NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ibrutinib for treating chronic lymphocytic leukaemia

This premeeting briefing presents:

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

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness:

- Is the company's assumption of physician choice in line with UK clinical practice?
- The clinical evidence of the efficacy of ibrutinib in people with CLL with the 17p deletion mutation data who have not received treatment before is very limited. Although there limited data from a single arm study, the company has used the 17p deletion population who have previously received treatment from the RESONATE trial as a proxy for those who have never received treatment before. Is this a reasonable assumption? Is the overall evidence base for the subgroup sufficient?
- People with the TP53 mutation were not included in the RESONATE trial. Is it possible for the data from the17p deletion population to be generalisable to people with the TP53 mutation?

- The company has not provided any comparisons with fludarabine in combination with cyclophosphamide and rituximab (FCR). NICE technology appraisal 174 recommends FCR as first line treatment for patients who are able to take fludarabine-containing regimens. For people with relapsed or refractory CLL NICE technology appraisal 193 recommends FCR, unless the disease is has not responded to fludarabine or has relapsed within 6 months of treatment with fludarabine, or has previously been treated with rituximab. Does the exclusion of FCR as a comparator restrict decision-making to people who cannot have FCR?
- The ERG consider that given that the data inputs from the other trials in the network were not adjusted for crossover, it would be more consistent methodology to use the ITT estimates from all studies, including RESONATE. The ERG presented revised estimates – are these more appropriate?
- The ERG notes that there is some uncertainty in the magnitude of the indirect treatment comparison and matching-adjusted indirect comparison results calculated by the company.

Cost effectiveness

- The company chose a Weibull parametric curve to extrapolate the progression-free survival for ibrutinib compared with ofatumumab. To extrapolate overall survival data, the company used a lognormal parametric curve for the first 3 years of the model and an exponential fit thereafter. The company did a sensitivity analysis using an exponential fit in both arms for the extrapolation of progression-free survival and overall survival. The ERG suggested that the Weibull function models too low a proportion of patients remaining in progression-free survival for the overall survival curve to be credible. Which parametric function is most appropriate to use for extrapolating progression-free and overall survival?
- The company treated the drug and administration costs differently in its model (which resulted in reduced costs in the ibrutinib arm). The company did this because ibrutinib is the only oral monotherapy in the model and so it believed that the costs should be reduced compared to other treatments. Is this a plausible assumption?
- Is it appropriate for the company to assume that patients will receive biopsies as part of routine follow-up, and that routine follow-up will be differentiated by response status.

- Are the end of life criteria met? Are the estimates presented by the company robust?

1 Remit and decision problems

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

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	• Adults with chronic lymphocytic leukaemia who have received at least 1 therapy • Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable			As per scope
Intervention	Ibrutinib			
Comparator	For adults with CLL who have received at least 1 prior therapy: • Fludarabine in combination with cyclophosphamide and rituximab • Bendamustine (with or without rituximab) • Chlorambucil (with or without rituximab) • Corticosteroids (with or without rituximab) • Idelalisib in combination with rituximab • Rituximab alone (for refractory disease) • Best supportive care For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable: • Alemtuzumab with or without corticosteroids • Idelalisib in combination with rituximab • Best supportive care	For adults with CLL who have received at least 1 prior therapy: • Physician's choice • Bendamustine (with or without rituximab) • Idelalisib in combination with rituximab • Ofatumumab For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable: • Alemtuzumab with or without corticosteroids • Idelalisib in combination with rituximab • Best supportive care	"Physician's choice" aims to accurately reflect that there is currently no clear standard of care for patients with relapsed or refractory CLL Clinical opinion strongly suggests that ofatumumab, despite no longer being funded by the Cancer Drugs Fund, remains a relevant comparator in the UK	
Outcomes	Overall survival, progression-free survival, response rates, adverse effects of treatment, health-related quality of life			

2 The technology and the treatment pathway

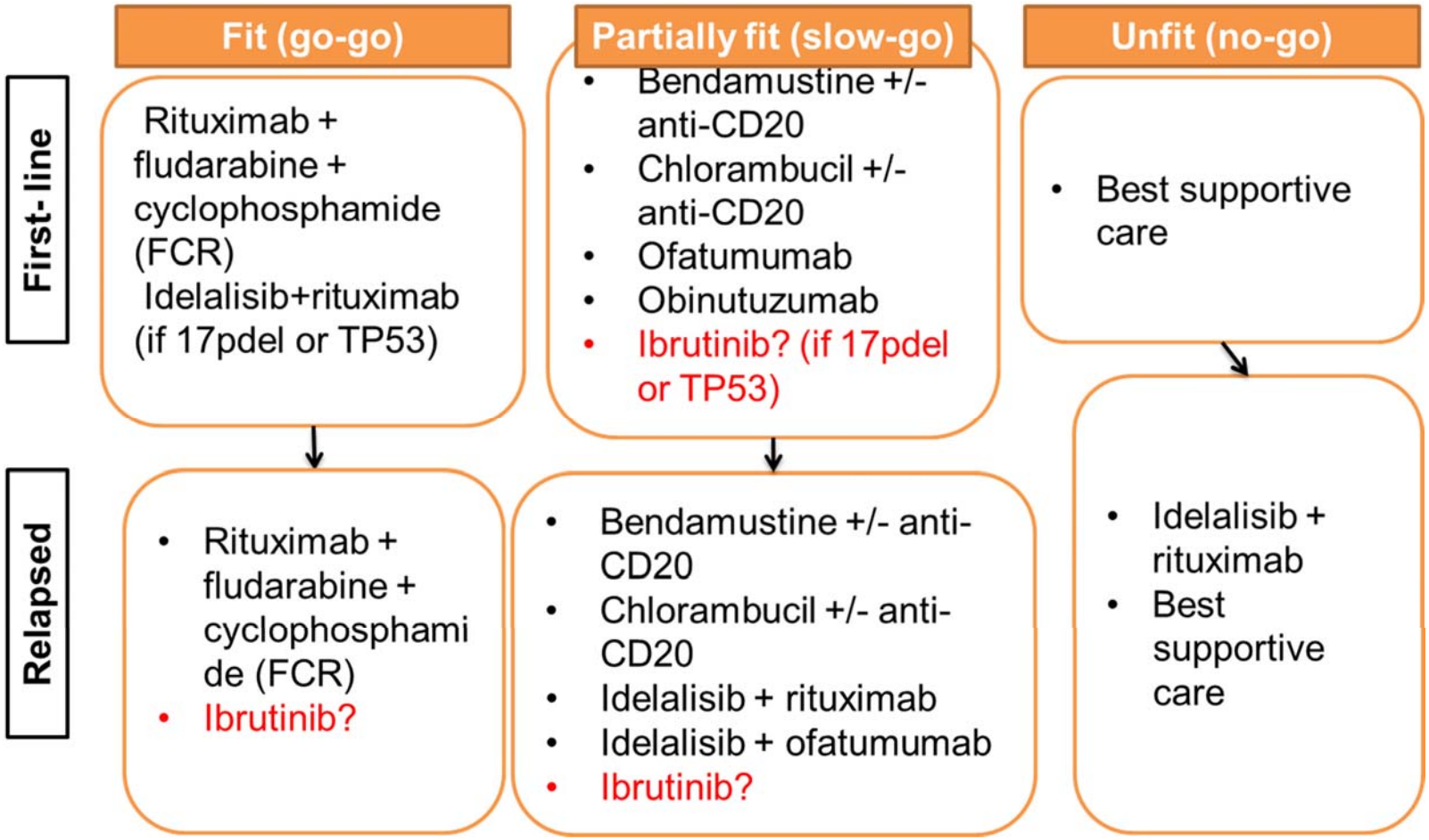


Figure 1 Treatment pathway adapted from the British Committee for Standards in Haematology interim guideline on CLL

Table 2 Technologies

	Ibrutinib	Ofatumumab	Idelalisib in combination with rituximab	Bendamustine in combination with rituximab
Marketing authorisation	It is indicated for the treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	**Previously untreated CLL:** Ofatumumab in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy. **Refractory CLL:** Ofatumumab is indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.	Idelalisib is indicated in combination with rituximab for the treatment of adult patients with CLL: • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	First-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
Administration method	3 capsules, once a day	Intravenous infusion with monitoring for AEs	150 mg, taken orally, twice daily	intravenous infusion over 30 - 60 minutes
BNF price	£51.10 per capsule ([redacted])	£182.00 per vial ([redacted])	£51.91 per capsule and £174.63 (rituximab) ([redacted])	£69.45 and £174.63 (rituximab)

See summary of product characteristics for details on adverse reactions and contraindications.

For details of all comparators, see company submission, page 144, table 59.

3 Comments from consultees

3.1 Consultees stated that CLL is a heterogeneous disease and there will be a small number of patients who have high risk, poor prognosis disease which is unlikely to respond to available therapies. Moreover, following relapse any further responses to treatment courses tend to provide shorter remission periods with increasing complications and side effects.

3.2 Consultees stated that in the absence of a cure, patients living with CLL want treatments that provide a lengthy remission with minimum side effects and long term toxicity. It was noted that ibrutinib produces durable remissions using an easily administered oral drug which offers convenience, reduced travel to hospital, no need for infusions with the potential for infusion reactions, less hospital time and most importantly, promotes patient independence. All these benefits lead to improvements in quality of life including less anxiety, in addition to the physiological benefits induced by the drug itself. It was highlighted that this was particularly a step change for treatment-naive patients with 17p- or TP53 mutation/deletion who have no approved treatment options. It was highlighted that ibrutinib was innovative as it is the first in class compound, targeting Bruton's Tyrosine Kinase (BTK) and can be delivered orally.

3.3 One patient organisation was concerned about the long duration of treatment, as ibrutinib is administered until progression. Consultees expressed concern about higher frequency of certain adverse events (as per the clinical trial data) – including bleeding-related adverse events and atrial fibrillation. The clinical expert also stated that there is evidence from several patients that arthralgia and myalgia are areas of significant concern, particularly in the first year of treatment. Also, neutropenia has been an issue especially in patients who have been treated with several chemo immunotherapy regimens, and complication from infection is the most frequent cause of death in CLL.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic literature review and identified 1 randomised controlled trial including ibrutinib. The RESONATE trial (n=391) was an open label multicentre trial (including the UK) comparing ibrutinib with ofatumumab in people with relapsing or refractory CLL, with ibrutinib administered orally and ofatumumab is administered using IV injection. The trial included 109 people with 17p deletion, 63 of whom received ibrutinib and 46 received ofatumumab. The trial was terminated early, at 146 progression free survival events, due to a positive interim analysis, with a median time on study of 9.4 months. All 195 patients in the ibrutinib group and 191 of the 196 people in the ofatumumab group received the assigned treatment (4 withdrew consent and 1 patient died).

4.2 The primary outcome of RESONATE was progression free survival according to the criteria of the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL), which require CT scans to evaluate response. It was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first. Secondary outcomes included overall survival and overall response rate. Overall response rate was based on IWCLL criteria and included complete response, complete response with incomplete haematopoietic recovery, partial response with and without lymphocytosis, stable disease and progressive disease.

4.3 The company stated that the despite being an open label trial, the risk of bias was low because assessment of progressive disease for the primary end-point and responses were assessed by the independent research committee, members of which were blinded to both study treatment and absolute lymphocyte count. The ERG noted that after 9.4 months outcomes were only investigator assessed (and therefore not blinded) but stated that the trial protocol was rigorous and reduced risk of bias.

4.4 Of the 191 patients who received ofatumumab, 116 patients with documented disease progression crossed over to ibrutinib at the time of the September 2014 data cut and extraction. The primary analysis was adjusted for crossover in the ofatumumab arm at the date of first dose of crossover to ibrutinib using RPSFT method. A sensitivity analysis was conducted in which crossover was not censored at the date of first dose of ibrutinib.

4.5 RESONATE included patients with the 17p deletion but not TP53 mutation. However, the company stated that these mutations have the same impact on cell biology, disease prognosis and treatment outcomes. Therefore, the company has stated that the results in patients with 17p deletion were generalisable to patients with the TP53 mutation. The company has also suggested that although RESONATE only included patients with the 17p deletion who had previously received treatment, the results for this population could be generalised to the 17p deletion population who had not been treated before.

Clinical trial results

4.6 The results of the RESONATE trial in the overall population showed that at 6 months, 88% of people in the ibrutinib group had no disease progression compared with 65% in the ofatumumab group. At a median follow-up of 16 months, investigator-assessed progression-free survival was longer for ibrutinib compared with ofatumumab - median progression-free survival had not been reached with ibrutinib whereas the median progression-free survival was 8.1 months for ofatumumab (hazard ratio 0.106, 95% confidence interval I 0.073 to 0.153, p<0.0001). The 12-month investigator-assessed progression-free survival rates were 84% for ibrutinib and 19% for ofatumumab. Full details of the outcomes from the RESONATE study are included in table 1table 3.

4.7 The results of the RESONATE trial in patients with the 17p deletion showed that at 6 months, 83% of people in the ibrutinib group had no disease progression compared with 49% in the ofatumumab group. At a

median follow up of 16-months, 79% of people with 17p deletion had no disease progression for 12 months compared with 17% of people receiving ofatumumab (hazard ratio not reported, p<0.001).

4.8 The company presented the results of the secondary outcomes analyses from RESONATE which were censored at the time of crossover. The overall survival rate at 12 months was 90% for ibrutinib and 81% for ofatumumab (hazard ratio 0.43, 95% confidence interval 0.24 to -0.79; p=0.005). When uncensored, the analysis showed similar results: hazard ratio 0.39 (p=0.001) and an overall survival rate at 12 months of 90% for ibrutinib and 79% for ofatumumab. The censored overall survival rate at 18 months was 85% for ibrutinib and 78% for ofatumumab, despite crossover of 120 patients (61%) from ofatumumab to ibrutinib, who were censored at crossover. The proportion of patients with lymphocytosis (an elevated level of lymphocytes in the blood) was observed in 69% of patients treated with ibrutinib. It was not considered to be disease progression according to the study protocol and resolved in 77% of these patients during follow-up. According to the company, lymphocytosis does not have an impact on clinical outcomes and resolves completely once treatment with ibrutinib is stopped. Further details of secondary outcomes results are given on pages 88-93 of the company submission.

Table 3 Outcomes from RESONATE study (for the overall population)

Outcome		**RESONATE**	
		Ibrutinib (n=195)	**Ofatumumab (n=196)**
Progression-Free Survival (ITT analysis)			
Follow-up of 9.4 months (Independent reviewer assessed)	Median: months (95% CI)	not reached	8.1; (4.0, 7.3)
	HR (95% CI)	0.22 (95%CI 0.15 to 0.32; p=<0.001) for overall population 0.25 (95%CI 0.15 to 0.45; p value not reported) for 17 p deletion population	
	Progression-free survival rate (at 6 mo)	88% for overall population 83% for 17p deletion population	65% for overall population 49% for 17p deletion population

Outcome		RESONATE	
		Ibrutinib (n=195)	**Ofatumumab (n=196)**
Follow-up of 16 months (Investigator-assessed)	HR (95% CI)	0.106 (95%CI 0.073 to 0.153; p<0.0001) for overall population	
	Progression-free survival rate	84% for overall population 79% for 17p deletion population	19% for overall population 17% for 17p deletion population
Overall Survival [ITT analysis] data censored for crossover			
Follow-up at 12 months	HR (95% CI)	0.43 (95% CI: 0.24 to 0.79; p=0.005) for overall population	
	Overall survival rate at 12 months	90% for overall population	81% for overall population
Follow-up of 16 months	Crossover-adjusted HR (95% CI) using RPSFT	[redacted] for overall population for 17 p deletion subgroup	
	Overall survival rate at 18 months	85% for overall population	78% for overall population
Key: CI, confidence interval; HR. Hazard Ratio; ITT, intention to treat, RPSFT, rank preserving structural failure time.			

Non RCT evidence

4.9 The company included the results from 4 non randomised controlled studies. PCYC1102 (n=85) was a multicentre, open label, dose ranging study of ibrutinib (420 mg or 840 mg) in patients with relapsed or refractory CLL or small lymphocytic leukaemia with safety as its primary outcome and progression-free survival, overall response rate as secondary outcomes. There were 36 patients with 17p deletion in PCYC1102 (2 of whom had not previously received treatment). Of the 85 patients enrolled, 54 patients remained on treatment at median follow-up of 20.9 months. The 26-month progression-free survival rate for the overall population and 17p deletion population as estimated by the company was 75% and 57%, respectively for the 420 mg and 840 mg doses combined. The estimated overall survival rate for the overall population and 17p deletion population was 83% and 70%, respectively for the 420 mg and 840 mg doses combined.

4.10 PCYC1103 (n=57) was the long-term extension study to PCYC1102 with a follow-up to 45 months. Of the 57 patients in the study, 23 had the 17p deletion mutation. Median progression-free and overall survival had not been reached for the overall population, but the 30-month progression-free survival rate as estimated by the company for patients receiving 420 mg of ibrutinib was 76% (95% CI 62.5 to 85.1). The median progression-free survival for the 17p deletion mutation population was reached at 32.4 months. The 30-month overall survival rate was estimated by the company for the overall population and the 17p deletion population at 87% (95% CI 75.8 to 93.3) and 81%, respectively.

4.11 PCYC1117 (n=144) was an open-label, single arm, multicentre study of ibrutinib in patients with relapsed or refractory CLL with the 17p deletion mutation. Patients in this study had a median of 2 previous treatments (range 1-7), and 39% of patients had 3 or more previous treatments. Median progression-free and overall survival had not been reached, but the 12-month progression-free and overall survival rates as estimated by the company were 79% and 84%, respectively.

4.12 A single-arm, investigator-initiated study (n=51) in patients with untreated (n=35) or relapsed or refractory CLL (n=16) and 17p deletions (n=47) and TP53 mutations (n=4) by Farooqui et al. (2014) was also included in the company's submission. As with most of the PCYC studies, median progression-free and overall survival were not reached, but the estimated progression-free survival at 24-months as estimated by the company was 82% for all patients included in the study. The estimated overall survival rate at 24 months as estimated by the company was 84% for patients who had not received treatment before, and 74% for patients who had received treatment previously.

ERG comments

4.13 The ERG stated that the baseline characteristics in the trials were well balanced and that the population was representative of the UK population. The ERG considered that the company's approach to censoring was

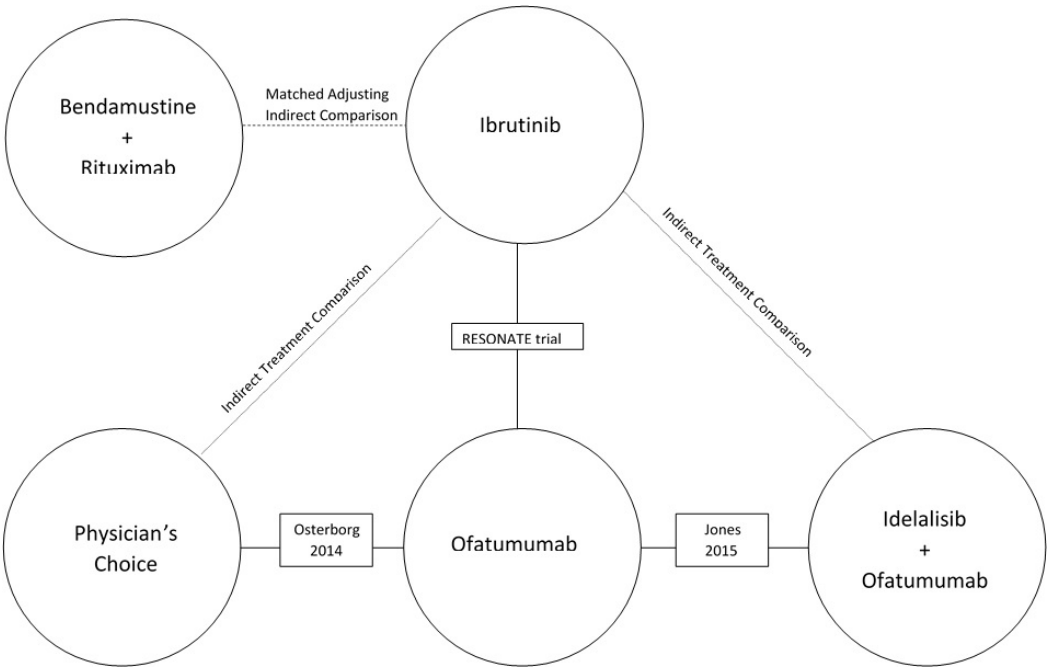
appropriate though noting that the risk of bias associated with unmeasured confounders would remain. The ERG commented that the overall survival and progression-free survival results suggest a marked, statistically significant improvement for patients receiving ibrutinib compared with ofatumumab whether crossover was adjusted for or not.

4.14 The ERG commented that the non-randomised studies showed similar efficacy profile for progression-free survival, overall survival and response rates as the ibrutinib treatment arm in the RESONATE study.

4.15 The ERG agreed with the company that the results in patients with 17p deletion were generalisable to patients with the TP53 mutation.

Indirect comparisons

Figure 2 Network diagram of studies used by the company (ERG report, figure 20, page 104)



4.16 The company presented pairwise indirect treatment comparisons based on Bucher et al. comparing ibrutinib with physician choice (Osterborg, 2014) and idelalisib and ofatumumab (Jones 2015). The company also conducted a matched-adjusted indirect comparison (MAIC) using methodology published by Signorovitch to compare a single arm study

(Fischer, 2011) of bendamustine in combination with rituximab in people with relapsing or refractory CLL with the patient level data from RESONATE. See figure 2.

4.17 The indirect analyses show significant effects in favour of ibrutinib compared with physician's choice and compared with bendamustine in combination with rituximab, for objective response rate, progression free survival and overall survival. Compared with idelalisib in combination with ofatumumab, ibrutinib showed a statistically significant improvement only in progression free survival (see table 4, which also includes the ERG's revised ITT estimates from all studies including RESONATE [see section 4.24]).

Table 4 Summary of results of company's indirect treatment comparison and matching-adjusted treatment comparison for the overall population of the studies (company submission, table 33, page 72 and table 28 from ERG report, page 103)

Comparison	Analysis type	Data sources	OR ORR (95% CI)	HR progression-free survival (95% CI)	HR overall survival (95% CI)	ERG HR overall survival (95% CI)
Ibrutinib vs. physician's choice	ITC, Bucher method	RESONATE vs. Osterborg, 2014	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib vs. idelalisib +/- ofatumumab	ITC, Bucher method	RESONATE vs. Jones, 2015	1.65 (0.66, 4.10)	0.39 (0.23, 0.66)	0.50 (0.24, 1.04)	0.58 (0.26-1.30)
Ibrutinib vs. bendamustine +/- rituximab	MAIC	RESONATE vs. Fischer, 2011	[redacted]	[redacted]	[redacted]	[redacted]

4.18 The company noted that indirect comparisons are assumed to generate unbiased results as long as no differences across trials exist that act as a treatment effect modifier. The company stated that the Osterborg study enrolled patients with more severe disease. When the company calculated the HR estimates in a subgroup from the RESONATE study similar to those in the Osterborg study, the progression-free and overall survival HRs

[redacted]

[redacted] To account for this potential bias, the company recalculated the HRs for RESONATE as input in the Bucher method which resulted in HR estimates for progression-free and overall survival were [redacted].

4.19 The company validated the outputs of the indirect treatment comparisons and MAIC using an indirect comparison based on a multivariate Cox model of pooled patient-level trial data. This methodology uses 2 sets of patient-level data which are adjusted for patient population difference using pooled patient level data from both RESONATE and the comparator study. The comparator studies included:

- a retrospective observational study conducted in Sweden by the Karolinska Institute which allows for an alternative comparison to be made for ibrutinib compared with physicians choice.
- the bendamustine with rituximab arm of the HELIOS study.

4.20 No indirect comparison was conducted for patients with the 17p deletion mutation who had not received treatment previously due to a lack of data. As a result, the company used the efficacy estimates from RESONATE from the 17p deletion mutation population who have previously received treatment as a proxy for those who have not been treated previously.

ERG comments

4.21 As noted by the company, the patients in the Osterborg study (comparing ofatumumab with physician's choice) appeared to include patients with a poorer prognosis than those in RESONATE. The ERG noted that the company's analysis restricting the RESONATE population to a similar population to Osterborg resulted in HR estimates which the ERG stated were more relevant for the comparison between ibrutinib and physician's choice (see section 4.17). The ERG commented although the indirect treatment comparisons suggest that ibrutinib is more clinically effective

than physician's choice and bendamustine and rituximab, the sensitivity analyses undertaken by the company shows that there is significant uncertainty over the magnitude of the difference between ibrutinib and its comparators.

4.22 The ERG noted that the company did not adjust the indirect comparison of RESONATE and Jones et al. for patient characteristics because they enrolled similar patient populations. The ERG noted, however, that there were some differences, particularly in the proportion of patients with the 17p deletion in each trial (32.3% of people receiving ibrutinib and 32.7% receiving ofatumumab in RESONATE, compared with 26.4% of people receiving idelalisib and 21.8% of people receiving ofatumumab in Jones et al.). According to the ERG, this indicates that the RESONATE study recruited people with a poorer prognosis, therefore, the effect of ibrutinib might appear greater in an indirect comparison with the population in the Jones study. Additionally, the ERG noted that no adjustment for crossover was conducted on the data from the Jones study.

4.23 The ERG stated that the company provided abstract and poster details on 2 ofatumumab trials which were used to form a network for indirect treatment comparisons and a single arm study of bendamustine and rituximab. The ERG stated that abstracts and poster details are generally insufficient information for it to fully assess these studies and the risk of bias.

4.24 The ERG commented on the sensitivity analysis presented by the company using an alternative indirect comparison approach (see section 4.18). The ERG were unable to identify a clear reason for the selection of the 2 studies used in the sensitivity analyses and therefore whether other studies may have been available. The ERG also noted that if the multivariate Cox model or the MAIC was the preferred approach, then it may have been possible for the company to have performed an MAIC analysis using the idelalisib plus rituximab compared with rituximab plus placebo trial. Such an analysis could have provided reassurance that the

current estimate of benefit of ibrutinib compared to idelalisib in the network is robust. The ERG also noted that the HELIOS study included less severe patients than RESONATE and so may have been biased in favour of bendamustine and rituximab.

4.25 The ERG question whether the adjusted-for-crossover hazard ratio of overall survival from the RESONATE trial should be used as the data input in the indirect treatment comparisons. Given that the data inputs from the other trials in the network were not adjusted for crossover, the ERG stated that it would be more consistent methodology to use the ITT estimates from all studies, including RESONATE. The ERG's revised estimates are shown in table 4 above. All data inputs are the same as the company estimates except for ibrutinib compared with ofatumumab where the ITT hazard ratio for overall survival (ITT) of 0.43 (95%CI 0.24-0.79) was used instead of [redacted]. The ERG was unable to make any amendments to the ibrutinib versus bendamustine and rituximab estimate as it did not have access to the individual patient data from RESONATE.

4.26 The ERG also commented that the data provided on treatment-naïve patients with the 17p deletion mutation comes from 33 patients in a single non-RCT (see section 4.12) although a benefit with ibrutinib had been demonstrated within that study.

Adverse effects of treatment

4.27 The most common adverse event in RESONATE was diarrhoea, occurring in approximately half of the patients. They were generally grade 1 or 2 in severity, managed with standard treatment and resulted in very few discontinuations (<15% across the studies). In comparison with ofatumumab in the RESONATE trial, infection rates were higher with ibrutinib (70% v 54%), but rates of grade 3 or above infections was similar. Serious adverse events were reported in 40-61% of patients, most were infection-related although there were a small number of cases of atrial fibrillation. The majority of serious adverse events were described as not related to ibrutinib.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a de novo economic model for people with chronic lymphocytic leukaemia who have received at least 1 prior therapy. The base case analysis modelled the following:

- Ibrutinib compared with idelalisib and rituximab
- Ibrutinib compared with ofatumumab
- Ibrutinib compared with physician choice
- Ibrutinib compared with bendamustine and rituximab

'Physician choice' was composed of the following treatments: rituximab plus cyclophosphamide, doxorubicin, and prednisolone (also known as R-CHOP, [redacted] bendamustine and rituximab [redacted]), fludarabine and cyclophosphamide and rituximab [redacted] Rituximab plus high dose methylprednisolone [redacted] and chlorambucil [redacted] This composition reflects the therapies in the physician choice arm of the Osterborg (2014) study, but the cost of the therapies were adjusted by the company so that only treatments relevant to UK clinical practice are included in the model.

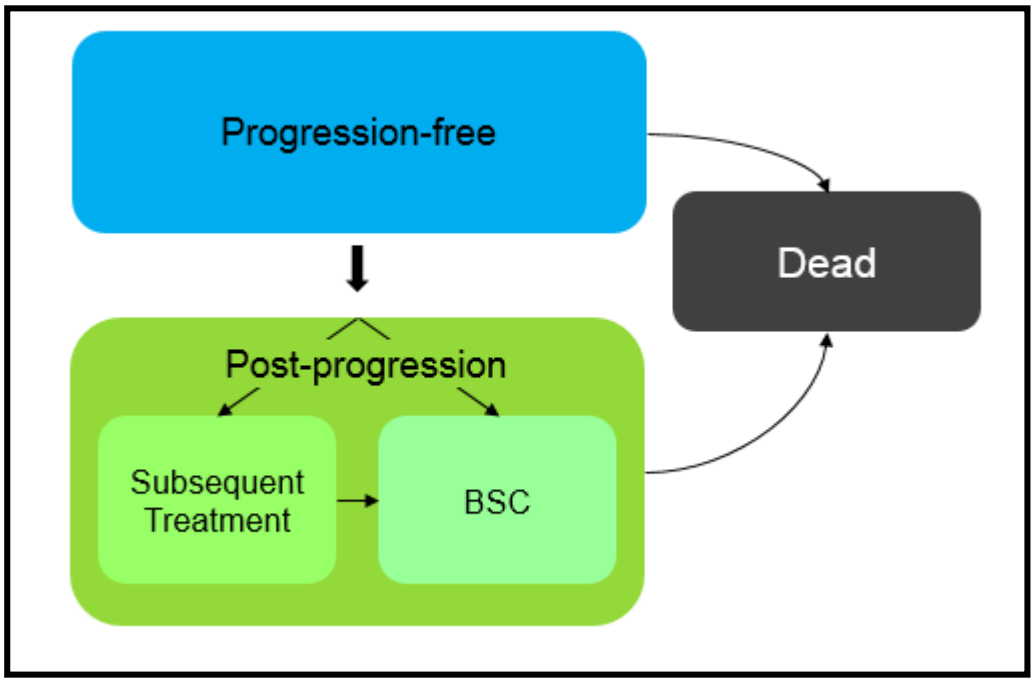
5.2 The company used a Markov model with time-dependent transition probabilities. It used 4-week cycle lengths (with half-cycle corrections) with a time horizon of 20 years. The mean age of patients entering the model was 71. A discount rate of 3.5% was applied to costs and health benefits and the analysis was conducted from an NHS and personal social services perspective.

5.3 The model consisted of 3 health states, 'progression free', 'post progression', and 'death', (see figure 3). The progression free health state was directly informed by the progression free survival curves projected based on parametric fitting to RESONATE trial data. The post-progression state was defined as all patients surviving (overall survival) less those who remain progression free. Overall survival was informed by overall survival

curves projected based on parametric fitting to RESONATE trial data and the hazard ratios for the comparators which were calculated using indirect comparisons. The mortality state was calculated as 1 minus overall survival. The area under the progression-free and overall survival curve was used to calculate the proportion of patients in health states at given time points. A constant mortality hazard was applied for each 4-week model cycle for patients in the progression-free health states. The company used the Weibull parametric function in its base case, and used the exponential function in a sensitivity analysis. Age-dependent general population mortality was incorporated into the model. Within each model cycle, the probability of death experienced by people with CLL could not be less than the general population.

5.4 In the post-progression health state, a proportion of patients were modelled to receive a subsequent line of active treatment following progression. The remainder were modelled to receive best supportive care (symptom management without active intervention) immediately upon entering the post-progression health state. Once patients on their subsequent line of therapy progressed, they then received best supportive care until death or model end. Costs in progression-free survival were assigned according to the distribution of patients' best eventual response.

Figure 3 Company's model diagram (CS, figure 27, page 105)



BSC- best supportive care.

5.5 The quality of life value for progression-free survival was based on post baseline EQ-5D-5L data collected during the RESONATE trial. The quality of life value for post progression survival and best supportive care was estimated by applying a percentage quality of life reduction associated with progression, drawn from the literature, to the baseline EQ-5D-5L average of the RESONATE trial. Serious adverse events were modelled as having cost and quality of life impacts, and are assumed to last for 14 days.

5.6 Ibrutinib and idelalisib are assumed to be taken for the entire period of progression free survival. The other first line treatments were administered to a given schedule for a maximum of up to 5 model cycles. The company applied a half cycle correction and discounting from the first cycle to the ibrutinib arm which resulted in a reduction in treatment costs for ibrutinib.

5.7 Drug costs were based on the British National Formulary (online). See CS, table 59, page 144. Because not all patients in the RESONATE trial

and other clinical trials received full doses of treatment throughout the duration of the trial, the company calculated the relative dose 'intensity' from the clinical trials to determine the cost for ibrutinib and its comparators. The company used these values to ensure that the doses in the model match the trials. See CS, table 60, page 145.

5.8 The company has proposed a confidential patient access scheme for ibrutinib, which [redacted]. Given a daily dose requirement of 420mg, this reduces its annual cost from £55,955 [redacted], assuming 100% dosing. The companies who hold the marketing authorisation for idelalisib and ofatumumab have agreed a patient access scheme with the Department of Health. [redacted].

5.9 No drug administration costs were included for ibrutinib whereas these were included for all comparators. The routine follow-up costs while in progression free survival are determined by treatment specific proportions of patients achieving complete response, partial response and being in stable disease. Terminal care costs are applied when patients die.

5.10 The company was unable to conduct an economic evaluation of ibrutinib in the subgroup of people with the 17p deletion who have not received treatment before due to a lack of robust clinical trial data. The company was able to conduct a scenario analysis based on the 17p deletion mutation subgroup data from RESONATE as it provided the best available estimate of efficacy associated with ibrutinib in CLL patients with 17p deletion who have not been treated before. In the scenario, ibrutinib was compared with ofatumumab, using the same assumptions that were used in the company's base case analysis.

5.11 The company used the results of the RESONATE study to inform its model for the comparison of ibrutinib with ofatumumab in people with CLL. The results of the indirect treatment comparisons were used to inform the

model for the comparison of ibrutinib and physician's choice (the company's base case comparator) and idelalisib with ofatumumab (as a proxy for idelalisib with rituximab). The company used the results of the matched-adjusted indirect comparison for ibrutinib compared with bendamustine with rituximab (see section 4.15-4.16).

5.12 For the comparison of ibrutinib with ofatumumab in the overall population, the company used parametric curves to project the progression-free and overall survival Kaplan-Meier trial data beyond the trial period. The ofatumumab overall survival curve was estimated by applying a crossover-adjusted hazard ratio to the ibrutinib overall survival, as a large proportion of patients in the ofatumumab arm of the RESONATE trial crossed over to the ibrutinib arm (n=116, 56%). The curves were then used as a reference to which hazard ratios were applied to derive the progression-free and overall survival for the comparators. The indirect treatment comparison using ofatumumab as the common arm and Osterborg et al. and Jones et al. were used to derive the relative treatment effect of ibrutinib compared with physician's choice (used in the company's base case) and idelalisib with ofatumumab (used as a proxy for idelalisib with rituximab), respectively, on progression-free and overall survival. The company used the results of the matched-adjusted indirect comparison using Fischer et al. to derive the relative treatment effect of ibrutinib compared with bendamustine with rituximab on progression-free and overall survival. EQ-5D trial data from RESONATE informed baseline utility and utility during PFS.

