NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Obinutuzumab for previously untreated chronic lymphocytic leukaemia

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1 Contents

Instructions for manufacturers and sponsors 3
Executive summary 6
Section A – Decision problem 16
1 Description of technology under assessment 16
2 Context 22
3 Equality 29
4 Innovation 29
5 Statement of the decision problem 32
Section B – Clinical and cost effectiveness 33
6 Clinical evidence 34
7 Cost effectiveness 127
Section C – Implementation 208
8 Assessment of factors relevant to the NHS and other parties 208
9 References 211
10 Appendices 234
11 Related procedures for evidence submission 309

2 List of figures

Figure 1 Study design: patient treatment and assessment 8
Figure A2 Mechanism of action of obinutuzumab (GA101) 17
Figure A3 Number of eligible people for obinutuzumab per annum in the UK 23
Figure A4 Example of the place obinutuzumab could occupy in the clinical pathway in chronic lymphocytic leukaemia 25
Figure B5 PRISMA Statement Flow Diagram 36
Figure B6 Study design: patient treatment and assessment 41
Figure B7 Disposition of patients in stage 1a (ITT) 58
Figure B8 Disposition of patients in stage 1b (ITT) 59
Figure B9 Disposition of patients in stage 2 (ITT) 60
Figure B10 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 1a (ITT) 65
Figure B11 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 1b (ITT) 66
Figure B12 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 1a (ITT) 67
Figure B13 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 1b (ITT) 67
Figure B14 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 2 (ITT) 68
Figure B15 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 2 (ITT) 69
Figure B16 Forest plot for PFS by subgroup: GClb vs. Clb (ITT) - Stage 1a (ITT) 70
Figure B17 Forest plot for PFS by subgroup: RClb vs. Clb (ITT) - Stage 1b (ITT) 70
Figure B18 Forest plot for PFS by subgroup: GClb vs. RClb (ITT) - Stage 2 (ITT) 71
Figure B19 PFS by MRD status in patients treated with GClb (Stage 2) 74
Figure B20 Study selection flow – PRISMA diagram (1992 until September 2013) 78
Figure B21 Study selection flow – PRISMA diagram (updated searches 2013 until 16 April 2014) 79

Figure B22 Diagram of evidence for large network for MTC (all 17 RCTs in 1L CLL included) 99
Figure B23 Diagram of evidence for small network for MTC (only RCTs in 1L CLL included if enrolled patients were ineligible for fludarabine-based therapy) 100
Figure B24 All grade and grade 3–4* infusion-related reactions by day of infusion†114
Figure B25 PRISMA flow for economic evaluation studies identified through database searches 129
Figure B26 Model Structure 133
Figure B27 March 2014 Kaplan-Meier estimates of investigator-assessed progression free survival for GClb (Stage 2) vs RClb (Stage 2) vs Clb (Stage 1) 138
Figure B28 CLL11 PFS Cumulative Hazard Plots 139
Figure B29 CLL11 PFS Log-cumulative Hazard Plots 140
Figure B30 PFS curves – KM estimates and log-logistic extrapolation 142
Figure B31 PFS curves – KM estimates and Weibull extrapolation 143
Figure B32 PFS curves – KM estimates and Gamma extrapolation**Error! Bookmark not defined.**
Figure B33 Base case modelled PFS curves – KM estimates with Gamma tails at 30, 36 and 37 months in the Clb, RClb and GClb arms respectively 144
Figure B34 Knauf trial – KM PFS estimates for Benda vs Clb at 2010 follow-up 146
Figure B35 Base case modelled PFS curves for Clb and Benda 147
Figure B36 Kaplan-Meier estimates of overall survival GClb (Stage 2) vs RClb (Stage 2) vs Clb (Stage 1) 150
Figure B37 Kaplan Meier curves of post progression survival in CLL5 152
Figure B38 Extrapolation of post progression survival in CLL5 153
Figure B39 Weekly probability of death as a function of age at progression 155
Figure B40 OS KM curves and base case modelled curves over lifetime horizon (20 years) 156
Figure B41 OS KM curves and base case modelled curves over duration of KM data available 157
Figure B42 Base case modelled OS curves for Clb, Benda and GClb 158
Figure B43 PRISMA flow for utility studies identified through database searches ..165
Figure B44 PRISMA flow for resource utilisation studies identified through database searches 179
Figure B45 Probabilistic sensitivity analysis scatterplot 202
Figure B46 Cost effectiveness acceptability curves 202

3 List of tables

Table 1 CLL11 PFS Results 10
Table 2 CLL11 OS Results 10
Table 3 Base-case results (costs, LYG and QALYs) 13
Table 4 Incremental cost-effectiveness results 13
Table 5 Incremental cost-effectiveness results versus Clb (compared against status quo to remove dominated and extended dominated interventions) 14
Table 6 Final simultaneous incremental cost-effectiveness results 14
Table A7 Additional evidence available within next 12 months 18
Table A8 Unit costs of technology being appraised 19
Table A9 Premedication to be administered before obinutuzumab infusion to reduce the risk of infusion-related reactions 20
Table A10 Median age at diagnosis and incidence rate of CLL in the UK (per 100 000 population) 22
Table A11 Relevant guidance and protocols for first line treatment of CLL 24
Table A12 Standard infusion rate of obinutuzumab in the absence of infusion reactions/hypersensitivity 27

Table A13 Innovative aspects of obinutuzumab 30
Table B14 List of eligible publications and relevant RCTs 38
Table B15 Dosage and administration of study treatments 43
Table B16 CLL inclusion criteria.....44
Table B17 CLL exclusion criteria.....45
Table B18 Characteristics of participants in CLL11 across randomised groups (stage 1a, stage 1b, and stage 2) 47
Table B19 Quality assessment results for CLL11.....62
Table B20 Secondary efficacy endpoints results for CLL11 (stage 1a, stage 1b, May 2013 data cut-off).....71
Table B21 Secondary efficacy endpoints results for CLL11 (stage 2).....72
Table B22 Overall survival results for CLL11 (stage 1a, stage 1b and stage 2, March 2014 cut off).....74
Table B23 Summary of the 42 RCTs meeting the inclusion criteria 80
Table B24 Summary of the trials used to conduct the indirect comparison.....88
Table B25 List of included non-randomised controlled trials.....96
Table B26 Summary of PFS and OS results of the 17 RCTs identified in the SR 97
Table B27 Summary of results in the trials used to conduct the indirect comparison102
Table B28 Summary of MTC results for obinutuzumab vs Bendamustine 108
Table B29 Probability of being best treatment.....108
Table B30 Adverse events of any grade (Safety Population*) 112
Table B31 Adverse events of Grade 3 or higher (Safety Population*) 113
Table B32 Serious adverse events (Safety Population*) 113
Table B33 Infusion related reactions during GClb treatment† by baseline characteristics 115
Table B34 Impact of study protocol amendments on infusion-related reactions during GClb treatment.....115
Table B35 Newly diagnosed malignant, benign or unspecified neoplasms starting 6 months after first study drug intake by treatment comparison*.....116
Table B36 Impact of infusion-related reactions and tumour lysis syndrome on clinical course 117
Table B37 List of grade 5 adverse events 118
Table B38 Inclusion and exclusion criteria for cost-effectiveness search.....128
Table B39 Summary list of other cost-effectiveness evaluations 130
Table B40 Key features of analysis.....135
Table B41 Investigator-assessed progression free survival (March 2014 data cut) 137
Table B42 Model Fit Akaike Information Criterion (AIC) estimates 141
Table B43 Overall survival 149
Table B44 Akaike Information Criterion (AIC) for CLL5 post progression survival ..152
Table B45 Likelihood ratio test for inclusion of parameters into the model with exponential distribution (CLL5).....154
Table B46 Weekly age-adjusted probability of death by treatment arm 155
Table B47Summary of variables applied in the economic model.....160
Table B48: Inclusion and exclusion criteria for utility studies 165
Table B49 Assessment of suitability of published literature detailing utility values in 1L CLL 167
Table B50 Health state titles and definitions.....174
Table B51 Results of utility elicitation study and relevance within economic model 174
Table B52 Base case utility weights for the progressed health state 175
Table B53 Final base case utilities used within model.....175
Table B54 Inclusion and exclusion criteria for resource utilisation studies.....179
Table B55 Unit costs associated with the technology in the economic model.....181
Table B56 List of health states and associated costs in the economic model.....185
Table B57 List of adverse events and summary of costs included in the economic model 187
Table B58 Total adverse event cost by treatment arm 189
Table B59 Summary of model results compared with clinical data 193

Table B60 Model outputs by clinical outcomes....194
Table B61 Summary of QALY gain in PFS....194
Table B62 Summary of QALY gain in PD....194
Table B63 Summary of costs in PFS....195
Table B64 Summary of costs in PD....195
Table B65 Summary of predicted resource use by category of cost: mean treatment cost 195
Table B66 Summary of predicted resource use by category of cost: administration cost 195
Table B67 Summary of predicted resource use by category of cost: mean costs supportive care PFS....196
Table B68 Base-case results (costs, LYG and QALYs)....196
Table B69 Incremental cost-effectiveness results 197
Table B70 Incremental cost-effectiveness results versus Clb (compared against status quo to remove dominated and extended dominated interventions) 197
Table B71 Final simultaneous incremental cost-effectiveness results 197
Table B72 Deterministic sensitivity analyses....199
Table B73 Eligible population by year 208
Table B74 Market share assumptions by year 209
Table B75 Budget impact by year 210

Executive summary

1L CLL for fludarabine-unsuitable patients

CLL is the most common form of adult leukaemia in Western Europe, accounting for 31%–37% of all leukaemias (1) with approximately 2–6 new cases in every 100 000 individuals per year (2-4). In the UK, the average incidence rate is 8.9 in males and 5.1 in females per 100 000 (5). On average only 44% of male patients and 52% of female patients will live for 5 years or more after being diagnosed (6).

The incidence and prevalence of CLL is higher in the elderly, with an estimated median age at first diagnosis reported at 71-72 years (4;5;7) and a median age of 75 at the time therapy is initiated (8). Since 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, such as cardiac or renal problems, that impact on the prognosis of CLL and are associated with shorter survival (9;10). As a result, these patients have limited treatment options since the standard of care in fit CLL patients, fludarabine, cyclophosphamide, and rituximab (FCR), is not well tolerated and often withheld from patients with comorbidities and age-related changes in organ function (8;9).

There is therefore a significant need for effective new treatment options for patients with cormorbidities who are typically unsuitable for fludarabine-based therapy, in order to improve their overall survival and health-related quality of life.

The current treatment pathway

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 (11), elderly patients with comorbidities are representative of a typical CLL patient. However, this population of CLL patients is underrepresented in clinical trials and subsequently is not optimally treated in clinical practice (12). According to real world data from clinical practice in the UK, chlorambucil (Clb) (±rituximab) is the most common first line treatment used in approximately 36% of patients. In contrast, bendamustine (±rituximab) makes up only 14% of treatment share (13).

Therefore, although there is no defined standard of care for patients with CLL who are ineligible for full-dose fludarabine-based treatment, Clb would appear to be the main therapeutic approach for these patients in UK practice. As yet, no first line treatment for CLL has proved to be superior to Clb in terms of overall survival (OS) in a typical, older patient population with coexisting conditions (14;15).

Obinutuzumab is a step change in the treatment of 1L CLL for fludarabine-unsuitable patients

Obinutuzumab is a new treatment anticipated to be indicated in combination with Clb for adult patients with previously untreated CLL for whom full-dose fludarabine-based therapy is not appropriate.

What is obinutuzumab?

Obinutuzumab is a first-in-class Type II glycoengineered anti-CD20 antibody with a mode of action based on enhanced antibody dependent cellular cytotoxicity, increased direct cell death, and a lower degree of complement dependent cytotoxicity compared with non-glycoengineered, Type I antibodies such as rituximab and ofatumumab. The combination of obinutuzumab and chlorambucil combines targeting the CD20 antigen with chemotherapy.

The result is an innovative treatment that significantly improves outcomes for older CLL patients with coexisting conditions, including progression free survival, response rate, and overall survival.

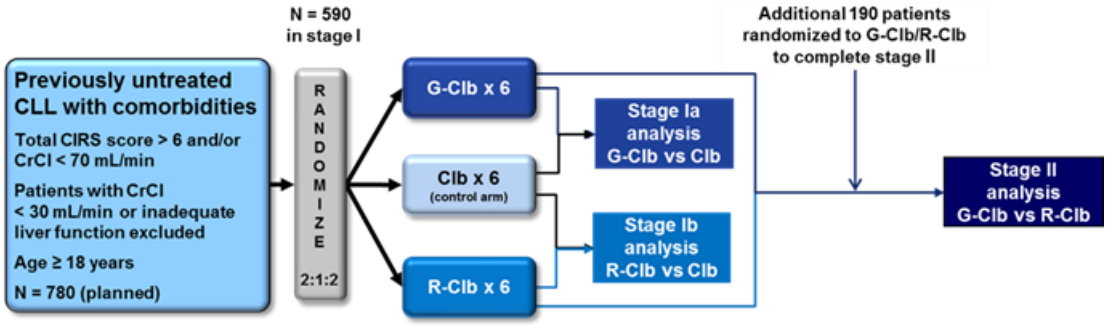
How efficacious is obinutuzumab?

The pivotal study supporting the use of obinutuzumab is the CLL11 trial. This is a phase III, randomised, double-blind, international, multicentre, three-arm study designed to evaluate the efficacy and safety of obinutuzumab and chlorambucil (GClb) compared with rituximab plus chlorambucil (RClb) or chlorambucil (Clb) in people with previously untreated CLL for whom full-dose fludarabine based therapy is not appropriate.

The study was designed to include two stages and 3 primary analysis time points (Figure 1):

- Stage 1 randomised patients 2:2:1 GClb:RClb:Clb and was split into two primary analysis time points:
    - Stage 1a: final analysis for GClb vs. Clb and futility and efficacy interim analysis for GClb vs. RClb
    - Stage 1b: final analysis for RClb v Clb
- Stage 2: final analysis for GClb vs. RClb (randomization) (1:1) continued into the GClb and RClb treatment arms only

Figure 1 Study design: patient treatment and assessment



CIRS: Cumulative Illness Rating Scale; Clb: Chlorambucil; CrCl: Creatinine Clearance; G: Obinutuzumab; R: Rituximab

The primary endpoint of the study was investigator-assessed progression free survival (PFS). PFS is a validated surrogate endpoint for overall survival (OS). CLL is an indolent disease with a death rate of about 50% after 5 years of diagnosis. Therefore a trial with OS as the primary endpoint in CLL would need a median observation time and number of patients required to demonstrate a significant benefit that would be prohibitively high. Secondary endpoints included time−to−event endpoints [i.e. event free survival (EFS), disease free survival (DFS), duration of response (DOR), time to re−treatment /new anti−leukaemic therapy and overall OS] and were analysed in a manner similar to the primary analysis.

PFS (9th May 2013 data cut)

The primary analysis took place with a clinical data cut off of 9th May 2013. The data presented immediately below are from this cut off, sourced from the CLL11 publication (10) or from the CLL11 trial CSRs (16-19).

At the time of the final stage 1a analysis, the addition of obinutuzumab to Clb (GClb) resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS (stratified Hazard Ratio (HR) 0.19 [95% CI: 0.14 - 0.27]). The Kaplan−Meier estimated median PFS was 11.1 months in the Clb arm and 26.7 months in the GClb arm (p<0.0001). This represents a 15.6 month improvement in PFS compared to the most commonly used regimen in the UK for this patient population.

In stage 2, the addition of obinutuzumab to Clb (GClb) resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS compared to RClb (stratified HR 0.39 [95% CI: 0.31 - 0.49]).The Kaplan-Meier estimated median PFS was 15.2 months in RClb arm and 26.7 months in GClb arm; an 11.5 month improvement.

Update to PFS (3rd March 2014 data cut-off)

Recently a new data cut (3rd March 2014) has been analysed for which neither an updated CSR nor publication is yet available. However given the increased maturity of this data and the potential value of this to the appraisal, this information is presented within this submission. This data should be regarded as commercial in confidence until formally presented.

The PFS results from this new data cut [redacted] stage 1a GClb showed [redacted]

The Kaplan-Meier estimated median PFS was [redacted] months in the Clb arm, versus [redacted] months in the GClb arm.

[redacted]

The Kaplan-Meier estimated median PFS was [redacted] months in RClb arm and [redacted] months in GClb arm.

Table 1 below summarises the main PFS results from both data cuts.

Table 1 CLL11 PFS Results

Data Cut	Stage 1a Analysis			Stage 2 Analysis		
	Median PFS (Mos)		HR (95% CI)	Median PFS (Mos)		HR (95% CI)
	Clb	*GClb*		*RClb*	*GClb*	
9th May 2013	11.1	26.7	0.19 (0.14 - 0.27)	15.2	26.7	0.39 (0.31 - 0.49)
3rd March 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; Clb: Chlorambucil; G: Obinutuzumab; HR: Hazard Ratio; Mos: Months; PFS: Progression-free Survival; R: Rituximab

OS (9th May 2013 data cut)

At the time of the final stage 1a analysis, the addition of obinutuzumab to Clb (GClb) resulted in a clinically meaningful and statistically significant (not adjusted for multiplicity) improvement in the secondary endpoint of OS (HR 0.41 [95% CI: 0.23 - 0.74]). In Stage 2, (GClb vs RClb) statistically significant improvement in OS was not achieved; (HR 0.66 [95% CI: 0.41 – 1.06], p=0.0849).

Update to OS (3rd March 2014 data cut-off)

This latest cut-off shows [redacted]. Table 2 below summarises the main OS results from both data cuts.

Table 2 CLL11 OS Results

Data Cut	Stage 1a Analysis			Stage 2 Analysis		
	Median OS (Mos)		HR (95% CI)	Median OS (Mos)		HR (95% CI)
	Clb	*GClb*		*RClb*	*GClb*	
9th May 2013	NR	NR	0.41 (0.23 - 0.74)	NR	NR	0.66 (0.41 – 1.06)
3rd March 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; Clb: Chlorambucil; G: Obinutuzumab; HR: Hazard Ratio; Mos: Months; NR: Not Reported; OS: Overall Survival; R: Rituximab

Safety

Adverse events occurred more frequently in the GClb and RClb groups than in the Clb alone group and were most frequent with GClb treatment. The incidence of grade 3 or 4 neutropenia was highest with the combination of obinutuzumab and chlorambucil and was lowest with Clb 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 GClb treatment than with RClb treatment. In the GClb 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.

How is obintuzumab administered?

Obinutuzumab is 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, 1000mg is administered by intravenous infusion, the first dose administered as a split infusion over day 1 (100mg) and day 2 (900mg).

The list price of one 1000mg vial of obinutuzumab is £3,312.

Cost-effectiveness

A cost utility analysis was conducted utilising data from the 3rd March 2014 data cut of the CLL11 study in order to evaluate the cost effectiveness of obinutuzumab in patients with previously untreated chronic lymphocytic leukaemia.

Comparators considered included Clb monotherapy, rituximab in combination with Clb (RClb), bendamustine (Benda) monotherapy and rituximab in combination with bendamustine (RBenda). As Benda and RBenda were not comparators in the CLL11 trial, a mixed treatment comparison was conducted and incorporated into the model.

A three state partitioned survival model (PFS, progressed disease, and death) was implemented which models the transition from the PFS health state using Kaplan−Meier PFS data directly from the CLL11 trial, whilst the transition from the progressed disease health state employs a Markov trace, due to the relatively immature OS trial data. This model structure has been utilised in numerous previous NICE technology appraisals in haematology. In accordance with the NICE reference case an NHS and personal social

services perspective was used, and a 3.5% discount rate per annum for costs and QALYs was applied. A 20 year time horizon was utilised in order to capture all differences between the arms compared. A cycle length of one week was used in order to incorporate the 28-day dosing of obinutuzumab and a half cycle correction where appropriate.

Resource use in each health state was based on ESMO guidelines (Eichhorst et al., 2011). Costs were taken from BNF 65, PSSRU 2013 and NHS references costs 2012/13. The utilities were based on a utility elicitation study conducted with the UK general public to derive societal preferences for quality of life associated with CLL.

The latest available data from CLL11 was utilised in order to develop the model (3rd March 2014). As the survival data from CLL11 is not complete, it was necessary to apply parametric extrapolation in order to derive mean survival with and without the intervention.

In line with best practice in extrapolation, modelling was informed via interpretation of the CLL11 cumulative hazard plots, consultation with a panel of clinical and academic modelling experts and validated through comparison with external data. The model has strong face validity when compared with the data available. Similarly the mixed treatment comparison was conducted in accordance with NICE recommended methods and consulted and validated with clinical and modelling experts.

A simultaneous incremental analysis of all comparators was utilised in order to define the efficiency frontier and ensure that only relevant therapies were considered when evaluating the cost-effectiveness of obinutuzumab.

The cost-effectiveness results are presented in Table 3, Table 4, Table 5 and Table 6.

Table 3 Base-case results (costs, LYG and QALYs)

	GClb	RBenda	RClb	Benda	Clb
Technology acquisition cost	£23,157	£15,243	£9,545	£4,745	£286
Other costs	£11,732	£11,972	£10,457	£10,812	£7,735
Total costs	£34,888	£27,215	£20,002	£15,557	£8,020
Difference in total costs	-	£6,576	£13,789	£18,234	£25,771
LYG	5.79	5.42	5.08	5.04	4.60
LYG difference	-	0.36	0.70	0.74	1.19
QALYs	4.03	3.65	3.33	3.30	2.92
QALY difference	-	0.38	0.70	0.73	1.11
ICER	-	£20,076	£21,275	£26,463	£24,256

Benda; Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY(s), quality-adjusted life year(s); R: Rituximab.

Table 3 shows the base case results for obinutuzumab versus each comparator. It shows that obinutuzumab is more effective but more costly than all other comparators.

Table 4 Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
RClb	£20,002	5.08	3.33	£4,445	0.04	0.03	£144,269
RBenda	£27,215	5.42	3.65	£7,213	0.34	0.32	£22,718
GClb	£34,888	5.79	4.03	£7,637	0.36	0.38	£20,076

Benda; Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY(s), quality-adjusted life year(s); R: Rituximab

Table 5 Incremental cost-effectiveness results versus Clb (compared against status quo to remove dominated and extended dominated interventions)

Technologies	Incremental costs vs Clb (£)	Incremental LYG vs Clb	Incremental QALYs vs Clb	ICER (£/QALY gained)	Remove from analysis
Clb	£0	0.00	0.00	£0	No
Benda	£7,536	0.45	0.38	£19,983	No
RClb	£11,982	0.48	0.41	£29,369	Yes – extendedly dominated
RBenda	£19,195	0.83	0.73	£26,458	Yes – extendedly dominated
GClb	£26,868	1.19	1.11	£24,256	No

Benda; Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY(s), quality-adjusted life year(s); R: Rituximab

The results in Table 4 demonstrate the incremental analysis.

Table 5 details all interventions against Clb (the status quo) in order to be able to determine the cost-effectiveness plane and eliminate all interventions that are either dominated or extended dominated. It can be seen that RClb and RBenda are both extended dominated because they result in ICERs that are greater than GClb.

Table 6 Final simultaneous incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
GClb	£34,888	5.79	4.03	£19,331	0.74	0.73	£26,463

The efficiency frontier therefore consists of only Clb, Benda and GClb as can be seen in Table 6. The comparison of Benda versus Clb results in ICER of £19,983. Since this is at a level that would typically be deemed cost-effective by NICE, Benda becomes the relevant comparator for GClb. The comparison of GClb versus Benda also results in a cost-effective ICER at £26,463. GClb therefore represents an efficient use of NHS resources compared to current standards of care.

Extensive deterministic sensitivity analyses were conducted – in the vast majority of these the ICER remained below £30,000 per QALY gained. These analyses indicate that the key

drivers of the model are the results of the mixed treatment comparison and the post-progression death rate.

A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate. The probabilistic sensitivity analysis (PSA) indicates that obinutuzumab has a 63.4% chance of being the most cost-effective at a threshold of £30,000 per QALY gained. This is more than twice that for the next most cost-effective treatment option (bendamustine at a probability of 28.5%).

Conclusion

Obinutuzmab offers a step change in the clinical management of previously untreated CLL for comorbid patients, who presently have few treatment options available to them.

The pivotal trial conducted demonstrates the substantial improvement in progression free and overall survival of obinutuzumab plus Clb compared with current standards of care; the PFS hazard ratios are exceptional and demonstrate the significant impact obinutuzumab can have on patients' lives.

The cost-effectiveness analysis presented demonstrates that obinutuzumab is cost-effective compared to currently used treatments and that this conclusion is robust when subject to sensitivity analysis.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Obinutuzumab (GA101, RG1759, Gazyvaro), a glycoengineered Type II humanised anti-CD20 monoclonal antibody of the IgG1 subclass, ATC code: L01XC15.

1.2 What is the principal mechanism of action of the technology?

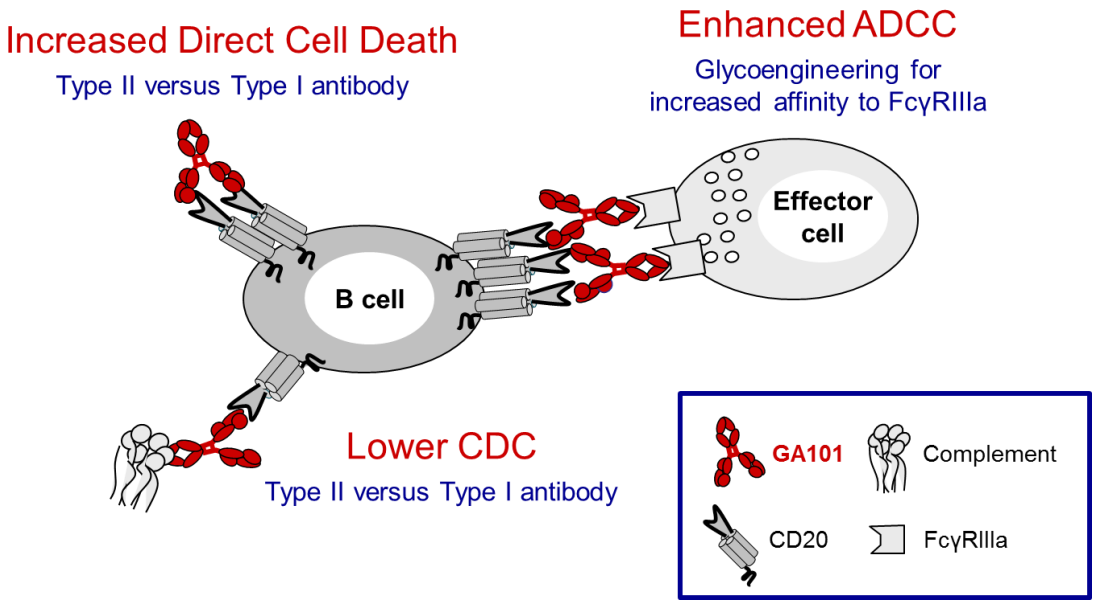
CD20 is an important target for the treatment of B-cell malignancies such as chronic lymphocytic leukaemia (20). Antibodies against CD20 deplete B-cells in lymphoid tissue (21;22) and as a result, improve response rates, depth of remission, progression-free, and overall survival in CLL patients compared with chemotherapy alone (10;23).

Obinutuzumab, as a Type II anti-CD20 antibody, specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue (24).

Obinutuzumab induces direct cell death and enhances antibody-dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells (22;24). In addition, obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC) cells (22;24). The mode of action of Type II antibodies results in a greater direct cell death compared with Type I antibodies (25). In addition, glycoengineering of the Fc part of obinutuzumab has resulted in a higher affinity for FcγRIII receptors on immune effector cells as compared to non-

glycoengineered antibodies, thereby enhancing ADCC (Figure A2), which translates into superior B cell depletion and anti-tumour efficacy (22;24).

Figure A2 Mechanism of action of obinutuzumab (GA101)



SOURCE: (26)

ADCC: Antibody-dependent Cellular Cytotoxicity; CDC: Complement Dependent Cytotoxicity; CD20: B-lymphocyte antigen CD20; FcγRIII: Receptor III for the Fc Region of Immunoglobulin G; GA101: Obinutuzumab

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A European Marketing Authorisation procedure has been submitted for obinutuzumab. A CHMP positive opinion is expected in May 2014. This opinion is expected to be converted into a marketing authorisation for the treatment of previously untreated CLL in July 2014.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The regulatory procedure is still ongoing and the draft assessment report is not yet available. To date, Roche has received day 150 questions from the regulatory agency and the main issue highlighted during the regulatory process is the need to provide data comparing obinutuzumab + chlorambucil vs. rituximab + chlorambucil which were not available at the time of the submission. Roche has prepared detailed responses to address this and provided the updated clinical study report containing the requested data.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Anticipated indication:

[Obinutuzumab] in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Table A7 Additional evidence available within next 12 months

Status	Details
Ongoing (updates on efficacy when available)	**CLL11 (BO21004; NCT01010061)** - Phase III, open-label, three arm randomised, multicentre, international, clinical trial to evaluate obinutuzumab + chlorambucil compared to rituximab + chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities
Ongoing (data available in Q4 2014)	**MaBLe (MO22468; NCT01056510)** - Phase IV, open-label, parallel group randomised, multicentre, international, clinical trial to evaluate rituximab added to either bendamustine or chlorambucil in patients with CLL

CLL: Chronic Lymphocytic Leukaemia

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Obinutuzumab is expected to be available in the UK in July 2014.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Obinutuzumab (Gazyva™) has been approved by the Food and Drug Administration (FDA) on the 1st of November 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated CLL.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

An SMC appraisal of obinutuzumab is expected at the earliest by July 2014 with guidance expected by October 2014.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A8 Unit costs of technology being appraised

Pharmaceutical formulation	Powder for concentrate for solution for infusion
Acquisition cost (excluding VAT)	£3,312 per 1000mg vial (*provisional price - subject to confirmation prior to launch*)
Method of administration	Intravenous infusion
Doses	1000mg fixed dose
Dosing frequency	Cycle 1: The First 1000mg infusion is split over days 1 and 2 (100mg day 1, 900mg day 2), with subsequent 1000mg infusions on days 8 and 15. Cycles 2-6: 1000mg on day 1 of each cycle All cycles are 28-days in duration
Average length of a course of treatment	6 cycles
Average cost of a course of treatment	£9,936 cycle 1 £3,312 per cycle thereafter
Anticipated average interval between courses of treatments	A person with previously untreated CLL will receive only one course of treatment with obinutuzumab
Anticipated number of repeat courses of treatments	A person with previously untreated CLL will receive only one course of treatment with obinutuzumab
Dose adjustments	Dose reductions are not recommended

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Other than the current routine clinical tests to confirm diagnosis of CD20-positive CLL, no additional tests are required for treatment with an obinutuzumab based regimen, or prior to the administration of obinutuzumab.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Monitoring of patients over and above usual clinical practice for obinutuzumab is not required.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Obinutuzumab is indicated for use in combination with chlorambucil (Clb).

In addition, premedication according to the schedule in Table A9 is required for all patients prior to treatment with obinutuzumab.

Prophylaxis and Premedication for Infusion-Related Reactions (IRR)

Table A9 Premedication to be administered before obinutuzumab infusion to reduce the risk of infusion-related reactions

Day of Treatment Cycle	Patients requiring Premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histaminic medicine[3]	
Cycle 1: Day 2	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab
		Anti-histaminic medicine[3]	

			infusion.
Cycle 1: **Day 8,** **Day 15** **Cycles 2-6:** **Day 1**	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/l prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine[3]	

SOURCE: (24)

IRR: Infusion Related Reaction. [1]100 mg prednisone/prednisolone or 20mg dexamethasone or 80mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR. [2] e.g. 1000 mg acetaminophen/paracetamol. [3] e.g. 50 mg diphenhydramine.

Hypotension, as a symptom of IRR, may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration (24).

Prophylaxis for Tumour Lysis Syndrome (TLS)

In patients with high circulating lymphocyte count (>25 x 10^9/L) prophylaxis with adequate hydration and administration of uricostatics (e.g. allopurinol) starting 12–24 hours prior to start of therapy is recommended to reduce the risk of tumour lysis syndrome (10;24).

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

CLL is the most common form of adult leukaemia in Western Europe, accounting for 31%–37% of all leukaemias (1) with approximately 2–6 new cases in every 100 000 individuals per year (2-4). In the UK, the average incidence rate is 8.9 in males and 5.1 in females per 100 000 population (Table A10) (5). The incidence and prevalence of CLL is higher in the elderly (Table A10), with an estimated median age at first diagnosis reported at 71-72 years (Table A10) (4;5;7) and a median age of 75 at the time therapy is initiated (8).

Table A10 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: (5)

CLL: Chronic Lymphocytic Leukaemia

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 (4).

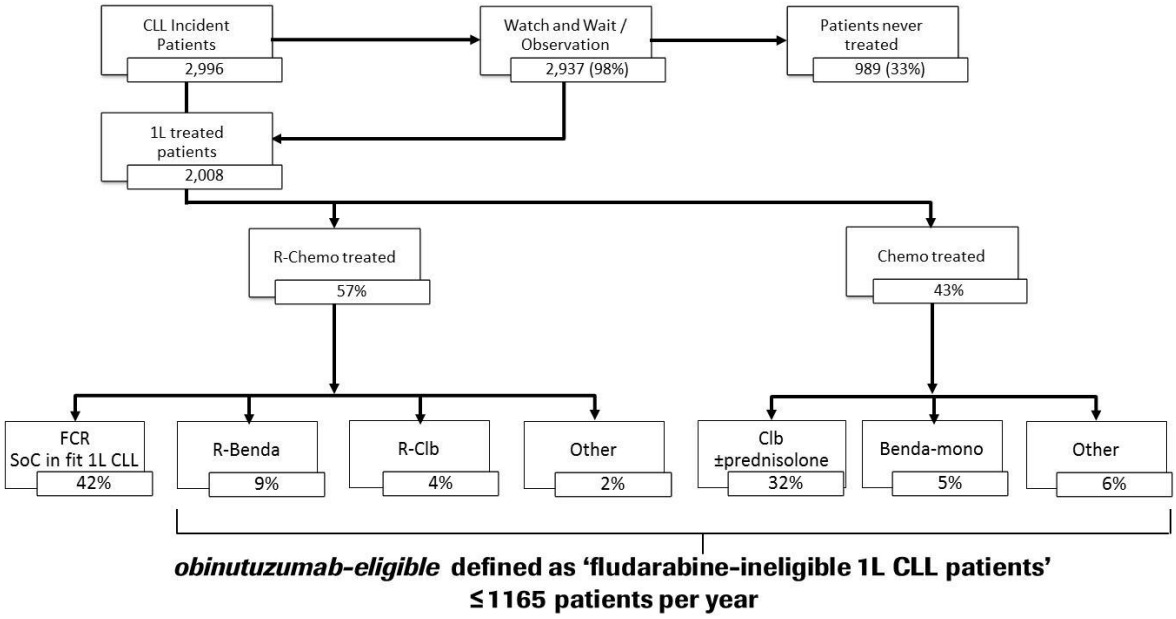
As CLL is a disease that typically affects the elderly (>70 years of age), a high proportion of patients with CLL suffer from co-existing medical conditions. An analysis from the Mayo Clinic Database (from 1995 to 2006) revealed that nearly 90% of CLL patients had one or more comorbidities and 46% of patients had at least 1 major comorbidity (9). Medical conditions, such as cardiac or renal problems, have an impact on the prognosis of CLL and are associated with shorter survival (9;10). As a result, 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 (8;9). 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 (27). In addition, a sustained remission for patients with CLL is associated with long-term health-related QoL benefit (28;29).

To effectively treat the typical CLL patient, 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.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Figure A3 Number of eligible people for obinutuzumab per annum in the UK



SOURCE: Based on Roche internal forecasting assumptions and CLL patient algorithms (13)
Benda: Bendamustine; Benda-mono: Bendamustine monotherapy; Chemo: Chemotherapy; Clb: Chlorambucil; Clb-mono: Chlorambucil monotherapy; CLL: Chronic Lymphocytic Leukaemia; FCR: Rituximab in combination with Fludarabine and Cyclophosphamide; R: Rituximab; R-Benda: Rituximab in combination with Bendamustine; R-Clb; Rituximab in combination with Chlorambucil; SoC: Standard of Care; 1L: First line; 17p del: 17p deletion

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

For CLL patients, the median survival from diagnosis varies between 18 months and over 10 years (4). In the UK, the median survival is 9.53 years (95%CI [8.20 to 10.18]), for all stages of CLL combined (30). However, on average only 44% of male patients and 52% of female

patients will live for 5 years or more after being diagnosed (6). 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 (14;15).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Table A11 Relevant guidance and protocols for first line treatment of CLL

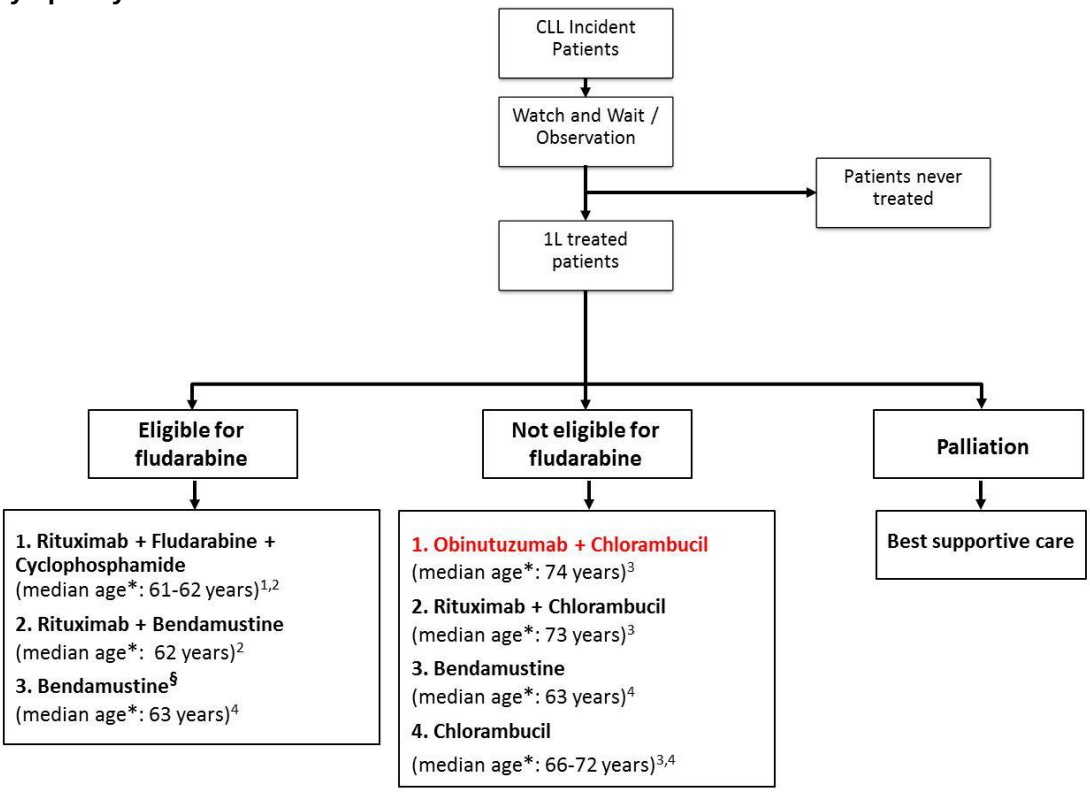
Guidelines	Year	Guidance
NICE		
No 174 'Rituximab for the first-line treatment of chronic lymphocytic leukaemia'	2009	TA 174 recommends rituximab in combination with fludarabine and cyclophosphamide as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate
No 216 'Bendamustine for the first-line treatment of chronic lymphocytic leukaemia'	2011	TA 216 recommends bendamustine as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
SMC		
Rituximab No. 540/09	2009	The SMC recommends rituximab for first-line treatment of patients with CLL in combination with fludarabine and cyclophosphamide
Bendamustine hydrochloride No. 694/11	2011	The 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
BCSH		
Guidelines on the diagnosis, investigation and management of CLL Brit J Haem. 2012, 159: 541–564	2012	BCSH recommends FCR as initial therapy for previously untreated fit patients outside clinical trials. Options for patients unfit for FCR include chlorambucil or bendamustine
NCCN		
Clinical Practice Guidelines in Oncology – Non-Hodgkins Lymphomas v.1.2014	2013	NCCN recommends rituximab in combination with fludarabine and cyclophosphamide for patients <70 years of age and without significant comorbidities. The NCCN recommends obinutuzumab and chlorambucil for patients ≥ 70 years of age or younger with comorbidities
ESMO		
Chronic lymphocytic leukemia Ann Oncol. 2011; 22 (suppl 6): vi50-vi54	2011	In physically active patients (no major health problems and normal renal function) rituximab in combination with fludarabine and cyclophosphamide is the standard first-line therapy. In patients with relevant co-morbidity, chlorambucil seems to be the standard therapy

SOURCE: (4;31-36)
BCSH: British Committee for Standards in Haematology Guidelines for CLL; CLL: Chronic Lymphocytic Leukaemia; ESMO: European Society for Medical Oncology; FCR: Rituximab in combination with Fludarabine and Cyclophosphamide ; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Obinutuzumab is anticipated to be indicated in combination with Clb for the treatment of adult patients with previously untreated CLL for whom full-dose fludarabine based therapy is unsuitable. This population is in accordance with the population included in the obinutuzumab pivotal clinical trial CLL11. Figure A4 depicts the treatment pathway in the UK for the treatment of patients with CLL, based on real-world data (market research) and clinical trials, to which obinutuzumab is added.

Figure A4 Example of the place obinutuzumab could occupy in the clinical pathway in chronic lymphocytic leukaemia



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

*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.**

CLL: Chronic Lymphocytic Leukaemia; 1L: First Line

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best 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 (11), elderly patients with comorbidities represent the typical CLL patients. However, this population of CLL patients is significantly underrepresented in clinical trials and subsequently is not optimally treated in clinical practice (12). According to real world data from clinical practice in the UK, Clb (±rituximab) occupies 36% of treatment share in first line treatment of CLL patients, compared with only 14% for bendamustine (±rituximab) (13). Therefore, although there is no defined standard of care for patients with CLL who are ineligible for full-dose fludarabine-based treatment, it seems clear that Clb is the main therapeutic approach for these patients in UK practice. Importantly, in this context, no first line treatment for CLL has yet proved to be superior to Clb in terms of overall survival (OS), in a typical, older patient population with coexisting conditions (14;15).

2.7 Please identify the main comparator(s) and justify their selection.

The main comparator identified is Clb as CLL patients considered ineligible for fludarabine-based immunochemotherapy because of co-morbidity and/or other age-related problems, are most frequently treated with Clb and sometimes with Clb combined with rituximab (RClb) (13;41;42). Rituximab in combination with chlorambucil has recently been added as a treatment for unfit CLL patients in the NCCN guidelines (36).

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 (40). Another limitation is the lack of comorbidity burden assessment in the patient population enrolled (43). 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. We therefore recommend bendamustine to be reserved as clinical comparator in patients eligible for fludarabine-based therapy, which is outside the scope of this appraisal.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The safety of obinutuzumab has been evaluated in more than 900 people in Phase I, Phase II, and Phase III trials.

In addition to IRRs (grade 1-4), in the pivotal trial CLL11 the most common adverse drug reactions (grade 3, 4, or 5) which occurred in 10% or more trial participants were neutropenia and thrombocytopenia (10) (Section 6.9).

The majority of adverse events were managed by delaying or reducing the dose of obinutuzumab (24). Therapies for the management of adverse events are listed in section 1.14.

The cost associated with treatment of adverse events will be considered in the economic analysis.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Obinutuzumab is administered on a 28 day cycle basis. On days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-6, 1000mg are administered by intravenous infusion, the first administered as a split infusion over days 1 and 2. The infusion rates are presented in Table A12. These infusions typically take place in a hospital with an established oncology unit, which has the staffing and infrastructure required for administration of cancer treatments.

Table A12 Standard infusion rate of obinutuzumab in the absence of infusion reactions/hypersensitivity

Cycle	Day of Treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2 (900 mg)	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	
Cycles 2 – 6	Day 1	

SOURCE: (24)

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 **Please let us know if you think that this appraisal:**

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues have been identified.

3.1.2 **How has the analysis addressed these issues?**

No equality issues have been identified.

4 Innovation

4.1.1 **Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.**

Obinutuzumab has an innovative design which has a direct impact on its mode of action and results in a step-change in the treatment of CLL.

Although there is no defined standard of care for patients with CLL who are ineligible for full-dose fludarabine-based treatment, it seems clear that Clb is the main therapeutic approach for these patients in UK practice (Section 2.6) (13). Importantly, in this context, no first line treatment for CLL has yet proved to be superior to Clb in terms of OS, in a typical, older patient population with coexisting conditions (14;15).

Obinutuzumab is a first-in-class Type II glycoengineered anti-CD20 antibody with a mode of action based on enhanced antibody dependent cellular cytotoxicity, increased direct cell death, and a lower degree of complement dependent cytotoxicity compared with non-glycoengineered, Type I antibodies such as rituximab and ofatumumab. The combination of obinutuzumab and chlorambucil combines targeting the CD20 antigen with chemotherapy.

The result is an innovative treatment significantly improving outcomes of older CLL patients with coexisting conditions, as demonstrated by improved progression free survival, response rate, and improved overall survival in the pivotal CLL11 trial (Table A13). This improvement in OS represents the first significant improvement in OS against Clb in a Phase 3 trial.

Table A13 Innovative aspects of obinutuzumab

Innovation area	Result
Design	• It is a first-in-class Type II glycoengineered anti-CD20 antibody, which compared to Type I antibodies, increases direct cell death with a lower degree of complement dependent cytotoxicity (Section 1.2) • It is glycoengineered, which results in a higher affinity for FcγRIII receptors on immune effector cells as compared to non-glycoengineered antibodies, leading to enhanced ADCC (Section 1.2)
Step-change in the treatment of CLL	• Improved PFS (26.7 months vs. 11.1 months, hazard ratio: 0.18 [95%CI: 0.13 to 0.24], p<0.001; versus Clb) (10) • Improved ORR (p<0.001; versus Clb) (10) • Longer time to next treatment (hazard ratio: 0.24 [95% CI: 0.16 – 0.35], p<0.0001; versus Clb) • Landmark improvement in OS (hazard ratio for death: 0.41 [95%CI: 0.23 to 0.74], p=0.002 versus Clb and 0.66 [95%CI: 0.41 to 1.06], p=0.08 versus R-Clb) (10). This result represents the first significant improvement in OS against Clb in a Phase 3 trial

SOURCE: (10;24)
ADCC: Antibody-dependent Cellular Cytotoxicity; Clb: Chlorambucil; CLL: Chronic Lymphocytic Leukaemia; FcγRIII: Receptor III for the Fc region of Immunoglobulin G; OS: Overall Survival; PFS: Progression-free Survival; R-Clb: Rituximab and chlorambucil; RR: Response Rate

4.1.2 **Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.**

All health-related benefits are likely to be captured in the QALY calculation.

4.1.3 **Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.**

Not applicable.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	To appraise the clinical and cost effectiveness of obinutuzumab within its licensed indication for previously untreated chronic lymphocytic leukaemia.	As per scope.	n/a
Intervention	Obinutuzumab	As per scope.	n/a
Comparator(s)	• Chlorambucil (Clb) • Rituximab in combination with chlorambucil (RClb) • Bendamustine (Benda) • Rituximab in combination with bendamustine (RBenda)	As per scope.	n/a
Outcomes	• overall survival • progression-free survival • response rates • minimal residual disease negativity • adverse effects of treatment • health-related quality of life	As per scope.	n/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope.	n/a
Subgroups to be considered	No subgroups identified.	As per scope.	n/a
Special considerations, including issues related to equity or equality	No potential equity or equality issues identified	As per scope.	n/a

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.**

A systematic review was undertaken in order to identify all randomised evidence relevant to the decision problem.

Searches used index and text words which included obinutuzumab and CLL as descriptors. The search was restricted to include only documents relating to humans and clinical trials, and excluded reviews when the inclusion criteria were not met. Only publications written in English were assessed. The search was restricted to CLL. The search was further restricted manually according to inclusion/exclusion criteria in Section 10.2.6.

Full details of the searches conducted and terms used are provided in Appendix 2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in Section 10.2.7.

6.2 Study selection

6.2.1 **Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A**

justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Inclusion Criteria:

Published papers or abstracts which evaluated the following were included:

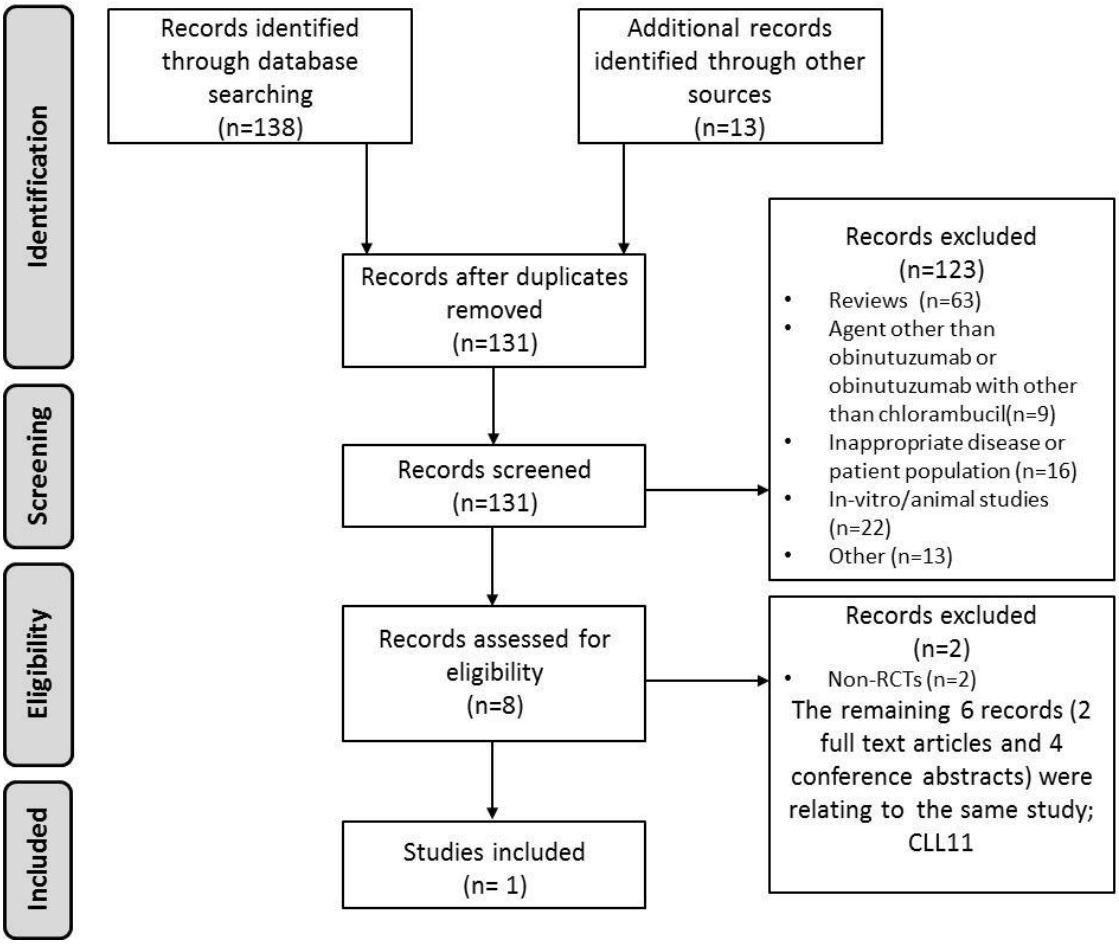
- GA101 (obinutuzumab) has to be the major focus of the study, in order to eliminate references which merely mentioned obinutuzumab as part of a discussion of treatments for CLL or other cancers, for example review articles
- CLL is the major focus of the study, in order to eliminate papers addressing the use of obinutuzumab in other cancers
- The relevant population is previously untreated patients
- Data addressing the efficacy of obinutuzumab in combination with agents other than chlorambucil are not in line with this submission
- Documents relating to humans – since work in animal models is not relevant to this submission

Exclusion criteria:

- References which were not randomised controlled trials
- Studies where obinutuzumab was not included
- Studies which were in non-relevant populations ie. Relapsing or refractory CLL
- Studies which included agents in combination with obinutuzumab other than chlorambucil

6.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.**

Figure B5 PRISMA Statement Flow Diagram



6.2.3 **When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

One RCT was identified – the CLL11 study. The list of all eligible publications can be found in Table B14 in Section 6.2.4.

Complete list of relevant RCTs

6.2.4 **Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.**

CLL11 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 coexisting conditions.