5.13 The baseline utility for patients in the progression-free survival state ([redacted]) was informed by an analysis of EQ-5D-5L data collected in RESONATE and represents the weighted average EQ-5D-5L score for patients who remained in the progression-free survival health state from weeks 4 to 60. The utility value was not age-adjusted as it was collected from the RESONATE trial directly, representing the median age of a relapsing or refractory CLL patient population. After progressing and entering the post-progression health state, patients in the model were assigned a utility

value informed by the baseline EQ-5D-5L score of patients entering the RESONATE trial ([redacted]) minus a utility decrement associated with progression (0.098), resulting in a utility value of [redacted] for the post-progression health state. Utility decrements associated with adverse effects of treatment (ranging from 0.123 to 0.195) were applied to patients as they experienced adverse events in the model. The utility decrements associated with progression and adverse events were based on published literature, as analysis of RESONATE EQ-5D-5L data did not identify differences for these events. In the base case, utility increments associated with response were not incorporated, but instead the weighted average utility score of patients remaining in progression-free survival informed utility for the progression-free survival health state, which the company considers some benefit of response. Published utility increments associated with response were tested in a sensitivity analysis.

ERG comments

5.14 The ERG noted that the company appear to treat the drug and administration costs in the model asymmetrically and this reduces costs in the ibrutinib arm. In its factual accuracy response to the ERG report, the company stated that the differences in costs applied in the model were justified primarily because ibrutinib is the only oral monotherapy treatment in the model.

5.15 The ERG stated that it noted there were uncertainties around the response rates, their definitions across the trials of the indirect treatment comparison and how the rates were derived for the comparator treatments. The ERG noted that it appeared that the response rates which were used for differentiating ongoing resource use were the peak response rates for ibrutinib and ofatumumab, while no data on time to response or response duration was included in the company's submission In response to NICE's clarification questions, the company provided the mean times to initial response and to best response from the PCYC1102 trial which were [redacted] months and [redacted] months, respectively. The company

also stated that the [redacted] for the PCYC1103 trial [redacted]. It was unclear to the ERG whether the company had defined the duration of response data presented as the duration of peak response or duration of overall response. The ERG expert opinion also suggested that patients would not receive ongoing biopsies as part of routine follow-up, and that routine follow-up would not be differentiated by response status. In the light of this, the ERG considered that it was not appropriate to differentiate non-drug routine follow up costs by treatment.

5.16 The ERG commented on the subgroup analysis conducted by the company on people with CLL who have the 17p deletion. As stated in section 5.10, the company used the subgroup results from the RESONATE study which were conducted on people with CLL with the 17p deletion who had been treated for CLL. The company stated that the cost effectiveness estimate in the previously treated 17p deletion mutation subgroup should provide a plausible and conservative estimate of ibrutinib's value in the subgroup population who has never received treatment before. It was unclear to the ERG why this estimate would be conservative assuming that people with the 17p deletion who have not been treated before may live longer (and receive ibrutinib longer possibly leading to higher costs) compared to the17p deletion mutation subgroup of the RESONATE trial who had been treated before. The ERG noted that there was considerable uncertainty with respect to the results of the scenario analysis presented by the company for this subgroup.

5.17 The ERG noted that the results from the indirect comparison were included in the model and reiterated its concerns with these analyses (see sections 4.20-25)

5.18 The ERG stated that, based on advice from its clinical experts, the company's assumption of proportions of treatments within physician choice were unlikely to reflect clinical practice in the UK. In particular, idelalisib plus rituximab was not included whereas it is used in

approximately 30% of patients. Additionally, usage of R-CHOP [redacted] and rituximab plus high dose methylprednisolone [redacted] is likely to be overestimated.

5.19 The ERG noted that the company model suggests that by 20 years a little over [redacted] of patients in the ibrutinib arm would be alive, but only around [redacted] in the idelalisib plus rituximab arm and effectively none in the other comparator arms. The ERG's clinical experts did not find the estimate of [redacted] for ibrutinib to be unreasonable, but they considered the [redacted] estimate for idelalisib plus rituximab unreasonably low. The ERG considered the overall survival estimate for idelalisib plus rituximab ([redacted] years) and bendamustine plus rituximab ([redacted] years) to be too low when compared with the estimate for ibrutinib ([redacted] years). The ERG stated that bendamustine plus rituximab was likely to have a similar life expectancy as ofatumumab ([redacted] years).

5.20 The ERG stated that of 2 parametric functions applied to the RESONATE overall survival Kaplan-Meier data, the more plausible of the 2 is the exponential function. The ERG stated that the Weibull function projects too low a proportion of patients remaining in progression-free survival for the overall survival curve to be credible. The ERG commented that the reasonableness of the progression-free survival curve can only be judged against the associated overall survival curve. Therefore, the ERG use the exponential function in their exploratory base case.

Company's base-case results and sensitivity analysis

5.21 The company's base case results are presented in tables 5 to 7 below. The ICERs presented have been calculated by the ERG using the company's base case assumptions but using prices based on the confidential patient access schemes for ibrutinib, idelalisib and ofatumumab. All results are commercial-in-confidence.

Table 5 Company's base case deterministic modelling results: all patients (ERG report, table 44, page 134 and ERG confidential appendix, table 1, page 2)

	Ibrutinib	Physician's Choice	Ofatumumab	Idelalisib+ Rituximab	Benda-mustine + Rituximab
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost	..	£149,589	£120,487	£86,718	£151,595
Total undiscounted LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental undiscounted LY	..	5.783	4.693	3.561	6.350
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	..	3.289	2.647	1.934	3.608
ICER	..	£45,486	£45,525	£44,836	£42,016
ICER including all PASes (Calculated by the ERG)		[redacted]	[redacted]	[redacted]	[redacted]

Table 6 Company's probabilistic modelling mean estimates: all patients (ERG confidential appendix, table 2, page 2)

	Ibrutinib	Physician's choice	Ofatumumab	Idelalisib+ Rituximab	Bend.+ Rituximab
Including all patient access schemes (calculated by the ERG)					
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7 Company's deterministic modelling results: scenario for 17p deletion mutation subgroup (ERG report, table 49, page 155 and ERG confidential appendix, table 4, page 4)

	Ibrutinib	Physician's choice	Ofatumumab	Idelalisib+ Rituximab	Bendamustine+ Rituximab
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost		£128,939	£102,596	£73,989	£130,618
Total undiscounted LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental undiscounted LY		4.727	4.592	3.051	5.133
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs		2.800	2.690	1.722	3.036
ICER		£46,045	£38,145	£42,967	£43,028
ICER with all patient access schemes (Calculated by the ERG)		[redacted]	[redacted]	[redacted]	[redacted]

5.22 Probabilistic modelling results were not calculated for the 17p deletion mutation subgroup.

5.23 Results of the one-way sensitivity analysis demonstrated time horizon was the biggest driver of results. When the time horizon was reduced from 20 to 10 years, the ICER for ibrutinib compared with physician's choice increased from £45,486 per QALY gained (company's base case ICER) to £57,630 per QALY gained without any of the patient access schemes applied. The remainder of the sensitivity analyses have minimal impact on the ICER (+/- 2% of base case ICER).

Company scenarios

5.24 The company conducted a scenario analysis varying the parametric distribution used for progression-free survival projection. When the company used an exponential distribution, it led to a higher ICER (for example, £62,296 per QALY gained for ibrutinib compared with physician's choice) without any of the patient access schemes applied. The company explained that this is because an exponential fit leads to a longer projection of progression-free survival, which results in longer time accruing the cost of ibrutinib treatment. The company stated that based on the AIC and BIC, it considered the Weibull distribution used in the analysis to be the best fit.

5.25 The company explored a scenario in which ibrutinib's treatment benefit is limited to 5 years; this resulted in an increased ICER (£62,128 per QALY gained for ibrutinib compared with physician's choice) without any of the patient access schemes applied. The company also explored a scenario assuming that the follow up cost for the progression-free survival health state is the same as the follow up cost of stable disease for all comparators, and removing the cost benefit associated with a high response rate. This resulted in an ICER of approximately £50,000 per QALY gained.

ERG exploratory analyses

5.26 The ERG present a fully incremental analysis using the company's base case assumptions comparing ibrutinib with each of the comparators and taking all the patient access schemes into account. The resulting ICER for ibrutinib compared with idelalisib plus rituximab for the overall population was [redacted] per QALY gained and [redacted] per QALY gained for the 17p deletion mutation subgroup. See table 8.

Table 8 Incremental cost effectiveness analysis using company's base-case assumption including all PASes (calculated by ERG) (see ERG confidential addendum)

	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
All comparators: All patients					
Bendamustine + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelalisib + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All comparators: 17p deletion mutation subgroup					
Bendamustine + R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phys. Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelalisib + R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.27 The ERG considered that the only relevant comparators that should be included in the incremental analysis are bendamustine with rituximab and idelalisib with rituximab, as ofatumumab is no longer available through the Cancer Drugs Fund and physician's choice is problematic as a blended comparator. As a result, it also calculated the incremental cost effectiveness analysis results using only these comparators. However, the

ICERs remain the same for both the overall group and the 17p deletion mutation subgroup.

5.28 The ERG conducted exploratory analyses. The main changes applied by the ERG's in its preferred analyses were:

- Apply the ITT overall survival hazard ratios for physician choice and idelalisib plus rituximab (see section 4.25).
- Apply exponential overall survival and exponential progression-free survival curves (see section 5.18).
- Remove the asymmetries in the treatment of ibrutinib drug and administration costs (see section 5.10).
- Not differentiate the non-drug routine costs of care by treatment (see section 5.11).
- Remove the costs of ongoing biopsies from the non-drug routine costs of care (see section 5.11).

Using these adjustments, the ICER for ibrutinib compared with idelalisib plus rituximab for the overall population is [redacted] per QALY gained taking into account all the patient access schemes. The results of the ERG's preferred analysis is shown below in with all applicable patient access schemes applied.

5.29 The ERG calculated the ICERs for the subgroup with the 17p deletion for ibrutinib compared with physician choice, idelalisib plus rituximab and bendamustine plus rituximab by applying 'all patient' hazard ratios for ibrutinib to the 17p deletion mutation subgroup progression free and overall survival and progression free survival curves. Using these adjustments, the ICER for ibrutinib compared with idelalisib plus rituximab for the overall population is [redacted] per QALY gained including all patient access schemes.The ERG's results are shown below in table 9 with all applicable patient access schemes applied.

Table 9 ERG's exploratory incremental cost effectiveness analysis including all PASes (see ERG confidential addendum)

	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
All comparators: All patients					
Bendamustine + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelalisib + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All comparators: 17p deletion mutation subgroup					
Bendamustine + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelalisib + Rituximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Innovation

5.30 The company stated that ibrutinib is innovative because:

- of its mode of administration (monotherapy, oral tablets, once daily) and mechanism of action (first in class Bruton's tyrosine kinase inhibitor).
- it has a well-tolerated safety profile
- it has a high level of efficacy compared with existing treatments
- it fulfils an unmet need, in particular for people with a 17p deletion or TP53 mutation. There is currently no standard of care available for patients with the 17p deletion or TP53 mutations.

Additionally, the company stated that some benefits of ibrutinib may not be fully captured in the modelling, such as the impact on carers and the wider society as a result of patients with CLL and their carers taking time off work. The impact is likely to increase as the disease progresses.

6 End-of-life considerations

Table 10 End-of-life considerations

Criterion	Company's comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	For patients with relapsing or refractory CLL, life expectancy is less than 24 months. The company presents a [redacted] as indicated by real-world retrospective data collected from 2009 to 2014 from a Swedish population (unpublished data from Karolinska Institute) For patients with the 17p deletion mutation, median life expectancy is less than 2 to 3 years from the time of initial diagnosis (Dohner et al., 2000)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The RESONATE data show a statistically significant improvement in overall survival for ibrutinib compared to ofatumumab based on 16 months of median follow-up. As median survival had not been reached in either arm and there was a high degree of crossover from the ofatumumab to the ibrutinib arm, precise incremental benefit has not been shown, but extrapolation suggests that this is in excess of 3 months. The company's base case modelling estimates for median survival in the overall population are [redacted] for ibrutinib, physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab respectively. The mean survival estimates are [redacted]. The median survival estimates for the 17p deletion mutation subgroup were not calculated.
The treatment is licensed or otherwise indicated for small patient populations	The estimated incidence for CLL in England is 7 per 100,000 people giving a total of 3,843 cases per year assuming an NHS England population of 54.9 million. One third of CLL patients never require treatment, another third have an indolent phase followed by disease progression; the remaining third exhibit aggressive disease at onset and require immediate treatment.

	Therefore, 2,562 with CLL will require active treatment (page 97 of company submission, Dighiero, 2003).

7 Equality issues

7.1 The company stated that ibrutinib may alleviate a potential equality issue within the current CLL treatment pathway. The company state that the current, most effective therapies available for treatment of CLL are most suited to young and fit patients (BresMed, unpublished summary report from Advisory Board, 2015), whereas ibrutinib is suitable for a wider population, including older and high-risk patients. The company, therefore, states that the addition of ibrutinib into the treatment pathway would address equality issues regarding the availability of suitable treatments for an older, frailer population. The ERG believes there are currently other combinations of treatments available in the UK for older, frailer populations such as idelalisib in combination with rituximab.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

2.8.4. Conclusions on the clinical efficacy

Initially the MAH (marketing authorisation holder) requested a conditional MA as on the basis on the available data at the time of the submission. However with the availability of the updates of trial 1104 where a consistent effect in terms of responses and duration of response is noted in MCL and the data made available during the procedure from the interim analysis of study 1112 in CLL, the CHMP agreed that enough reassurance was provided to support the clinical efficacy of ibrutinib in the CLL and MCL indications as described in the SmPC.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003791/WC500177777.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating chronic lymphocytic leukaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ibrutinib within its licensed indication for chronic lymphocytic leukaemia.

Background

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). It causes anaemia, swollen lymph nodes, spleen enlargement, weight loss and increased susceptibility to infection. CLL is the most common form of leukaemia.

In England around 2,700 people were diagnosed with CLL in 2011.[1] The risk of developing CLL increases with age and it is more common in men. Median survival ranges from about 3 to over 10 years depending on the genetic subtype and the stage at which the disease is diagnosed.[2]

Approximately 5% to 10% of people diagnosed with CLL are considered to have 'high-risk' disease characterised by the presence of cytogenetic mutations or abnormalities (that is, 17p deletion or TP53 mutation).[3] The presence of 17p deletion or TP53 mutation influences the rate of cell growth as well as the resistance of the disease to treatment. People with the 17p deletion or TP53 mutation have a median survival of 2 to 3 years.[3]

Treatment options vary depending on factors such as stage of CLL, performance status and co-morbidities. The appraisal includes 2 groups of people with CLL:

- People who have received at least 1 therapy; and
- People with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable.

Chemo-immunotherapy is a combination of chemotherapy medicines and treatments that stimulate the immune system to kill cancer cells.

For **people who have received at least 1 therapy**, treatment options include fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine with or without rituximab, chlorambucil with or without rituximab and idelalisib.

- NICE technology appraisal guidance 193 recommends FCR as an option for people with relapsed or refractory CLL unless the disease is refractory to fludarabine or has been previously treated with rituximab.

- Bendamustine does not have a UK marketing authorisation for previously treated CLL, but it is currently used with or without rituximab in clinical practice in England through the Cancer Drugs Fund.

- Chlorambucil has a UK marketing authorisation for CLL and is used in clinical practice, with or without rituximab, in relapsed or refractory CLL where FCR is unsuitable.

- Idelalisib in combination with rituximab is the subject of an ongoing NICE technology appraisal, and is currently funded by the Cancer Drugs Fund for relapsed or refractory CLL.

- Rituximab alone may be used for refractory disease.
- Other options may include corticosteroids (with or without rituximab) or best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support).

There are limited treatment options for **people with untreated CLL associated with 17p deletion or TP53 mutation** for whom chemo-immunotherapy is not suitable.

- Alemtuzumab does not have a marketing authorisation for CLL in the European Union because its marketing authorisation for this indication was withdrawn at the request of the company for commercial reasons. However alemtuzumab is currently available in England through a patient access programme agreed by the company and the European Medicines Agency.

- Idelalisib in combination with rituximab has a UK marketing authorisation for this indication and is the subject of an ongoing NICE technology appraisal. Idelalisib is not currently funded by the Cancer Drugs Fund for untreated CLL.

- Other options may include best supportive care.

The technology

Ibrutinib (Imbruvica, Janssen) is an oral inhibitor of a protein called Bruton's Tyrosine Kinase, which stops B-cell (lymphocyte) proliferation and promotes cell death.

Ibrutinib has a marketing authorisation in the UK for treating adult patients with CLL 'who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy'.

Intervention(s)	Ibrutinib
Population(s)	• Adults with chronic lymphocytic leukaemia who have received at least 1 therapy • Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable
Comparators	For adults with chronic lymphocytic leukaemia who have received at least 1 prior therapy: • Fludarabine in combination with cyclophosphamide and rituximab • Bendamustine (with or without rituximab) [not licensed in the UK for this indication, funded by the CDF] • Chlorambucil (with or without rituximab) • Corticosteroids (with or without rituximab) • Idelalisib in combination with rituximab (NICE guidance is in development, funded by the CDF in the interim) • Rituximab alone (for refractory disease) • Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support). For adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable: • Alemtuzumab with or without corticosteroids • Idelalisib in combination with rituximab (subject to ongoing NICE technology appraisal, *not* funded by the CDF in the interim) • Best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support).

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
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. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If the evidence allows, the following subgroups will be considered for adults with untreated chronic lymphocytic leukaemia: • Presence or absence of 17p deletion. • Presence or absence of TP53 mutation. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 202, October 2010, 'Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab'. Review Proposal Date TBC. Technology Appraisal No. 193, July 2010, 'Rituximab for the treatment of relapsed chronic lymphocytic leukamia'.

	Moved to the static list, March 2014. Appraisals in development: Idelalisib for treating chronic lymphocytic leukaemia. NICE technology appraisals guidance. ID764. Publication expected October 2015. Proposed appraisal: Idelalisib in combination with ofatumumab for chronic lymphocytic leukaemia. Proposed NICE technology appraisal ID 817. Publication date to be confirmed. Related Guidelines: NICE cancer service guidance (2003). Improving outcomes in haematological cancers. Related NICE Pathways: NICE pathway on blood and bone marrow cancers, available at: http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	National service framework: 'Improving outcomes: a strategy for cancer', Jan 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/135516/dh_123394.pdf.pdf NHS England Manual for prescribed specialised services 2013/2014. Specialist cancer services (adults) [section 105, page 234]: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England 2013/14 NHS standard contract for cancer: chemotherapy (adult). Section B part 1- service specifications: http://www.england.nhs.uk/wp-content/uploads/2013/06/b15-cancr-chemoth.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

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3. Eichhorst B, Dreyling M, Robak T et al. on behalf of the European Society for Medical Oncology (ESMO) Guidelines Working Group (2011). Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 22 (S6): vi50–vi54.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Manufacturers/sponsors • Janssen (ibrutinib) Patient/carer groups • Afiya Trust • African Caribbean Leukaemia Trust • Anthony Nolan • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • Chronic Lymphocytic Leukaemia Support Association • Chronic Myeloid Leukaemia Support Group • Equalities National Council • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma AssociationMacmillan Cancer Support • Maggie's Centres • Marie Curie Cancer CareMuslim Council of Britain • Myeloma UK • Muslim Health Network • National Council for Palliative Care • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus • United Kingdom Chronic Lymphocytic Leukaemia Forum	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator manufacturers • Accord Healthcare (fludarabine) • Actavis UK (fludarabine • Aspen Pharma (chlorambucil) • Baxter Healthcare (cyclophosphamide) • Genzyme (alemtuzumab, fludarabine) • Gilead Sciences (idelalisib) • GlaxoSmithKline (chlorambucil, ofatumumab) • Hospira UK (fludarabine • Napp Pharmaceuticals (bendamustine) • Pfizer (cyclophosphamide) • Roche Products (rituximab) • Sandoz (cyclophosphamide) • Sanofi (fludarabine) • Teva UK (fludarabine)

Consultees	**Commentators (no right to submit or appeal)**
Professional groups • Association of Cancer Physicians • British Blood Transfusion Society • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society for Haematology • British Transplantation Society • Cancer Network Pharmacists Forum • Cancer Research UK • National Blood Service • NHS Blood & Transplant • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiography • United Kingdom Clinical Pharmacy Association • UK Health Forum • United Kingdom Oncology Nursing Society Others • Department of Health • NHS England • Welsh Government	Relevant research groups • Clinical Trials Research Unit • Cochrane Haematological Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • Leukaemia & Lymphoma Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research Evidence Review Group • Aberdeen Health Technology Assessment Group • National Institute for Health Research Health Technology Assessment Programme Associated Guideline Groups • National Collaborating Centre for Cancer Associated Public Health Groups • Public Health England • Public Health Wales NHS Trust

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-manufacturer/sponsor consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-manufacturers/sponsors commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the manufacturer/sponsor evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID749]

Company evidence submission

October 2015

File name	Version	Contains confidential information	Date
ID749_Janssen_ibrutinib_Submission_30oct15_ Redacted	1.0	Yes	30th October 2015

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List of abbreviations

AACR	American Association for Cancer Research
AE	Adverse events
AF	Atrial fibrillation
AIC	Akaike information criteria
ASCO	American Society of Clinical Oncology
ASCT	Allogeneic stem cell transplant
ASH	American Society for Hematology
BCR	B cell receptor
BCSH	British Committee for Standards in Haematology
BIC	Bayesian information criteria
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
BTK	Bruton's tyrosine kinase
CAP	Cyclophosphamide, doxorubicin and prednisolone
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisolone
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRi	Complete response with incomplete haematopoietic recovery
CSR	Clinical study report
CT	Computed tomography
CVP	Cyclophosphamide, vincristine and prednisolone
DH	Department of Health
EAIR	Exposure-adjusted of incidence rates
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EHA	European Hematology Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence review group
ESMO	European Society of Medical Oncology
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue
FAD	Final Appraisal Determination
FCR	Fludarabine and cyclophosphamide and rituximab
FISH	Fluorescence in situ hybridization
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IGHV	Immunoglobulin variable region heavy chain gene
IO	Idelalisib and ofatumumab
IPCW	Inverse probability of censoring weights
IPE	Iterative parameter estimation
IR	Idelalisib and rituximab
IRC	Independent research committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive web response system
KM	Kaplan Meier
LY	Life year
LYG	Life years gained
MAA	Marketing authorisation application
MAIC	Matching adjusted treatment comparison
MCL	Mantle cell lymphoma
MMRM	Mixed model for repeated measures
MRD	Minimal residual disease
MRU	Medical resource use
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nPR	Nodular partial response
NR	Non responder
Od	Once daily
OR	Odds ratios
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PASLU	Patient access scheme liaison unit
PC	Physician's choice
PCR	Pentostatin, cyclophosphamide, fludarabine
PD	Progressive disease
PFS	Progression free survival
PPS	Post-progression survival
PSS	Personal social services
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QOL	Quality of life
R/R	Relapsed/refractory
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, and prednisolone
RCT	Randomised controlled trial
R-HDMP	Rituximab plus high dose methylprednisolone
RPSFT	Rank-preserving structural failure time
SD	Stable disease
SLR	Systematic literature review
SSL	Small lymphocytic leukaemia
STA	Single Technology Appraisal
TA	Technology Appraisal
TP	Transition probability
TTF	Time to treatment failure
TTP	Time to progression

uCR	Unconfirmed complete response
WM	Waldenström's macroglobulinaemia

1 Executive summary

1.1 *Statement of decision problem*

Table 1 presents the decision problem associated with this submission and includes the final scope provided by the National Institute for Health and Care Excellence (NICE), the scope of this submission dossier and the rationale for any differences between the two. In summary, the scope of the current submission is a Single Technology Appraisal (STA) of ibrutinib in two patient populations:

- Adults with chronic lymphocytic leukaemia (CLL) who have received at least one therapy;
- Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	As per the final scope: • Adults with CLL who have received at least one therapy • Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable		
Intervention	As per the final scope: • Ibrutinib		
Comparator (s)	<u>For adults with CLL who have received at least one prior therapy:</u> • Fludarabine in combination with cyclophosphamide and rituximab (FCR) • Bendamustine with or without rituximab (BR or B) • Chlorambucil with or without rituximab • Corticosteroids with or without rituximab • Idelalisib in combination with rituximab (IR) • Rituximab alone for refractory disease • Best supportive care (BSC) <u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom</u>	<u>For adults with CLL who have received at least one prior therapy:</u> • Physician's Choice (PC) • BR • IR • Ofatumumab <u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-</u>	<u>For adults with CLL who have received at least one prior therapy:</u> PC aims to accurately reflect the fact that there is currently no clear standard of care for patients with R/R CLL. It is comprised of the comparators listed within the final NICE scope except for (a) IR which is compared to independently and (b) rituximab monotherapy which is not licensed and not widely used in UK clinical practice. Ofatumumab is an important comparator as it is licensed for use in Europe for R/R CLL (while rituximab is not), it is the comparator within the pivotal phase III trial for ibrutinib (RESONATE), as it was the only licensed treatment within R/R CLL at the time of trial initiation, and most importantly, clinical opinion strongly suggests that it remains a relevant comparator in the UK for R/R CLL (1). <u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable:</u>

	chemo-immunotherapy is not suitable: • Alemtuzumab with or without corticosteroids • IR • BSC	immunotherapy is not suitable: • Alemtuzumab with or without corticosteroids • IR • BSC	As scope.
Outcomes	As per the final scope: Overall survival (OS), progression-free survival (PFS), response rates, adverse effects (AE) of treatment, health-related quality of life (HRQOL)		
Economic analysis	As per the final scope: the reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY); 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 (PSS) perspective; if appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices; and the availability of any patient access schemes (PAS) for the intervention or comparator technologies should be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered for adults with untreated CLL: Presence or absence of 17p deletion. Presence or absence of TP53 mutation.	Presence or absence of 17p deletion in untreated CLL. Presence or absence of 17p deletion in R/R CLL.	Clinical data are limited and disparate for these subgroups. The ibrutinib pivotal trial collected 17p deletion but not TP53 mutation status and thus analyses can be performed for 17p deletion only. However, as these mutations have the same impact on the cell biology, disease prognosis and treatment outcomes, ibrutinib data in patients with 17p deletion are used as a proxy for ibrutinib's efficacy in TP53 mutation. Where cost-effectiveness is demonstrated in the 17p deletion subgroup, it can be assumed to apply equally to the patient subgroup with TP53 mutation. This assumption is reflected in the BCSH interim guidelines which make no distinction in treatment recommendations between the two cytogenetic abnormalities, and use the encompassing term 'TP53 disruption' (2)

			Data for other comparators as above are limited and thus subgroup comparisons against PC, BR and IR are not feasible.
Special considerations including issues related to equity or equality	The current, most effective therapies available for the treatment of CLL are most suited to young and fit patients (1). However, ibrutinib is suitable for a wider patient population, including high-risk and older patients. The addition of ibrutinib into the treatment pathway will likely address equality issues regarding the availability of suitable treatments for an older, frailer population.		Introduction of ibrutinib may alleviate a potential equality issue within the current treatment pathway of CLL.
Key: CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; BR, bendamustine plus rituximab; IR, Idelalisib in combination with rituximab; BSC, best supportive care; PC, physicians' choice; R+HDMP, rituximab plus high dose methylprednisolone; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin and prednisolone; PFS, progression free survival; OS, overall survival; AE, adverse event; HRQOL, health related quality of life; QALY, quality adjusted life year.			

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Ibrutinib Brand name: Imbruvica®
Marketing authorisation/CE mark status	Committee for Medicinal Products for Human Use (CHMP) positive opinion for Imbruvica® (ibrutinib) was granted on 24th July 2014 and a final European Commission decision was granted on 21st October 2014.
Indications and any restriction(s) as described in the summary of product characteristics	Ibrutinib is indicated for the treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Ibrutinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. Use of preparations containing St. John's Wort is contraindicated in patients treated with ibrutinib.
Method of administration and dosage	The dose is three 140 mg capsules (420 mg in total) once daily (od). Ibrutinib is administered as a monotherapy.
Key: CLL, chronic lymphocytic leukaemia; od, once daily	

1.3 Summary of the clinical effectiveness analysis

Disease overview and burden

CLL is a cancer of the blood and results from monoclonal expansion of mature malignant B lymphocytes in bone marrow, which eventually stream into the blood and lymphatic system and other organs in the body (3). Malignant lymphocytes accumulate in the lymphatic system and bone marrow and prevent the development of normal white blood cells, red blood cells and platelets.

CLL is an incurable disease and is extremely variable in its clinical course (4). Symptoms of the disease include anaemia, bleeding, a tendency to prolonged and recurrent infections, enlarged lymph nodes, and the so called "B symptoms" (night sweats, fever, rapid and unexplained weight loss). It is a debilitating condition which has a major negative impact on patients' quality of life, particularly affecting patients' emotional wellbeing and fatigue (5).

Despite being the most common B-cell malignancy in adults, the annual incidence of CLL is only 3.7 to 7 new cases per 100,000 (6-8), with 2,712 new cases reported in England in 2011 (7). Although not exclusively a disease of the elderly, disease incidence increases with age. Following diagnosis, one third of patients with CLL will never require treatment because they remain asymptomatic (9), therefore the population of patients within the scope of this appraisal is relatively small, and thus ibrutinib has been granted "orphan" designation by the European Medicines Agency (EMA) in this patient population (10).

CLL is genetically heterogeneous within each affected patient. As mutations accumulate over the course of the disease, CLL becomes more difficult to treat with time (11). Patients with R/R disease and/or adverse cytogenetics (for example 17p deletion or TP53 mutation) are the most difficult to treat and have particularly poor outcomes (12).

There is no current standard of care for the treatment of CLL, particularly relapsed or refractory (R/R) CLL (2, 13). Patients with R/R disease are treated based on their disease biology, fitness status, comorbidities and previous treatment. Outcomes are very poor in the sub-group of R/R CLL patients who relapse early (up to 36 months) following treatment (and are therefore ineligible for further treatment with fludarabine), and for those with 17p deletion or TP53 mutation. The median OS in these patients is less than 2 years with the current standard of treatment (14). Consistent with this, recent real-world retrospective data collected from 2009 to 2014 from a Swedish population of CLL patients for whom fludarabine-based regimens were inappropriate showed median OS of [redacted], Figure 1 below (15).

[redacted]

Of note, patients with 17p deletion or TP53 mutation are unsuitable for chemo-immunotherapy regardless of line of therapy, as both those cytogenetic alterations affect a gene whose mutation confers resistance to chemotherapy agents (12) and as a result no standard of care exist for these sub-groups.

Ibrutinib

Ibrutinib is a potent, non-chemotherapy agent and first-in-class inhibitor of Bruton's tyrosine kinase (BTK). This is a novel therapeutic target and critical signalling kinase in the B cell receptor (BCR) pathway and its activity is essential for tumour cell survival and proliferation. BTK's inhibition therefore represents a step-change in the therapeutic armamentarium of clinicians treating CLL (16) (17).

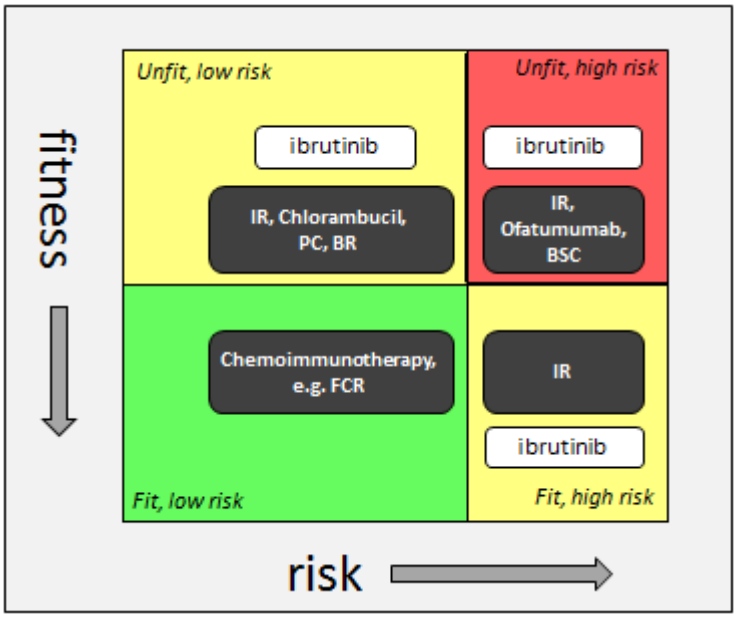
Ibrutinib is administered as monotherapy and does not require associated intravenous (IV) monoclonal antibody administration. It also does not require pre-medication or prophylactic treatments to prevent side effects. The mechanism of action of ibrutinib is independent from the integrity of the TP53 gene and other cytogenetic alterations commonly found in patients with CLL; this translates into a highly consistent efficacy profile across patient subgroups, including those carrying cytogenetic abnormalities (18).

Ibrutinib's potency and pharmacologic properties (i.e., specificity to BTK with very little off-target binding, oral bioavailability, irreversible binding to BTK (19) (20) (16)) make it an extremely attractive therapeutic option in CLL. This is reflected in its unprecedented efficacy, generally well tolerated safety profile and convenience to patients across all subgroups.

Place in therapy

The treatment decision for R/R CLL patients can be considered according to fitness and cytogenetic risk factors. Figure 2 below illustrates how the current treatment regimens used will differ by quadrant. It is proposed that ibrutinib is suitable for use in all quadrants, with the exception of those patients (being the fit, low cytogenetic risk) for whom treatment with fludarabine-containing chemoimmunotherapy is appropriate.

Figure 2: Place in therapy for ibrutinib



Key: FCR, fludarabine, cyclophosphamide + rituximab; IR, idelalisib + rituximab; PC, Physicians' choice; BR, bendamustine + rituximab

EFFICACY

R/R population

Ibrutinib has demonstrated a consistent and unprecedented survival benefit across all R/R patient subgroups, with more than 50% of patients still alive and free of progression at the end of all published clinical trials, including one with a follow-up of up to 44 months (18, 21-25). As a result of this unprecedented efficacy, ibrutinib was granted FDA breakthrough status and accelerated approval in February 2014, closely followed by the European Medicines Agency (EMA) in October 2014. It is worth noting a few of the quotes taken directly from the European Public Assessment Report (EPAR) that characterise the importance of the clinical trial results:

"The results from studies conducted in CLL indication are of ***high clinical relevance***. Of major importance in the assessment of benefit is the consistently shown ***dramatic activity*** of ibrutinib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with MCL and CLL."

"In patients with del17p/TP53 mutations limited options such as fludarabine or alemtuzumab combination regimens may be available; however these regimens are too toxic for large proportions of patients, therefore benefit-risk is considered ***clearly favourable*** for patients non-suitable for immuno-chemotherapy in case of mutations del17p/TP53, regardless of prior treatment experience."