Table B14 List of eligible publications and relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
CLL11 (BO21004; NCT01010061) (stage 1 and stage 2 results)	Obinutuzumab and chlorambucil (n= 238 for stage 1 and n=333 for stage 2) Obinutuzumab: 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Rituximab and chlorambucil (n=238 for stage 1 and n=330 for stage 2) or chlorambucil alone (n=118) Rituximab: 375 mg/m^2 of body-surface area on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Patients with previously untreated CLL and a CIRS score > 6 or an estimated creatinine clearance of 30 to 69 ml/min	**Goede 2014 (10)** Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. N Engl J Med. 370: 1101-1110 and Supplementary Appendix.
CLL11 (BO21004; NCT01010061) (Final stage 2 results)	Obinutuzumab and chlorambucil (n=333) Obinutuzumab: 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Rituximab and chlorambucil (n=330) or chlorambucil alone (n=118) Rituximab: 375 mg/m^2 of body-surface area on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Patients with previously untreated CLL and a CIRS score > 6 or an estimated creatinine clearance of 30 to 69 ml/min	**Goede 2013 (26)** Head-to-head comparison of obinutuzumab (GA101) plus chlorambucil (CLB) versus rituximab plus CLB in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final stage 2 results of the CLL11 trial. 55th ASH annual meeting, New Orleans, LA, USA. Blood 122 (21): Abstract 6
CLL11 (BO21004; NCT01010061) (safety run-in phase)	Obinutuzumab and chlorambucil (n=6) Obinutuzumab: 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	NA (safety run-in phase)	Patients with previously untreated CLL and a CIRS score > 6 or an estimated creatinine clearance of 30 to 69 ml/min	**Goede 2013(44)** Chemoimmunotherapy with chlorambucil and the type II CD20-antibody GA101 in patients with chronic lymphocytic leukemia and comorbidity: Results of the run-in phase of the CLL11 (BO21004) trial. Leukemia. 27:1172-1174

CLL11 (BO21004; NCT01010061) (Final stage 1 results)	Obinutuzumab and chlorambucil (n=238) Obinutuzumab: 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Rituximab and chlorambucil (n=233) or chlorambucil alone (n=118) Rituximab: 375 mg/m^2 of body-surface area on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Patients with previously untreated CLL and a CIRS score > 6 or an estimated creatinine clearance of 30 to 69 ml/min	**Goede 2013(45)** Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial. 49th ASCO Annual Meeting, Chicago. J Clin Oncol 31 (Suppl): Abstract 7004
CLL11 (BO21004; NCT01010061) (Final stage 1 results)	Obinutuzumab and chlorambucil (n=238) Obinutuzumab: 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Rituximab and chlorambucil (n=233) or chlorambucil alone (n=118) Rituximab: 375 mg/m^2 of body-surface area on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 through 6 Chlorambucil: 0.5 mg/kg of body weight on days 1 and 15 of each cycle	Patients with previously untreated CLL and a CIRS score > 6 or an estimated creatinine clearance of 30 to 69 ml/min	**Goede 2013 (46)** Obinutuzumab (GA101)+chlorambucil (CLB) or rituximab (r) + Clb versus Clb alone in patients with chronic lymphocytic leukaemia (CLL) and pre-existing medical conditions (comorbidities): Final stage 1 results of the CLL11 phase 3 trial 18th Congress of EHA. Abstr S567 **Hallek 2013 (47)** Obinutuzumab (GA101)+chlorambucil (CLB) or rituximab (r) + Clb versus Clb alone in patients with chronic lymphocytic leukaemia (CLL) and pre-existing medical conditions (comorbidities): Final stage 1 results of the CLL11 (bo21004) phase 3 trial 12th International Conference on Malignant Lymphoma, Lugano, Switzerland

ASCO: American Society of Clinical Oncology, ASH: American Society of Hematology; CIRS: Cumulative Illness Rating Scale; CLL: Chronic Lymphocytic Leukaemia

6.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

CLL11 is a phase III, multicentre, open-label, randomised, three-arm study comparing the intervention of interest with rituximab plus chlorambucil or chlorambucil alone. This study is directly relevant to the decision problem.

6.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

No identified studies have been excluded.

List of relevant non-RCTs

6.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

Due to the availability of randomised placebo-controlled double-blind data on the relative efficacy directly relevant to the decision problem no non-RCT evidence has been presented in this submission.

6.3 Summary of methodology of relevant RCTs

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers**

(www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 **Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

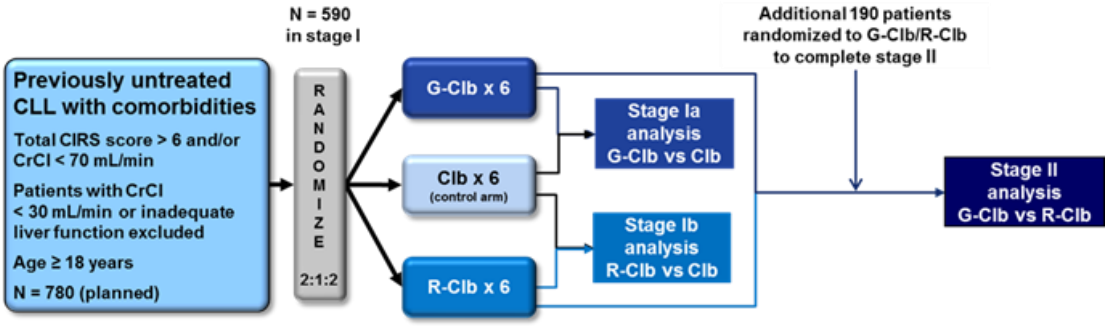
Summary of the CLL11 study

All the information presented below is sourced from the CLL11 publication (10) or the CLL11 trial CSRs (16-19).

Study design

CLL11 is a phase III, randomised, double-blind, international, multicentre, three-arm study designed to evaluate the efficacy and safety of obinutuzumab and chlorambucil (GClb) compared with rituximab plus chlorambucil (RClb) or chlorambucil (Clb) in people with previously untreated CLL for whom full-dose fludarabine based therapy is not appropriate.

Figure B6 Study design: patient treatment and assessment



SOURCE: (10)

CCL: Chronic Lymphocytic Leukaemia; CrCl: Creatinine Clearance; Clb: Chlorambucil; G-Clb: Obinutuzumab and chlorambucil; R-Clb: Rituximab and chlorambucil

The study enrolled 781 patients; 589 patients were randomised in Stage 1 on a 2:2:1 (GClb:RClb: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.

The study was designed to include two stages and 3 primary analysis time points (Figure B6):

- Stage 1 randomised patients 2:2:1 GClb:RClb:Clb and was split into two primary analysis time points:
    - Stage 1a: final analysis for GClb vs. Clb and futility and efficacy interim analysis for GClb vs. RClb
    - Stage 1b: final analysis of RClb v Clb
- Stage 2: final analysis for GClb vs. RClb (randomisation (1:1) continued into the GClb and RClb treatment arms only

Prior to the start of enrolment into the randomised 3-arm portion of the study, 6 patients entered a safety run-in with obinutuzumab to assess the safety of the combination therapy. All adverse events (AE) and serious adverse events (SAE) as well as laboratory data were reviewed by the sponsor (Roche) and the German CLL study group (GCLLSG) on an ongoing basis and a formal review took place after the sixth patient completed 28 days of treatment. If a treatment-related death had been reported, or 3 or more patients experienced febrile neutropenia or documented infection requiring intravenous (IV) antibiotics in the presence of Grade 3 or 4 neutropenia (CTC version 4), the GClb treatment arm would not have been opened for recruitment.

Study treatments

Table B15 Dosage and administration of study treatments

Obinutuzumab	• All 6 patients entering the safety run-in and all patients randomised to the GClb treatment arm received 1000 mg 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 (1000 mg) as an IV infusion on Day 1 only (Cycle 2 to 6).
Rituximab	• All patients randomised to the RClb arm received 375 mg/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).
Chlorambucil	• All patients entering the study received 0.5 mg/kg body weight of Clb given orally on Day 1 and Day 15 of all treatment cycles (Cycles 1 to 6). • In patients with a BMI >35 (Grade 2 obesity) the dose of Clb was capped at a maximum limit associated with a BMI of 35.

SOURCE: (10)

BMI: Body Mass Index; Clb: Chlorambucil; IV: Intravenous; GClb: Obinutuzumab and Chlorambucil; RClb: Rituximab and Chlorambucil

As there is no clear standard of care dose for Clb, the dose of Clb was based on the dose used in the CLL5 trial (15). Although lower than in other CLL trials (40;48-50), the dose of Clb in CLL11 was the same in all three arms of the trial. This dose was chosen due to the CLL5 population being deemed most similar to the proposed CLL11 population, offering a balance of efficacy and toxicity. The trials mentioned above involved mainly significantly younger, fitter patients than those anticipated for CLL11.

Peripheral blood counts, bone marrow biopsy results, reports of physical examination, and other relevant data relating to disease assessments were sent to the independent review facility on an on-going basis. Once a participant was assessed to have progressed by the investigator, the independent review facility was notified. If progression was confirmed by the independent review facility, the investigator was notified that the participant no longer required tumour assessments in the study. If progression was not confirmed, the investigator was informed that the patient continue to be examined, as per protocol.

The primary analysis of efficacy is progression-free survival based on a stratified (Binet stage at baseline), two-sided log-rank test of PFS as assessed by the investigator. Key secondary endpoints are PFS assessed by an independent review committee, 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.

The statistical analyses of the primary and secondary efficacy data was performed from a clinical data cut-off on 9 May 2013. This analysis of the data forms the basis of the Goede New England Journal of Medicine publication March 2014 (10). A subsequent analysis of PFS and OS data with a clinical cut-off of 03 March has been performed but has not been published in any form and is presented in this document as data that are commercial in confidence.

Participants

6.3.3 **Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.**

The study population for this trial comprised previously untreated adult patients 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.

The population for the study reflects people who would normally be eligible for obinutuzumab-based treatment outside of the clinical trial setting. See Table B16 and Table B17 for full details of the inclusion and exclusion criteria for the study.

Table B16 CLL inclusion criteria

Inclusion criteria
• Have documented CD20+ B−CLL according to National Cancer Institute (NCI) criteria • Previously untreated CLL requiring treatment according to the NCI criteria • Total cumulative illness rating scale (CIRS) Score >6*, or creatinine clearance <70 mL/min • Absolute neutrophil count ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L unless cytopenia is caused by the underlying disease, i.e., no evidence of additional bone marrow dysfunction (e.g., myelodysplastic syndrome, hypoplastic bone marrow) • Age 18 years or older • Life expectancy >6 months • Able and willing to provide written informed consent and to comply with the study protocol procedures

SOURCE: (10)

* scoring due to underlying CLL disease was not considered

B-CLL: B cell-Chronic Lymphocytic Leukaemia; CD-20+: B-lymphocyte antigen CD20 positive; NCI: National Cancer Institute

Table B17 CLL exclusion criteria

Exclusion criteria
• Patients who have received previous CLL therapy • Transformation of CLL to aggressive NHL (Richter's transformation) • One or more individual organ/system impairment Score of 4 as assessed by the CIRS definition, excluding the eyes, ears, nose, throat and larynx organ system • Inadequate renal function: creatinine clearance <30 mL/min • Inadequate liver function: NCI Common Toxicity Criteria Grade 3 liver function tests (aspartate transaminase [AST], alanine transaminase [ALT] >5 × upper limit of normal [ULN] for >2 weeks; bilirubin >3 × ULN) unless due to underlying disease • History of other malignancies which could affect compliance with the protocol or interpretation of results. Patients with a history of malignancy that had been treated, but not with curative intent, were excluded, unless the malignancy had been in remission without treatment for ≥2 years prior to enrolment. Patients with a history of adequately treated carcinoma in situ of the cervix; basal or squamous cell skin cancer; low grade, early stage localised prostate cancer treated surgically with curative intent; good prognosis ductal carcinoma in situ of the breast treated with lumpectomy alone with curative intent were eligible • Patients with active bacterial, viral, or fungal infection requiring systemic treatment • Patients with known infection with human immunodeficiency virus or Human T-cell Leukaemia Virus 1 • Positive hepatitis serology: Hepatitis B: Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen or Hepatitis B core antibody (anti- HBc). Patients positive for anti−HBc may be included if Hepatitis B viral DNA is not detectable. Hepatitis C (HCV): Patients with positive Hepatitis C serology unless HCV (RNA) is confirmed negative • History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies. Known sensitivity or allergy to murine products • Hypersensitivity to Clb or to any of the excipients • Women who are pregnant or lactating • Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥2 years after the onset of menopause (2) willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 12 months after end of antibody treatment and male patients for 6 months after end of chlorambucil treatment • Vaccination with a live vaccine a minimum of 28 days prior to randomisation

SOURCE: (10)

AST: Aspartate Transaminase; ALT: Alanine Transaminase; CIRS: Cumulative Illness Rating Scale; Clb: Chlorambucil; CLL: Chronic Lymphocytic leukaemia; HBc: Hepatitis B core antibody; HCV: Hepatitis C Virus; NCI: National Cancer Institute; NHL: Non-Hodgkin Lymphoma; ULN: Upper Limit of Normal; RNA: Ribonucleic Acid

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The treatment groups were generally comparable with respect to demographic characteristics (Table B18).

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 GClb arm and 78% in the chlorambucil, 79% RClb arm). The age of this recruited population is older than the ages of participants recruited in previous landmark CLL studies (37;48;51;52) and typical of the general CLL population (8;9;12). The majority of people were categorised as either White (96% in the GClb arm compared with 92%

in the Clb arm, and 95% in the RClb arm) or Asian (2% in the GClb arm compared with 5% in the Clb arm, and 3% in the RClb arm).

The patients had a CIRS score >7 at baseline. Most patients (82%) had more than three coexisting conditions, and nearly one third (27%) had at least one coexisting 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 GClb arm and 78% in the RClb arm). The majority of people were categorised as either White (95% in both arms) or Asian (2% in both arms).

Table B18 Characteristics of participants in CLL11 across randomised groups (stage 1a, stage 1b, and stage 2)

	Obinutuzumab and chlorambucil (n=238)	**Chlorambucil (n=118)**	**Rituximab and chlorambucil (n=233)**	**Obinutuzumab and chlorambucil (n=333)**	**Rituximab and chlorambucil (n=330)**
Age (years, 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%)
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%)

SOURCE: (10)

CIRS: Cumulative Illness Rating Scale; SD: Standard Deviation

Outcomes

6.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

This study was conducted in full conformance with the principles of the Declaration of Helsinki and its subsequent amendments or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study adhered to the principles outlined in the Guideline for Good Clinical Practice ICH (International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use) Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the subject. In other countries where guidelines for good clinical practice existed, the sponsor and the investigators were to strictly ensure adherence to the stated provisions. The study was designed by the senior academic authors and representatives of the sponsor. The data were collected and analysed by the sponsor in collaboration with senior academics, who confirm the completeness and accuracy of the data and analyses, and the fidelity of the study to the protocol.

Primary endpoint

Progression-free survival

PFS 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

Secondary endpoints

Event-free survival

Event-free survival (EFS) is defined as the time between date of randomisation and the date of disease progression/relapse, death, or start of a new anti-leukaemic therapy.

Disease-free survival

Disease-free survival (DFS) is defined for all patients with complete response at any time from 56 days after end of treatment onwards. DFS extends from the date the complete response was first recorded to the date on which progressive disease (PD) is first noted or the date of death due to any cause.

Duration of response

Duration of response (DOR) is defined similarly for complete and partial responders at any time from 56 days after end of treatment onwards. DOR starts at the date the response (either complete response [CR] or partial response [PR]) was first recorded until the date on which PD is first noted or the date of death due to any cause.

Time to re-treatment / new anti-leukaemic therapy

Time to re-treatment/new anti-leukaemic therapy is defined as time between the date of randomization and the date of first intake of re-treatment or new anti-leukaemic therapy.

Overall survival

OS is defined as the time between the date of randomization and the date of death due to any cause.

End of treatment response

End of treatment response is defined as the response occurring at the end of treatment (first assessment that occurred more than 56 days after the end of treatment) before start of new anti−leukaemia treatment. If the only response assessment after treatment end is PD, it was included irrespective of when it occurred (i.e., even if earlier than 56 days after the end of treatment). Overall response rate for end of treatment response (end of treatment response rate) is defined as percentage of patients with CR, incomplete CR (CRi), nodular partial response (nPR), or PR at end of treatment response.

Best overall response

Best overall response is defined as the best response recorded from 56 days after end of treatment onwards before start of new anti-leukemic treatment. Overall response rate for best overall response (best overall response rate) is defined as percentage of patients with CR, CRi, PR, or nPR as best overall response.

Best overall response within 1 year of start of study treatment

Best overall response within 1 year of start of study treatment is defined as the best response recorded from 56 days after end of treatment onwards until disease progression, death, or 6 months (190 days) after last administration of last component of study drug, whichever occurs first. Overall response rate for best overall response (best overall response rate within 1 year of start of study treatment) is defined as percentage of patients with CR, CRi, PR, or nPR as best overall response.

Molecular remission

Molecular remission is defined as an MRD-negative result (defined as a result below 0.0001, representing less than 1 in 10 000 detectable CLL cells to every healthy cell) at the end of treatment (assessment that occurred between 56 days and 6 months of last treatment).

Safety reporting and analyses

People who received any amount of any component of study treatment were included in safety analyses (safety analysis population), this will be discussed in Section 6.9.

Safety assessments included adverse events (including serious adverse events), standard laboratory assessments and vital signs.

All adverse events and serious adverse events occurring after study entry (i.e., date of informed consent) were recorded up to 28 days after completion of study treatment. New Grade 3 and 4 adverse events continue to be reported until 6 months after end of therapy. All unrelated serious adverse events are to be reported up to one year and Grade 3 or 4 infections will be reported up to two years after treatment or until a new anti−leukaemic treatment is instituted.

All adverse events and routine laboratory parameters were assessed according to the NCI CTCAE version 4.0 grading system.

Patient reported outcomes/ health-related quality of life analyses

Health-related quality of life assessments were used to derive pre-specified global and domain scores according to the European Organisation for Research and Treatment of Cancer (EORTC) QLQC30 and QLQ-CLL-16 module scoring manuals.

In addition to the outcomes cited above, pharmacodynamic and pharmacokinetic analyses have been conducted. All patients (approximately 100 patients) enrolled up until the time of the “50 patient safety review meeting” had samples collected for immunophenotyping (T cell subsets and CD19+ B-cell) during treatment. During follow-up all patients had samples collected for B-cell recovery. In addition, B-cell depletion and immunoglobulin depletion were also analysed

Statistical analysis and definition of study groups

6.3.6 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was**

undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

All the information presented below is sourced from the CLL11 publication (10) or the CLL11 trial CSRs (16-19).

OBJECTIVE:

The primary objective of the study is to compare the following three hypotheses listed below.

- PFS of GClb versus Clb alone:
  H_0: GClb = Clb versus H_1: GClb ≠ Clb (Stage 1a)
- PFS of RClb versus Clb alone:
  H_0: RClb = Clb versus H_1: RClb ≠ Clb (Stage 1b)
- PFS of GClb versus RClb:
  H_0: GClb = RClb versus H_1: GClb ≠ RClb (Stage 2)

The primary endpoint of investigator-assessed PFS was used to determine the sample size for the study. However, PFS based on IRC assessments was also analysed to support the primary analysis.

STUDY POPULATIONS:

Depending on the treatment group comparison, two different sets of patients were to form the basis for the analysis:

• Stage 1: Patients randomised in parallel to all three treatment groups (approximately 590 patients). This set of patients was used for the global test of any difference between any of the three treatment groups. For all comparisons of GClb or RClb against Clb, only Stage 1 patients are used.

• Stage 1 + 2: Patients randomised at any time during the trial (781 patients). The patients randomised to GClb and RClb arms (663 patients) were used for the Stage 2 analyses of comparison of GClb versus RClb.

However, stage 2 was compared to stage 1 in the cost-effectiveness analysis (section 7)

Intent-to-treat (ITT) population: The ITT population was the primary analysis population for the primary endpoint, and consisted of all patients who were randomised.

In addition, a per protocol (PP) population was used for a sensitivity analysis of PFS. The PP population comprised all patients who completed the study therapy (defined as having received at least three cycles of study therapy) and patients who terminated treatment before three cycles because of disease progression or death. Patients in this analysis population fulfilled all the inclusion criteria and had no major protocol violations.

All efficacy endpoints were analysed based on the ITT population.

Safety analysis population (SAP): Safety analyses were performed on the treated population, defined as patients who received at least one dose of study medication.

Safety analyses were based on the actual treatment received.

EFFICACY ANALYSIS:

Primary efficacy endpoint

Data for patients without disease progression or death will be censored at the time of the last response assessment, or, if no response assessments were performed after the baseline visit, at the time of randomisation plus one day.

Adjustments for multiplicity were done using a three-arm closed-test procedure. 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 above mentioned hypotheses (i.e., GClb versus Clb alone, GClb versus RClb, and RClb versus Clb alone) were enabled at the 5% alpha level without α-inflation (53).

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. PFS rates for 1 and 2 years after randomisation with 95% confidence intervals are reported. Estimates of the treatment effect are expressed as HRs including 95% confidence limits. A secondary

multivariate analysis of PFS used a Cox regression model to assess the treatment effect after adjustment for baseline prognostic factors.

In addition sensitivity analyses for PFS were performed:

- The impact of patients starting a new anti-leukaemic treatment without meeting the criteria of disease progression was assessed by censoring these patients at the start date of the new anti-leukemic treatment. Stopping only one component of the randomised study treatment was not considered a reason for censoring patients.
- Although there was no reason to believe study investigators were biased in favour of the GClb or RClb treatment arm when assessing disease progression, an analysis was conducted to assess the potential investigator bias on PFS in this unblended study. For this analysis, objective assessments from the IRC were used.
- The impact of late death cases was assessed for the analysis of PFS based on investigator as well as IRC assessment. Patients who died more than 6 months after last treatment and showed no sign of progression were censored at the last available tumour assessment.
- In order to explore a potential bias from releasing the results of the Stage 1 analysis (publication of GClb vs. Clb and RClb vs. Clb data) separate evaluations of Stage 1 and Stage 2 were conducted for the treatment comparison of GClb versus RClb using only patients randomised and data collected during each stage. Point estimates of the stage-wise HRs as well as stage-wise Kaplan-Meier estimates were determined and compared with the primary analyses outlined above. However, Stage 2 was compared to stage 1 in the cost-effectiveness analysis (section 7)
- An analysis to study the impact of missing response assessments was conducted. In the analysis, patients who discontinued the study for any reason other than disease progression or death were counted as having progressed at the time of withdrawal. Furthermore, patients who missed/had an incomplete response assessment prior to a PD or the cut-off for the analysis were counted as having progressed at the time of the missed/incomplete response assessment.

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 (i.e. EFS, DFS, DOR, time to re−treatment /new anti−leukaemic therapy and OS) were analysed in a manner similar to the primary analysis. However, no formal comparisons can be made for DOR and DFS as the underlying subpopulations of responding patients were no longer randomised, and therefore, do not control confounding factors. Patients who crossed over from Clb to GClb were handled in all time−to−event analyses like patients who started second-line therapy. Best overall response rates and end of treatment response rates in the treatment groups were compared using a chi-square test with continuity correction (Shouten). In addition, 95% confidence limits for the difference using the Anderson-Hauck approach are 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 (CR, CRi, PR, SD, and PD) by treatment group is presented. The effect of prognostic factors is assessed in an exploratory analysis using logistic regression

Determination of sample size and power

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 GClb and Clb, 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 RClb and Clb (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 GClb vs. RClb vs. Clb 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 GClb and RClb, approximately 406 events were required to achieve 80% power at a two-sided significance level of 0.5%.

Assumptions

The primary stage 1a PFS analysis was estimated to occur approximately 28 months from FPI. Stage 1b data comparing RClb with Clb will be blinded until all patients (stage 1 and stage 2) have been randomised and have finished their treatment. At

the end of stage 1a, a futility analysis of GClb vs. RClb will be conducted when 125 of the PFS events on the combination treatment arms will have been observed. PFS stage 2 interim analysis will be performed at the time of the PFS analysis. The second PFS stage 2 interim analysis will be performed when all patients have been randomised, have finished the randomised study therapy, and the end of treatment response is available. This will happen approximately 45 months after the first patient has been randomised and approximately 74% of the total of 406 events have been observed. The final stage 2 analysis for the comparison of GClb versus RClb will be done after 406 PFS events have been observed in the two treatment arms, approximately 63 months after the first randomisation

Handling of missing data points

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 will be censored at the date of last response assessment. In case no response assessment is available patients will conservatively be censored at the date of randomisation plus one day.

Patients with no documented progression after CR/CRi will be 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 will be 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 will be 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 are still alive, OS will be 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) will be

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) will be considered non-responders in the analysis of end of treatment response rates.

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

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

All the information presented below is sourced from the CLL11 publication (10) or the CLL11 trial CSRs (16-19).

Subgroup analyses were pre-planned for the study. Analyses for independent review facility determined progression-free survival were performed for the following pre-defined categorical covariates:

- Age-group (< 65, ≥ 65, <75, ≥ 75 years)
- Race (White, Other)
- Binet stage at baseline (A, B, C)
- Total CIRS score at baseline (≤6 or >6)
- Calculated creatinine clearance (<50, ≥50, <70, ≥70 mL/min)
- Beta2-microglobulin (<3.5 or ≥3.5)
- IVGH mutational status
- Hierarchical model at baseline (17P, 11Q, +12, 13Q, abnormal, normal)
- Time from diagnosis to randomisation (≤12 months, 13 – 24 months, >24 months)
- FCγRIIa (131HH, 131HR, 131RR)
- FCγRIIIa (158FF, 158FV, 158VV)
- Circulating lymphocyte count at baseline (<$25x10^9$ cells/L or ≥$25x10^9$ cells/L)

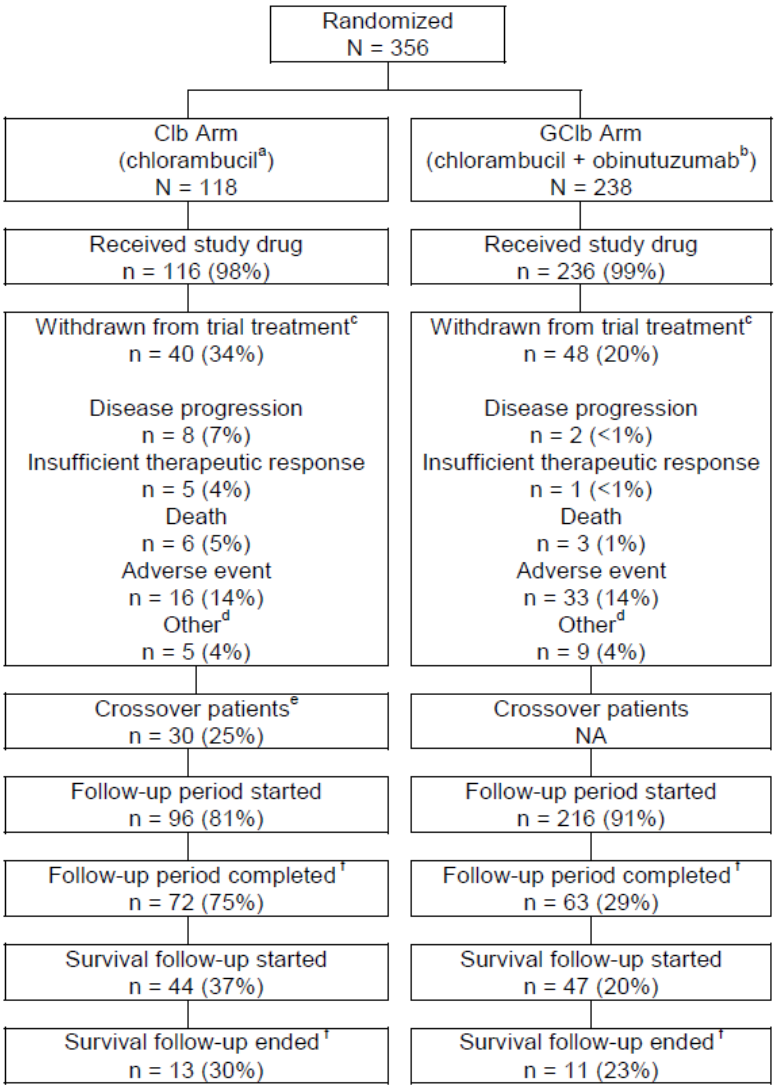
Forest plots of the HR and corresponding (1-α) % CI were produced for all subgroups.

Participant flow

6.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

All the information presented below is sourced from the CLL11 publication (10) or the CLL11 trial CSRs (16-19).

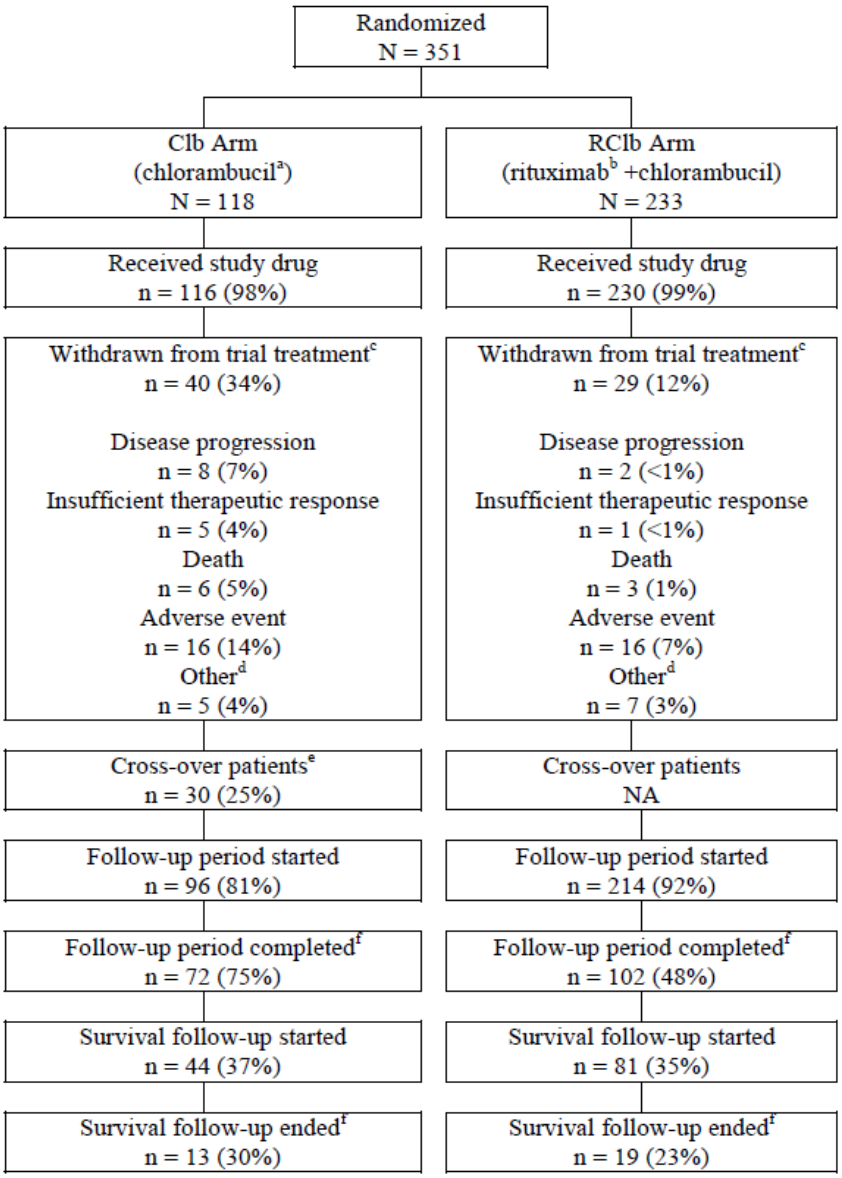
Figure B7 Disposition of patients in stage 1a (ITT)



SOURCE: (10;18) [Figure 2]
Clb: Chlorambucil; G: obinutuzumab; NA = not applicable; R: Rituximab
[a] Clb was administered orally on Days 1 and 15 of each cycle at 0.5 mg/kg body weight
[b] Patients received 1000 mg of obinutuzumab as an IV. infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). For subsequent cycles patients received obinutuzumab (1000 mg) as an IV infusion on Day 1 only (Cycle 2 – 6). Following protocol amendment G (dated 9 December, 2011) the first infusion of obinutuzumab was given over two days (100 mg Day 1, 900 mg Day 2).
[c] Includes the two patients in each treatment arm who did not receive study drug.
[d] Includes withdrew consent, administrative/other, other protocol violation, refused treatment/did not cooperate, violation of selection criteria at entry.
[e] Patients with PD during Clb treatment or within 6 months of follow-up.

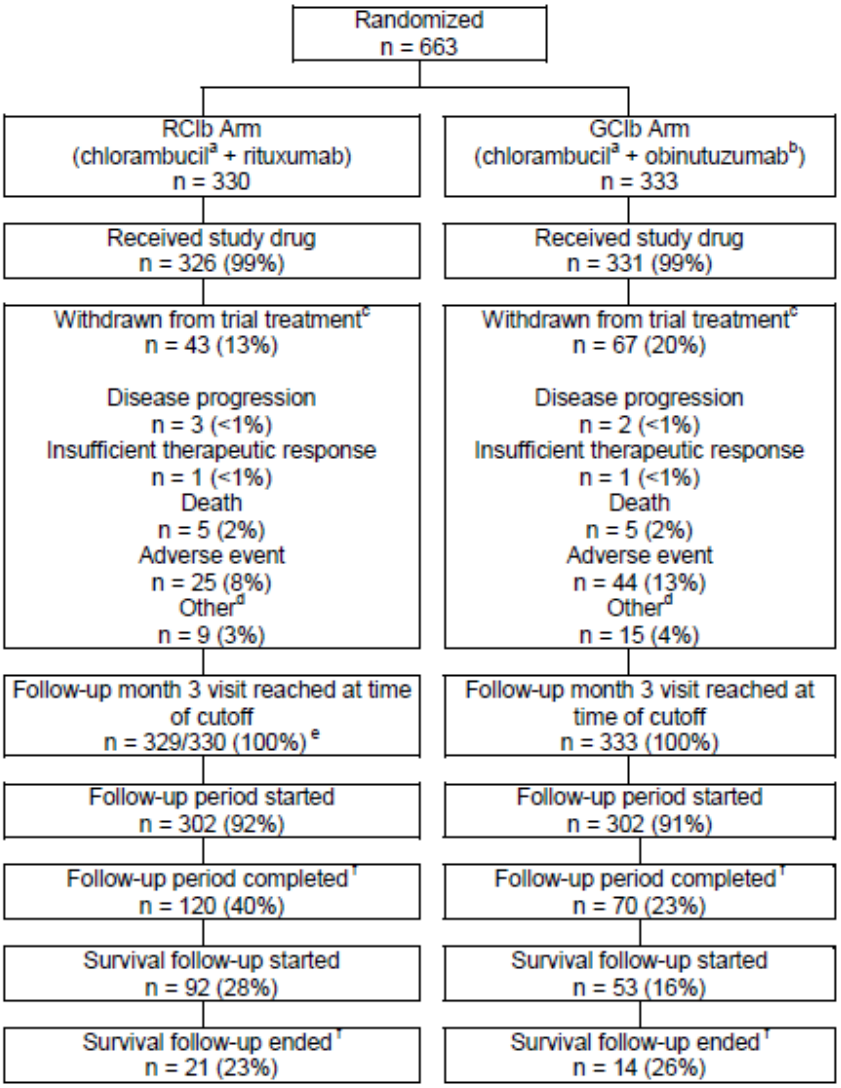
[f] Please note percentages are based on the number of patients entering this period of the study

Figure B8 Disposition of patients in stage 1b (ITT)



SOURCE: (10;18) [Figure 8]
Clb: Chlorambucil; G: obinutuzumab; NA = not applicable; R: Rituximab
[a] Clb was administered orally on Days 1 and 15 of each cycle at 0.5 mg/kg body weight
[b] Patients received 375 mg/m2 of rituximab by IV infusion on Day 1 of Cycle 1, and 500mg/m2 of rituximab by IV infusion on Day 1 of Cycles 2-6.
[c] Includes the two patients in Clb arm and the three patients in the RClb arm who did not receive study drug.
[d] Includes withdrew consent, administrative/other, other protocol violation, refused treatment/did not cooperate, violation of selection criteria at entry
[e] Patients with PD during Clb treatment or within 6 months of follow-up were allowed to cross over and receive treatment with obinutuzumab plus chlorambucil (GClb).
[f] Note percentages are based on the number of patients entering this period of the study

Figure B9 Disposition of patients in stage 2 (ITT)



SOURCE: (10;19)} [Figure 3]
Clb: Chlorambucil; G: obinutuzumab; NA = not applicable; R: Rituximab
[a] Clb was administered orally on Days 1 and 15 of each cycle at 0.5 mg/kg body weight
[b] Patients received 1000 mg of obinutuzumab as an IV. infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). For subsequent cycles patients received obinutuzumab (1000 mg) as an IV infusion on Day 1 only (Cycle 2 – 6). Following protocol amendment G (dated 9 December, 2011) the first infusion of obinutuzumab was given over two days (100 mg Day 1, 900 mg Day 2)
[c] Includes the 4 patients in the RClb arm and 2 patients in GClb arm who did not receive study drug.
[d] Includes withdrew consent, administrative/other, other protocol violation, refused treatment/did not cooperate, violation of selection criteria at entry
[e] One patient had not reached follow-up month 3 at the time of the cut-off and has no ETR response assessment available; this patient is not included in the analysis of response rates and MRD
[f] Percentages are based on the number of patients entering this period of the study

6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.**

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

Data for this study were recorded through an electronic data capture system using eCRFs. Accurate and reliable data collection was assured by verification and cross-checking of the eCRFs against the investigator's records by the study monitor (source document verification), and by the maintenance of a drug-dispensing log by the investigator. Data were transcribed by the site from the paper source documents onto the eCRF. A comprehensive validation check program utilising front-end checks in the eCRF and back-end checks in the Roche database was used to verify the data, and discrepancy reports were generated accordingly. These were transferred electronically to the eCRF at the site for resolution by the investigator.

Table B19 Quality assessment results for CLL11

Study question	How is the question addressed in the study?	Grade (yes/no/ not clear/N/ A)
Was randomisation carried out appropriately?	After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment arm from the interactive voice response system (IVRS). A complete block randomisation scheme was applied to achieve balance in treatment assignment within each of the strata, as defined by Binet stage and region (Asia and Oceania, Europe Group 1, Europe Group 2, North and Central America and Caribbean, South America and South Atlantic).	Yes
Was the concealment of treatment allocation adequate?	Concealment of treatment allocation was achieved by IVRS.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	The patient demographics and characteristics were generally well balanced in all arms and stages of the study.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This trial was an open-label study which does introduce the possibility of bias, 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 PFS by investigator review. There is a chance that these results may be biased by additional unscheduled assessments and knowledge of treatment allocation, but the IRC assessment of the results should reduce the risk for bias. OS is unlikely to be affected by bias.	No
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances in drop outs	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on people who received at least one dose of study medication	Yes

SOURCE: (16-19)

IRC: Independent Review Committee; IVRS: Interactive Voice Response System; OS: Overall Survival; PFS: Progression-free Survival

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.**

See section 10.5 (Appendix 5).

6.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.**

Not appropriate as there is only one RCT.

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

6.5.3 **For each outcome for each included RCT, the following information should be provided.**

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**

- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

The primary analysis took place with a clinical data cut off of 9th May 2013. All the information for this cut-off is presented below is sourced from the CLL11 publication (10) or from the CLL11 trial CSRs (16-19). For stage 1a, the overall median observation time (randomisation to last available assessment) at the time of clinical data cut-off was 22.8 months; 20.4 months (0.2 - 35.2 months) for patients in the Clb arm and 23.2 months (0.1 - 36.9 months) for patients in the GClb arm. For stage 1b, the overall median observation time (randomisation to last available assessment) at the time of clinical data cut-off was 22.7 months; 20.4 months (0.2 - 35.2 months) for patients in the Clb arm and 23.2 months (0.5 - 35.9 months) for patients in the RClb arm. Finally for stage 2, the overall median observation time (randomisation to last available assessment) at the time of clinical cut-off was 18.7 months; 18.6 months (0 - 35.9 months) for patients in the RClb arm and 18.8 months (0.1 - 36.9 months) for patients in the GClb arm.

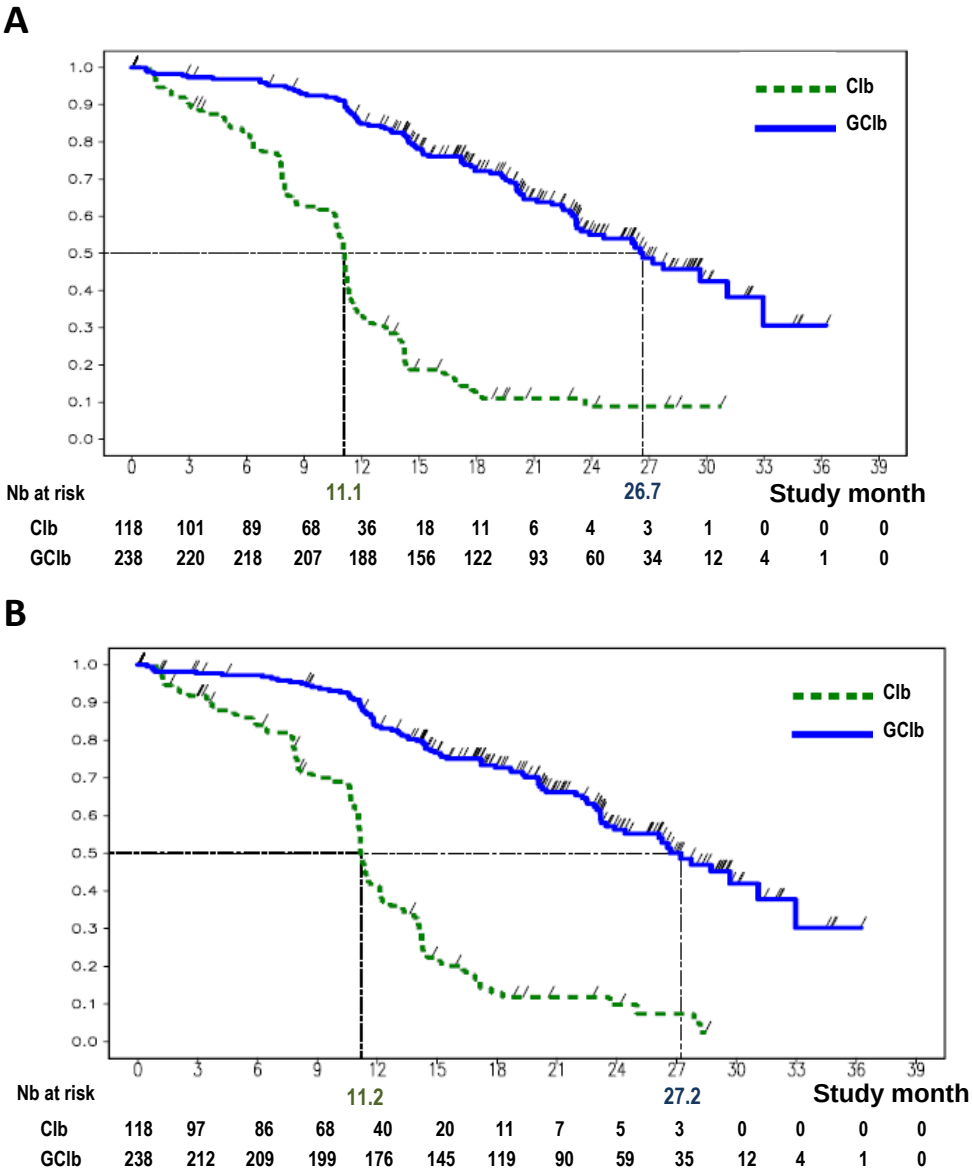
Updated PFS figure from the latest unpublished data cut-off (03 March 2014) is presented at the end of the Primary endpoint and Secondary endpoint sections. These latest PFS data should be considered commercial in confidence.

Primary Endpoint

The study met its primary endpoint in all stages of the study.

At the time of the final stage 1a analysis, the addition of obinutuzumab to Clb (GClb) 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 Clb arm and 26.7 months in the GClb arm (p<0.001). Similar results were found based on the IRC data with an estimated median PFS of 11.2 months in the Clb arm and 27.2 months in the GClb arm (p<0.001) (Figure B10).

Figure B10 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 1a (ITT)



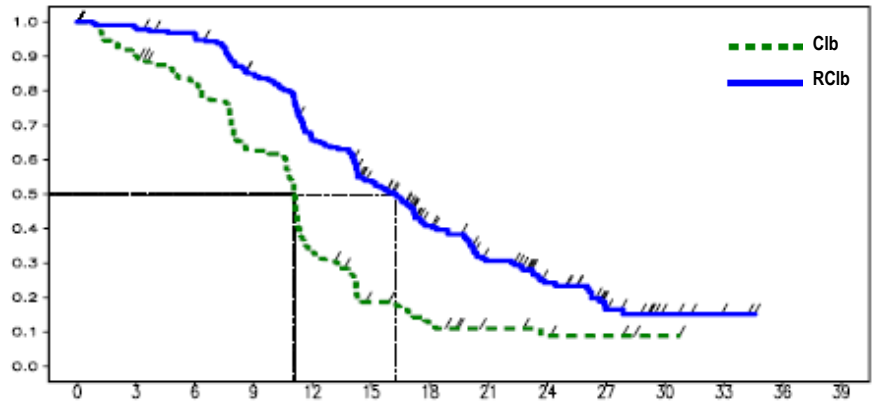
SOURCE: (10)

Clb: Chlorambucil; GClb: Obinutuzumab and Chlorambucil; IRC: Independent Review Committee; PFS: Progression-Free Survival

In stage 1b, the addition of rituximab to Clb (RClb) also resulted in a 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 Clb arm and 16.3 months in RClb arm (p<0.001). Similar results were found based on the IRC data with an estimated median PFS of 11.2 months in the Clb arm and 16.1 months in the RClb arm (p<0.001) (Figure B11).

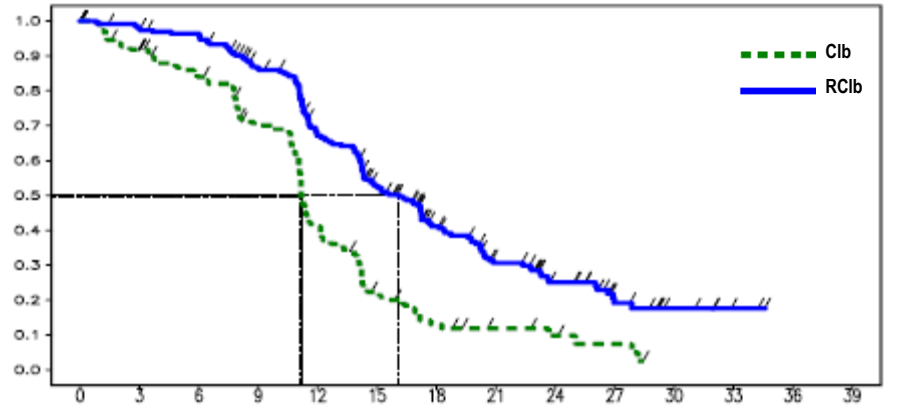
Figure B11 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 1b (ITT)

A



Nb at risk														
Clb	118	101	89	68	36	18	11	6	4	3	1	0	0	0
RClb	233	225	219	190	146	114	72	49	31	14	5	2	0	0

B



Nb at risk														
Clb	118	97	86	68	40	20	11	7	5	3	0	0	0	0
RClb	233	220	214	186	141	105	67	44	28	14	6	2	0	0

SOURCE: (10)

Clb: Chlorambucil; RClb: Rituximab and Chlorambucil; IRC: Independent Review Committee; PFS: Progression-Free Survival

Recent data from the latest cut-off (03 March 2014), show [redacted]

Figure B12 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 1a (ITT)

[redacted]

Clb: Chlorambucil; GClb: Obinutuzumab and Chlorambucil; PFS: Progression-Free Survival

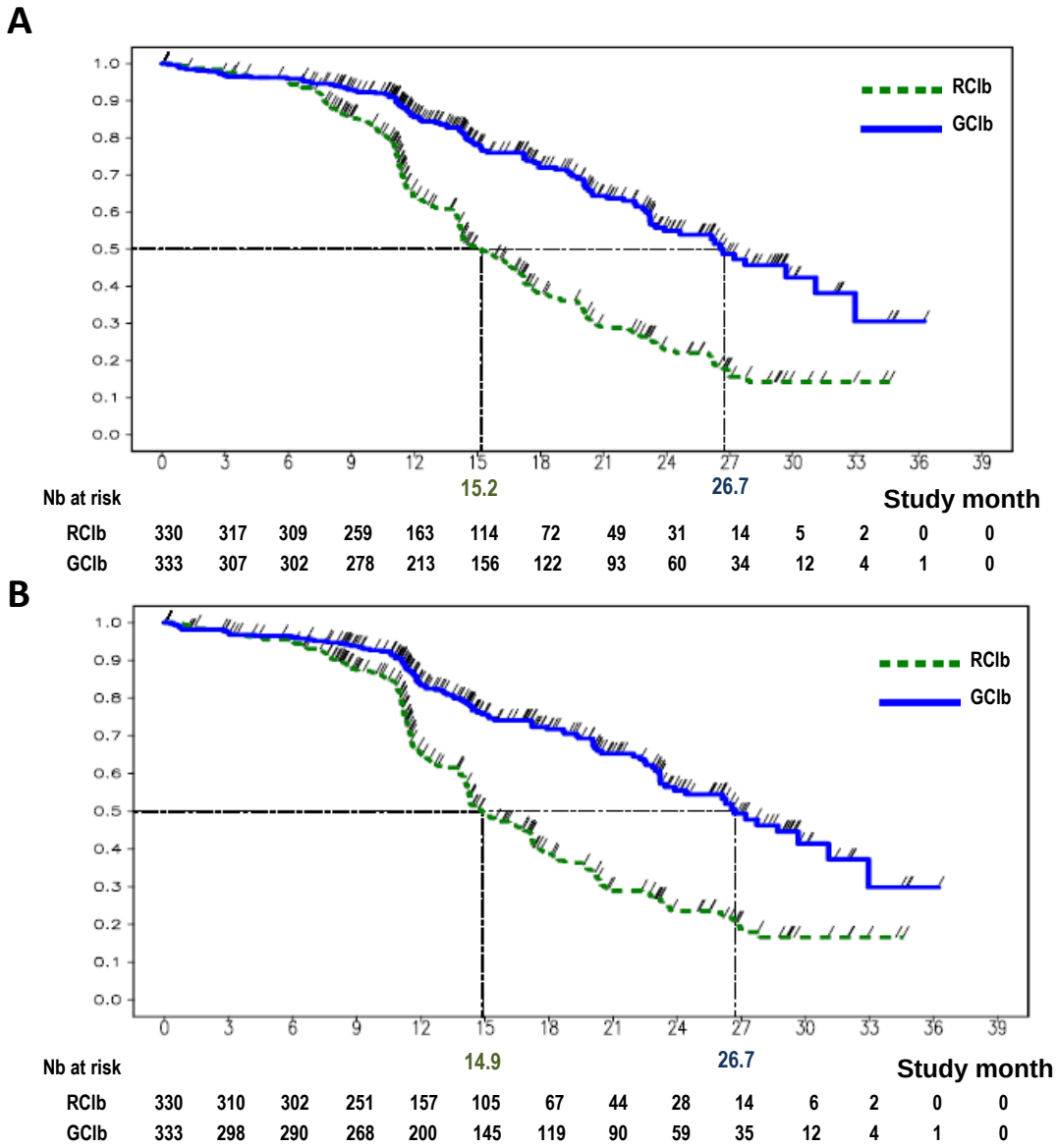
Figure B13 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 1b (ITT)

[redacted]

Clb: Chlorambucil; RClb: Rituximab and Chlorambucil; PFS: Progression-Free Survival

In stage 2, addition of obinutuzumab to Clb (GClb) resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS compared to RClb (stratified HR 0.39 [95% CI: 0.31 - 0.49]).The Kaplan-Meier estimated median PFS was 15.2 months in RClb arm and 26.7 months in GClb arm (p<0.001). Similar results were found based on the IRC data with an estimated median PFS of 14.9 months in the RClb arm and 26.7 months in the GClb arm (p<0.001) (Figure B14).

Figure B14 Kaplan-Meier plot of PFS (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 2 (ITT)



SOURCE: (10)

RClb: Rituximab and Chlorambucil; GClb: Obinutuzumab and Chlorambucil; IRC: Independent Review Committee; PFS: Progression-Free Survival

Recent data from the latest cut-off (03 March 2014), show [redacted] The Kaplan-Meier estimated median PFS was [redacted] months in RClb arm and [redacted] months in GClb arm (Figure B15). The median observation time was [redacted] months for GClb and [redacted] months for RClb.

Figure B15 Kaplan-Meier plot of PFS (as assessed by the investigator, March 2014 data cut-off) - Stage 2 (ITT)

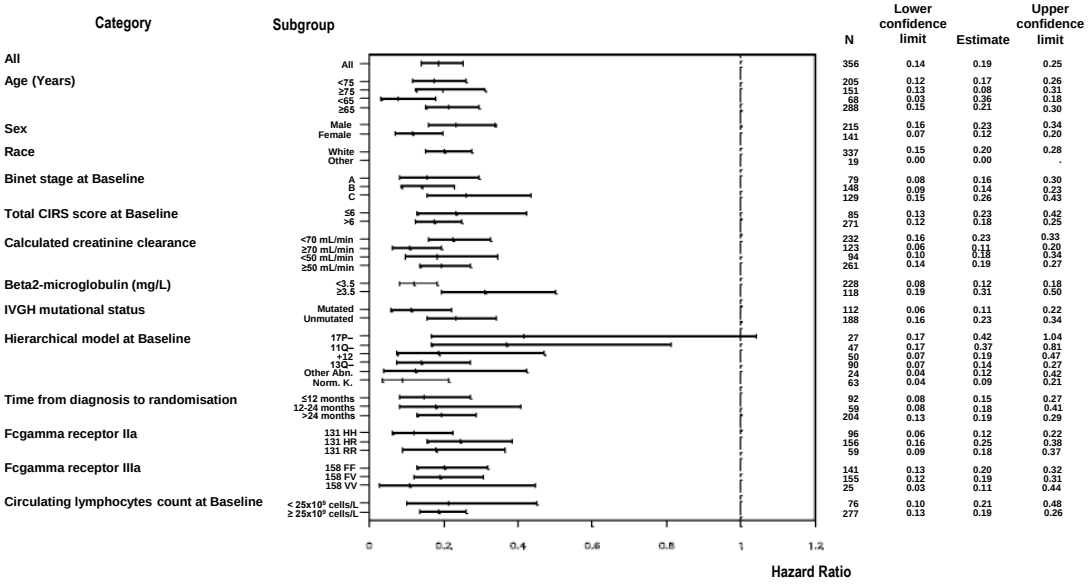
[redacted]

RClb: Rituximab and Chlorambucil; GClb: Obinutuzumab and Chlorambucil; IRC: Independent Review Committee; PFS: Progression-Free Survival

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 GClb over Clb alone (stage 1a), RClb over Clb alone (stage 1b), and GClb over RClb (stage 2) (Figure B16, Figure B17, and Figure B18). The same was true for the subgroup analysis based on IRC assessments of PFS.