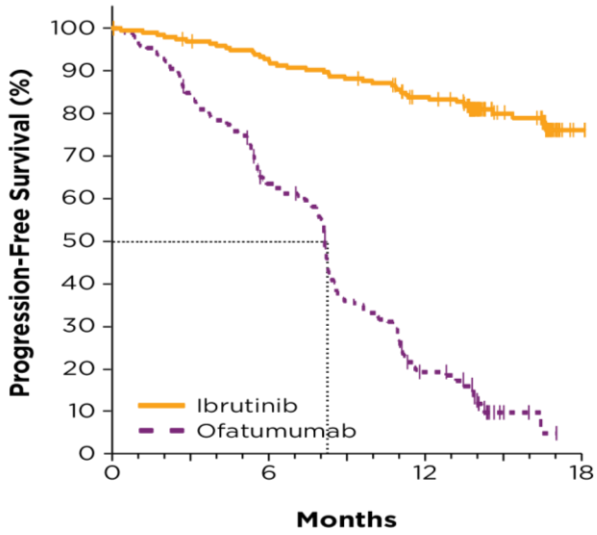
"The positive results in the high risk patients with 17p deletion/TP53 mutations are of particular importance and ***support indication in first line*** for those patients who are unsuitable for chemoimmunotherapy."

In the R/R setting, ibrutinib is listed in the American National Comprehensive Cancer Network (NCCN) guidelines as the *first* treatment option in order of preference, based on a level of evidence of 1 (this being defined as "*Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate*") (26) (27). Ibrutinib is also recommended in the British Committee for Standards in Haematology (BCSH) guidelines as a treatment option in relapsed patients inappropriate for fludarabine (2).

PROGRESSION FREE SURVIVAL

In the pivotal phase III randomised controlled trial (RCT; RESONATE), with 16 months median follow-up, more than 70% of patients in the ibrutinib arm were still alive and free of progression, compared to less than 20% in the ofatumumab arm, which reached median PFS at 8.1 months (Figure 3) (28).

Figure 3: Progression free survival of ibrutinib vs. ofatumumab(28)



	Ofa n=196	Ibr n=195
Median time (months)	8.1	NR
Hazard ratio	0.106	
(95% CI)	(0.073-0.153)	
Log-rank *P* value	*P*<0.0001	

Ibrutinib is also effective in the more difficult to treat patient population with 17p deletion or p53 mutation. In the R/R setting, 50% of patients were still alive and free of progression at 32.4 months (22) (23); as a measure of comparison, the median PFS for patients with 17p deletion treated with ofatumumab was 5.8 months in RESONATE (18).

OVERALL SURVIVAL

The unprecedented efficacy profile of ibrutinib has also translated into an advantage in OS in all patient subgroups, with more than 70% of patients still alive in all published clinical trials. In a phase II trial, 87% of patients were still alive at a median duration of follow up of 30 months (22, 23).

In RESONATE, a highly statistically significant difference in OS was also observed between the two arms, despite the fact that 61% of patients had crossed over from the ofatumumab arm on to ibrutinib. This crossover was recommended by the steering committee based on highly promising data from the phase II study. A protocol amendment allowed patients in the ofatumumab group who had disease progression to receive ibrutinib.

ADDITIONAL EVIDENCE

Indirect treatment comparisons (ITC) were performed across available clinical trials. Although very few comparative studies in R/R CLL have been conducted, a side by side comparison of PFS shows the step-change in efficacy that ibrutinib offers (Table 3). Despite being a naïve comparison, this conveys the superiority of ibrutinib versus its main comparators. (21-24).

Table 3: Summary of available data of PFS in R/R CLL trials

Treatment	Median PFS (months)	Source
Ofatumumab	8.1	RESONATE (18)
Bendamustine+rituximab (BR)	14.7	Fischer et al. (29).
Idelalisib+rituximab (IR)	19.4	Study 116 (30)
Ibrutinib	>30	Coutre et al.(22, 23)
It should be noted that PFS data above are not adjusted for trial characteristics.		

Treatment-naïve 17p deletion population

The use of ibrutinib was tested in a population of previously untreated patients with 17p deletion. In this population with high unmet need, ibrutinib demonstrated a strong efficacy profile, with 84% of patients alive at 24 months (25). Formal comparison with other treatments is not feasible because idelalisib plus rituximab (IR) has a very limited dataset in this patient group and the only other effective treatment (alemtuzumab) was withdrawn from the UK market for CLL in 2012 and has only been available since then on a compassionate basis. However, efficacy of current treatments in *treatment-naïve* 17p deletion patients, ranging from 2.2 to 18.3 months median PFS, is clearly exceeded by the 32.4 months median PFS observed with ibrutinib in *R/R* 17p deletion patients (22, 31). It can be inferred that the efficacy of ibrutinib in treatment-naïve 17p deletion patients will at least be equivalent to that observed in R/R 17p deletion patients and thus represents a major step change in the treatment of treatment-naïve 17p deletion CLL.

In this population, ibrutinib is listed in the NCCN guidelines (26) (27) as the *first* treatment option in order of preference, based on a level of evidence of 2A (this being defined as "*Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate*"). BCSH guidelines also recommend ibrutinib as a treatment option in treatment-naïve 17p deletion patients (2).

SAFETY

The safety profile of ibrutinib has been well characterised in the clinical programme, and can be safely administered even in a heavily pre-treated and elderly population with baseline coexisting conditions (18, 21-25, 32).

AEs are usually predictable, of low grade and can be effectively managed with supportive therapy; their incidence decreases over time and rarely results in need for discontinuation (7% in RESONATE in the 16 months follow up (28)) or dose reduction. This is in contrast to agents commonly used in this setting, e.g. chemotherapy agents with a known poor tolerability profile or even newer targeted agents (33).

1.4 Summary of the cost-effectiveness analysis

Methods and inputs

The cost-effectiveness of ibrutinib was assessed in the R/R CLL population and in the high-risk subgroup of R/R 17p deletion patients. The economic analysis was based on a three-health state (PFS, post-progression and death) partition survival model designed to best capture the unique aspects of the disease and treatment pathway, and to make the best use of clinical trial data available. The structure of the model is consistent with previous published models in this disease area, which have been previously accepted by NICE (34-36).

The comparators included in the analysis are detailed in Table 1 above. Clinical data inputs were informed by the most rigorous available data, using direct comparative trial data where possible (ibrutinib vs. ofatumumab). Indirect treatment comparisons (ITCs) were conducted where a common comparator was available (ibrutinib vs. PC and vs. IR) and, where no common comparator was found (ibrutinib vs. BR), matching-adjusted indirect comparisons (MAICs) were conducted, triangulating multiple data sources to demonstrate a consistent trend in comparative efficacy, Table 4 below. Utility values were informed by the analysis of

EQ-5D data from the RESONATE trial and published literature. Medical resource use was elicited from clinical experts.

Table 4: Summary of results of ITCs and MAICs

Comparison	Analysis type	Data sources	HR PFS (95% CI)	HR OS (95% CI)
Ibrutinib vs. PC	ITC, Bucher method	RESONATE (28) vs. Osterborg, 2014 (37, 38)	[redacted]	[redacted]
	ITC, multivariate Cox model	RESONATE (28) vs. Karolinksa Institute (15)	[redacted]	[redacted]
Ibrutinib vs. BR	MAIC	RESONATE (28) vs. Fischer, 2011 (29)	[redacted]	[redacted]
Ibrutinib vs. IR	ITC, Bucher method	RESONATE (28) vs. Jones, 2015 (39)	[redacted]	[redacted]
Ibrutinib vs. ofatumumab	RCT	RESONATE (28)	0.11 (0.07-0.15)	[redacted]

Key: ITC, indirect treatment comparison; MAIC, matched adjusted treatment comparison; HR, hazard ratio; PFS, progression free survival; OS, overall survival; PC, physicians' choice; BR, bendamustine+rituximab; IR, idelalisib+rituximab

Base case results for CLL patients who have received at least one therapy

Ibrutinib was consistently associated with substantially longer PFS and OS versus all comparators and across all sensitivity analyses. The demonstrated effect of ibrutinib on prolonging PFS represents a major clinical breakthrough and consequently, the drug remains cost-effective (with ICERs/QALY below £50,000) in the base case at list price (Table 5 to Table 8) and across all plausible one-way sensitivity and scenario analyses.

Table 5: Incremental cost-effectiveness results, base case results vs. PC without PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
PC	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	149,589	3.29	45,486

Key: PC, physicians' choice; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 6: Incremental cost-effectiveness results, base case results vs. BR without PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
BR	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	151,595	3.61	42,016

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BR, bendamustine plus rituximab

Table 7: Incremental cost-effectiveness results, base case results vs. IR without PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
IR	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	86,718	1.93	44,836
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; idelalisib plus rituximab					

Table 8: Incremental cost-effectiveness results, base case results vs. ofatumumab without PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
Ofatumumab	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	120,487	2.65	34,345
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Subgroup analysis results for CLL patients with 17p deletion or TP53 mutation who have received at least one therapy

The cost-effectiveness of ibrutinib vs. ofatumumab was tested in a R/R CLL 17p deletion subgroup for which there was comparative efficacy data from the phase III RESONATE study (18). Ibrutinib is cost-effective in this sub-population (Table 9).

Cost-effectiveness analysis against other comparators in this subgroup is not feasible due to lack of data. However, few treatments in current practice are effective for patients with 17p. deletion; the ICERs of ibrutinib vs. other comparators, especially PC and BR, in this subgroup are therefore likely to be lower than the ICERs associated with the full R/R patient population.

Clinical expert opinion indicates that cost-effectiveness results in the R/R 17p deletion population should provide a plausible, although conservative, estimate of ibrutinib's value for money in a first-line 17p deletion subgroup (1). In addition, IR has a similar license to ibrutinib and has recently gained a positive Final Appraisal Determination (FAD) from NICE for the use in frontline 17p deletion and TP53 patients due to the acknowledged high level of clinical need in this patient population (40, 41)

Table 9: Incremental cost-effectiveness results, subgroup results vs. ofatumumab without PAS

Technology (and comparator)	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
Ofatumumab	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	102,596	2.69	38,145
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Patient Access Scheme

A PAS has been submitted to the Department of Health. [redacted] The results with the PAS are presented in Table 10 to Table 14 below.

Table 10: Incremental cost-effectiveness results, base case results vs. PC with PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
PC	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	3.29	[redacted]
Key: PC, physicians' choice; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 11: Incremental cost-effectiveness results, base case results vs. BR with PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
BR	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	3.61	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BR, bendamustine plus rituximab					

Table 12: Incremental cost-effectiveness results, base case results vs. IR with PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
IR	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	1.93	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; idelalisib plus rituximab					

Table 13: Incremental cost-effectiveness results, base case results vs. ofatumumab with PAS

Technology and comparator	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
Ofatumumab	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	2.65	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 14: Incremental cost-effectiveness results, <u>subgroup</u> results vs. ofatumumab with PAS

Technology (and comparator)	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
Ofatumumab	[redacted]	[redacted]			
Ibrutinib	[redacted]	[redacted]	[redacted]	2.69	[redacted]
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Conclusion

Ibrutinib is highly cost-effective as an end of life therapy in patients who have received at least one therapy and for whom fludarabine is inappropriate. Base case ICERs with the PAS incorporated vs. PC, IR, BR and ofatumumab are [redacted], [redacted], [redacted] and [redacted] per QALY, respectively. Ibrutinib is also highly cost-effective in the subgroup of R/R CLL patients with 17p deletion, with an ICER vs. ofatumumab of [redacted]/QALY. Although no formal analysis was possible in the treatment naïve 17p deletion population, clinical data for ibrutinib are compelling and it can be inferred that the clinical and cost-effectiveness will be at least equivalent to that of ibrutinib in the R/R 17p deletion patient population.

2 The technology

2.1 Description of the technology

Ibrutinib is a first-in-class inhibitor of Bruton's tyrosine kinase (BTK), a critical signalling kinase in the B cell receptor (BCR) pathway for tumour cell survival and proliferation.

Table 15: Details of ibrutinib

Approved name	Ibrutinib
Brand name	Imbruvica®
Therapeutic class	Anti-neoplastic agents, protein kinase inhibitors
ATC code	L01XE27
Pharmaceutical form(s)	Capsule
Strengths available	140 mg
Route of administration	Oral
Pack/Package size	90 hard capsules 120 hard capsules
Manufacturer	Janssen

Mechanism of action

Since its identification, BTK has represented an attractive therapeutic target for B-cell malignancies, for its proven, prominent role in B-cell development and function, cytoplasmic expression and selective expression in B-cells (42) (17) (43).

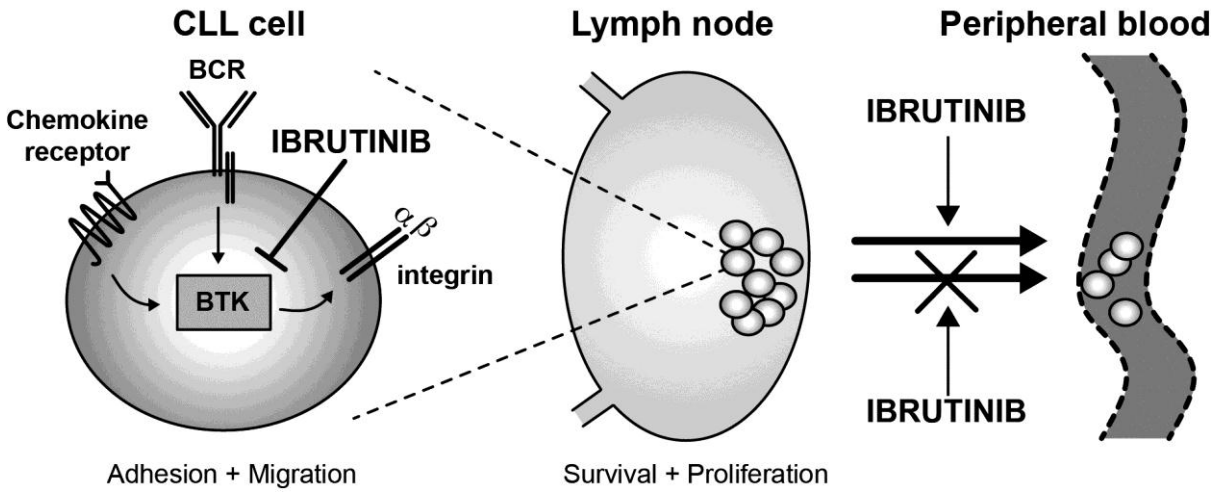
BTK belongs to the "Tec kinase family", which are involved in pathogenesis of several B-cell malignancies, including chronic lymphocytic leukaemia (CLL), and is a key component of the BCR signalling pathway (16) (17).

The BCR plays an important role in normal B cell development. The BCR regulates multiple cellular processes, including proliferation, differentiation, apoptosis and cell migration, all of which are essential for the functioning and survival of both normal and malignant B cells (17) (16) (42) (44) (45) (46).

BTK also regulates B cell migration and homing independently of BCR signalling, affecting chemokine-controlled mechanisms of adhesion and migration as well as integrin expression (see Figure 4). Constant migration of mature lymphocytes between blood and tissues is a physiological occurrence but also provides malignant lymphocytes such as CLL cells with protective niches in the bone marrow and lymph nodes. Whilst in the protective niches, CLL cells receive survival and proliferation signals from the microenvironment (47). BTK protein and mRNA are significantly over expressed in CLL compared with normal B cells (48).

Ibrutinib is a potent, orally bioavailable, highly specific inhibitor of BTK, with which it forms a stable covalent bond within BTK's active site Cys-48,1producing a sustained inhibition of its enzymatic activity. By blocking BTK, ibrutinib disrupts the BCR signalling pathway and prevents proliferation and survival of B cells.

Figure 4: Mechanism of action of ibrutinib in CLL (49)



Pharmacodynamic data from the phase Ib-II study (21) revealed that once daily (od) ibrutinib provided effective and complete occupancy of BTK. The median occupancy of BTK was 96% to 99%. Full occupancy was observed as early as 4 hours after the dose was given and was maintained for 24 hours.

As discussed, treatment with ibrutinib impairs the adhesion of CLL cells within the protective niches in the bone marrow and lymph nodes and migration of CLL cells to the protective niches. This results in egress of CLL cells into the circulation where the cells eventually die (49). This movement of lymphocytes into the circulation results in lymphocytosis, an increase in the number or proportion of lymphocytes in the blood. This observed lymphocytosis is a pharmacodynamic effect and is not a sign of progressive disease in the absence of other clinical findings.

Lymphocytosis is observed in the majority of patients receiving ibrutinib. It tends to resolve within 8 months of treatment; however, a minority of patients have lymphocytosis lasting >12 months (50). Lymphocytosis does not have an impact on clinical outcomes and resolves completely once treatment with ibrutinib is stopped (51).

Ibrutinib is not a cytotoxic agent; it exerts an anti-neoplastic effect by modest induction of apoptosis, inhibition of cell proliferation, and blockage of survival pathways in CLL cells (48). As a consequence of this, the majority of adverse events (AE) observed with ibrutinib are transient and manageable, decreasing over time and rarely results in the need for discontinuation (7% in the 16-months follow-up RESONATE trial) or dose reduction (28). Treatment with ibrutinib allows the majority of patients with CLL, even those with adverse cytogenetic features, to enter remission for many months with minimal toxicities (47).

2.2 Marketing authorisation and health technology assessment

Ibrutinib is indicated for the treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

Ibrutinib is also indicated for the treatment of adult patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL) and for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

The Summary of Product Characteristics is provided in Appendix 1.

In the US, in February 2014, the FDA granted breakthrough status and accelerated approval for ibrutinib to treat CLL based on the demonstrable effect of ibrutinib on overall response rate (ORR). In July 2014, new labelling was issued which reflected that clinical benefit had been verified and expanded the approval to include patients with 17p deletion. Ibrutinib is also approved outside the UK and Europe, including the US, Canada, Australia, Switzerland and Israel. The marketing authorisation application (MAA) was submitted to the European Medicines Agency (EMA) on 30th October 2013. Positive Committee for Medicinal Products for Human Use (CHMP) opinion for Imbruvica® (ibrutinib) was obtained on 24th July 2014, and a final European Commission decision was obtained on 21st October 2014.

The ibrutinib EMA approval was achieved earlier than expected following initial submission of single arm phase II data because of the recognition by the EMA of the promise shown by ibrutinib in a disease area of considerable unmet need.

It is noteworthy to highlight the most significant extracts from the CHMP report related to the CLL submission, as it reflects the regulators' opinion on the clinical value of ibrutinib.

"The results from studies conducted in CLL indication are of *high clinical relevance*. Of major importance in the assessment of benefit is the consistently shown *dramatic activity* of ibrutinib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with MCL and CLL."

"In patients with del17p/TP53 mutations limited options such as fludarabine or alemtuzumab combination regimens may be available; however these regimens are too toxic for large proportions of patients, therefore benefit-risk is considered CLEARLY FAVOURABLE for patients non-suitable for immuno-chemotherapy in case of mutations del17p/TP53, regardless of prior treatment experience."

"The positive results in the high risk patients with 17p deletion/TP53 mutations are of particular importance and support indication in first line for those patients who are unsuitable for chemo-immunotherapy."

"The study is considered WELL-CONDUCTED but was TERMINATED EARLY, at 146 PFS events, due to a positive interim analysis, with a median time on study at 9.6 and 9.2 months for the ibrutinib and ofatumumab arms, respectively. The primary PFS analysis, based on IRC assessment, shows a LARGE AND STATISTICALLY HIGHLY SIGNIFICANT SUPERIORITY for the ibrutinib arm, $p < 0.0001$, HR = 0.215, 95% CI: 0.146, 0.317."

"These results are ROBUST AND CONVINCING, with a p-value of 0.0049 and a HR of 0.434 (95% CI: 0.238, 0.789) in the primary analysis, and supportive sensitivity analyses and a relatively consistent result across subgroups…"

The European public assessment report (EPAR) was therefore extremely positive for ibrutinib. The full EPAR is provided in Appendix 1.

It should be noted that the current submission only focuses on the use of ibrutinib for the licenced indications in CLL as per the scope (6).

Ibrutinib will be assessed by NICE for MCL. The submission date for the MCL assessment is April 2016, with a decision anticipated by January 2017.

Ibrutinib will be assessed by SMC for CLL and MCL. The submission date for both appraisals is December 2015 with decisions anticipated by April 2016.

Ibrutinib will be assessed by AWMSG for both MCL and CLL. The submission date for both appraisals is December 2015 with decisions anticipated by June 2016.

2.3 Administration and costs of the technology

Ibrutinib is administered orally once daily at the patient's home, does not require any pre-medication or associated treatment administration, and therefore has no administration costs. Table 16 summarises the anticipated costs of treatment with ibrutinib.

With respect to the acquisition cost of ibrutinib, Janssen have proposed a confidential Patient Access Scheme (PAS) to the Patient Access Scheme Liaison Unit (PASLU) and the Department of Health (DH). Details of this scheme and the related cost-effectiveness results incorporating the scheme are provided in Appendix 14.

Table 16: Costs of the technology being appraised

	Cost	**Source**
Pharmaceutical formulation	140 mg capsule, administered as monotherapy	SmPC (52)
Acquisition cost (excluding VAT) *	£51.10 per capsule	British National Formulary (53)
Method of administration	Oral	SmPC (52)
Doses	Three 140 mg capsules per day for CLL	SmPC (52)
Dosing frequency	Once daily (od)	SmPC (52)
Average length of a course of treatment	Treatment is until disease progression or unacceptable toxicity. As median PFS has not yet been reached in R/R CLL patients treated with ibrutinib, it is difficult to estimate the average length of treatment; however, in the phase II extension study (PCYC1103), median duration of treatment was 30.4 months and 21.9 months in the treatment-naïve and R/R populations, respectively (22, 23). Median PFS has been reached in patients with 17p deletion in the PCYC1103 study and was	SmPC (52) Coutre 2015 (22, 23)

	32.4 months (23).	
Average cost of a course of treatment	The cost per year of treatment is £55,954.50.	Calculated based on list price and dosing regimen.
Anticipated average interval between courses of treatments	Ibrutinib is administered continuously until disease progression or unacceptable toxicity. Patients may discontinue treatment briefly in specific circumstances; for example, treatment should be held for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.	SmPC (52)
Anticipated number of repeat courses of treatments	Ibrutinib is administered continuously until disease progression or unacceptable toxicity.	SmPC (52)
Dose adjustments	Ibrutinib dose should be lowered to 140 mg od (one capsule) when used concomitantly with moderate CYP3A4 inhibitors. Ibrutinib dose should be reduced to 140 mg od (one capsule) or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors. Ibrutinib therapy should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity, ≥ grade 3 neutropenia with infection or fever or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), treatment may be reinitiated at the starting dose. If the toxicity reoccurs, the od dose should be reduced by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg od (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg od (one capsule).	SmPC (52)
Anticipated care setting	The anticipated setting of care would be secondary care as CLL, a haematological malignancy, is managed in this care setting. Treatment with ibrutinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.	SmPC (52)
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

Ibrutinib's pharmacological properties, together with its efficacy and its safety profile will have a noticeable positive impact on the changes in service provision and management. Ibrutinib is self-administered by the patient at home as it is an oral monotherapy. Ibrutinib has no further administration requirements and does not require any premedication, unlike the majority of existing treatments for CLL which are either fully administered as an infusion or are in combination with treatments requiring infusion. It is therefore reasonable to assume a steep reduction in infusion service requirements for patients on ibrutinib.

Ibrutinib's licence in treatment-naïve patients is restricted to those with 17p deletion or TP53 mutation not eligible for chemo-immunotherapy; however, testing for both these common genetic abnormalities is current practice and no additional testing will be required for ibrutinib. No additional infrastructure, no change to the current standard of care testing and no further monitoring over and above current clinical practice is anticipated with this application. There are no concomitant therapies specified in the marketing authorisation or used in the key clinical trials.

A full evaluation of the resource use and costs associated with treatment can be found in Section 6.

2.5 Innovation

Ibrutinib is a first-in-class, oral, highly selective BTK inhibitor that offers a substantial step-change in the management of CLL. This is corroborated through five key considerations:

Ibrutinib's mode and mechanism of action ease the patient and NHS burden associated with current CLL treatments

Ibrutinib is a potent, novel therapeutic target and a critical signalling kinase in the BCR pathway for tumour cell survival and proliferation (16) (17).

Ibrutinib is administered orally, once daily which provides an ease of administration to patients and has the added benefit of avoidance of chemotherapy. This translates to reduced time burden for patients and carers related to infusions, avoids the side-effects and psychological impact of chemotherapy for patients and frees up NHS resources otherwise associated with chemotherapy administration and management.

Ibrutinib's mechanism of action is independent from the integrity of the TP53 gene and other cytogenetic alteration commonly found in patients with CLL; this translates into a consistent efficacy profile across patient sub-groups carrying cytogenetic abnormalities (18) (28).

Unlike other targeted agents, ibrutinib is administered as monotherapy and does not require an associated intravenous (IV) monoclonal antibody administration. It also does not require premedication or prophylactic treatment to prevent side effects. No other oral monotherapies are currently recommended by NICE for CLL patients, whether in the R/R setting or otherwise.

As discussed throughout this section, ibrutinib's pharmacologic properties (e.g. oral bioavailability, potency, high specificity with little off target effect, ideal elimination kinetic, etc.) leads to an unprecedented efficacy and safety profile, representing a true step-change in the treatment of B-cell malignancies, and CLL in particular.

Ibrutinib has a robust evidence base demonstrating unprecedented clinical efficacy

The efficacy of ibrutinib in CLL has been investigated in a number of clinical studies, in both the R/R population and in the treatment-naïve population who have 17p deletion or TP53 mutation.

In the phase III pivotal trial, ibrutinib reduced the risk of death by 57% compared to ofatumumab and reduced the risk of death or progression by 88%. These results are highly statistically significant and were not affected by subgroup analyses (18) (28).

In a phase II trial of ibrutinib with a follow-up of up to 45 months (median time on study 22 months) 87% of patients with R/R CLL treated with ibrutinib remain alive while an unprecedented 76% remain alive and free of progression (22, 23). These data substantiate the long-term efficacy of ibrutinib. Furthermore, a summary of the median PFS for common treatments used in R/R CLL as listed in Table 17 demonstrates the step-change in efficacy that ibrutinib offers.

Table 17: Summary of available data of PFS in R/R CLL trials

Treatment	Median PFS (months)	Source
Bendamustine+rituximab (BR)	14.7	Fischer et al (29)
Idelalisib+rituximab (IR)	19.4	Study 116 (30)
Ofatumumab	8.1	RESONATE (18)
Ibrutinib	>30	Coutre et al (22, 23)
Note that PFS above is not adjusted for trial characteristics		

In a population of treatment-naïve patients with 17p deletion, ibrutinib continued to demonstrate a strong efficacy profile with 84% of patients remaining alive at 24 months (25). Ibrutinib has proved to be effective across all patient subgroups, including those with unfavourable cytogenetic and other negative prognostic factors, frail patients and those with comorbidities and patients with advanced disease (18) (28).

Sustained disease remission with a good tolerability profile has also been demonstrated in these patient when on treatment with ibrutinib (47).

Section 4 provides further details supporting the substantial clinical efficacy of ibrutinib.

Ibrutinib demonstrates a well-tolerated safety profile which keeps patients on therapy

The safety profile of ibrutinib has been well characterised in the clinical programme and the drug can be safely administered even in a heavily pre-treated and/or elderly population with baseline comorbidities.

AEs are generally predictable, of low grade and can be effectively managed with supportive therapy. The incidence of AEs decrease over time and rarely results in need for discontinuation (7% in the 16-months follow-up RESONATE trial) or dose reduction (28).

Ibrutinib's manageable and predictable safety profile allows patients to remain on therapy which consequently ensures that treatment remains uninterrupted and efficacy is not impacted by tolerability. This is in contrast to agents commonly used in this setting (e.g. chemotherapy agents with a known poor tolerability profile or even newer targeted agents) (33).

Section 4 reports the detailed safety data associated with ibrutinib.

Ibrutinib significantly and substantially addresses unmet need within the CLL treatment pathway

There is currently no standard of care for the R/R CLL population or treatment-naïve CLL patients with 17p deletion or TP53 mutation as indicated by the list of relevant comparators included within the Final Scope and CLL treatment guidelines (13) (54) (26, 27) (55). CLL remains incurable (4) and despite the current relatively efficacious regimens available for treatment-naïve patients with no adverse cytogenetics, all patients will eventually relapse. At relapse, outcomes of patients who relapse within 36 months from frontline intensive chemo-immunotherapy are poor, with a median overall survival (OS) of less than 2 years (14) (15).

In addition to being administered orally and as a monotherapy, ibrutinib further overcomes the limitations of current cytotoxic therapy and newer targeted agents by inhibiting a molecule specific to B-cells which are an ideal candidate for targeted therapy (52). The treatment of patients with adverse cytogenetics (mainly 17p deletion and TP53 mutation) was, up until recently, largely ineffective with the only recommended agent (alemtuzumab) now withdrawn from the market for the CLL indication and only available on a named patient compassionate basis (4).

The National Comprehensive Cancer Network (NCCN) and Swedish CLL guidelines have recently been updated and recognise the innovative nature of ibrutinib as both guidelines now recommend this step-change therapy (26) (27) (55). The NCCN recommend ibrutinib as a first line option for both the R/R CLL population as well as for the treatment-naïve 17p deletion/TP53 mutation population and consider the respective level of evidence associated with ibrutinib to be level 1 (high-level evidence; uniform NCCN consensus that the intervention is appropriate) and Level 2A (lower-level evidence; uniform NCCN consensus that the intervention is appropriate). The Swedish guidelines recommend ibrutinib as a first option and differentiate it as the preferred option compared to other targeted therapies and anti CD-20 antibodies (e.g. idelalisib in combination with rituximab, alemtuzumab, ofatumumab) (55).

The British Committee for Standards in Haematology (BCSH) produce UK-specific guidance with respect to the management of CLL (13). An update to the current guideline is expected before the end of 2015; however, an interim statement was issued in July 2015 recommending ibrutinib in treatment-naïve patients with TP53 abnormality and in high risk patients (i.e. those with TP53 mutation/17p deletion or those who fail fludarabine combination therapy within 2 years).

Section 3 describes the current treatment landscape and demonstrates in further detail the significant impact that ibrutinib will make.

Benefits of ibrutinib may not be fully captured by the quality adjusted life year (QALY) metric

CLL is a debilitating condition and has been associated with more sick leave in affected patients as compared with the general population (56). It is therefore assumed that CLL will

also impact on carers and the wider society as a result of patients with CLL and their carers taking time off work. The impact is likely to increase as the disease progresses. Such impacts will not be captured in the QALY calculation.

Oral administration means that patients are able to return to work and normal activities.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Clinical condition

CLL results from clonal proliferation and accumulation of mature CD5+, CD23+ B lymphocytes in the blood, lymph nodes and bone marrow, which prevent the development of normal white blood cells, red blood cells and platelets (3). Historically, CLL was classified separately from small lymphocytic lymphoma (SLL), but both are now considered the same entity with a different clinical presentation (4) and BCSH guidance recommend that SLL is managed in the same way as CLL (13).

CLL is a life-threatening disease due to development of cytopenias and impaired production of normal immunoglobulin. Current treatment options for patients with R/R CLL are poor, particularly for high-risk groups for whom no standard of care exists, such as patients with short initial duration of remission or certain cytogenetic aberrations (e.g. TP53 mutations ± 17p deletion, 11q deletion, or complex karyotypes).

Risk factors identified as poor prognostic factors include advanced stage at diagnosis, advanced age, male sex, diffuse pattern of bone marrow infiltration, poor response to therapy or short duration of response and short lymphocyte doubling time (4).

17p deletion and TP53 mutation

CLL is genetically heterogeneous and contains subclonal populations with diverse cytogenetics. Genetic abnormalities and mutations develop over the course of disease which makes CLL difficult to treat (11).

The TP53 tumour suppressor gene plays a critical role in cancer development and in response to chemotherapy. The TP53 tumour suppressor gene is located at 17p13.1 on chromosome 17 (57). Disruption of TP53 can occur when part of the gene sequence is mutated (TP53 mutation) or when 17p deletion (deletion of the area of the chromosome 17 where TP53 is located) is missing or deleted.

The clinical impact of TP53 mutation or 17p deletion is significant. Patients present with more advanced disease at diagnosis (58) and have a poor prognosis with short survival and resistance to conventional DNA-damaging chemotherapy (12).

Diagnosis

CLL often remains undiagnosed either until it is well advanced, or until a chance test shows abnormally high levels of lymphocytes in the blood. More than 80% of early-stage diagnoses occur in patients following an incidental finding on a routine full blood count (59).

CLL is diagnosed by the detection of a clonal population of small B cells and mature lymphocytes in a biopsy of a lymph node, tissue or bone marrow. The diagnosis of CLL requires the presence of ≥5 x 10^9 B lymphocytes/L (5,000/μL) for ≥3 months in the peripheral

blood (60). The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.

Additional investigations, including cytogenetic analysis and histology, may be required to obtain a definitive diagnosis (61). Fluorescence in situ hybridisation (FISH) can identify cytogenetic lesions in approximately 80% of CLL cases (58). The FISH technique uses fluorescently-labelled deoxyribonucleic acid (DNA) probes to detect chromosomal aberrations where TP53 or the 17p arm is missing; however, it is unable to detect cases where the TP53 gene is mutated but 17p remains intact. A FISH analysis is recommended in both international and UK guidelines (13) (54).

Staging

Staging systems based on the results of physical examination and blood tests are used to evaluate a patient at diagnosis to determine prognosis and decide on therapy (54). There are two staging systems: the Binet system is most commonly used in Europe and the Rai system which is used in the US and Japan (54) (13).

Symptoms and clinical consequences of disease

CLL has a highly variable disease course ranging from no treatment to early death due to development of cytopenias and impaired production of normal immunoglobulin (62) (63).

The clinical characteristics of CLL patients are shown in Table 18.

Table 18: Clinical characteristics of CLL patients (60) (64) (13)

Non-specific symptoms may include:	Clinical signs may include:	In advanced disease patients may experience:
Weakness Fatigue Abdominal discomfort Night sweats Fever	Abnormal enlargement of lymph nodes (lymphadenopathy) Abnormal enlargement of organs (organomegaly), e.g. spleen (splenomegaly) or liver enlargement (hepatomegaly) Ecchymoses (bruising) Swelling and redness of joints	Weight loss Recurrent infections Bleeding secondary to thrombocytopenia Symptomatic anaemia

Natural history

CLL is preceded by a premalignant B-cell proliferative disorder known as monoclonal B-cell lymphocytosis. The accumulation of genetic lesions and interactions of leukemic cells with antigen through the B-cell receptor and the microenvironment are believed to promote cell proliferation and inhibit apoptosis (65).

The prognosis of patients with CLL depends on a variety of patient-related (age, gender, comorbidities, performance status), disease-related (disease stage, cytogenetics, marrow

failure, immunodeficiency, lymphomatous transformation, biomarkers), and treatment-related (type of treatment, response, toxicity, minimal residual disease [MRD] status) factors (13).

CLL is considered generally incurable, with limited treatment options. Progression-free survival (PFS) and OS have been shown to be significantly shorter in patients with R/R CLL with poor-risk features. The predominant poor-risk feature in CLL is the presence of the 17p deletion cytogenetic abnormality which increases among patients with relapsed CLL (13) and has been statistically linked to be the strongest predictor of death with a hazard ratio of 8.08 (58).

Life expectancy for patients with R/R CLL is less than 24 months as indicated by recent real-world retrospective data collected from 2009 to 2014 from a Swedish population [redacted]

Furthermore, 17p deletion is associated with a median life expectancy of less than 2 to 3 years from the time of initial diagnosis (58). Recent NICE Final Appraisal Determination documentation pertaining to R/R CLL have also concluded that the disease meets NICE's short life expectancy criteria in determining whether new therapies are considered as end-of-life treatments (40).

[redacted]

Epidemiology

Relapsed and refractory CLL

CLL is relatively rare, with an incidence of 4 to 7.5 per 100,000 persons per year (66) (7). Incidence increases with age and is higher in men than in women (13).

CLL is incurable and is extremely heterogeneous in its clinical course (4). Approximately one-third of CLL patients live for decades without treatment, one-third have an indolent phase followed by disease progression and one-third have extremely aggressive disease at onset with a poor response to treatment and a relapsing/remitting course of disease (4, 9).

Treatment-naïve CLL with 17p deletion

In most cases (approximately 80%), 17p deletion is also associated with concomitant TP53 mutations (12). 17p deletion is present in 7% to 10% of patients with newly diagnosed CLL (58, 67) and the prevalence rises to one-third in patients with R/R disease.

3.2 Effect on patients, carers and society

The clinical sequelae of CLL can have substantial negative impacts on patients' QOL as a result of disease-related symptoms, treatment-related AEs, and the psychological, socioeconomic and functional effects of living with the disease.

In patients with progressive disease, CLL can be chronically debilitating with symptoms including enlargement of the lymph nodes, liver and spleen; weight loss; night sweats; fatigue; cytopenias (anaemia, thrombocytopenia); and infection (68). Approximately 20% of patients present with advanced disease and have anaemia and thrombocytopenia at presentation (4) with symptoms worsening as the disease progresses.

The emotional well-being of patients with CLL has been shown to be significantly lower than that of the general population, as well as that of patients with other types of cancer (p=0.001), due to the emotional distress of the incurable and uncertain nature of the disease and the fatigue associated with it (5). In the same study, patients with CLL reported statistically significantly higher rates of fatigue than the general population; patient-reported fatigue increased with disease stage (5).

Recent progress has been made in understanding the effect of treatment on the QOL of patients with CLL. In a recently published study of 777 previously untreated patients randomised to receive different first-line treatments, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) was used to assess the impact of CLL on patients over a 5-year period (69). Results of the study indicated that patients aged over 70 years reported statistically significantly worse scores in physical functioning compared with younger patients (69). Older patients also reported significantly lower scores in the role functioning domain (mean 63 points vs 73 points; 95% CI: 69, 77; p=0.006) and in the global health-related quality of life (HRQOL) score (mean 54 points vs 67 points; 95% CI: 48, 59; p=0.00001) (69). Research further suggests that the negative impact of CLL on QOL is greater during active treatment (5, 70).

Patients and their carers can find it difficult to accept a diagnosis of an incurable condition, particularly as patients may be asymptomatic with uncertainty around timing and impact of disease progression and subsequent treatments. This uncertainty is likely to have a considerable impact on QOL (71).

The impact of CLL on society was investigated in a study carried out in Germany which reported that patients with CLL who were still within working age took significantly more sick days than those without the disease, impacting on work productivity (56). In addition, as the disease progresses, the impact on carers' QOL will consequentially increase as they will be

required to take more time off work or be unable to work at all having a further impact from the societal perspective.

3.3 Current treatment landscape and anticipated positioning of ibrutinib

This submission addresses the following two patient populations which are included within ibrutinib's marketing authorisation:

- **Adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate**: This patient population is highly heterogeneous and includes relatively unfit patients who do not have numerous treatment options, as well as much frailer patients who are refractory to, or have a rapid relapse following cytotoxic agents, with/without rituximab, with multiple comorbidities, and who have few, if any, active treatment options remaining.

- **Adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation**: This patient population with poor prognostic markers do not respond well to chemo-immunotherapy as these high-risk cells are resistant to this treatment regimen.

CLL remains incurable with chemo-immunotherapy and it is a disease of repeated relapse. Some patients follow an aggressive course from the outset, which is associated with poor treatment outcomes. Throughout treatment, the primary aim remains improved survival and patient QOL. However, at times these aims are driven by individual patient characteristics; for physically fit patients, the goal may be increased OS while for patients with reduced physical fitness, the time to progression or improved HRQOL may be more suitable goals (60).

Treatment options range from chemo-immunotherapy using single agents and combination regimens consisting of chemotherapy (e.g. purine analogues, alkylating agents), monoclonal antibodies, and more recently, targeted therapies (see Table 19) (26) (27).

Table 19: Therapies for CLL

Drug class	Drug therapy	Mechanism of action
Cytotoxic therapies	Chlorambucil	Alkylating agent
	Fludarabine	Purine analogue
	Bendamustine	Alkylating agent, purine analogue
Monoclonal antibodies	Rituximab	Anti-CD20 monoclonal antibody
	Ofatumumab	Anti-CD20 monoclonal antibody
	Obinutuzumab	Anti-CD20 monoclonal antibody
	Alemtuzumab	Anti-CD52 monoclonal antibody
Targeted therapies	Ibrutinib	BTK inhibitor
	Idelalisib	PI3Kδ inhibitor

NICE guidance

NICE have carried out a series of technology appraisals in CLL. These are detailed in Table 20 and have also been summarised in a pathway issued by NICE (72).

For CLL patients who are treatment-naïve, as initial therapy NICE recommends fludarabine, cyclophosphamide and rituximab (FCR) for patients who are able to take fludarabine-containing regimens. For patients who are unsuitable for fludarabine-containing regimens, bendamustine is the current recommended option (73).

For patients with R/R CLL, guidance as to the choice of NICE-recommended treatments is limited. NICE recommends repeat administration of FCR unless the patient is refractory to fludarabine or has been previously treated with rituximab outside of the context of a clinical trial. As an alternative, NICE recommends oral fludarabine for patients who have failed on or are intolerant to first-line chemotherapy who would otherwise have received standard combination chemotherapy (i.e. cyclophosphamide, doxorubicin, vincristine and prednisolone [CHOP], cyclophosphamide, doxorubicin and prednisolone [CAP] or cyclophosphamide vincristine and prednisolone [CVP]).

NICE currently does not provide any specific treatment pathways for patients with a 17p deletion or TP53 mutation; therefore, these patients are treated using the same guidance as the wider CLL patient population. This highlights a poorly-addressed patient population and a high unmet need. It is important to note that as per the final scope of this appraisal, NICE recognises the need to specifically address this patient population (6).

Table 20: Treatments considered in the NICE CLL pathway and their technology appraisals

Agent	NICE Guidance
Initial treatment	
Rituximab (given as FCR) TA174, July 2009 (34)	Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of CLL.
Bendamustine TA216 February 2011 (73)	Bendamustine is recommended 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.
Obinutuzumab, in combination with chlorambucil TA343 June 2015 (74).	Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if • Bendamustine-based therapy is not suitable and • the company provides obinutuzumab with the discount agreed in the patient access scheme
Ofatumumab, in combination with chlorambucil TA344 June 2015 (75)	Ofatumumab in combination with chlorambucil is recommended as an option for untreated CLL only if: • the person is ineligible for fludarabine-based therapy and • bendamustine is not suitable and • the company provides ofatumumab with the discount agreed in the patient access scheme
Fludarabine monotherapy	Fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of CLL.

TA119 February 2007 (76)	
R/R treatment	
Rituximab (given as FCR) TA193 July193 (34)	Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with R/R CLL except when the condition: • is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or • has previously been treated with rituximab, unless: o in the context of a clinical trial, at a dose lower than the dose currently licensed for CLL or o in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide.
Fludarabine monotherapy TA29 September 2001 (77)	Oral fludarabine is recommended as second line therapy for B-cell CLL for patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either: • CHOP • CAP • CVP
Ofatumumab TA202 October 2010 (35)	Ofatumumab is not recommended for the treatment of CLL that is refractory to fludarabine and alemtuzumab.
Idelalisib, in combination with rituximab FAD September 2015 (TAG pending) (40)	Idelalisib, in combination with rituximab, is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed within 24 months. Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

Clinical guidelines

The BCSH has issued UK-specific guidance with respect to the management of CLL (13). A wide range of treatment options are suggested based on fitness to tolerate FCR chemo-immunotherapy and whether patients are previously untreated or have relapsed or high-risk disease but there is no clear standard of care for the treatment of CLL, particularly R/R CLL. The recommendation that R/R patients should be offered entry into clinical trials wherever possible is indicative of the poor efficacy of existing treatment options.

The BCSH guidance is summarised by patient population in Table 21. A recent interim statement aims to update the guidance in response to the advances in CLL treatments which have become available (2). The additions include a recommendation to use ibrutinib in treatment-naïve patients with TP53 abnormality and in high risk patients (i.e. those with TP53 mutation/17p deletion or those who fail fludarabine combination therapy within 2 years). The revised BCSH CLL guidelines are expected before the end of 2015.

Table 21: Summary of BCSH guidelines updated with the interim 2015 statement (2) (13)

Patient population	Summary of guidance
First-line treatment of patients without TP53 abnormality who are fit enough to receive fludarabine	• FCR is recommended • Bendamustine plus rituximab is an alternative option in patients in whom FCR is contraindicated
First-line treatment of patients without TP53 abnormality who are not fit enough to receive fludarabine	• Chlorambucil in combination with ofatumumab or obinutuzumab • Chlorambucil in combination with rituximab is an alternative treatment if access to ofatumumab or obinutuzumab is restricted. • In particularly frail patients, chlorambucil is the treatment of choice for palliating frail patients, but bendamustine monotherapy is an option
First-line treatment of patients with TP53 abnormality	• Ibrutinib monotherapy or IR. • If not available, alemtuzumab with or without corticosteroids are preferable to chemotherapy
R/R CLL	• Patients relapsing ≥2 years after fludarabine-containing regimens who remain fit enough to receive fludarabine, should receive FCR. • Bendamustine plus rituximab is an alternative option • Patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR. • Patients relapsing after chlorambucil can be retreated with chlorambucil, with/without an anti-CD20 antibody. • For patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy, options include high-dose steroids, alone or in combination with rituximab and alemtuzumab.
High risk (TP53 mutation/17p deletion or failing fludarabine combination therapy within 2 years) patients	• Ibrutinib monotherapy or IR. • If not available, alemtuzumab with or without corticosteroids are preferable to chemotherapy
CLL with autoimmune cytopenias as a complication	• Steroids as first-line treatment • cyclosporine, intravenous immunoglobulin, thrombopoietin mimetic agents, low-dose cyclophosphamide, rituximab, alemtuzumab and splenectomy for patients unable to take steroids
CLL with infections as a complication	• Anti-microbial prophylaxis in patients at high risk of infection • Immunoglobulin replacement therapy may be considered to reduce bacterial infections in patients with a low serum IgG level with previous infection despite prophylaxis

With respect to infections, it is important to note that these are common and 50% of all CLL-related deaths are associated with infection-related complications (13).

The guidelines issued by the European Society of Medical Oncology (ESMO) for the management of CLL in Europe also recommend a wide range of strategies for managing relapsed CLL (54). In line with the BCSH guidelines, ESMO recommends that first-line treatment of patients with a 17p deletion or TP53 mutation should be offered alemtuzumab

followed by autologous stem cell transplantation (ASCT). However, alemtuzumab does not have a marketing authorisation in the EU and is only available via a PAS agreed between EMA and the manufacturer; therefore, it is unclear how long alemtuzumab will be available to patients in this indication and it is important to note that alemtuzumab tolerability can be challenging (78).

The Swedish Association of Haematology guidelines (55) recommend ibrutinib as a first option and differentiate it as the preferred option compared to other targeted therapies and anti CD-20 antibodies (e.g. IR, alemtuzumab, ofatumumab).

Guidelines issued by the NCCN for the management of CLL in the US are similar to the BSCH guidance in that there are no clear standards for treatment of R/R CLL (27). While a range of treatment options have been previously recommended for this group of patients, dependent on the fitness and age of patients and the length of time to relapse, the guidelines were recently updated to recommend ibrutinib as the first option in patients with R/R CLL (with or without 17p deletion) and as initial treatment in patients with untreated CLL with 17p deletion (27) (26).

In summary, although the treatment recommendations for first-line CLL patients are fairly clear and consistent across the various guidelines, the advice for R/R CLL patients remains unclear with a range of treatment regimens being recommended and an even wider range being used in clinical practice. In acknowledgement of the wide range of unique treatment regimens being used in clinical practice, it can be concluded that there is no existing standard of care for patients with R/R CLL in England.

With respect to patients with 17p deletion or TP53 mutation, response to chemo-immunotherapy remains poor and as such, current treatment options are very limited for this patient population. Alemtuzumab tolerability can be challenging (78) and the majority of CLL patients are not suitable for ASCT. Management of these patients remains an area of high unmet need.

Issues relating to current clinical practice

Despite the existence of UK recommendations for the management of CLL, these are not entirely reflective of current clinical practice. Guidelines from the BCSH were published in 2012 (13) and clinical practice in this area has since advanced. Table 22 and Table 23 summarise the treatments listed in the Final Scope of this submission, the patient population in whom these treatments are used, the extent of use of these treatments in the UK, and any issues associated with them.

Table 22: Therapies in NICE final scope and use in clinical practice: Relapsed CLL

Drug class	Treatment in scope	Patients who receive treatment	Use in clinical practice	Issues
Cytotoxic therapies for patients fit enough to receive fludarabine	FCR	Patients relapsing after fludarabine or chlorambucil within 2 years who are fit enough to receive fludarabine	Most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset (79)	Clinical experts suggested that FCR would not be used to treat patients who relapse early and it is not an option in older patients and those with significant comorbidities. Experts agreed that chemo-immunotherapy regimens such as this would not be suitable for relapsed patients with a 17p deletion or TP53 mutation (1).
Cytotoxic therapies for patients unable to receive fludarabine	Chlorambucil (with or without rituximab)	Patients relapsing after chlorambucil treatment, with or without an anti-CD20 antibody	Chlorambucil monotherapy is the third most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset (79). Chlorambucil in combination with rituximab is also used.	Clinical experts agreed that chlorambucil±R is used sparingly in R/R CLL. Furthermore, data are limited in the R/R setting making it difficult to estimate relative efficacy. The experts also noted that using chlorambucil±R in relapsed patients with a 17p deletion or TP53 mutation would be unlikely (1).

	Bendamustine (with or without rituximab)	Patients relapsing after chlorambucil treatment, with or without an anti-CD20 antibody	BR is the second most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset (79). Bendamustine monotherapy is also used.	Clinical experts agreed that B±R is an appropriate option in R/R CLL. However, data are limited in the R/R setting making it difficult to estimate relative efficacy. The experts also noted that using B±R in relapsed patients with a 17p deletion or TP53 mutation would be unlikely (1).
Anti-CD20 antibodies	Rituximab monotherapy	Not recommended as monotherapy	Clinical advice suggests this is not used as single agent in current practice (1). Clinical advice further suggests rituximab would be expected to have a similar efficacy to ofatumumab, the seventh most commonly used regimen in England as reported in the Systemic Anti-Cancer Therapy Dataset (79)	Not assessed by NICE in this population and not licensed for use as monotherapy in this population.
Targeted therapies	Idelalisib in combination with rituximab (IR)	Patients relapsed within 24 months	Based on the therapies available through the Cancer Drug Fund (CDF) for CLL in the R/R setting, IR is the second most commonly used regimen (49 or 17% of notifications) behind ibrutinib (178 or 62%) as reported by the CDF for the first quarter of 2015. The other funded CLL therapies are bendamustine (48; 17%) and ofatumumab (13; 5%) (80)	NICE have recently completed appraisal of this therapy and issued a FAD recommending use in untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed within 24 months. The final TAG expected in November 2015 at the earliest.

Supportive therapies	Corticosteroids (with or without rituximab)	Patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy	Steroid use is not certain and not captured in the Systemic Anti-Cancer Therapy Dataset (79)	Not assessed by NICE in this population.
	Best supportive care (BSC) (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)	In patients not fit enough to receive any of the above treatments, or where all other treatment options have been exhausted.	BSC consists of a wide range of therapies. Recent NICE appraisal documents reported that BSC would be comprised of outpatient review, blood/red cell transfusion for anaemia, inpatient stays, platelet transfusion for thrombocytopenia, immunoglobulin replacement, and plasmaphoresis. Additionally, there would be high use of anti-infective agents (e.g. antimicrobial, antifungals, and antivirals) (40).	Not assessed by NICE in this population.

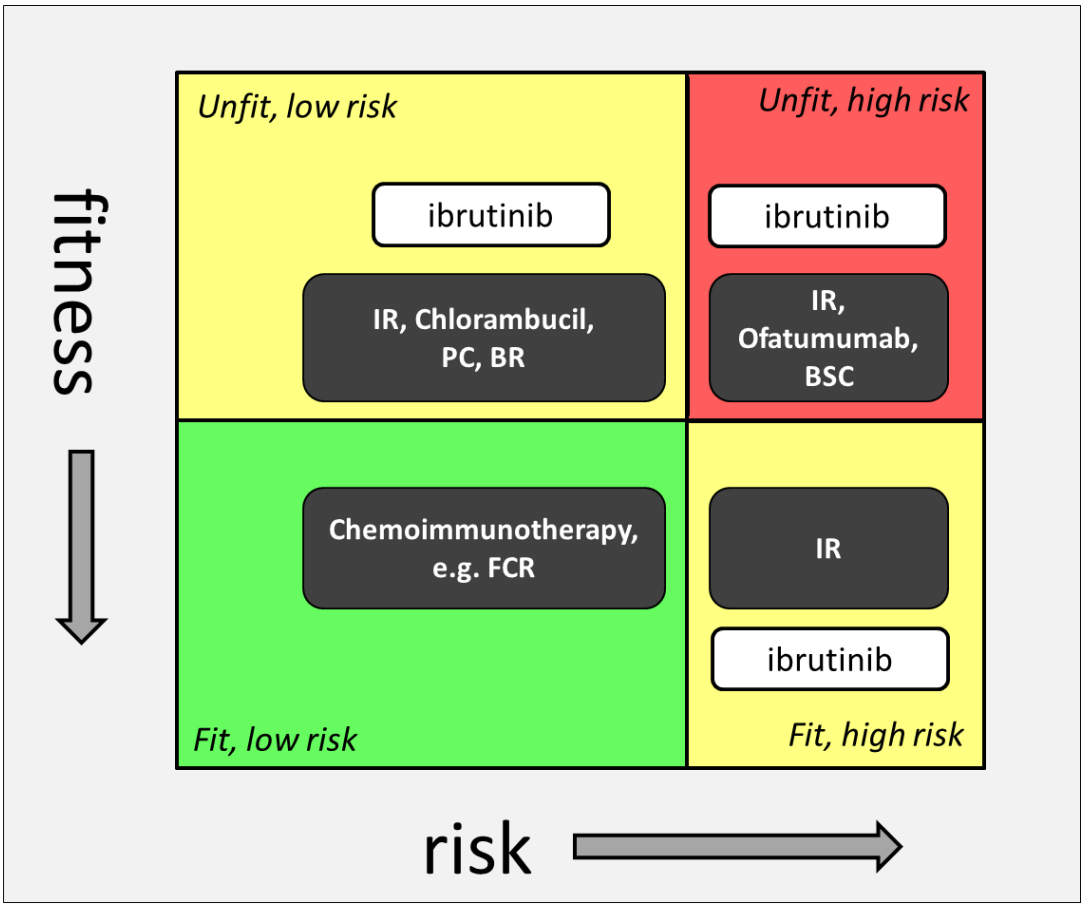
Table 23: Therapies in NICE final scope and use in clinical practice: Treatment-naïve patients with 17p deletion or TP53 mutation

Drug class	Treatment in scope	Patients who receive treatment	Use in clinical practice	Issues
Anti-CD20 antibodies	Alemtuzumab	Patients for whom chemo-immunotherapy is not an option, but who are able to receive ASCT, used in combination with pulsed high-dose glucocorticoids	No data available in this patient group.	Clinical experts recognise alemtuzumab as a relevant comparator but it does not have a marketing authorisation in the EU and is only available via a compassionate use scheme agreed between EMA and the manufacturer. It is unclear how long alemtuzumab will be available in this manner (1). Alemtuzumab is associated with considerable toxicity as a result of immunosuppression such as reactivation of cytomegalovirus and is not suitable for unfit patients (78).
Targeted therapies	Idelalisib in combination with rituximab	Untreated patients with a 17p deletion or TP53 mutation	Data specific to this patient group is not available. However, based on the therapies available through the CDF for CLL in the R/R setting, IR is the second most commonly used regimen (49 or 17% of notifications) behind ibrutinib (178 or 62%) as reported by the CDF for the first quarter of 2015. The other funded CLL therapies are bendamustine (48; 17%) and ofatumumab (13; 5%) (80).	NICE have recently completed appraisal of this therapy and issued a FAD recommending use in untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed within 24 months. The final TAG expected in November 2015 at the earliest.

Supportive therapies	BSC (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)	In patients not fit enough to receive any of the above treatments, or where all other treatment options have been exhausted.	BSC consists of a wide range of therapies. Recent NICE appraisal documents reported that BSC would be comprised of outpatient review, blood/red cell transfusion for anaemia, inpatient stays, platelet transfusion for thrombocytopenia, immunoglobulin replacement, and plasmaphoresis. Additionally, there would be high use of anti-infective agents (e.g. antimicrobial, antifungals, and antivirals) (40).	Not assessed by NICE in this population.

The treatment decision for R/R CLL patients can be considered according to fitness and cytogenetic risk factors. Figure 6 below illustrates how the current treatment regimens used will differ by quadrant. It is proposed that ibrutinib is suitable for use in all quadrants, with the exception of those patients (being the fit, low cytogenetic risk) for whom treatment with fludarabine-containing chemoimmunotherapy is appropriate.

Figure 6: Place in therapy for ibrutinib



Key: FCR, fludarabine, cyclophosphamide + rituximab; IR, idelalisib + rituximab; PC, Physicians' choice; BR, bendamustine + rituximab

The BCSH guidelines and interim statement (2, 13) recognise that the clinical heterogeneity of CLL means that there is no standard approach to treatment. This is echoed by the ESMO (54) and NCCN guidelines (26) (27) which include recommendations for enrolment into clinical trials for difficult to treat patients. The lack of a standard of care and a remaining unmet need in this disease is further supported by the comprehensive list of comparators included in the Final Scope of this appraisal (6).

Consequently, as a result of the lack of clear standard of care, and in discussion with clinical experts (1) we have considered four comparators to be relevant to this appraisal: Physician's Choice (PC), idelalisib in combination with rituximab (IR), bendamustine with rituximab (BR) and ofatumumab.

Physician's choice

PC aims to accurately reflect the fact that there is currently no clear standard of care for patients with R/R CLL. It is the main comparator within this appraisal and is comprised of the relevant comparators listed within the final NICE scope: BR; rituximab in combination with high-dose steroids (R+HDMP); chlorambucil and rituximab plus cyclophosphamide, doxorubicin, and prednisolone (R-CHOP); and chlorambucil with rituximab and FCR (1). Clinical evidence leveraged in order to estimate relative efficacy vs ibrutinib in R/R CLL is based on a phase III randomised controlled trial (RCT) comparing PC with ofatumumab (37, 81). Details of this analysis are presented in Section 4.10.

Idelalisib plus rituximab

IR is a new combination therapy which has recently received positive NICE Final Appraisal Determination (FAD) for untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed within 24 months (40).

Clinical evidence for idelalisib in combination with anti-CD20 antibody therapy in R/R CLL is available from three studies:

- Study 116 (30) compares IR to placebo with rituximab in patients with clinically significant coexisting medical conditions (decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses)

- Study 117 (82) which was an open-label extension study to 116

- Study 119 (NCT 01659021) (39) which was an open-label, randomised phase III trial, which compared idelalisib plus ofatumumab (IO) with ofatumumab

Median PFS was reached within Study 116/117 (5.5 months for placebo with rituximab; 19.4 months for IR). The extension study, Study 117, randomised patients to either the standard dose (150 mg bd) or a double dose (300 mg bd) of idelalisib monotherapy (following completion of the rituximab treatment regimen); therefore, it is difficult to interpret the long-term data since the licenced dose of idelalisib 150 mg bd plus rituximab was not used.

Median PFS was reached within Study 119 (8.0 months with ofatumumab; 16.3 months for IO, $p<0.0001$) (39).

Further to the efficacy data, safety data on IR suggests that the combination is not only associated with late onset of grade ≥3 diarrhoea or colitis but also, the events increase over time (83). Furthermore, a high overall discontinuation rate of 20% is reported within idelalisib's EPAR (33).

Bendamustine with rituximab (BR)

BR is not recommended for R/R CLL by NICE; however, clinical experts indicated that this combination is used in clinical practice in this patient population as limited alternatives are available (1). Data to support a comparison to BR were leveraged from a phase II study (29) in 78 patients with R/R disease.

Ofatumumab

Although ofatumumab does not appear as a comparator within the final scope (note that it appeared in the previous version of the scope) and is not recommended by NICE for the treatment of R/R CLL (35), Janssen strongly feel it is a relevant comparator for the following reasons:

- Ofatumumab is the comparator within the pivotal phase III trial for ibrutinib (RESONATE), as it was the only licensed treatment for R/R CLL at the time of trial initiation (18).
- Ofatumumab remains licensed for use in Europe for R/R CLL.
- Rituximab monotherapy is not licensed and not widely used in UK clinical practice; however, it remains within the final scope. Given NICE has accepted that ofatumumab and rituximab are equivalent in terms of efficacy (40, 41) ofatumumab should be considered an appropriate comparator.
- Most importantly, clinical opinion strongly suggests that it remains a relevant comparator in the UK for R/R CLL (1).

3.4 Equality issues

The current, most effective treatments for CLL are generally more suitable for young and fit patients as these treatments are myelosuppressive and/or immunosuppressive which are unsuitable for patients with a poor performance status and/or significant comorbidities. Poor performance status and comorbidities increase with age and an age threshold of approximately 70 years is often set as an upper limit for administering FCR, since few patients above this age have adequate renal function to allow for FCR and many have comorbidities (84).

In contrast, ibrutinib is suitable for patients regardless of their performance status or comorbidities. It is not a cytotoxic agent and is well tolerated with a consistent survival benefit demonstrated across all patient groups (18, 21-25, 32).

Furthermore, data from the clinical trials report that most AEs are grade 1 or 2 in severity, are clinically manageable, and reduce over time.

Ibrutinib provides an effective treatment option for all R/R CLL patients including those who cannot receive cytotoxic therapies due to their advanced age, performance status, comorbidities, fitness, or mutation status. Equality issues which may currently exist for older, frailer patients would be alleviated with the addition of ibrutinib to the current treatment landscape.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted in order to identify and select studies relevant for consideration within this submission.

Search strategy

The search strategy was developed and tested as part of the *a priori* protocol to identify relevant studies. The search algorithms used were generated under the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) and in line with the research question. A summary of the search strings and the rationale for their design is in Appendix 2.

The literature search for the review of clinical evidence was conducted in May 2014 and updated on 03 June 2015. The precise syntax and search settings used for the update search conducted in June 2015 differed slightly from those used in the original May 2014 searches to take into account additional efficiencies possible in the search interfaces that improved the specificity of searches without negatively impacting their sensitivity (especially for the search of relevant in-process citations via Embase.com). The actual search terms (i.e., keywords, text strings, indexing terms, etc.) remained the same. The search strategies used for the electronic literature database searches for the May 2014 search and the June 2015 update are shown in Appendix 2.

The databases searched without date limits were as follow:

- MEDLINE (via PubMed) and MEDLINE In-Process (via PubMed)
- Embase (via Embase.com) and Embase In-Process (via Embase.com)
- Cochrane Collaboration Central Register of Clinical Trials (CENTRAL, via the Cochrane Library).

To capture new trials that were not yet indexed, PubMed and Embase.com searches were run without limitations (i.e. no limitations such as title-abstract designations, Medical Subject Headings [MeSH] terminology, etc.) to identify new publications from December 2014 through June 2015.

Searches were also performed via the Cochrane Library and the other databases noted above to identify any high-quality, recently conducted SLRs (published from 2011 to 2015) to serve as supplemental data sources. Bibliographies of relevant systematic review articles published since 2011 and the bibliographies of accepted studies were also reviewed to identify any additional, relevant publications.

In addition to the databases listed above, ‘grey’ literature (i.e., material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for meeting abstracts or conference posters presenting any relevant information on the outcomes of interest. Proceedings from the past 3 years (if available) for the following key conferences were screened for relevant abstracts:

- American Society of Clinical Oncology (ASCO) 2013–2015: http://am.asco.org/
- ASH 2012–2014: http://www.hematology.org/Annual-Meeting/

- European Hematology Association (EHA) 2013–2015: http://www.ehaweb.org/
- ESMO 2012–2013: http://www.esmo.org/Conferences/ESMO-2014-Congress
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2013–2015 (International, Europe, and Latin America Meetings): http://www.ispor.org/

Study selection

The SLR focused on trials of R/R CLL patients reporting efficacy outcomes (OS, PFS, response to treatment, response duration, time to first response, event-free survival [EFS], time to treatment failure [TTF], time to progression [TTP]), and safety outcomes (AEs, discontinuations of interest). The search was not limited by date or language; however, all non-English-language publications with English abstracts were reviewed at the abstract level, and those that met the abstract inclusion criteria were noted separately (rejected as "Language other than English") and were not assessed further in the review. Publications without titles and abstracts in English were title screened and categorised according to the available information. All publications identified provided English-translated titles.

All randomised trials and non-randomised trials reporting on a comparator of interest were assessed for their study design, patient population (in order to be sufficiently comparable to the ibrutinib trial), and how the outcome of interest was reported.

The pre-specific inclusion and exclusion criteria used to identify studies relevant for inclusion in this review (along with their rationale) are described in Appendix 2.

After the initial removal of duplicate citations, abstracts were screened by two independent investigators using the pre-specified inclusion and exclusion criteria. Any discrepancies between the two investigators were reviewed and resolved by a third investigator before proceeding to full-text article retrieval. In this initial screening phase, studies were not excluded based on intervention/comparators of interest.

Full-text articles were reviewed by a single investigator, and all articles rejected at the full-text screening level were independently verified by a second, senior-level investigator based on the reason for rejection and whether the rejection was correct. Accepted full-text articles were further validated for inclusion during data extraction. The inclusion/exclusion criteria for the interventions/comparators of interest were applied during full-text screening.

Flow diagram

After the initial removal of duplicate citations, 3,961 abstracts were screened according to the pre-specified inclusion and exclusion criteria. A table presenting the number of references yielded from each database search conducted on 03 June 2015 is provided in Appendix 2.

Of the 3,961 abstracts screened, 3,110 were excluded at the title/abstract screening level. Among the 851 publications for which full texts were retrieved and screened, 641 were rejected and 210 publications reporting on 121 trials were accepted.

The SLR was initially designed to have a greater scope than just to identify evidence to support the clinical effectiveness of ibrutinib in line with the final scope issued by NICE. Consequently the following studies initially included in the review are not considered further in the current assessment of the clinical effectiveness of ibrutinib (i.e., are not relevant to subsections 4.2–4.9, 4.11, and/or 4.12 of this submission):

- ASCT was evaluated in 11 unique studies (presented in 14 publications). Publications on ASCT were unlike other accepted publications both in terms of the population (i.e., younger, fit patients) and outcome reporting (response to consolidated induction treatment followed by ASCT for patients responding to induction treatment). Given the clinical differences compared to the ibrutinib and other non-ASCT trials, these studies were not included in the current report.

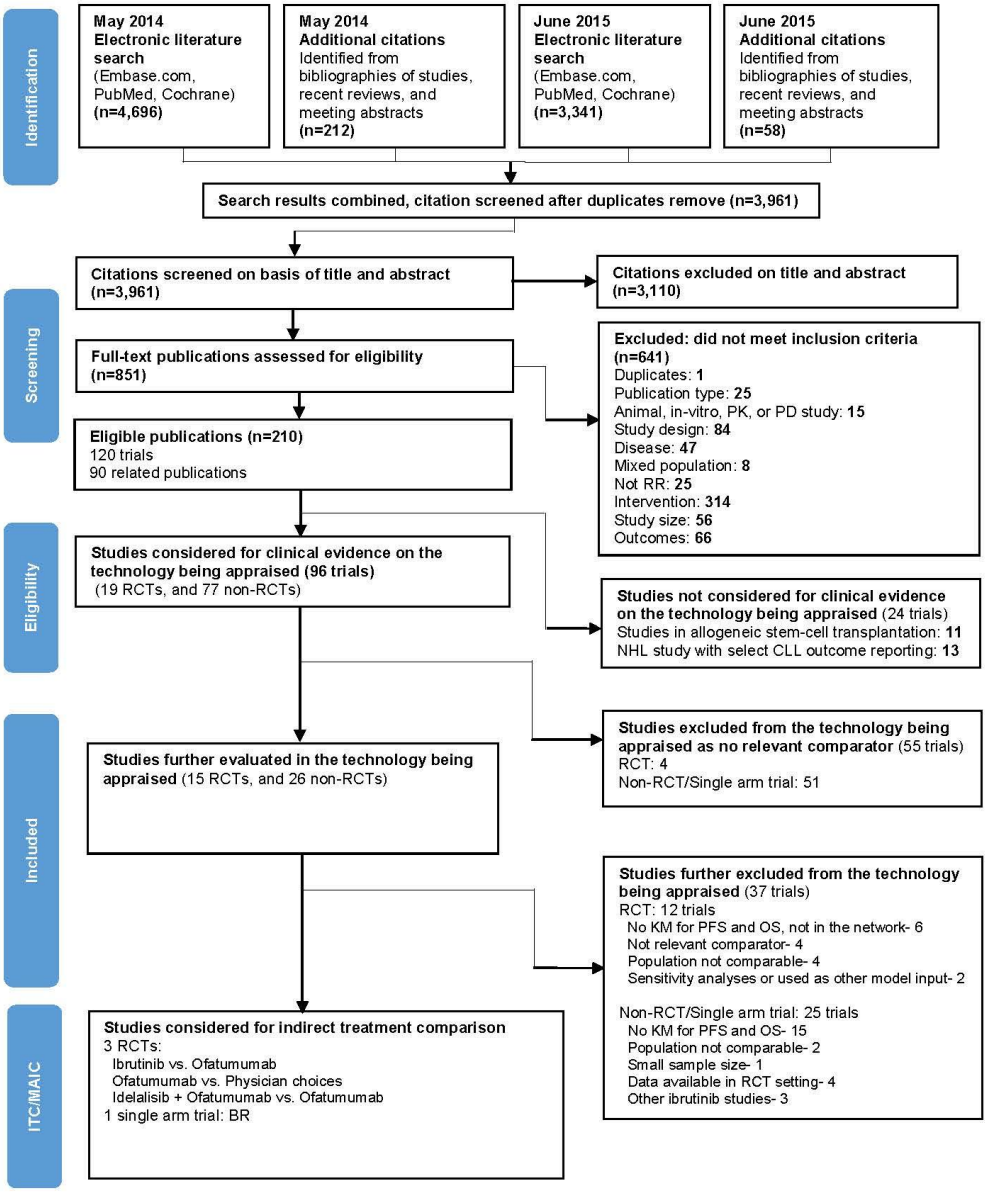
- Studies reporting CLL as subgroups presented lower-quality data that were not accurately reflected in associated descriptions of methods. Studies were not powered for these types of subgroup analyses and lacked the delineation of baseline patient characteristics that is necessary for trial population comparability estimation. Subsequently, studies with CLL as a subgroup of Non-Hodgkin's lymphoma (NHL), where the publication focused on the NHL population as a whole, were not assessed along with the CLL publications, and were excluded from further review.

- Of the remaining 97 studies (presented in 175 publications), 31 studies were only available in abstract form without accompanying full-text publications. The conference proceedings often represented interim data and lack sufficient evidence to adequately assess trial and population comparability.