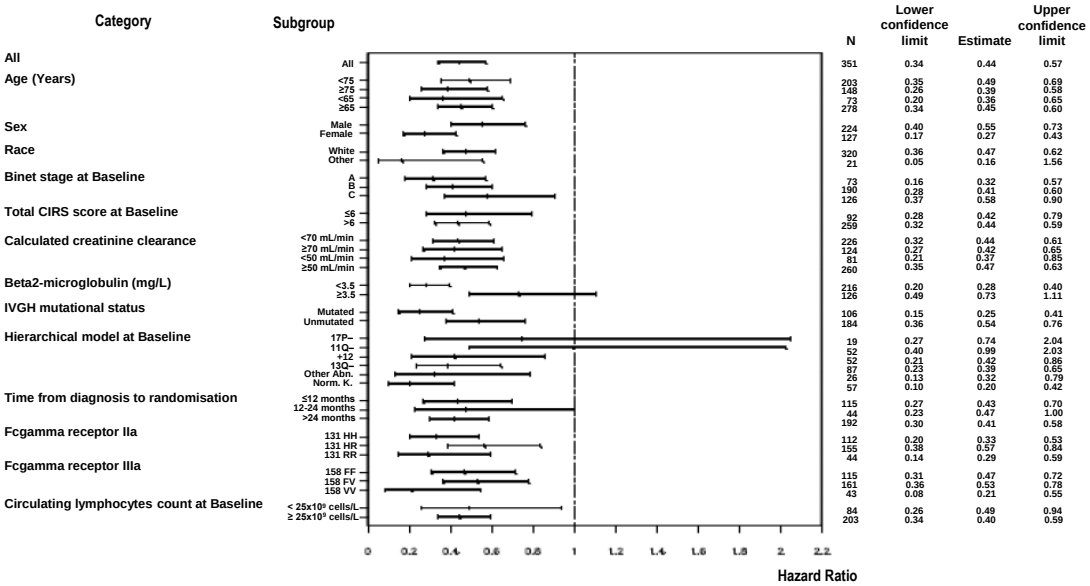
In stage 1a only, for some subgroups the upper limit of the 95% confidence interval was above 1 (race “other”, cytogenetics 17p deletion and other abnormalities, FCγIIa 131RR and FCγIIIa 158VV). However, it is of note that in some of these subgroups the number of patients is low, and the study was not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

Figure B16 Forest plot for PFS by subgroup: GClb vs. Clb (ITT) - Stage 1a (ITT)



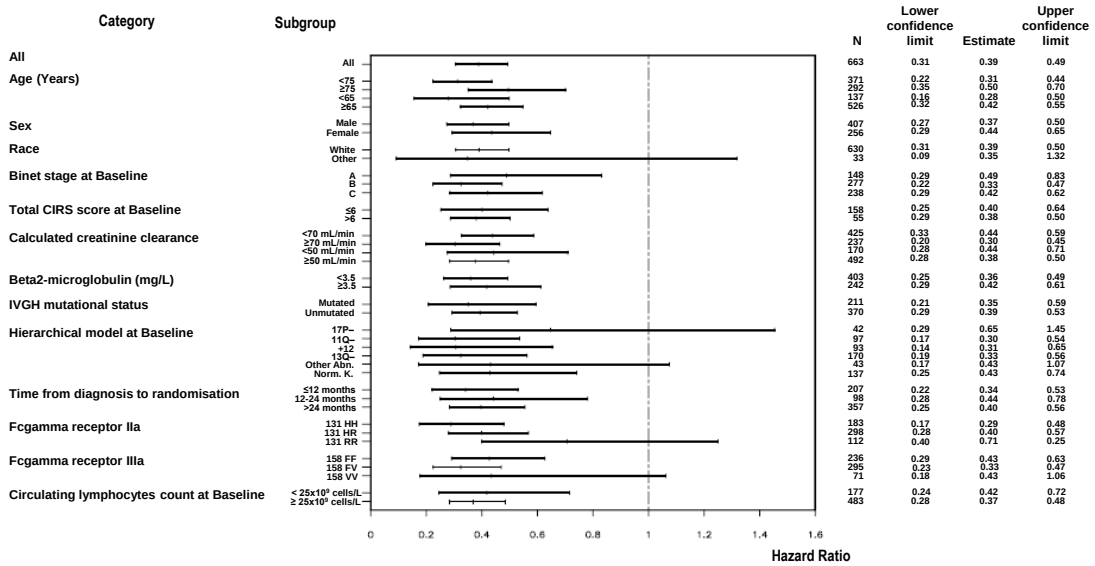
SOURCE: (10;18) [Figure 7]

Figure B17 Forest plot for PFS by subgroup: RClb vs. Clb (ITT) - Stage 1b (ITT)



SOURCE: (10;18) [Figure 13]

Figure B18 Forest plot for PFS by subgroup: GClb vs. RClb (ITT) - Stage 2 (ITT)



SOURCE: (10;19) [Figure 9]

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 B20 and Table B21). However for stage 1a GClb vs Clb was significant (p=0.0022). Disease-free survival and patient-reported quality of life were outcomes for which the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made.

Table B20 Secondary efficacy endpoints results for CLL11 (stage 1a, stage 1b, May 2013 data cut-off)

	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 %)
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

SOURCE: (10;18) [Table 10, Table 14, Table 18; Table 48, Table 52, Table 56]

Clb: Chlorambucil; GClb: Obinutuzumab and Chlorambucil; RClb: Rituximab and chlorambucil

including censored observations, ** 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

In stage 2, among all patients for whom a result for minimal residual disease was available plus 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 GClb treatment than after RClb treatment (bone marrow, 19.5% vs. 2.6%; blood, 37.7% vs. 3.3%, respectively) (10). Negative testing for minimal residual disease in blood after GClb treatment was associated with a favourable disease course during follow-up (Figure B19).

Table B21 Secondary efficacy endpoints results for CLL11 (stage 2)

	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]

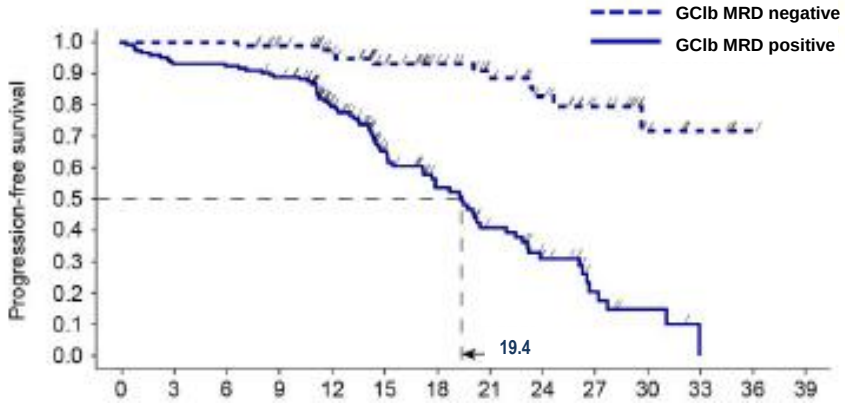
Hazard Ratio (unstratified) 95%CI	-	0.42 [0.33 – 0.54]
Overall survival		
Patients with event	41 (12.4 %)	28 (8.4 %)
Patients without event**	289 (87.6 %)	305 (91.6 %)
P-value	-	**p=0.0849**
Hazard Ratio (stratified[##]) 95%CI	-	0.66 [0.41 - 1.06]
End of treatment response		
Responders	214 (65.0 %)	261 (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**
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**

SOURCE: (10) (19) [Table 21, Table 27, Table 30]

GClb: Obinutuzumab and Chlorambucil; RClb: Rituximab and chlorambucil

[##] including censored observations, ** 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

Figure B19 PFS by MRD status in patients treated with GClb (Stage 2)



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

SOURCE: (10)
Clb: Chlorambucil; G: obinutuzumab; MRD: Minimal Residual Disease

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

Table B22 Overall survival results for CLL11 (stage 1a, stage 1b and stage 2, March 2014 cut off)

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]

Clb: Chlorambucil; GClb: Obinutuzumab and Chlorambucil; RClb: Rituximab and chlorambucil

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

A meta-analysis was not considered necessary given that only one relevant trial was identified.

6.6.2 **If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal**.

Not applicable

6.6.3 **If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

Not applicable

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.**

The CLL11 trial evaluates the efficacy of obinutuzumab plus chlorambucil (GClb) versus rituximab plus chlorambucil (RClb) and chlorambucil alone (Clb). However given the need to compare against other interventions of interest (bendamustine [Benda] and rituximab plus bendamustine [RBenda]), an indirect treatment comparison (ITC) needs to be conducted to assess its efficacy against these treatments. Further, where both direct and indirect evidence is available, this indicates a potential for undertaking mixed treatment comparison (MTC). MTC, a special case of network meta-analysis (NMA), combines direct with indirect evidence for particular pair-wise comparisons thereby synthesising a greater share of the available evidence than traditional meta-analysis. MTC as compared with ITC has two important characteristics including strengthening the inference for relative efficacy determinations and facilitating the ranking or simultaneous comparisons of all the treatments. Given the modelling approach used in section 7 – a Markov structure as opposed to an Area Under the Curve model was used due to the immaturity of OS data in CLL11 – an MTC was undertaken to determine the relative efficacy of obinutuzumab versus different interventions in 1L CLL, in terms of PFS only. In other words this means it is necessary to identify all RCTs reporting a hazard ratio for PFS in order to inform the network.

All studies that might inform the MTC were identified via the search detailed below.

The systematic review (SR) was conducted to identify randomised controlled trials (RCTs) and non-randomised clinical trials (n-RCTs) using MEDLINE, EMBASE, MEDLINE In-process, and Cochrane Library. The databases searched studies published from 1992 to April 2014.

The following relevant conferences were hand searched for a review of the abstracts, covering, as a minimum, the past three years:

- American Society of Clinical Oncology (ASCO) Annual meeting (2011-2014)
- American Society of Hematology (ASH) Annual meeting (2011-2014)
- European Haematology Association (EHA) Annual meeting (2011-2014)

Searches used index and text words which included investigational agents in untreated CLL and CLL as descriptors. The search was restricted to include only documents relating to humans and clinical trials, and excluded reviews when the inclusion criteria were not met. Only publications written in English were assessed. The search was restricted to CLL. The search was further restricted manually according to inclusion/exclusion criteria in Section 10.4.6.

Citations were screened by two independent reviewers first, based on the abstract supplied with each citation and subsequently based on the full-text citations. Any discrepancies between reviewers were reconciled by a third independent reviewer.

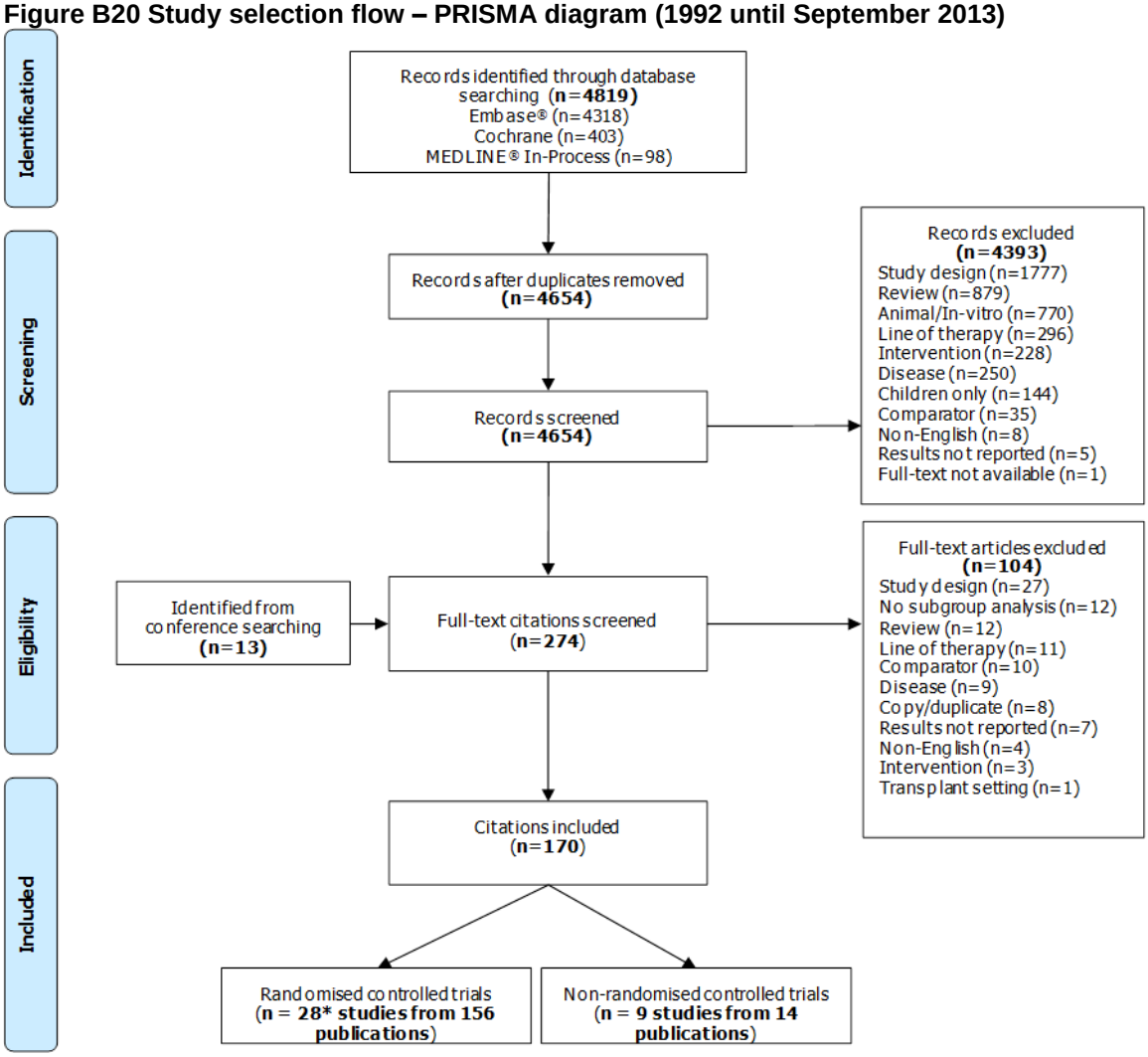
Full details of the searches conducted and terms used are provided in Appendix 4, section 10.4. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in Section 6.3.3.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The search strategies for the systematic review are presented in section 10.3.4 and the inclusion and exclusion criteria are summarised in section 10.3.6. Figure B20 and Figure B21 show the flow of studies through the systematic review process. The initial search was conducted until September 2013. In order to have conducted a search within 6 months of the submission, an updated search was run until April 16th 2014. However due to time constraints, this updated search was only included since this data was deemed most significant to identify for the MTC (i.e. in order to be most

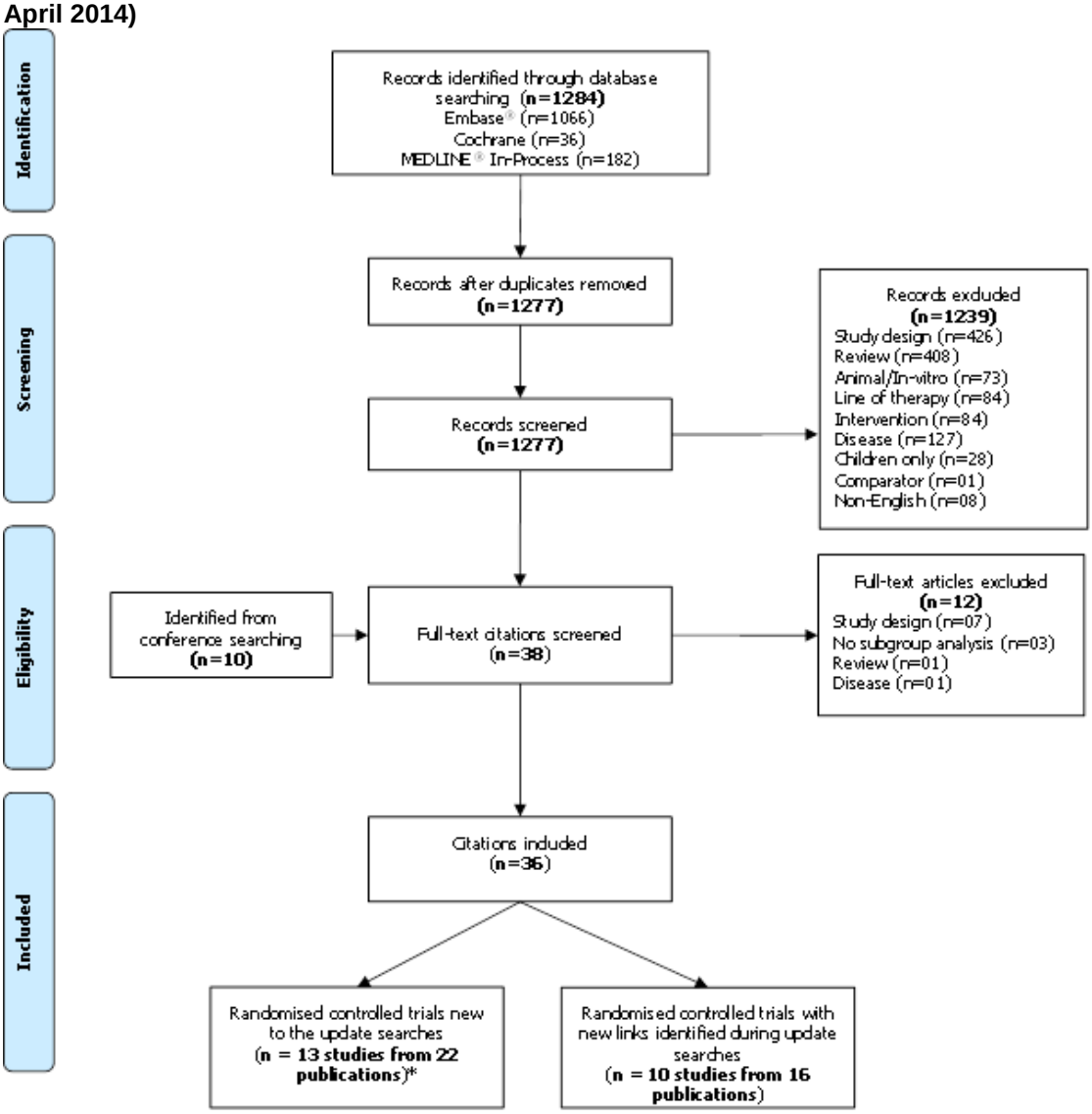
efficient non-RCTs were not searched since any data from non-RCTs would not be used in the MTC anyway).

Figure B20 Study selection flow – PRISMA diagram (1992 until September 2013)



*One study reported data for two trials

Figure B21 Study selection flow – PRISMA diagram (updated searches 2013 until 16 April 2014)



3.1.1.1.1 *Represents two additional references for studies that were identified in the original review but were not extracted due to the unavailability of results

In the initial search a total of 28 studies (29 full RCTs since one study in the initial search reported data for two trials) were identified as meeting the inclusion criteria for the review (Table B23). In the updated search an additional 13 new studies were identified (10 studies from the initial search with new links (sources) were also identified). Therefore in total, 41 studies (42 full RCTs since one study in the initial search reported data for two trials) with data reported in 178 publications were identified.

Table B23 Summary of the 42 RCTs meeting the inclusion criteria

Study	Treatment details	Study country	N*	Primary study	Linked publications
Induction					
Brugiatelli 1995	Chlorambucil (early treatment) vs. Chlorambucil (deferred treatment)	Croatia, Italy	148	(54)	-
CALGB 9011 trial	Chlorambucil + Fludarabine vs. Chlorambucil vs. Fludarabine	Not reported	544	(49)	(14;55-65)
CAM307 study	Alemtuzumab vs. Chlorambucil	Croatia, Czech Republic, Estonia, France, Ireland, Italy, Lithuania, Netherlands, Poland, Serbia, Slovakia, United Kingdom, United States	297	(50)	(66-71;71-77)
CLL2007FMP trial	Alemtuzumab + Fludarabine + Cyclophosphamide vs. Fludarabine + Rituximab + Cyclophosphamide	France and Belgium	165	(78)	(79-83)
CLL5 trial	Fludarabine vs. Chlorambucil	Germany	206	(15)	(84-88)
CLLARC CLL5 trial	Fludarabine (24mg/m^2, d1-5) + Rituximab vs. Fludarabine (24mg/m^2, d1-5) +	Australia and New Zealand	120	(89)	(90;91)

	Rituximab + Cyclophosphamide vs. Fludarabine (24mg/m^2, d1-3) + Rituximab + Cyclophosphamide				
Dighiero 1998 (Trial 1)	Chlorambucil vs. No treatment	France	609	(92)	-
Dighiero 1998 (Trial 2)	Chlorambucil + Prednisone vs. No treatment	France	926	(93)	-
US E2997 trial	Fludarabine vs. Fludarabine + Cyclophosphamide	United States	278	(92)	(94-99)
EORTC LCG trial	Fludarabine vs. Chlorambucil	Not reported	88	(100)	(101-103)
Eradat 2012	Rituximab vs. Rituximab + Navitoclax (for 12 weeks) vs. Rituximab + Navitoclax (until disease progression, relapse or unacceptable toxicity)	Not reported	118	(104)	(105)
French Group CLL trial	Fludarabine vs. CHOP	France	938	(106)	(107-112)
GCLLSG CLL7trial	Early vs. Deferred Fludarabine + Rituximab + Cyclophosphamide	Germany, France	824	(113)	-
GCLLSG CLL8 trial	Fludarabine + Cyclophosphamide vs. Fludarabine + Rituximab + Cyclophosphamide	Australia, Austria, Belgium, Czech Republic, Denmark, France,	817	(37)	(114-131)

		Germany, Israel, Italy, New Zealand, Spain			
GCLLSG CLL10 trial	Bendamustine + Fludarabine vs. Fludarabine + Rituximab + Cyclophosphamide	Germany, Austria, Switzerland, Denmark and Czech Republic	688	(38)	-
German group CLL4 trial	Fludarabine + Cyclophosphamide vs. Fludarabine	Austria and Germany	375	(132)	(133-139)(133-139)(133-139)(133-139)(134-140)(135-141) (133-139)
HOVON68 CLL trial	Alemtuzumab + Fludarabine + Cyclophosphamide vs. Fludarabine + Cyclophosphamide	Not reported	281	(140)	(141;142)
Hx-CD20-407 trial	Fludarabine + Ofatumumab (500 mg) + Cyclophosphamide vs. Fludarabine + Ofatumumab (1000 mg) + Cyclophosphamide	USA, UK, Germany, Czech Republic	61	(143)	(144-149)
Karlsson 2007	Cladribine vs. Chlorambucil vs. Fludarabine	Australia, Scandinavia, UK	221	(150-152)	
Knauf 2009	Bendamustine vs. Chlorambucil	Austria, Bulgaria, France, Germany, Italy, Spain, Sweden, and the United Kingdom	319	(40)	(43;51;153-155)
MaBLe study	Bendamustine +	Not reported	339	(156)	

	Rituximab vs. Chlorambucil + Rituximab				
PALG CLL1 trial	Cladribine + Prednisone vs. Chlorambucil + Prednisone	Poland	-	(157)	(158-164)
PALG CLL2 trial	Cladribine vs. Cladribine + Cyclophosphamide vs. Cladribine + Cyclophosphamide + mitoxantrone	Poland	508	(165)	(166-169)
PALG-CLL3 study	Cladribine + Cyclophosphamide vs. Fludarabine + Cyclophosphamide	Not reported	423	(170)	(75;76;171-174)
PALG CLL4 trial	Fludarabine + Rituximab + Cyclophosphamide followed bymaintenance treatment with Rituximab vs. no further treatment,	Poland	128	(175)	-
Rummel 2003	Fludarabine vs. Fludarabine + Epirubicin	Germany	161	(176)	(177-179)
Spriano 2000	Fludarabine vs. Chlorambucil + Prednisone	Italy	150	(180)	-
THE OWN STUDY	Cladribine + Cyclophosphamide vs. Fludarabine + Cyclophosphamide	Poland	38	(181)	-

UK LRF CLL4 trial	Fludarabine + Cyclophosphamide vs. Fludarabine vs. Chlorambucil	UK, Argentina, Croatia, Greece, Ireland, Italy, New Zealand and Russia	783	(48)	(182-192)
LLC 2007 SA trial	Abbreviated Fludarabine + Cyclophosphamide and dose-dense Rituximab	France	194	(193)	-
Mulligan 2014	Cladribine vs. Fludarabine vs. Chlorambucil	Sweden, Norway, Denmark, Finland, Australia, United Kingdom, South Africa		(130)	-
ARCTIC trial	Mitoxantrone + Fludarabine + Cyclophosphamide + attenuated dose Rituximab vs. Rituximab + Fludarabine + Cyclophosphamide	United Kingdom	206	(194)	-
OMB110911 trial (COMPLEMENT 1)	Ofatumumab + Chlorambucil vs. Chlorambucil	Belgium, Brazil, Canada, Chech Republic, Germany, Greece, India, Ireland, Italy, Netherlands, Poland, Russia, Spain, Sweden, United Kingdom, United States	447	(52)	(195)
Nikitin 2013	Rituximab +	Russia	97	(196)	-

	Fludarabine + Cyclophosphamide lite vs. Chlorambucil				
ADMIRE trial	Mitoxantrone + Fludarabine + Cyclophosphamide + Rituximab vs. Rituximab + Fludarabine + Cyclophosphamide	United Kingdom	215	(197)	-
CLL11 trial	Obinutuzumab + Chlorambucil vs. Rituximab + Chlorambucil vs. Chlormabucil	Argentina, Austria, Australia, Brazil, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany , Great Britain, Hong Kong, Italy, Mexico, Romania, Russian Federation, Slovakia, Spain, Switzerland, Thailand, New Zealand, USA	781	(10)	(26;45-47;198)
CLLM1 trial	Lenolamide as maintenance after Rituximab + Fludarabine + Cyclophosphamide vs. after Rituximab + Bendamustine	Germany	37	(199)	(200)
CLL1 trial	Early risk-adapted	Unclear	710	(201)	(202;203)

	therapy with Fludarabine monotherapy vs. watch and wait				
Foa 2014	Chlorambucil + Rituximab as first-line induction treatment with or without Rituximab as maintenance	Unclear	85	(204)	-
Induction + Consolidation					
CALGB 9712 trial	Fludarabine + Rituximab (concurrent regimen) vs. Fludarabine + Rituximab (sequential regimen)	USA	104	(65)	(205-210)
IGCI CLL-02 trial	CHOP vs. Chlorambucil	Croatia, Czech Republic, Hungary, Italy, Poland, Vienna	228	(211)	(212)
Consolidation					
Schweighofer 2009	Alemtuzumab vs. Observation alone	Germany and Austria	23	(213)	(214-217)

*Represents patient population of interest to the review; CHOP: Cyclophosphamide + Adriamycin + Oncovin + Prednisone; UK: United Kingdom; USA: United States of America

List of relevant RCTs identified through literature review

The systematic review (SR) identified a total of 42 studies (41 RCTs in total since one study reported data for two trials). However, only 8 studies reported the HR for PFS. In order to minimise outcome reporting bias, the HR was approximated for another 8 RCTs, based on additional PFS information reported in the manuscripts. Hence, the network of evidence includes a total of 17 RCTs (including CLL11), encompassing 14 different pharmacological interventions. Therefore, a total 17 RCTs were included in the NMA to estimate the (indirect) comparative effectiveness of obinutuzumab against another 13 pharmacological interventions in terms of PFS. The MaBLe study is expected to have an HR reported in the near future when available and has therefore been included in the network but not, as yet, in the analysis. Once the HR for MaBLe is reported the MTC will be updated accordingly.

A brief summary of each of the 17 RCTs (16 + MaBLe) used to inform the MTC is given below, whilst Table B24 details the PFS and OS (where available) results in tabular form for comparative purposes.

Table B24 Summary of the trials used to conduct the indirect comparison

	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

	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 randomisation	Adequate	Unclear	Unclear	Unclear	Unclear
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:	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

age					
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

	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 C	• Binet stage A, B, and C	• Binet stage A, B, and C	• Binet stage A, B, and C

CLL stage			• Rai Stage 0, I, II, III and IV	• Rai Stage 0, I, II, III and IV	
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

	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

List of relevant non-RCTs identified through literature review

A total of 9 nRCTs with data reported in 14 publications were identified in the main systematic review as meeting the inclusion criteria (Table B25). However, only RCTs were included into the network as evidence from non-RCTs is not considered robust where RCTs are available. The update of the systematic review did not include searches for non-RCTs.

Table B25 List of included non-randomised controlled trials

Study	Intervention	Comparator	N*	Primary study	Linked publications
Induction therapy					
Byrd 2012	Ibrutinib 420 mg	Ibrutinib 840 mg	31	(219)	(O'Brien 2012)
Molica 2005	Fludarabine	Chlorambucil	12	(220)	-
Robak 2000	Cladribine + prednisone	Cladribine	378	(221)	-
SAWYER (BO25341) study	Fludarabine + rituximab (1400 mg SC in cycle 6) + cyclophosphamide	Fludarabine + rituximab (1600 mg SC in cycle 6) + cyclophosphamide	64	(222)	-
		Fludarabine + rituximab (1870 mg SC in cycle 6) + cyclophosphamide			
Stadnik 2010	Fludarabine + cyclophosphamide	Fludarabine + Rituximab + cyclophosphamide	90	(223)	(Stadnik 2011)
Badea 2000	Fludarabine	Chlorambucil + prednisone	67	(224)	-
Tasic 2002	CHOP	Chlorambucil	130	(225)	-
Consolidation/Maintenance					
CALGB19901 trial	Alemtuzumab (iv)	Alemtuzumab (sc)	59	(226)	-
Del Poeta 2008	Rituximab	Observation (MRD positive patients)	138	(227)	-
		Observation (MRD negative patients)			

*Represents patient population of interest to the review; CHOP: Cyclophosphamide + Hydroxydaunorubicin + Oncovin + Prednisone; iv: Intravenous; MRD: Minimal Residual Disease; sc: Subcutaneous

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A total of 17 RCTs were included in the network meta-analysis (NMA) to evaluate the comparative effectiveness of obinutuzumab in terms of PFS. The results of these RCTs are presented in Table B26.

Table B26 Summary of PFS and OS results of the 17 RCTs identified in the SR

Trial	Comparison	PFS			OS		
		Median (months)	HR	95% CI (Lower - Upper)	Median (months) (p-value)	HR	95% CI (Lower - Upper)
GCLLSG CLL8	RFC vs FC	51.8 vs. 32.8 (p<0.0001)	0.560	0.46-0.69	NR vs. 86.0 (p=0.0001)	0.67	0.48–0.92 p=0.012
CLL5	F vs. Clb	19 vs. 18 (p=0.7)	0.951	0.70-1.29	46 vs. 64 (p=0.15)	NA	NA
Knauf	Benda vs. Clb	21.2 vs. 8.8 (p<0.0001)	0.353	0.27-0.46	NR vs. 78.8	1.30	0.89- 1.91, p=0.1801
CAM307	Alm vs. Clb	14.6 vs. 11.7 (p=0.0001)	0.580	0.43-0.77	NR vs. NR	NA	NA
UK LRF CLL4	F vs.Clb	Clb: 20 Flu: 23 FC: 40 (p<0.00005).	0.860	0.71-1.04	NA	1.18	0.92–1.51 p=0.20
	FC vs.Clb		0.450	0.37-0.54	NA	1.18	0.92–1.51 p=0.20
	FC vs.F		0.450	0.35-0.59	NA	0.93	0.67–1.30 p=0.70
CALGB 9011	F vs. Clb	20 vs. 14 (p<0.001)	0.680	0.55-0.86	66 vs 56 (p=0.10)	NA	NA
CLL11	GClb vs. Clb	26.7 vs. 11.1 (p<0.001)	0.183	0.137-0.244	NA	0.41	0.23- 0.74 p=0.002
	RClb vs. Clb	16.3 vs. 11.1 (p<0.001)	0.458	0.358-0.586	NA	0.66	0.39- 1.11 p=0.11
	GClb vs. RClb	26.7 vs. 15.2 (p<0.001)	0.388	0.306-0.493	NA	0.66	0.41- 1.06 p=0.08
COMPLEMENT 1	Ofa+Clb vs. Clb	22.4 vs. 13.1 (p<0.001)	0.570	0.45-0.73	NR vs. NR (p=0.666)	NA	NA
CLL10	RFC vs. RBenda	NR vs. 36.5 (p=0.016)	NA	NA	NA (p=0.593)	0.842	NA
LLC 2007	Cla or F vs. Clb	25 vs. 10 vs. 9 (p=0.0005 [Cla vs. F] and p=0.0038 [Cla vs. Clb])	NA	NA	96 vs. 82 vs. 91 (p not significant)	NA	NA
HOVON68	AlmFC vs. FC	37 vs. 31 (p=0.08)	NA	NA	NR	NA	NA
CLL207FMP	AlmFC vs. RFC	NR	NA	NA	NR	NA	NA

Nikitin 2013	RFC-lite vs. Clb	NR vs. 25.3 (p=0.0042)	NA	NA	NA	NA	NA
PALG-CLL3	RFC vs. FC	30.6 vs 20.6 (p<0.001)	0.65	0.51-0.82	NR vs. 52 (p=0.2874)	0.83	0.59-1.17
GCLLSG CLL4	FC vs. F	48.0 vs. 20.0 (p=0.001)	NA	NA	NR (p= 0.74)	NA	NA
US E2997	FC vs. F	31.6 vs. 19.2 (p<0.0001)	NA	NA	NA	NA	NA
MaBLe	RBenda vs. RClb	NA	NA	NA	NA	NA	NA

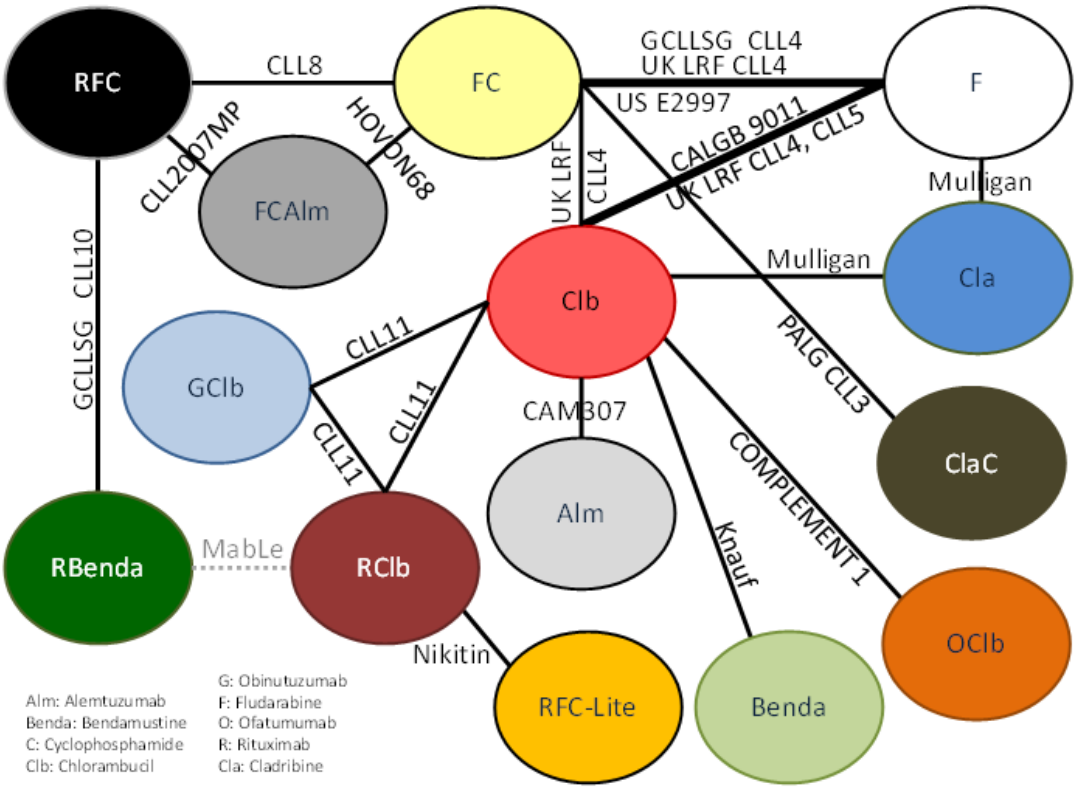
*Mean age was preferred over median age (whenever available/reported)
Alm: Alemtuzumab; Benda: Bendamustine; Cla: Cladrabine; Clb: Chlorambucil; C: Cyclophosphamide; F: Fludarabine; G: Obinutuzumab; HR: Hazard Ratio; lnHR: natural logarithm of the reported Hazard Ratio; NA: Not available; NR: Not reached; Ofa: Ofatumumab; R: Rituximab; se(lnHR): standard error of lnHR

Based on these 17 RCTs two different networks were built to represent differing scenarios with regard to the suitability of patients for fludarabine based therapy in line with the label of obinutuzumab (Section 1.5):

"Obinutuzumab in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with co morbidities making them unsuitable for full-dose fludarabine based therapy."

One scenario (large network, Figure B22) includes all 17 studies identified in the systematic review of the literature (i.e. those that have reported/will report a HR for PFS), regardless of the patients' suitability for full-dose fludarabine based therapy. In the second scenario (small network, Figure B23) studies are only included if they **enrolled patients ineligible for fludarabine-based therapy** (i.e. according to the predefined inclusion/exclusion criteria) in line with obinutuzumab's licensed indication.

Figure B22 Diagram of evidence for large network for MTC (all 17 RCTs in 1L CLL included)

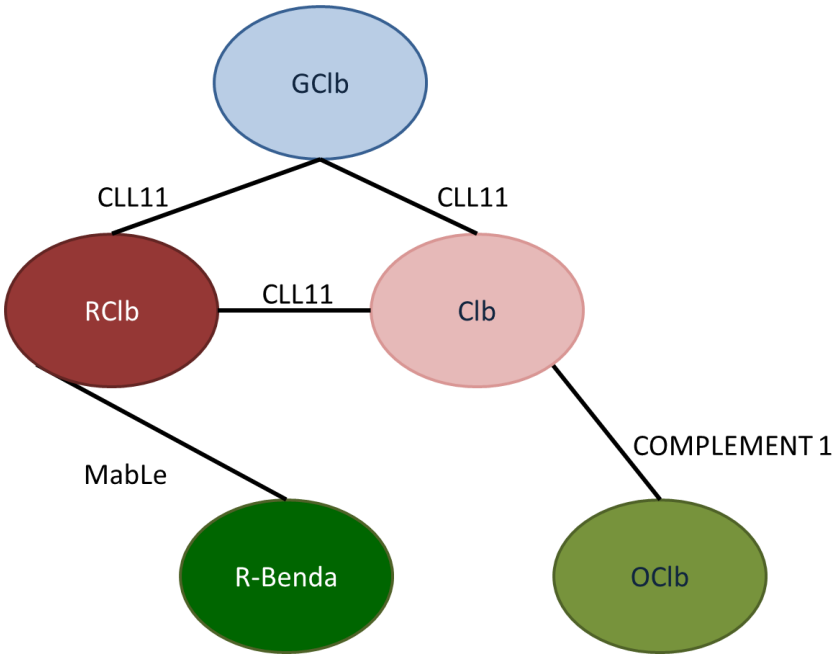


Alm: Alemtuzumab; Benda: Bendamustine; C: Cyclophosphamide; Cla: Cladribine; Clb: Chlorambucil; F: Fludarabine; G: Obinutuzumab; O: Ofatumumab; R: Rituximab

The large network includes all RCTs identified in the systematic review that reported a HR for PFS or for which a HR for PFS could be calculated. This network includes all studies irrespective of eligibility of patients to fludarabine-based therapy. A total of

17 studies have been included in this network diagram (see section 6.7.2). The present MTC analysis does not include MaBLe. The MaBLe study (RBenda vs RClb) will be added to the MTC once the trial results are published.

Figure B23 Diagram of evidence for small network for MTC (only RCTs in 1L CLL included if enrolled patients were ineligible for fludarabine-based therapy)



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

The small network corresponds to studies enrolling patients ineligible for fludarabine-based therapy (Figure B23). This network includes studies that explicitly excluded patients ineligible for fludarabine-based therapy. A total of three studies have been included in this network diagram: CLL11, COMPLEMENT 1 and MaBLe. The present MTC analysis only includes the first two studies; it will be updated once the MaBLe study (RBenda vs RClb) trial results become available.

Although bendamustine (Benda) has a licensed indication for patients ineligible to fludarabine-based therapy it is excluded from the small network since the Knauf study did not explicitly include or exclude patients based on fludarabine eligibility. Further, the study patients had a median age of 63, and in the absence of any formal measures to signify fludarabine-ineligiblity, it should be assumed such patients would in reality be considered eligible for fludarabine-based care. This is evidenced by the trial having a median age comparable with other trials for medically fit 1L CLL patients (i.e. suitable for fludarabine, such as CLL8, CLL10 and CLL4) as opposed to the median ages in trials where fludarabine suitability was a specific exclusion

criterion (e.g. CLL11, COMPLEMENT-1, MaBLe) (see Table B26). To reinforce this assessment of the Knauf study being inappropriate for the small network, 96% of the patients had a WHO performance status of 0 or 1, and the oldest patient recruited into the trial was only 78, all suggestive that the majority of these patients would be considered 'fit' and eligible for fludarabine-based therapy.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

For CLL11, individual patient level data was available and hence three unstratified HRs for PFS were estimated using the stage 2 data where possible, corresponding to the three comparisons arms of the trial. For all other trials, aggregate data (study-level summary statistics) from publications were used.

Table B27 summarises the key input data used for the MTC analysis. Natural logarithms of the HRs (lnHR) were inputted into the WinBUGS code (see section 6.7.5). The age for which an age-adjusted large network analysis was conducted are also presented (see section 6.7.5).

Table B27 Summary of results in the trials used to conduct the indirect 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						

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.

‡When 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.

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

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The following section describes the methods used to synthesise the network of evidence in a Bayesian framework using WinBUGS software. The WinBUGS code used here was originally published in the NICE DSU technical support document 2 as "Program 7" (228) and adapted to the underlying situation here (http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%20Mar2013.pdf).

The WinBUGS code used to parameterise the NMA model uses the natural logarithm (ln) of the HR as the (continuous) outcome variable. These are available from the clinical trials together with the corresponding standard errors (se). The parameters of interest are the trial-specific mean lnHR. Trial results are available as trial-based summary measures in the form of ln-hazard ratios (lnHR) and its corresponding standard error (se). The NMA model assumes a normal distribution for the lnHR of arm k relative to arm 1 in trial i, y_{ik} , with variance v_{ik} . The methodology is fully described in section 3.5 from the same Dias et al. DSU document 2 (228).

CLL11, UK LRF CLL4 and Mulligan 2014 are three-arm trials that provide three pairwise comparisons. When results from multi-arm trials are presented as (continuous) treatment differences relative to the control arm (arm 1), a correlation between the treatment effects is induced because all differences are taken relative to the same control arm. This correlation is inherent in the data, and so requires an adjustment to the likelihood – which has been done in the WinBUGS code used for these ITCs. A trial with n arms produces n-1 treatment effects that are correlated. For example, in CLL11, the comparisons GClb vs. Clb, RClb vs. Clb are correlated. The covariance between differences taken with respect to the same control arm is equal to the observed variance for the common control arm. For example, when the treatment differences are given as lnHRs, se2i1 is the variance of the ln-Hazard for arm 1 (reference arm) of trial i. CLL11 is a three-arm trial and the WinBUGS code uses the Clb arm as the reference arm. The se2i1 of the Chlorambucil arm (reference arm) in CLL11 is estimated based on the formula n.7 published by (229):

$$se_b = \sqrt{\left(\left(se^2_{k_1,b} + se^2_{k_2,b} - se^2_{k_1,k_2} \right) / 2 \right)}$$

Where se2i,j is the variance of the ln hazard ratio comparing arm i to arm j and sei is the standard error of the ln hazard for arm i.

The likelihood adjusted for the correlation in the WinBUGS code used here for CLL11 and UK LRF CLL4. However, this adjustment was not possible for Mulligan 2014. The variance for the common control arm in Mulligan 2014 could not be estimated because the manuscript did not report the necessary information for the calculation (i.e. PFS data for all arms). Hence, the variance for the common control arm in the Mulligan study was assumed equal to zero.

In addition to a standard fixed-effect (FE) model, the presence of between-study heterogeneity was investigated through a random-effect (RE) NMA model.

While a random-effect (RE) NMA model was implemented to account for heterogeneity, a meta-regression NMA model was used to investigate and explain the heterogeneity potentially caused by differential age between studies. Age was considered as a potential confounder of PFS through treatment effect (14) and therefore a source of heterogeneity in the network. The average patient age varies markedly across trials in the large network. This is likely to bias the MTC results because older patients have higher competing mortality risks compared to younger patients, and consequently this difference in mortality risks between studies is likely to bias the relative treatment estimates derived from the MTC.

MTC analyses considered

Small network

Two models were applied to the small network:

- Fixed-effect (FE) model (base case)
- Random-effects (RE) model with a weakly-informative prior distribution to induce heterogeneity

The FE model applied to the small network assumes that there is no heterogeneity between trials. Note that each pairwise comparison in the small network is informed by a single study. This prevents the MTC model from identifying the between-study variance. Because of the limited number of studies in the network (and particularly because there is only a single study informing each pairwise comparison) the

implementation of a RE model is not feasible based solely on the available sample data.

A potential limitation of this FE model is the small number of RCTs in the network of evidence, which prevents investigation of potential sources of heterogeneity between trials. That is, the use of meta-regression is not feasible due to:

1) Limited number of studies to inform the relationship between age and treatment effect, and;

2) The median age reported in the two trials that make up the network (CLL11 and COMPLEMENT-1) differ by little (73 and 69.5)[1].

Therefore a FE model with no adjustment made for between trial heterogeneity is used as the base case for the small network. The WinBUGS model code and the full set of results (WinBUGS output) can be found in Appendix 10.14.

As a sensitivity analysis, an RE model was implemented. This is achieved by replacing the vague prior distribution of the between-study standard deviation with a weakly informative prior distribution. A standard reference prior distribution for the between-study standard deviation is Uniform (0,2), as suggested by the NICE DSU Technical Support Document 2 (Evidence Synthesis series) (228). However, this implies that extreme heterogeneity is equally plausible to mild heterogeneity. This approach forces the model to rely solely on the sample data to estimate the size of heterogeneity, which is not possible with such a small network.

To overcome this problem, a weakly-informative prior distribution (i.e. a Half-Normal (0, 0.322)) for the between-study standard deviation is suggested in the NICE DSU Technical Support Document 3 (Evidence Synthesis Series) (230). Since there is no sample data to inform this model parameter, the prior distribution drives the posterior distribution. As the size of the induced heterogeneity grows, the relative benefit between different interventions is eroded, making their HRs more and more similar in relation to a common comparator. The WinBUGS model code and the full set of results (WinBUGS output) can be found in Appendix 10.14.

Large network

Three models were applied to the large network:

[1] This refers to being able to perform a meta-regression and not the fitness of patients where a difference of 3.5 years is not an insignificant amount.

- FE model with meta-regression on age (base case)
- FE model
- RE model with a weakly-informative prior distribution to induce heterogeneity

The large network allows the investigation of age as a potential source of heterogeneity between trials. Age is a potential confounder of treatment effect (as measured by the PFS HR) since studies with older patients have a higher (baseline) risk of death than studies with younger patients. 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 MTC.

An FE model both with and without an age adjustment was therefore implemented. However the FE meta-regression on age MTC model is used for the base case of the large network because the age adjustment is believed to minimise potential bias (as explained above) in the MTC results. The age-adjustment network and methodology was presented at an advisory board where clinicians and health economists agreed that this was a reasonable way to try to compensate for between trial heterogeneity given the data available. For the RE model, only an analysis without an age adjustment was implemented since a meta-regression MTC model could not identify the posterior distribution of the age coefficient due to the limited number of studies available.

In the FE meta-regression MTC model age was centered around the median age observed in the CLL11 trial (73 years). The median was preferred because all publications reported the median, but only a few reported the mean value. By centering the covariate, the mixing of the Markov Chain Monte Carlo (MCMC) chains is improved. Treatment effects are estimated at the median covariate value, and so the MTC results can be interpreted for a hypothetical population with a median age of 73 years. Assuming a positive correlation between age and comorbidities (14), adjusting for age within the large network allows for a fairer comparison of treatments, since older patients inherently have higher competing mortality risks compared to younger patients due to having more comorbidities. Removing this difference in mortality risks therefore helps to eliminate bias in the relative treatment effect estimates.

As a sensitivity analysis, the FE and RE models (without age adjustment) were run. The RE MTC model is fitted with the same weakly informative prior distribution

described previously. The RE NMA model was also fitted with a vague prior and the results were consistent with the RE NMA model with a weakly informative prior distribution (it has therefore not been included in submission). Note that although the number of studies in the large network is 16 (compared to 2 in the small network), most pairwise comparisons are still informed by a single study (except the comparisons Fludarabine (F) vs. Chlorambucil (Clb); and Chlorambucil (Clb) vs. Fludarabine+Cyclophosphamide (FC), which are informed by three studies each).

The WinBUGS model code and the full set of results (WinBUGS output) for all models can be found in Appendix 10.14.

6.7.6 **Please present the results of the analysis.**

GClb was always shown to be always the most effective treatment against any potential comparator, in all analyses undertaken in both in the small and large networks. When the MTC was adjusted for age in the large network, the performance of GClb improved relative to the other treatments.

Table B28 below presents the results from all possible models for the comparators of interest (i.e. bendamustine and within the large network only since it did not figure in the small network; full results for all comparators can be found in the WinBUGS code in Appendix 10.14). In the base case, the age-adjusted FE model MTC for GClb vs Benda resulted in a HR (95% CI) of 0.399 (0.218 to 0.672). Without an age adjustment the HR for GClb vs Benda was higher in both the FE and RE model (0.546 and 0.554 respectively) but still statistically significant in both cases. The impact on the ICER of taking a HR for GClb vs Benda without adjusting for age is explored in the sensitivity analysis.

The results of the MTC were presented to clinicians at an advisory board and they agreed that an approximately ~27% reduction in the HR after adjusting for age seemed plausible.

Table B28 Summary of MTC results for obinutuzumab vs Bendamustine

Comparison	Model	Mean PFS HR	Lower 95%CI	Upper 95%CI
GClb vs Benda	FE model with age adjustment	**0.399**	0.218	0.672
	FE model	**0.546**	0.367	0.783
	RE model	**0.554**	0.322	0.892

In all models GClb was consistently ranked the best treatment. The probability of it being best ranged from 0.607 in the RE model to 0.694 in the FE model with age adjustment.[2]

Table B29 Probability of being best treatment

Comparator	FE model with age adjustment		FE model		RE model	
	Prob. Best Tx	Ranking	Prob. Best Tx	Ranking	Prob. Best Tx	Ranking
Clb	0.000	12.790	0.000	14.000	0.000	13.970
Benda	0.000	6.598	0.000	5.751	0.004	5.891
OClb	0.000	10.000	0.000	11.230	0.000	10.970
F	0.000	13.370	0.000	12.980	0.000	12.920
Alm	0.000	12.640	0.000	11.280	0.000	11.030
FC	0.000	9.744	0.000	9.099	0.000	8.946
RFC	0.008	3.211	0.035	2.822	0.065	2.944
RClb	0.000	5.745	0.000	8.882	0.000	8.743
GClb	0.694	1.314	0.667	1.364	0.607	1.508
FCAlm	0.000	6.915	0.000	6.321	0.001	6.358
RBenda	0.000	6.423	0.002	5.903	0.008	6.096
RFC-Lite	0.296	1.891	0.291	2.333	0.303	2.517
ClaC	0.000	8.364	0.000	7.760	0.001	7.696
Cla	0.001	5.992	0.005	5.272	0.011	5.405

Given that the MTC did not provide a HR for the comparison of GClb vs RBenda (since MaBLe data was not available to be input into the analysis) an assumption for this HR has been made in order to input into the cost-effectiveness model.

[2]It should be noted that although R-FC-Lite has a ~30% of being the best treatment, information about this comparator comes from an interim analysis reported in a conference abstract (Nikitin 2013). The median PFS was not available for the R-FC-Lite arm because the data were not mature enough by the time of the publication and no PFS HR was reported either. Therefore for the MTC, an HR was approximated from other PFS reported data. Specifically, the 72.6% PFS at 2 years for the R-FC-Lite arm compared against a median PFS of 25.3 months in the R-Clb arm.

The HR for GClb vs RClb from the latest data cut (March 2014) was [redacted] and the percentage of complete responders was 20.7% and 7% respectively (see Table B21); in others words there were approximately 2.96 times as many responders in the GClb arm versus the RClb arm. In the MaBLe protocol the sample size calculation for the primary endpoint (primary endpoint is “confirmed complete response rates” after 6 cycles) on first-line patients is based on estimates of 30% and 15% in the R-Benda arm and the RClb arm respectively (231); a multiple of 2.

Assuming a full correlation between the difference in complete responders and the PFS HR, if a multiple of [redacted] leads to a [redacted] reduction in the risk of progression for GClb versus RClb (HR = [redacted]), then a multiple of [redacted] might lead to a [redacted] in the risk of progression for RBenda versus RClb or a HR of [redacted] This then enables an indirect comparison of GClb versus RBenda where [redacted], giving a final HR of 0.68. A HR of 0.68 for GClb versus RBenda is therefore used as the base case in the cost-effectiveness model.

It should be noted that the interim analysis of MaBLe (156) validates the percentages sought in the protocol with the percentage of first line complete responders being 30% in the RBenda arm versus 13% in the RClb arm (p=0.054); a multiple of approximately 2.31. Using the same rationale as above, a 2.31 multiple might lead to a 46% (2.31/2.96 * 59%) reduction in the risk of progression for R-Benda versus RClb or a HR of 0.54, giving a final HR GClb versus RBenda of 0.76 [ln(HR) = ln(0.41) – ln(0.54)]. However since the p-value was not significant and that the analysis of complete responders was for only approximately one third of the total target number (85 out of a final 240 previously untreated patients), the complete response rates targeted in the protocol (30% and 15%) were used as the base case to estimate an HR for GClb versus RBenda. However given the uncertainty of this parameter, varying the HR of GClb versus RBenda is explored in the sensitivity analysis.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

No formal statistical assessment of heterogeneity was undertaken.

6.7.8 **If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

N/A

6.7.9 **Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies**.

The base case was the FE model with meta-regression on age; having adjusted for age a consistency assessment was not deemed appropriate and hence not undertaken.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 **If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

There are no non-RCTs which are relevant to the decision problem.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

Safety was an endpoint in the CLL11 trial. In light of this no additional searches have been undertaken.

6.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.**

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 (10).

Adverse events occurred more frequently in the GClb and RClb groups than in the Clb alone group and were most frequent with GClb treatment (Table B30,Table B31, Table B32). The incidence of grade 3 or 4 neutropenia was highest with the

combination of obinutuzumab and chlorambucil and was lowest with Clb 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 B30 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)
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)

SOURCE: (10)

*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.

AE: Adverse Event; Clb: Chlorambucil; GClb: Obinutuzumab and chlorambucil; RClb: Rituximab and chlorambucil

Table B31 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%)

SOURCE: (10)

* 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.

AE: Adverse Event; Clb: Chlorambucil; GClb: Obinutuzumab and chlorambucil; RClb: Rituximab and chlorambucil

The most frequent serious adverse events were infections, infusion-related reactions, and neoplasms (Table B32).

Table B32 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 anaemia	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)

SOURCE: (10)

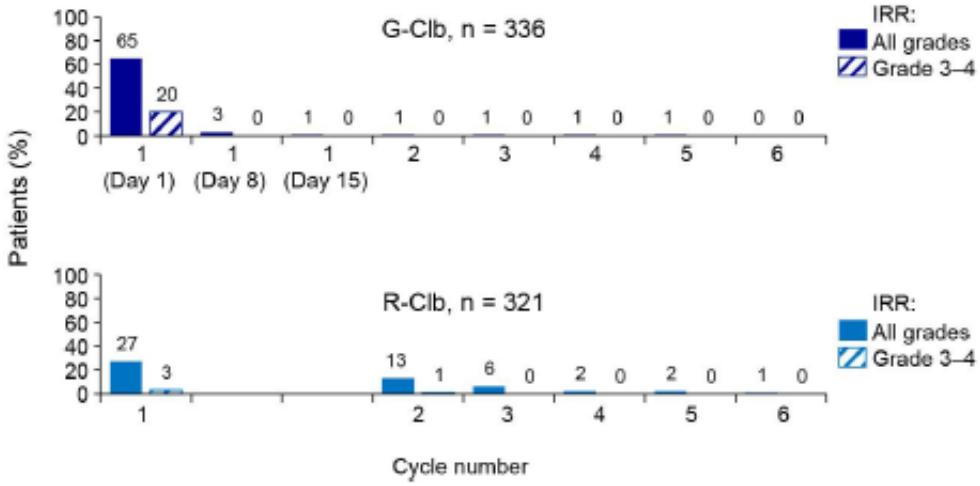
*Safety analysis population (included all patients who received at least one dose of study medication). All AE irrespective of grade, and whether considered related or unrelated to treatment by investigators, were collected and used to calculate the incidence of AE. †Incidence rate of ≥1% in any treatment arm.

AE: Adverse Event; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab; SAE: Serious Adverse Event.

Infusion-related reactions:

Infusion-related reactions were more frequent with GClb treatment than with RClb treatment. In the GClb 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 B24). No deaths were associated with infusion-related reactions. 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 B33). Prophylactic measures had only a moderate effect on the frequency of infusion-related reactions (Table B34).

Figure B24 All grade and grade 3–4* infusion-related reactions by day of infusion†



SOURCE: (10)

*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).

Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Table B33 Infusion related reactions during GClb treatment† by baseline characteristics

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)

SOURCE: (10)
*There were no grade 5 infusion-related reactions. †Stage 2 analysis.
CIRS, Cumulative Illness Rating Scale; CrCl, Creatinine Clearance; GClb: Obinutuzumab and chlorambucil; SPD, Sum of the Products of the Diameters.

Table B34 Impact of study protocol amendments on infusion-related reactions during GClb treatment

Baseline characteristic	Enrolled n	All grades n (%)	Grade 3-4 n (%)
Date of enrolment			
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)

SOURCE: (10)
*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 B35).

Table B35 Newly diagnosed malignant, benign or unspecified neoplasms starting 6 months after first study drug intake by treatment comparison*

	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)
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)

SOURCE: (10)

*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.

AE: Adverse Event; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Discontinuations:

As compared with both patients receiving GClb and those receiving Clb alone, patients receiving RClb were less likely to discontinue therapy early owing to adverse events. This imbalance between the GClb group and the RClb group was primarily due to infusion-related reactions in the GClb group (Table B36).

Table B36 Impact of infusion-related reactions and tumour lysis syndrome on clinical course

	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

SOURCE: (10)
*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 GClb and RClb groups and infections in the Clb group (Table B37). The incidence of haemorrhagic events was similar between arms (GClb 4 deaths/336, RClb 3 deaths/321, Clb 2 deaths/116). However, all 4 fatal haemorrhagic events in GClb patients occurred in Cycle 1, compared to none in RClb patients and 1 in Clb patients.

Table B37 List of grade 5 adverse events

Adverse event*	Treatment received G-Clb, n=336 R-Clb, 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 haemorrhage	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
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

SOURCE: (10)
*Safety analysis population (included all patients who received at least one dose of study medication). †As assessed by investigator.
Clb: Chlorambucil; G: Obinutuzumab; NK: not known; R: Rituximab

Give a brief overview of the safety of the technology in relation to the decision problem.

The safety profile of obinutuzumab in combination with Clb 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 for obinutuzumab and 0.5 mg/kg body weight for Clb, 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 GClb arm compared with the RClb arm. This difference was mainly due to IRRs

- The high incidence of IRR's in the GClb 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 GClb arm were low grade in intensity and were clinically manageable. No deaths were associated with IRRs.

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

- Adverse events leading to death were more frequent in the RClb (n=21) and GClb (n=15) arms compared with the Clb arm (n=11)

In CLL11, overall, GClb was comparable to RClb and Clb alone in terms of the severity of AEs, discontinuations due to AEs, and AEs leading to death.

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-Clb than with rituximab-Clb, 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 RClb or Clb arms of the study. Serious

infections, however, were more common in the Clb arm and more people died in that arm, mainly due to progressive disease.

Overall in stage 2 of the CLL11 study, 166/241 patients (69%) in the GClb arm and 88/225 patients (39%) in the RClb arm experienced an IRR, although the majority of IRRs were Grade 1-2 (20% of patients in the GClb arm and 4% of patients in the RClb arm had a Grade 3-4 IRR). Of the 221 GClb-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 RClb-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.

In stage 1, SAE neutropenia occurred more frequently in GClb-treated patients than in Clb-treated patients. The incidence of SAE neutropenia was 1% in GClb-treated patients compared to 0% in RClb-treated patients and 0% in Clb treated patients. In stage 2, SAE neutropenia occurred more frequently in GClb-treated patients than in Clb-treated patients with an incidence of 1% for GClb and <1% for RClb.

In stage 1 incidence of SAE thrombocytopenia was <1% in GClb-treated patients and <1% in RClb-treated patients, in stage 1. In stage 2, the incidence was 1% for GClb and <1% for RClb. There were no fatalities because of neutropenia or thrombocytopenia in the study.

The incidence of infection (SAE) was balanced between the treatment arms with 13% of patients in the GClb arm (stage 2), 14% of patients in the RClb arm (stage 2) and 15% in the Clb 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 Clb arm than in the GClb arm and balanced in the RClb arm. However,

for 5 patients in the Clb arm (stage 1), 2 patients in the GClb arm (stage 2) and 2 patients in the RClb arm (stage 2), the infection was fatal.

In summary, these data indicate that GClb is well tolerated with manageable additional toxicity. The observed effect of rapid and profound B cell depletion by obinutuzumab (232) 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. Consequently obinutuzumab is not expected to add any significant burden to patients, their healthcare professionals or cost to the NHS.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The typical CLL patient is >70 years of age and suffers from co-existing medical conditions (9). Medical conditions, such as cardiac or renal problems, have an impact on the prognosis of CLL and are associated with shorter survival (9). Since patients with coexisting medical conditions have been under-represented in clinical trials, it is unclear how these patients should be best managed. As a result, these patients have limited treatment options since 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 (8;9).

Patients with CLL who are not eligible for fludarabine-based therapy due to coexisting medical conditions and/or other age-related problems are frequently treated with the alkylating drug Clb as monotherapy and this is still considered as Standard of Care for such patients in US and European treatment guidelines(4;36).

Although Clb is generally well tolerated, complete responses are rare and remission durations are usually shorter than 1.5 years (48;49). CLL11 is the first study investigating alternative immunotherapeutic regimens combining cytostatic drugs and monoclonal antibodies in CLL patients with coexisting medical conditions.

Obinutuzumab is a first-in-class Type II glycoengineered anti-CD20 monoclonal antibody (mAb), derived by humanisation of the parental B-Ly1 mouse antibody and subsequent glyco-engineering leading to the following characteristics:

- High affinity Type II binding to the CD20 epitope
- Increased antibody−dependent cellular cytotoxicity (ADCC) by FcγRIIIa−expressing cells (natural killer cells, monocytes, and macrophages) and increased antibody−dependent cellular phagocytosis by FcγRIIIa−expressing phagocytic cells (monocytes and macrophages) and

FcγRIIIb−expressing polymorphonuclear neutrophils, compared to non−glycoengineered wild-type antibodies related to obinutuzumab. Obinutuzumab is a glycoengineered antibody with enhanced affinity for FcγRIIIa and FcγRIIIb

- Low complement−dependent cytotoxicity (CDC) activity related to the recognition of the CD20 type II epitope and the lack of CD20 localisation into lipid rafts after binding of obinutuzumab to CD20

- Increased direct cell death induction through a novel type of non-apoptotic lysosome-mediated cell death compared to type I CD20 antibodies

The combination of obinutuzumab and chlorambucil combines targeting the CD20 antigen with chemotherapy.

In the CLL11 trial, obinutuzumab showed a clinically meaningful and statistically significant improvement in progression-free survival when compared with Clb and RClb (27). PFS was 26.7 months in the GClb arm compared with 11.1 months in the Clb arm and 14.9 months in the RClb arm (HR:0.65, 95% CI [0.55 - 0.77], p <0.0001 and HR: 0.39, [95% CI: 0.31 - 0.49]), p <0.0001, respectively). This corresponds to a >50% increase in median PFS. 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 GClb arm was observed when compared with Clb (HR: 0.41 [95%CI: 0.23 to 0.74], p=0.002). When GClb was compared with RClb, the hazard ratio was of 0.66 ([95%CI: 0.41 to 1.06], p=0.08). This improvement in survival observed with GClb represents the first significant improvement in OS against Clb in a Phase 3 trial in 1L CLL to date.

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

The safety profile of obinutuzumab was generally comparable to that of RClb and Clb alone in terms of the severity of AEs, discontinuations due to 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 RClb or Clb arms of the study. Serious infections, however, were more common in the Clb arm and more people died in that arm, mainly due to progressive disease.

Conclusion

The CLL11 study demonstrates that obinutuzumab in combination with Clb offers substantial and consistent clinically relevant benefits as a therapy for previously-untreated CLL patients who are not eligible for fludarabine-based therapy. These benefits included significant improvements in the proportions of people responding to treatment, and progression-free survival and in prolonged overall survival. Importantly these efficacy gains are delivered without a significant increase in overall toxicity or adverse effects on patient-reported quality of life.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths - The CLL11 study is a robust, high quality, adequately powered, centrally randomised trial that compared the intervention directly with the current standard treatment. It is also the biggest clinical trial in this population to date.

The study was developed with the aid of EMA scientific advice, investigator feedback, early phase studies, and published data. The study was conducted in 250 centres in 25 countries with a total of 781 patients randomised to GClb arm (n=336), Clb arm (n=118), or RClb arm (n=321).

The study incorporated many of the standard features of clinical studies in people with CLL, with additional safety measures for monitoring IRR, tumour lysis syndrome, prophylaxis, and hypersensitivity. The safety of participants in each study was overseen by an independent Data Safety Monitoring Board (DSMB).

The international nature of the studies ensured that all major race groups and ages were enrolled. Benefit with the GClb treatment was seen across these groups and this would be expected in the clinical setting.

The comparator treatment in the CLL11 study, chlorambucil, is a licensed regimen and is considered to be standard of care for CLL patients such as those in the CLL11 study who are not eligible for fludarabine-based therapy.

The trials presented within the submission investigated the efficacy and safety of obinutuzumab for the treatment of CLL. The outcomes assessed were consistent with the EMA guidelines on the evaluation of anticancer medicinal product in man (233), and are thus considered relevant for the clinical practice. The primary endpoint was PFS (investigator-assessed) and the secondary endpoints included PFS (independent review committee), OS, DFS, and ORR. Further, MRD (in blood and bone marrow) and TTNT were used to assess disease stabilisation.

Limitations – Due to the routes of administration of treatment in each arm in CLL11 – obinutuzumab and rituximab were delivered IV and Clb is delivered orally - the number of placebos required to double blind these studies was considered prohibitive and unethical. This study was therefore open label.

In CLL11 the primary efficacy parameter, investigator-assessed progression-free survival, with Independent Review committee-assessed progression-free survival a secondary efficacy endpoint, which is considered to be of relevance to routine clinical practice in the UK. The data from independent review and investigator assessment were very similar, indicative of the quality of data collection.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The primary and secondary outcomes adopted to assess efficacy and safety in the pivotal study have been well established in CLL, are familiar to haematologists, and are relevant to people with CLL.

The main treatment challenge in clinical practice is how to increase the patient's life expectancy while still maintaining their quality of life; in particular, older patients with comorbidities who are not eligible for fludarabine-based therapy do not have access to optimal treatment. The efficacy endpoint of progression-free survival, has been accepted as an endpoint for registration of products for the treatment of CLL (37;43;170). Prolongation of progression-free survival in itself provides a meaningful

clinical benefit to people by extending the time without disease progression and its associated symptoms.

Overall survival is arguably the outcome of greatest relevance to the treatment of all people with cancer. Further, a majority of patients beginning treatment for CLL will die as a direct result of the disease or its complications (8;234). CLL is an indolent disease and as the follow-up was short at the time of the clinical data cut-off the median was not expected to be achieved. Despite the fact that data are not yet available for median OS, the CLL11 study shows a statistically significant and clinically meaningful hazard ratio for death versus Clb and RClb (0.41 [95%CI: 0.23 to 0.74], p=0.002 and 0.66 [95%CI: 0.41 to 1.06], p=0.08, respectively).

Other secondary endpoints such as response rate, minimal residual disease, and time to next treatment are highly pertinent to people and their clinicians when discussing treatment options at the onset of the disease.

The outcomes assessed in CLL11, therefore, are expected to have a significant beneficial effect on people in clinical practice as GClb has been shown to increase the proportion of patients responding to treatment and that this response is durable as seen by the significant increase in progression-free survival with an associated significant lower hazard ratio for death. For patients who are not eligible for fludarabine-based treatment being treated with GClb would mean a higher likelihood of a positive response to treatment, the disease being controlled for a longer period of time, a delay in the time when the next anti-lymphoma treatment is required, and a subsequently longer life expectancy.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

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 in the UK. The performance status and comorbidity burden of patients in the CLL11 trial

(CIRS >6 [moderate to severe comorbidity]) was reflective of the typical CLL patient population.

Patients in the CLL11 trial did not receive any prior treatment which could influence the validity of the results in the study.

What proportion of the evidence base is for the dose(s) given in the SPC?

The doses in cycle 1 (1000mg day 1/2, 1000mg day 8, 1000mg day 15), and cycles 2-6 (1000mg day 1)were established in a dose escalation study (235). These doses have been used in all phase II or III trials with obinutuzumab and are reflected in the SPC (100mg day 1, 900mg day 2, 1000mg day 8, 1000mg day 15).

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), and NHS EED were searched for studies assessing the cost-effectiveness of obinutuzumab. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. The search included all papers in each database and the search strategy is provided in section 10.10 The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Key word strategies were developed using key references retrieved through initial scoping searches. ProQuest was used to search EMYY, EMBA and MEYY whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York) on 13th May 2014. Each search result's title and abstract were assessed for relevance according to pre-defined inclusion and exclusion criteria (Table B38).

Table B38 Inclusion and exclusion criteria for cost-effectiveness search

Parameter	Inclusion Criteria	Exclusion Criteria
Population	1L CLL patients	Non CLL, non-1L
Intervention	Obinutuzumab (GA101)	-
Comparator	Chlorambucil, Rituximab plus Chlorambucil, Bendamustine, Rituximab plus Bendamustine	-
Outcome	Cost per QALY gained, Cost per LY gained	-
Study Design	Economic Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

CLL: Chronic Lymphocytic Leukaemia; LY: Life Year; QUALY: Quality Adjusted Life Year; RCT: Randomised Clinical Trial

The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

One study was identified across the four databases. This was determined as relevant by the independent reviewers after being assessed against the inclusion criteria. One cost-effectiveness study of obinutuzumab (GA101) was thus identified.

Figure B25 PRISMA flow for economic evaluation studies identified through database searches

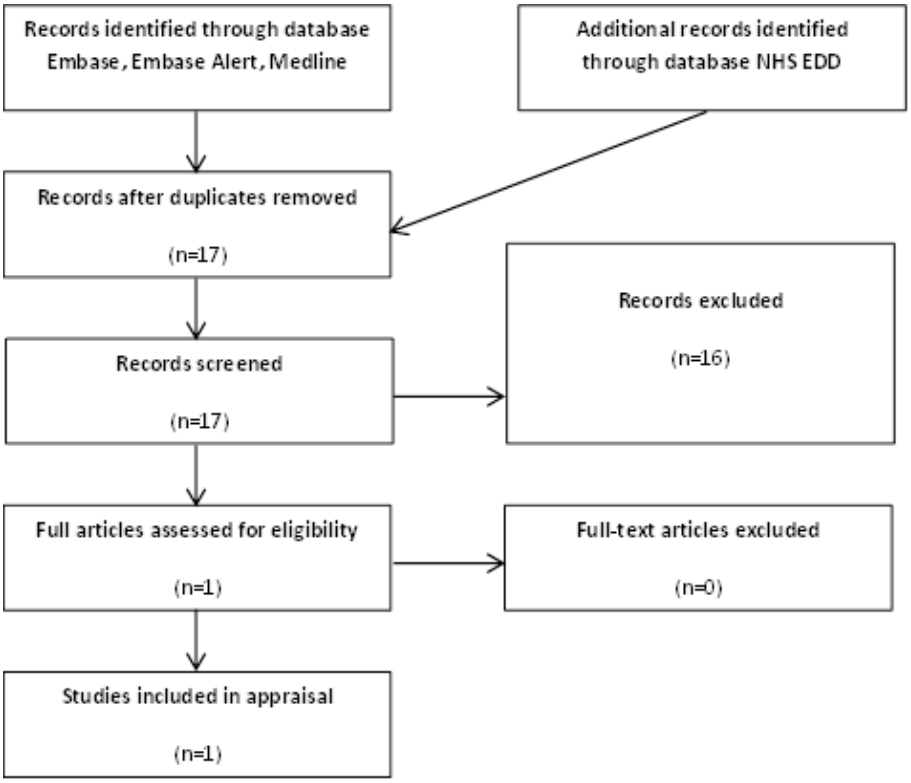


Figure B25 above illustrates the literature search in terms of identified and included/excluded cost-effectiveness studies.

Description of identified studies

7.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

Table B39 Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
The potential cost-effectiveness of obinutuzumab in combination with chlorambucil in CLL	2013	UK	4-state Markov lifetime model	Not stated	GClb = 3.6 RClb = 3.2 Clb = 2.8	GClb = £21k to £25.6k R-Clb = £13k Clb = £1.4k	GClb vs RClb = £21k to £33.6k GClb vs Clb = £25.5k to £31.5k

Clb: Chlorambucil; CLL: Chronic Lymphocytic Leukaemia; G: Obinutuzumab; ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); R: Rituximab; UK: United Kingdom

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[3] or Philips et al. (2004)[4]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

[3] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[4] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

	Study name	
The potential cost-effectiveness of GA101 in combination with chlorambucil in CLL	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Not justified.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Pivotal trial (CLL11) comparators used
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Utilities based on NICE TA174
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	
18. Were currency and price data recorded?	Not clear	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	

23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	The key driver for the uncertainty was seen in the assumption of the parametric function and utility values for PFS for which further research is needed.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

7.2 De novo analysis

Patients

7.2.1 **What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

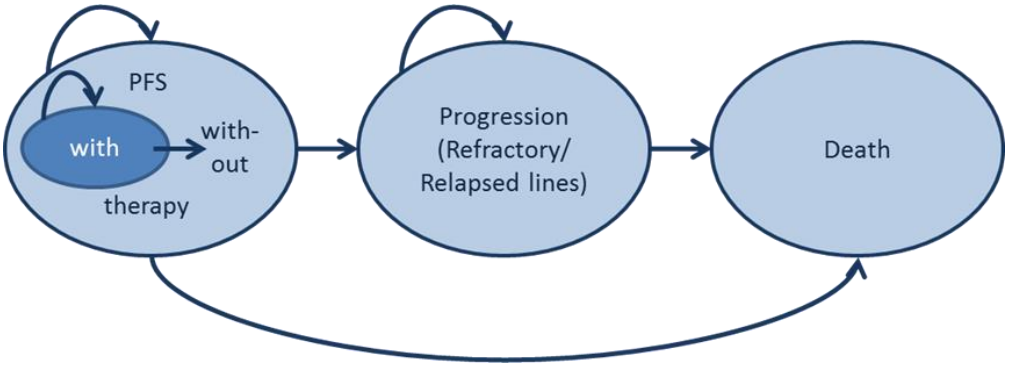
One cost-effectiveness model was identified in the search outlined in Section 7.1. This model and analysis was conducted by Roche and served as a preliminary model subject to change prior to finalisation and submission to relevant HTA bodies

worldwide. As such an updated version of the same model is used in this submission. It is a *de novo* economic model to assess the clinical and cost effectiveness of GA101 in previously untreated CLL in patients with co-morbidities who are unsuitable for full-dose fludarabine. The model is thus aligned with the marketing authorization GA101 and captures the key outcomes from the ITT population of the CLL11 trial.

Model structure

7.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

Figure B26 Model Structure



PFS: Progression-free Survival

7.2.3 **Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5**.

The model was constructed using Excel® featuring three health states; progression-free, progressed and death. The health states mirrored the main endpoints measured in the CLL11 trial. The structure of stratifying the clinical outcomes of people with cancer into progression-free, progression, and death is common practice in the economic evaluation of oncology interventions. The health states align with the key objectives of treatment within this disease area: to extend duration of progression-free and overall survival for as long as possible.

The PFS health state is divided into two parts – PFS whilst on therapy (with) and PFS whilst not on therapy (without) to take account of potential differences in health-related quality of life that may arise whilst a patient is on and off treatment.

The progressed health state represents the duration from progression until death and therefore includes the possible sequence of remission and relapse following further lines of treatments common to CLL. Disease progression is represented in the model

by people who are no longer classified as “progression free”, as defined by the CLL11 protocol.

7.2.4 Please define what the health states in the model are meant to capture.

All people in the model start in the progression-free health state. At the end of each discrete weekly cycle a person either remains in progression-free survival, moves to the progressed health state or dies. Once a person is within the progressed health state, they may remain in that health state or die at the end of each weekly cycle. People cannot move from the progressed health state back to progression-free survival health state in the model. Death is an absorbing health state in the model.

The model uses a partitioned survival approach, in which inputs are taken as estimated as a parametric survival function for progression-free survival and as a function of this via the selected post-progression death rate for overall survival. The proportion of the initial cohort in the progressed state at each cycle is the difference between the proportion that is alive and the proportion that is progression-free. The area between these two curves is the mean life-years of people with progressed disease. This approach allows the model to be accurately calibrated with the trial results for progression-free survival whilst overall survival is modelled entirely.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The structure of stratifying the clinical outcomes of oncology patients into progression-free, progression, and death is common practice in the economic evaluation of oncology. The health states align with one of the key objectives of treatment within this disease area: to place a patient into a progression-free health state for the longest period possible. Furthermore, the main outcomes of the clinical trial could be stratified into one of these 3 heath states: progression-free survival, progressed patients and death. Disease progression was represented by all patients no longer being classified as “progression free” within the CLL11 trial, as defined by the CLL11 protocol.

7.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below**.

Table B40 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (equating to a maximum of 20 years)	NICE reference case At 20 years there are approximately 1% of patients remaining alive in the comparator arm of the model	NICE methods guide
Cycle length	1 week	The four-weekly administration of drugs in the model supports the use of a weekly cycle length.	NICE methods guide
Half-cycle correction	Yes (half cycle correction is not applied to drug, administration and pharmacy costs)	NICE reference case	NICE methods guide
Were health effects measured in QALYs; if not, what was used?	QALY	NICE reference case	NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE methods guide
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE methods guide

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services; QALYs: Quality-adjusted Life Years

Technology

7.2.7 **Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?**

The intervention and comparators are in line with the decision problem set out in the NICE scope. More details on the implementation of the technologies within the models can be found in Section 5.

7.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment**

strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**
- **Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

No treatment continuation rule has been applied in the economic model.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 **Please demonstrate how the clinical data were implemented into the model**.

A partitioned survival model was implemented which models the transition from the PFS health state using data from both the CLL11 trial and background mortality directly, whilst the transition from the progressed health state employs a Markov trace, due to the relatively immature OS trial data.

In CLL11, two PFS assessments are available: by the investigator and by the Independent Review Committee (IRC). In the cost-effectiveness model, the investigator assessed PFS is used as this corresponds to the primary endpoint of the trial.

7.3.1.1 CLL11 Data Cuts

The clinical cut-off date was 11 July 2012 for Stage 1a, 10th August 2012 for Stage 1b and 9th May 2013 for Stage 2. However updates to the Stage 1a/b data were triggered by the Stage 2 analysis. Therefore the latest official data cut for all arms is therefore that of 9th May 2013.

However a new update from 3rd March 2014 has been included in this submission as commercial in confidence (see section 6.5). Given the increased maturity of this data (see section 6.5) and the potential value of this to the appraisal, this information is presented within this submission. However this data should be regarded as commercial in confidence until formally presented. This data cut includes updated OS and PFS analyses for all stages (see section 6.5). Given that this data is more mature than the previous data cut, the 3rd March 2014 data has been used in the cost-effectiveness model i.e. for the basis of PFS modelling in all arms and for the validation of OS modelling (insofar as appropriate) in all arms.

7.3.1.2 PFS Modelling

Table B41 summarises the results of the March 2014 PFS analyses of the different stages of CLL11 relevant to GClb (see section 6.5 for a full summary of results). It can be seen that PFS for GClb was [redacted]

Table B41 Investigator-assessed progression free survival (March 2014 data cut)

Data Cut	Stage 1a Analysis			Stage 2 Analysis		
	Median PFS (Mos)		HR (95% CI)	Median PFS (Mos)		HR (95% CI)
	Clb	*GClb*		*RClb*	*GClb*	
3rd March 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The PFS Kaplan-Meier curves for each pairwise comparison can be found in section 6.5. Figure B27 below shows the KM PFS curves plotted together (Stage 2 data for G-Clb and R-Clb and Stage 1 data for Clb.)

Figure B27 March 2014 Kaplan-Meier estimates of investigator-assessed progression free survival for GClb (Stage 2) vs RClb (Stage 2) vs Clb (Stage 1)

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Whilst survival data is typically presented in the form of Kaplan-Meier plots, the production of cumulative hazard and log-cumulative hazard plots allows simple examination of the trends in the data that can be difficult to interpret using Kaplan-Meier data alone.

A cumulative hazard plot details the negative log of the survival function versus time. The slope of the cumulative hazard plot at any point in time can be interpreted as the hazard of the event of interest occurring at that point in time. The steeper a cumulative hazard plot is the higher the hazard of the event occurring and the flatter a cumulative hazard plot is the lower the hazard of the event occurring is. This property allows consideration of how the risk of an event occurring changes over time (i.e. how does the slope change over time) and the way in which the impact of some intervention changes over time (i.e. how much does the ratio of the two slopes (the hazard ratio) change over time). This method of analysing the data is important when considering extrapolation as it can inform both the extrapolation of the baseline risk without the intervention (i.e. if the slope (hazard) of the cumulative hazard plot for the non-intervention curve has been straight for the period observed it may be reasonable to continue with a straight hazard beyond this point in time) and how the intervention arm may differ from that baseline risk if further follow-up were available (i.e. if the ratio of the two slopes (hazard ratio) has been constant throughout the data it may be reasonable to continue that ratio beyond the period of follow-up).

7.3.2 Similarly log-cumulative hazard plots allow a close inspection of whether hazards are monotonic, non-monotonic or constant and where significant changes in the observed hazard occur, by plotting the log of the negative log of the survival function versus the log of time. In particular they allow for the testing of the suitability of the Weibull and exponential distributions. In addition, such plots allow an evaluation of whether the proportional hazards assumption – important when conducting an indirect treatment comparison – holds.

Figure B28 and Figure B29 below show the cumulative hazard and log cumulative hazard plots using the March 2014 data cut from CLL11.

Figure B28 CLL11 PFS Cumulative Hazard Plots

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; PFS: Progression Free Survival; R: Rituximab

Figure B29 CLL11 PFS Log-cumulative Hazard Plots

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; PFS: Progression Free Survival; R: Rituximab

The cumulative hazard plot (see Figure B28) shows that [redacted]

[redacted]

Table B42 shows the model fit Akaike Information Criterion (AIC) estimates and corresponding ranks where the lower the number represents the best fit. For the Clb and RClb arms a log-logistic fit is best although Weibull and Gamma distributions also represent strong fits in the Clb arm. In the GClb arm a Weibull represents the best fit followed by the log-logistic function.

Table B42 Model Fit Akaike Information Criterion (AIC) estimates

	AIC Estimates			Rank of AIC estimates		
Parametric distribution	**Clb**	**GClb**	**RClb**	**Clb**	**GClb**	**RClb**
Exponential	281.31	668.99	767.39	6	6	6
Weibull	255.56	**637.62**	671.16	2	**1**	4
Log Normal	266.14	663.96	665.69	4	5	3
Gamma	256.20	639.49	658.31	3	3	2
Log Logistic	**255.40**	639.48	**642.93**	**1**	2	**1**
Gompertz	269.43	643.21	718.35	5	4	5

AIC: Akaike Information Criterion; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Given the above in the first instance a log-logistic distribution was fitted to all arms (the same distribution was preferred in order to try and maintain the assumption of proportional hazards). The resulting PFS curves are depicted Figure B30.

Whilst the log-logistic distribution provides a reasonable visual fit to the GClb and RClb KM data, it is less convincing for the Clb arm first overestimating it, then underestimating before finally overestimating again. Additionally, in all arms the log-logistic extrapolation leads to implausibly fat tails particularly in the GClb arm. Given the age and frailty of the CLL11 trial population it is unlikely that such a high percentage (~7%) would not have progressed at 10 years. Furthermore clinicians at an advisory board hypothesised that in the Clb arm it would be highly unlikely that there would be any patients of this type who had not progressed within three to four years.

Figure B30 PFS curves – KM estimates and log-logistic extrapolation

Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; PFS: Progression Free Survival; R: Rituximab

Next, Weibull and Gamma distributions were fitted for visual inspection based on their strong AIC ranks as can be seen in Figure B31 and **Error! Reference source not found.**. Although both distributions again provided a strong fit to the GClb and RClb arms (with the Gamma function appearing slightly better for RClb), neither were convincing with respect to the Clb arm. When other functions were tested, visual fits were worse than those described previously. Further, independent fits for each arms were tested (log-logistic for Clb and RClb, and Weibull for GClb) but were ruled out due to both the log-logistic not fitting the Clb data well and the implausibly fat tails for Clb and RClb.

Figure B31 PFS curves – KM estimates and Weibull extrapolation

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; PFS: Progression Free Survival; R: Rituximab

Figure B32 PFS curves – KM estimates and Gamma extrapolation

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; PFS: Progression Free Survival; R: Rituximab

Given that no distribution provided a strong fit to the Clb arm and that the CLL11 data was relatively mature in all arms in terms of the occurrence of events with little censoring [redacted], it was decided to use the KM data for as long as reasonable in order to minimise error from a poor fit. The time points in each arm up until which to use the KM data were decided based on deviations in the cumulative hazard plots (see Figure B28) as explained previously and visual inspection of the applied tail to the preceding KM data. As such the time points chosen were [redacted] months in the Clb, RClb and GClb arms respectively. A gamma distribution was chosen as the base case to fit the tail based on the strongest visual fit above. This represents the base case modelled PFS. However it is equally plausible that a Weibull distribution could have been fitted fully (i.e. to the whole curve) and the impact of this as an alternative base case is tested. Further a number of other alternative distributions for both the tail only and the whole curve are explored extensively as sensitivity analyses.

Figure B33 Base case modelled PFS curves – KM estimates with Gamma tails in the Clb, RClb and GClb arms

[redacted]

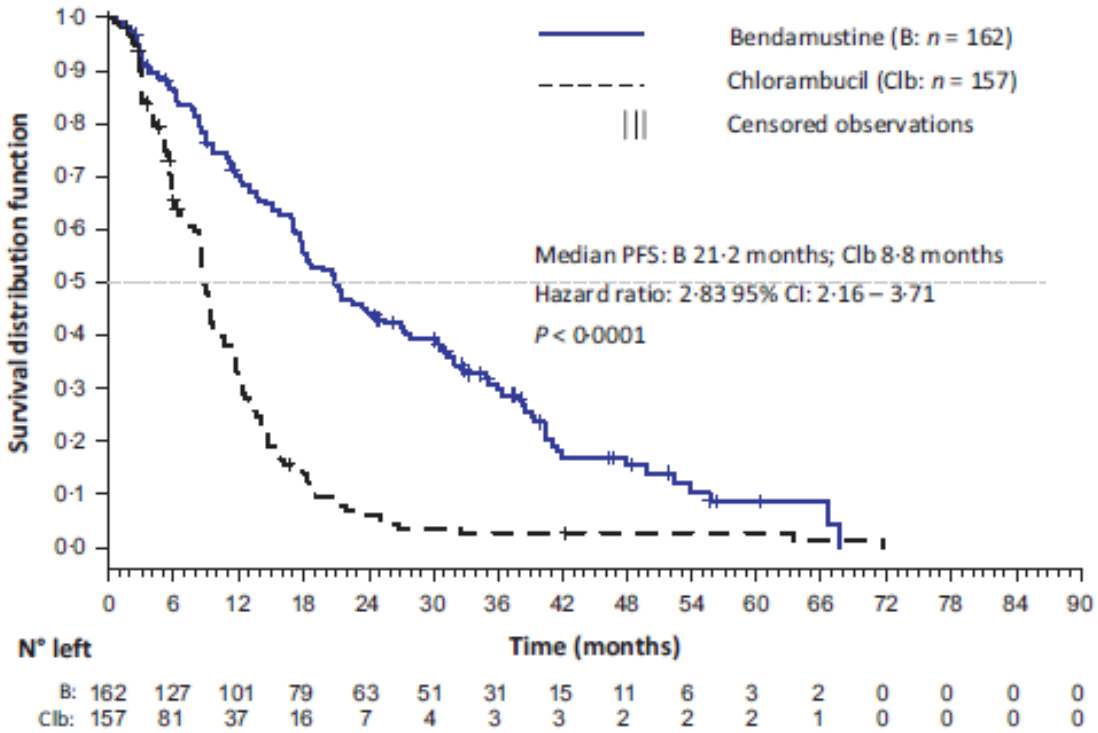
Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; PFS: Progression Free Survival; R: Rituximab

External validation of the tails of the PFS curves is difficult since there is a dearth of long-term follow-up data in this patient population. Naturally there is none for the GClb arm given it is a new intervention whilst for the RClb arm, there was little registry data available where patients received this as a first line treatment option and the CLL208 trial (a single-arm study of RClb in a 1L CLL comorbid population;

Hillmen, 2014), had a median follow-up time of only 30 months. Therefore external validation is most appropriate for the Clb arm but again there was a dearth of registry data with the necessary duration of follow-up available for patients who were receiving this as first-line treatment option. (For example a Roche sponsored retrospective analysis of a UK hospital's data for approximately 60 first-line comorbid CLL patients yielded only 4 patients who received Clb monotherapy).

In the absence of registry data, one source for validation is the Knauf trial of Benda vs Clb – with the caveat of differences in trial populations as discussed extensively in section 6.7 - where the median follow-up in the 2010 updated analysis was 50 months. Figure B34 and Figure B35 show the Knauf PFS trial data at median follow up of 50 months and the modelled arms of Clb and Benda (via MTC as explained in section 6.7) respectively. In the Knauf trial at approximately 5 years (60 months) there are between 1-2% of patients in the Clb arm and approximately 7-8% of patients in the Benda arm who have not progressed. Given the patient population in CLL11 is much more unfit, it is therefore reassuring to see that at 5 years, the modelled percentage of patients who have not progressed is 0% in the Clb arm and 0.5% in the Benda arm. As noted previously clinicians at an advisory board hypothesised that in the Clb arm it would be highly unlikely that there would be any patients of this type who had not progressed within three to four years and hence the modelling approach used aligns with this.

Figure B34 Knauf trial – KM PFS estimates for Benda vs Clb at 2010 follow-up



CI: Confidence Interval; Clb: Chlorambucil; PFS: Progression Free Survival

Figure B35 Base case modelled PFS curves for Clb and Benda

Benda: Bendamustine; Chb: Chlorambucil; KM: Kaplan Meier; PFS: Progression Free Survival

7.3.2.1 OS Modelling

The progressed health state within the model (see Figure B26) represents the duration from progression until death and therefore includes the possible sequence of remission and relapse following further lines of treatments common to CLL. Disease progression is represented in the model by people who are no longer classified as “progression free”, as defined by the CLL11 protocol.

Due to the limited data on PPS and OS in the CLL11 trial (i.e. the data was not mature and had not reached the median in any arm), OS was modelled using the maximum of a constant post-progression death rate or background mortality. In other words, the OS KM data from CLL11 were not used directly in the cost-effectiveness model and the transition from progression to death was modelled using a post-progression survival rate from outside of CLL11.

In order to be able to use post-progression survival data from other 1L CLL trials it had to be readily available (i.e. there had to be post-progression data with enough follow-up time either in publication form or as a patient-level data set which Roche could access or request analyses from). Datasets from two trials - CLL8 and CLL5 - were available. Yet both of these trials enrolled patients who were eligible for fludarabine in contrast to CLL11. However in the absence of other data, clinicians at an advisory board advised that the CLL5 post-progression death rates were most appropriate to use due to two factors. Firstly, the CLL5 trial population was thought to mirror most closely the CLL11 trial population, particularly in terms of having a similar median age (70 to 71 in CLL5 and 72 to 74 in CLL11; see Table B24). Secondly, clinicians advised that there was a large number of deaths from fludarabine intolerability in CLL8 and so this data was less appropriate to use.

However it should be noted that the baseline risk for CLL11 patients is likely to be worse than for both CLL5 and CLL8 patients as shown by patient age and comorbidities in Table B24. It is therefore not unreasonable to assume that given the lesser fitness and greater median age of the CLL11 population, the post-progression death rate from both CLL5 and CLL8 are too low even after adjusting for age (see below) (i.e. if followed up for a longer time period patients in CLL11 may die at a faster rate than those in CLL5 and CLL8 due to having a worse baseline risk). Given the uncertainty regarding the true post-progression death rate, varying this parameter was explored extensively during the sensitivity analyses. The modelling of PPS and OS is explained in further detail below.

Table B43 summarise the results of the OS analyses of the different stages of CLL11.[redacted]. The hazard ratio for GClb vs. RClb was [redacted]

A full summary of the results and Kaplan-Meier curves for each pairwise comparison can be found in section 6.5.

Table B43 Overall survival

Data Cut	Stage 1a Analysis			Stage 2 Analysis		
	Median PFS (Mos)		HR (95% CI)	Median PFS (Mos)		HR (95% CI)
	Clb	*GClb*		*RClb*	*GClb*	
3rd March 2014	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; Clb: Chlorambucil; G: Obinutuzumab; HR: Hazard Ratio; Mos: Months: NR: Not Reached; PFS: Progression-free Survival; R: Rituximab

Figure B36 below shows the KM OS curves plotted together (Stage 2 data for GClb and RClb and Stage 1 data for Clb.)

Figure B36 Kaplan-Meier estimates of overall survival GClb (Stage 2) vs RClb (Stage 2) vs Clb (Stage 1)

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Given the immature OS data, the probability of death following disease progression within the model was estimated using Kaplan-Meier PPS product limit estimates from the CLL5 trial. These were generated for patients who had experienced disease progression (those with a defined PFS event, excluding death). As described above, both the CLL5 trial and CLL8 trial had post-progression survival data which was readily available but the CLL5 trial was thought to mirror more closely the CLL11 trial population and hence was used as the base case.

The approach to estimate PPS for CLL5 (and CLL8) was as follows:

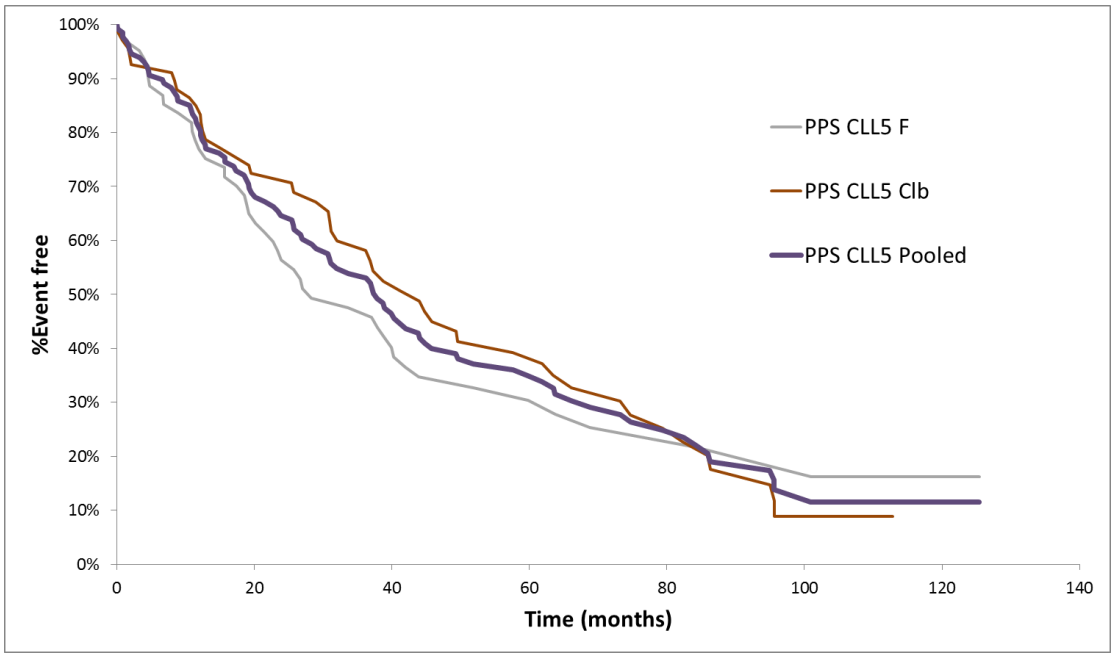
1. Exclude all patients without a PFS event.
2. Exclude all patients with death event without having progressed first.
3. Test whether the treatment received first line had an effect on PPS.
4. If not, pool data across treatment arms.
5. Fit parametric survival functions (Exponential, Weibull, Log-logistic, Log-normal, Gamma and Gompertz) to estimate the probability of transitioning to Death.
6. Determine which parametric function provides the best fit to the existing data and the most plausible extrapolation beyond the observed period.
7. Test whether other covariates have a significant impact on PPS.
    a. If no, then use a simple model without covariates.

b. If yes, then check whether the distribution of this covariate is similar among the trial considered (CLL5 or CLL8) and CLL11. If the distribution of this covariate is similar, then no explicit adjustment for this covariate needs to be done. If the distribution is different, then this should be adjusted for and a model with a covariate should be used.

Post-progression survival from CLL5

In CLL5, fludarabine (F) was compared to chlorambucil (Clb). It can be seen in Figure B37 that PPS is very similar for the two treatment arms. A likelihood-ratio test for the inclusion of the treatment arm indicator parameters in a model using an exponential distribution showed no significant treatment effect (p-value=0.63). Therefore it was decided to estimate PPS by using data from both treatment arms in a pooled fashion.

Figure B37 Kaplan Meier curves of post progression survival in CLL5



Clb: Chlorambucil; CLL: Chronic Lymphocytic Leukaemia; F: Fludarabine; PPS: Post Progression Survival

Using the post progression survival time and survival censoring information from both treatment arms together, parametric survival functions (Exponential, Weibull, Log-logistic, Log-normal, Gamma and Gompertz) were fitted to estimate the probability of transitioning to Death. The mathematical goodness of fit to the observed data can be expressed via the Akaike Information Criterion (AIC) and is shown in Table B44 where the exponential provides the best fit.

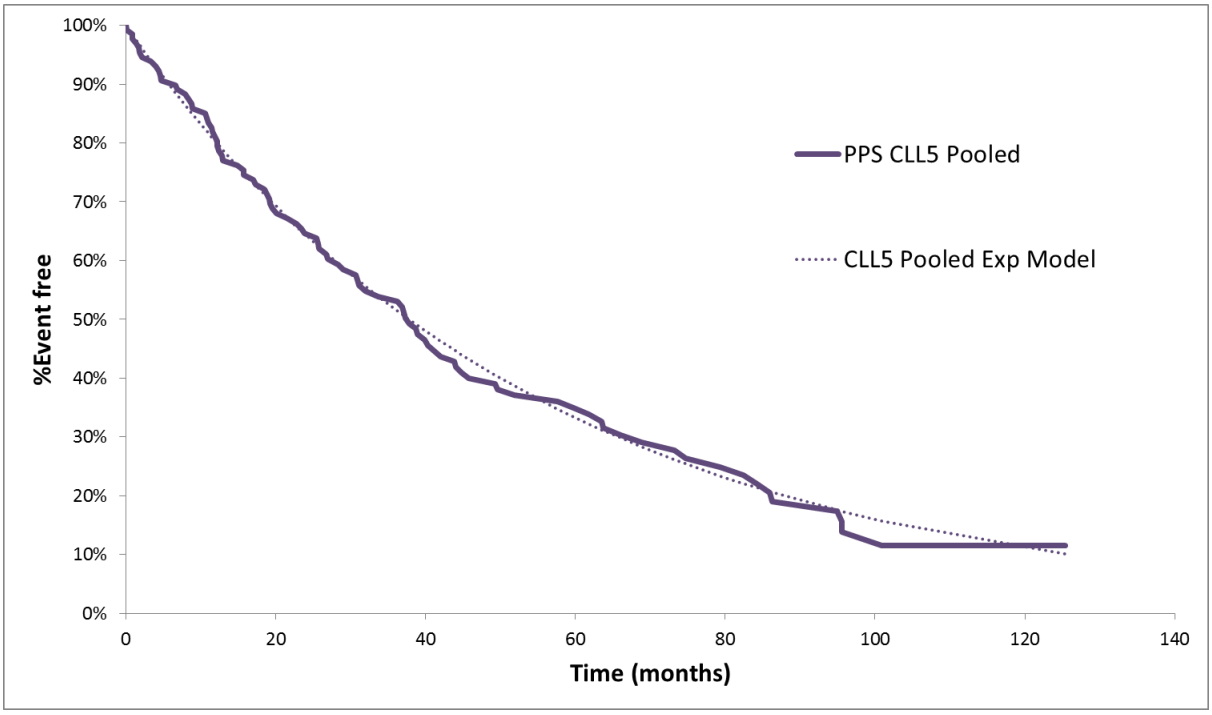
Table B44 Akaike Information Criterion (AIC) for CLL5 post progression survival

Distribution for CLL5 PPS data	AIC
Exponential	368.52
Weibull	370.44
Log-normal	382.81
Gamma	370.41
Log-logistic	375.59
Gompertz	370.39

AIC: Akaike Information Criterion; CLL: Chronic Lymphocytic Leukaemia

Figure B38 illustrates graphically that the exponential distribution provides a strong fit to the KM PPS data from CLL5.

Figure B38 Extrapolation of post progression survival in CLL5



PPS: Post Progression Survival

The impact of covariates on PPS was also explored. Table B45 shows that only one of the covariates (Del 17p, p-value = 0.0049) had a significant impact on PPS within CLL5. Given the percentage of patients with this mutation is broadly similar in CLL11 no specific adjustment was made for this.

Table B45 Likelihood ratio test for inclusion of parameters into the model with exponential distribution (CLL5)

Baseline: model with just intercept	p-value
Addition of randomised treatment	0.6257
Addition of age at progression	0.1954
Addition of sex	0.2366
Addition of Binet stage	0.7698
Addition of Del 13q Mutation	0.6464
Addition of Del 11q Mutation	0.3923
Addition of Del 17p Mutation	0.0049
Addition of Trisomy 12 Mutation	0.1091
Addition of IgVH Mutation	0.7530
Addition of Creatinine Clearance >= 70 ml/min	0.6485
Addition of ECOG status	0.5648
Addition of number of comorbidities	0.8088
Addition of comorbidities (Yes/No)	0.7015
Addition of Serum thymidine kinase	0.1233
Addition of Serum thymidine kinase <=10 U/l	0.7164
Addition of beta 2 microglobuline	0.6198
Addition of beta 2 microglobuline <=3.5 mg/l	0.2359

ECOG: Eastern Cooperative Oncology Group

Although age at progression is not significant with a p-value of 0.1954, median age of patients in CLL5 is between 1 to 4 years younger than CLL11 depending on which arms are compared (see Table B24). Given age is likely to be correlated with comorbidities (see section 2.1), an age adjustment in the estimation of PPS was therefore incorporated and the weekly probability of death expressed as a function of age at progression can be found in Figure B39. The average age at progression is then calculated as the average at baseline plus the mean estimated time spent in PFS for the respective treatment arm within the model where time spent in PFS is derived via the model. This then accounts for the difference in length of PFS among the treatment arms which in turn impacts on PPS, since it is a function of age. This leads to the Clb arm having the longest PPS, followed by the RClb arm and the GClb arm with the shortest PPS. Further this adjustment is also translated to the age of progression of the comparators of the MTC; Benda and R-Benda. The weekly age-adjusted probabilities used in the model are detailed in Table B46.

Figure B39 Weekly probability of death as a function of age at progression

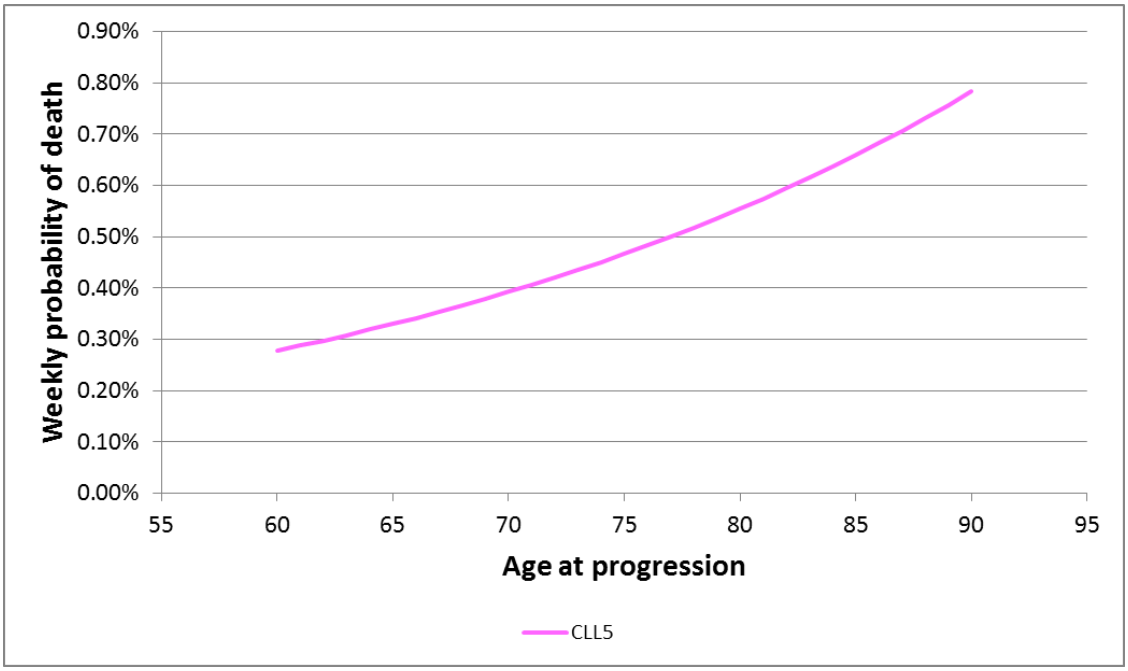


Table B46 Weekly age-adjusted probability of death by treatment arm

Treatment arm	Weekly probability of death
GClb (Stage 2)	0.4534%
RClb (Stage 2)	0.4369%
Clb (Stage 1)	0.4294%
Benda (Stage 2)	0.4369%
RBenda (Stage 2)	0.4448%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Derived OS curves

Figure B40 below shows the KM OS curves and the resulting modelled extrapolations for each arm, over the lifetime horizon of the model. At 20 years only approximately 1% of patients remain alive in the Clb and approximately 1.5% in the RClb and GClb arms. Figure B41 shows the same data and modelled curves over only a 5 year period in order to allow for a closer visual inspection of the extrapolations against the CLL11 KM data.