- Of the remaining studies, 62 did not investigate treatment with ibrutinib within its licensed indication (i.e., monotherapy) and so were not considered further in subsections 4.2–4.9, 4.11, and 4.12 of this submission. (These studies were initially included in the review as the review was initially designed to also identify studies which can contribute relevant clinical data to indirect analyses for the comparison of ibrutinib to relevant comparators).

Figure 7 illustrates the process of eliminating references based on the systematic review protocol and the subsequent exclusion of studies from the present consideration of clinical evidence for ibrutinib (Figure 7 is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram template) (85).

Figure 7: PRISMA flow diagram for the review



Multiple publications from one study

When any particular study or trial had multiple publications associated with it, this was identified during study linking/related-publication identification and taken into account in the review trial flow (as shown in Figure 7, where a clear distinction has been made between numbers of included *studies* and numbers of included *publications* at the relevant stages). In order to avoid double-counting of data, when data from a single study presented in this clinical effectiveness section were drawn from more than one source/publications, or when studies were linked, the relevant publications associated with the actual study itself are shown (i.e. are listed in Sections 4.2 and 4.11 of this submission).

4.2 List of relevant randomised controlled trials

Table 24: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
PCYC1112 RESONATE	Ibrutinib	Ofatumumab	Patients with R/R CLL	Published paper Byrd, 2014 (18)

The RESONATE study compares ibrutinib (n=195) with ofatumumab (n=196) in patients with CLL who have received at least one prior treatment. The study also includes a subgroup of patients with the 17p deletion, 63 of whom received ibrutinib and 64 of whom received ofatumumab.

Trial
RESONATE - Study of Ibrutinib vs. Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

Publication
Byrd JC, Brown JR, O'Brien S et al for the RESONATE Investigators. Ibrutinib vs. ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014;371(3):213-223 (18)

Data sources
The data presented in this section are drawn from the published paper (18) and from the CSR (86).Wherever possible, the published paper is referenced and any additional relevant information is drawn from the CSR. Updated data available from a poster and abstract presented at ASH in December 2014 (28) are also presented to further supplement the data related to RESONATE.

4.3 Summary of methodology of the relevant randomised controlled trials

Table 25: Summary of methodology of RESONATE

	RESONATE
Location	Europe (UK, France, Ireland, Italy, Poland, Spain, Austria), the US and Australia US, Germany, Denmark, The Netherlands
UK patients	73 patients from the UK from 12 units; 34 patients were randomised to ibrutinib and 39 were randomised to ofatumumab.
Trial design	Multicentre open label controlled study
Enrolment	From June 2012 to April 2013, 391 patients were enrolled at 67 sites
Randomisation and blinding	Randomisation was via an interactive web response system (IWRS). Two randomisation schemes were generated: one for each geographical region (US vs. non-US). Under each scheme, patients were stratified according to resistance to purine analogue chemo-immunotherapy within 12 months of the last dose of a purine analogue and the presence/absence of 17p13.1. Given that the study was open-label in design, neither the subjects nor the investigators were blinded to treatment. However, it is important to note that progressive disease for the primary end-point and responses were assessed by the Independent Review Committee (IRC), members of which were blinded to both study treatment and absolute lymphocyte count. In addition, access to data was controlled so that the sponsor did not have access to aggregated efficacy data by treatment arm until unblinding (86).
Eligibility criteria	• Patients with CLL or SLL with R/R disease • Patients with CLL or SLL who had received at least one prior therapy and were considered inappropriate candidates for purine analogue treatment (e.g. fludarabine), due to a short PFS after immunochemotherapy, were aged 70 years or more or with a chromosome 17p13.1 deletion. • ECOG performance score of less than 2 (ECOG scores from 0 for least disability to 5 for greatest disability). • Absolute neutrophil count of at least 750 cells/µl. • Platelet count of at least 3,000 cells/µl. • Adequate liver and kidney function.
Exclusion criteria	• Patients receiving warfarin or strong CYP3A4/5 inhibitors
Trial drugs	Patients were randomised in a 1:1 ratio to receive oral ibrutinib (420 mg od) until disease progression or unacceptable toxicity (n=195) or IV ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by 2,000 mg weekly for 7 weeks, and then every 4 weeks for 16 weeks (n=196). Promising data from a phase II study (21) resulted in a revision in the study protocol which allowed patients on ofatumumab with disease progression to crossover to the ibrutinib arm see **Accounting for crossover in RESONATE** later in this section.
Monitoring	Patients were monitored each week for the first 8 weeks, then every 4 weeks until month 6 and then every 12 weeks.
Primary outcome	Duration of PFS, as assessed by the IRC
Secondary outcomes	Duration of OS Overall response rate (defined as the proportion of patients achieving a best overall response of either CR, CRi (CR with incomplete haematopoietic recovery), nPR or PR (86).). CT scans were used to evaluate response and persistent improvement for at least 2 months to confirm response.

PRO outcomes	Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) EORTC QlQ-C30 EQ-5D
Adherence	Adherence to ibrutinib was assessed by the site pharmacist or designee at each visit using direct questioning, examination of patient diaries and capsule counts. Ofatumumab was administered at the clinical site, and adherence was checked by the site pharmacist or designee.
Pre-planned subgroups for PFS	• Age (<65 vs. ≥65) • Gender (Male, Female) • Race (White, Non-White) • Geographical region (US, Other) • Rai Stage at screening (Stage 0-II, III-IV) • ECOG at randomisation (0, 1) • Bulky disease (<5 cm, ≥5 cm) • Number of prior treatment lines (<3, ≥3) • Refractory disease to purine analogues as recorded in IWRS (Yes, No) • 17p deletion as recorded in IWRS (Yes, No) • 11q deletion (Yes, No) • β2-microglobulin at baseline (≤3.5 mg/l, >3.5 mg/l)
Pre-planned subgroups for PFS	Age, gender, race, region, 17p deletion, and disease refractory to purine analogues (86).

The primary end-point was the duration of PFS, as assessed by the IRC according to the criteria of the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL), which require CT scans to evaluate response. It should be noted that treatment-related lymphocytosis was not considered to be progressive disease. PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first (86)(60).

Secondary end-points included duration of OS and ORR. Further details on the end-points are discussed below.

PFS was assessed by both IRC and investigators for the first 9.4 months (interim analysis); after that PFS was only assessed by the investigators.

OS was defined as the time from the date of randomisation to the date of death from any cause (86). CT scans were used to evaluate response and persistent improvement for at least 2 months to confirm response.

ORR comprises of complete response (CR) and partial response (PR). The protocol criteria for response were based on the criteria from IWCLL 2008 (60); the definitions of the various levels of response are shown in Table 26 and the criteria are shown in Table 27.

Table 26: Explanation of the various levels of response

Level of response	Explanation
CR	All of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow aspiration is required to confirm CR

CRi	Defined as CR with incomplete hematopoietic recovery (patients who fulfil all the criteria for a CR but who have persistent anaemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity)
PR	Requires two criteria from Group A, if abnormal at baseline to respond plus 1 of the criteria from Group B must be met. Improvement in Group B criteria must be in absence of growth factor or transfusion support. If all group B criteria normal at baseline, criteria must continue to remain within these limits. Note if all PR criteria with the exception of ALC are met this is consistent with a PR with lymphocytosis.
SD	The absence of PD and the failure to achieve a CR, CRi, nPR, PR, or PR with lymphocytosis.
PD	At least one of the above criteria from Group A or B are met or development of transformation to a more aggressive histology

Table 27: Protocol criteria for response were based on the criteria from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 (18, 60, 87)

Parameter	CR	PR	PD
Group A - defines the tumour load			
Lymphadenopathy[a]	None; ≤1.5cm	Decrease ≥50%	Increase ≥50% or any new lesion >1.5 cm
Hepatomegaly	None	Decrease ≥50%	Increase ≥50% or new hepatomegaly
Splenomegaly	None	Decrease ≥50%	Increase ≥50% or new splenomegaly
Blood lymphocytes	<4,000/µl	Decrease ≥50% from baseline	Increase ≥50% over baseline[c] or > 5000/µl
Marrow[b]	Normocellular, <30% lymphocytes, no B lymphoid nodules, no clonal infiltrate. Hypocellular defines Cri		
Group B - defines the function of the haematopoietic system			
Platelet count	>100,000/µl	>100,000/µl or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Haemoglobin	>110 g/l	>110 g/l or increase ≥50% over baseline	Decrease of >20 g/l from baseline secondary to CLL
Neutrophils	>1500/µl	1500/µl or increase ≥50% over baseline	N/A

a) Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node
b) This parameter is not relevant for the PD category unless confirming cytopaenic progression.
c) Patients with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease
d) Patients meeting all criteria for a CR with B-lymphocyte nodules on bone marrow exam will be considered nPR

Patient reported outcomes (PRO) were also explored as a secondary end-point using Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue).

The FACIT measurement system is a comprehensive compilation of questions that measure health-related quality of life in patients with cancer and other chronic diseases (http://www.facit.org). The core of the FACIT system is the Functional Assessment of Cancer Therapy-General, a 27-item general version of the questionnaire. Thirteen fatigue-related questions (FACIT fatigue) are added to the Functional Assessment of Cancer Therapy-General to form the FACIT-F. The responses to the 13 items on the FACIT fatigue questionnaire are each measured on a 4-point Likert scale. Thus, the total score ranges from 0 to 52. High scores represent less fatigue.

EQ-5D is a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the five separate items are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. UK weights were used to generate patient utilities from the five dimensions of the EQ-5D.

EORTC-QLQ-C30 includes 30 separate items resulting in five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), one Global Health Status scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Table 28 lists the reliability, validity and current use in clinical practice of each outcome.

Table 28: Outcomes and reliability/validity/current use in clinical practice

Outcome	Reliability/validity/current use in clinical practice
Primary end-point	
PFS	PFS is used in clinical practice and is a benefit in itself. Unlike OS, PFS is not affected by crossover or by subsequent treatments. However, PFS is affected by the timing of assessments and can be prone to investigator bias unless strict criteria for response evaluation are used, which were implemented in RESONATE
Secondary end-points	
OS	OS is the gold standard end-point for studies in cancer. Death is definitive, is easily compared across disease sites and is not subject to investigator bias. However, results may be diluted by crossover and contaminated by subsequent agents.
Response rate	Response rate provides an indication of the patients who will benefit from treatment. Not all patients who respond to treatment will benefit from treatment, but patients must have an initial response in order to benefit.
FACIT-Fatigue	The FACIT-Fatigue score has been validated in patients with cancer and has been shown to be a reliable and valid measure of fatigue (88). Fatigue is a key concern for patients undergoing treatment for cancer, including CLL.
EQ-5D	QOL is an important measure in CLL, an incurable condition with a R/R nature.
EORTC-QLQ-C30	

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

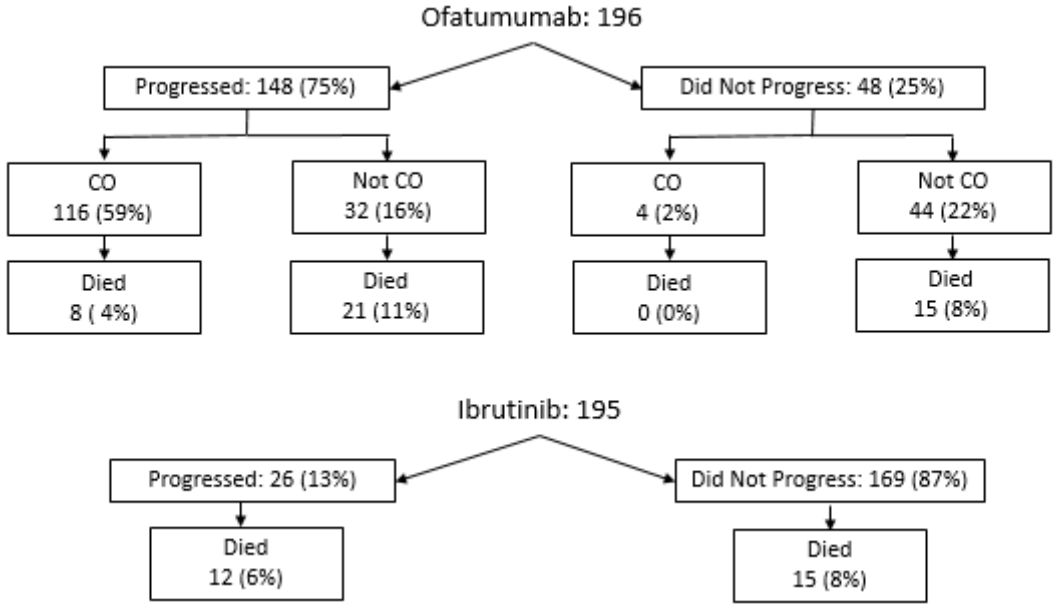
Table 29: Pre-specified statistical analysis in RESONATE

Primary hypothesis	Patients with R/R CLL treated with od ibrutinib would have improved PFS compared to patients treated with ofatumumab.
Calculation of study sample size	The number of required PFS events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%. The efficacy boundary (two-sided $p<0.028$) was crossed at the pre-planned interim analysis, and the results from that analysis are presented in the published paper.
Primary analysis	Two-sided log-rank test stratified according to the presence or absence of 17p deletion and the disease refractory status at randomisation. The type I error was controlled through adjustment of the significance level with the use of the O'Brien-Fleming boundary for the interim analysis and with the use of a hierarchical closed-testing procedure for primary and ordered secondary end-points. The primary analysis censored crossover subjects in the ofatumumab arm at the date of first dose of crossover to ibrutinib. A sensitivity analysis was conducted in which crossover subjects were not censored at the date of first dose of ibrutinib (86).
ITT population	The ITT population included all randomised patients; data were analysed according to the treatment to which patients were randomised. The ITT population was used for analysis of all efficacy and PRO end-points and baseline characteristics. A per protocol analysis was not carried out. The safety population was defined as all randomised patients who received at least one dose of study drug and patients were analysed according to the actual treatment received (86).

Accounting for crossover in RESONATE

The RESONATE trial allowed patients treated with ofatumumab to crossover or start receiving treatment with ibrutinib after developing progressive disease. Figure 8 illustrates the extent of crossover in RESONATE, detailing the number of patients who progressed, crossed over, and died in both treatment arms. As illustrated, at the time of the data cut (7 September 2014 data cut and extraction), 59% (n=116) of ofatumumab patients had progressed and crossed over to ibrutinib. It is important to note that the four patients who had not progressed but crossed from the ofatumumab to ibrutinib arms were protocol violations.

Figure 8: Diagram of RESONATE crossover



CO= crossover

While PFS outcomes are not impacted by crossover (given that progression precedes crossover), crossover can cause bias in OS analyses because the survival observed in the ofatumumab arm reflects the mixed effects of standard care after randomisation and after crossover to treatment with ibrutinib. If ibrutinib is effective and truly prolongs survival, crossover will lead to a gradual attenuation of differences in OS. For this reason, a traditional ITT analysis, in which data are analysed according to the arms to which patients were originally randomised, will underestimate ibrutinib's relative treatment effect on OS.

Accordingly, methods to adjust for the impact of crossover were tested, including rank-preserving structural failure time (RPSFT) models, inverse probability of censoring weights (IPCW) method, the iterative parameter estimation (IPE) algorithm, and novel two-stage methods. The RPSFT model was ultimately selected as the most robust method for adjusting for crossover. RPSFT models were designed specifically in the context of RCTs, and are often used when the data available are unlikely to capture all the factors that predict both treatment changes and outcome. This approach can therefore be used in situations where high rates of switching occur and may be associated with prognostic factors. This was the same technique used for crossover adjustment in the recent IR NICE submission (41). The resulting HR comparing ibrutinib vs. ofatumumab OS outcomes in the overall R/R CLL RESONATE population was [redacted]. In the 17p deletion subgroup of the RESONATE population, the OS HR comparing ibrutinib vs. ofatumumab adjusting for crossover was [redacted]. Full details of the adjustment for crossover are in Appendix 4.

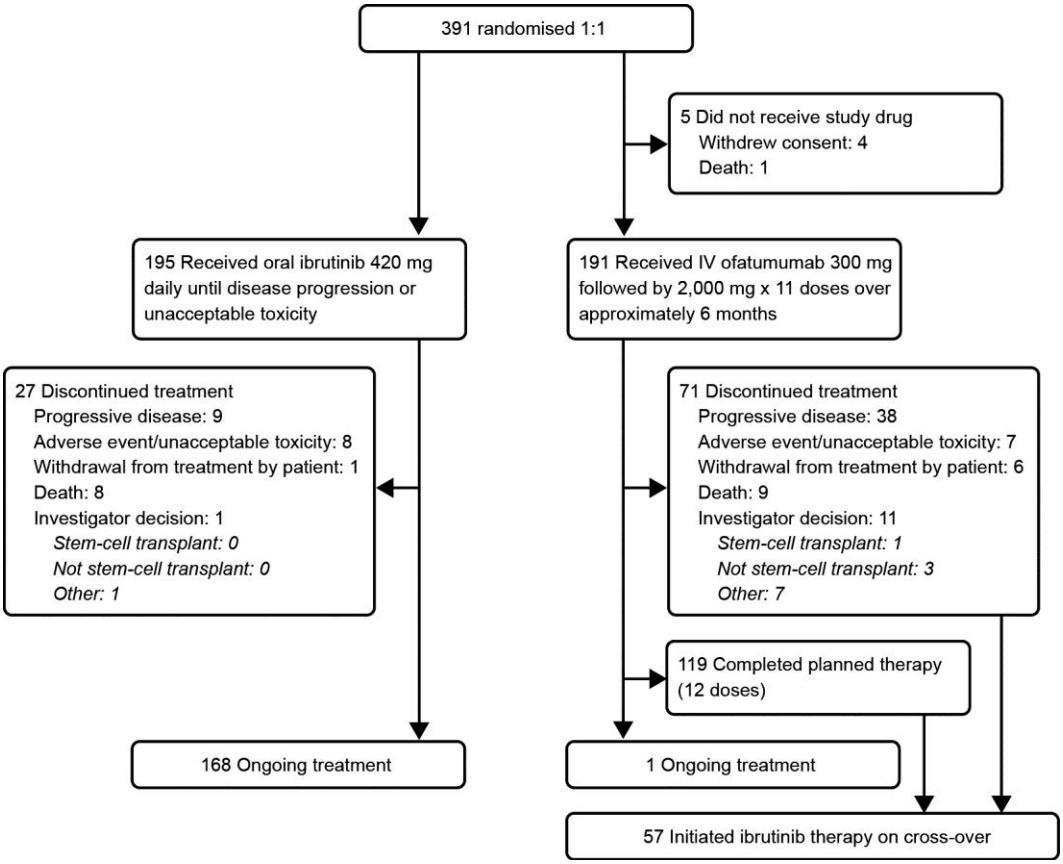
4.5 Participant flow in the relevant randomised controlled trials

Participant flow

RESONATE enrolled 391 patients at 67 sites; 195 patients were randomised to ibrutinib and 196 to ofatumumab. All patients randomised to ibrutinib received treatment; however, five

patients randomised to ofatumumab did not receive treatment. Of the 191 patients who received ofatumumab, 57 patients with documented disease progression crossed over to ibrutinib, see Figure 9.

Figure 9: CONSORT flow chart (18)



Patient characteristics

The characteristics of the patients were generally well balanced between the two arms. There were no significant differences between the two arms apart from the presence of bulky disease (64% in ibrutinib arm vs. 52% in the ofatumumab arm, p=0.04) and median time from last therapy (8 months vs. 12 months, p=0.02), both of which confer a poor prognosis. Patients in the ibrutinib arm had received treatment with a median of three prior treatments vs. two treatments in the ofatumumab arm.

Table 30 shows the patient characteristics at baseline.

Table 30: Patient characteristics at baseline in RESONATE.

Characteristic	Ibrutinib (n=195)	Ofatumumab (n=196)
Patients with SLL, number (%)	10 (5%)	8 (4%)
Median age (range), year	67 (30–86)	67 (37–88)
Male sex, number (%)	129 (66%)	137 (70%)
Cumulative Illness Rating Scale score >6, number (%)	38 (32%)	39 (32%)
Creatinine clearance <60 ml/min, number (%)	62 (32%)	61 (31%)
Median haemoglobin (range) g/l	110 (70–160)	110 (60–160)
Median platelet count (range), per mm^3	116,500 (20,000–441,000)	122,000 (23,000–345,000)
Median lymphocyte count (range), per mm^3	29,470 (90–467,700)	29,930 (290–551,030)
ECOG performance status 0, number (%)	79 (41%)	80 (41%)
ECOG performance status 1, number (%)	116 (59%)	116 (59%)
Bulky disease ≥5 cm, number (%)	124 (64%)	101 (52%)
Interphase cytogenetic abnormalities, number (%)		
Chromosome 11q22.3 deletion	63 (32%)	59 (30%)
Chromosome 17p13.1 deletion	63 (32%)	64 (33%)
β2-microglobulin >3.5 mg/l, number (%)	153 (78%)	145 (74%)
Previous therapies		
Median number (range)	3 (1–12)	2 (1–13)
≥3, number (%)	103 (53%)	90 (46%)
Type of therapy, number (%)		
Alkylator	181 (93%)	173 (88%)
Bendamustine	84 (43%)	73 (37%)
Purine analogue	166 (85%)	151 (77%)
Anti-CD20	183 (94%)	176 (90%)
Alemtuzumab	40 (21%)	33 (17%)
Allogeneic transplantation	3 (2)	1 (1)
Median time from last therapy (range), months	8 (1–140)	12 (0–184)
Resistance to purine analogues, number (%)	87 (45)	88 (45)

4.6 Quality assessment of the relevant randomised controlled trials

The quality assessment for RESONATE is provided in Table 31.

Table 31: RCT quality assessment of RESONATE

Parameter	Comment
Was the randomisation method adequate?	Yes, the randomisation method was adequate; patients were randomised using a central IWRS
Was the allocation adequately concealed?	Yes, allocation was adequately concealed; patients were randomised using a central IWRS
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes, patients were generally well balanced between the two arms. There were no significant differences between the two arms apart from the presence of bulky disease (64% in ibrutinib arm vs. 52% in the ofatumumab arm, p=0.04) and median time from last therapy (8 months vs. 12 months, p=0.02). Patients in the ibrutinib arm had received treatment with a median of three prior treatments vs. two treatments in the ofatumumab arm.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Given that the study was open-label in design and treatment was administered using two different methods (oral or IV); neither the subjects nor the investigators were blinded to treatment. However, the likely impact on the risk of bias is low since assessment of progressive disease for the primary end-point and responses were assessed by the IRC, members of which were blinded to both study treatment and absolute lymphocyte count.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	All patients randomised to ibrutinib received treatment; however, five patients randomised to ofatumumab did not receive treatment. Of the 191 patients who received ofatumumab, 57 patients with documented disease progression crossed over to ibrutinib. The primary analysis censored crossover subjects in the ofatumumab arm at the date of first dose of crossover to ibrutinib. A sensitivity analysis was conducted in which crossover subjects were not censored at the date of first dose of ibrutinib.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population included all randomised patients; data were analysed according to the treatment to which patients were randomised. The ITT population was used for analysis of all efficacy and PRO end-points and baseline characteristics.
Consider how closely the RCT(s) reflects routine clinical practice in England.	RESONATE compares ibrutinib with ofatumumab. Ofatumumab is not recommended by NICE for the treatment of R/R CLL in England. However clinical opinion suggests that ofatumumab is used in some patients and remains a relevant comparator (1). Further details can be found in section 3.3

4.7 Clinical effectiveness results of the relevant randomised controlled trials

RESONATE median follow-up was 9.4 months (range 0.1-16.6) and 86% of patients were still receiving ibrutinib at the time of the published analysis (18). Updated data with median follow-up of 16 months are presented in a poster at ASH 2014 (28).

RESONATE Primary end-point: PFS

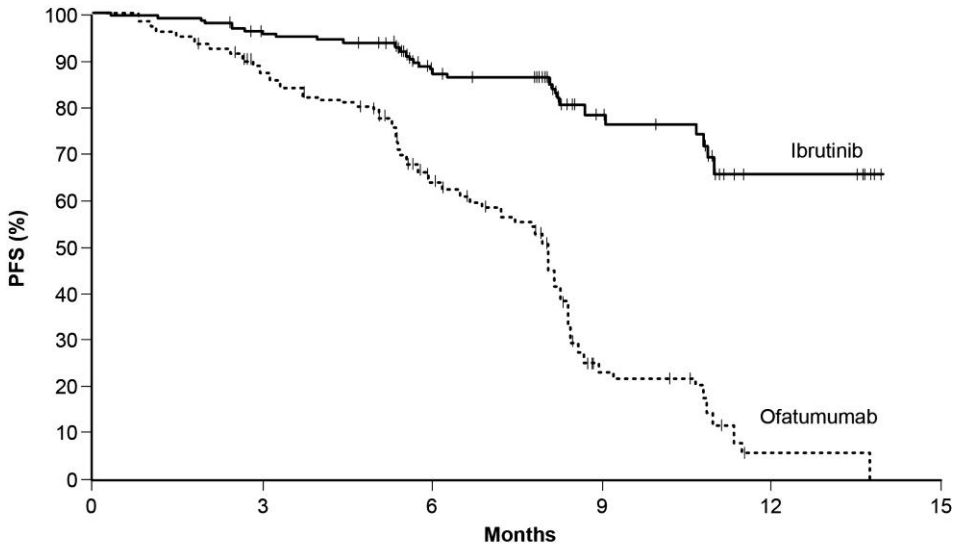
Ibrutinib significantly extended the duration of PFS compared with ofatumumab. With ibrutinib the median PFS was not reached after a median follow-up of 9.4 months vs. a median duration of PFS of 8.1 months with ofatumumab, see Figure 10.

The HR for progression or death in the ibrutinib group was 0.22 (95% CI, 0.15 to 0.32; p<0.001). This represents a 78% reduction in the risk of progression or death among patients treated with ibrutinib vs. ofatumumab.

At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression vs. 65% in the ofatumumab group.

These results demonstrate that ibrutinib provides an impressive and unprecedented benefit on PFS.

Figure 10: KM curve of PFS in RESONATE, IRC assessment (ITT analysis).

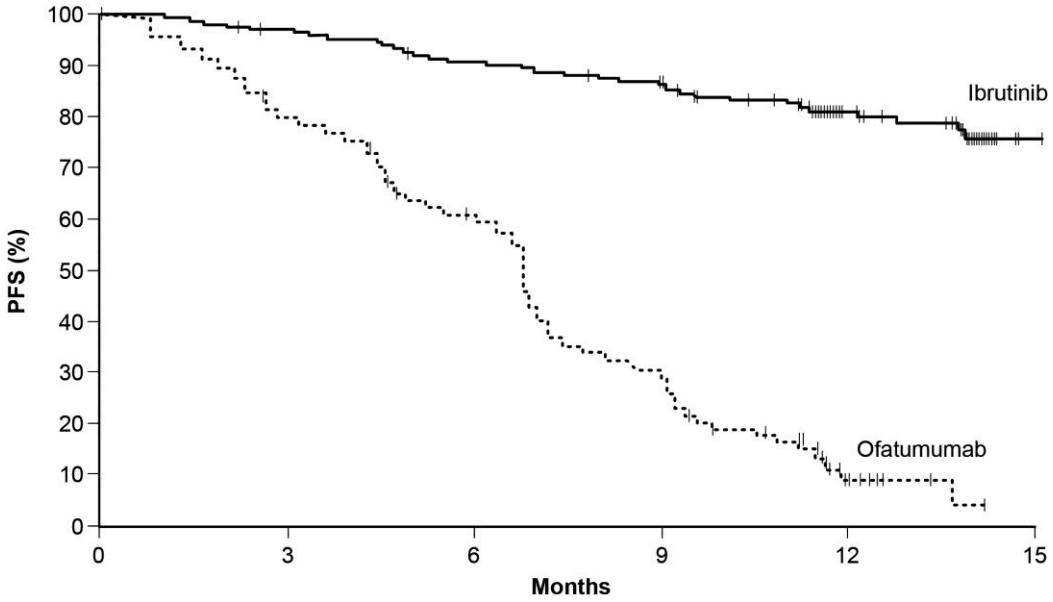


Updated data with a median follow-up of 16 months are available from a poster presented at ASH, 2014 (28).

Investigator-assessed PFS was significantly longer for ibrutinib vs. ofatumumab; median PFS had not been reached with ibrutinib vs. 8.1 months with ofatumumab, HR 0.106, 95%CI 0.073-0.153, p<0.0001, see Figure 11.

The 12-month investigator-assessed PFS rates were 84% for ibrutinib and 19% for ofatumumab.

Figure 11: KM curve of PFS in RESONATE (ITT analysis): 16 month follow-up



RESONATE Secondary end-points:

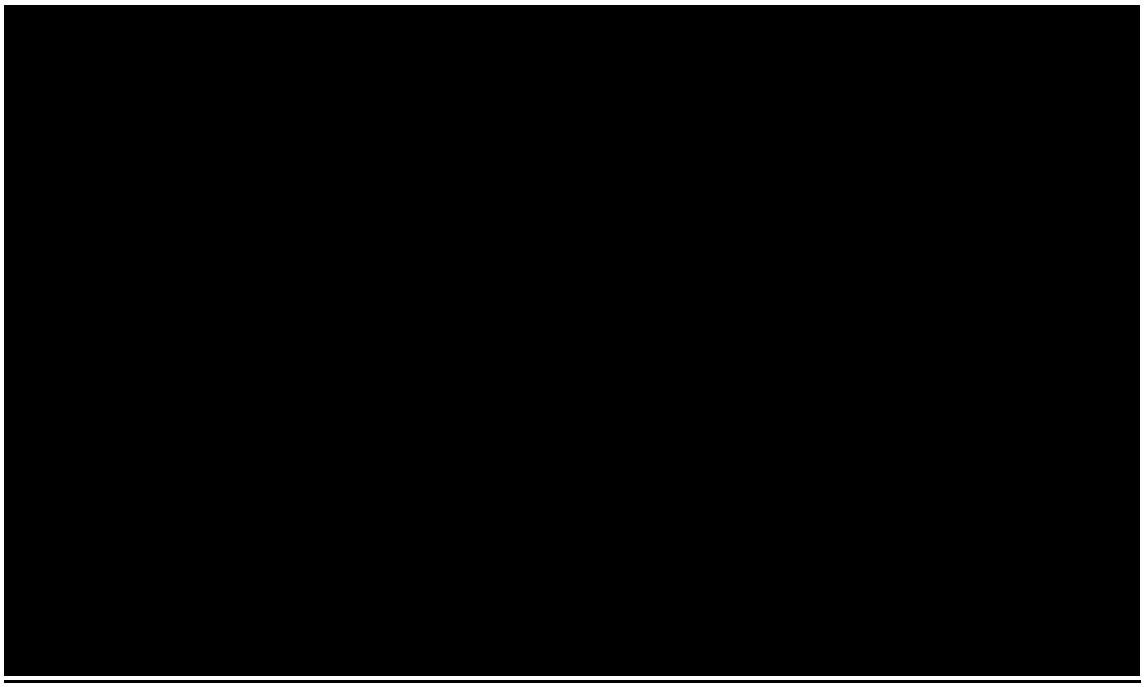
OS

At the time of the first published analysis, 57 patients in the ofatumumab group had crossed over to receive ibrutinib after confirmed disease progression. The survival effect was based on an analysis in which data were censored at the time of crossover.

OS was significantly prolonged with ibrutinib vs. ofatumumab: hazard ratio for death in the ibrutinib group was 0.43 (95% CI: 0.24 to 0.79; p=0.005), with the risk of death reduced by 57%, see Figure 12.

These results provide further confirmation of the unprecedented survival benefit with ibrutinib.

[redacted]



At 12 months, the OS rate was 90% in the ibrutinib group vs. 81% in the ofatumumab group.

The uncensored sensitivity analysis showed similar results: hazard ratio for death of 0.39 (p=0.001), OS rate 90% vs. 79%.

After 16 months follow-up, OS remained significantly superior for ibrutinib vs. ofatumumab with 18-month OS rates of 85% and 78% respectively, despite crossover of 120 patients (61%) from ofatumumab to ibrutinib, who were censored at crossover (28). As crossover leads to an overestimation of the survival benefit of ofatumumab, statistical methods were employed to adjust for the impact of crossover (see Section 4.4 and Appendix 4). The crossover adjusted OS HRs using the RPSFT approach are [redacted] for the overall R/R CLL population, and [redacted] for the 17p deletion subgroup. Figure 13 below presents the 16 month KM data for ibrutinib and ofatumumab for the overall R/R CLL population, in which the ofatumumab curve has been adjusted for crossover using an OS HR (ibrutinib vs. ofatumumab) of [redacted].

[redacted]

[redacted]

Response

Response rates were consistently higher in the ibrutinib arm compared to the ofatumumab arm, regardless of whether they were independently assessed or investigator assessed, see Table 32.

The ORR was significantly higher in the ibrutinib group vs. the ofatumumab group, 43% vs. 4% (odds ratio, 17.4; 95% CI, 8.1 to 37.3; p<0.0001). In addition, 20% of the patients receiving ibrutinib had a PR with lymphocytosis (resulting in a 63% ORR with lymphocytosis). The ORR by investigator assessment was significantly higher in the ibrutinib group vs. the ofatumumab group, 70% vs. 21%, p<0.0001.

Lymphocytosis was observed in 69% of patients treated with ibrutinib and was not considered to be disease progression according to the study protocol. Lymphocytosis resolved in 77% of these patients during follow-up.

Lymphocytosis is observed in the majority of patients receiving ibrutinib. It tends to resolve within 8 months of treatment; however, a minority of patients have lymphocytosis lasting >12 months (50). Lymphocytosis does not have an impact on clinical outcomes and resolves completely once treatment with ibrutinib is stopped (51).

Table 32: Best response to treatment in RESONATE

	Ibrutinib (n=195)	**Ofatumumab (n=196)**	**Ibrutinib (n=195)**	**Ofatumumab (n=196)**
	Independent assessment, n(%)		**Investigator assessment, n(%)**	
ORR	83 (43%)	8 (4%)	136 (70%)	42 (21%)
ORR with PR with lymphocytosis	122 (63%)	8 (4%)	162 (83%)	46 (23%)
CR or CR with incomplete haemopoietin recovery			4 (2%)	1 (1%)
PR	83 (43%)	8 (4%)	132 (68%)	41 (21%)
PR with lymphocytosis	39 (20%)	0	30 (15%)	4 (2%)

Stable disease	63 (32%)	153 (78%)	22 (11%)	106 (54%)
Progressive disease	5 (3%)	20 (10%)	2 (1%)	27 (14%)

Patient reported outcomes (PROs)

A poster and abstract presented at ASH 2014 provides information on PROs (89, 90); data on EQ-5D is sourced from the RESONATE CSR (86).

EORTC QLQ-C30

A clinically meaningful improvement in EORTC QLQ-C30 global health scores was observed in both arms, although more patients had a clinically meaningful improvement in the ibrutinib arm, 47% vs. 40%, OR:1.3, p=0.2049 (89, 90).

EQ-5D

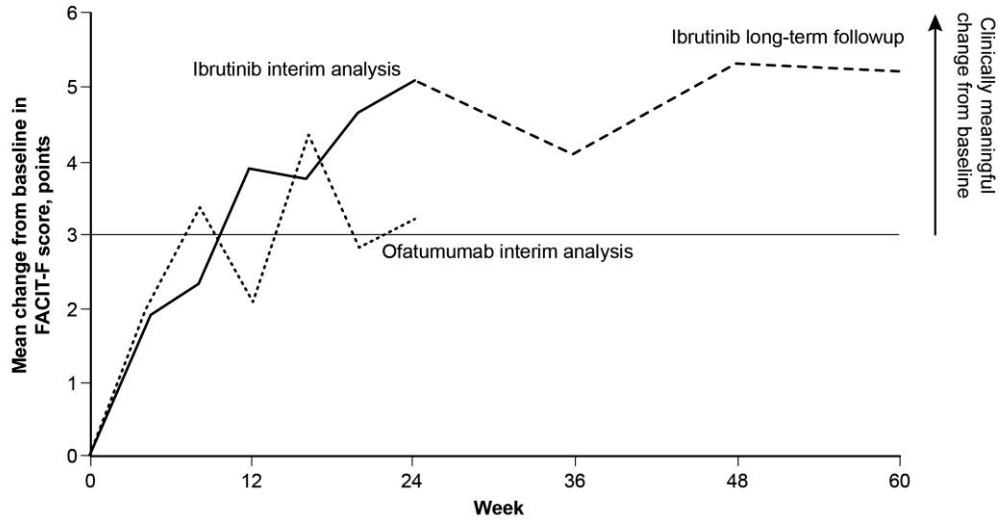
[redacted]

FACIT-Fatigue

More patients achieved a clinically meaningful improvement in FACIT-Fatigue score (increase of ≥3 points) with ibrutinib than with ofatumumab (56% vs. 43%, OR: 1.69, p=0.0101). Clinically meaningful deterioration was reported by 14% vs. 24% respectively, p=0.08, see Figure 15 (89, 90).

A clinically meaningful improvement in fatigue (≥10 points) was also observed on the EORTC Fatigue Subscale Score from baseline to week 24: mean -11 vs. 0 observed.

Figure 15: Improvement in FACIT-Fatigue by treatment arm in RESONATE.



Number at risk										
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**60**
Ibrutinib	165	121	131	122	116	112	115	97	53	23
Ofatumumab	154	101	102	97	91	80	87			

4.8 Subgroup analysis

The subgroup analyses presented in this section were pre-planned to determine whether baseline clinical characteristics or molecular features had an impact on the efficacy of ibrutinib:

Pre-planned subgroups for PFS included the following potential prognostic variables at screening or baseline:

- Age (<65 vs. ≥65)
- Gender (Male, Female)
- Race (White, Non-White)
- Geographical region (US, Other)
- Rai Stage at screening (Stage 0-II, III-IV)
- ECOG at randomisation (0, 1)
- Bulky disease (<5 cm, ≥5 cm)
- Number of prior treatment lines (<3, ≥3)
- Refractory disease to purine analogues as recorded in IWRS (Yes, No)
- 17p deletion as recorded in IWRS (Yes, No)

- 11q deletion (Yes, No)
- β2-microglobulin at baseline (≤3.5 mg/l, >3.5 mg/l)

Subgroup analysis for OS and ORR included age, gender, race, region, 17p deletion, and refractory disease to purine analogues (86).

Importantly, the effect of ibrutinib on PFS was consistent regardless of baseline clinical characteristics or molecular features - see Figure 16.

The only significant test for heterogeneity was geographical region (p=0.02). In order to address this, a multivariate Cox proportional hazard analysis was employed, using a comprehensive list of baseline prognostic variables as covariates. After adjustment for the baseline covariates, the HR was 0.22 (0.085, 0.564) for US and 0.20 (0.092, 0.451) for Europe/other. The selected covariates were considered clinically appropriate and while acknowledging the caveats of the presented post-hoc analysis there is no reason to anticipate major differences between the regions (66).

The consistent benefit in all subgroups was maintained after 16 month follow-up, rates of 12-month PFS were significantly better with ibrutinib than ofatumumab regardless of lymphocytosis, number of prior lines of therapy, presence of 17p deletion or other adverse cytogenetics (28).

In line with PFS, the difference in OS was preserved in all subgroups, see Figure 17 .

Figure 16: Subgroup analyses of PFS in RESONATE

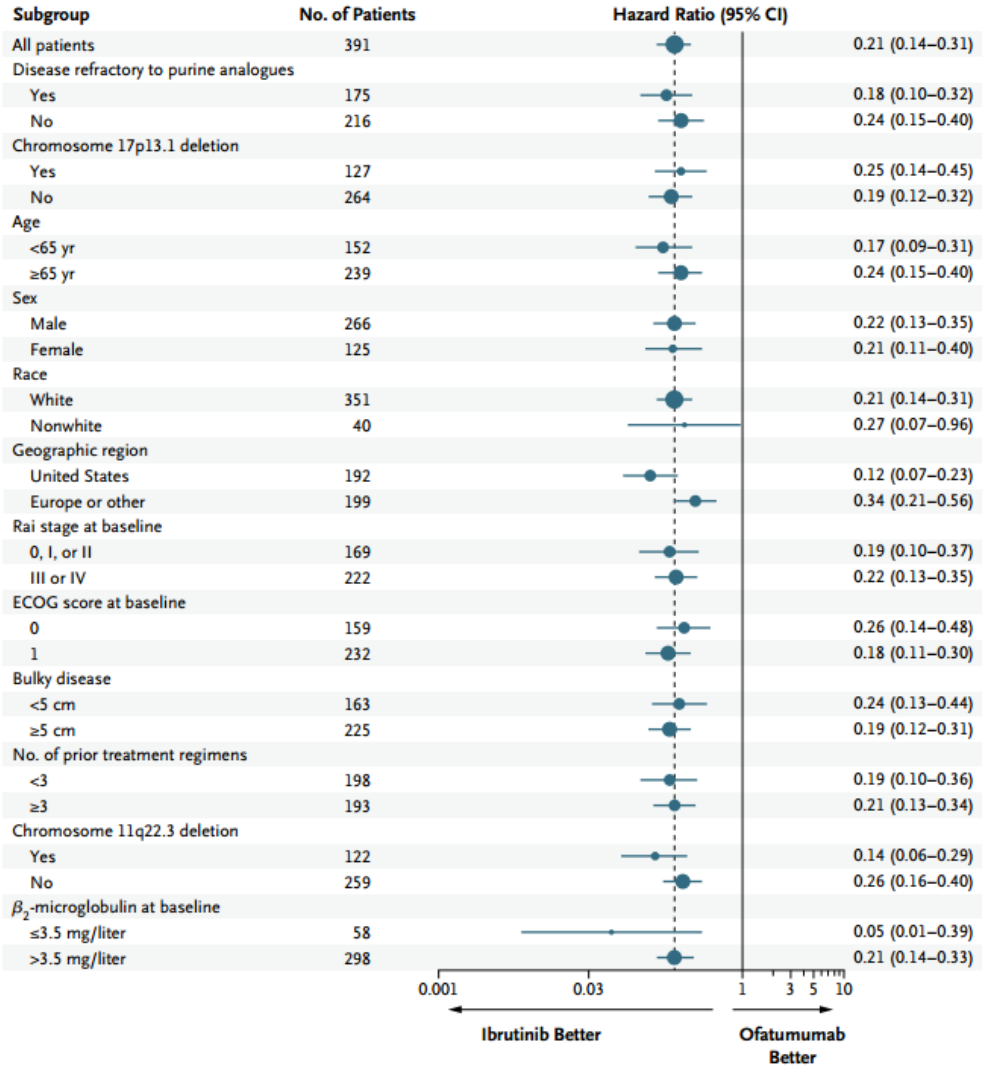
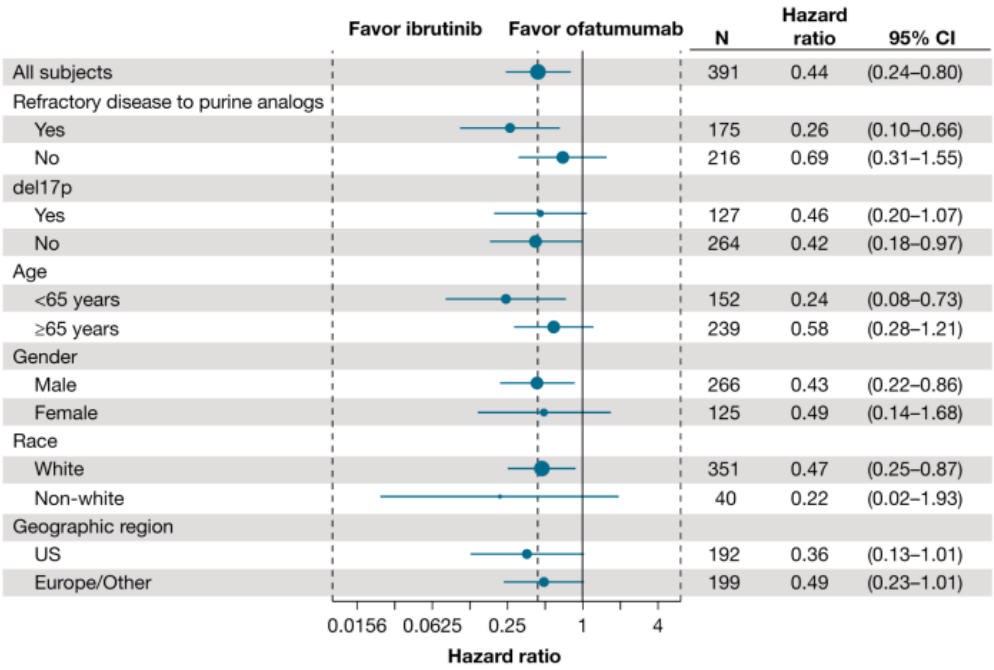


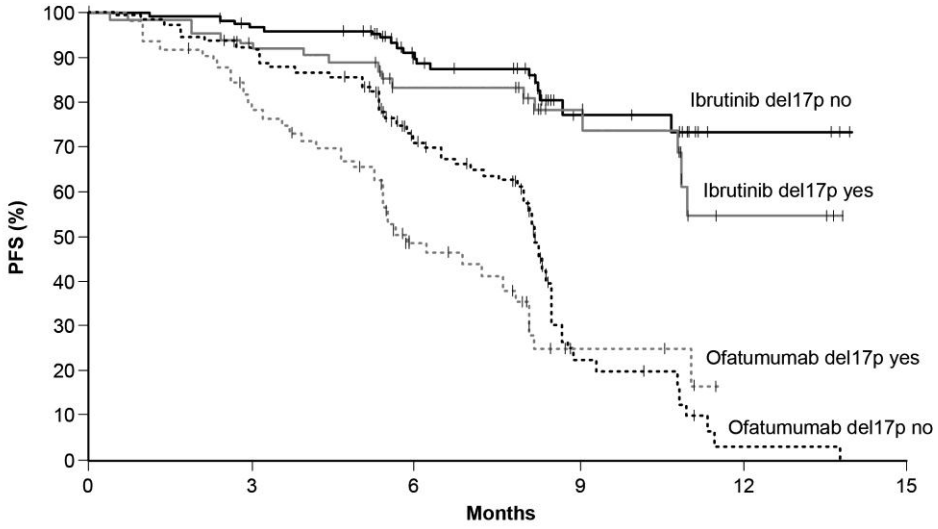
Figure 17: Subgroup analyses of OS in RESONATE.



Further data are available for patients with the 17p deletion; median PFS was not reached in the ibrutinib arm vs. a median PFS of 5.8 months in the ofatumumab arm (HR for progression or death, 0.25; 95% CI 0.14-0.45). At 6 months, 83% of patients in the ibrutinib arm were alive with no disease progression vs. 49% of those in the ofatumumab arm.

Figure 18 shows the KM curves for PFS for patients with and without 17p deletion.

Figure 18: KM curves for PFS for patients with and without 17p13.1 deletion in RESONATE.



Number at risk

Ibrutinib del17p no:	132	125	75	21	3	
Ibrutinib del17p yes:	63	58	41	17	4	
Ofatumumab del17p no:	132	115	63	11	1	0
Ofatumumab del17p yes:	64	46	20	4		

Data from the 16-month median follow-up analysis revealed 12-month PFS of 79% for patients with 17p deletion receiving ibrutinib vs. 17% in those receiving ofatumumab, p<0.001 (28).

4.9 Meta-analysis

At the time of this application, only one ibrutinib monotherapy RCT was available (Section 4.2) and therefore, a meta-analysis was not possible.

4.10 Indirect and mixed treatment comparisons

4.10.1 Search strategy

An SLR was conducted to identify and select all clinical studies relevant for this appraisal, including those for consideration in indirect comparison to ibrutinib. The methodology of the SLR is detailed in Section 4.1; the search strategies and quality assessment conducted on the included studies are provided in Appendix 2 and Appendix 5.

4.10.2 Study selection

The clinical SLR identified and reviewed 41 trials (15 RCTs and 26 single-arm trials) which evaluated treatments listed as comparators within the final NICE Scope (Table 1). The review evaluated whether these studies could be leveraged for an indirect or a mixed treatment comparison. Consideration was given to the data reported (e.g. KM data for OS and PFS, baseline characteristics, and study design) and a full assessment of their comparability is provided in Appendix 3.

Once these trials were evaluated for data relevant to economic modelling and indirect comparison analysis, only four trials (three RCTs and one single-arm trial) were included:

1. RESONATE: RCT of ibrutinib vs ofatumumab (18) (28)
2. Osterborg et al, 2015: RCT of PC vs. ofatumumab (37) (38)
3. Jones et al, 2015: RCT of IO vs ofatumumab (39)
4. Fischer et al, 2011: Single-arm trial of BR (29)

4.10.3 Analysis and presentation of results - summary

With such limited RCT data available, all of which are further confounded by differences in trial designs and patient populations, a network meta-analysis was not possible.

For the RCTs with a common arm to RESONATE, standard and widely accepted pair-wise indirect treatment comparisons (ITCs) were conducted based on the Bucher methodology (92) versus the key comparators to establish ibrutinib's relative treatment efficacy. In summary, two analyses were possible using ITC methodology:

- ITC of ibrutinib vs PC using the common ofatumumab treatment arm across the two trials (18) (28) (37) (38).
- ITC of ibrutinib vs IO using the common ofatumumab treatment arm across the two trials (18) (28) (39).

For a comparison vs the single-arm BR trial (29), a matched-adjusted indirect comparison (MAIC) based on the methodology published by Signorovitch (93, 94) was used to compare the patient level data from RESONATE to the aggregate KM data available from the published BR trial. While an ITC would be the preferred analysis for indirect comparisons, the lack of published data does not allow for it and the alternative of a naïve comparison is not acceptable. As such, the MAIC method was selected as it allows for relative efficacy to be explored where no common comparator arms are available and a network cannot be established. In summary, one analysis was possible using MAIC methodology:

- MAIC of ibrutinib vs BR by adjusting the RESONATE patient-level data in order to match the ibrutinib population to the BR population as represented by the published aggregate KM data (18) (28) (29).

The above summarizes the three main analyses conducted to support the three comparisons presented in this appraisal. In order to further validate the outputs of these analyses, a third indirect comparison methodology was explored. An indirect comparison based on multivariate Cox model of pooled patient-level trial data is a methodology where two sets of patient-level data are adjusted for patient population difference using pooled patient level data from both RESONATE and the comparator study. Janssen have access to patient-level data from a retrospective observational study conducted in the Stockholm area in Sweden by the Karolinska Institute which allows for an alternative comparison to be made vs PC (15). Furthermore, Janssen are able to leverage patient-level data from the BR arm of the HELIOS trial (95), which is outside the scope of this decision problem and not yet published but it allows for an alternative comparison to be made vs BR. In summary, two analyses were possible using this methodology:

- Indirect comparison based on multivariate Cox model of pooled patient-level trial data of ibrutinib vs PC using data from the Karolinska Institute (18) (28) (15).
- Indirect comparison based on multivariate Cox model of pooled patient-level trial data of ibrutinib vs BR using data from the BR arm of HELIOS (18) (28) (95).

The final results of the three main analyses are summarised in Table 33 and show a remarkable consistency in ibrutinib's comparative efficacy versus key comparators, triangulating different data sources for validation wherever possible.

All of the analyses were based on investigator-assessed PFS, OS and ORR outcomes from the 16 month follow-up RESONATE data (28), representing the most mature, comparative trial data available for ibrutinib, and based upon assessments that most closely reflect real world clinical practice. Inputs for the non-comparative trials were based on available KM data for PFS and OS.

Table 33: Summary of results of ITCs and MAICs

Comparison	Analysis type	Data sources	OR ORR (95% CI)	HR PFS (95% CI)	HR OS (95% CI)
Ibrutinib vs. PC	ITC, Bucher method	RESONATE (28) vs. Osterborg, 2014 (37, 38)	[redacted]	[redacted]	[redacted]
Ibrutinib vs. IO	ITC, Bucher method	RESONATE (28) vs. Jones, 2015 (39)	[redacted]	[redacted]	[redacted]
Ibrutinib vs. BR	MAIC	RESONATE (28) vs. Fischer, 2011 (29)	[redacted]	[redacted]	[redacted]

Each of the five analyses introduced above (i.e. the three main and two alternatives carried out for validation) are discussed further in the following sub-sections including details on the methods and outcomes of the included studies, consideration of the risk of bias, and the results. Full descriptions of the three statistical method of analysis (i.e. ITC, MAIC and the multivariate pooled analysis) are provided in Appendix 6.

4.10.4 Analysis and presentation of results - details

Ibrutinib vs. PC (Bucher Method)

Overall methods: ibrutinib vs. PC

Österborg, 2014 (37) (38), was an open-label, randomised, phase III study, that compared ofatumumab with PC. This made it possible to conduct an ITC using the Bucher methodology (92), resulting in relative efficacy estimates of ibrutinib vs. PC (RESONATE vs. Österborg, 2014). The trial designs, patient characteristics, outcomes, and other details of the two trials included in the ITC were compared using the PICOs (population, intervention, comparator, outcomes, and study design) construct to evaluate comparability.

Data inputs: ibrutinib vs. PC

Table 34 presents the data inputs used in the ITC.

Table 34: Inputs used in ITC – Ibrutinib vs. PC

	OR ORR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
Ibrutinib vs. ofatumumab	26.25 (14.93-46.16) [1]^	0.106 (0.07-0.15)[1] p<0.0001	[redacted][2]
Ofatumumab vs. PC	3.15 (1.24-7.97)[3]	0.56 (0.38-0.82)[4] p=0.003	0.68 (0.41-1.15)[5] p = 0.1295

^ The OR was derived with the best overall response presented in Brown 2014 (28), i.e. including patients who achieved response and subsequently lost it during the follow-up
1. Brown, 2014 (28)
2. OS HR adjusted for crossover (see Section 4.4)
3. Österborg, 2014a (37)
4. Österborg, 2014b (38)
5. Clinicaltrials.gov (96)

Results of PICOS: ibrutinib vs. PC

Results of the PICOS analysis (Table 35) identified key differences in trial eligibility criteria and patient populations. The Österborg 2014 trial enrolled a more severe patient population compared to RESONATE. Specifically, Österborg enrolled only fludarabine-refractory patients with at least two lines of prior therapy and bulky disease (>5 cm). RESONATE required that patients received at least prior therapy and only 45% of patients were refractory to purine analogue treatments. RESONATE also enrolled more patients with 17p deletion compared with Österborg.

Indirect comparisons are assumed to generate unbiased results, as long as no differences across trials exist that act as a treatment effect modifier. This may not be the case here, as Österborg enrolled more severe patients. Results of the PICOS analysis (Table 34) identified key differences in trial eligibility criteria and patient populations. Patients in Österborg had refractory status, bulky disease and at least two prior lines of therapy as trial inclusion criteria while RESONATE also included non-refractory patients, patients without bulky disease, and patients with one prior line of treatment. The relative treatment effects are substantially higher in these more severe patients; HR-estimates in RESONATE on the subset of patients similar to those in Österborg, were [redacted], compared to the entire trial population. To account for this potential bias due to this relative treatment effect modification, the indirect comparison was rerun, using these re-estimated HRs for RESONATE as input in the Bucher methodology. [redacted]. These additional results illustrate that the base case results were biased in favour of PC.

Table 35: PICOS results comparing Byrd (2014) and Österborg (2014)

PICOS Factor	Parameter	RESONATE Byrd et al., 2014 Brown, 2014		Österborg et al., 2014	
		Ibrutinib	Ofatumumab	Ofatumumab	Physician's choice
Population	**Median age (range)**	67 (30–86)	67(37-88)	61.5 (46 to 82)	63.0 (40 to76)
	≥65, n (%)	118 (60.5%)	121 (61.7%)	Not reported	Not reported
	Del 17p	63 (32.3%)	64 (32.7%)	15 (18.9%)	9 (20.9%)
	Del 11q	63 (32.3%)	59 (30.1%)	21 (27%)	12 (28%)
	Median # of prior therapies (range)	3 (1–12)	3 (1 to 13)	4 (2 to 16)	3 (2 to 11)
	≥3	103 (52.8%)	90 (45.9%)	NR	NR
	Bulky disease (≥5cm)	124 (63.6%)	101 (51.5%)	NR (assumed 100% according to eligibility criteria)	NR (assumed 100% according to eligibility criteria)
	Refractory disease	87 (45%)*	88 (45%)*	NR (assumed 100% according to eligibility criteria)~	NR (assumed 100% according to eligibility criteria)~
	Rai Stage				
	0,I, or II	86 (44.1%)	83 (42.3%)	33 (42%)	18 (42%)
	III or IV	109 (55.9%)	113 (57.7%)	43 (54%)	24 (56%)
Interventions		Ibrutinib, 420 mg daily		Ofatumumab, 300 mg week 1; 2000 mg week 2,3,4,5,6,7,8,12, 16,20,24	
Comparators			Ofatumumab, 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks		Physician's choice; dosing details not reported

			for 16 weeks		
Outcomes	**Median PFS**	Not reached	8.1 months	7.0 months	4.5 months
	Median OS	Not reached (90% at 12 months)	Not reached (81% at 12 months)	11.5 months	6.5 months
Study design	**Sample size**	195	196	79	43
	Trial design	RCT, phase II		RCT, phase III	
	Eligibility criteria	**Inclusion criteria** • Active CLL • At least one previous therapy • Inappropriate for purine analogue therapy (due to short progression-free interval after chemo-immunotherapy or coexisting illnesses, age ≥70, or del 17p) • ECOG score PS <2 • Absolute neutrophil count ≥750 cells per microliter • Platelet count ≥30,000 cells per microliter • Adequate liver and kidney function. **Exclusion criteria** • Patients requiring warfarin or strong CYP3A4/5 inhibitors		**Inclusion criteria** • Active fludarabine-refractory CLL requiring therapy • At least 2 prior therapies • Bulky (>5 cm) lymph nodes • ECOG PS 0-2 **Exclusion criteria** • Prior allogeneic stem cell transplantation • Known Richter's transformation • Prolymphocytic leukemia • Autoimmune haemolytic anaemia unless with PD • Active infection	
*Purine analogue-refractory ~Fludarabine-refractory					

Results of ITC: ibrutinib vs. PC

Results of the ITC comparing ibrutinib vs. PC are presented in Table 33 and demonstrate ibrutinib's superiority to PC in terms of ORR, PFS, and OS. In the absence of direct, head-to-head trial evidence, this ITC provides strong evidence of ibrutinib's relative efficacy versus a mix of treatments commonly used in the UK to treat R/R CLL.

Ibrutinib vs idelalisib + anti-CD20 monoclonal antibody (Bucher method)

Overall methods: ibrutinib vs. idelalisib + anti-CD20 monoclonal antibody

IR has received preliminary guidance by NICE to be recommended for use in the R/R CLL setting and is included in ibrutinib's Final Scope; however, it was not possible to create a comparison of ibrutinib vs. IR using published trial data due to differences in trial design and follow-up.

The Jones, 2015 (39) publication of Study 119 (NCT 01659021), an open-label, randomised phase III trial, which compared IO with ofatumumab, provided an opportunity to compare ibrutinib to IO, using ofatumumab as a common comparator. An ITC using the Bucher methodology (92) was therefore conducted to estimate the relative efficacy of ibrutinib vs. IO (RESONATE vs. Jones, 2015). This ITC was considered to provide an estimate of ibrutinib's relative efficacy to idelalisib + an anti-CD20 monoclonal antibody. The trial designs, patient characteristics, outcomes, and other details of the two trials included in the ITC were compared using the PICOS construct to evaluate comparability.

Data inputs: ibrutinib vs. idelalisib + anti-CD20 monoclonal antibody

Table 36 presents the data inputs used in the ITC.

Table 36: Inputs used in ITC – Ibrutinib vs. Idelalisib + anti-CD20 monoclonal antibody

	OR ORR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
Ibrutinib vs. ofatumumab	26.25 (14.93-46.16)^+	0.106 (0.07-0.15)[1+] p<0.0001	[redacted]
IO vs. ofatumumab	15.94 (7.80-32.58) [3]*	0.27 (0.19-0.39)[3]* p<0.0001	0.74 (0.44-1.25) [3] p=0.27

^ The OR was derived with the best overall response presented in Brown 2014 (28), i.e. including patients who achieved response and subsequently lost it during the follow-up.

\+ Assessed by investigators

* Assessed by independent review committee (IRC)

1. Brown, 2014 (28)
2. OS HR adjusted for crossover (see Section 4.4)
3. Jones, 2014 (39)

Results of PICOS: ibrutinib vs. idelalisib + anti-CD20 monoclonal antibody

The PICOS analysis indicated that RESONATE and Study 119 enrolled very similar patient populations and that characteristics expected to modify treatment effect (such as age, 17p deletion cytogenetic status, median prior lines of therapy) did not differ between the two trials Table 37. Based on the strong similarities between these trial populations, it was concluded that no adjustment for patient characteristics was necessary.

Table 37: PICOS results comparing RESONATE and Study 119 (39) (18) (28)

PICOS Factor	Parameter	RESONATE Byrd et al., 2014 Brown, et al., 2014		Study 119 Jones et al., 2015	
		Ibrutinib	Ofatumumab	IO	Ofatumumab
Population	**Median age (range)**	67 (30–86)	67(37-88)	68 (40-85)	67 (36-84)
	≥65, n (%)	118 (60.5%)	121 (61.7%)	107 (61.5%)	60 (69%)
	Del 17p	63 (32.3%)	64 (32.7%)	48 (26.4%)	19 (21.8%)
	Median # of prior therapies	3 (1–12)	3 (1 to 13)	3 (1-11)	3 (1-11)

	(range)				
	IGVH unmutated	98 (73%)	83 (63%)	137 (78.7%)	68 (78.2%)
	% male	66%	70%	71.3	71.3
	Refractory disease	87 (45%)*	88 (45%)*	82 (47%)	47 (54%)
	Rai Stage				
	II	30 (15.4%)	39 (19.9%)	15%	24%
	III	23 (11.8%)	35 (17.9%)	14%	12%
	IV	86 (44.1%)	78 (39.8%)	53%	45%
Interventions		Ibrutinib, 420 mg daily		Idelalisib: 150 mg bd Ofatumumab: 300 mg Week 1; then 1,000 mg weekly x7 and then every 4 weeks x 4 (total 12 doses; finishing Week 24)	
Comparators			Ofatumumab, 300 mg at week 1, followed by a dose of 2,000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks		Ofatumumab: 300 mg Week 1; then 2,000 mg weekly x 7 and then every 4 weeks x 4 (total 12 doses; finishing Week 24)
Outcomes	**Median PFS**	Not reached+	8.1 months+	16.3 months^	8.0 months^
	Median OS	Not reached (90% at 12 months)	Not reached (81% at 12 months)	20.9 months	19.4 months
Study design	**Sample size**	195	196	174	87
	Trial design	RCT, phase III		RCT, phase III	
	Eligibility criteria	**Inclusion criteria** • Active CLL requiring therapy with at least one previous therapy • Inappropriate for purine analogue therapy (due to short progression-free interval after chemo-immunotherapy or coexisting illnesses, age ≥70, or del 17p) • ECOG score PS <2 • Absolute neutrophil count ≥750 cells per microliter • Platelet count ≥30,000 cells per microliter • Adequate liver and kidney function.		**Inclusion criteria** • Diagnosis of B-cell CLL and requiring treatment, per International • Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria2 • CLL progression <24 months from completion of last therapy • Prior therapy: ≥2 cycles of a purine analogue or bendamustine • Karnofsky score ≥60 • Complete blood count: any values	

		Exclusion criteria • Patients requiring warfarin or strong CYP3A4/5 inhibitors	• Estimated creatinine clearance (eCrCl) >30 mL/min (Cockcroft-Gault) **Exclusion criteria** • Prior therapy with inhibitor of AKT, BTK, JAK, mTOR, PI3K, or SYK • Prior allogeneic stem cell or solid organ transplantation • Progression within 6 months of last ofatumumab dose
*Purine analogue-refractory ~del17p and/or TP53 mutation +Investigator-assessed outcome ^Independent review committee-assessed outcome			

Results of ITC: ibrutinib vs. idelalisib + anti-CD20 monoclonal antibody

Results of the ITC comparing ibrutinib vs. IO are presented in Table 33 and demonstrate ibrutinib's superiority to IO in ORR, PFS and OS. Close similarity in patient populations between RESONATE and Study 119 is demonstrated, suggesting trial outcomes can be compared without adjusting for differences in patient characteristics. The similarities can be clearly observed when comparing the PFS and OS KM data from RESONATE and Jones, 2015. Figure 19 and Figure 20 clearly illustrate that the ofatumumab PFS KM curves are very similar between the two trials (median of 8 months in both) as are ofatumumab OS KM curves up to 9 months' follow-up, after which point the curves separate due to crossover from ofatumumab to ibrutinib in RESONATE.

A limitation of this ITC is that in Study 119, IRC assessed PFS is used while in RESONATE investigator-assessed PFS is only available at the longer-term follow-up. However, the PFS differences between the criteria used by investigators and IRC bodies may not be significant. As shown in the Figure 19 and Figure 20, the ofatumumab arms between the two trials are very similar. In addition, although full details of the IRC assessment are not available from the Jones publication, the IRC criteria as described in Study 116 (the trial assessing IR vs rituximab) indicate that there are likely to be important differences even in the IRC criteria that is available from the first interim analysis for RESONATE and the idelalisib combination therapy trials.

In the absence of direct, head-to-head trial evidence, this ITC provides strong evidence of ibrutinib's relative efficacy versus idelalisib + anti-CD20 monoclonal antibody.

[redacted]

[redacted]

[redacted]

Ibrutinib vs BR (MAIC method)

Rationale for MAIC

No trial comparing BR to ofatumumab was identified in the SLR, which made it impossible to use traditional ITC methods to compare ibrutinib to BR using the RESONATE data. The trial with the most robust data identified by the SLR to inform efficacy of BR was Fischer, 2011 (29) (see Section 4.1). However, naïve comparison of RESONATE and Fischer, 2011 outcomes would bias results against ibrutinib for a number of reasons given that the Fischer, 2011 trial enrolled a less severe population compared to RESONATE. This population difference is demonstrated by the smaller proportion of patients with three or more prior

therapies and a smaller proportion with 17p deletion (see Table 38). Therefore, MAIC was used to derive estimates of ibrutinib's treatment effect vs. BR.

Table 38: Comparison of Byrd (2014) (18) and Fischer, 2011(29)

Regimen	**Ibrutinib**	**BR**
Author (Year)	Byrd, 2014 Brown, 2014	Fischer, 2011
Trial/Study Characteristics		
Study Design	RCT	Single-arm
Phase	Phase: III	Phase: II
Country	Australia, US, 7 European countries	Germany
Primary endpoint	PFS	OR
Publication Type	Full Publication	Full Publication
Patient Characteristics		
N Evaluated for Efficacy	195	78
Inclusion Criteria	Received at least one previous therapy, and inappropriate candidates for purine analogue treatment	Had received at least one but not more than three previous treatments
Age Median (Range)	67 (30 to 86)	66.5 (42 to 86)
Age strata, n (%)	≥65 118 (60.5%)	> 65, 24 (30.8%)
17p Deletion n (%)	63 (32.3)	14 (17.9)
Number of Prior Tx Median (Range)	3 (1 to 12)	2 (1 to 5*)
1/ 2 / ≥3 prior Tx (% of patients)	17.9 / 29.2 / 52.8	46.2 / 28.2 / 23.1
% of patients with other number of prior therapies	193 (49%)	20 (25.6%)
Relapsed/ Refractory / Flud Refractory (%)	--- / ---[b] / ---	--- / --- / 28.2
Outcomes		
ORR (%)	90%(INV)	59
Median PFS (months)	Not reached	15.2
Median PFS 95%CI	N/A	12.5 to 17.9
% Achieving PFS (time point for assessment (month))		---
Median OS (months)	Not reached	33.9
Median OS 95%CI	N/A	25.5 to 42.1
% Survival (time point for assessment (months))	85% (18)	---

Regimen	Ibrutinib	BR
Author (Year)	Byrd, 2014 Brown, 2014	Fischer, 2011
OS/PFS KM graph available	Yes/Yes	Yes/No
Median Follow-Up (months)	9.4	24
Outcome Criteria	IWCLL-NCI 2008 (Hallek 2008), and Cheson 2012	NCI-WG 1996 (Cheson 1996)

Overall methods: ibrutinib vs. BR

There is a precedent for the use of MAIC in HTA submissions. The approach has been employed in a number of oncology technology assessments submitted to and accepted by NICE, including those evaluating bortezomib for induction treatment of multiple myeloma (97) and dasatinib, nilotinib, and standard-dose imatinib (NICE TA 70/251) for frontline treatment of chronic myeloid leukaemia (98). It has also been used and accepted in other disease areas where a lack of head-to-head data was demonstrated (99).

MAIC is a method developed by Signorovitch (93, 94) for indirect comparison of competing treatments across trials. Frequently, indirect treatment comparisons rely on the aggregate data (AD) reported in the trial publications, which may be biased by differences across trial population characteristics. While individual patient-level data (IPD) for all trials is rarely available, IPD for at least one comparator (in this case, for ibrutinib) may be available. MAIC leverages the IPD to re-weight patients in the data set so that their average baseline characteristics match those reported in the comparator trial, thereby reducing the bias of the indirect comparison.

An MAIC approach was employed in order to compare ibrutinib to BR using the IPD from RESONATE closely following the steps set forth by Signorovitch (93, 94).

The first step in the process was the alignment of the inclusion and exclusion criteria between the two trials being compared. Patients that would have been excluded from the Fischer study were also excluded from the RESONATE population.

In the next step, the remaining IPD data from RESONATE were matched to the Fischer trial using all clinically relevant baseline characteristics that were available for both trials. This process involved re-weighting patients in the RESONATE trial so that their baseline characteristics match those reported for the comparator treatment. The actual weights represent the inverse odds of being enrolled in RESONATE versus being enrolled in the Fischer trial. After matching, the average (in case of continuous variable) or % (in case of categorical variable) for a certain baseline characteristic will be similar between the two trials and treatment outcomes can be compared across balanced trial populations. Clinical experts reviewed the matching approach used in this analysis as well as the list of characteristics included in matching and the results of the MAIC.

Results of the matching process and MAIC: ibrutinib vs. BR

Results of the MAIC comparing ibrutinib vs. BR are presented in Table 33 and demonstrate ibrutinib's superiority to BR in ORR, PFS, and OS. Additional detail on the matching process and results of the MAIC are presented in Appendix 6.

Validation of ITC and MAIC results

ITC and MAIC provide useful estimates of comparative efficacy; however, both techniques have certain limitations. In an effort to validate the results of the ITCs and MAIC presented above and to triangulate different data sources wherever possible, two additional analyses were conducted. These analyses took the form of an ITCs using a multivariate Cox model to compare two sets of patient-level data, adjusting for patient population differences using pooled patient level data from both RESONATE and the comparator study.