The depictions show that although the modelled OS curve for GClb provides a reasonably good fit to the trial data, the fit is less convincing for the RClb and in particular the Clb arm with the curves seeming to overestimate then underestimate the KM data. However this divergence could be explained in a number of ways.

Firstly, it is possible that OS does not follow the same distribution as inferred by modelling PFS with a constant post-progression death rate. However given the immaturity of the KM OS data and the difficulty extrapolating this over a long period given the low number of events (see below), it was thought more appropriate to use a Markov structure (albeit with no tunnel states) rather than a full Area Under the Curve (AUC) model, as has been accepted in previous NICE Technology Appraisals in 1L CLL (TA174, 2009).

Secondly it is highly likely that the KM data does not represent the true survival estimates of each arm of the CLL11 trial. The numbers of events occurring in each arm are low particularly in relation to the numbers censored [redacted] It is therefore highly likely that the KM OS data in the Clb arm is an overestimate of the true survival function.

Figure B40 OS KM curves and base case modelled curves over lifetime horizon (20 years)

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; OS: Overall Survival; R: Rituximab

Figure B41 OS KM curves and base case modelled curves over duration of KM data available

[redacted]

Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; OS: Overall Survival; R: Rituximab

Once again, external validation of the extrapolated OS curves is difficult since there is a dearth of long-term follow-up data in this patient population and registry data for patients whose first line treatment was Clb or RClb could not be located. However the CLL5 and Knauf trials do offer significant follow-up in terms of having reached median OS to compare the modelled results against. In the CLL5 trial the median OS in the Clb arm was 64 months (15). In the Knauf trial OS had not been reached in the Benda arm and was 78.8 months in the Clb arm. However in the "patients over 65 years" subgroup – those more similar age-wise to the CLL5 and CLL11 populations – median OS was reached in both arms. In the Benda arm it was 72.8 months and 65.4 months in the Clb arm; an overall difference of 7.4 months.

Figure B42 shows the modelled OS Curves for Clb, Benda (via MTC) and GClb. The resulting predicted median OS in the Clb, Benda and GClb arms is [redacted] This offers some degree of face validity to the modelling method employed since there is no strong reason as to why the relative difference between the arms should not remain. Further when the

projected OS curves were presented to clinicians, they agreed that the reduced medians but constant difference suggested that the modelling method employed was reasonable.

Figure B42 Base case modelled OS curves for Clb, Benda and GClb

[redacted]

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; KM: Kaplan Meier; OS: Overall Survival

7.3.3 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The PFS hazards were estimated using data from CLL11 and OS hazards using PPS data from CLL5 as described in Section 7.3.2.1, and were converted into weekly probabilities prior to inclusion in the model.

For comparisons of GClb versus the two treatments that were not part of the CLL11 trial but in NICE's scope (Benda and R-Benda), the results of the base case MTC in section 6.7.6 were used.

The derived HRs from the MTC for both PFS for each comparator were then applied in the model using the GClb curves as the baseline. Therefore in the base case, for PFS, the GClb KM curve with Weibull extrapolation was used as the base curve, and for OS, the resultant OS curve as modelled using PPS data from CLL5, was used as the base curve. From these baselines, estimates of the PFS and OS relative efficacy for each of the two comparators were calculated.

7.3.4 **Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

Data from the CLL11 trial appears to show that the hazards for progression free survival and overall survival may increase with time (see section 7.3.1.2 above).

7.3.5 **Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?**

The relationship between PFS and OS via PPS data from CLL5 has been described in section 7.3.2.1 above.

7.3.6 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical specialists were consulted in an advisory board in the development of the submission and economic model. The clinical experts gave their opinion on the validity of the PFS extrapolation conducted and the use of PPS data from the CLL5

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

trial to model OS. The experts also validated the approach and methodology of the MTC conducted detailed in section 6.7.

Summary of selected values

7.3.7 **Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below**.

Table B47Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Transition Probabilities		
Progression-free survival distribution in obinutuzumab arm	CLL11 KM PFS data with Gamma tail	7.3.1
Progression-free survival distribution in RClb arm	CLL11 KM PFS data with Gamma tail	7.3.1
Progression-free survival distribution in Clb arm	CLL11 KM PFS data with Gamma tail	7.3.1
Progression-free survival distribution in Benda arm	HR = 2.5 (1/0.40) vs GClb	6.7
Progression-free survival distribution in RBenda arm	HR = 1.47 (1/0.68) GClb	6.7
Overall survival distribution in obinutuzumab arm	Modelled using CLL5 PPS data	7.3.1
Overall survival distribution in RClb arm	Modelled using CLL5 PPS data	7.3.1
Overall survival distribution in Clb arm	Modelled using CLL5 PPS data	7.3.1
Overall survival distribution in Benda arm	Modelled using CLL5 PPS data	7.3.1
Overall survival distribution in RBenda arm	Modelled using CLL5 PPS data	7.3.1
Utility Values		
Progression-free survival under oral treatment	0.71	7.4.9
Progression-free survival under IV treatment	0.67	7.4.9
Progression-free survival on initial therapy with increased hospital visits	0.55	7.4.9
Progression-free survival after initial treatment is completed	0.82	7.4.9
Progressed disease	0.60	7.4.9
Costs (£)		
Supportive care costs PFS per week (all arms)	£8.13	7.5.6
Supportive care costs PD		7.5.6
Supportive care costs PD inc. post-progression treatments per week (RClb arm)	£24.38	7.5.6
Post-progression treatment costs	£369.45	7.5.6
Administration costs (£)		
Initial dose if at least one IV dose present	£514	7.5.5
All subsequent doses if at least one IV treatment present	£343	7.5.5
All doses if no IV treatment present (i.e. only oral treatment)	£136	7.5.5
Clinical haematologist cost of first cycle consultation (30 mins)	£134	7.5.5
Clinical haematologist cost of subsequent cycles consultations (30 mins)	£53	7.5.5

Pharmacy costs per dispensing for IV treatment (15 minutes)	£16.75	7.5.5
Pharmacy costs per dispensing for oral treatment (5 minutes)	£5.58	7.5.5
Adverse event costs (£)		
Anaemia	£2,088	7.5.7
Febrile neutropenia	£3,894	7.5.7
Infusion-related reaction	£359	7.5.7
Leukopenia	£942	7.5.7
Lymphopenia	£942	7.5.7
Neutropenia	£3,894	7.5.7
Pneumonia	£1,353	7.5.7
Rash Maculo-Papular	£500	7.5.7
Thrombocytopenia	£1,847	7.5.7
Drug costs(£)		
Obinutuzumab	£3,153.29 per 1000mg vial	7.5.5
Rituximab	£174.73 per 100mg vial £873.15 per 500mg vial	7.5.5
Chlorambucil	£40.51 per 25-tab pack	7.5.5
Bendamustine	£69.45 per 25mg vial £275.81 per 100mg vial	7.5.5
Discount rate (%)		
Costs	3.5	NICE Methods Guide
QALYs	3.5	NICE Methods Guide
Patient characteristics		
Age (years)	71.7	CLL11
Weight (kg)	73.7	CLL11
Body surface area (m^2)	1.85	CLL11

Benda: Bendamustine; Clb: Chlorambucil; CLL: Chronic Lymphocytic Leukaemia; G: Obinutuzumab; HR: Hazard Ratio; IV: Intravenous; KM: Kaplan Meier; NICE: National Institute for Health and Care Excellence; PFS: Progression Free Survival; PPS: Post Progression Survival; QALY: Quality Adjusted Life Years; R: Rituximab

7.3.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

See section 7.3.1

7.3.9 Provide a list of all assumptions in the de novo economic model and a justification for each assumption

Assumption 1: Following treatment failure, patients enter the progressed health state. The subsequent weekly risk of death from this health state is assumed equal in all arms of the model except for an age adjustment (see section 7.3.2.1).

Assumption 2: Following first relapse, all patients are assumed to have the same sequence of further health care resource use. Once patients in the GClb and comparator arms have progressed they are subject to the same 2L treatment options (only 2L treatment is modelled; section7.5.5). Consequently, weekly healthcare costs

are assumed to be the same in all arms following first-line relapse. Although in CLL11 patients were allowed to cross-over to GClb on progression in the RClb and Clb arms, OS has not been modelled using data from the CLL11 (see Assumption 1) and GClb is pursuing an indication for use as a first line treatment. It is therefore reasonable to assume that the same treatment options would be available to all patients irrespective of their first-line treatment. The assumed healthcare costs for the "progressed" health state are outlined in more detail in section 7.5.5below.

Assumption 3: Only adverse events with over 2% incidence in either treatment arm of CLL11 or any treatment arm of a comparator-related pivotal trial (Knauf and MaBLe studies) 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 as opposed to random chance.

Assumption 4: Where two treatments are administered concomitantly and one is oral and one is IV, only the (more expensive) NHS reference cost code for the IV treatment is applied and clinician consultation is assumed, whilst a separate pharmacy cost to dispense each drug is incorporated.

Assumption 5: The HR for GClb for RBenda is 0.68. See section 6.7 for a full explanation.

Assumption 6: Complete adverse event (AE) data for RBenda from the MaBLe study (RBenda vs RClb) is not yet available, The profile and cost of AEs for RBenda is therefore assumed to be equal to Stage 2 RClb from the CLL11 trial based on the MaBLe abstract which states that safety was similar between the two arms.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous

variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 **Please outline the aspects of the condition that most affect patients' quality of life**.

Studies have found that cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (236) and the most important distress factor among people with cancer has been found to be the fear of disease progression (237).

7.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition**.

Health-related quality of life is expected to decrease with each line of treatment failure due to disease progression.

HRQL data derived from clinical trials

7.4.3 **If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals**.

A disease specific measurement (EORTC-QLQ-C30) collected changes in quality of life in the CLL11 study. The NICE reference case specifies use of a generic quality of life measurement, preferably EQ-5D, to capture changes in quality of life.

Mapping

7.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique**.

Since currently no validated mapping function exists for EORTC-QLQ-C30 to EQ-5D, quality of life data collected in the CLL11 trial could not be used in the economic model.

HRQL studies

7.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)[6] and NHS EED were searched for studies assessing utility values for different health states in CLL. The searches were conducted on the 28th January 2014 and were designed to evaluate all potentially relevant utility scores that have been used in CLL health technology evaluations. The complete search strategy is provided in section 10.12. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008). If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

[6] Note Medline-In-Process is now nested within Medline in the new ProQuest.

Table B48: Inclusion and exclusion criteria for utility studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously untreated Chronic Lymphocytic Leukemia (CLL)	Non CLL patients
Intervention	Any	-
Comparator	Any	-
Outcome	Utilities derived via a recognised preference based instrument (EQ5D or SF6D), standard gamble or time trade off conducted using a sample of the general public	Other non-preference based HRQoL measures
Study Design	Utility Studies, Cost-Effectiveness studies containing utility values	-

CLL: Chronic Lymphocytic Leukaemia; EQ5D: EuroQOL five dimensions questionnaire; HRQoL: Health Related Quality of Life; SF6D: six-dimensional health state short form

In total 55 records were identified across the 4 databases. Of these, 46 were excluded by the independent reviewers whilst 9 were deemed potentially relevant and read in full. These 9 were included after being assessed against the exclusion criteria.

Figure B43 PRISMA flow for utility studies identified through database searches

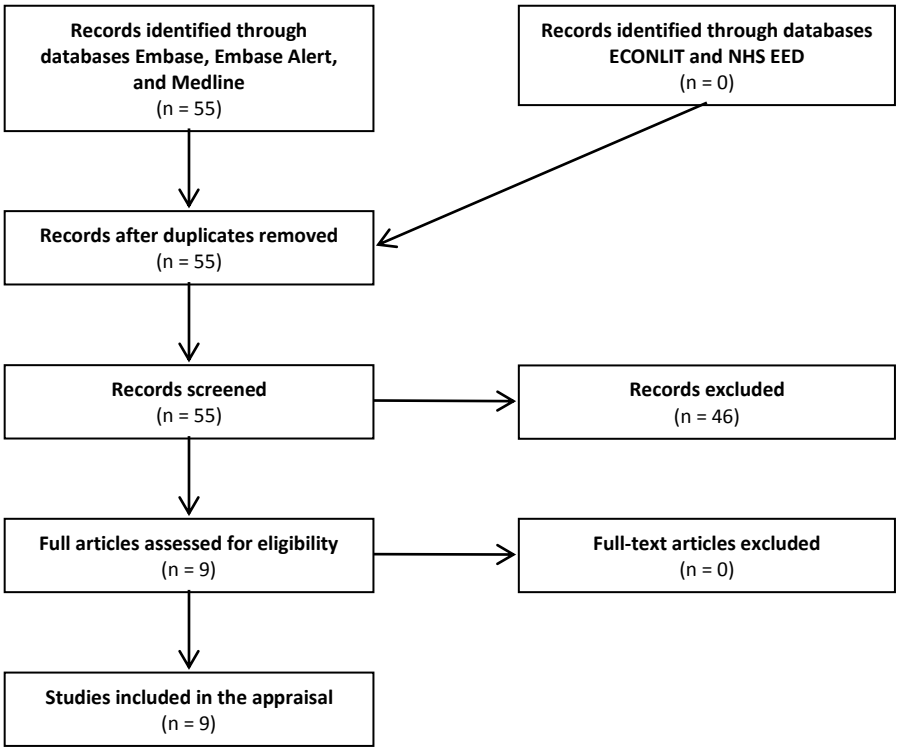


Figure B43 above illustrates the literature search in terms of identified and included/excluded utility studies.

7.4.6 **Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.**

- **Population in which health effects were measured.**
- **Information on recruitment.**
- **Interventions and comparators.**
- **Sample size.**
- **Response rates.**
- **Description of health states.**
- **Adverse events.**
- **Appropriateness of health states given condition and treatment pathway.**
- **Method of elicitation.**
- **Method of valuation.**
- **Mapping.**
- **Uncertainty around values.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**
- **Appropriateness of the study for cost-effectiveness analysis**.

Table B49 Assessment of suitability of published literature detailing utility values in 1L 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 leukaemia Walzer 2013 (238)	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(239) *	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 (240)	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
Long-term outcomes and quality of life in critically ill patients with haematological or solid malignancies: A single centre study Oeyen 2013 (241)	Not clear	Patients with haematological (HM) or solid malignancies admitted to the medical or surgical ICU of a university hospital	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	N/A	No utility values for PFS and/or PD

		N=483 (478 on admission, 392 after 3 months and 331 after 1 year)				HM: p = 0.041		
Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: A cost-utility analysis Woods 2012 (242)	Benda vs. Clb	Previously untreated patients with CLL N=Not clear Patients with inoperable oesophaegal 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 diarrhoea: 0.70±0.19 No change + 3–4 anaemia: 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(243)	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	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 (243)	Standard gamble rather than TTO methodology used in Beusterien 2010

Hornberger 2012								
Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia Tolley 2013 (244)	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
Population preference values for treatment outcomes in chronic lymphocytic leukaemia: A cross-sectional utility study	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	N/A	Standard gamble rather than TTO methodology used

Beusterien 2010 (243)						(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 Diarrhoea: 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)		
Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia Scott 2007 (245)	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 (246)	3L CLL
Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia	Intravenous immune globulin vs. no immune globulin	CLL N=Not clear Physicians (to elicit	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	N/A	Line of treatment not clear, small sample size, non-societal preferences, no PFS/PD values

Weeks 1991 (247)		utility values) N=10				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)		

Two original references (Hancock 2002 and Beusterien 2010) in Table B54 provide utilities that are arguably suitable within the model since they give values for both the PFS and PD health states. However both of these studies had limitations with regard to the elicitation method used. Hancock 2002 were originally derived from expert opinion and therefore may not reflect societal preferences. Beusterien 2010 uses the standard gamble method as opposed to the time trade-off (TTO) methodology and there is considerable evidence that yields higher estimates of preference than the TTO approach (248). Furthermore the utilities from both references lacked a certain refinement with respect to a number of key aspects that would have made them more appropriate for use within the model. These include the following:

- Lack of distinction between PFS utility whilst on treatment and PFS utility whilst off treatment. Given that in a disease such as CLL, treatments are typically given for a fixed period (as opposed to until progression) and that the period for which an average patient remains in PFS is longer than treatment duration, it may be reasonable to assumes that PFS QoL may be different whilst on and off treatment due to the side effects and possible angst associated with therapy.

- Lack of distinction between PFS utility on an IV treatment versus an oral treatment. Patient side effects and angst may differ based on whether the treatment is given orally or via intravenous infusion.

- 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 GA101 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. The QoL of a patient who has relapsed after multiple lines of treatment and then only perhaps as palliative care as a treatment option is likely to be vastly different to a patient who has had a first line treatment and after a long remission has only just relapsed.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No utility values were taken from CLL11.

Adverse events

7.4.8 **Please describe how adverse events have an impact on HRQL**.

Utility losses due to specific adverse events in the CLL trial - only Grade 3 or 4 adverse events are considered as impacting on HRQL - are not explicitly taken into account. However PFS for treatments that may require more hospitalisations due to adverse events/side effects is adjusted accordingly by having a separate value attributed to it compared to PFS on treatment (with no hospitalisations) or PFS off treatment. In other words, given that in the GA101 arm 20% of patients had Grade 3 or 4 infusion related reactions during the first infusion (there were no Grade 3 or 4 adverse events for subsequent infusions; see section 6.9), the PFS utility value for the first dose of GA101 is attributed a lower value than for subsequent doses. Details of the utilities used are explained fully in section 7.4.9.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case**.

Given the limitations of the utility values in the existing published literature (see section 7.4.6, a utility elicitation study was conducted with the UK general public to derive societal preferences for QoL associated with CLL, to employ within the model (249).

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. A total of nine health states were developed related to CLL and are presented in Table B50.

Table B50 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.

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 (TTO) was employed to elicit utility scores. The results of the study and their relevance within the model are shown in Table B51**.**

Table B51 Results of utility elicitation study and relevance within economic model

Health state	Mean Utility	SD	95% Confidence Intervals (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	

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

The last five health states in Table B52 represent the progression health state of the model. In order to obtain one utility value for this state w, a weighted average of the utility values of the five health states has to be calculated. Ideally the weights should be proportional to the time spent by an average patient in this health state. In Table B52, the weights used in the base case scenario can be found. 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 have been obtained through a discussion with Dr. Barbara Eichhorst who is a CLL specialist working at the Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany (personal communication with Dr. Eichhorst).

Table B52 Base case utility weights for the progressed health state

Health state	Weight for utility for all lines of Tx
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

PFS: Progression Free Survival; Tx: Treatment

Table B53 details the final base case utility values as applied in the economic model.

Table B53 Final base case utilities used within model

Health state within model	Treatment arm	Mean utility
PFS on initial therapy oral treatment	Clb	0.71
PFS on initial therapy IV treatment	RClb Benda RBenda	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

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

7.4.10 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical specialists were consulted upon the development of vignettes for the elicitation study. The impact of varying utility values on the ICER has been explored in the sensitivity analysis.

7.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

Patient experience is described in section 7.4.1.

7.4.12 **Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

All relevant health effects identified in the literature and reasons for exclusion have been described in section 7.4.6

7.4.13 **If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The baseline quality of life has been assumed to be different in treatment arms of the economic evaluation (see section 7.4.9 for justification). All people in the progressed health state are characterised as being progressed.

7.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time**.

HRQL is assumed to be constant over time within each health state in the model.

7.4.15 **Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

The methodology used to alter utility values (specifically, to generate one value for the progressed disease health state) has been described in section 7.4.9.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2**.

ESMO guidelines (4), recommend that follow up of asymptomatic patients should include a blood cell count every 3 to 12 months, as well as a regular examinations of lymph nodes, liver and spleen. It is assumed that once progressed frequency of visits would increase to one per month. This has formed the basis of the costing assumptions for disease management in the model.

7.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised**.

NHS reference costs are the most appropriate source of cost data for this appraisal.

Resource identification, measurement and valuation studies

7.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)[8] and NHS EED were searched for studies regarding resource use and costs related to CLL. The complete search strategy is provided in section 10.13. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008).

ProQuest was used to search EMYY, EMBA and MEYY and NHS EED was searched using The Centre for Reviews and Dissemination's website. All searches were undertaken on the 13th May 2014. Titles and abstracts were assessed for relevance according to the pre-defined inclusion and exclusion criteria.

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in Table B54.

[8] Note Medline-In-Process is now nested within Medline in the new ProQuest.

Table B54 Inclusion and exclusion criteria for resource utilisation studies

Inclusion criteria	Exclusion criteria
CLL Resource utilisation from a UK NHS Perspective	Non-CLL hematological malignancies Resource utilisation from a private/US setting and any other non-UK country. Costs derived from studies more than 5 years old.

CLL: Chronic Lymphocytic Leukaemia

In total 40 articles were identified across the four databases. All were excluded by the independent reviewers.

Figure B44 PRISMA flow for resource utilisation studies identified through database searches

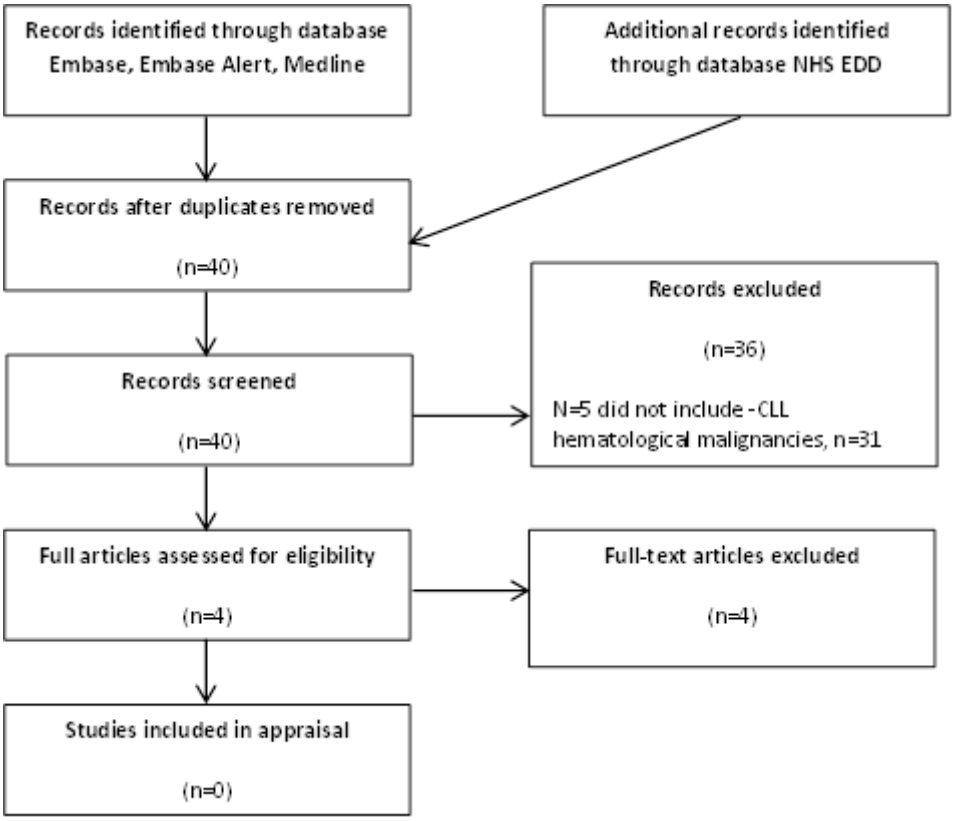


Figure B44 above illustrates the literature search in terms of identified and included/excluded studies.

7.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[9]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

N/A

Intervention and comparators' costs

7.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

[9] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B55 Unit costs associated with the technology in the economic model

Items	Obinutuzumab	Rituximab	Bendamustine	Chlorambucil
Technology cost	£3,312 per 1000 mg vial	£174.63 per 100mg vial £873.15 per 500mg vial	£69.45 per 25mg vial £275.81 per 100mg vial	£40.51 per 25 x 2mg pack
Cost/mg	£3.31	£1.75	£2.76	£0.81
Cost per treatment course	£26,496	£9,953.91	£5,809.92	£369.45
Administration cost	£514 for first infusion £343 for subsequent infusions	£514 for first infusion £343 for subsequent infusions	£514 for first infusion £343 for subsequent infusions	£136
Pharmacy cost	£16.75 (15mins)	£16.75 (15mins)	£16.75 (15mins)	£5.58 (5mins)

All drugs in the model requiring dosing in relation to body weight or body surface area (BSA) 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. In the CLL11 trial, the mean patient weight is 73.68kg, mean height is 166.70cm and mean BSA therefore 1.85m^2. For all intravenously administered drugs, an assumption of no vial sharing is made and therefore all calculations include drug wastage.

All costs are presented below according to planned treatment duration (i.e. maximum number of cycles as per label) and planned dose (i.e. full dose as per label). Note however the model base case uses the actual treatment duration and actual dose from the relevant trials (i.e. CLL11 for GClb, RClb and Clb, Knauf for bendamustine, and MaBLe for RBenda) so costs within the model are adjusted accordingly.

Obintuzumab drug cost

Obintuzumab is administered by intravenous infusion over six 28 day cycles with the first cycle including 3 doses on days 1,8 and 15, at a fixed 1000mg dose per infusion. Obintuzumab can be purchased in a 1000 mg vial for £3,153.29. This equates to a cost of £26,496 per course of treatment.

Rituximab drug cost

Rituximab is administered by intravenous infusion over six 28 day cycles with the first cycle given at 375mg/m^2 and the next five cycles at 500mg/m^2. Rituximab can be

purchased in a 100mg vial for £174.63 and 500mg vial for £873.15 respectively. This equates to a cost of £9953.91 per course of treatment.

Bendamustine drug cost

Bendamustine is administered by separate intravenous infusions on days 1 and 2, every 4 weeks at 100mg/m^2 for up to 6 cycles. Bendamustine can be purchased in a 25mg vial for £69.45 and 100mg vial for £275.81 respectively. This equates to a cost of £6619.44 per course of treatment. The Knauf trial states that a mean 4.9 out of 6 cycles were administered at an average of 90% dose intensity (40).

When given in combination with rituximab, bendamustine is administered by intravenous infusion on day 1 and 2 every 4 weeks at 90mg/m^2 for up to 6 cycles. This equates to a cost of £5 809.92 per course of treatment. Given that the MaBLe study has not yet been fully published, it is assumed that duration and dose intensity are as per trial protocol.

Chlorambucil drug cost

Chlorambucil is administered orally on day 1 and 15 over six 28 day cycles at 0.5mg/kg. The cost of chlorambucil is £40.51 per 25 pack of 2mg tablets. This equates to a cost of £369.45 per course of treatment.

Administration and pharmacy cost

Obinutuzumab, rituximab and bendamustine are administered by intravenous infusion in a hospital. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the technologies (typically within a hospital setting). The administration cost of the first dose for each technology is based on NHS Reference costs 2012-13 DH HRG SB14Z Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (£514). The administration cost of subsequent doses (i.e. all remaining doses within the first cycle and all subsequent cycles thereafter) is obtained from NHS Reference costs 2012/13 (SB15Z): Deliver subsequent elements of a chemotherapy cycle (£343). For obinutuzumab it is possible that the first dose of the cycle 1 is given as a split dose over two days to limit infusion related reactions (see section 1). However given that the intention is to deliver obinutuzumab in one dose (as per the SPC), only one administration cost is attributed to obinutuzumab for delivery of the first dose (as in line with NHS delivery specifications; see example on p11 Chemotherapy Regimens Clinical Coding Standards and Guidance OPCS-4 (250)). In contrast, the delivery of

bendamustine is intended to be over two days per cycle (as per the SPC). Two separate administration costs have therefore been attributed to the delivery of bendamustine for days 1 and 2 of each cycle (as in line with NHS delivery specifications; see example on p11 Chemotherapy Regimens Clinical Coding Standards and Guidance OPCS-4 (250)).

The pharmacy time required for dispensing an intravenous drug is assumed to be 15 minutes (validated with clinicians at a previous advisory board). One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £67 (PSSRU, 2013). The cost of dispensing of intravenous treatments in the economic model is estimated to be £16.75 (£67 x 15/60) per administration, based on 15 minutes of pharmacist preparation time.

Chlorambucil is administered orally and again there is a cost associated with both the pharmacy preparation of the oral drug and the administration of the technologies (typically within a hospital setting). The administration cost of delivering an oral therapy is obtained from NHS Reference costs 2012/13 (SB11Z): Deliver exclusively oral chemotherapy (£136). The pharmacy time required for dispensing an oral drug is assumed to be 5 minutes (validated with clinicians at a previous advisory board). One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £67 (PSSRU, 2013). The cost of dispensing of intravenous treatments in the economic model is estimated to be £5.58 (£67 x 5/60) per administration, based on 5 minutes of pharmacist preparation time.

For all treatments it is assumed that there is a 30 minute consultation with a clinical hematologist per cycle, as confirmed at an independent advisory board with hematology clinicians. This is obtained from NHS Reference costs 2012/13 (Treatment function 303 where a first outpatient attendance with a clinical hematologist costs £268/hr and subsequent outpatient attendances cost £106/hr.

Where a treatment is given in conjunction with another treatment (i.e. GClb, RClb, RBenda) only 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).

Post-progression treatment costs

Given the modelling method employed for OS (PPS death rates from CLL5 were used; see Section 7.3.2.1), it was considered most appropriate to use post-progression treatments from CLL5. In CLL5, patients across both arms received a

range of treatments on relapse, including most typically fludarabine, bendamustine or chlorambucil. Similarly, at an independent advisory board of clinical experts, it was advised that for CLL11-type patients, treatment on progression could vary widely and may or may not depend on first line remission as equally as the individual patient's characteristics. Furthermore clinical experts advised that given the initial age and comorbidities of CLL11-type patients, second line treatment may not even be appropriate once the patient progresses emphasised further by the large difference between median TTNT and median PFS (see section 6.5), thus suggesting that it is appropriate to include in the model one treatment post-progression.

Therefore, in the absence of any strong justification as to why second line treatment might differ across arms in the CLL11 trial, a conservative approach was taken by assuming that patients across each arm would receive a course of chlorambucil treatment. This was conservative in the sense that there was crossover to obinutuzumab from the chlorambucil arm but no retreatment with obinutuzumab in the obinutuzumab arm, and so had post-progression treated been modelled accordingly, this would strongly favour the cost-effectiveness of obinutuzumab versus chlorambucil. Nonetheless this scenario (i.e. crossover to obinutuzumab), a scenario where the post-progression treatment was bendamustine for all arms and a scenario where no post-progression treatment was assumed were all run as sensitivity analyses.

In each instance, the cost of post-progression treatment was divided by the mean time spent in progressed disease in each arms was and converted to a weekly supportive care cost in the progressed health state that therefore included post-progression treatment.

Health-state costs

7.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.**

Table B56 List of health states and associated costs in the economic model

Health states	Items	Frequency	Unit cost (£)	Total Cost per week (£)
Progression-free survival best supportive care	Follow-up attendance with clinical haematologist	Once every 3 months	106	8.13
Post progression survival best supportive care	Follow-up attendance with clinical haematologist	Once per month	106	24.38

ESMO guidelines (4) state that follow-up of asymptomatic patients is recommended every 3 (-12) months and should include a blood cell count every three months, as well as a regular examinations of lymph nodes, liver and spleen. The PFS health state therefore assumes one 1 hour outpatient attendance every 3 months at a cost of £106/hr. It was assumed in the progressed health state that the frequency of these visits would increase to one per month. These frequencies were confirmed with haematology clinicians at an independent advisory board.

Adverse-event costs

7.5.7 **Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Grade 3, 4 or 5 adverse events occurring in 2% or more people in any arm of the CLL11 trial, or the Benda and R-Benda arms of the Knauf and MaBLe trials respectively are incorporated into the model (see Table B57). In all instances the most recent NHS reference costs (non-elective spell tariffs) are used (NHS References costs 2012/13) (see Table B57). The cost of adverse 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 arm was then applied as a one off event in the first cycle of each Markov trace.

Table B57 List of adverse events and summary of 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 (£)	Source: NHS reference cost 2012/13 (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 (PA45Z)
NEUTROPENIA	4	13.8%	9.7%	7.6%		0.0%	3,894	Febrile Neutropenia with Malignancy (PA45Z)
PNEUMONIA	3	1.5%	2.1%	0.8%	0.0%	0.0%	1,353	Lobar, Atypical or Viral Pneumonia, without CC (DZ11C)
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)

*No AE data yet from MabLe

AE: Adverse Event; Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; HRG: Healthcare Resource Groups; NHS: National Health Service; R: Rituximab

Table B58 summarises the total adverse event cost in each arm as applied in the economic model. Varying the AE costs by treatment arm are explored as sensitivity analyses.

Table B58 Total adverse event cost by treatment arm

Treatment arm	Total Adverse Event Cost Per Patient (£)
GClb	£2544.04
RClb	£1693.78
Clb	£1035.51
Benda	£1361.78
RBenda*	£1693.78

*No AE data yet for MabLe so assumed to be same as RClb based on MaBLe abstract which states that safety was similar between the two arms

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs are present.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 **Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis**.

The three state model structure used in this model has been used in previous NICE Technology Appraisals in haematology and is accepted as an appropriate method of modelling CLL, therefore no structural sensitivity analysis of the model has been undertaken.

7.6.2 **Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.**

Deterministic sensitivity analysis was carried out on a range of parameters as listed in Table B72. The impact on the ICER of using different parametric functions to model progression-free survival was explored. Further the impact of varying the post-progression death rate to model overall survival and subsequent impact on the ICER was also explored. In addition derived hazard ratios from the MTC were also varied. Significant costs were varied and the impact of varying utility values was also analysed. Finally the discount rate for both costs and outcomes was varied according to standard methods and the time horizon altered.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A PSA was undertaken over 1000 iterations. In order to be able sample a distribution around the PFS data which is not possible within the model when using KM data and fitting a parametric tail, the base case PFS curves in all arms were set to Gamma distributions (within the PSA analysis only). Fitting a Gamma distribution to the whole dataset for each arm as opposed to only the tails has minimal impact on the ICERs as can be seen in Table B72.

The following parameters were given distributions (in brackets) and applied within the PSA:

- Utility values (Beta distribution)
- Parameter estimates for the parametric PFS and PPS function (Multivariate normal distribution)
- Number of adverse event (Log-normal distribution)
- Costs of adverse events (Log-normal distribution)
- Monthly supportive care costs for the PFS and Progressed health states (Log-normal distribution)
- Administration costs (Log-normal distribution)
- Hazard ratio of the indirect treatment comparisons (Log-normal distribution)

No distribution was applied to the cost of study drugs.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included**.

Table B59 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
GClb		
Progression-free survival	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]
RClb		
Progression-free survival	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]
Clb		
Progression-free survival	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]

Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Table B59 indicates that the model predicts exactly the median progression-free survival observed in the CLL11 trial. This is due to the use of KM progression-free survival curves from the study applied directly in the model until the start of extrapolation (which began after median progression-free survival). Given that the median OS has not been reached in any arm of the trial, the model predicted OS cannot be compared to the trial. Validation of the OS modelling has been discussed in section 7.3.2.1.

The model predicts a mean OS gain to PFS gain multiple of 70% for GClb versus Clb and 67% for GClb versus Clb. Clinical consensus was that this is reasonable in haematology where one would not expect to see all of the PFS gain necessarily translated into an OS gain, particularly in a patient population such as that of CLL11.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The model runs for 20 years on a weekly cycle length for five interventions. Reproducing the Markov trace would substantially lengthen the submission and thus has not been reproduced within the template. The trace is available within the model and can be provided as a separate appendix document if required.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

See response to 7.7.2.

7.7.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:**

Table B60 Model outputs by clinical outcomes

Technologies	Outcome	Life Years	QALYs
GClb	Progression-free survival	2.69	2.18
	Progressed disease	3.10	1.84
	Overall survival	5.79	4.03
RBenda	Progression-free survival	2.15	1.70
	Progressed disease	3.27	1.95
	Overall survival	5.42	3.65
RClb	Progression-free survival	1.63	1.28
	Progressed disease	3.45	2.05
	Overall survival	5.08	3.33
Benda	Progression-free survival	1.56	1.23
	Progressed disease	3.48	2.07
	Overall survival	5.04	3.30
Clb	Progression-free survival	0.99	0.77
	Progressed disease	3.61	2.15
	Overall survival	4.60	2.92

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; QALY, quality-adjusted life year; R: Rituximab

7.7.5 **Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below**.

Table B61 Summary of QALY gain in PFS

Technologies	QALY gain PFS	Increment	(% absolute increment)
Clb	0.77	-	-
Benda	1.23	0.45	59%
RClb	1.28	0.05	4%
RBenda	1.70	0.42	33%
GClb	1.84	0.14	9%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; PFS: Progression Free Survival; QALY, quality-adjusted life year; R: Rituximab

Table B62 Summary of QALY gain in PD

Technologies	QALY gain PD	Increment	(% absolute increment)
GClb	1.84	-	-
RBenda	1.95	0.10	6%
RClb	2.05	0.11	5%
Benda	2.07	0.02	1%
Clb	2.15	0.08	4%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; QALY, quality-adjusted life year; R: Rituximab

Table B63 Summary of costs in PFS

Technologies	Costs PFS	Increment	(% absolute increment)
Clb	£3,061	-	-
Benda	£10,761	£7,700	252%
RClb	£15,246	£4,485	42%
RBenda	£22,687	£7,441	49%
GClb	£30,577	£7,890	35%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; PFS: Progression Free Survival; R: Rituximab

Table B64 Summary of costs in PD

Technologies	Costs Progressed	Increment	(% absolute increment)
GClb	£4,311	-	-
RBenda	£4,529	£217	5%
RClb	£4,756	£228	5%
Benda	£4,796	£40	1%
Clb	£4,959	£163	3%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Table B65 Summary of predicted resource use by category of cost: mean treatment cost

Technologies	Costs of treatment	Increment	(% absolute increment)
Clb	£286	-	-
Benda	£4,745	£4,459	1559%
RClb	£9,545	£4,800	101%
RBenda	£15,243	£5,698	60%
GClb	£23,157	£7,913	52%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Table B66 Summary of predicted resource use by category of cost: administration cost

Technologies	Cost - administration	Increment	(% absolute increment)
Clb	£1,320	-	-
RClb	£3,314	£1,994	151%
GClb	£3,736	£422	13%
Benda	£3,991	£255	7%
RBenda	£4,836	£845	21%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Table B67 Summary of predicted resource use by category of cost: mean costs supportive care PFS

Technologies	Costs - mean supportive care PFS	Increment	(% absolute increment)
Clb	£420	-	-
Benda	£663	£243	58%
RClb	£693	£30	4%
RBenda	£914	£220	32%
GClb	£1,140	£226	25%

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Base-case analysis

7.7.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

The cost-effectiveness results are presented in Table B68, Table B69, Table B70 and Table B71.

Table B68 Base-case results (costs, LYG and QALYs)

	GClb	RBenda	RClb	Benda	Clb
Technology acquisition cost	£23,157	£15,243	£9,545	£4,745	£286
Other costs	£11,732	£11,972	£10,457	£10,812	£7,735
Total costs	£34,888	£27,215	£20,002	£15,557	£8,020
Difference in total costs	-	£7,673	£14,886	£19,331	£26,868
LYG	5.79	5.42	5.08	5.04	4.60
LYG difference	-	0.36	0.70	0.74	1.19
QALYs	4.03	3.65	3.33	3.30	2.92
QALY difference	-	0.38	0.70	0.73	1.11
ICER	-	£20,076	£21,275	£26,463	£24,256

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

Table B69 Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
RClb	£20,002	5.08	3.33	£4,445	0.04	0.03	£144,269
RBenda	£27,215	5.42	3.65	£7,213	0.34	0.32	£22,718
GClb	£34,888	5.79	4.03	£7,673	0.36	0.38	£20,076

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

Table B70 Incremental cost-effectiveness results versus Clb (compared against status quo to remove dominated and extended dominated interventions)

Technologies	Incremental costs vs Clb (£)	Incremental LYG vs Clb	Incremental QALYs vs Clb	ICER (£/QALY gained)	Remove from analysis
Clb	£0	0.00	0.00	£0	No
Benda	£7,536	0.45	0.38	£19,983	No
RClb	£11,982	0.48	0.41	£29,369	Yes – extendedly dominated
RBenda	£19,195	0.83	0.73	£26,458	Yes – extendedly dominated
GClb	£26,868	1.19	1.11	£24,256	No

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

Table B71 Final simultaneous incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
GClb	£34,888	5.79	4.03	£19,331	0.74	0.73	£26,463

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

Table B70 shows the base case results for obinutuzumab versus each comparator. It shows that obinutuzumab is more effective but more costly than all other comparators.

The results in Table B71 demonstrate the incremental analysis. Table B71 details all interventions against Clb (the status quo) in order to be able to determine the cost-effectiveness plane and eliminate all interventions that are either dominated or extended dominated. It can be seen that RClb and RBenda are both extended dominated because they result in ICERs that are greater than GClb.

The efficiency frontier therefore consists of only Clb, Benda and GClb as can be seen in Table B71. The comparison of Benda versus Clb results in ICER of £19,983. Since this is at a level that would typically be deemed cost-effective by NICE (i.e. less than £30,000/QALY gained), Benda becomes the relevant comparator for GClb. The comparison of GClb versus Benda also results in a cost-effective ICER at £26,463. GClb therefore represents an efficient use of NHS resources compared to current standards of care.

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

Table B72 Deterministic sensitivity analyses

Variable	Base Case Value (BCV)	Sensitivity Analysis Value (SAV)	Clb	Benda	RClb	RBenda	GClb
Transition Probabilities: PFS	KM PFS with Gamma tail (in all arms)	KM PFS with Weibull tail (in all arms)	-	£19,755 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£25,745 (vs Benda)
		KM PFS with Log-logistic tail (in all arms)	-	Extendedly Dominated	Extendedly Dominated	Extendedly Dominated	£18,402 (vs Clb)
		KM PFS with Gompertz tail (in all arms)	-	£20,375 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£30,828 (vs Benda)
		PFS Gamma distribution (in all arms)	-	£19,751 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£27,567 (vs Benda)
		PFS Weibull distribution (in all arms)	-	£19,463 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,751 (vs Benda)
		PFS Gompertz distribution (in all arms)	-	£20,303 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£31,872 (vs Benda)
		PFS Log-logistic distribution (in all arms)	-	Extendedly Dominated	Extendedly Dominated	Extendedly Dominated	£18,907 (vs Clb)
Transition Probabilities: OS	Age adjusted post-progression (PP) death rate from CLL5 (all arms)	Non-age adjusted post-progression (PP) death rate from CLL5 (all arms)	-	£18,464 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£24,460 (vs Benda)
		BCV x 50% (all arms)	-	£22,854 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£33,133 (vs Benda)
		BCV x 75% (all arms)	-	£20,979 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£28,645 (vs Benda)
		BCV x 125% (all arms)	-	£19,383 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£25,221 (vs Benda)
		BCV x 150% (all arms)	-	£18,985 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£24,406 (vs Benda)

		BCV x 90% (Clb only)	-	£18,985 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,463 (vs Benda)
PFS HR: GClb vs Benda	0.40	0.54 (FE model without age adjustment)	-	£13,308 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£35,684 (vs Benda)
		0.55 (RE model without age adjustment)	-	£13,019 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£36,527 (vs Benda)
PFS HR: GClb vs RBenda	0.68	0.82 (BCV x 1.2)	-	£19,983 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£32,145 (vs Benda)
		0.55 (BCV x 0.8)	-	£19,983 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,463 (vs Benda)
Treatment dose	Actual	Planned	-	£21,733 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£25,590 (vs Benda)
Treatment duration	Actual	According to label	-	£22,964 (vs Clb)	Extendedly Dominated	£29,033 (vs Benda)	£29,704 (vs RBenda)
Utility: PFS off treatment	0.82	0.92 (BCV +0.1)	-	£17,417 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£22,148 (vs Benda)
		0.72 (BCV -0.1)	-	£23,434 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£32,865 (vs Benda)
Utility: PD	0.60	0.70 (BCV +0.1)	-	£20,720 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£27,990 (vs Benda)
		0.50 (BCV -0.1)	-	£19,355 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£25,210 (vs Benda)
PP treatment costs (all arms)	£369 (Clb in all arms)	£5,810 (Benda)	-	£20,014 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,527 (vs Benda)
		£25,226 (GClb)	-	£20,014 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,527 (vs Benda)

Adverse event costs (Clb)		£0 (No AEs)	-	£22,728 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,463 (vs Benda)
Adverse event costs (Benda)		£0 (No AEs)	-	£26,372 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£28,327 (vs Benda)
Adverse event costs (RBenda)		£0 (No AEs)	-	£19,983 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£26,463 (vs Benda)
Adverse event costs (GClb)		£1272 (BCV x 0.5)	-	£19,983 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£24,721 (vs Benda)
		£3816 (BCV x 1.5)	-	£19,983 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£28,204 (vs Benda)
Time Horizon	20 years	10 years	-	£21,037 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£28,430 (vs Benda)
Discount rate: Costs and Outcomes	3.5%	6%	-	£21,540 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£29,106 (vs Benda)
Adverse event costs (RBenda)	£1,694	0%	-	£17,798 (vs Clb)	Extendedly Dominated	Extendedly Dominated	£22,861 (vs Benda)

7.7.8 **Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves**.

A 1,000 iteration probabilistic sensitivity analysis was conducted in order to determine the uncertainty surrounding the base-case ICERs.

Figure B45 Probabilistic sensitivity analysis scatterplot

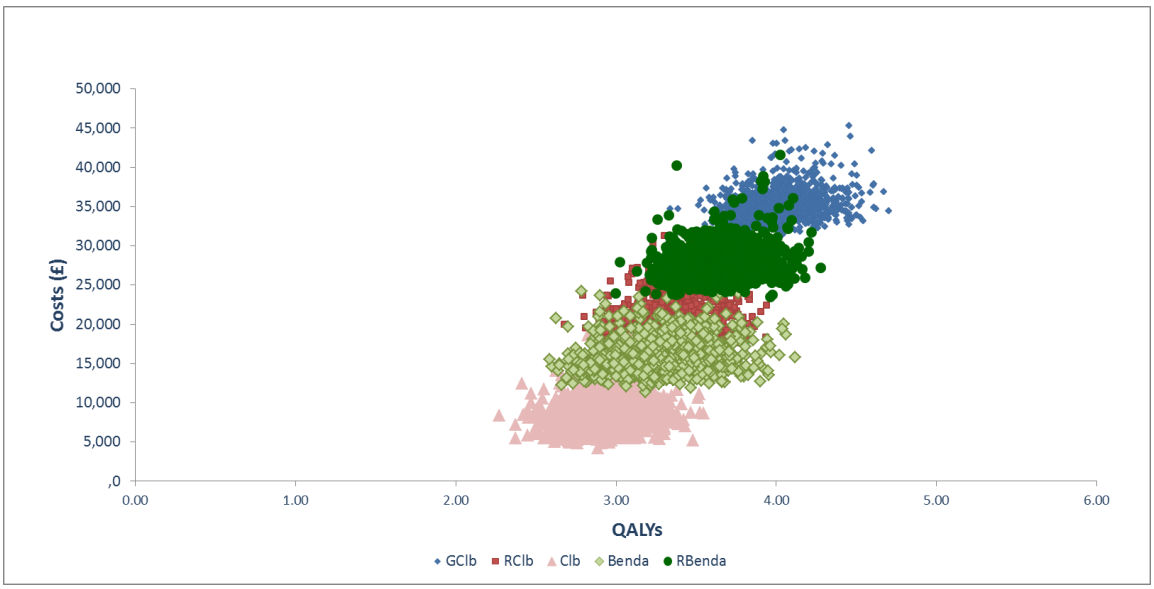
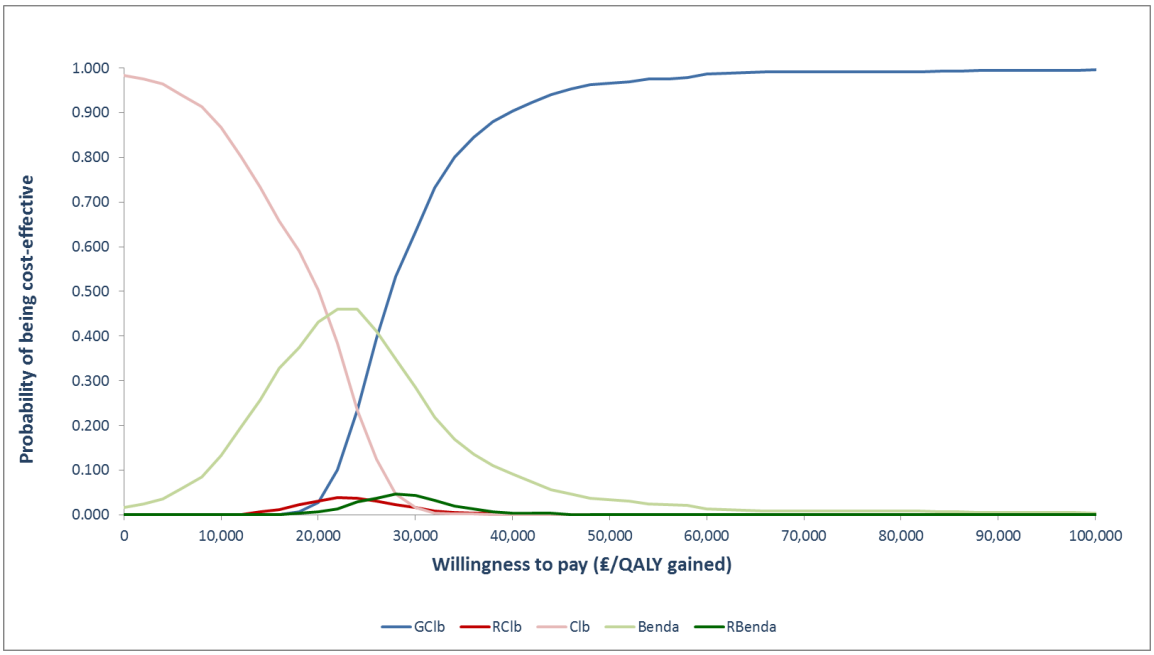


Figure B46 Cost effectiveness acceptability curves



This analysis indicated that obinutuzumab in combination with chlorambucil had a 63.4% chance of being the most cost-effective treatment option at a threshold of £30,000/QALY gained. This was more than twice as high as that observed for the next most cost-effective treatment option (bendamustine at a probability of 28.5%). The probabilistic base-case ICER was comparable to the deterministic base-case at £25,779/QALY gained.

In addition to this analysis PSA was also run for an alternative base-case (using a Weibull function in its interity rather than using KM data followed by parametric extrapolation). This resulted in a probabilistic ICER of £26,206 and a 62.8% of obinutuzumab being the most cost-effective treatment option.

7.7.9 **Please present the results of scenario analysis. Include details of structural sensitivity analysis**.

Structural sensitivity analyses can be found in Table B72.

7.7.10 **What were the main findings of each of the sensitivity analyses?**

The deterministic sensitivity analyses demonstrate that even with variation in each of the model parameters chlorambucil, bedamustine and obinutuzumab in combination with chlorambucil remain the regimens on the efficiency frontier in the vast majority of scenarios.

Both the deterministic and probabilistic analyses demonstrate that high probability of being considered cost-effective at a threshold of £30,000/QALY gained.

7.7.11 **What are the key drivers of the cost-effectiveness results?**

The key drivers of the model are the long term projection of progression-free survival, the post-progression death rate, the results of the MTC and the utility values used.

7.8 Validation

7.8.1 **Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.**

The modelling methodology, assumptions and clinical inputs employed were validated at an advisory board meeting and by an independent health economics academic, whilst the model functionality was validated by an external consultancy. Further the model was externally validated insofar as possible against existing data; this included PFS and OS validation of the modelled chlorambucil and bendamustine curves against the Knauf 2009 trial data in the over 65 age group, and the modelled OS chlorambucil curves against the CLL5 trial chlorambucil arm (see section7.3.2.1).

The extrapolations conducted were discussed with an academic health economists and a panel of expert CLL clinicians. All noted that whilst subject to uncertainty the extrapolation approach employed appeared reasonable given the evidence currently available.

The model also went an internal and external quality check by an external agency.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 **Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.**

No subgroup analysis was undertaken.

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

N/A

7.9.3 **Please describe how the statistical analysis was undertaken.**

N/A

7.9.4 **What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).**

N/A

7.9.5 **Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

N/A

7.10 Interpretation of economic evidence

7.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

There are no economic evaluations in this indication and patient population with which these results may be compared (see Section 7 for more details of the search of cost-effectiveness studies undertaken).

7.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?**

The evaluation is founded upon the CLL11 trial and so should be representative of all people who participated in the CLL11 trial.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The model uses data from the pivotal clinical trial (CLL11) wherever possible, and resource use and costs based on ESMO clinical guidelines and NHS reference costs.

2. CLL11 is a robust and well conducted study in people broadly representative of the population expected to be treated in England and Wales.

3. The extrapolated overall survival curves demonstrate external validity when compared against existing data of people with CLL.

Weaknesses

1. The model is heavily reliant upon long-term projection of overall survival.

2. For comparisons against interventions not included in the CLL11 trial the model is reliant on an indirect treatment comparison and thus all the caveats associated with making cross-trial comparisons. Whilst every effort has been made to only compare with data from trials that have a similar population to CLL11 (via the inclusion and exclusion criteria of the systematic literature review and subsequent age adjustment), it is inevitable that there are some underlying differences between the populations of each trial and this therefore might distort the efficacy data imputed versus had RCTs against each comparator being conducted.

3. There is currently a lack of data on RBenda which means that the relative efficacy of GClb versus this treatment option is subject to considerable uncertainty.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Key drivers in the model are the extrapolation of overall survival and progression-free survival, and the utility values used to estimate the quality of life of people with the disease. Robustness of the model would be improved by the incorporation of more mature data on the baseline risk of death and the longer term treatment effect

associated with GA101. Collection of EQ-5D values from participants in the trial itself would improve the estimates of the quality of life impact within the progression-free survival and progressed health states.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that approximately 1,034 people per annum will be eligible to receive obinutuzumab. The derivation of this number is provided in Figure A3 and adjusted accordingly for the population of England and Wales. At a population growth rate of 0.5% per annum this results in the following yearly eligible populations

Table B73 Eligible population by year

Year	1	2	3	4	5
Eligible population	1034	1039	1044	1050	1055

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The analysis considers only the absolute budget impact of obinutuzumab (i.e. the costs of any technologies displaced are not considered and hence the budget impact is conservative).

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that 30% of eligible people in the year following NICE approval would receive obinutuzumab with that figure rising to 70% in the fifth year following approval. The market share figures used are presented in Table B74.

Table B74 Market share assumptions by year

Year	1	2	3	4	5
% people treated with trastuzumab emtansine	30%	40%	50%	60%	70%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact calculations include all the additional costs of treatment with obinutuzumab as included in the de novo economic model and discussed in the cost-effectiveness section.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The budget impact calculations are based upon the output of the economic model.

8.6 Were there any estimates of resource savings? If so, what were they?

No.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table B75 Budget impact by year

Year	1	2	3	4	5
Budget impact - drug cost	£7,184,018	£9,626,584	£12,093,396	£14,584,636	£17,100,486
Budget impact - non-drug cost	£3,639,580	£4,877,038	£6,126,779	£7,388,895	£8,663,480
Total budget impact	**£10,823,598**	**£14,503,622**	**£18,220,175**	**£21,973,531**	**£25,763,965**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter):

The following databases were searched:

- Medline (Embase.com; http://www.embase.com/)
- Embase (Embase.com; http://www.embase.com/)
- Medline In-process (PubMed ; http://www.ncbi.nlm.nih.gov)
- The Cochrane Library (http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html)
- American Society of Clinical Oncology (ASCO) Abstracts
- American Society of Hematology (ASH) Abstracts
- European Haematology Association (EHA) Abstracts

10.2.2 The date on which the search was conducted.

All searches were performed on the 8th of April 2014 Except the Embase searches which were performed on the 9th of April 2014.

10.2.3 The date span of the search.

Database	**Date span of search**
Medline	1992 to 8 April 2014
Embase	1992 to 9 April 2014
MEDLINE In-process	1992 to 9 April 2014
The Cochrane Library	1992 to 8 April 2014
American Society of Clinical Oncology (ASCO) American Society of Hematology (ASH) European Haematology Association (EHA)	Entries from 2011 to 8 April 2014

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

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

The Embase Library was searched between 1992 and 8 April 2014. The search was conducted using the search terms summarised in the table below.

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 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	10525641
#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

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

The Pubmed Library was searched between 1992 and 8 April 2014. The search was conducted using the search terms summarised in the table below.

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

Search strategy for Cochrane Library – 8 April 2014

The Cochrane Library was searched between 1992 and 8 April 2014. The search was conducted using the search terms summarised in the table below. Two references were located, which referred to agents not being considered for this submission.

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

In order to identify articles (and other items, e.g. letters) which have not yet been included in electronic databases, three conference proceedings were searched manually from January 2011 until 8 April 2014

Search strategy for ASCO abstracts: January 2011 – 8 April 2014

The Journal of Clinical Oncology archive was searched for ASCO annual meetings 2011-2014. ASCO Meeting Abstracts was specified as the source to search. The search was conducted through the JCO archive rather than the ASCO website as the search tool on the website has restricted function compared with the JCO archive which allows compound searching in multiple fields. The search was conducted using the terms *"GA101"* in the Title and "*GA101 and CLL"* in the Abstract Body. Searching for obinutuzumab did not yield any additional publications. There was 1 result which related to the CLL study.

Search strategy for ASH abstracts: January 2011 – 8 April 2014

The Blood journal archive was searched for ASH annual meetings 2011-2014. ASH Meeting Abstracts was specified as the source to search. The search was conducted through the journal's archive rather than the ASH website as the search tool on the website has restricted function compared with the JCO archive which allows compound searching in multiple fields. The search was conducted using the terms *"GA101"* in the Title and "*GA101 and CLL"* in the Abstract Body. Searching for obinutuzumab did not yield any additional publications. There were 10 results, 1 of which related to the CLL study, the other 9 related to other trials (e.g. GAUSS) or pre-clinical data, or combinations with agents other than chlorambucil, all of which were not being considered for this submission.

Search strategy for EHA abstracts: January 2011 – 8 April 2014

The EHA website was searched for EHA annual meetings 2011-2014. Each year's archive (2011 - 2014) was searched within the 'chronic lymphocytic leukemia-Clinical' category. The search was conducted using the term "GA101" as a Keyword and in the Title and the Abstract Body. Searching for obinutuzumab did not yield any additional publications. There were 2 results, 1 which related to relapsed/refractory CLL which was not being considered for this submission and 1 which related to the CLL study.

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

None

10.2.6 The inclusion and exclusion criteria.

Inclusion Criteria:

Published papers or abstracts which evaluated the following were included:

- Obinutuzumab had to be the major focus of the study, in order to eliminate references which merely mentioned obinutuzumab as part of a discussion of treatments for CLL or other blood cancers, for example review articles

- CLL had to be the major focus of the study, in order to eliminate papers addressing the use of obinutuzumab in other blood cancers
- Studies in which patients received study therapy for the first-line treatment of CLL, to be consistent with the anticipated obinutuzumab licence
- Studies in which patients receiving obinutuzumab therapy in combination with chlorambucil, to be consistent with the anticipated obinutuzumab licence. Data addressing the efficacy of obinutuzumab in combination with agents other than chlorambucil are not in line with this submission
- Efficacy endpoints associated with the treatment of CLL were the focus for the data ie. Progression-free survival, overall survival and response rates
- Clinical trial data, not case reports, retrospective reviews, etc.
- Documents relating to humans – since work in animal models was not relevant to this submission.

Exclusion criteria:

- References which were not randomised, controlled trials
- Studies where obinutuzumab was not included
- Studies which were in non-relevant populations ie. relapsing or refractory CLL
- Studies which included agents in combination with obinutuzumab other than chlorambucil

10.2.7 The data abstraction strategy.

Exclusion key

References which were not randomised, controlled phase II/III trials (such as phase I, single arm studies, reviews and meta-analyses).	**RAN**
Studies where obinutuzumab is not the intervention or is used in combination with agents other than chlorambucil	**INV**
Studies which were in non-relevant populations, i.e. refractory/relapsed CLL	**POP**

Search results from Medline/Embase 1992 to 9 April 2014

Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
1	None given	2009	No	RAN
2	None given	2014	No	RAN
3	None given	2014	No	RAN
4	Ashforth,E	2008	No	RAN
5	Badoux,X	2011	No	RAN
6	Bologna,L	2010	No	RAN
7	Bologna,L	2011	No	RAN
8	Bologna,L	2013	No	INV
9	bou-Nassar,K	2010	No	RAN
10	Brown,J.R	2013	No	INV
11	Brugger,W	2013	No	INV
12	Cameron,F	2014	No	RAN
13	Cartron,G	2009	No	RAN/POP
14	Chamuleau,M.E.D	2010	No	RAN
15	Chang,J.E	2012	No	INV
16	Cheson,B.D	2008	No	RAN
17	Cheson,B.D	2009	No	RAN
18	Cheson,B.D	2010	No	RAN
19	Chiappella,A	2011	No	RAN
20	Chiappella,A	2011	No	RAN
21	Coiffier,L.K.B	2013	No	RAN/POP
22	Comer,B	2014	No	RAN
23	Davids,M.S	2013	No	RAN
24	Delgado,J	2009	No	RAN
25	Delgado,J	2012	No	RAN
26	Desai,S	2012	No	RAN
27	Dyer,M.J.S	2013	No	RAN
28	Fine,G	2011	No	RAN
29	Fong,S	2013	No	RAN
30	Fox,J.	2010	No	RAN
31	Fox,J.	2010	No	Duplicate
32	Friedberg,J.W	2010	No	RAN
33	Goede,V	2010	Yes	
34	Goede,V	2011	No	RAN
35	Goede,V	2013	Yes	
36	Goede,V	2013	Yes	
37	Goede,V	2014	Yes	
38	Golay,J	2013	No	RAN
39	Hallek,M	2010	No	RAN
40	Hallek,M	2011	No	RAN
41	Hallek,M	2013	No	RAN

42	Hallek,M	2013	Yes	
43	Helwick,C	2013	No	RAN
44	Honeychurch,J	2012	No	RAN
45	Houlton,S	2013	No	RAN
46	Jaglowski,S.M	2012	No	RAN
47	Jak,M	2011	No	RAN
48	Kahl,B.S	2010	No	RAN
49	Karlin,L	2011	No	RAN
50	Kassam,S	2009	No	RAN
51	Kempin,S	2013	No	RAN
52	Klein,C	2013	No	RAN
53	Laprevotte,E	2013	No	RAN
54	Laurenti,L	2011	No	RAN
55	Leonard,J.P	2008	No	RAN
56	Lugovskoy,A.A	2012	No	RAN
57	Mehta,D	2010	No	RAN/POP
58	Melchardt,T	2011	No	RAN/POP
59	Meneses-Lorente,G	2010	No	RAN/POP
60	Merli,M	2013	No	RAN/POP
61	Milani,C	2009	No	RAN/POP/INV
62	Molica,S	2014	No	RAN
63	Morschhauser,F	2009	No	POP
64	Morschhauser,F	2011	No	POP
65	Mullard,A	2013	No	RAN
66	Mulligan,S.P	2012	No	RAN
67	Obholz,K.L	2013	No	RAN
68	Owen,C	2012	No	RAN
69	Parikh,S.A	2010	No	RAN
70	Patz,M	2009	No	RAN
71	Patz,M	2010	No	RAN
72	Patz,M	2011	No	RAN
73	Pauwels,P.J	2012	No	RAN
74	Pievani,A	2010	No	RAN
75	Quintas-Cardama,A	2010	No	RAN
76	Rafiq,S	2011	No	RAN
77	Rafiq,S	2013	No	RAN
78	Reslan,L	2010	No	RAN
79	Rummel,M.J	2011	No	INV
80	Salles,G.A	2011	No	POP
81	Sampath,D	2013	No	RAN/INV
82	Sehn,L.H	2012	No	POP
83	Seiler,T	2012	No	RAN
84	Sellner,L	2013	No	RAN
85	Slabicki,M	2013	No	RAN
86	Smolej,L	2012	No	RAN

87	Stathis,A	2012	No	RAN
88	Steurer,M	2009	No	RAN
89	Stilgenbauer,S	2010	No	RAN
90	Tiwari,A.A	2012	No	POP
91	Tobinai,K	2010	No	POP
92	van der Jagt,R	2012	No	RAN/INV
93	van Meerten,T	2010	No	RAN
94	Van Oers,M.H.J	2012	No	RAN
95	Walzer,S	2013	No	RAN
96	Walzer,S	2013	No	RAN
97	Woyach,J.A	2012	No	POP
98	Wu,H.S	2013	No	RAN
99	Younes,A	2012	No	RAN
100	Ysebaert,L	2010	No	RAN
101	Ysebaert,L	2010	No	RAN
102	Ysebaert,L	2013	No	RAN
103	Zhang,B	2009	No	RAN

Search results from Medline In Process Library – 1992 - 8 April 2014

Result number	Publication author/ Title if no author	Publication year	Relevant RCT	Reason for exclusion
1	None given	2014	No	RAN
2	None given	2014	No	RAN
3	Bagcchi. S	2014	No	RAN
4	Bologna, L	2011	No	RAN
5	bou-Nassar,K	2010	No	RAN
6	Cameron,F	2014	No	RAN
7	Cheney,C.M	2014	No	INV
8	Cuneo,A	2014	No	RAN
9	Goede,V	2011	No	RAN
10	Goede,V	2013	Yes	Duplicate
11	Goede,V	2014	Yes	Duplicate
12	Golay,J	2013	No	RAN
13	Goldenberg,M.M	2014	No	RAN
14	Hallek,M	2013	No	RAN
15	Hallek,M	2013	Yes	Duplicate
16	Honeychurch,J	2012	No	RAN
17	Jaglowski,S.M	2010	No	RAN
18	Jain,P	2013	No	RAN
19	Jak,M	2011	No	RAN
20	Kahl,B.S	2010	No	RAN
21	Klein,C	2013	No	RAN
22	Laprevotte,E	2013	No	RAN
23	Laprevotte,E	2013	No	RAN
24	Maruyama,D	2011	No	RAN
25	Patz,M	2011	No	RAN
26	Rafiq,S	2013	No	RAN
27	Reslan,L	2014	No	RAN
28	Robak,T	2009	No	RAN
29	Robak,T	2013	No	RAN
30	Robak,T	2014	No	RAN/INV
31	Sehn,L.H	2012	No	RAN/POP
32	Smolej,L	2012	No	RAN
33	van Oers,M.H	2012	No	RAN
34	Wendtner,C.M	2013	No	RAN

Search results from Cochrane Library – 1992 - 8 April 2014

Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
1	Bauer,K	2012	No	RAN
2	Parikh,S.A	2010	No	RAN

Search results from ASCO Library – January 2011 - 8 April 2014

The one retrieved article was relevant (CLL11 trial).

Search results from ASH Library – January 2011 - 8 April 2014

Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
1	Beroual,D	2011	No	RAN
2	Da Roit,F	2013	No	RAN
3	Goede, V	2013	Yes	Duplicate
4	Honeychurch,J	2011	No	RAN
5	O'Brien,S	2013	No	INV
6	Rafiq,S	2011	No	RAN
7	Sampath,D	2013	No	RAN/INV
8	Sehn,L	2011	No	RAN/POP
9	Yasuhiro,T	2013	No	RAN
10	Ysebaert,L	2011	No	RAN

Search results from EHA Library – January 2011 - 8 April 2014

Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
1	Cartron,G	2011	No	RAN/POP
2	Goede, V	2013	Yes	

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study question	**How is the question addressed in the study?**	**Grade (yes/no/ not clear/N/ A)**
Was randomisation carried out appropriately?	After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment arm from the interactive voice response system (IVRS). A complete block randomisation scheme was applied to achieve balance in treatment assignment within each of the strata, as defined by binet stage and region (Asia and Oceania, Europe Group 1, Europe Group 2, North and Central America and Caribbean, South America and South Atlantic).	Yes
Was the concealment of treatment allocation adequate?	Concealment of treatment allocation was achieved by IVRS.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	The patient demographics and characteristics were generally well balanced in all arms and stages of the study.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	This trial was an open-label study which does introduce the possibility of bias, 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 PFS by investigator review. There is a chance that these results may be biased by additional unscheduled assessments and knowledge of treatment allocation, but the ICR assessment of the results should reduce the risk for bias. OS is unlikely to be affected by bias.	No
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances in drop outs	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on people who received at least one dose of study medication	Yes

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched:

- Medline (Embase.com; http://www.embase.com/)
- Embase (Embase.com; http://www.embase.com/)
- Medline In-process (PubMed ; http://www.ncbi.nlm.nih.gov)
- The Cochrane Library (http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html)
- American Society of Clinical Oncology (ASCO) Abstracts
- American Society of Hematology (ASH) Abstracts
- European Haematology Association (EHA) Abstracts

10.4.2 The date on which the search was conducted.

All searches for the original systematic review were performed on 27 February 2013 for RCTs and non-RCTS and in March 2013 for the abstracts from conference proceedings. Searches for the update of the systematic review were performed on 16 April 2014.

10.4.3 The date span of the search.

Database	**Date span of search**
MAIN SYSTEMATIC REVIEW	
Medline	1992 to 27 February 2013
Embase	1992 to 27 February 2013
MEDLINE In-process	1992 to 27 February 2013
The Cochrane Library	1992 to 27 February 2013
American Society of Clinical Oncology (ASCO) American Society of Hematology (ASH) European Haematology Association (EHA)	Entries from 2010 to March 2013
SYSTEMATIC REVIEW UPDATE	
Medline	2013 to 16 April 2014
Embase	2013 to 16 April 2014
MEDLINE In-process	2013 to 16 April 2014

American Society of Clinical Oncology (ASCO) American Society of Hematology (ASH) European Haematology Association (EHA)	Entries from 2011 to April 2014

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategies for the systematic review

Search strategy for Embase® and MEDLINE® – Year 1992 – 27 February 2013

The Embase Library was searched between 1992 and 27 February 2013. The search was conducted using the search terms summarised in the table below.

No.	Query	Results
1	'clinical trial'/exp	940 678
2	'randomization'/de	60 237
3	'controlled study'/de	3 972 102
4	'comparative study'/de	662 870
5	'single blind procedure'/de	16 468
6	'double blind procedure'/de	112 466
7	'crossover procedure'/de	35 411
8	'placebo'/de	227 169
9	'clinical trial'	1 082 859
10	'clinical trials'	191 470
11	'controlled clinical trial'	472 240
12	'controlled clinical trials'	11 789
13	'randomised controlled trial'	12 409
14	'randomized controlled trial'	368 714
15	'controlled trials'	59 891
16	'randomized controlled trials'	29 448
17	'randomisation'	5181
18	'randomization'	73 289
19	random*	909 291
20	rct	13 190
21	'random allocation'	1342
22	'randomly allocated'	18 522
23	'allocated randomly'	1864
24	allocated NEAR/2 random	797
25	assign* NEAR/2 random*	76 504
26	randomi*	617 058
27	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	196 738
28	placebo*	305 678
29	'prospective study'/de	216 805

30	Nrct	46
31	'n rct'	1
32	n?rct	24
33	'controlled clinical trial'/exp	439 628
34	'prospective study'/exp	216 805
35	'intervention study'/exp	15 627
36	(clinical NEXT/1 trial*):ab,ti	250 077
37	'major clinical study'/exp	2 049 241
38	compar*:ab,ti	3 992 223
39	group*:ab,ti	2 909 497
40	OR/1-39	9 600 141
41	'case study'/de	20 489
42	'case report'	1 943 789
43	'abstract report'/de	89 565
44	'letter'/de	781 077
45	OR/41-44	2 669 114
46	#40 NOT #45	9 343 300
47	'chronic lymphatic leukemia'/de	21 060
48	'b cell leukemia'/exp	4973
49	lymphom* near/2 lymphocyt*	6862
50	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast*	417 736
51	(chronic OR cronic OR 'well differential')	964 357
52	#50 AND #51	50 117
53	OR/47-49, 52	64 003
54	'chlorambucil'/syn OR amboclorin OR ‘cb 1348’ OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088	16 346
55	'fludarabine'/syn OR fludara	16 123
56	'cladribine'/syn OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR ‘rwj 26251’ OR rwj26251	4787
57	'bendamustine'/syn OR ‘cimet 3393’ OR cytostasan OR cytostasan r OR cytostasane OR ‘imet 3393’ OR levact OR ribomustin OR treanda	1521
58	'alemtuzumab'/syn OR campath OR ‘ldp 103’ OR ‘ldp103’ OR lemtrada OR mabcampath	8902
59	'rituximab'/syn OR ‘idec c2b8’ OR mabthera OR reditux OR rituxan OR rituxin	32 061
60	'ofatumumab'/syn OR arzerra OR ‘gsk 1841157’ OR gsk1841157 OR ‘humac CD20’ OR HuMax-CD20 OR ‘HuMax CD20’ OR HuMaxCD20	876
61	'lenalidomide'/syn OR ‘cc 5013’ OR cc5013 OR ‘cdc 501’ OR cdc 5013 OR cdc501 OR cdc5013 OR ‘enmd 0997’ OR enmd0997 OR ‘imid 3’ OR imid3 OR revimid OR revlimid	6597
62	'gs 1101'/syn OR ‘cal 101’ OR cal101 OR ‘gs 1101’ OR gs1101 OR idelalisib	265
63	'obinutuzumab'/syn OR afutuzumab OR ‘ga 101’ OR ga101 OR r 7159 OR r7159 OR ‘ro 5072759’ OR ro5072759	270
64	'cyclophosphamide'/syn OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR ‘cyclofos amide’ OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR ‘cyclophosphamide isopac’ OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan	164 147

	OR ‘cytoxan lyophilized’ OR ‘endocyclo phosphate’ OR endoxan OR endoxan-asta OR ‘endoxan asta’ OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR ‘lyophilized cytoxan’ OR mitoxan OR neosan OR neosar OR noristan OR ‘nsc 26271’ OR ‘nsc 2671’ OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid	
65	cop NEAR/2 regimen	70
66	chop NEAR/2 regimen	701
67	Or/54-66	204 213
68	#46 AND #53 AND #67 AND [1992-2013]/py AND AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR	4318

Search strategy for Medline - In Process (via PubMed) – Year 1992 – 27 February 2013

The Pubmed Library was searched between 1992 and 27 February 2013. The search was conducted using the search terms summarised in the table below.

No	Query	Results
1	"Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh terms]	10 777
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]	17 425
3	Search (#1 or #2)	17 425
4	(chlorambucil OR amboclorin OR ‘cb 1348’ OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088)	4570
5	(fludarabine OR fludara)	3988
6	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR ‘rwj 26251’ OR rwj26251)	1886
7	(bendamustine OR ‘cimet 3393’ OR cytostasan OR cytostasan r OR cytostasane OR ‘imet 3393’ OR levact OR ribomustin OR treanda)	529
8	(alemtuzumab OR campath OR ‘ldp 103’ OR ‘ldp103’ OR lemtrada OR mabcampath)	2066
9	(rituximab OR ‘idec c2b8’ OR mabthera OR reditux OR rituxan OR rituxin)	10 846
10	(ofatumumab OR arzerra OR ‘gsk 1841157’ OR gsk1841157 OR ‘humac CD20’ OR HuMax-CD20 OR ‘HuMax CD20’ OR HuMaxCD20)	6980
11	(lenalidomide OR ‘cc 5013’ OR cc5013 OR ‘cdc 501’ OR cdc 5013 OR cdc501 OR cdc5013 OR ‘enmd 0997’ OR enmd0997 OR ‘imid 3’ OR imid3 OR revimid OR revlimid)	1729
12	(‘gs 1101' OR ‘cal 101’ OR cal101 OR ‘gs 1101’ OR gs1101 OR idelalisib)	35
13	(obinutuzumab OR afutuzumab OR ‘ga 101’ OR ga101 OR r 7159 OR r7159 OR ‘ro 5072759’ OR ro5072759)	49
14	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR ‘cyclofos amide’ OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR ‘cyclophosphamide isopac’ OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR ‘cytoxan lyophilized’ OR ‘endocyclo phosphate’ OR endoxan OR endoxan-asta OR ‘endoxan asta’ OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR ‘lyophilized cytoxan’ OR mitoxan OR neosan OR neosar OR noristan OR ‘nsc 26271’ OR ‘nsc	496 503

	2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid)	
15	"cop regimen"	43
16	"chop regimen"	340
17	OR/4-16	527 769
18	Search (#3 AND #17)	3955
19	Search (#18 AND (in process[sb] OR pubstatusaheadofprint))	98

Search strategy for Cochrane Library – Year 1992 - 27 February 2013

The Cochrane Library was searched between 1992 and 27 February 2013. The search was conducted using the search terms summarised in the table below.

No.	**Query**	**Results**
1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees	197
2	'b cell leukaemia' OR 'b cell leukemia'	1294
3	lymphom* near/2 lymphocyt*	81
4	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR	11 116
5	(chronic OR cronic OR 'well differential')	58 350
6	#4 AND #5	1878
7	OR/1-3, 6	2857
8	MeSH descriptor: [Chlorambucil] explode all trees	214
9	(chlorambucil OR amboclorin OR 'cb 1348' OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088):ab,ti,kw	402
10	(fludarabine OR fludara):ab,ti,kw	340
11	MeSH descriptor: [Cladribine] explode all trees	1
12	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR 'rwj 26251' OR rwj26251): ab,ti,kw	125
13	(bendamustine OR 'cimet 3393' OR cytostasan OR cytostasan r OR cytostasane OR 'imet 3393' OR levact OR ribomustin OR treanda): ab,ti,kw	34
14	(alemtuzumab OR campath OR 'ldp 103' OR 'ldp103' OR lemtrada OR mabcampath): ab,ti,kw	157
15	(rituximab OR 'idec c2b8' OR mabthera OR reditux OR rituxan OR rituxin): ab,ti,kw	648
16	(ofatumumab OR arzerra OR 'gsk 1841157' OR gsk1841157 OR 'humac CD20' OR HuMax-CD20 OR 'HuMax CD20' OR HuMaxCD20): ab,ti,kw	16
17	(lenalidomide OR 'cc 5013' OR cc5013 OR 'cdc 501' OR cdc 5013 OR cdc501 OR cdc5013 OR 'enmd 0997' OR enmd0997 OR 'imid 3' OR imid3 OR revimid OR revlimid): ab,ti,kw	106
18	('gs 1101' OR 'cal 101' OR cal101 OR 'gs 1101' OR gs1101 OR idelalisib): ab,ti,kw	2
19	(obinutuzumab OR afutuzumab OR 'ga 101' OR ga101 OR r 7159 OR r7159 OR 'ro 5072759' OR ro5072759): ab,ti,kw	12

No.	Query	Results
20	MeSH descriptor: [Cyclophosphamide] explode all trees	3719
21	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'cytoxan lyophilized' OR 'endocyclo phosphate' OR endoxan OR endoxan-asta OR 'endoxan asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR 'lyophilized cytoxan' OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR 'nsc 2671' OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid): ab,ti,kw	6416
22	cop NEAR/2 regimen	21
23	chop NEAR/2 regimen	120
24	OR/8-23	8002
25	#7 and #24 from 1992 to 2013, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	403

Search strategies for the update of the systematic review

Search strategy for Embase® and MEDLINE® – Year 2013 – 16 April 2014

The Embase Library was searched between 2013 and 16 April 2014. The search was conducted using the search terms summarised in the table below.

3.1.1.2	3.1.1.3 Search History	3.1.1.4 acet	3.1.1.5 R esults
1	'clinical trial'/exp	Study design (RCTs)	959,334
2	'randomization'/de		61,404
3	'controlled study'/de		4,272,155
4	'comparative study'/de		620,235
5	'single blind procedure'/de		17,819
6	'double blind procedure'/de		114,150
7	'crossover procedure'/de		38,298
8	'placebo'/de		249,504
9	'clinical trial' OR 'clinical trials'		1,222,268
10	'controlled clinical trial' OR 'controlled clinical trials'		515,580
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'		25,783
12	'randomisation' OR 'randomization'		79,186
13	Rct		15,927
14	'random allocation'		1,425
15	'randomly allocated'		20,107
16	'allocated randomly'		1,912

17	allocated NEAR/2 random		789
18	random* NEAR/1 assign*		83,002
19	random*		1,003,174
20	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)		204,768
21	placebo*		326,122
22	'prospective study'/de		242,980
23	#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		5,725,012
24	'case study'/de		26,670
25	'case report'		1,936,427
26	'abstract report'/de		89,606
27	'letter'/de		808,910
28	#22 OR #23 OR #24 OR #25		2,693,461
29	#23 NOT #28		5869229
30	'chronic lymphatic leukemia'/de	Disease facet	23252
31	'b cell leukemia'/exp		5032
32	lymphom* near/2 lymphocyt*		7459
33	(leuk?em* OR leu?em* OR lymph*) near/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')		1133958
34	(chronic OR cronic OR 'well differential')		1223310
35	#33 AND #34		117134
36	OR/30-32, 35		127883
37	'chlorambucil'/syn OR amboclorin OR ‘cb 1348’ OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR 'nsc 3088' OR nsc3088	Intervention facet	16597
38	'fludarabine'/syn OR fludara		17996
39	'cladribine'/syn OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR ‘rwj 26251’ OR rwj26251		5070
40	'bendamustine'/syn OR ‘cimet 3393’ OR cytostasan OR cytostasan OR cytostasane OR ‘imet 3393’ OR levact OR ribomustin OR treanda		2122
41	'alemtuzumab'/syn OR campath OR ‘ldp 103’ OR ‘ldp103’ OR lemtrada OR mabcampath		10140
42	'rituximab'/syn OR ‘idec c2b8’ OR mabthera OR reditux OR rituxan OR rituxin		39132
43	'ofatumumab'/syn OR arzerra OR ‘gsk 1841157’ OR gsk1841157 OR ‘humac CD20’ OR HuMax-CD20 OR ‘HuMax CD20’ OR HuMaxCD20		1175
44	'lenalidomide'/syn OR ‘cc 5013’ OR cc5013 OR ‘cdc 501’ OR 'cdc 5013' OR cdc501 OR cdc5013 OR ‘enmd 0997’ OR enmd0997 OR ‘imid 3’ OR imid3 OR revimid OR revlimid		8459

45	'gs 1101'/syn OR ‘cal 101’ OR cal101 OR ‘gs 1101’ OR gs1101 OR idelalisib		511
46	'obinutuzumab'/syn OR afutuzumab OR ‘ga 101’ OR ga101 OR 'r 7159' OR r7159 OR ‘ro 5072759’ OR ro5072759		405
47	'cyclophosphamide'/syn OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR ‘cyclofos amide’ OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR ‘cyclophosphamide isopac’ OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR ‘cytoxan lyophilized’ OR ‘endocyclo phosphate’ OR endoxan OR endoxan-asta OR ‘endoxan asta’ OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR ‘lyophilized cytoxan’ OR mitoxan OR neosan OR neosar OR noristan OR ‘nsc 26271’ OR ‘nsc 2671’ OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid		171998
48	cop NEAR/2 regimen		75
49	chop NEAR/2 regimen		800
50	Or/37-49		219215
49	#27 AND #34 AND #48 AND [27-2-2013]/sd NOT [16-4-2014]/sd	Combined results	1066

Search strategy for Medline - In Process (via PubMed) – Year 2013 – 16 April 2014

The Pubmed Library was searched between 2013 and 16 April 2014. The search was conducted using the search terms summarised in the table below.

3.1.1.6 No	3.1.1.7 Query	3.1.1.8 Results
1	"Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh terms]	11520
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]	18564
3	Search (#1 or #2)	18564
4	(chlorambucil OR amboclorin OR ‘cb 1348’ OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088)	4654
5	(fludarabine OR fludara)	4300
6	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR ‘rwj 26251’ OR rwj26251)	1628
7	(bendamustine OR ‘cimet 3393’ OR cytostasan	499

	OR cytostasan r OR cytostasane OR ‘imet 3393’ OR levact OR ribomustin OR treanda)	
8	(alemtuzumab OR campath OR ‘ldp 103’ OR ‘ldp103’ OR lemtrada OR mabcampath)	2291
9	(rituximab OR ‘idec c2b8’ OR mabthera OR reditux OR rituxan OR rituxin)	12250
10	(ofatumumab OR arzerra OR ‘gsk 1841157’ OR gsk1841157 OR ‘humac CD20’ OR HuMax-CD20 OR ‘HuMax CD20’ OR HuMaxCD20)	7838
11	(lenalidomide OR ‘cc 5013’ OR cc5013 OR ‘cdc 501’ OR cdc 5013 OR cdc501 OR cdc5013 OR ‘enmd 0997’ OR enmd0997 OR ‘imid 3’ OR imid3 OR revimid OR revlimid)	2150
12	(‘gs 1101' OR ‘cal 101’ OR cal101 OR ‘gs 1101’ OR gs1101 OR idelalisib)	74
13	(obinutuzumab OR afutuzumab OR ‘ga 101’ OR ga101 OR r 7159 OR r7159 OR ‘ro 5072759’ OR ro5072759)	81
14	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR ‘cyclofos amide’ OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR ‘cyclophosphamide isopac’ OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR ‘cytoxan lyophilized’ OR ‘endocyclo phosphate’ OR endoxan OR endoxan-asta OR ‘endoxan asta’ OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR ‘lyophilized cytoxan’ OR mitoxan OR neosan OR neosar OR noristan OR ‘nsc 26271’ OR ‘nsc 2671’ OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid)	2690626
15	“cop regimen”	44
16	“chop regimen”	374
17	OR/4-16	2713294
18	Search (#3 AND #17)	5078
19	Search (#18 AND (in process[sb] OR pubstatusaheadofprint))	182

Search strategy for Cochrane Library – Year 2013 – 16 April 2014

The Cochrane Library was searched between 2013 and 16 April 2014. The search was conducted using the search terms summarised in the table below.

3.1.1.9 No.	**3.1.1.10 Query**	**3.1.1.11 Results**
1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic,	22
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	12836
5	(chronic OR cronic OR 'well differential')	67410

3.1.1.9 No.	3.1.1.10 Query	3.1.1.11 Results
6	#4 AND #5	2129
7	OR/1-3, 6	3174
8	MeSH descriptor: [Chlorambucil] explode all trees	227
9	(chlorambucil OR amboclorin OR ‘cb 1348’ OR cb1348 OR chlorambacil OR chloraminophene OR chlorbutin OR chloroambucil OR chorambucil OR ecloril OR leuceran OR leukeran OR linfolysin OR lympholysin OR nsc 3088 OR nsc3088):ab,ti,kw	436
10	(fludarabine OR fludara):ab,ti,kw	442
11	MeSH descriptor: [Cladribine] explode all trees	65
12	(cladribine OR biodribin OR ntocel OR leustat OR leustatin OR leustatine OR litak OR litax OR movectro OR mylinax OR ‘rwj 26251’ OR rwj26251): ab,ti,kw	148
13	(bendamustine OR ‘cimet 3393’ OR cytostasan OR cytostasan r OR cytostasane OR ‘imet 3393’ OR levact OR ribomustin OR treanda): ab,ti,kw	50
14	(alemtuzumab OR campath OR ‘ldp 103’ OR ‘ldp103’ OR lemtrada OR mabcampath): ab,ti,kw	222
15	(rituximab OR ‘idec c2b8’ OR mabthera OR reditux OR rituxan OR rituxin): ab,ti,kw	889
16	(ofatumumab OR arzerra OR ‘gsk 1841157’ OR gsk1841157 OR ‘humac CD20’ OR HuMax-CD20 OR ‘HuMax CD20’ OR HuMaxCD20): ab,ti,kw	28
17	(lenalidomide OR ‘cc 5013’ OR cc5013 OR ‘cdc 501’ OR cdc 5013 OR cdc501 OR cdc5013 OR ‘enmd 0997’ OR enmd0997 OR ‘imid 3’ OR imid3 OR revimid OR revlimid): ab,ti,kw	166
18	(‘gs 1101' OR ‘cal 101’ OR cal101 OR ‘gs 1101’ OR gs1101 OR idelalisib): ab,ti,kw	5
19	(obinutuzumab OR afutuzumab OR ‘ga 101’ OR ga101 OR r 7159 OR r7159 OR ‘ro 5072759’ OR ro5072759): ab,ti,kw	19
20	MeSH descriptor: [Cyclophosphamide] explode all trees	3888
21	(cyclophosphamide OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR ‘cyclofos amide’ OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR ‘cyclophosphamide isopac’ OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cyclostin n OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR ‘cytoxan lyophilized’ OR ‘endocyclo phosphate’ OR endoxan OR endoxan-asta OR ‘endoxan asta’ OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR ‘lyophilized cytoxan’ OR mitoxan OR neosan OR neosar OR noristan OR ‘nsc 26271’ OR ‘nsc 2671’ OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid): ab,ti,kw	6763

3.1.1.9 No.	3.1.1.10 Query	3.1.1.11 Results
22	cop NEAR/2 regimen	21
23	chop NEAR/2 regimen	129
24	OR/8-23	8653
25	#7 and #24 from 2013 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	36

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

None

10.4.6 The inclusion and exclusion criteria.

Only studies with the full-text published in English language were included in the review. Studies with an English abstract where the full-text is in non-English language were not included in the review. Other inclusion and exclusion criteria used in the systematic review and in the update are summarised in the table below.

3.1.1.12	3.1.1.13 Inclusion	3.1.1.14 Rationale/comments
3.1.1.15 Study design		
Controlled clinical trials (randomised and non-randomised, any blinding status and phase of study)	Include	• RCTs are the gold standard of clinical evidence, minimising the risk of confounding factors and allowing the comparison of the relative efficacy of the interventions • Non-RCTs (comparative clinical trials without randomisation) will supplement evidence provided by the RCTs
Prospective cohort studies	Exclude	• Observational studies have a higher risk of bias
Retrospective cohort studies		
Single-arm studies		
Case studies		
Case reports		
Case-control study		
Cross-sectional study		
Population		
Age	Adults	CLL is usually diagnosed in adult patients, with median age of diagnosis being 70 years. CLL is rarely diagnosed in children
Gender	Both women and men	CLL can occur both in males and females
Race	Any	Focusing the inclusion on a particular race(s) would pose problems in conducting reviews and would limit the findings of the review to a particular race only. Moreover, the objective of the review does not restrict it to any particular race
Disease		
Untreated CLL	Include	Studies which enroll a mixed population of CLL and other types of cancers (e.g. follicular lymphoma) will only be included if there is a

		subgroup data for the disease of interest
Line of therapy		
untreated CLL or receiving first-line treatment (i.e. treatment-naïve patients)	Include	Studies that enroll a mixed population of both treatment naïve and pre-treated patients will only be included if subgroup data for the first-line therapy is reported.
Patients with relapsed/refractory CLL or those receiving second-line or later-lines of treatment (i.e. pre-treated for CLL)	Exclude	
Interventions		
• Studies investigating the role of radiotherapy, chemo-radiotherapy • Interventions used to control the symptoms of the disease such as erythropoietin to treat anaemia, antibiotics to treat infections, and various types of pain medication • Adjuvant or neo-adjuvant therapy	Exclude	
• Interventions will be included both as monotherapies and as combination therapies with any other pharmacological intervention • Studies evaluating different doses of the same intervention will be included • Inclusion will not be restricted to the licensed dose of intervention	Include	See table of included interventions (below)
Comparators		
• Another active included intervention (i.e. head-to-head trials of included interventions) • Placebo/best supportive care (BSC)	Include	See table of included comparators (below)

Included interventions (in combination or as single agent)

3.1.1.16 Generic name	3.1.1.17 Brand name
Chlorambucil	Leukeran®, Chloraminophen®
Fludarabine	Fludara®
Cladribine	Leustat®, LITAK®
COP	-
CHOP	-
Bendamustine	Levact®
Alemtuzumab	Campath®, MabCampath®

Rituximab	Rituxan®, MabThera®
Ofatumumab	Arzerra®, HuMax-CD20®
Lenalidomide	Revlimid®
Ibrutinib	-
GS-1101	-
GA101 (obinutuzumab)	-

Included comparators

3.1.1.18 Intervention	**3.1.1.19 Comparator**	**3.1.1.20 Included or not included?**
Intervention list drug A (e.g. rituximab)	Intervention list drug B (e.g. alemtuzumab)	Include
Intervention list drug A (e.g. rituximab)	Non-intervention list drug (e.g. oblimersen)	Exclude (comparator not of interest)
Intervention list drug A + Other intervention list drug B (e.g. rituximab + alemtuzumab)	Intervention list drug C (e.g. fludaribine)	Include
Intervention list drug A + Other intervention list drug B (e.g. rituximab + alemtuzumab)	Intervention list drug A (e.g. rituximab)	Include
Intervention list drug A + Non-intervention list drug (e.g. rituximab + oblimersen)	Intervention list drug A (e.g. rituximab)	Include
Intervention list drug A + Non-intervention list drug (e.g. rituximab + oblimersen)	Non-intervention list drug (e.g. oblimersen)	Exclude (comparator not of interest)
Intervention list drug dose 1 (e.g. rituximab)	Intervention list drug dose 2 (e.g. rituximab)	Include
Intervention list drug (e.g. rituximab)	Placebo	Include
Intervention list drug (e.g. rituximab)	BSC	Include
Intervention list drug A (e.g. rituximab)	Intervention list drug B + BSC (e.g. fludaribine + BSC)	Include
Intervention list drug (e.g. rituximab)	Non-drug intervention (radiotherapy/surgery)	Exclude (comparator not of interest)
Non-drug intervention (e.g. radiotherapy)	Surgery	Exclude (intervention and comparator not of interest)
Adjuvant intervention drug A (e.g. rituximab)*	Placebo/BSC	Exclude (intervention not of interest)
Intervention list drug A + Non-drug intervention (e.g. rituximab + Surgergy/radiotherapy)	Intervention list drug B (e.g. fludaribine)	Exclude (combination with intervention not of interest)
Intervention list drug (e.g. rituximab)	No treatment or wait and watch principle	Include

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study name	Randomisation and allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcomes selection and reporting	Statistical analysis
Systematic review						
MaBLe study	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported.	Low risk; Patient characteristics between the two treatment arms were well balanced.	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Not clear; Withdrawals and reasons for withdrawals were not reported.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study.	Not clear; This was a conference abstract. No data for method of analysis and handling of missing data were reported.
CLLARC CLL5 trial	Not clear; This was a randomised trial. Method of randomisation and allocation concealment was not reported.	Not clear; Information regarding blinding was not reported. This was a conference abstract thus limited information was reported.	Not clear; It was not clear whether the baseline characteristics were comparable across the treatment groups.	Not clear; The reasons for withdrawals were not reported.	Not clear; It was not clear whether the authors measured more outcomes than reported in the protocol.	Not clear; The method of efficacy and safety analysis was not reported.
Eradat 2012	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported. Stratification was done by Binet stage and high-risk cytogenetic features and then randomised.	Low risk; Baseline characteristics and prognostic factors for the randomised patients were generally balanced among the three treatment arms.	High risk; This was an open label trial.	Not clear; Withdrawals were not reported.	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not.	Not clear; Efficacy and safety analysis type was unclear.

CLL2007FMP trial	Not clear; This was a randomised study, but method of generation of randomisation was not reported. Randomisation was done centrally through a central dynamic randomisation process using IGHV mutational status and 11q deletion as stratification factors	Low risk; There were no significant differences regarding the main clinical features and risk categories.	Not clear; Details regarding blinding was not reported.	Low risk; Withdrawals and reasons for withdrawals were adequately reported.	Low risk; With reference to 'NCT00564512', authors measured all the outcomes that were pre-specified in the protocol.	Low risk; mITT analysis was used for efficacy and ITT analysis was used for safety outcomes. Statistical details and sample size calculations were reported
HOVON68 CLL trial	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported.	Low risk; Both the arms were comparable between the baseline characteristics	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Not clear; Withdrawals and reasons for withdrawals were not reported.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study.	Not clear; The number of patients randomised to each treatment arm was unclear. No data for method of analysis and handling of missing data were reported.
Hx-CD20-407 trial	Not clear; This was a randomised study. Method of randomisation and allocation concealment not reported.	Low risk; Treatments groups were generally similar in terms of baseline characteristics.	Not clear; This was an open-label study but response was assessed by IRC	Low risk; The withdrawals were adequately reported for the treatment groups. ITT analysis was employed for safety as well as efficacy analysis.	High risk; The authors measured lesser outcomes as reported in clinical trial protocol (NCT00410163).	Low risk; ITT analysis was carried out for safety and efficacy analysis.

GCLLSG CLL8 trial	Low risk; This was a randomised study. Patients were randomly assigned in a one-to-one ratio in a block size of four stratified by centre, and then by country and Binet stage since the first amendment (July 27, 2004), using a randomisation list that was computer generated.	Low risk; The treatment groups were generally similar in terms of baseline characteristics.	High risk; This was an open-label study.	Low risk; An ITT analysis was used for efficacy evaluations. The reasons for discontinuations were not fully reported.	Low risk; According to NCT00281918, the authors measured all the outcomes as reported in the protocol.	Low risk; Efficacy and safety analyses were performed on ITT and mITT population. Exploratory analyses of the secondary endpoints were also done. To confirm the primary analysis, a two-sided log-rank test stratified by Binet stage was done before treatment.
PALG-CLL3 study	Not clear; This was a randomised study. Method of randomisation was not reported. Central randomisation was performed in the Department of Hematology, Medical University of Lodz, and the participating centres were informed about treatment assignment by phone or fax.	Low risk; The treatment arms were well balanced in regard to patients' age, sex, CLL stage, blood counts, and prognostic factors.	Not clear; Details regardig blinding were not clear	Low risk; Withdrawals were adequately reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not.	Low risk; Efficacy and safety analyses were performed on mITT population.
CLL-5 trial	Not clear; This was a randomised study, but method of generation of randomisation was not reported. Randomisation was done centrally.	Low risk; There were no significant differences regarding the main clinical features and risk categories.	Not clear; Details regarding blinding was not reported.	Low risk; Data regarding withdrawals was well reported.	Low risk; With reference to 'ISRCTN 36294212', authors measured all the outcomes that were pre-specified in the protocol.	Low risk; mITT analysis was used both for efficacy and safety outcomes.

Knauf 2009	Not clear; This was a randomised study. Method of randomisation and concealment allocation was not described.	Low risk; Authors mentioned that overall, patient characteristics were well balanced between the groups.	Not clear; This was an open-label study, but response was assessed by IRC while other outcomes OS, PFS was investigator`s assessed.	Not clear; Withdrawals were reported but reasons for withdrawals were not described adequately.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study as protocol or clinical trial registry.	Low risk; The statistical analysis was performed on the intention-to-treat (ITT) patient population. The safety population consisted of all patients who received at least one dose of study medication.
THE OWN STUDY	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported.	Not clear; Baseline characteristics were not separately for treatment groups.	Not clear; Details regarding blinding were not reported	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Not clear; Analysis type was unclear.
CAM307 study	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported.	Low risk; Baseline demographic and disease characteristics were well balanced between the groups.	Low risk; This was an open label study, 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	Not clear; Withdrawals and reasons for withdrawals were not appropriately reported.	Low risk; According to NCT00046683, the authors measured all the outcomes as they reported in the protocol	Low risk; Efficacy analysis and safety analysis were performed on ITT and modified ITT population, respectively.

UK LRF CLL4 trial	Low risk; This was a randomised trial. Patients were randomised by computer and was balanced over by stage, age (younger than 60 years, 60-69 years and 70 years and older) and sex by the method of minimisation. Clinicians telephoned the clinical trial service unit for treatment allocation	Low risk; The treatment arms were balanced in terms of baseline and disease characteristics	Not clear; It was unclear whether patients were blinded to the treatment or not. However, the clinicians treating the patients and assessing the response were not blinded	Low risk; An mITT analysis was used for efficacy evaluations. Details of withdrawals were not reported adequately	Low risk; The authors reported those outcomes as measured in the protocol number, NCT58585610	Low risk; Efficacy and safety analysis were reported by mITT population
E2997 trial	Not clear; This was a randomised study and the randomisation process was done centrally.	Low risk; There were no significant differences regarding the main clinical features and risk categories.	Not clear; Details regarding blinding was not reported.	Not clear; The reasons for withdrawals were not adequately reported.	Not clear; It was not clear whether the authors measured more or less outcomes than reported in the protocol.	Low risk; mITT analysis was used both for efficacy and safety outcomes.
PALG CLL2 trial	Not clear; This was a randomised trial but the method of randomisation was not reported but allocation concealment was adequate with randomisation centrally done	Low risk; The author reported demographics and clinical characteristics which were similar with respect to age, sex distribution, disease stage, and peripheral blood count parameters in all the three groups	Not clear; Details regarding blinding were not reported	Low risk; Reasons for withdrawals were reported	Not clear; It was not clear whether authors measured more outcomes than they reported in the study as protocol or clinical trial registry record was not provided	Low risk; response rates were measured by mITT analysis

German group CLL4 trial	Not clear; The method of generation of randomisation was not reported. However, concealment of treatment allocation was adequate as randomisation was performed by the Institute of Medical Statistics & Epidemiology, Technical University, Germany.	Low risk; Comparison of patients in the two treatment arms indicated no significant difference regarding the main clinical features and the risk categories.	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Not clear; The withdrawals, completers and the specific reasons for withdrawal were not adequately reported.	Low risk; According to NCT00276848, the authors measure all the outcomes as they reported in protocol.	Not clear; No data for method of analysis and handling of missing data were reported.
PALG CLL1 trial	Not clear; this was a randomised study, but method of generation of randomisation was not reported. Central randomisation procedure for the assignment to either treatment arm was done by telephone, fax, or e-mail.	Low risk; There were no significant differences regarding the main clinical features between the two groups.	High risk; This was an open label study.	Not clear; Overall Withdrawals and reasons for withdrawals were not reported.	Not clear; It was unclear if the authors measured more outcomes than reported.	Not clear; Method of analysis was unclear.
French Group CLL trial	Not clear; The study was randomised but the method of randomisation was not reported. Allocation concealment was adequate performed centrally by telephone	Low risk; The author reported about demographics and clinical characteristics as per the disease stage for all the arms	High risk; It was reported that the procedure of randomisation to the three arms was not blinded	Not clear; Reasons for withdrawals were not reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; The safety analysis was done using ITT population while efficacy analysis type was not clear

CALGB 9011 trial	Not clear; The study was randomised. However, the method of randomisation was not reported. The allocation concealment was adequate as it was accomplished centrally.	Low risk; There were no imbalances among the three groups with respect to clinical features and risk categories.	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Low risk; An ITT analysis was used for efficacy and mITT for safety evaluation. However, resons for witdrawals were not reported adequately.	Not clear; It was unclear whether author measured more outcomes than they reported.	Low risk; An ITT analysis was used for efficacy and mITT for safety evaluation.
Dighiero 1998	Not clear; The study was randomised but the method of randomisation was not reported. Allocation concealment was adequate performed centrally by telephone	Low Risk; There were no significant differences between the groups in either trial at the time of randomisation	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Not clear; Withdrawals and reasons for withdrawals were not reported.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study.	Not clear; No data for method of analysis and handling of missing data were reported.
Brugiatelli 1995	Not clear; This was a randomised study, but method of randomisation and allocation concealment were not reported	Low risk; Both treatment groups were well balanced.	Not clear; Details regrding blinding was not reported	Not clear; Withdrawals were not reported	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; ITT analysis was used for efficacy measures.
EORTC LCG trial	Not clear; The method of generation of randomisation and concealment of treatment allocation was not reported	Low risk; All baseline parameters were well balanced between the treatment groups	Not clear; Blinding details were not reported	Not clear; Withdrawals were not reported	Not clear; There was no evidence to suggest that the authors measured more than they reported in the protocol	Not clear; Analysis type for efficacy and safety unclear
Spriano 2000	Not clear; This was a randomised study. Method of randomisation and allocation concealment was not reported.	Not clear; This was a conference abstract and author has not reported the demographic and baseline characteristics of included patients.	Not clear; It was not reported whether the care providers, participants, or outcome assessors were blinded to treatment allocation.	Not clear; Withdrawals and reasons for withdrawals were not reported.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study.	Not clear; This was a conference abstract. No data for method of analysis and handling of missing data were reported.