Indirect comparison using multivariate Cox model of pooled patient-level data, ibrutinib vs. BR

An ITC using a multivariate Cox model was conducted based on patient-level data from the ibrutinib arm of RESONATE and the BR arm from HELIOS (HELIOS compares ibrutinib + BR vs. BR and reports IRC-assessed PFS and OS). HELIOS enrolled a much healthier and less heavily treated population compared to RESONATE (median of 2 versus 3 lines of prior therapy; patients with 17p deletion excluded versus 32% of patients with 17p deletion in RESONATE). Given the large differences between the RESONATE and HELIOS populations, results of this ITC should be considered to represent ibrutinib's comparative efficacy in a fit, low risk population, and may not be as applicable to the current decision problem. Details of the patient-level ITC methodology and the outputs of this analysis are presented in Appendix 6 and impact of this alternative data is explored through scenario analysis in Section 5.8.

Results of the comparison vs BR from HELIOS are presented in Table 39.

Table 39: Summary of results of Ibrutinib vs BR (multivariate cox method)

Comparison	Analysis type	Data sources	OR ORR (95% CI)	HR PFS (95% CI)	HR OS (95% CI)
Ibrutinib vs. BR	ITC, multivariate Cox model	RESONATE (28) vs. HELIOS (95)	Not available	[redacted]	[redacted]

Indirect comparison using multivariate Cox model of pooled patient-level data, ibrutinib vs. PC

An ITC using a multivariate Cox model was conducted based on patient-level data from RESONATE compared with patient-level data from a retrospective observational study conducted in the Stockholm area in Sweden by the Karolinska Institute (15). The retrospective Swedish study collected efficacy and safety data from a detailed, in-depth retrospective review of individual patient files from 148 consecutively identified patients with R/R CLL initiated on second or later line treatment between 2009 and 2014 at the four CLL-treating centres in Stockholm, Sweden, with complete follow-up. The data set was adjusted

to include only treatment options relevant to the population appraised within this appraisal (R/R patients who are inappropriate for fludarabine-based regimens) and therefore, patients who received fludarabine-based regimens were removed from the data prior to the analysis. Longitudinal follow-up by treatment line was available for patients in second line (n=86), third (n=54), fourth (n=32), fifth (n=23), and sixth (n=10) line, and individual patients could contribute information to the analysis for multiple lines of therapy, with baseline defined as the date of initiation of the actual treatment line. A multivariate cox proportional hazards model was generated to compare PFS and OS between treatments, including line of therapy, age, gender, Binet stage, ECOG, and refractory disease as covariates.

Results of the comparison vs PC from the Swedish data set are summarized in Table 40.

Table 40. Summary of results of Ibrutinib vs PC (multivariate cox method)

Comparison	Analysis type	Data sources	OR ORR (95% CI)	HR PFS (95% CI)	HR OS (95% CI)
Ibrutinib vs. PC	ITC, multivariate Cox model	RESONATE (28) vs. Karolinksa Institute (15)	Not available	[redacted]	[redacted]

Details of this analysis are presented in Appendix 6 and impact of these alternative data on cost effectiveness is explored through scenario analysis in Section 5.8.

4.11 Non-randomised and non-controlled evidence

Table 41: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
PCYC1102	Ibrutinib	R/R CLL and untreated patients	Efficacy and safety	Published paper Byrd, 2013 (21)	Phase II studies have longer follow-up than the phase III study PCYC1103 provides 45 month follow up in R/R patients
PCYC1103	Ibrutinib	R/R CLL	Efficacy and safety	Presentation at AACR 2015 (22) (23) Published paper (32)	
PCYC1117	Ibrutinib	R/R CLL with 17p deletion	Efficacy and safety	CSR (24),	Provides additional evidence in patients with 17p deletion
Farooqui, 2014	Ibrutinib	R/R and untreated CLL and with TP53 aberrations (including 17p deletion)	Efficacy and safety	Published paper Farooqui, 2014 (25)	Provides additional evidence in patients with TP53 mutation or 17p deletion Provides evidence in previously untreated patients with 17p deletion

Data from the four non-RCT studies listed in Table 41 provide confirmatory evidence that:

- The survival benefit with ibrutinib is maintained over the long-term; R/R patients in the PCYC1103 study receiving ibrutinib 420 mg have follow-up over a maximum of 45 months

- The survival benefit with ibrutinib is observed regardless of adverse cytogenetics (17p deletion and/or TP53 mutation).

The Farooqui study demonstrates that the survival benefit is greater still in previously untreated patients with the 17p deletion or TP53 mutation (25).

The study methodology, statistical analysis, assessment of study quality, patient baseline characteristics, and additional results for each study can be found in Appendix 7.

R/R patients: PCYC1102/1103

The phase Ib-II study, PCYC1102, of ibrutinib has been published: Byrd JC, Furman RR, Coutre SE et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013;369(1):32-42 (21).

This study also included 31 patients with treatment-naïve CLL, two of whom had 17p deletion (100). Data on patients with treatment-naïve CLL are not included in this submission since it falls outside the scope, apart from the two patients with 17p deletion whose data is presented amalgamated with the R/R patients.

Data in this section are predominantly drawn from the published paper (21), the CSR (101) and the CSR Appendix (91).The published paper is used wherever possible, with additional information drawn from the CSR.

Patients without disease progression in PCYC1102 were able to enrol into the long-term extension study PCYC1103.

PCYC1102 was an open label phase II study which enrolled 85 patients with R/R disease; patients received either the licensed 420 mg dose (n=51) or 840 mg (n=34). Endpoint data are not available for the two doses separately in PCYC1102; however, separate data for the 420 mg dose are available in PCYC1103.

PCYC1103 provides updated data on outcomes with follow-up out to 45 months for R/R patients. Data for R/R patients receiving ibrutinib 420 mg (n=67) was presented at the AACR annual meeting in 2015 (22, 23). Additional information is taken from the 3-year follow-up which includes patients treated with ibrutinib at the 420 mg and 840 mg dose and has been published: Byrd JC, Furman RR, Coutre SE et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood* 2015;125(16):2497-2506 (32).

Of the 85 patients who entered PCYC1102, 54 patients remained on treatment at median follow-up of 20.9 months. Eleven patients discontinued treatment due to disease progression and 20 due to other reasons; AE (n=7), stem cell transplant (n=5), patient decision (n=5) and investigator decision (n=3).

Patients enrolled in PCYC1102 had high risk disease and had received a median of four previous treatments, 65% had advanced stage disease, 33% had 17p13.1 deletions and 36% had 11q22.3 deletions. Given that PCYC1103 was a roll-over study, patient characteristics were similar to PCYC1102.

The key results from PCYC1102/PCYC1103 are shown in Table 42 and demonstrate that the survival benefit with ibrutinib observed in the pivotal phase III trial, RESONATE is maintained over the long-term.

Table 42: Key results from PCYC1102/PCYC1103

	PCYC1102 (21)		**PCYC1103 (23)**
Variable	**Ibrutinib 420 mg (n=51)**	**Ibrutinib 840 mg (n=34)**	**Ibrutinib 420 mg (n=67)**
Best response, no (%)			
ORR (CR + PR)	36 (71%)	24 (71%)	61 (91%)
CR	2 (4%)		6 (9%)
PR	34 (67%)	24 (71%)	55 (82%)
PR with lymphocytosis	10 (20%)	5 (15%)	2 (3%)
	PCYC1102 (all patients)		
PFS			
Median (months)	Not reached		Not reached
Estimated PFS	75% (26 months)		76% (30 months)
OS			
Median (months)	Not reached		Not reached
Estimated OS	83% (26 months)		87% (30 months)

In PCYC1102, median PFS and OS was not reached. 26-month estimated PFS was 75% and estimated OS was 83% for the 420 mg and 840 mg doses combined, see Figure 21 and Figure 22.

Figure 21: KM curve of PFS in PCYC1102 (all patients) (21)

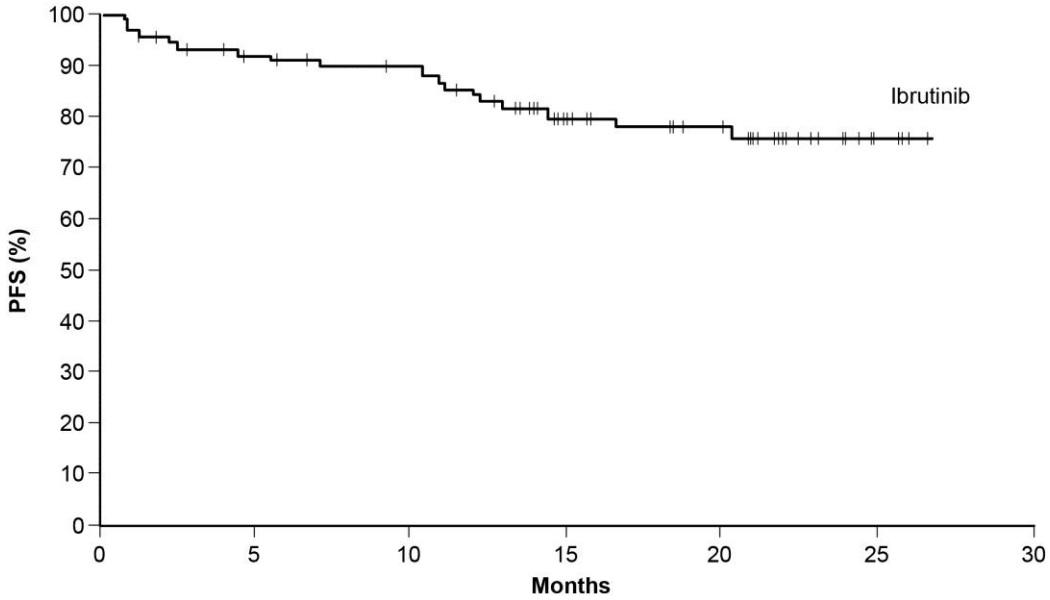
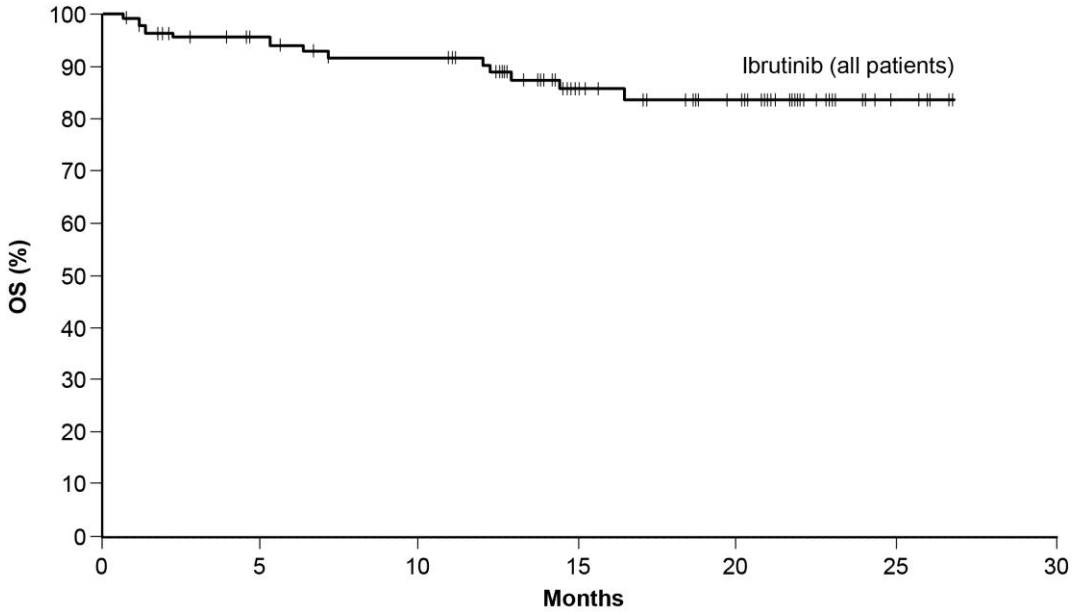
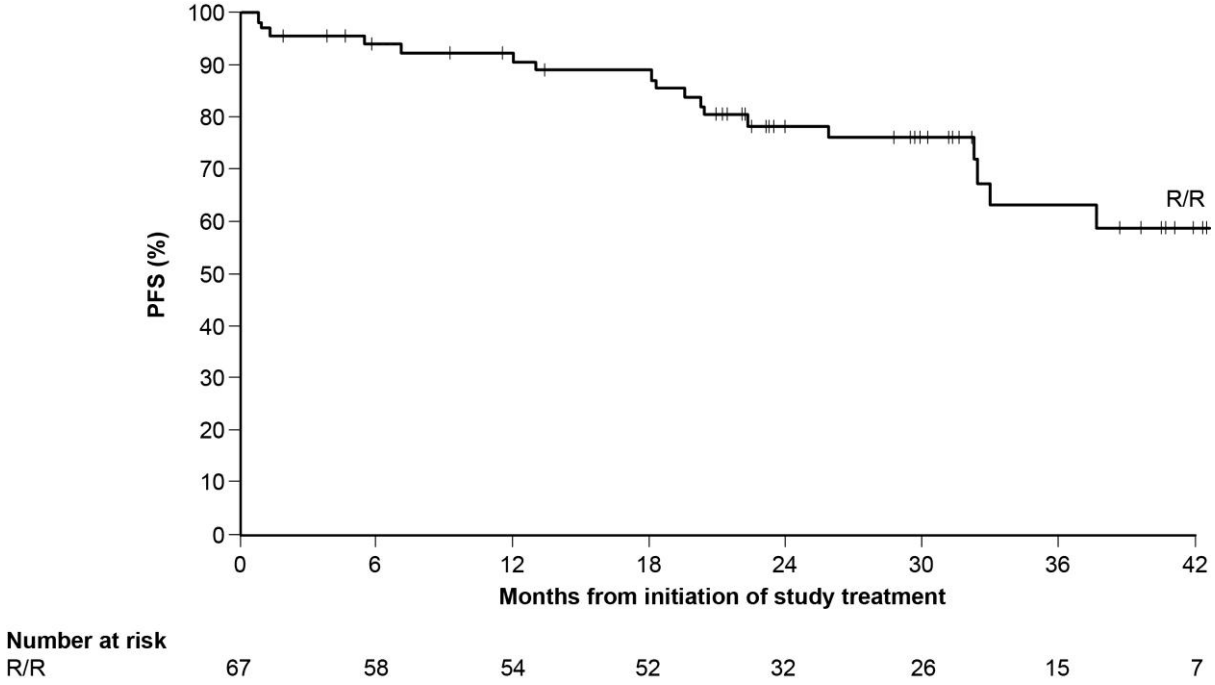


Figure 22: KM curve of OS in PCYC1102 (all patients) (21)



Median PFS or OS were not reached at 45 month follow-up for patients receiving either dose (32). The 30-month PFS for patients receiving ibrutinib 420 mg was 76% (95% CI 62.5%-85.1%) and the 30-month OS was 87% (95% CI 75.8%-93.3%,see Figure 23. These data are highly clinically relevant, given that not reaching median indicates that over 50% of the patient population remain alive at the longest follow-up available.

Figure 23: KM curve of PFS in PCYC1103 (23)



Patients with 17p deletion

Data are available on 262 patients with 17p deletion. There were 36 patients with 17p deletion in PCYC1102 (two of whom had not previously received treatment) and 23 patients in PCYC1103, the follow-up study to PCYC1102.

A phase II study, PCYC1117, assessed ibrutinib in 144 patients with 17p deletion. These data have not yet been published and data are drawn from the CSR (24), the protocol (102) and data presented at ASH, 2014 which provides data with a median 13 month follow-up (103) (104).

An investigator initiated study in patients with untreated or R/R CLL and TP53 mutation has been published: Farooqui MZ, Valdez J, Martyr S, Aue G, Saba N, Niemann CU, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol* 2014 (25). Data in this section are drawn from the published paper and associated appendix. The study included 35 patients with untreated CLL and 16 with R/R disease.

Patients were high risk in both studies:

- In PCYC1117, patients had high risk disease, a median of two previous treatments (range 1-7), and 39% of patients had three or more previous treatments.

- In Farooqui 2014, patients had high risk disease; patients with R/R disease had a median of four previous treatments (range 1-7).

The results are shown in Table 43 and demonstrate a consistent survival benefit across all four studies for R/R and previously untreated patients

Median PFS is yet to be reached in all but one study; median PFS was reached at 32.4 months in a small subgroup of PCYC1103 (n=23).

In patients with previously untreated disease in the Farooqui study (25), both ORR and survival were greater than that observed in the studies in patients with R/R disease: ORR was 82% and 84% of patients remained alive at 24 months. For comparison, the R/R patients in this study had an ORR of [redacted] and estimated OS of 74% at 24 months.

Table 43: Key results from studies including patients with 17p deletion

Study	**PCYC1102* (subgroup) (91)**		**PCYC1103 (subgroup) (105)**	**PCYC1117 (CSR) (24)**	**Farooqui** (25)**	
Patient group	R/R	R/R	R/R	R/R	R/R	Previously untreated
n	25	11	34	144	15	35 (33 evaluable)
Dose	Ibrutinib 420 mg	Ibrutinib 840 mg	Ibrutinib 420 mg and 840 mg	Ibrutinib 420 mg	Ibrutinib 420 mg	Ibrutinib 420 mg
Best response, no (%)						
ORR (CR + PR)	[redacted]	[redacted]	24 (71%)	[redacted]	10 (67%)	27 (82%)
CR	[redacted]	[redacted]	2 (3%)	[redacted]	1 (7%)	4 (12%)
PR	[redacted]	[redacted]	22 (65%)	[redacted]	9 (60%)	23 (70%)
PR with lymphocytosis	[redacted]	[redacted]	3 (9%)	[redacted]	3 (20%)	14 (42%)
	Ibrutinib 420 mg and 840 mg (21)		**Ibrutinib 420 mg (n=23) (23)**	**(104)**		
PFS						
Median (months)	Not reached		32.4 months	Not reached	Not reached	
Estimated PFS	57% (26 months)			79% (12 months)	82% (24 months)	
OS						
Median (months)	Not reached		Not reached	Not reached	Not reached	Not reached
Estimated OS	70% (26 months)		81% (30 months)	84% (12 months)	74% (24 months)	84% (24 months)

*Includes 2 patients with 17p deletion and untreated prior to ibrutinib
** 17p deletion and TP53 mutation

4.12 Adverse reactions

Adverse reactions in RESONATE

Data in this section are drawn from the RESONATE publication (18) and from the CSR (86).The published paper is used wherever possible, with additional information drawn from the CSR.

An updated analysis after a median of 16 months follow-up was presented at ASH 2014 (28) and is included below.

Due to ibrutinib being taken until disease progression or unacceptable toxicity while ofatumumab is administered for a set course, it should be noted that exposure to treatment was longer in patients receiving ibrutinib than in patients receiving ofatumumab (8.6 months vs. 5.3 months). Analysis of exposure-adjusted incidence rates (EAIR) of AE was performed and showed that [redacted]

Discontinuation of treatment due to AE occurred in 4% of patients in each arm, a low discontinuation rate. Dose reduction due to AE occurred in 4% of ibrutinib patients and 0.5% of ofatumumab patients.

The most common AEs in the ibrutinib group were diarrhoea, fatigue, pyrexia and anaemia. The most common AEs in the ofatumumab group were fatigue, infusion site reactions and cough, see Table 44.

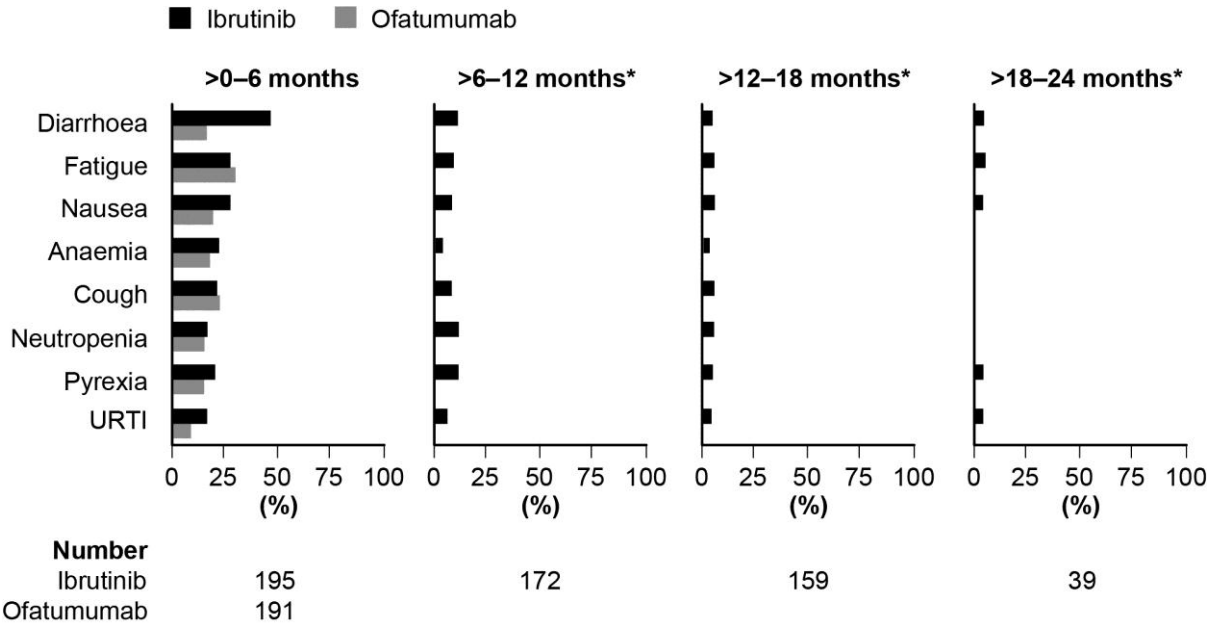
Table 44: AE in the RESONATE study reported in at least 10% of patients in either arm of the study.

AE	Ibrutinib (n=195)	Ofatumumab (n=191)	Relative risk (95% CI)
Any AE occurring during treatment	194 (99%)	187 (98%)	1.02 (0.99-1.04)
Diarrhoea	93 (48%)	34 (18%)	2.68 (1.91-3.76)
Fatigue	54 (28%)	57 (30%)	0.93 (0.68-1.27)
Nausea	51 (26%)	35 (18%)	1.43 (0.97-2.09)
Pyrexia	46 (24%)	28 (15%)	1.61 (1.05-2.46)
Anaemia	44 (23%)	33 (17%)	1.31 (0.87-1.96)
Neutropenia	42 (22%)	28 (15%)	1.47 (0.95-2.27)
Cough	38 (19%)	44 (23%)	0.85 (0.58-1.24)
Thrombocytopenia	33 (17%)	22 (12%)	1.47 (0.89-2.43)
Arthralgia	34 (17%)	13 (7%)	2.56 (1.40-4.70)
Upper respiratory tract infection	31 (16%)	20 (10%)	1.52 (0.90-2.57)
Constipation	30 (15%)	18 (9%)	1.63 (0.94-2.83)
Vomiting	28 (14%)	12 (6%)	2.29 (1.20-4.36)
Headache	27 (14%)	11 (6%)	2.40 (1.23-4.71)
Petechiae	27 (14%)	2 (1%)	13.22 (3.19-54.84)
Muscle spasm	25 (13%)	16 (8%)	1.53 (0.84-2.77)
Dysponea	23 (12%)	20 (10%)	1.13 (0.64-1.98)

Peripheral oedema	22 (11%)	15 (8%)	1.44 (0.77-2.68)
Back pain	22 (11%)	12 (6%)	1.80 (0.91-3.53)
Sinusitis	21 (11%)	12 (6%)	1.71 (0.87-3.39)
Dizziness	22 (11%)	10 (5%)	2.15 (1.05-4.43)
Contusion	21 (11%)	6 (3%)	3.43 (1.41-8.31)
Stomatitis	21 (11%)	4 (2%)	5.14 (1.80-14.70)
Pain in limb	20 (10%)	8 (4%)	2.45 (1.11-5.42)
Pneumonia	19 (10%)	13 (7%)	1.43 (0.73-2.82)
Urinary tract infection	19 (10%)	10 (5%)	1.86 (0.89-3.90)
Myalgia	19 (10%)	7 (4%)	2.66 (1.14-6.18)
Blurred vision	19 (10%)	6 (3%)	3.10 (1.27-7.60)
Night sweats	10 (5%)	24 (13%)	0.41 (0.20-0.83)
Peripheral sensory neuropathy	8 (4%)	24 (13%)	0.33 (0.15-0.71)
Infusion-related reaction	0	53 (28%)	Not calculated

It should be noted that ofatumumab was only administered for 24 weeks and therefore AE after 6 months in the ofatumumab arm were rare as patients were not receiving treatment at that point. A similar picture was observed with AE ≥ grade 3, the most common of which were cytopenias and pneumonia in both arms. Data from long-term follow-up (90) reveal that most AEs in patients treated with ibrutinib occurred early in treatment, mostly within the first year, see Figure 24.

Figure 24: AE (all grades) by time to event onset in RESONATE (90)



Serious AE were reported in 42% of ibrutinib patients and 30% of ofatumumab patients. The majority were infection-related (56% of serious AE with ibrutinib and 67% of those with ofatumumab). Other serious AE included febrile neutropenia, anaemia, cardiac disorders and general disorders and administration site conditions.

AE of grade 3 or higher severity were observed in 57% of ibrutinib patients and 47% of ofatumumab patients. Rates of grade 3 or higher diarrhoea and atrial fibrillation (AF) were higher with ibrutinib than with ofatumumab (4% vs. 2% and 3% vs. 0%).

AF was observed in 10 (5%) patients receiving ibrutinib vs. one (0.5%) patient receiving ofatumumab. AF was severe or grade 3 or higher in seven patients. However, only one case was considered to be treatment related and only one patient discontinued treatment due to AF. Most of the patients who experienced AF were older (aged over 70 years) and all of them had risk factors for AF (including a prior history in three patients). The ibrutinib SMPC advises to periodically monitor all patients clinically for AF and to perform an ECG for those who develop arrhythmic symptoms or new onset of dyspnoea (52).

In RESONATE, 50% of patients were receiving anticoagulants or antiplatelet agents in the ibrutinib arm. While bleeding-related AE were more common in the ibrutinib arm (44% vs. 12%), major haemorrhage (defined as any haemorrhagic event grade 3 or higher requiring hospitalisation or blood transfusion) was unusual and observed in two (1%) ibrutinib patients and three (2%) ofatumumab patients. The frequency of both any bleeding and major bleeding also decreases with time (107). The findings above suggest that, while care should be exercised in patients treated with ibrutinib and concomitant anticoagulants/antiplatelet agents, the overall rate of major bleeding is low and was not increased in the ibrutinib arm compared to the ofatumumab arm.

Other AE which were more common with ibrutinib than ofatumumab were rash (8% vs. 4%), pyrexia (24% vs. 15%) and blurred vision (10% vs. 3%). Most of these events were grade 1 or 2 in severity. The incidence of cataracts was 3% vs. 1%.

Infection of any grade was more common in the ibrutinib group (70% vs. 54%), however, rates of grade 3 or above infection were similar (24% vs. 22%). Infusion site reactions, peripheral sensory neuropathy, urticaria, night sweats and pruritus were all more common with ofatumumab than ibrutinib.

Of the patients enrolled in the study, 63% had some form of cytopenia at baseline (45% were anaemic, 35% had thrombocytopenia and 20% neutropenia). There was a sustained improvement in cytopenia(s) in both arms, although the improvement was significantly greater in the ibrutinib arm vs. the ofatumumab arm (69% of patients vs. 43%, $p<0.0001$) (89).

There were eight deaths (4%) in the ibrutinib group and nine (5%) in the ofatumumab group. Most deaths were due to infection (pneumonia or sepsis) or disease progression.

Data from the updated analysis (28) revealed that AEs were consistent with those reported above. In an updated analysis with a median follow up period of 16 months, the majority of patients were still receiving ibrutinib. Discontinuation rates remained relatively low, with 11% of patients (n=47) discontinuing ibrutinib due to adverse events. There were two additional deaths in the ibrutinib arm, making a total of ten deaths at median 16 month follow-up.

Adverse reactions in non-RCT

Data are presented for the long-term follow-up of PCYC1103, below. Specific AE results for PCYC1102, PCYC1117 and Farooqui are detailed in Appendix 7.

The most up to date data are from the 44 month follow-up abstract and presentation from the American Association for Cancer Research Annual Meeting in 2015 (22, 23).

The presentation focused on AE of grade 3 and above in R/R patients receiving the 420 mg dose of ibrutinib only; 82% (n=55) experienced AE of grade 3 or greater severity. Overall, 48% (n=32) patients experienced an infection of which 25 (78%) were deemed to be ibrutinib-related by the investigators. Serious grade ≥3 AE occurred in 69% (n=46) patients, of which eight (17%) were deemed to be ibrutinib-related by the investigators. Dose reductions occurred in seven patients, all but one during the first year of treatment. There were seven deaths on study.

Additional data are provided for both doses of ibrutinib used in the study with 3-years of follow-up (32). Data are presented for treatment-naïve and R/R patients unless specified otherwise.

Most patients were able to continue treatment with ibrutinib. Most discontinuations due to AEs were observed in the first year of treatment (11/132 patients, 8%), falling steeply in the second (4/103, 4%) and third years (2/71, 2%).

AE led to dose reduction in 10% (n=13) of patients, and occurred primarily in the first year.

The most common AEs observed over the 3-year follow-up period were hypertension (20% R/R), pneumonia (25% R/R), neutropenia (18% R/R), infection (13% R/R) and thrombocytopenia (10% R/R). For AEs occurring in >5% of patients, during years 1, 2, 3, and 4 on therapy, the frequency of infections (pneumonia and sepsis), cytopenias, diarrhoea, and fatigue decreased over time, while the frequency of hypertension and atrial fibrillation appeared constant.

For AEs requiring treatment discontinuation, only four were possibly related to ibrutinib treatment (grade 3 haematoma in an R/R patient, grade 3 influenza in an R/R patient, grade 3 pruritic rash in a treatment-naïve patient, and grade 3 fatigue in a treatment-naïve patient), and all resolved on discontinuation of ibrutinib.

Diarrhoea, which was observed in 55% of R/R patients was the most frequent any-grade AE. Looking at both treatment-naïve and R/R patients, the median number of diarrhoea events per patient was one (range, 1-6). Eight patients experienced 12 events of grade 3 diarrhoea. There were no grade 4 or 5 events. Most of the grade 3 events were of short duration, with only five events lasting longer than 5 days. The majority of episodes resolved without additional therapy, while symptomatic management was generally successful in treating diarrhoea. One grade 3 diarrhoea event led to study treatment discontinuation.

Safety overview

In summary, ibrutinib has a predictable safety profile, AEs tend to be self-limiting and their incidence decreases over time. Ibrutinib does not require prophylactic measures or medication, and the number of discontinuation due to AEs remains low in the most up-to-date follow up.

4.13 Interpretation of clinical effectiveness and safety evidence

Clinical benefits and harms

Ibrutinib provides an unprecedented and consistent benefit in survival across all patients

Ibrutinib is supported by clinical trial data from five clinical trials, all of which show a consistent efficacy profile in the overall population and across each subgroup analysed. More than 50% of patients are still alive and progression free at the time of data cut in all trials with follow up of up to 45 months in patients with R/R disease (18, 21-25).

When compared to ofatumumab, a licensed product that is recommended in clinical guidelines, the incremental efficacy of ibrutinib in PFS and OS were remarkable and highly statistically significant (28)

The survival benefit was observed regardless of cytogenetic status and across all subgroups. Significant survival benefit was observed in older patients, those with poor performance score, advanced disease and heavily pre-treated patients: all characteristics which impact on fitness and/or risk and traditionally make treatment more challenging.

Of note, in the more difficult-to-treat patient population with 17p deletion, ibrutinib's efficacy profile remained ground-breaking and the PFS and OS benefit against ofatumumab was maintained in a highly statistically significant manner (18).

The survival benefit in patients with 17p deletion is clarified in phase II studies which report 32.4 months median PFS observed with ibrutinib in R/R 17p deletion patients (21-23, 25, 104).

In addition, data from the ITC demonstrate a consistent benefit with ibrutinib and improved survival benefit against comparators including PC, BR and IO (as a proxy for IR), as demonstrated by the hazard ratios derived from these analyses (Section 4.10).

Ibrutinib also demonstrates benefit in patients with previously untreated disease and TP53 mutation or 17p deletion (25). A cohort of patients within the Farooqui trial was untreated (n=33) and showed benefit with ibrutinib. Indeed, previously untreated patients had improved responses compared with R/R patients: ORR, 82% vs. 67% and estimated OS at 24 months of 84% vs. 74%.

Efficacy of current treatments in *treatment-naïve 17p deletion patients*, ranging from 2.2 to 18.3 months median PFS, is clearly exceeded by the 32.4 months median PFS observed with ibrutinib in *R/R 17p deletion patients* (22, 31). It can be inferred that the efficacy of ibrutinib in treatment-naïve 17p deletion patients will at least be equivalent to that observed in R/R 17p deletion patients and thus represents a step change in the treatment of treatment-naïve 17p deletion CLL.

There is currently no other oral single or combination agent whose efficacy results match those shown by patients treated with ibrutinib in this patient population. Very few other cancer treatments have been able to show a degree of improvement over a comparator of this magnitude.

Ibrutinib has a manageable tolerability profile and most patients remain on treatment

AE were consistent and predictable across all studies, most were grade 1 and 2, and were manageable with standard supportive treatments. Ibrutinib does not require any routine pre-medication or additional monitoring.

The majority of patients are able to continue on treatment with ibrutinib, as discontinuations due to AE within the clinical study programme are low (<15%) with an incidence rate that reduces over time.

When assessing ibrutinib's safety profile against its comparator in the pivotal phase III trial, it must be borne in mind that patients in the ibrutinib arm had a >50% longer AE reporting period than those on ofatumumab (8.6 vs. 5.3 months, respectively).

The most common AE in each study was diarrhoea, which occurred in around one-half of patients. Almost all cases occurred early in treatment, were grade 1 or 2 in severity, were managed with standard treatment and responsive to loperamide, and resulted in very few discontinuations. Cases of diarrhoea were of short duration (<5 days) and most patients experienced only one case. In RESONATE, infection rates were higher with ibrutinib (70% vs. 54%); however, rates of grade 3 or above infection were similar with both agents (24% vs. 22%). Grade 3 or above infection rates fell by approximated 50% with ibrutinib after 6 months of treatment.

Serious AE were reported in 40-61% of patients; most were infection-related although AF was also reported. Most cases of AF were in patients with risk factors or pre-existing disease. The majority of serious AEs were not related to ibrutinib.

Ibrutinib results in a transient and non-clinically significant (i.e. does not require treatment, investigation, or drug discontinuation and does not affect the efficacy of the drug) increase in blood lymphocyte levels, which usually resolves with continued treatment (18, 21). Lymphocytosis has been observed with other agents that target B-cell receptor signalling and is not a sign of progressive disease (108).

Ibrutinib has a measurable positive impact of patients' HRQOL

Patients feel well on ibrutinib treatment, with a reduction in disease-related symptoms, fatigue and disease bulk. In RESONATE, a reduction in disease-related symptoms (defined as a change of at least one grade post-baseline reported for at least two consecutive assessments) was observed more often with ibrutinib than with ofatumumab. Disease-related symptoms included weight loss (reduction of 100% vs. 87%), fatigue (79% vs. 64%), night sweats (89% vs. 77%), abdominal pain (96% vs. 75%) and anorexia (100% vs. 64%) (90). There was also a reduction in disease bulk (90).