Karlsson 2007	Not clear; This was a conference abstract with limited information	Low risk; There was no significant differnce in baseline and disease characteristics between the treatment groups	Not clear; This was a conference abstract with limited information	Not clear; An ITT analysis was used for efficacy evaluations	Not clear; This was a conference abstract with limited information	Low risk; An ITT analysis was used for efficacy evaluations
Rummel 2003	Not clear; This was a randomised trial. Method of randomisation and allocation was not reported in this conference abstract	Not clear; It was unclear whether both treatment arms were balanced or not on baseline characteristics. However, it was reported that cytogenetic abnormalities were well balanced between the group	Not clear; Details regarding blinding was not reported	Not clear; This was a conference abstract. The reasons for withdrawals were not reported.	Not clear; It was not clear whether the authors measured more or less outcomes than reported in the protocol.	Not clear; Total number of patients randomised was reported. However, number of patients randomised to each treatment arm was not reported.
CALGB 9712 trial	Not clear; The study was randomised. However, the method of randomisation and allocation concealment were not reported.	Low risk; The baseline characteristics were comparable across the treatment groups.	Not clear; Information regarding blinding was not reported.	Not clear; The reasons for withdrawals were not reported.	Not clear; It was not clear whether the authors measured more outcomes than reported in the protocol.	Low risk; The efficacy and safety analysis were based on ITT population.
IGCI CLL-02 trial	Not clear; The study was randomised. However, the method of randomisation and allocation concealment was not reported.	Low risk; Binet stage was significantly differeny across the two groups. (p=0.004)	Not clear; Information regarding blinding was not reported.	Not clear; The reasons for withdrawals were not reported.	Not clear; It was not clear whether the authors measured more outcomes than reported in the protocol.	Low risk; The efficacy analysis was carried out by ITT whereas safety analysis method was unclear.
Schweighofer 2009	Not clear; This was a randomised trial. Method of randomisation and allocation concealment was not reported	Low risk; There was no significant difference in the baseline characteristics reported between the two treatment arms	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The safety and efficacy analysis was done using mITT population
Update of the systematic review						

GCLLSG CLL10 trial	Not clear; The study was randomised. However, the method of randomisation was not reported.	Low risk; There were significantly more pts with unmutated IGVH in the BR arm (68%) in comparison to the FCR arm (55%; p=0.003). All other characteristics including median age were well balanced	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The efficacy analysis was carried out by ITT whereas safety analysis method was unclear
PALG CLL4 trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups.	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Not clear; Total number of patients randomised was reported. However, number of patients randomised to each treatment arm was not reported
GCLLSG CLL7 trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups.	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The efficacy and safety analysis was carried out by ITT
LLC 2007 SA trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Not clear; It was unclear whether both treatment arms were balanced or not on baseline characteristics.	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Not clear; Total number of patients randomised was reported. However, number of patients randomised to each treatment arm was not reported

Mulligan 2014	Low risk; This was a randomised trial. Patients were randomised using closed envelopes	Low risk; There was no signifi cant difference in age, sex, clinical stage by either Rai or Binet system or performance status between the three treatment cohorts	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The efficacy and safety analysis was carried out by ITT
ARCTIC trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups	Low risk; This was an open label study, however an independent response review panel, determined response for each patient	Not clear; Withdrawals and reasons for withdrawals were not reported	High risk; The authors measured lesser outcomes as reported in clinical trial protocol (NCT00254410)	Low risk; The efficacy and safety analysis was carried out by ITT
OMB110911 trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups	Low risk; This was an open label study, however an independent response review panel, determined PFS for each patient	Not clear; Withdrawals and reasons for withdrawals were not reported	High risk; The authors measured lesser outcomes as reported in clinical trial protocol (NCT00748189)	Not clear; Total number of patients randomised was reported. However, number of patients randomised to each treatment arm was not reported
Nikitin 2013	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups	Not clear; Blinding was not reported	Low risk; An ITT analysis was used for efficacy and mITT for safety evaluation. Reasons for witdrawals were reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The efficacy and safety analysis was carried out by ITT

ADMIRE trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups	Low risk; This was an open label study, however an independent response review panel, determined response for each patient	Not clear; Rasons for withdrawals were not reported	High risk; The authors measured lesser outcomes as reported in clinical trial protocol (NCT00410163)	Low risk; The efficacy and safety analysis was carried out by ITT
CLL11 trial	Low risk; This was a randomised trial. Patients were randomised by computer. Clinicians telephoned the clinical trial service unit for treatment allocation	Low risk; The baseline characteristics were comparable across the treatment groups	Low risk; This was an open label study, 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	Low risk; An ITT analysis was used for efficacy and mITT for safety evaluation	Low risk; According to NCT01010061, NCT01998880, and NCT02053610, the authors measure all the outcomes as they reported in protocol	Low risk; The efficacy and safety analysis was carried out by ITT and SAP
CLL M1 trial	Not clear; Recruitment is still ongoing for this study	Not clear; Recruitment is still ongoing for this study	Low risk; This was a double-blind trial	Not clear; Recruitment is still ongoing for this study	Not clear; Recruitment is still ongoing for this study	Not clear; Recruitment is still ongoing for this study
CLL1 trial	Not clear; The study was randomised. However, the method of randomisation was not reported	Not clear; It was unclear whether both treatment arms were balanced or not on baseline characteristics.	High risk; This was an open label study	Not clear; Withdrawals and reasons for withdrawals were not reported	Not clear; It was unclear if the authors measured more outcomes than reported	Low risk; The efficacy and safety analysis was carried out by ITT and SAP
Foa 2014	Not clear; The study was randomised. However, the method of randomisation was not reported	Low risk; The baseline characteristics were comparable across the treatment groups	High risk; This was an open label study	Low risk; An ITT analysis was used for efficacy and mITT for safety evaluation	Low risk; According to NCT00738374, the authors measure all the outcomes as they reported in protocol	Low risk; The efficacy and safety analysis was carried out by ITT

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

(NOTE: not all sections may be applicable)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

There are no non-RCTs which are relevant to the decision problem therefore no additional searches were undertaken.

10.6.2 The date on which the search was conducted.

No searches were undertaken.

10.6.3 The date span of the search.

No searches were undertaken.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No searches were undertaken.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No searches were undertaken.

10.6.6 The inclusion and exclusion criteria.

No searches were undertaken.

10.6.7 The data abstraction strategy.

No searches were undertaken.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No searches were undertaken.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Safety was a secondary endpoint in the CLL11 study therefore no additional searches were undertaken.

10.8.2 The date on which the search was conducted.

No searches were undertaken.

10.8.3 The date span of the search.

No searches were undertaken.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No searches were undertaken.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No searches were undertaken.

10.8.6 The inclusion and exclusion criteria.

No searches were undertaken.

10.8.7 The data abstraction strategy.

No searches were undertaken.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No searches were undertaken.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

- NHS EED.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY) and NHS EED were searched for studies assessing the cost-effectiveness of obinutuzumab.

10.10.2 The date on which the search was conducted.

The Centre for Reviews and Dissemination's website and the PROQUEST website were searched on 13 May 2014.

10.10.3 The date span of the search.

1992 – 13 May 2014

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy for Embase® and MEDLINE® – Year 1992 – 13 May 2014.

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised in the table below.

3.1.1.21	**3.1.1.22 Search History**	**3.1.1.23 Facet**	**3.1.1.24 Results**
S1	(cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness) AND la.exact("ENG")	Modelling	820607
S2	(economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost[*1] OR direct ADJ cost[*1] OR direct ADJ service ADJ cost[*1] OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util[*3] OR quality ADJ of ADJ life OR QALY OR QALYs OR QOL OR economic$1 ADJ models OR medical ADJ economics OR pharmaceutical ADJ economics) AND la.exact("ENG")		873648
S3	(Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR/4 Evaluation) OR EMB.EXACT.EXPLODE("ECONOMIC EVALUATION") OR EMB.EXACT.EXPLODE("PHARMACOECONOMICS") OR		387763

	EMB.EXACT.EXPLODE(“COST UTILITY ANALYSIS”) OR EMB.EXACT.EXPLODE(“QUALITY ADJUSTED LIFE YEAR”) AND la.exact("ENG")		
S4	(TI(Markov OR decision ADJ analys[*2]) OR AB(Markov OR decision ADJ analys[*2])) AND la.exact("ENG")		25963
S5	S1 OR S2 OR S3 OR S4		1453220
S6	chronic lymphocitic leukemia	Disease Facet	18
S7	chronic lymphatic leukemia		22411
S8	S6 OR S7		22422
S9	'obinutuzumab'/syn OR afutuzumab OR ‘ga 101’ OR ga101 OR r 7159 OR r7159 OR ‘ro 5072759’ OR ro5072759	Intervention Facet	23758
S10	S5 AND S8 AND S9	Combined Result	17

Search strategy for NHS EED and EconLIT – Year 1992 – 13 May 2014

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised below.

“COST EFFECTIVENESS ANALYSIS” OR “COST UTILITY ANALYSIS” OR “COST BENEFIT ANALYSIS” OR “ECONOMIC MODEL” OR “DE NOVO MODELLING” OR “COST MINIMISATION ANALYSIS” AND (LEUKEMIA OR LYMPHOCYTIC OR CHRONIC OR B-CELL) AND (OBINUTUZUMAB OR AFUTUZUMAB OR GA 101)

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

One study was identified across the four databases. This was determined as relevant by the independent reviewers after being assessed against the inclusion criteria. The quality assessment of the one cost-effectiveness study of GA101 is presented below.

Quality assessment of cost-effectiveness studies

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Not justified.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Pivotal trial (CLL11) comparators used
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Utilities based on NICE TA174
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Not clear	
18. Were currency and price data recorded?	Not clear	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY) and NHS EED were searched for retrieving utility values in CLL (Chronic Lymphocytic Leukemia) in order to inform a health economic model.

10.12.2 The date on which the search was conducted.

The searches were conducted on the 28th January 2014.

10.12.3 The date span of the search.

1992 – 28th January 2014

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Set#	**Searched for**	**Databases**	**Results**
S1	QUALITY-ADJUSTED-LIFE-YEAR OR QALY[*2] OR QALIES	Embase®, Embase® Alert, MEDLINE®	15930*
S2	SF-6D OR EQ-5D OR EQ-5D-5L OR EUROQOL	Embase®, Embase® Alert, MEDLINE®	6968*
S3	"UTILITY VALUES" OR "UTILITY SCORES"	Embase®, Embase® Alert, MEDLINE®	1667*
S4	"TIME TRADE OFF" OR "STANDARD GAMBLE"	Embase®, Embase® Alert, MEDLINE®	1470*
S5	S1 OR S2 OR S3 OR S4	Embase®, Embase® Alert, MEDLINE®	23112*
S6	CHRONIC LYMPHOCITIC LEUKEMIA	Embase®, Embase® Alert, MEDLINE®	19*
S7	CHRONIC LYMPHATIC LEUKEMIA	Embase®, Embase® Alert, MEDLINE®	30459*
S8	S6 OR S7	Embase®, Embase® Alert, MEDLINE®	30465*

S9	S5 AND S8	Embase®, Embase® Alert, MEDLINE®	55*
S13		Embase®, Embase® Alert	

* Duplicates are removed from your search, but included in your result count.

° Duplicates are removed from your search and from your result count.

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.12.6 The inclusion and exclusion criteria.

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in the table below.

Inclusion and exclusion criteria for vaualtion of health effects

Parameter	**Inclusion Criteria**	**Exclusion Criteria**
Population	Patients with previously untreated Chronic Lymphocytic Leukemia (CLL)	Non CLL patients
Intervention	Any	-
Comparator	Any	-
Outcome	Utilities derived via a recognised preference based instrument (EQ5D or SF6D), standard gamble or time trade off conducted using a sample of the general public	Other non-preference based HRQoL measures
Study Design	Utility Studies, Cost-Effectiveness studies containing utility values	-

10.12.7 The data abstraction strategy.

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes

over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), and NHS EED were searched for studies assessing resource use for different health states in CLL.

10.13.2 The date on which the search was conducted.

The Centre for Reviews and Dissemination's website and the PROQUEST website were searched on 13 May 2014.

10.13.3 The date span of the search.

1992 – 13 May 2014.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategy for Embase, Embase Alert and MEDLINE.

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised in the table below.

3.1.1.25 #	3.1.1.26 Search History	3.1.1.27 Facet	3.1.1.28 Results
S1	(socioeconomics OR cost ADJ benefit ADJ analysis OR cost ADJ effectiveness ADJ analysis OR cost ADJ of ADJ illness OR cost ADJ control OR economic ADJ aspect OR financial ADJ management OR health ADJ care ADJ cost OR health ADJ care ADJ financing OR health ADJ economics ADJ hospital ADJ cost OR (fiscal OR financial OR finance OR funding) OR cost ADJ minimi?ation ADJ analysis OR (cost ADJ ESTIMATE$) OR (cost ADJ variable$) OR (unit ADJ cost$)) AND la.exact("ENG")	Resource use	318343
S2	(resource ADJ utilis?ation OR nhs ADJ cost$1 OR resource) AND la.exact("ENG")		515877
S3	S1 OR S2		797095
S4	chronic lymphocitic leukemia	Disease Facet	18
S5	chronic lymphatic leukemia		22411
S6	S4 OR S5		22422
S7	(england OR wales OR scotland OR united ADJ kingom OR uk) AND la.exact("ENG")	Country Facet	4292082
S8	S3 AND S6 AND S7	Combined Result	33

Search strategy for NHS EED.

The libraries were searched between 1992 and 13 May 2014. The search was conducted using the search terms summarised below.

“RESOURCE UTILISATION OR NHS REFERENCE COSTS OR COST ANALYSIS” AND *TITLE ONLY* (LEUKEMIA OR LYMPHOCYTIC OR CHRONIC OR B-CELL)

AND *TITLE ONLY* (ENGLAND OR WALES OR SCOTLAND OR UNITED ADJ KINGOM OR UK).

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.13.6 The inclusion and exclusion criteria.

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in the table below.

Inclusion and exclusion criteria for resource identification

Is the paper in English?	No – Exclude
Does the abstract mention one or more resource use terms (Costs, Resources, Economics)?	No – Exclude
Do resources mentioned apply to the United Kingdom?	No – Exclude
Is the disease area CLL?	No – Exclude
Is the paper a literature review of existing resource use used in CLL?	Yes - Exclude
Once a record has made it to here, it is retrieved and read in entirety and assessed against the following criteria:	
Are resources derived directly from a large scale study (>100)?	No – Exclude
Is the study less than 5 years old?	No – Exclude

10.13.7 The data abstraction strategy

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

10.14 Appendix 14: WinBUGS code and outputs (sections 6 and 7)

When performing Bayesian analyses through Gibbs sampling it is important to check whether the model converged. This was done for three different sets of initial values. That is, three chains of widely different (yet possible) initial values were run for each Network Meta Analysis (NMA) model. The set of initial values can be found in this appendix. The diagnostics displayed by WinBUGS were used to visually inspect convergence. Posteriors from the three different chains were examined visually for spikes and unwanted peculiarities. They all sample from comparable posteriors.

The initial “burn-in” had 100,000 iterations. The posterior samples were drawn from 500,000 iterations. The Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation was observed to be very small, suggesting that the number of iterations was sufficiently large.

The choice of reference treatment in the NMA was Clb because it was the most common treatment in the network. The choice of prior distributions is shown in the WinBUGS code below.

The full set of results (WinBUGS output) can be found in this appendix after the WinBUGS model code next.

3.2 WinBUGS Code used for the NMAs

The below code was used to perform the NMA. It is based on the code published by (Dias, Welton, Sutton, & Ades, 2013)
http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%20Mar2013.pdf

Fixed effect NMA model (NOT adjusted for age)
Normal likelihood, identity link, trial-level data given as lnHRs.

```
model{
for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
        }
     }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
     }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
for(i in 1:(ns2+ns3)){                #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
     }
  }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
HR[c,k] <- exp(d[k] - d[c])
lnHR[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
 rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
}
# *** PROGRAM ENDS
```

Random effects NMA model (with vague prior for between-trial SD)

```
model{
for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
        }
     }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                              }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
for(i in 1:(ns2+ns3)){                    #   LOOP THROUGH ALL STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
     }
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,2)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
}
            # *** PROGRAM ENDS
```

Random effects NMA model (with weakly-informative prior for between-trial SD)

Same as RE NMA above but replacing the line:

```
sd ~ dunif(0,2)     # vague prior for between-trial SD
```

Replace with:

```
sd ~ dnorm(0,prec2)I(0,) # weakly-informative prior for between-trial SD
prec2<-pow(0.32,-2)
```

Fixed effect meta-regression NMA model (age-adjusted model)

Normal likelihood, identity link, trial-level data given as lnHRs.

```
model{
for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
        }
     }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
     }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
for(i in 1:(ns2+ns3)){                #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
# model for linear predictor, covariate effect relative to treat in arm 1 (centering at mean age in CLL11)
      delta[i,k] <- d[t[i,k]]-d[t[i,1]]+(beta[t[i,k]]-beta[t[i,1]])*(x[i]-mx)
     }
  }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1] <- 0    # treatment effect is zero for reference treatment
beta[1] <- 0 # covariate effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){
   d[k] ~ dnorm(0,.0001)
   beta[k] <- B # common covariate effect
  }
B ~ dnorm(0,.0001) # vague prior for covariate effect
# pairwise HRs and lnHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  {
# at mean value of covariate
      HR[c,k] <- exp(d[k] - d[c])
      lnHR[c,k] <- (d[k]-d[c])
                          }  }
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"
                                          # rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } #prob.treat k is h-th best
     }
           }  }
                    # *** PROGRAM ENDS
```

Data for the small network (only 1L CLL fludarabine ineligible trials)

```
# ns2= number of studies with two arms; # ns3= number of studies with three arms;
# nt=number of treatments; # V=variance of baseline arm; # y=lnHR
# t1:Clb; t2:OfaClb; t3:RClb; t4:GClb

list(ns2=1, ns3=1, nt=4)

t[,1]	t[,2]	t[,3]	y[,2]	y[,3]	se[,2]	se[,3]	na[]	V[]	#Study
Comparison
1	2	NA	-0.5620	NA	0.1234	NA	2	NA	#Compl1
Ofa+Clb vs. Clb
1	3	4	-0.7960	-1.6640	0.1190	0.1350	3	0.01079	#CLL11;RClb
vs.Clb/GClb vs.Clb
END
```

Data for the large network (all 1L CLL trials)

```
# ns2= number of studies with two arms; # ns3= number of studies with three arms;
# nt=number of treatments; # V=variance of baseline arm; # y=lnHR
# t1:Clb; t2:Benda; t3:OClb; t4:F; t5: Alm; t6: FC; t7: RFC; t8:RClb; t9:GClb; t10:FCAlm; t11:RBenda; t12:RFC-Lite;
t13:ClaC; t14:Cla

list(ns2=13, ns3=3, nt=14)

t[,1]	t[,2]	t[,3]	y[,2]	y[,3]	se[,2]	se[,3]	na[]	V[]	#Study name
Comparison
1	2	NA	-1.0403	NA	0.1380	NA	2	NA	#Knauf 2009
Benda vs Clb
1	3	NA	-0.5621	NA	0.1234	NA	2	NA	#Complement 1	OClb
vs Clb
1	4	NA	-0.0507	NA	0.1539	NA	2	NA	#CLL5	F vs
Clb
1	4	NA	-0.3857	NA	0.1140	NA	2	NA	#CALGB 9011	F vs
Clb
1	5	NA	-0.5447	NA	0.1486	NA	2	NA	#CAM307	Alm
vs Clb
4	6	NA	-0.5798	NA	0.1801	NA	2	NA	#GCLLSG CLL4	FC vs
F
4	6	NA	-0.5798	NA	0.1801	NA	2	NA	#US E2997	FC vs
F
6	7	NA	-0.5798	NA	0.1034	NA	2	NA	#GCLLSG CLL8	RFC
vs FC
6	10	NA	-0.1740	NA	0.1000	NA	2	NA	#HOVON68
FCAlm vs FC
6	13	NA	-0.0834	NA	0.1239	NA	2	NA	#PALG CLL3
ClaC vs FC
7	10	NA	0.2900	NA	0.2870	NA	2	NA	#CLL2007FMP	RFC
vs FCAlm
7	11	NA	0.3260	NA	0.1590	NA	2	NA	#GCLLSG CLL10
RBenda vs RFC
8	12	NA	-0.7230	NA	0.2520	NA	2	NA	#Nikitin 2013
RFC-Lite vs RClb
1	4	6	-0.1508	-0.7985	0.0974	0.0964	3	0.00052	#UK LRF CLL4
Fvs.Clb/FCvs.Clb
1	8	9	-0.7960	-1.6640	0.1190	0.1350	3	0.01079	#CLL11	RClb vs
Clb/GClbvsClb
14	1	4	1.0220	0.9160	0.3530	0.2260	3	0.00000	#Mulligan	Clb
vs.Cla/F vs.Cla
END
```

Data for the large network including the age variable (x)

```
# ns2= number of studies with two arms; # ns3= number of studies with three arms;
# nt=number of treatments; # V=variance of baseline arm; # y=lnHR
# t1:Clb; t2:Benda; t3:OClb; t4:F; t5: Alm; t6: FC; t7: RFC; t8:RClb; t9:GClb; t10:FCAlm; t11:RBenda; t12:RFC-Lite;
t13:ClaC; t14:Cla

list(ns2=13, ns3=3, nt=14, mx=73)

t[,1]	t[,2]	t[,3]	y[,2]	y[,3]	se[,2]	se[,3]	na[]	V[]	x[]	#Study name ; Comparison
1	2	NA	-1.0403	NA	0.1380	NA	2	NA	64.5	#Knauf 2009; Benda vs Clb
1	3	NA	-0.5621	NA	0.1234	NA	2	NA	69.5	#Complement 1; OClb vs
Clb
1	4	NA	-0.0507	NA	0.1539	NA	2	NA	70.5	#CLL5;	F vs Clb
1	4	NA	-0.3857	NA	0.1140	NA	2	NA	63.0	#CALGB 9011; F vs Clb
```

```
1	5	NA	-0.5447	NA	0.1486	NA	2	NA	59.5	#CAM307;  Alm vs Clb
4	6	NA	-0.5798	NA	0.1801	NA	2	NA	59.0	#GCLLSG CLL4; FC vs F
4	6	NA	-0.5798	NA	0.1801	NA	2	NA	61.0	#US E2997;	FC
vs F
6	7	NA	-0.5798	NA	0.1034	NA	2	NA	61.0	#GCLLSG CLL8; RFC vs
FC
6	10	NA	-0.1740	NA	0.1000	NA	2	NA	60.0	#HOVON68	;
FCAlm vs FC
6	13	NA	-0.0834	NA	0.1239	NA	2	NA	59.0	#PALG CLL3; ClaC vs FC
7	10	NA	0.2900	NA	0.2870	NA	2	NA	56.7	#CLL2007FMP; RFC vs
FCAlm
7	11	NA	0.3260	NA	0.1590	NA	2	NA	62.0	#GCLLSG CLL10; RBenda
vs RFC
8	12	NA	-0.7230	NA	0.2520	NA	2	NA	71.0	#Nikitin 2013; RFC-Lite vs
RClb
1	4	6	-0.1508	-0.7985	0.0974	0.0964	3	0.00052	65.0	#UK LRF CLL4;
Fvs.Clb/FCvs.Clb
1	8	9	-0.7960	-1.6640	0.1190	0.1350	3	0.01079	73.0	#CLL11; RClb vs
Clb/GClbvsClb
14	1	4	1.0220	0.9160	0.3530	0.2260	3	0.00000	63.0	#Mulligan; Clb vs.Cla/F
vs.Cla
END
```

Initial values for the small network under a FE NMA model

```
#chain 1
list(d=c( NA, 0,0,0))
#chain 2
list(d=c( NA, -1,-3,-1))
#chain 3
list(d=c( NA, 2,2,2))
```

Initial values for the small network under a RE NMA model (with weakly-informative prior for between-trial SD)

```
#chain 1
list(d=c( NA, 0,0,0), sd=1)
#chain 2
list(d=c( NA, -1,-3,-1), sd=2)
#chain 3
list(d=c( NA, 2,2,2), sd=0.5)
```

Initial values for the large network under a FE NMA model

```
#chain 1
list(d=c( NA, 0,0,0,0,0,0,0,0,0,0,0,0,0))
#chain 2
list(d=c( NA, -1,-3,-1,2,1,-3,-1,1, -1,-3,-1,2,1))
#chain 3
list(d=c( NA, 2,2,2,2,2,2,2,2,2,2,2,2,2))
```

Initial values for the large network under a RE NMA model (with weakly-informative prior for between-trial SD)

```
#chain 1
list(d=c( NA, 0,0,0,0,0,0,0,0,0,0,0,0,0),sd=1)
#chain 2
list(d=c( NA, -1,-3,-1,2,1,-3,-1,1, -1,-3,-1,2,1),sd=2)
#chain 3
list(d=c( NA, 2,2,2,2,2,2,2,2,2,2,2,2,2),sd=0.5)
```

Initial Values for the large network under a FE meta-regression NMA model

```
#chain 1
list(d=c( NA, 0,0,0,0,0,0,0,0,0,0,0,0,0), B=0)
#chain 2
list(d=c( NA, -1,-3,-1,2,1,-3,-1,1, -1,-3,-1,2,1), B=-2)
#chain 3
list(d=c( NA, 2,2,2,2,2,2,2,2,2,2,2,2,2), B=5)
```

3.3 WinBUGS results

The results from each of the different NMA models run are provided next. The tables below display the WinBUGS output for the different variable analyzed. These include the hazard ratio [HR], natural logarithm of the HR [lnHR], the HR compared to the reference treatment (Clb) [d], between-study standard deviation [sd], between-study standard precision [tau], probability of being the best treatment (i.e. most effective) [best] and the ranking of performance [rk].

Each variable is described by the mean, standard deviation, median and two quartiles (2.5% and 97.5%). The initial "burn-in" had 100,000 iterations [start]. The posterior samples were drawn from 500,000 iterations [sample].

Note that HR[x, y] indicates the hazard ratio of treatment y compared to treatment x. For example, the HR of GClb compared to Clb is *HR[1,4]* in the small network. In this example, a HR<1 indicates that GClb performs better than Clb.

The treatments were coded in the small network using the following numbers:

1: Clb
2: OfaClb
3: RClb
4: GClb

The treatments were coded in the large network using the following numbers:

1: Clb
2: Benda
3: OClb
4: F
5: Alm
6: FC
7: RFC
8: RClb
9: GClb
10: FCAlm
11: RBenda
12: RFC-Lite
13: ClaC
14: Cla

Results from the fixed effect NMA of the small network

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
HR[1,2]	0.5744	0.07111	9.01E-05	0.4475	0.57	0.726	100001	600000
HR[1,3]	0.4543	0.05434	1.14E-04	0.357	0.4511	0.5698	100001	600000
HR[1,4]	0.191	0.02593	5.45E-05	0.1452	0.1893	0.2467	100001	600000
HR[2,3]	0.803	0.1387	2.34E-04	0.5653	0.7914	1.107	100001	600000
HR[2,4]	0.3377	0.06234	1.08E-04	0.2323	0.3321	0.4755	100001	600000
HR[3,4]	0.422	0.04402	4.57E-05	0.3424	0.4197	0.5147	100001	600000
best[1]	0	0	7.45E-14	0	0	0	100001	600000
best[2]	0	0	7.45E-14	0	0	0	100001	600000
best[3]	0	0	7.45E-14	0	0	0	100001	600000
best[4]	1	0	7.45E-14	1	1	1	100001	600000
d[2]	-0.5621	0.1234	1.57E-04	-0.8042	-0.5621	-0.3203	100001	600000
d[3]	-0.7962	0.1192	2.51E-04	-1.03	-0.796	-0.5625	100001	600000
d[4]	-1.664	0.1351	2.85E-04	-1.929	-1.664	-1.4	100001	600000
lnHR[1,2]	-0.5621	0.1234	1.57E-04	-0.8042	-0.5621	-0.3203	100001	600000
lnHR[1,3]	-0.7962	0.1192	2.51E-04	-1.03	-0.796	-0.5625	100001	600000
lnHR[1,4]	-1.664	0.1351	2.85E-04	-1.929	-1.664	-1.4	100001	600000
lnHR[2,3]	-0.2341	0.1715	2.91E-04	-0.5704	-0.234	0.1019	100001	600000
lnHR[2,4]	-1.102	0.1829	3.19E-04	-1.46	-1.102	-0.7434	100001	600000
lnHR[3,4]	-0.8682	0.104	1.08E-04	-1.072	-0.8683	-0.6642	100001	600000
rk[1]	4	0.001291	1.67E-06	4	4	4	100001	600000
rk[2]	2.914	0.2802	3.99E-04	2	3	3	100001	600000
rk[3]	2.086	0.2802	3.99E-04	2	2	3	100001	600000
rk[4]	1	0	7.45E-14	1	1	1	100001	600000
totresdev	3.004	2.456	0.003804	0.2167	2.368	9.387	100001	600000

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	**Dhat**	**pD**	**DIC**
y	-4.530	-7.533	3.004	-1.526
total	-4.530	-7.533	3.004	-1.526

Adjusted DIC=totresdev+pD=3+3=6

Results from the random effects NMA model of the small network (with weakly-informative prior for between-trial SD)

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
HR[1,2]	0.6058	0.2597	4.30E-04	0.2764	0.5695	1.176	100001	600000
HR[1,3]	0.4804	0.2056	4.17E-04	0.2197	0.4518	0.9316	100001	600000
HR[1,4]	0.2019	0.08679	1.85E-04	0.09162	0.1897	0.3926	100001	600000
HR[2,3]	0.9021	0.7714	0.001359	0.2856	0.7936	2.21	100001	600000
HR[2,4]	0.379	0.3165	5.63E-04	0.1194	0.3331	0.9307	100001	600000
HR[3,4]	0.445	0.1925	2.86E-04	0.2044	0.4198	0.856	100001	600000
best[1]	1.42E-04	0.0119	1.60E-05	0	0	0	100001	600000
best[2]	0.01934	0.1377	2.28E-04	0	0	0	100001	600000
best[3]	0.01168	0.1074	1.60E-04	0	0	0	100001	600000
best[4]	0.9688	0.1737	3.19E-04	0	1	1	100001	600000
d[2]	-0.5626	0.3419	5.67E-04	-1.286	-0.5629	0.1621	100001	600000
d[3]	-0.7941	0.3405	7.35E-04	-1.515	-0.7946	-0.07087	100001	600000
d[4]	-1.663	0.3454	7.85E-04	-2.39	-1.663	-0.935	100001	600000
lnHR[1,2]	-0.5626	0.3419	5.67E-04	-1.286	-0.5629	0.1621	100001	600000
lnHR[1,3]	-0.7941	0.3405	7.35E-04	-1.515	-0.7946	-0.07087	100001	600000
lnHR[1,4]	-1.663	0.3454	7.85E-04	-2.39	-1.663	-0.935	100001	600000
lnHR[2,3]	-0.2315	0.4827	9.34E-04	-1.253	-0.2312	0.7932	100001	600000
lnHR[2,4]	-1.1	0.4857	9.69E-04	-2.125	-1.099	-0.0718	100001	600000
lnHR[3,4]	-0.8685	0.3351	4.35E-04	-1.588	-0.8679	-0.1555	100001	600000
md[1,2]	-0.5626	0.3419	5.67E-04	-1.286	-0.5629	0.1621	100001	600000
md[2,2]	-0.7941	0.3405	7.35E-04	-1.515	-0.7946	-0.07087	100001	600000
md[2,3]	-1.663	0.3067	6.45E-04	-2.304	-1.663	-1.024	100001	600000
rk[1]	3.933	0.265	5.35E-04	3	4	4	100001	600000
rk[2]	2.779	0.5483	0.001097	2	3	4	100001	600000
rk[3]	2.252	0.4969	0.001099	2	2	3	100001	600000
rk[4]	1.036	0.2105	3.87E-04	1	1	2	100001	600000
sd	0.2552	0.1923	8.58E-04	0.009923	0.2162	0.7155	100001	600000
tau	938100	1.18E+08	475900	1.953	21.4	10160	100001	600000
taud[1,2]	938100	1.18E+08	475900	1.953	21.4	10160	100001	600000
taud[2,2]	938100	1.18E+08	475900	1.953	21.4	10160	100001	600000
taud[2,3]	1.25E+06	1.58E+08	634500	2.605	28.54	13540	100001	600000
totresdev	2.997	2.444	0.005818	0.2176	2.365	9.324	100001	600000

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
sd	1.386	1.386	0	1.386
y	-4.536	-7.533	2.997	-1.54
total	-3.15	-6.147	2.997	-0.153

Adjusted DIC=totresdev+pD=3+3=6

Results from the fixed effect NMA of the large network

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
HR[1,2]	0.3567	0.04949	2.78E-05	0.2697	0.3533	0.4633	100001	600000
HR[1,3]	0.5744	0.07111	3.78E-05	0.4477	0.57	0.7257	100001	600000
HR[1,4]	0.8109	0.04981	3.25E-05	0.7176	0.8094	0.9129	100001	600000
HR[1,5]	0.5864	0.08772	4.83E-05	0.4332	0.5801	0.7767	100001	600000
HR[1,6]	0.4517	0.03643	4.24E-05	0.3846	0.4502	0.5273	100001	600000
HR[1,7]	0.2573	0.0327	3.48E-05	0.1993	0.2552	0.3271	100001	600000
HR[1,8]	0.4543	0.05429	4.66E-05	0.3573	0.4511	0.5697	100001	600000
HR[1,9]	0.1911	0.02591	2.13E-05	0.1452	0.1894	0.2468	100001	600000
HR[1,10]	0.3771	0.04713	4.67E-05	0.2931	0.3742	0.4776	100001	600000
HR[1,11]	0.361	0.07408	6.65E-05	0.2373	0.3537	0.5263	100001	600000
HR[1,12]	0.2276	0.06471	4.69E-05	0.1269	0.2188	0.3778	100001	600000
HR[1,13]	0.4188	0.06218	5.47E-05	0.3103	0.4143	0.5531	100001	600000
HR[1,14]	0.3403	0.06698	3.68E-05	0.2279	0.3339	0.4894	100001	600000
HR[2,3]	1.641	0.3063	1.75E-04	1.123	1.614	2.317	100001	600000
HR[2,4]	2.317	0.3521	2.04E-04	1.703	2.29	3.081	100001	600000
HR[2,5]	1.675	0.3435	2.05E-04	1.102	1.641	2.443	100001	600000
HR[2,6]	1.291	0.2076	1.55E-04	0.9316	1.274	1.743	100001	600000
HR[2,7]	0.735	0.1389	1.14E-04	0.5003	0.7223	1.042	100001	600000
HR[2,8]	1.298	0.2386	1.69E-04	0.8926	1.277	1.824	100001	600000
HR[2,9]	0.546	0.1065	7.58E-05	0.3671	0.536	0.7826	100001	600000
HR[2,10]	1.077	0.2021	1.59E-04	0.7349	1.059	1.524	100001	600000
HR[2,11]	1.031	0.257	2.08E-04	0.6184	1.001	1.618	100001	600000
HR[2,12]	0.6502	0.2074	1.51E-04	0.3363	0.6193	1.141	100001	600000
HR[2,13]	1.197	0.2444	1.83E-04	0.7886	1.173	1.745	100001	600000
HR[2,14]	0.9723	0.2358	1.40E-04	0.5917	0.9448	1.51	100001	600000
HR[3,4]	1.433	0.1983	1.13E-04	1.084	1.42	1.859	100001	600000
HR[3,5]	1.037	0.202	1.21E-04	0.6971	1.017	1.484	100001	600000
HR[3,6]	0.7985	0.1182	9.08E-05	0.592	0.7899	1.055	100001	600000
HR[3,7]	0.4548	0.08108	6.85E-05	0.3168	0.4479	0.6334	100001	600000
HR[3,8]	0.8031	0.1385	9.63E-05	0.5659	0.7915	1.107	100001	600000
HR[3,9]	0.3378	0.06229	4.33E-05	0.2321	0.3321	0.4755	100001	600000
HR[3,10]	0.6666	0.1177	9.43E-05	0.4655	0.6565	0.9254	100001	600000
HR[3,11]	0.6382	0.1539	1.26E-04	0.3894	0.6205	0.9893	100001	600000
HR[3,12]	0.4022	0.1253	9.17E-05	0.2119	0.3838	0.6971	100001	600000
HR[3,13]	0.7403	0.1436	1.08E-04	0.4992	0.7265	1.059	100001	600000
HR[3,14]	0.6016	0.1407	8.30E-05	0.3726	0.5857	0.9209	100001	600000
HR[4,5]	0.7259	0.1176	6.61E-05	0.5226	0.7167	0.9826	100001	600000
HR[4,6]	0.5583	0.04764	4.11E-05	0.4709	0.5563	0.6577	100001	600000
HR[4,7]	0.318	0.0414	3.72E-05	0.2446	0.3153	0.4067	100001	600000
HR[4,8]	0.5624	0.07566	6.19E-05	0.4288	0.5573	0.7251	100001	600000
HR[4,9]	0.2365	0.03527	2.82E-05	0.175	0.2339	0.3127	100001	600000
HR[4,10]	0.4661	0.05975	4.91E-05	0.3599	0.4623	0.5942	100001	600000
HR[4,11]	0.4462	0.09241	7.52E-05	0.2921	0.4369	0.6523	100001	600000
HR[4,12]	0.2817	0.08206	5.96E-05	0.1548	0.2704	0.4733	100001	600000
HR[4,13]	0.5177	0.0783	5.79E-05	0.3816	0.5117	0.6877	100001	600000

HR[4,14]	0.4201	0.08091	4.26E-05	0.284	0.4125	0.5995	100001	600000
HR[5,6]	0.7875	0.1341	9.50E-05	0.5572	0.7761	1.082	100001	600000
HR[5,7]	0.4485	0.08841	6.94E-05	0.3003	0.44	0.6456	100001	600000
HR[5,8]	0.792	0.1524	1.02E-04	0.5352	0.7777	1.13	100001	600000
HR[5,9]	0.3331	0.06754	4.55E-05	0.2205	0.3265	0.4839	100001	600000
HR[5,10]	0.6574	0.1288	9.66E-05	0.4414	0.645	0.9435	100001	600000
HR[5,11]	0.6294	0.1611	1.27E-04	0.372	0.6098	0.9993	100001	600000
HR[5,12]	0.3968	0.1289	9.21E-05	0.2033	0.3774	0.7017	100001	600000
HR[5,13]	0.7302	0.1547	1.14E-04	0.4737	0.7143	1.077	100001	600000
HR[5,14]	0.5933	0.1479	8.73E-05	0.3563	0.5758	0.9311	100001	600000
HR[6,7]	0.5695	0.05586	3.52E-05	0.4679	0.5667	0.6867	100001	600000
HR[6,8]	1.012	0.1462	1.42E-04	0.7556	1.002	1.328	100001	600000
HR[6,9]	0.4258	0.06733	6.25E-05	0.3089	0.4206	0.5723	100001	600000
HR[6,10]	0.8347	0.07949	4.15E-05	0.6898	0.8309	1.001	100001	600000
HR[6,11]	0.7991	0.1503	1.01E-04	0.544	0.7856	1.131	100001	600000
HR[6,12]	0.507	0.1503	1.17E-04	0.2756	0.486	0.8587	100001	600000
HR[6,13]	0.9272	0.1152	6.09E-05	0.7223	0.9201	1.173	100001	600000
HR[6,14]	0.7574	0.1574	1.00E-04	0.4957	0.7414	1.11	100001	600000
HR[7,8]	1.794	0.314	3.10E-04	1.258	1.768	2.483	100001	600000
HR[7,9]	0.7548	0.1409	1.34E-04	0.5161	0.742	1.066	100001	600000
HR[7,10]	1.478	0.1909	1.05E-04	1.139	1.466	1.886	100001	600000
HR[7,11]	1.403	0.2244	1.18E-04	1.014	1.386	1.893	100001	600000
HR[7,12]	0.8988	0.2817	2.29E-04	0.4713	0.8576	1.563	100001	600000
HR[7,13]	1.644	0.2607	1.52E-04	1.192	1.623	2.211	100001	600000
HR[7,14]	1.343	0.3098	2.19E-04	0.8369	1.308	2.044	100001	600000
HR[8,9]	0.4221	0.04401	1.87E-05	0.3425	0.4198	0.5148	100001	600000
HR[8,10]	0.8419	0.1462	1.36E-04	0.5921	0.8294	1.163	100001	600000
HR[8,11]	0.8059	0.1923	1.72E-04	0.4942	0.7842	1.243	100001	600000
HR[8,12]	0.5009	0.1281	7.88E-05	0.2963	0.4852	0.7959	100001	600000
HR[8,13]	0.9351	0.1791	1.56E-04	0.633	0.9182	1.333	100001	600000
HR[8,14]	0.7598	0.1758	1.15E-04	0.4734	0.7401	1.158	100001	600000
HR[9,10]	2.01	0.3723	3.35E-04	1.378	1.976	2.832	100001	600000
HR[9,11]	1.924	0.4763	4.20E-04	1.157	1.867	3.011	100001	600000
HR[9,12]	1.2	0.3328	2.28E-04	0.6783	1.155	1.972	100001	600000
HR[9,13]	2.232	0.4511	3.85E-04	1.479	2.188	3.239	100001	600000
HR[9,14]	1.814	0.4359	2.89E-04	1.109	1.763	2.806	100001	600000
HR[10,11]	0.9651	0.1992	1.25E-04	0.633	0.9456	1.409	100001	600000
HR[10,12]	0.613	0.1917	1.53E-04	0.3215	0.585	1.065	100001	600000
HR[10,13]	1.121	0.176	1.01E-04	0.8152	1.107	1.504	100001	600000
HR[10,14]	0.9156	0.2102	1.44E-04	0.5731	0.8922	1.391	100001	600000
HR[11,12]	0.657	0.2336	1.90E-04	0.3149	0.6186	1.218	100001	600000
HR[11,13]	1.201	0.2728	1.77E-04	0.7558	1.171	1.819	100001	600000
HR[11,14]	0.9813	0.2775	2.02E-04	0.5474	0.9441	1.627	100001	600000
HR[12,13]	1.989	0.6426	5.09E-04	1.02	1.893	3.508	100001	600000
HR[12,14]	1.616	0.5662	4.02E-04	0.7843	1.525	2.972	100001	600000
HR[13,14]	0.8296	0.2021	1.37E-04	0.5037	0.8059	1.29	100001	600000
best[1]	0	0	7.45E-14	0	0	0	100001	600000
best[2]	2.22E-04	0.01489	1.94E-05	0	0	0	100001	600000

best[3]	0	0	7.45E-14	0	0	0	100001	600000
best[4]	0	0	7.45E-14	0	0	0	100001	600000
best[5]	0	0	7.45E-14	0	0	0	100001	600000
best[6]	0	0	7.45E-14	0	0	0	100001	600000
best[7]	0.03548	0.185	2.45E-04	0	0	1	100001	600000
best[8]	0	0	7.45E-14	0	0	0	100001	600000
best[9]	0.6674	0.4711	5.29E-04	0	1	1	100001	600000
best[10]	3.33E-06	0.001826	2.35E-06	0	0	0	100001	600000
best[11]	0.001543	0.03925	5.12E-05	0	0	0	100001	600000
best[12]	0.2906	0.4541	5.25E-04	0	0	1	100001	600000
best[13]	1.67E-06	0.001291	1.67E-06	0	0	0	100001	600000
best[14]	0.004688	0.06831	8.93E-05	0	0	0	100001	600000
d[2]	-1.04	0.1381	7.10E-05	-1.311	-1.04	-0.7694	100001	600000
d[3]	-0.5621	0.1233	6.00E-05	-0.8037	-0.5621	-0.3207	100001	600000
d[4]	-0.2115	0.06137	3.97E-05	-0.3318	-0.2114	-0.09112	100001	600000
d[5]	-0.5447	0.1488	7.22E-05	-0.8366	-0.5446	-0.2527	100001	600000
d[6]	-0.7979	0.08052	9.36E-05	-0.9555	-0.798	-0.64	100001	600000
d[7]	-1.366	0.1266	1.34E-04	-1.613	-1.366	-1.117	100001	600000
d[8]	-0.7961	0.1191	1.01E-04	-1.029	-0.796	-0.5627	100001	600000
d[9]	-1.664	0.135	1.09E-04	-1.93	-1.664	-1.399	100001	600000
d[10]	-0.9831	0.1245	1.23E-04	-1.227	-0.983	-0.7389	100001	600000
d[11]	-1.04	0.2031	1.79E-04	-1.438	-1.039	-0.6418	100001	600000
d[12]	-1.519	0.2785	1.79E-04	-2.064	-1.519	-0.9734	100001	600000
d[13]	-0.8812	0.1476	1.29E-04	-1.17	-0.8811	-0.5922	100001	600000
d[14]	-1.097	0.1949	9.64E-05	-1.479	-1.097	-0.7147	100001	600000
lnHR[1,2]	-1.04	0.1381	7.10E-05	-1.311	-1.04	-0.7694	100001	600000
lnHR[1,3]	-0.5621	0.1233	6.00E-05	-0.8037	-0.5621	-0.3207	100001	600000
lnHR[1,4]	-0.2115	0.06137	3.97E-05	-0.3318	-0.2114	-0.09112	100001	600000
lnHR[1,5]	-0.5447	0.1488	7.22E-05	-0.8366	-0.5446	-0.2527	100001	600000
lnHR[1,6]	-0.7979	0.08052	9.36E-05	-0.9555	-0.798	-0.64	100001	600000
lnHR[1,7]	-1.366	0.1266	1.34E-04	-1.613	-1.366	-1.117	100001	600000
lnHR[1,8]	-0.7961	0.1191	1.01E-04	-1.029	-0.796	-0.5627	100001	600000
lnHR[1,9]	-1.664	0.135	1.09E-04	-1.93	-1.664	-1.399	100001	600000
lnHR[1,10]	-0.9831	0.1245	1.23E-04	-1.227	-0.983	-0.7389	100001	600000
lnHR[1,11]	-1.04	0.2031	1.79E-04	-1.438	-1.039	-0.6418	100001	600000
lnHR[1,12]	-1.519	0.2785	1.79E-04	-2.064	-1.519	-0.9734	100001	600000
lnHR[1,13]	-0.8812	0.1476	1.29E-04	-1.17	-0.8811	-0.5922	100001	600000
lnHR[1,14]	-1.097	0.1949	9.64E-05	-1.479	-1.097	-0.7147	100001	600000
lnHR[2,3]	0.4782	0.1851	9.29E-05	0.1156	0.4785	0.8404	100001	600000
lnHR[2,4]	0.8288	0.1511	8.11E-05	0.5324	0.8286	1.125	100001	600000
lnHR[2,5]	0.4955	0.2029	1.01E-04	0.09709	0.4955	0.8933	100001	600000
lnHR[2,6]	0.2424	0.1598	1.17E-04	-0.07088	0.2425	0.5558	100001	600000
lnHR[2,7]	-0.3254	0.1873	1.51E-04	-0.6926	-0.3253	0.04079	100001	600000
lnHR[2,8]	0.2442	0.1823	1.24E-04	-0.1136	0.2443	0.6013	100001	600000
lnHR[2,9]	-0.6238	0.1932	1.31E-04	-1.002	-0.6237	-0.2452	100001	600000
lnHR[2,10]	0.05719	0.186	1.41E-04	-0.308	0.05717	0.4214	100001	600000
lnHR[2,11]	7.51E-04	0.2454	1.91E-04	-0.4806	8.15E-04	0.481	100001	600000
lnHR[2,12]	-0.4788	0.311	1.90E-04	-1.09	-0.4792	0.1317	100001	600000

lnHR[2,13]	0.1591	0.2022	1.45E-04	-0.2375	0.1592	0.5566	100001	600000
lnHR[2,14]	-0.05661	0.239	1.20E-04	-0.5248	-0.05677	0.412	100001	600000
lnHR[3,4]	0.3506	0.1377	7.34E-05	0.081	0.3507	0.6203	100001	600000
lnHR[3,5]	0.01734	0.1931	9.61E-05	-0.3608	0.01721	0.395	100001	600000
lnHR[3,6]	-0.2358	0.1472	1.11E-04	-0.5243	-0.2358	0.05327	100001	600000
lnHR[3,7]	-0.8036	0.1768	1.47E-04	-1.15	-0.8033	-0.4567	100001	600000
lnHR[3,8]	-0.234	0.1713	1.16E-04	-0.5693	-0.2338	0.1014	100001	600000
lnHR[3,9]	-1.102	0.1828	1.23E-04	-1.461	-1.102	-0.7434	100001	600000
lnHR[3,10]	-0.421	0.1753	1.38E-04	-0.7646	-0.4209	-0.07757	100001	600000
lnHR[3,11]	-0.4774	0.2378	1.88E-04	-0.9432	-0.4773	-0.0108	100001	600000
lnHR[3,12]	-0.957	0.3041	1.87E-04	-1.552	-0.9577	-0.3608	100001	600000
lnHR[3,13]	-0.3191	0.1921	1.41E-04	-0.6948	-0.3196	0.05759	100001	600000
lnHR[3,14]	-0.5348	0.2308	1.15E-04	-0.9874	-0.5349	-0.0824	100001	600000
lnHR[4,5]	-0.3333	0.161	8.04E-05	-0.6489	-0.3331	-0.0176	100001	600000
lnHR[4,6]	-0.5864	0.08516	7.36E-05	-0.753	-0.5864	-0.419	100001	600000
lnHR[4,7]	-1.154	0.1296	1.16E-04	-1.408	-1.154	-0.8997	100001	600000
lnHR[4,8]	-0.5846	0.1339	1.09E-04	-0.8467	-0.5847	-0.3215	100001	600000
lnHR[4,9]	-1.453	0.1483	1.17E-04	-1.743	-1.453	-1.163	100001	600000
lnHR[4,10]	-0.7716	0.1277	1.05E-04	-1.022	-0.7715	-0.5206	100001	600000
lnHR[4,11]	-0.828	0.2049	1.63E-04	-1.231	-0.828	-0.4272	100001	600000
lnHR[4,12]	-1.308	0.2852	1.83E-04	-1.866	-1.308	-0.7481	100001	600000
lnHR[4,13]	-0.6697	0.1503	1.10E-04	-0.9634	-0.6699	-0.3744	100001	600000
lnHR[4,14]	-0.8854	0.1908	8.78E-05	-1.259	-0.8854	-0.5116	100001	600000
lnHR[5,6]	-0.2531	0.1691	1.15E-04	-0.5849	-0.2534	0.07858	100001	600000
lnHR[5,7]	-0.8209	0.1952	1.49E-04	-1.203	-0.8209	-0.4376	100001	600000
lnHR[5,8]	-0.2513	0.1906	1.23E-04	-0.6251	-0.2514	0.1224	100001	600000
lnHR[5,9]	-1.119	0.2007	1.29E-04	-1.512	-1.119	-0.7258	100001	600000
lnHR[5,10]	-0.4383	0.194	1.40E-04	-0.8177	-0.4385	-0.05812	100001	600000
lnHR[5,11]	-0.4948	0.2519	1.90E-04	-0.9889	-0.4946	-7.31E-04	100001	600000
lnHR[5,12]	-0.9743	0.3163	1.91E-04	-1.593	-0.9744	-0.3543	100001	600000
lnHR[5,13]	-0.3364	0.2095	1.45E-04	-0.7472	-0.3364	0.07428	100001	600000
lnHR[5,14]	-0.5521	0.2455	1.22E-04	-1.032	-0.5519	-0.07138	100001	600000
lnHR[6,7]	-0.5678	0.09784	6.08E-05	-0.7595	-0.568	-0.3759	100001	600000
lnHR[6,8]	0.001816	0.1438	1.38E-04	-0.2803	0.001967	0.2836	100001	600000
lnHR[6,9]	-0.8662	0.1572	1.43E-04	-1.175	-0.866	-0.5581	100001	600000
lnHR[6,10]	-0.1852	0.095	4.86E-05	-0.3714	-0.1852	0.001055	100001	600000
lnHR[6,11]	-0.2416	0.1865	1.20E-04	-0.6089	-0.2412	0.1231	100001	600000
lnHR[6,12]	-0.7212	0.2899	2.04E-04	-1.289	-0.7215	-0.1523	100001	600000
lnHR[6,13]	-0.0833	0.1238	6.24E-05	-0.3253	-0.08331	0.1594	100001	600000
lnHR[6,14]	-0.299	0.2057	1.20E-04	-0.7018	-0.2992	0.1045	100001	600000
lnHR[7,8]	0.5696	0.1737	1.69E-04	0.2292	0.5697	0.9096	100001	600000
lnHR[7,9]	-0.2984	0.1851	1.73E-04	-0.6615	-0.2985	0.06397	100001	600000
lnHR[7,10]	0.3826	0.1286	6.87E-05	0.1304	0.3826	0.6346	100001	600000
lnHR[7,11]	0.3261	0.1589	7.90E-05	0.01398	0.3261	0.6381	100001	600000
lnHR[7,12]	-0.1534	0.3058	2.26E-04	-0.7523	-0.1536	0.4464	100001	600000
lnHR[7,13]	0.4845	0.1577	8.68E-05	0.1753	0.4844	0.7934	100001	600000
lnHR[7,14]	0.2688	0.2278	1.52E-04	-0.1781	0.2686	0.7151	100001	600000
lnHR[8,9]	-0.868	0.104	4.24E-05	-1.072	-0.868	-0.6639	100001	600000

lnHR[8,10]	-0.187	0.1723	1.59E-04	-0.524	-0.1871	0.1512	100001	600000
lnHR[8,11]	-0.2434	0.2354	2.05E-04	-0.7048	-0.243	0.2173	100001	600000
lnHR[8,12]	-0.723	0.2517	1.24E-04	-1.216	-0.7233	-0.2283	100001	600000
lnHR[8,13]	-0.08511	0.1898	1.64E-04	-0.4572	-0.08536	0.2877	100001	600000
lnHR[8,14]	-0.3008	0.2284	1.41E-04	-0.7479	-0.3009	0.1464	100001	600000
lnHR[9,10]	0.681	0.1837	1.64E-04	0.3209	0.6808	1.041	100001	600000
lnHR[9,11]	0.6246	0.2439	2.09E-04	0.1458	0.6244	1.102	100001	600000
lnHR[9,12]	0.145	0.2721	1.38E-04	-0.3881	0.1444	0.679	100001	600000
lnHR[9,13]	0.7829	0.2001	1.69E-04	0.3914	0.783	1.175	100001	600000
lnHR[9,14]	0.5672	0.237	1.47E-04	0.1033	0.5671	1.032	100001	600000
lnHR[10,11]	-0.05644	0.2044	1.21E-04	-0.4573	-0.05599	0.3431	100001	600000
lnHR[10,12]	-0.536	0.3052	2.20E-04	-1.135	-0.5361	0.06279	100001	600000
lnHR[10,13]	0.1019	0.1561	8.12E-05	-0.2043	0.1019	0.408	100001	600000
lnHR[10,14]	-0.1138	0.2266	1.43E-04	-0.5567	-0.114	0.3303	100001	600000
lnHR[11,12]	-0.4796	0.3447	2.56E-04	-1.156	-0.4802	0.1972	100001	600000
lnHR[11,13]	0.1583	0.2241	1.36E-04	-0.2799	0.158	0.5983	100001	600000
lnHR[11,14]	-0.05736	0.2775	1.90E-04	-0.6027	-0.05755	0.487	100001	600000
lnHR[12,13]	0.6379	0.3153	2.25E-04	0.01976	0.6383	1.255	100001	600000
lnHR[12,14]	0.4222	0.3401	2.02E-04	-0.243	0.4221	1.089	100001	600000
lnHR[13,14]	-0.2157	0.2401	1.45E-04	-0.6858	-0.2158	0.2549	100001	600000
rk[1]	14	0.01962	2.61E-05	14	14	14	100001	600000
rk[2]	5.751	1.689	0.001523	3	6	10	100001	600000
rk[3]	11.23	0.9186	9.50E-04	9	11	12	100001	600000
rk[4]	12.98	0.1585	2.29E-04	13	13	13	100001	600000
rk[5]	11.28	1.051	0.001086	8	12	12	100001	600000
rk[6]	9.099	0.9741	0.001138	7	9	11	100001	600000
rk[7]	2.822	0.7423	8.65E-04	1	3	4	100001	600000
rk[8]	8.882	1.611	0.00165	5	9	11	100001	600000
rk[9]	1.364	0.5495	6.56E-04	1	1	3	100001	600000
rk[10]	6.321	1.393	0.001269	4	6	9	100001	600000
rk[11]	5.903	2.016	0.001772	3	6	10	100001	600000
rk[12]	2.333	1.423	0.001373	1	2	6	100001	600000
rk[13]	7.76	1.761	0.001453	4	8	11	100001	600000
rk[14]	5.272	1.987	0.001568	2	5	10	100001	600000
totresdev	17	5.103	0.01321	9.024	16.34	28.75	100001	600000

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
y	-20.488	-33.479	12.991	-7.497
total	-20.488	-33.479	12.991	-7.497

Adjusted DIC=totresdev+pD=17+13=30

Results from the random effects NMA model of the large network (with weakly-informative prior for between-trial SD)

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
HR[1,2]	0.3597	0.06778	2.10E-04	0.2461	0.3536	0.508	100001	600000
HR[1,3]	0.5791	0.1033	2.93E-04	0.4045	0.5707	0.8032	100001	600000
HR[1,4]	0.816	0.07472	2.45E-04	0.6809	0.812	0.9768	100001	600000
HR[1,5]	0.5908	0.1168	3.95E-04	0.3973	0.5798	0.8459	100001	600000
HR[1,6]	0.4528	0.05495	2.13E-04	0.3541	0.4496	0.5699	100001	600000
HR[1,7]	0.261	0.05074	2.07E-04	0.1775	0.2562	0.3732	100001	600000
HR[1,8]	0.4579	0.08037	3.27E-04	0.3226	0.4511	0.6331	100001	600000
HR[1,9]	0.1925	0.03582	1.38E-04	0.1324	0.1892	0.2708	100001	600000
HR[1,10]	0.3778	0.07238	2.86E-04	0.2555	0.3715	0.5349	100001	600000
HR[1,11]	0.3691	0.1085	4.64E-04	0.2073	0.3548	0.6151	100001	600000
HR[1,12]	0.2305	0.07945	3.90E-04	0.1148	0.2181	0.4163	100001	600000
HR[1,13]	0.4224	0.09288	3.07E-04	0.2725	0.4127	0.627	100001	600000
HR[1,14]	0.3434	0.08039	3.96E-04	0.2149	0.3342	0.525	100001	600000
HR[2,3]	1.666	0.4452	0.001388	0.9779	1.612	2.651	100001	600000
HR[2,4]	2.347	0.5003	0.001634	1.536	2.296	3.457	100001	600000
HR[2,5]	1.699	0.476	0.00144	0.9723	1.64	2.772	100001	600000
HR[2,6]	1.302	0.2971	9.90E-04	0.8243	1.27	1.962	100001	600000
HR[2,7]	0.7508	0.2102	7.43E-04	0.4335	0.724	1.225	100001	600000
HR[2,8]	1.317	0.3501	0.00121	0.7784	1.276	2.093	100001	600000
HR[2,9]	0.5536	0.1514	5.11E-04	0.3218	0.5349	0.8921	100001	600000
HR[2,10]	1.086	0.3003	0.001031	0.6238	1.05	1.753	100001	600000
HR[2,11]	1.062	0.3892	0.001526	0.5254	1.002	1.938	100001	600000
HR[2,12]	0.6631	0.2711	0.001217	0.2971	0.6166	1.293	100001	600000
HR[2,13]	1.215	0.3649	0.001156	0.6732	1.167	2.031	100001	600000
HR[2,14]	0.9879	0.3076	0.001261	0.5343	0.9452	1.692	100001	600000
HR[3,4]	1.452	0.2959	8.45E-04	0.9723	1.422	2.106	100001	600000
HR[3,5]	1.052	0.2882	9.10E-04	0.6106	1.016	1.699	100001	600000
HR[3,6]	0.806	0.178	5.66E-04	0.5193	0.7871	1.198	100001	600000
HR[3,7]	0.4647	0.1276	4.39E-04	0.273	0.4489	0.7489	100001	600000
HR[3,8]	0.8152	0.2113	7.34E-04	0.489	0.7906	1.282	100001	600000
HR[3,9]	0.3426	0.09078	3.08E-04	0.2025	0.3319	0.5453	100001	600000
HR[3,10]	0.6725	0.1816	6.10E-04	0.3924	0.6509	1.075	100001	600000
HR[3,11]	0.6573	0.2384	8.98E-04	0.3296	0.6216	1.187	100001	600000
HR[3,12]	0.4104	0.1655	7.26E-04	0.1848	0.3822	0.794	100001	600000
HR[3,13]	0.752	0.2215	6.87E-04	0.4222	0.7239	1.247	100001	600000
HR[3,14]	0.6112	0.1848	7.46E-04	0.3361	0.5859	1.032	100001	600000
HR[4,5]	0.73	0.1601	5.45E-04	0.4674	0.7143	1.081	100001	600000
HR[4,6]	0.5565	0.06161	2.54E-04	0.4435	0.5536	0.6858	100001	600000
HR[4,7]	0.3208	0.0597	2.46E-04	0.2206	0.3156	0.4518	100001	600000
HR[4,8]	0.5657	0.1127	4.33E-04	0.3774	0.5558	0.8117	100001	600000
HR[4,9]	0.2378	0.04974	1.83E-04	0.1555	0.2331	0.3466	100001	600000
HR[4,10]	0.4643	0.08507	3.35E-04	0.3178	0.4572	0.6484	100001	600000
HR[4,11]	0.4537	0.1301	5.78E-04	0.2568	0.437	0.7492	100001	600000
HR[4,12]	0.2848	0.1028	4.91E-04	0.1384	0.2685	0.5244	100001	600000
HR[4,13]	0.5192	0.1101	3.45E-04	0.3383	0.5085	0.7615	100001	600000

HR[4,14]	0.4219	0.09555	4.63E-04	0.2672	0.4113	0.636	100001	600000
HR[5,6]	0.7955	0.1884	6.82E-04	0.4963	0.7748	1.213	100001	600000
HR[5,7]	0.4587	0.1317	4.69E-04	0.2615	0.4418	0.7539	100001	600000
HR[5,8]	0.8046	0.2211	8.07E-04	0.4685	0.7778	1.292	100001	600000
HR[5,9]	0.3382	0.09538	3.33E-04	0.194	0.3263	0.5498	100001	600000
HR[5,10]	0.6637	0.1883	6.97E-04	0.3763	0.6399	1.084	100001	600000
HR[5,11]	0.6487	0.2412	8.90E-04	0.3178	0.6119	1.191	100001	600000
HR[5,12]	0.4051	0.1675	7.60E-04	0.1795	0.3763	0.7994	100001	600000
HR[5,13]	0.7423	0.2287	7.66E-04	0.4068	0.7124	1.251	100001	600000
HR[5,14]	0.6036	0.1914	8.27E-04	0.321	0.5761	1.039	100001	600000
HR[6,7]	0.5765	0.08501	3.06E-04	0.4307	0.5701	0.762	100001	600000
HR[6,8]	1.026	0.2239	9.16E-04	0.6651	1.004	1.518	100001	600000
HR[6,9]	0.4313	0.0983	3.86E-04	0.2733	0.4213	0.6476	100001	600000
HR[6,10]	0.8342	0.1201	3.81E-04	0.6196	0.8266	1.09	100001	600000
HR[6,11]	0.8152	0.2124	8.84E-04	0.488	0.7899	1.298	100001	600000
HR[6,12]	0.5167	0.194	9.32E-04	0.2443	0.485	0.9654	100001	600000
HR[6,13]	0.9331	0.1671	5.35E-04	0.6536	0.9186	1.298	100001	600000
HR[6,14]	0.7667	0.1941	8.94E-04	0.4627	0.743	1.202	100001	600000
HR[7,8]	1.818	0.5127	0.002078	1.061	1.762	2.898	100001	600000
HR[7,9]	0.7639	0.2161	8.68E-04	0.439	0.7388	1.232	100001	600000
HR[7,10]	1.47	0.264	0.001073	1.011	1.45	2.047	100001	600000
HR[7,11]	1.414	0.2909	0.001152	0.9339	1.386	2.06	100001	600000
HR[7,12]	0.9153	0.3843	0.001797	0.4047	0.8497	1.788	100001	600000
HR[7,13]	1.653	0.3903	0.001395	1.029	1.612	2.509	100001	600000
HR[7,14]	1.358	0.4085	0.001828	0.748	1.303	2.271	100001	600000
HR[8,9]	0.4249	0.07004	1.82E-04	0.3054	0.4195	0.5775	100001	600000
HR[8,10]	0.8495	0.2269	9.11E-04	0.4968	0.8234	1.351	100001	600000
HR[8,11]	0.8304	0.2977	0.001288	0.4178	0.7862	1.501	100001	600000
HR[8,12]	0.5033	0.1446	7.45E-04	0.2797	0.484	0.8378	100001	600000
HR[8,13]	0.9501	0.2785	9.77E-04	0.5353	0.9156	1.565	100001	600000
HR[8,14]	0.7725	0.2327	0.001081	0.4252	0.7396	1.304	100001	600000
HR[9,10]	2.029	0.5605	0.00224	1.168	1.962	3.276	100001	600000
HR[9,11]	1.983	0.724	0.003117	0.9846	1.875	3.618	100001	600000
HR[9,12]	1.215	0.4107	0.00178	0.6155	1.155	2.169	100001	600000
HR[9,13]	2.269	0.6747	0.002331	1.259	2.182	3.783	100001	600000
HR[9,14]	1.845	0.5675	0.002478	1.001	1.763	3.145	100001	600000
HR[10,11]	0.9926	0.2825	0.001199	0.568	0.9543	1.642	100001	600000
HR[10,12]	0.6325	0.2665	0.001227	0.2808	0.5875	1.242	100001	600000
HR[10,13]	1.142	0.2723	8.25E-04	0.7166	1.112	1.747	100001	600000
HR[10,14]	0.9382	0.28	0.001216	0.5205	0.899	1.576	100001	600000
HR[11,12]	0.6745	0.3346	0.001489	0.2636	0.6143	1.421	100001	600000
HR[11,13]	1.217	0.3946	0.001459	0.6374	1.164	2.103	100001	600000
HR[11,14]	1.001	0.3801	0.001617	0.4742	0.9406	1.862	100001	600000
HR[12,13]	2.041	0.8821	0.003806	0.8778	1.895	4.049	100001	600000
HR[12,14]	1.659	0.7207	0.003454	0.7046	1.532	3.358	100001	600000
HR[13,14]	0.847	0.2702	0.001084	0.4516	0.8097	1.458	100001	600000
best[1]	0	0	7.45E-14	0	0	0	100001	600000
best[2]	0.003743	0.06107	9.90E-05	0	0	0	100001	600000

best[3]	8.00E-05	0.008944	1.21E-05	0	0	0	100001	600000
best[4]	0	0	7.45E-14	0	0	0	100001	600000
best[5]	7.17E-05	0.008465	1.15E-05	0	0	0	100001	600000
best[6]	1.67E-06	0.001291	1.67E-06	0	0	0	100001	600000
best[7]	0.06508	0.2467	9.98E-04	0	0	1	100001	600000
best[8]	6.67E-06	0.002582	3.33E-06	0	0	0	100001	600000
best[9]	0.6069	0.4884	0.002324	0	1	1	100001	600000
best[10]	0.001117	0.0334	4.94E-05	0	0	0	100001	600000
best[11]	0.00824	0.0904	1.89E-04	0	0	0	100001	600000
best[12]	0.3026	0.4594	0.002237	0	0	1	100001	600000
best[13]	0.001288	0.03587	5.27E-05	0	0	0	100001	600000
best[14]	0.01088	0.1037	2.92E-04	0	0	0	100001	600000
d[2]	-1.039	0.1839	5.79E-04	-1.402	-1.04	-0.6774	100001	600000
d[3]	-0.5614	0.1736	4.98E-04	-0.9052	-0.5609	-0.2192	100001	600000
d[4]	-0.2075	0.09053	2.95E-04	-0.3843	-0.2083	-0.02346	100001	600000
d[5]	-0.5449	0.1926	6.61E-04	-0.9232	-0.545	-0.1673	100001	600000
d[6]	-0.7996	0.1197	4.69E-04	-1.038	-0.7993	-0.5622	100001	600000
d[7]	-1.361	0.1869	7.82E-04	-1.729	-1.362	-0.9858	100001	600000
d[8]	-0.7957	0.1702	7.02E-04	-1.131	-0.796	-0.4571	100001	600000
d[9]	-1.664	0.1814	7.09E-04	-2.022	-1.665	-1.306	100001	600000
d[10]	-0.9909	0.1863	7.42E-04	-1.365	-0.9901	-0.6256	100001	600000
d[11]	-1.035	0.2741	0.001187	-1.573	-1.036	-0.486	100001	600000
d[12]	-1.521	0.3263	0.001691	-2.165	-1.523	-0.8764	100001	600000
d[13]	-0.8841	0.2105	6.94E-04	-1.3	-0.885	-0.4668	100001	600000
d[14]	-1.095	0.2279	0.001139	-1.538	-1.096	-0.6444	100001	600000
lnHR[1,2]	-1.039	0.1839	5.79E-04	-1.402	-1.04	-0.6774	100001	600000
lnHR[1,3]	-0.5614	0.1736	4.98E-04	-0.9052	-0.5609	-0.2192	100001	600000
lnHR[1,4]	-0.2075	0.09053	2.95E-04	-0.3843	-0.2083	-0.02346	100001	600000
lnHR[1,5]	-0.5449	0.1926	6.61E-04	-0.9232	-0.545	-0.1673	100001	600000
lnHR[1,6]	-0.7996	0.1197	4.69E-04	-1.038	-0.7993	-0.5622	100001	600000
lnHR[1,7]	-1.361	0.1869	7.82E-04	-1.729	-1.362	-0.9858	100001	600000
lnHR[1,8]	-0.7957	0.1702	7.02E-04	-1.131	-0.796	-0.4571	100001	600000
lnHR[1,9]	-1.664	0.1814	7.09E-04	-2.022	-1.665	-1.306	100001	600000
lnHR[1,10]	-0.9909	0.1863	7.42E-04	-1.365	-0.9901	-0.6256	100001	600000
lnHR[1,11]	-1.035	0.2741	0.001187	-1.573	-1.036	-0.486	100001	600000
lnHR[1,12]	-1.521	0.3263	0.001691	-2.165	-1.523	-0.8764	100001	600000
lnHR[1,13]	-0.8841	0.2105	6.94E-04	-1.3	-0.885	-0.4668	100001	600000
lnHR[1,14]	-1.095	0.2279	0.001139	-1.538	-1.096	-0.6444	100001	600000
lnHR[2,3]	0.478	0.2528	7.89E-04	-0.02234	0.4776	0.975	100001	600000
lnHR[2,4]	0.832	0.2053	6.65E-04	0.4289	0.8311	1.24	100001	600000
lnHR[2,5]	0.4946	0.2658	8.25E-04	-0.02807	0.4944	1.02	100001	600000
lnHR[2,6]	0.2399	0.2193	7.30E-04	-0.1932	0.239	0.6739	100001	600000
lnHR[2,7]	-0.3213	0.2618	9.46E-04	-0.8358	-0.3229	0.2029	100001	600000
lnHR[2,8]	0.2437	0.2503	8.92E-04	-0.2505	0.2433	0.7386	100001	600000
lnHR[2,9]	-0.625	0.2581	8.91E-04	-1.134	-0.6257	-0.1142	100001	600000
lnHR[2,10]	0.04852	0.2612	9.07E-04	-0.4719	0.04907	0.5615	100001	600000
lnHR[2,11]	0.004713	0.3302	0.001301	-0.6435	0.002311	0.6615	100001	600000
lnHR[2,12]	-0.4819	0.3744	0.001785	-1.214	-0.4836	0.2568	100001	600000

lnHR[2,13]	0.1553	0.2791	8.98E-04	-0.3957	0.1549	0.7084	100001	600000
lnHR[2,14]	-0.05553	0.2929	0.001235	-0.6268	-0.05636	0.5259	100001	600000
lnHR[3,4]	0.3539	0.1954	5.57E-04	-0.0281	0.3523	0.7448	100001	600000
lnHR[3,5]	0.01654	0.2591	8.37E-04	-0.4933	0.01562	0.53	100001	600000
lnHR[3,6]	-0.2382	0.2108	6.77E-04	-0.6552	-0.2395	0.1809	100001	600000
lnHR[3,7]	-0.7994	0.255	9.10E-04	-1.298	-0.8008	-0.2892	100001	600000
lnHR[3,8]	-0.2343	0.2434	8.63E-04	-0.7154	-0.2349	0.2485	100001	600000
lnHR[3,9]	-1.103	0.2511	8.77E-04	-1.597	-1.103	-0.6064	100001	600000
lnHR[3,10]	-0.4295	0.2547	8.79E-04	-0.9356	-0.4293	0.0724	100001	600000
lnHR[3,11]	-0.4733	0.3244	0.001294	-1.11	-0.4754	0.1717	100001	600000
lnHR[3,12]	-0.9599	0.37	0.001762	-1.688	-0.9617	-0.2307	100001	600000
lnHR[3,13]	-0.3227	0.2726	8.62E-04	-0.8623	-0.3232	0.2204	100001	600000
lnHR[3,14]	-0.5336	0.2856	0.001199	-1.09	-0.5345	0.03189	100001	600000
lnHR[4,5]	-0.3374	0.2129	7.41E-04	-0.7605	-0.3364	0.07821	100001	600000
lnHR[4,6]	-0.5921	0.1103	4.54E-04	-0.8131	-0.5913	-0.3771	100001	600000
lnHR[4,7]	-1.153	0.181	7.67E-04	-1.511	-1.153	-0.7945	100001	600000
lnHR[4,8]	-0.5883	0.1928	7.51E-04	-0.9743	-0.5873	-0.2086	100001	600000
lnHR[4,9]	-1.457	0.2026	7.56E-04	-1.861	-1.456	-1.06	100001	600000
lnHR[4,10]	-0.7835	0.1801	7.07E-04	-1.146	-0.7827	-0.4332	100001	600000
lnHR[4,11]	-0.8273	0.2704	0.001192	-1.36	-0.8279	-0.2888	100001	600000
lnHR[4,12]	-1.314	0.3383	0.001699	-1.978	-1.315	-0.6455	100001	600000
lnHR[4,13]	-0.6766	0.205	6.42E-04	-1.084	-0.6762	-0.2724	100001	600000
lnHR[4,14]	-0.8875	0.221	0.001091	-1.32	-0.8885	-0.4526	100001	600000
lnHR[5,6]	-0.2547	0.2269	8.28E-04	-0.7005	-0.2552	0.1931	100001	600000
lnHR[5,7]	-0.8159	0.268	9.83E-04	-1.341	-0.817	-0.2824	100001	600000
lnHR[5,8]	-0.2509	0.2574	9.76E-04	-0.7582	-0.2513	0.2559	100001	600000
lnHR[5,9]	-1.12	0.2647	9.69E-04	-1.64	-1.12	-0.5982	100001	600000
lnHR[5,10]	-0.4461	0.2678	0.001008	-0.9774	-0.4465	0.08076	100001	600000
lnHR[5,11]	-0.4899	0.3349	0.001296	-1.146	-0.4911	0.1744	100001	600000
lnHR[5,12]	-0.9764	0.3791	0.001834	-1.718	-0.9775	-0.2238	100001	600000
lnHR[5,13]	-0.3392	0.2853	9.97E-04	-0.8995	-0.3391	0.2236	100001	600000
lnHR[5,14]	-0.5501	0.2992	0.001366	-1.136	-0.5514	0.03853	100001	600000
lnHR[6,7]	-0.5612	0.1437	5.22E-04	-0.8423	-0.5619	-0.2718	100001	600000
lnHR[6,8]	0.003846	0.2084	8.79E-04	-0.4078	0.004101	0.4173	100001	600000
lnHR[6,9]	-0.8648	0.2177	8.88E-04	-1.297	-0.8645	-0.4345	100001	600000
lnHR[6,10]	-0.1913	0.1422	4.56E-04	-0.4788	-0.1905	0.08652	100001	600000
lnHR[6,11]	-0.2351	0.2467	0.001016	-0.7175	-0.2358	0.2606	100001	600000
lnHR[6,12]	-0.7217	0.3486	0.001811	-1.409	-0.7236	-0.0352	100001	600000
lnHR[6,13]	-0.08452	0.1739	5.64E-04	-0.4252	-0.08492	0.2608	100001	600000
lnHR[6,14]	-0.2954	0.2432	0.001165	-0.7707	-0.297	0.1836	100001	600000
lnHR[7,8]	0.565	0.2532	0.001114	0.05934	0.5664	1.064	100001	600000
lnHR[7,9]	-0.3036	0.2608	0.001114	-0.8234	-0.3027	0.2087	100001	600000
lnHR[7,10]	0.3699	0.1776	7.28E-04	0.01069	0.3717	0.7164	100001	600000
lnHR[7,11]	0.326	0.2001	7.85E-04	-0.0684	0.3261	0.7227	100001	600000
lnHR[7,12]	-0.1605	0.3771	0.001954	-0.9046	-0.1628	0.581	100001	600000
lnHR[7,13]	0.4767	0.2259	8.30E-04	0.0286	0.4773	0.92	100001	600000
lnHR[7,14]	0.2658	0.2829	0.00134	-0.2904	0.2646	0.8202	100001	600000
lnHR[8,9]	-0.8687	0.1598	4.13E-04	-1.186	-0.8688	-0.5491	100001	600000

lnHR[8,10]	-0.1952	0.2525	0.001031	-0.6997	-0.1943	0.3007	100001	600000
lnHR[8,11]	-0.239	0.3229	0.001447	-0.8726	-0.2406	0.4058	100001	600000
lnHR[8,12]	-0.7256	0.2793	0.001504	-1.274	-0.7256	-0.177	100001	600000
lnHR[8,13]	-0.08836	0.2708	9.96E-04	-0.6249	-0.08822	0.4477	100001	600000
lnHR[8,14]	-0.2992	0.2852	0.00135	-0.8552	-0.3017	0.2653	100001	600000
lnHR[9,10]	0.6735	0.2601	0.001048	0.1555	0.6742	1.187	100001	600000
lnHR[9,11]	0.6297	0.329	0.001449	-0.01553	0.6286	1.286	100001	600000
lnHR[9,12]	0.1431	0.3212	0.001464	-0.4854	0.1438	0.7743	100001	600000
lnHR[9,13]	0.7803	0.278	0.001011	0.23	0.7804	1.331	100001	600000
lnHR[9,14]	0.5695	0.2912	0.001314	7.71E-04	0.5673	1.146	100001	600000
lnHR[10,11]	-0.04381	0.2678	0.001099	-0.5656	-0.04675	0.4958	100001	600000
lnHR[10,12]	-0.5304	0.3772	0.001948	-1.27	-0.5319	0.2164	100001	600000
lnHR[10,13]	0.1068	0.2252	7.01E-04	-0.3332	0.106	0.5578	100001	600000
lnHR[10,14]	-0.104	0.2821	0.001279	-0.6529	-0.1065	0.4552	100001	600000
lnHR[11,12]	-0.4866	0.4272	0.002206	-1.333	-0.4873	0.3515	100001	600000
lnHR[11,13]	0.1506	0.3019	0.001202	-0.4504	0.1515	0.7436	100001	600000
lnHR[11,14]	-0.06024	0.3476	0.001633	-0.746	-0.06126	0.6216	100001	600000
lnHR[12,13]	0.6372	0.3888	0.001836	-0.1303	0.639	1.398	100001	600000
lnHR[12,14]	0.4263	0.3973	0.001987	-0.3501	0.4264	1.211	100001	600000
lnHR[13,14]	-0.2109	0.2979	0.001274	-0.795	-0.2111	0.377	100001	600000
rk[1]	13.97	0.1874	5.76E-04	13	14	14	100001	600000
rk[2]	5.891	2.019	0.007285	3	6	10	100001	600000
rk[3]	10.97	1.414	0.005143	7	11	13	100001	600000
rk[4]	12.92	0.3628	0.001025	12	13	13	100001	600000
rk[5]	11.03	1.492	0.005479	7	11	13	100001	600000
rk[6]	8.946	1.196	0.005054	6	9	11	100001	600000
rk[7]	2.944	1.052	0.004447	1	3	5	100001	600000
rk[8]	8.743	1.934	0.0094	5	9	12	100001	600000
rk[9]	1.508	0.7858	0.003192	1	1	3	100001	600000
rk[10]	6.358	1.727	0.006531	3	6	10	100001	600000
rk[11]	6.096	2.385	0.01065	2	6	11	100001	600000
rk[12]	2.517	1.745	0.008547	1	2	7	100001	600000
rk[13]	7.696	2.087	0.007499	4	8	12	100001	600000
rk[14]	5.405	2.204	0.0109	2	5	10	100001	600000
Sd	0.09545	0.07554	7.75E-04	0.003975	0.07939	0.2829	100001	600000
Tau	575600	5.69E+07	3.54E+05	12.49	158.7	63300	100001	600000
totresdev	16.58	5.396	0.02844	7.903	15.93	28.84	100001	600000

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
sd	1.386	1.386	0	1.386
y	-20.914	-35.649	14.735	-6.18
total	-19.528	-34.263	14.735	-4.793

Adjusted DIC=totresdev+pD= 16.6+14.7=31.3

Results from the fixed effect meta-regression NMA model of the large network

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
B	0.03961	0.02508	6.72E-05	-0.00954	0.03959	0.08882	100001	600000
HR[1,2]	0.5111	0.132	3.01E-04	0.3008	0.4948	0.8137	100001	600000
HR[1,3]	0.6623	0.1008	1.61E-04	0.4868	0.6548	0.8808	100001	600000
HR[1,4]	1.123	0.2313	6.11E-04	0.738	1.1	1.64	100001	600000
HR[1,5]	1.06	0.406	0.001003	0.4795	0.9898	2.044	100001	600000
HR[1,6]	0.6299	0.1363	3.66E-04	0.405	0.6156	0.9364	100001	600000
HR[1,7]	0.3587	0.08556	2.15E-04	0.2201	0.3489	0.5532	100001	600000
HR[1,8]	0.4544	0.05429	3.00E-05	0.3573	0.4512	0.5697	100001	600000
HR[1,9]	0.1911	0.02593	1.37E-05	0.1454	0.1894	0.2469	100001	600000
HR[1,10]	0.5257	0.1247	3.11E-04	0.3234	0.5115	0.8092	100001	600000
HR[1,11]	0.5033	0.1458	3.07E-04	0.2771	0.4835	0.8435	100001	600000
HR[1,12]	0.2276	0.06471	2.98E-05	0.1268	0.2189	0.3783	100001	600000
HR[1,13]	0.584	0.1466	3.45E-04	0.3492	0.5664	0.9192	100001	600000
HR[1,14]	0.4853	0.1423	2.90E-04	0.2656	0.4658	0.8174	100001	600000
HR[2,3]	1.357	0.3071	4.70E-04	0.854	1.323	2.05	100001	600000
HR[2,4]	2.249	0.3446	1.49E-04	1.65	2.223	2.995	100001	600000
HR[2,5]	2.059	0.4984	7.23E-04	1.253	2.001	3.194	100001	600000
HR[2,6]	1.26	0.2038	8.29E-05	0.9083	1.244	1.704	100001	600000
HR[2,7]	0.7177	0.1363	6.04E-05	0.4882	0.705	1.02	100001	600000
HR[2,8]	0.9483	0.2713	5.53E-04	0.5261	0.9118	1.579	100001	600000
HR[2,9]	0.3989	0.1171	2.32E-04	0.2177	0.3827	0.6723	100001	600000
HR[2,10]	1.052	0.198	8.41E-05	0.7169	1.034	1.49	100001	600000
HR[2,11]	1.007	0.2518	1.14E-04	0.6028	0.977	1.582	100001	600000
HR[2,12]	0.4751	0.1859	2.84E-04	0.2114	0.4423	0.9275	100001	600000
HR[2,13]	1.168	0.2396	9.90E-05	0.7687	1.145	1.703	100001	600000
HR[2,14]	0.9685	0.2349	8.96E-05	0.5889	0.9412	1.504	100001	600000
HR[3,4]	1.706	0.2992	5.20E-04	1.194	1.68	2.363	100001	600000
HR[3,5]	1.59	0.5162	0.001107	0.813	1.512	2.813	100001	600000
HR[3,6]	0.9563	0.1774	3.26E-04	0.6554	0.9403	1.348	100001	600000
HR[3,7]	0.5446	0.1148	1.96E-04	0.3541	0.5328	0.8014	100001	600000
HR[3,8]	0.7019	0.1364	1.75E-04	0.4723	0.689	1.005	100001	600000
HR[3,9]	0.2952	0.06047	7.39E-05	0.1943	0.2892	0.4303	100001	600000
HR[3,10]	0.7981	0.1669	2.81E-04	0.5208	0.7813	1.172	100001	600000
HR[3,11]	0.7641	0.2041	2.86E-04	0.4417	0.7381	1.236	100001	600000
HR[3,12]	0.3516	0.1144	9.70E-05	0.1795	0.3343	0.623	100001	600000
HR[3,13]	0.8865	0.1991	3.13E-04	0.56	0.865	1.335	100001	600000
HR[3,14]	0.736	0.1955	2.65E-04	0.4265	0.7114	1.187	100001	600000
HR[4,5]	0.9213	0.2015	3.58E-04	0.5893	0.9	1.375	100001	600000
HR[4,6]	0.5617	0.04799	2.86E-05	0.4735	0.5597	0.6615	100001	600000
HR[4,7]	0.3199	0.04172	2.56E-05	0.2459	0.3172	0.4092	100001	600000
HR[4,8]	0.4217	0.1009	2.28E-04	0.2583	0.4102	0.6512	100001	600000
HR[4,9]	0.1774	0.044	9.58E-05	0.1066	0.1721	0.278	100001	600000
HR[4,10]	0.4688	0.0601	3.29E-05	0.3621	0.465	0.5972	100001	600000
HR[4,11]	0.4488	0.09315	4.93E-05	0.294	0.4394	0.6573	100001	600000
HR[4,12]	0.2112	0.07515	1.17E-04	0.1012	0.199	0.3916	100001	600000

HR[4,13]	0.5207	0.07877	3.85E-05	0.3833	0.5149	0.6911	100001	600000
HR[4,14]	0.4312	0.0834	3.62E-05	0.2908	0.4234	0.6162	100001	600000
HR[5,6]	0.637	0.1418	2.25E-04	0.4042	0.6218	0.9566	100001	600000
HR[5,7]	0.3628	0.08863	1.25E-04	0.2198	0.3524	0.5647	100001	600000
HR[5,8]	0.4914	0.1981	4.56E-04	0.2128	0.4558	0.9752	100001	600000
HR[5,9]	0.2067	0.08455	1.92E-04	0.08847	0.1913	0.4136	100001	600000
HR[5,10]	0.5317	0.1291	1.85E-04	0.323	0.5169	0.8259	100001	600000
HR[5,11]	0.509	0.1501	1.75E-04	0.2774	0.4882	0.8595	100001	600000
HR[5,12]	0.2461	0.1202	2.30E-04	0.08923	0.2212	0.5479	100001	600000
HR[5,13]	0.5906	0.1515	2.07E-04	0.3487	0.5721	0.9378	100001	600000
HR[5,14]	0.4887	0.1378	1.69E-04	0.2737	0.4705	0.8089	100001	600000
HR[6,7]	0.5695	0.05588	2.31E-05	0.4678	0.5669	0.6865	100001	600000
HR[6,8]	0.7551	0.1876	4.34E-04	0.4539	0.7328	1.184	100001	600000
HR[6,9]	0.3176	0.08163	1.83E-04	0.1874	0.3076	0.5053	100001	600000
HR[6,10]	0.8346	0.07943	2.61E-05	0.6898	0.8309	1.001	100001	600000
HR[6,11]	0.799	0.1505	6.36E-05	0.5447	0.7852	1.133	100001	600000
HR[6,12]	0.3783	0.1371	2.22E-04	0.1787	0.3556	0.7083	100001	600000
HR[6,13]	0.9271	0.1153	3.75E-05	0.7217	0.92	1.173	100001	600000
HR[6,14]	0.7728	0.1611	6.44E-05	0.5049	0.7565	1.134	100001	600000
HR[7,8]	1.339	0.3591	7.92E-04	0.7712	1.293	2.169	100001	600000
HR[7,9]	0.5631	0.1556	3.33E-04	0.3189	0.5427	0.924	100001	600000
HR[7,10]	1.478	0.1908	6.96E-05	1.139	1.466	1.886	100001	600000
HR[7,11]	1.403	0.2244	7.25E-05	1.014	1.386	1.891	100001	600000
HR[7,12]	0.6706	0.2529	4.04E-04	0.3069	0.6273	1.283	100001	600000
HR[7,13]	1.644	0.2613	9.55E-05	1.191	1.623	2.212	100001	600000
HR[7,14]	1.37	0.3169	1.35E-04	0.8526	1.335	2.088	100001	600000
HR[8,9]	0.422	0.04402	1.17E-05	0.3423	0.4198	0.5148	100001	600000
HR[8,10]	1.174	0.3134	6.96E-04	0.6777	1.134	1.896	100001	600000
HR[8,11]	1.123	0.3541	6.88E-04	0.5858	1.071	1.96	100001	600000
HR[8,12]	0.5009	0.1283	4.87E-05	0.2962	0.4852	0.7951	100001	600000
HR[8,13]	1.304	0.3646	7.74E-04	0.7332	1.255	2.148	100001	600000
HR[8,14]	1.083	0.345	6.49E-04	0.5616	1.032	1.899	100001	600000
HR[9,10]	2.801	0.7706	0.001663	1.59	2.701	4.586	100001	600000
HR[9,11]	2.682	0.8643	0.001643	1.379	2.553	4.731	100001	600000
HR[9,12]	1.2	0.3333	1.41E-04	0.6775	1.156	1.971	100001	600000
HR[9,13]	3.112	0.8942	0.00185	1.721	2.991	5.194	100001	600000
HR[9,14]	2.586	0.842	0.001549	1.321	2.46	4.581	100001	600000
HR[10,11]	0.965	0.1994	8.03E-05	0.6332	0.945	1.412	100001	600000
HR[10,12]	0.4573	0.1722	2.73E-04	0.2098	0.4279	0.8737	100001	600000
HR[10,13]	1.121	0.176	6.19E-05	0.8157	1.107	1.503	100001	600000
HR[10,14]	0.9343	0.215	8.78E-05	0.5835	0.9105	1.421	100001	600000
HR[11,12]	0.4902	0.203	3.02E-04	0.2075	0.4526	0.9881	100001	600000
HR[11,13]	1.201	0.2725	1.11E-04	0.7549	1.172	1.817	100001	600000
HR[11,14]	1.001	0.2839	1.26E-04	0.5583	0.9636	1.662	100001	600000
HR[12,13]	2.773	1.071	0.001689	1.247	2.587	5.371	100001	600000
HR[12,14]	2.304	0.9595	0.00142	0.9716	2.127	4.654	100001	600000
HR[13,14]	0.8465	0.2067	8.46E-05	0.5135	0.8224	1.318	100001	600000
best[1]	0	0	4.71E-14	0	0	0	100001	600000

best[2]	8.73E-05	0.009345	7.63E-06	0	0	0	100001	600000
best[3]	0	0	4.71E-14	0	0	0	100001	600000
best[4]	0	0	4.71E-14	0	0	0	100001	600000
best[5]	6.67E-07	8.17E-04	6.66E-07	0	0	0	100001	600000
best[6]	0	0	4.71E-14	0	0	0	100001	600000
best[7]	0.008392	0.09122	1.02E-04	0	0	0	100001	600000
best[8]	0	0	4.71E-14	0	0	0	100001	600000
best[9]	0.6938	0.4609	3.23E-04	0	1	1	100001	600000
best[10]	6.67E-07	8.17E-04	6.67E-07	0	0	0	100001	600000
best[11]	3.57E-04	0.0189	1.55E-05	0	0	0	100001	600000
best[12]	0.2962	0.4566	3.16E-04	0	0	1	100001	600000
best[13]	6.67E-07	8.17E-04	6.67E-07	0	0	0	100001	600000
best[14]	0.001141	0.03375	2.88E-05	0	0	0	100001	600000
d[2]	-0.7035	0.254	5.80E-04	-1.201	-0.7037	-0.2061	100001	600000
d[3]	-0.4234	0.1513	2.41E-04	-0.7199	-0.4234	-0.1269	100001	600000
d[4]	0.09537	0.2038	5.38E-04	-0.3039	0.09528	0.495	100001	600000
d[5]	-0.00993	0.3699	9.19E-04	-0.7351	-0.01025	0.7148	100001	600000
d[6]	-0.4851	0.2139	5.72E-04	-0.904	-0.4852	-0.06575	100001	600000
d[7]	-1.053	0.2353	5.89E-04	-1.514	-1.053	-0.5921	100001	600000
d[8]	-0.796	0.1191	6.49E-05	-1.029	-0.7959	-0.5626	100001	600000
d[9]	-1.664	0.135	7.02E-05	-1.929	-1.664	-1.399	100001	600000
d[10]	-0.6704	0.2341	5.82E-04	-1.129	-0.6704	-0.2117	100001	600000
d[11]	-0.7269	0.2839	6.00E-04	-1.283	-0.7268	-0.1702	100001	600000
d[12]	-1.519	0.2789	1.15E-04	-2.066	-1.519	-0.9722	100001	600000
d[13]	-0.5685	0.2472	5.82E-04	-1.052	-0.5685	-0.0843	100001	600000
d[14]	-0.7641	0.2871	5.87E-04	-1.326	-0.764	-0.2016	100001	600000
lnHR[1,2]	-0.7035	0.254	5.80E-04	-1.201	-0.7037	-0.2061	100001	600000
lnHR[1,3]	-0.4234	0.1513	2.41E-04	-0.7199	-0.4234	-0.1269	100001	600000
lnHR[1,4]	0.09537	0.2038	5.38E-04	-0.3039	0.09528	0.495	100001	600000
lnHR[1,5]	-0.00993	0.3699	9.19E-04	-0.7351	-0.01025	0.7148	100001	600000
lnHR[1,6]	-0.4851	0.2139	5.72E-04	-0.904	-0.4852	-0.06575	100001	600000
lnHR[1,7]	-1.053	0.2353	5.89E-04	-1.514	-1.053	-0.5921	100001	600000
lnHR[1,8]	-0.796	0.1191	6.49E-05	-1.029	-0.7959	-0.5626	100001	600000
lnHR[1,9]	-1.664	0.135	7.02E-05	-1.929	-1.664	-1.399	100001	600000
lnHR[1,10]	-0.6704	0.2341	5.82E-04	-1.129	-0.6704	-0.2117	100001	600000
lnHR[1,11]	-0.7269	0.2839	6.00E-04	-1.283	-0.7268	-0.1702	100001	600000
lnHR[1,12]	-1.519	0.2789	1.15E-04	-2.066	-1.519	-0.9722	100001	600000
lnHR[1,13]	-0.5685	0.2472	5.82E-04	-1.052	-0.5685	-0.0843	100001	600000
lnHR[1,14]	-0.7641	0.2871	5.87E-04	-1.326	-0.764	-0.2016	100001	600000
lnHR[2,3]	0.2801	0.2236	3.46E-04	-0.1579	0.2801	0.7179	100001	600000
lnHR[2,4]	0.7989	0.1523	6.33E-05	0.5005	0.7987	1.097	100001	600000
lnHR[2,5]	0.6936	0.2386	3.45E-04	0.2256	0.6935	1.161	100001	600000
lnHR[2,6]	0.2184	0.1607	6.29E-05	-0.09614	0.2182	0.5332	100001	600000
lnHR[2,7]	-0.3494	0.1881	8.10E-05	-0.717	-0.3495	0.01976	100001	600000
lnHR[2,8]	-0.09242	0.2806	5.83E-04	-0.6422	-0.09232	0.4568	100001	600000
lnHR[2,9]	-0.9605	0.2877	5.82E-04	-1.525	-0.9604	-0.397	100001	600000
lnHR[2,10]	0.03316	0.1866	7.54E-05	-0.3328	0.03321	0.3989	100001	600000
lnHR[2,11]	-0.02336	0.2463	1.06E-04	-0.5061	-0.0233	0.459	100001	600000

lnHR[2,12]	-0.8155	0.3775	5.92E-04	-1.554	-0.8158	-0.0753	100001	600000
lnHR[2,13]	0.135	0.203	7.82E-05	-0.263	0.135	0.5326	100001	600000
lnHR[2,14]	-0.06057	0.239	7.60E-05	-0.5295	-0.06064	0.408	100001	600000
lnHR[3,4]	0.5188	0.1741	3.03E-04	0.1777	0.5189	0.8601	100001	600000
lnHR[3,5]	0.4135	0.3166	6.83E-04	-0.2071	0.4131	1.034	100001	600000
lnHR[3,6]	-0.06165	0.184	3.38E-04	-0.4225	-0.06155	0.2988	100001	600000
lnHR[3,7]	-0.6294	0.2085	3.56E-04	-1.038	-0.6295	-0.2214	100001	600000
lnHR[3,8]	-0.3725	0.1925	2.48E-04	-0.7501	-0.3726	0.004721	100001	600000
lnHR[3,9]	-1.241	0.2028	2.49E-04	-1.638	-1.241	-0.8433	100001	600000
lnHR[3,10]	-0.2469	0.2069	3.48E-04	-0.6525	-0.2468	0.1588	100001	600000
lnHR[3,11]	-0.3034	0.2624	3.69E-04	-0.817	-0.3037	0.2118	100001	600000
lnHR[3,12]	-1.096	0.3174	2.67E-04	-1.718	-1.096	-0.4733	100001	600000
lnHR[3,13]	-0.145	0.2219	3.49E-04	-0.5798	-0.145	0.2889	100001	600000
lnHR[3,14]	-0.3407	0.2611	3.53E-04	-0.8522	-0.3405	0.1711	100001	600000
lnHR[4,5]	-0.1053	0.2161	3.84E-04	-0.5287	-0.1053	0.3182	100001	600000
lnHR[4,6]	-0.5805	0.08528	5.07E-05	-0.7476	-0.5804	-0.4133	100001	600000
lnHR[4,7]	-1.148	0.1298	7.90E-05	-1.403	-1.148	-0.8936	100001	600000
lnHR[4,8]	-0.8913	0.236	5.40E-04	-1.354	-0.8911	-0.4289	100001	600000
lnHR[4,9]	-1.759	0.2445	5.40E-04	-2.239	-1.759	-1.28	100001	600000
lnHR[4,10]	-0.7657	0.1277	6.92E-05	-1.016	-0.7658	-0.5155	100001	600000
lnHR[4,11]	-0.8223	0.2053	1.07E-04	-1.224	-0.8225	-0.4196	100001	600000
lnHR[4,12]	-1.614	0.3453	5.50E-04	-2.291	-1.614	-0.9374	100001	600000
lnHR[4,13]	-0.6638	0.1504	7.24E-05	-0.9589	-0.6638	-0.3694	100001	600000
lnHR[4,14]	-0.8595	0.1916	7.46E-05	-1.235	-0.8594	-0.4842	100001	600000
lnHR[5,6]	-0.4752	0.22	3.54E-04	-0.9058	-0.4751	-0.04437	100001	600000
lnHR[5,7]	-1.043	0.2408	3.43E-04	-1.515	-1.043	-0.5714	100001	600000
lnHR[5,8]	-0.786	0.3886	9.20E-04	-1.547	-0.7856	-0.02513	100001	600000
lnHR[5,9]	-1.654	0.3938	9.20E-04	-2.425	-1.654	-0.8829	100001	600000
lnHR[5,10]	-0.6604	0.2395	3.48E-04	-1.13	-0.66	-0.1913	100001	600000
lnHR[5,11]	-0.717	0.2886	3.43E-04	-1.282	-0.717	-0.1514	100001	600000
lnHR[5,12]	-1.509	0.4631	9.27E-04	-2.417	-1.509	-0.6017	100001	600000
lnHR[5,13]	-0.5585	0.2525	3.49E-04	-1.054	-0.5584	-0.06419	100001	600000
lnHR[5,14]	-0.7542	0.2766	3.43E-04	-1.296	-0.7541	-0.2121	100001	600000
lnHR[6,7]	-0.5678	0.09791	4.03E-05	-0.7598	-0.5676	-0.3762	100001	600000
lnHR[6,8]	-0.3109	0.2447	5.75E-04	-0.7899	-0.3109	0.1689	100001	600000
lnHR[6,9]	-1.179	0.2529	5.75E-04	-1.674	-1.179	-0.6826	100001	600000
lnHR[6,10]	-0.1853	0.09496	3.05E-05	-0.3714	-0.1852	0.00101	100001	600000
lnHR[6,11]	-0.2418	0.1867	7.62E-05	-0.6076	-0.2419	0.1248	100001	600000
lnHR[6,12]	-1.034	0.3514	5.84E-04	-1.722	-1.034	-0.3449	100001	600000
lnHR[6,13]	-0.08338	0.1239	3.84E-05	-0.3261	-0.08338	0.1592	100001	600000
lnHR[6,14]	-0.279	0.2063	7.47E-05	-0.6834	-0.279	0.1255	100001	600000
lnHR[7,8]	0.2569	0.2636	5.92E-04	-0.2598	0.2568	0.7742	100001	600000
lnHR[7,9]	-0.6111	0.2712	5.91E-04	-1.143	-0.6112	-0.07909	100001	600000
lnHR[7,10]	0.3825	0.1285	4.54E-05	0.1305	0.3825	0.6343	100001	600000
lnHR[7,11]	0.326	0.1589	4.82E-05	0.01431	0.3261	0.6374	100001	600000
lnHR[7,12]	-0.4661	0.3648	6.01E-04	-1.181	-0.4663	0.2493	100001	600000
lnHR[7,13]	0.4844	0.158	5.49E-05	0.1748	0.4845	0.7938	100001	600000
lnHR[7,14]	0.2888	0.2283	8.98E-05	-0.1595	0.2889	0.7363	100001	600000

lnHR[8,9]	-0.868	0.104	2.64E-05	-1.072	-0.8681	-0.664	100001	600000
lnHR[8,10]	0.1256	0.2625	5.85E-04	-0.389	0.1258	0.6397	100001	600000
lnHR[8,11]	0.06907	0.3078	6.02E-04	-0.5347	0.06904	0.6727	100001	600000
lnHR[8,12]	-0.723	0.2521	7.80E-05	-1.217	-0.7231	-0.2292	100001	600000
lnHR[8,13]	0.2275	0.2744	5.85E-04	-0.3103	0.2273	0.7646	100001	600000
lnHR[8,14]	0.03185	0.3108	5.89E-04	-0.577	0.03172	0.6413	100001	600000
lnHR[9,10]	0.9936	0.2701	5.84E-04	0.464	0.9937	1.523	100001	600000
lnHR[9,11]	0.9371	0.3143	6.02E-04	0.3211	0.9372	1.554	100001	600000
lnHR[9,12]	0.145	0.2727	8.58E-05	-0.3893	0.1447	0.6787	100001	600000
lnHR[9,13]	1.096	0.2817	5.85E-04	0.5428	1.096	1.648	100001	600000
lnHR[9,14]	0.8999	0.3173	5.89E-04	0.2786	0.9001	1.522	100001	600000
lnHR[10,11]	-0.05652	0.2045	7.76E-05	-0.457	-0.0566	0.3447	100001	600000
lnHR[10,12]	-0.8486	0.3639	5.94E-04	-1.561	-0.8488	-0.135	100001	600000
lnHR[10,13]	0.1019	0.1561	4.77E-05	-0.2038	0.1017	0.4077	100001	600000
lnHR[10,14]	-0.09374	0.2272	8.41E-05	-0.5388	-0.09375	0.3517	100001	600000
lnHR[11,12]	-0.7921	0.3979	6.11E-04	-1.573	-0.7927	-0.01201	100001	600000
lnHR[11,13]	0.1584	0.2241	8.49E-05	-0.2812	0.1587	0.5974	100001	600000
lnHR[11,14]	-0.03722	0.2782	1.13E-04	-0.5829	-0.03706	0.5078	100001	600000
lnHR[12,13]	0.9505	0.3726	5.94E-04	0.2206	0.9504	1.681	100001	600000
lnHR[12,14]	0.7549	0.3999	5.99E-04	-0.02881	0.7549	1.538	100001	600000
lnHR[13,14]	-0.1956	0.2406	8.77E-05	-0.6665	-0.1955	0.2758	100001	600000
rk[1]	12.79	0.945	0.002243	12	13	14	100001	600000
rk[2]	6.598	1.903	0.001408	4	6	11	100001	600000
rk[3]	10	1.609	0.002771	6	11	12	100001	600000
rk[4]	13.37	0.5498	6.20E-04	12	13	14	100001	600000
rk[5]	12.64	1.16	0.002332	10	13	14	100001	600000
rk[6]	9.744	0.9708	0.001227	8	10	11	100001	600000
rk[7]	3.211	0.7128	0.001042	2	3	5	100001	600000
rk[8]	5.745	2.236	0.00492	3	5	11	100001	600000
rk[9]	1.314	0.4856	3.66E-04	1	1	2	100001	600000
rk[10]	6.915	1.507	0.001403	4	7	10	100001	600000
rk[11]	6.423	2.109	0.001655	3	6	11	100001	600000
rk[12]	1.891	0.8889	8.44E-04	1	2	4	100001	600000
rk[13]	8.364	1.778	0.001418	5	8	11	100001	600000
rk[14]	5.992	2.169	0.001503	3	6	11	100001	600000
totresdev	15.52	5.29	0.008593	7.167	14.86	27.67	100001	600000

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
y	-21.969	-35.969	14.001	-7.968
total	-21.969	-35.969	14.001	-7.968

Adjusted DIC=totresdev+pD=15.5+14.0=29.5

In order to display the results of the MTC in an easy to read format, results for both large network FE models only are displayed in the matrices below.

Mean HR results from the fixed effect NMA of the large network (NOT age adjusted)

	Clb	Benda	OClb	F	Alm	FC	RFC	RClb	GClb	FCAlm	RBenda	RFC-Lite	ClaC
Benda	0.36												
Oclb	0.57	1.64											
F	0.81	2.32	1.43										
Alm	0.59	1.68	1.04	0.73									
FC	0.45	1.29	0.80	0.558	0.788								
RFC	0.26	0.74	0.46	0.32	0.45	0.57							
RClb	0.45	1.30	0.80	0.56	0.79	1.01	1.79						
GClb	0.19	0.55	0.34	0.24	0.33	0.43	0.76	0.42					
FCAlm	0.38	1.08	0.67	0.47	0.66	0.84	1.48	0.84	2.01				
RBenda	0.36	1.03	0.64	0.45	0.63	0.80	1.40	0.81	1.92	0.97			
RFC-Lite	0.23	0.65	0.40	0.28	0.40	0.51	0.90	0.50	1.20	0.61	0.66		
ClaC	0.42	1.20	0.74	0.52	0.73	0.93	1.64	0.94	2.23	1.12	1.20	1.99	
Cla	0.34	0.97	0.60	0.42	0.59	0.76	1.34	0.76	1.81	0.92	0.98	1.62	0.83

A value of HR<1 indicates that the treatment on the left-hand side column performs better than the treatment on the top row

Mean HR results from the fixed effect meta-regression NMA of the large network (age adjusted)

	Clb	Benda	OClb	F	Alm	FC	RFC	RClb	GClb	FCAlm	RBenda	RFC-Lite	ClaC
Benda	0.51												
Oclb	0.66	1.36											
F	1.12	2.25	1.71										
Alm	1.06	2.06	1.59	0.92									
FC	0.63	1.26	0.96	0.562	0.637								
RFC	0.36	0.72	0.55	0.32	0.36	0.57							
RClb	0.45	0.95	0.70	0.42	0.49	0.76	1.34						
GClb	0.19	0.40	0.30	0.18	0.21	0.32	0.56	0.42					
FCAlm	0.53	1.05	0.80	0.47	0.53	0.84	1.48	1.17	2.80				
RBenda	0.50	1.01	0.76	0.45	0.51	0.80	1.40	1.12	2.68	0.97			
RFC-Lite	0.23	0.48	0.35	0.21	0.25	0.38	0.67	0.50	1.20	0.46	0.49		
ClaC	0.58	1.17	0.89	0.52	0.59	0.93	1.64	1.30	3.11	1.12	1.20	2.77	
Cla	0.49	0.97	0.74	0.43	0.49	0.77	1.37	1.08	2.59	0.93	1.00	2.30	0.85

A value of HR<1 indicates that the treatment on the left-hand side column performs better than the treatment on the top row

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be

completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.