[redacted]

[redacted]

Strengths and limitations

Consistent evidence of survival benefit

The clinical trial evidence to support the survival benefit with ibrutinib is consistent across five clinical trials and in all patient subgroups.

The evidence supporting this appraisal for patients with R/R disease comes from one randomised study vs. ofatumumab (RESONATE) and four open studies (PCYC1102, PCYC1103, PCYC1117 and Farooqui, 2014 (18, 21-25)).

The evidence for this appraisal for first-line use of ibrutinib in patients with 17p deletion or TP 53 mutation comes from an open study which included 33 untreated patients (25). Two additional patients in study PCYC1102 were treatment-naïve with 17p deletion (100). Clearly, this is a small patient population in an uncontrolled study; nevertheless, it demonstrates that patients with 17p deletion or TP 53 mutation do benefit from treatment with ibrutinib as first-line treatment. Clinical opinion from an advisory board convened by Janssen suggests that addition to the current evidence base available for treatment-naïve patients with 17p deletion, the data for ibrutinib in R/R patients with 17p deletion provide a strong argument to support first-line use of ibrutinib in the 17p deletion or TP 53 mutation populations (1).

Comparative evidence to support ibrutinib comes from ITC, MAIC and pooled analyses, which show a highly consistent survival benefit with ibrutinib over comparators, regardless of the methods used or the comparator assessed.

Robust evidence base

All five clinical studies have robust internal validity as demonstrated by strong critical appraisal scores.

A number of factors influence external validity and are listed below:

- Data from RESONATE demonstrate that the positive effect of ibrutinib on OS is robust and highly statistically significant, despite the crossover of 57 patients to the ibrutinib arm after disease progression on ofatumumab at the primary analysis time-point and crossover of 122 patients at the 16-month follow-up point (28)

- Reduced clonal evolution of aggressive subclones, and patients maintaining health on ibrutinib: recent work looking at subclonal populations of CLL cells suggests that mutations increase over time and with conventional treatment with rituximab or fludarabine, agents which are less active against cells with adverse cytogenetics (11). Conventional chemotherapy typically leads to mass extinction of the incumbent clone which allows the more aggressive (and difficult to treat) subclones to multiply. This may explain why patients who relapse after first-line treatment do less well with each subsequent treatment. Ibrutinib is active against all CLL cells, regardless of cytogenetics,

therefore, we hypothesise that clonal evolution of aggressive subclones is less likely with ibrutinib than with conventional therapy and benefit will be continued post-progression. The manageable tolerability profile observed with ibrutinib also means that when patients do eventually progress on treatment, they are physiologically fitter and well placed to withstand progressive disease and further lines of treatment.

Few limitations to the evidence-base

- In study PCYC1102/1103, 34 (40%) patients received an unlicensed dose (840 mg). There was no difference in efficacy; however AE rates were higher in patients receiving the 840 mg dose. In this submission we have presented data for the licenced dose wherever possible (21-23), although in some cases this has not been possible due to study reporting.

- As expected in clinical trials, the study populations exclude patients with significant cardiovascular disease, those taking warfarin, patients with prior malignancy, patients with significant infection and those with a poor performance score.

- The studies were carried out around the world; 87 patients in the study programme were from the UK (73 from RESONATE and 14 from PCYC1117). For the most part, patients were recruited from countries with similar demographics to the UK (Europe, North America and Australia/New Zealand). Clinical opinion from an advisory board convened by Janssen is that that the only difference between UK patients in clinical practice and those in RESONATE is that they are likely to be slightly older (mid/late-70s) than those observed in the RESONATE trial (67 years) (1).

- While ibrutinib's license covers patients with either 17p deletion or TP53 mutation, RESONATE collected 17p deletion status but not TP53 mutation status and so analyses can be made for 17p deletion but not the TP53 mutation subgroups. However, as these mutations have the same impact on the cell biology, disease prognosis and treatment outcomes, ibrutinib data in patients with 17p deletion are used as a proxy for ibrutinib's efficacy in TP53 mutation. This assumption is reflected in the BCSH interim guidelines which make no distinction in treatment recommendations between the two cytogenetic abnormalities, and use the encompassing term 'TP53 disruption' to address both abnormalities (2).

Table 45: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A recent NICE appraisal of idelalisib with rituximab in CLL patients who relapse within 24 months of prior therapy concluded that this patient group met the end of life criteria, which included a median OS of less than 24 months (40), For the R/R patient population considered in this submission, which is patients who have received one prior treatment and for whom fludarabine is inappropriate, the median OS based on a real world study was [redacted] (15) (see Section 3, Figure 5). This low survival is confirmed in the literature, where outcomes of patients who relapse within 36 months from frontline intensive chemo-immunotherapy are poor, with a median overall survival of less than 2 years (14).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The RESONATE data show a statistically significant improvement in OS for ibrutinib compared to ofatumumab based on 16 months of median follow-up (28). As median survival has not been reached in either arm and there was a high degree of crossover from the ofatumumab to the ibrutinib arm, precise incremental benefit has not been shown, but extrapolation suggests this to be well in excess of 3 months.
The treatment is licensed or otherwise indicated for small patient populations	The estimated incidence for CLL in England is 7 per 100,000 population giving a total of 3,843 cases per year assuming an NHS England population of 54.9 million. One third of CLL patients never require treatment and have long survival, another third have an indolent phase followed by disease progression; the remaining third exhibit aggressive disease at onset and require immediate treatment. Thus, two thirds of patients (2,562) with CLL will require active treatment at some point (9).

4.14 Ongoing studies

There are currently no ongoing company-sponsored ibrutinib studies in R/R CLL or treatment-naïve CLL with 17p deletion or TP53 mutation.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

Identification of studies

5.1.1 Describe the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England from published NICE technology appraisals, the published literature and from unpublished data held by the company. Justify the methods used with reference to the decision problem and the NICE reference case. Provide sufficient detail to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used. Provide the search strategy used in an **appendix**.

A SLR was conducted based on a pre-approved protocol in literature databases (listed below) to identify economic models, and studies reporting economic outcomes and data related to the treatment of R/R CLL patients with any chemotherapeutic, biologic or investigational pharmaceutical agents. The databases searched included:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed),
- Embase, and Embase In-process
- CENTRAL
- Database of Abstracts of Reviews of Effects (DARE)
- National Health Service Economic Evaluation Database (NHS EED)
- National Health Services Health Technology assessment (HTA) database,
- EconLit

The search algorithms used in these databases were generated using the PICOS (109) framework (Population, Intervention, Comparators, Outcomes, Study design) in line with the research question. Search algorithms were tailored to identify studies published as of 03 June 2015. All searches were run without limitations (e.g. no date or language limits). Non-relevant designs (i.e., comments or editorials) were removed from the search hits prior to review of the abstracts.

Additional searches were conducted via the Cochrane Library and the above databases for high-quality, recently conducted systematic reviews (published from 2011 to 2015) to serve as supplemental data sources.

Finally, bibliographies of relevant systematic review articles published since 2011 and the bibliographies of accepted studies were also reviewed to obtain any additional, relevant references.

In addition to the above searches within key databases, 'grey' literature (i.e., material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for relevant meeting abstracts or posters. Proceedings from the past three years (as available) for the follow key conferences were reviewed:

- ASCO (2013–2015): http://am.asco.org/
- ASH (2012–2014): http://www.hematology.org/Annual-Meeting/
- EHA (2013–2015): http://www.ehaweb.org/
- ESMO (2012–2013): http://www.esmo.org/Conferences/ESMO-2014-Congress
- ISPOR (2013–2015): http://www.ispor.org/

Search strategies were developed in line with the NICE Methods Guide and are provided in Appendix 8

Records identified from the searches underwent two rounds of screening according to pre-specified inclusion/exclusion criteria shown in Appendix 8. In the first round, two independent investigators evaluated the title/abstracts of all unique records. In the second round, full-texts/publications of all records that met the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a record to have passed this level. During both rounds of the screening process, discrepancies were resolved through consensus by a third investigator.

Relevant data elements were extracted by one investigator and validated by a second independent investigator. All discrepancies were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcomes measures to be extracted from the full papers. The results of this process are presented in the section that follows, Section 5.1.2.

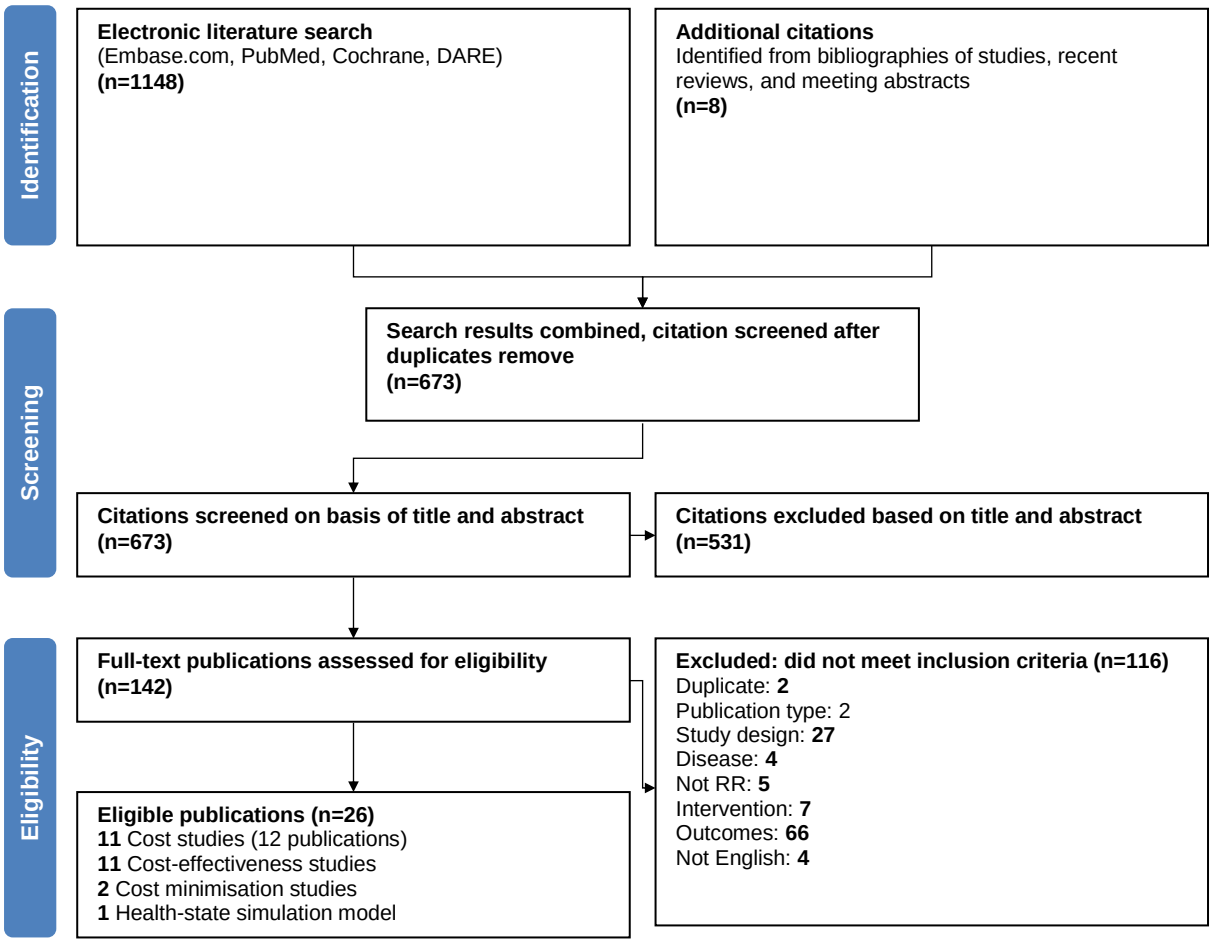
Description of identified studies

5.1.2 Provide a brief overview of each cost-effectiveness study only if it is relevant to decision-making in England. Describe the aims, methods and results for each study. Each study's results should be interpreted with reference to a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than 1 study is identified, please present the information in a table as suggested below.

After the initial removal of duplicate citations, 673 citations were screened according to the pre-specified inclusion and exclusion criteria. Of these, 531 citations were excluded at the abstract level. Among the 142 citations remaining, 116 were rejected following further application of the inclusion/exclusion criteria to full-text citations and 24 citations were finally

accepted into the review: 11 cost studies (12 publications), 11 cost-effectiveness analyses, and two cost-minimisation publications. Figure 25 below illustrates the process of eliminating references based on the protocol.

Figure 25: PRISMA Economic Analyses Flow Diagram



Of the 24 studies identified, there were 11 cost-effectiveness studies (110-120) and 11 resource identification studies (121-131). Additionally, two cost-minimisation studies (132, 133) and one health-state simulation model (19) were identified. The cost-minimisation studies were excluded from this discussion due to the fact that no health or QOL outcomes were analysed and the health-state simulation model study did not report any cost.

Four of the 11 cost-effectiveness analyses took the perspective of the UK. However, no full-text publications were available for these 11 studies (only abstracts) with the exception of Hoyle et al. 2010 (119); therefore, very limited information was available regarding the studies' methods and inputs. Details on the model, patient populations, and results of the four studies relevant to the UK are presented in Table 46. The remaining seven cost-effectiveness studies, three of which were only available as abstracts, took the perspectives of Australia (110), Canada, (113, 115) the US (114, 117), Portugal (118), and Poland (116), which limits their relevance to decision-making in England and Wales.

Table 46: Summary list of published cost-effectiveness studies

Study Reference	Country	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Almond et al. 2013 (abstract only) (111)	UK	Cost-effectiveness model from TA202 (comparing ofatumumab with BSC) was reproduced and populated with alternative survival data from the perspective of the UK NHS. Individual patient-level data were reconstructed from KM curves using a published algorithm. Plausible survivor functions were fitted to the data using Markov chain Monte-Carlo simulation.	NR	NR	NR	ICER comparing ofatumumab vs. BSC: £52,400 (compared to £49,252 reported in TA202).
Batty et al. 2010 (abstract only) (112)	UK	Cost-effectiveness of ofatumumab vs. BSC was evaluated in the UK national healthcare setting using a partitioned survival analysis model. PFS and OS for ofatumumab were estimated by fitting a Weibull curve to trial data; no similar data could be identified for BSC, therefore Cox regression models were fit to non-responder data vs. all fludarabine-refractory patients. Costs and utilities were taken from published and unpublished sources.	Not listed.	BSC patients (approximated by non-responders): 0.50 QALYs Ofatumumab patients: 0.77 QALYs	BSC: £4,876 Ofatumumab: £43,828	Ofatumumab vs. BSC: £144,266.66/ QALY
Hoyle et al. 2010 (134)	UK	An 'area under the curve' or 'partitioned-survival' model was used to project expected clinical and economic outcomes for patients with DR CLL who were assumed to receive ofatumumab or BSC. The model had a three-state structure: 'alive pre-progression', 'alive post progression' and 'dead'.	NR	No QALYs reported	NR	£38,241 per QALY
Dretzke et al. 2010 (120)	UK	The objective of the model was to assess the cost per QALY of R-FC compared to FC based on clinical parameters taken from the REACH trial. The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.	CLL (median age: 63 years)	No QALYs reported	NR	Base case - £15,593/QALY
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); BSC, BSC; DR, double refractory						

5.1.3 Provide a complete quality assessment for each relevant cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. Please provide these assessments in an **appendix**.

A complete quality assessment of the relevant cost-effectiveness studies is provided in Appendix 9.

5.2 *De novo analysis*

Patient population

5.2.1 State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials. If there are differences, please provide the rationale. Explain the implications of this for the relevance of the evidence base to the decision problem. For example, indicate if the population in the economic model is different from that described in the (draft) summary of product characteristics (SmPC) or information for use (IFU) and included in the trials.

The licensed indication for ibrutinib is for the treatment of adult patients with CLL who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

Figure 26 presents the current treatment paradigm as recommended in BCSH guidelines (13) with ibrutinib added as indicated. Introduction of ibrutinib is anticipated to alter the treatment paradigm in the following ways:

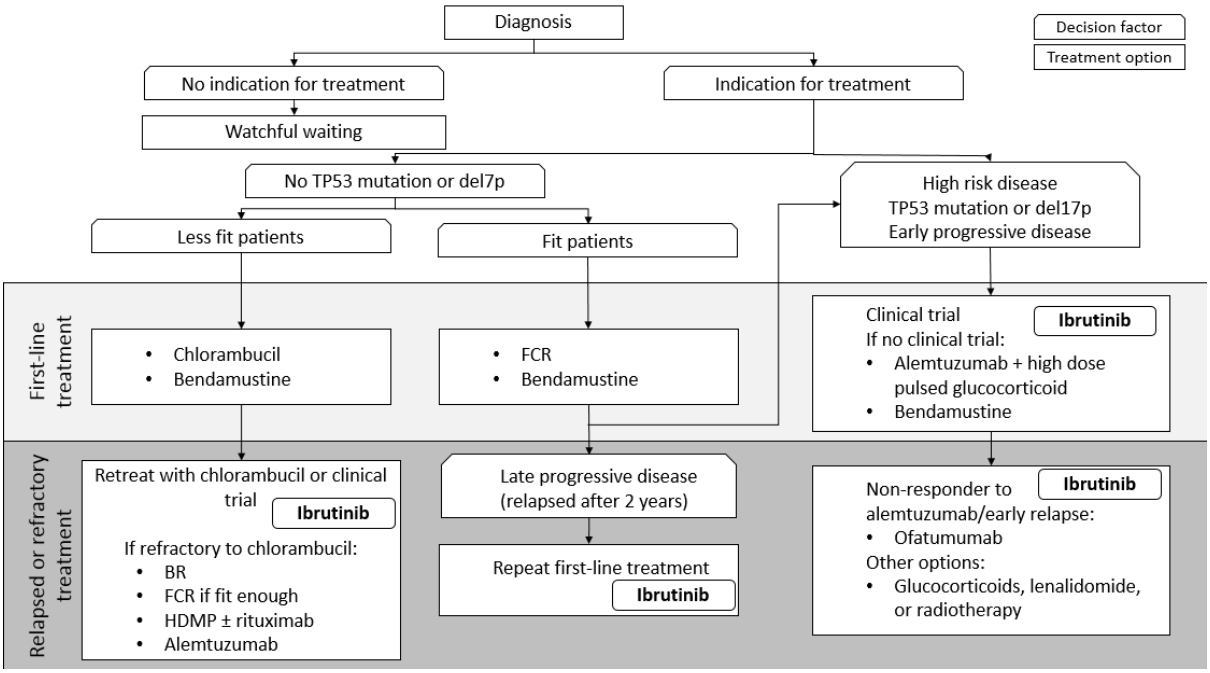
- Providing a much more effective treatment option for multiple CLL populations, including hard-to-treat and high risk groups

[1] 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

[2] 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.

- By prolonging the PFS period, use of ibrutinib delays the use of other more toxic treatments

Figure 26: CLL treatment paradigm including ibrutinib



The patient population in the economic model reflects the population in which ibrutinib would be used in UK clinical practice (described in Section 3.3). Baseline characteristics used in modelling (e.g. age and % male) reflect the RESONATE trial population, to ensure alignment with the most rigorous source of clinical evidence of ibrutinib's efficacy.

Ibrutinib's licence and scope also include treatment-naïve patients with 17p deletion or TP53 mutation unsuitable for chemo-immunotherapy. Ibrutinib is currently being evaluated in treatment-naïve patients compared to chlorambucil (PCYC1115), but the trial excludes patients with 17p deletion. Accordingly, only very limited data on treatment-naïve CLL patients with 17p deletion (n=2) are available from PCYC-1102/1103 (see Section 4.11). An analysis of the RESONATE 17p deletion subgroup (n=127/391, 32.5%) is presented as a scenario. In the absence of robust trial data of ibrutinib in treatment-naïve 17p deletion population, this scenario provides the best estimate of ibrutinib's comparative efficacy in this population. Clinical experts agreed that in the absence of data for first-line use of ibrutinib in patients with 17p deletion, data for ibrutinib in R/R CLL patients with 17p deletion constitute a strong argument to support treatment-naïve use in the 17p deletion population (1). Outcomes in the R/R population with 17p deletion are expected to be similar, if not better, to R/R patients without 17p deletion based on Landau et al. (2012) (11). IR has a similar license to ibrutinib and has recently gained a positive FAD from NICE for use in frontline 17p deletion and TP53 patients due to the acknowledged high level of clinical need in this patient population (40) (41).

Model structure

5.2.2 Describe the model structure and provide a diagram of the model submitted, including the following:

- Type of de novo analysis (for example, decision tree, Markov model, discrete event simulation model).
- Justification of the chosen structure in line with the clinical pathway of care described in section 3.3.
- How the model structure and its health states capture the disease or condition for patients identified in section 3.3.
- Where appropriate, state the cycle length and whether a half-cycle correction has been applied.

PFS and OS are key clinical endpoints. After a median of 16-months follow-up in the RESONATE trial, 91.8% of ibrutinib patients were still alive and 82.1% were still alive and progression free (28); even with up to 45 months in PCY1102/1103, median PFS and OS still has not been reached (23). PFS and OS outcomes in the hard-to-treat 17p deletion subgroup in RESONATE were similarly prolonged. Therefore, it was critical to structure the model in a way that could capture these outcomes.

Accordingly, a *de novo* survival partition model structure was developed with the following three health states (see Figure 27 for model diagram):

- PFS
- PPS
- Death

This three health state model is a highly accepted structure within oncology and was considered appropriate in multiple NICE submissions within CLL (34-36). The recent submissions evaluating IR for treatment of R/R CLL (40) and obinutuzumab + chlorambucil for untreated CLL (74) used similar health states, but with additional functionality to capture time spent “on” and “off-treatment” within the PFS period, based on the dosing schedules of the interventions. The model described in this submission also captures this distinction within the PFS health state.

In the PPS health state, a proportion of patients were modelled to receive a subsequent line of active treatment following progression. The remainder were modelled to receive BSC (symptom management without active intervention) immediately upon entering the PPS health state. Once patients on their subsequent line of therapy progressed, they then received BSC until death or

model end. Stratification of the PPS period by “subsequent line of treatment” and “BSC” was included in the current analysis to add face validity in this disease area where patients will experience multiple lines of therapy over the course of their treatment. Of note, NICE has previously favoured inclusion of subsequent lines of treatment for similar indications (e.g. first-line CLL and follicular NHL) (135, 136).

Costs and health effects (i.e. utility values) were assigned to each health state. A 4-week model cycle was used, based on the 4-week dosing schedule for most of the relevant comparators. Costs in PFS were assigned according to the distribution of patients’ best eventual response. A half-cycle correction was used to adjust for the distribution of costs and benefits accrued throughout the cycle.

Figure 27: Model diagram

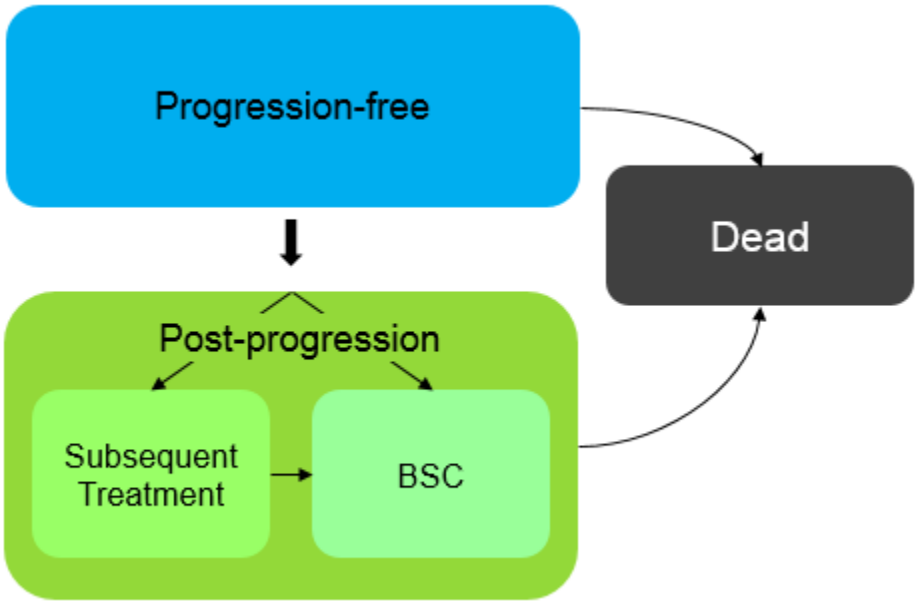


Table 47: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	20 years	Patients with relapsed or refractory CLL can live for many years and may receive multiple lines of therapy. Median survival for patients treated with ibrutinib in PCYC-1102/1103 had not been reached after 44 months (30 month OS 87.1% in R/R CLL 420mg patients) (23) (23). The projected median survival from the modelling of ibrutinib was approximately 6.4 years, with an estimated 10% of patients remaining alive at 20 years. A 20 year time horizon was considered to be sufficient to fully capture the costs and benefits associated with ibrutinib and to adequately simulate the treatment pathway of patients with R/R CLL, while minimising the uncertainty of projecting long-term health outcomes as per the NICE methods guide.
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in both QALYs and Lys	OS is the ultimate outcome in late-stage oncology trials. As a result, life-years gained by patients receiving one treatment compared to another are a critical measurement. In addition, we consider the possibility that HRQOL is differs at different phases of disease and with different treatment regimens. To measure this impact, time spent in each treatment phase was adjusted by utility to determine QALYs
Discount of 3.5% for utilities and costs	Health and cost outcomes were discounted by 3.5%	The discount rate applied to both costs and outcomes in the reference case was 3.5% per year as per the NICE methods guide.
Perspective (NHS/PSS)	The model took the perspective of the NHS and PSS	The model takes the perspective of the NHS in England and Wales.
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.3 Intervention technology and comparators

5.2.3.1 Intervention

Ibrutinib was implemented in the economic model per its SmPC (52) and in accordance with its usage in the RESONATE trial: 420 mg/day (3 capsules) administered until disease progression or until no longer tolerated by the patient (18). A dose intensity of 94.8% based on usage of ibrutinib in RESONATE was applied to the full cost of the drug to account for patients who temporarily reduced the dose of ibrutinib or discontinued treatment due to tolerability issues.

5.2.3.2 Selection of comparators

The selection of comparators for inclusion in the economic model was based upon consideration of the following criteria, in accordance with the NICE Methods Guide, Section 5.1.6:

Relevance to UK clinical practice, based on NICE Final Scope input from UK clinical experts

As noted in Section 1.0, the NICE Final Scope for ibrutinib for treating R/R CLL (July 2015) (6) recommended the following comparators: FCR; bendamustine (with or without rituximab); chlorambucil (with or without rituximab); corticosteroids (with or without rituximab); IR; and BSC. However, clinical guidelines (see Section 3.3) and an advisory board of UK haematologists (1) confirm that there is no established standard of care for patients with R/R CLL in the UK.

Quality and rigour of data for establishing relative treatment effects

The following hierarchy of data was considered. Wherever possible, multiple sources of data were leveraged to validate estimates of relative treatment effect and to show consistency of the superior treatment benefit of ibrutinib over comparators (see Section 4.10 and Appendix 6 for details).

1. The most rigorous source of comparative efficacy is a head-to-head, comparative, RCT.

2. In the absence of RCT data, the NICE Methods Guide recommends establishing a NMA or, if not all comparators can be included in one network, an ITC using common treatment arms. Such methods are considered to generate unbiased estimates of the relative treatment effect, under the assumption of relative treatment effects being similar across heterogeneity of trial characteristics.

3. When indirect comparisons cannot be conducted due to a lack of a common comparator, alternative statistical methods, such as MAIC and pooled multivariate analysis, can be employed to estimate relative treatment efficacy between two treatments, adjusting for population differences between trials and therefore improving on naïve, unadjusted comparisons that can be introduce bias.

5.2.3.3 Comparators included in the economic model

PC is the most relevant comparator for ibrutinib, as demonstrated by the lack of a standard of care in clinical guidelines (13) (2) and clinical expert opinion (1). Numerous treatment options are used depending on a patient's risk factors, age, and fitness levels; moreover, clinicians often enrol patients in clinical trials if they see fit. BR, IO (as a proxy for IR), and ofatumumab were included as secondary comparators. Table 48 presents the comparators selected in the economic model and an assessment of these key factors considered for inclusion (see Section 3.3 and Figure 6 for an overview of the disease and place in therapy for ibrutinib).

PC was composed of the following treatments: R-CHOP (10%), BR (35%), FCR (10%), R+HDMP (25%), and chlorambucil (20%). This composition reflects the mix and proportion of therapies that were used in the PC arm of Österborg, 2014 (37) (38) but was adjusted further to include only treatments relevant to UK clinical practice (1). Clinicians indicated that it would be

appropriate to use the ITC results to inform relative treatment efficacy of ibrutinib vs. the current practice in the UK (1).

As noted in Section 4.10, it was not possible to establish ibrutinib's efficacy vs. IR based upon the publication of the phase III Study 116 (Furman, 2014) (30). Instead, ibrutinib's efficacy vs. IO was established through an ITC comparing RESONATE vs. Jones, 2015 (39). UK clinicians supported that the efficacy of IR and IO were interchangeable (1). Moreover, the recent appraisal of IR employed the same assumption of interchangeability of efficacy for rituximab and ofatumumab and this which was accepted by NICE (40).

When analysing ibrutinib in the R/R CLL 17p deletion subgroup, it was only possible to compare ibrutinib against ofatumumab, as PFS and OS data specific to that subgroup were not published for any of the other comparators relevant to the UK.

Table 48: Justification of comparators in economic model

Comparator	Included in NICE Scope?	Relevance to UK clinical practice?	Rigour of data available for modelling
PC (primary comparator)	No	High; clinical guidelines (Section 3.3) and UK clinicians (1) indicated there is no standard of care and patients are treated with a wide variety of treatment options.	High Primary source: ITC based on RESONATE vs. Österborg, 2014 Validation source: ITC of RESONATE vs. Karolinska real-world evidence (Section 4.10, Appendix 6)
BR (secondary comparator)	Yes	High; UK clinicians indicated BR is frequently used (1)	Medium Primary source: MAIC of RESONATE vs. Fischer, 2011 Validation source: ITC of RESONATE and HELIOS (Section 4.10, Appendix 6)
IO as proxy for IR (secondary comparator)	Yes	High; recently recommended (FAD stage) by NICE for the same indication as ibrutinib (40)	Medium ITC based on RESONATE vs. Jones (2015); requires assumption that IO has the same efficacy as IR (Section 4.10, Appendix 6)
Ofatumumab	No	Medium; UK clinicians indicated that ofatumumab is relevant to UK clinical practice (1)	High; RESONATE is a head-to-head RCT comparing ibrutinib vs. ofatumumab

5.2.4 If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations/CE marking, describe how and why there

are differences. Make it clear whether the intervention and comparator(s) included in the model reflect the decision problem. If not, briefly describe how and why, cross-referencing to the decision problem section in your submission.

The dosing and continuation rules for ibrutinib have been implemented in accordance with the market authorisation. Due to a lack of robust data of ibrutinib's efficacy in a frontline 17p deletion population, the cost-effectiveness of ibrutinib has instead been tested in a R/R CLL 17p deletion subgroup. It is expected that results from this subgroup analysis would be indicative of that of the treatment-naïve 17p deletion population. This is consistent with the approach taken and accepted by NICE in the recent IR NICE submission in the same patient population (41).

Comparators are implemented in the model as per their marketing authorisations. The dosing regimen and continuation rules for ibrutinib and the relevant comparators are summarised in Table 49. The intervention and comparators reflect the decision problem as they are the most representative treatment options currently in use for the patient population under appraisal.

Table 49: Dosing regimen and continuation rules

Treatment		Dosing regimen	Source	Continuation rules as per MA/SmPC	Continuation rules implemented in the model	Justification implementation in the model
Ibrutinib		420 mg/day (3 capsules) daily	Ibrutinib SmPC (52)	Treatment should continue until disease progression or no longer tolerated by the patient.	Patients continue treatment with ibrutinib until progression; treatment discontinuation is informed by treatment discontinuation KM data from RESONATE, which takes into account dose reduction or discontinuation due to tolerability	Implemented as per SmPC and RESONATE trial observation
Physician's Choice	BR	See BR below	See BR below	See BR below	See BR below	Based on Österborg, 2014; customized by clinical experts to fit UK clinical practice
	R-CHOP	Rituximab: 375 mg/m^2, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP Cyclophosphamide: 750 mg/m^2 Doxorubicin: 50 mg/m^2 Vincristine: 1.4 mg/m^2 up to a maximum of 2 mg on day 1 Prednisone: 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles	Mabthera (rituximab) EMA label (137)	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration.	Treatment should continue until disease progression, or maximum treatment duration.	Implemented as per Rituximab SmPC

	FCR	Fludarabine: 25 mg/m^2 on days 2-4, every 4 weeks for 6 cycles Cyclophosphamide: 250 mg/m2 on days 1-3, every 4 weeks for 6 cycles Rituximab: 375 mg/m^2 on day 0 of Cycle 1 followed by 500 mg/m^2 on day 1 of each subsequent cycle, for 6 cycles (per cycle = 28 days)	Badoux (2011) (138)	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration.	Treatment should continue until disease progression, or maximum treatment duration.	Implemented as per Badoux trial
	Chlorambucil	12 mg/m^2/day for 7 consecutive days, every month for 3 cycles (per cycle = 4 weeks)	Robak (2005) (139)	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration.	Treatment should continue until disease progression, or maximum treatment duration.	Implemented as per Robak trial
	R+HDMP	Methylprednisolone: 1 g/m^2 daily for day 1 to day 5 days of each 3 week treatment cycle Rituximab: 375 mg/m^2 on day 1, 500 mg/m^2 on day 5, day 22 and day 26. Then starting from day 43, 500 mg/m^2 repeat every 3 week cycles for 4 times.	Pileckyte (2011) (140)	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration.	Treatment should continue until disease progression, or maximum treatment duration.	Implemented as per Pileckyte trial
BR		Bendamustine: 70 mg/IV on days 1 and 2 every 28 days, for 6 cycles (per cycle=28 days Rituximab: 375 mg/m^2 on day 0 of cycle 1 followed by 500 mg/m^2 on day 1 of each subsequent cycle	Fischer (2011) (29)	Bendamustine: on days 1 and 2 every 28 days, for 6 cycles (per cycle=28 days) Rituximab: 375 mg/m^2 on day 0 of cycle 1 followed by 500 mg/m^2 on day 1 of each subsequent cycle	Patients continue incurring cost of BR treatment until 24 weeks, or until progression, whichever occurs sooner.	Implemented as per Fischer, 2011 trial

IO (proxy for IR)	Idelalisib: 150 mg orally, twice daily Rituximab: 375 mg/m^2 on day 0 of cycle 1 followed by 500 mg/m^2 on day 1 of each subsequent cycle	Idelalisib SmPC (141)	Idelalisib: Treatment should continue until disease progression or unacceptable toxicity Rituximab: 375 mg/m^2 on day 0 of cycle 1 followed by 500 mg/m^2 on day 1 of each subsequent cycle	Patients continue incurring the cost of rituximab until 24 weeks, or until progression, whichever occurs sooner. Patients continue incurring the cost of idelalisib until progression, as informed by PFS from Jones, 2014 (39).	The use of PFS as a proxy for treatment discontinuation was vetted by UK clinicians (1).
Ofatumumab	300 mg on Day 1 of week 1, 2,000 mg weekly from week 2 to week 8, 2,000 mg every 4 weeks from week 12 to week 24	Ofatumumab SmPC (142)	Infusion schedule is 8 consecutive weekly infusions followed 4-5 weeks later by 4 consecutive monthly infusions	Patients continue incurring cost of ofatumumab treatment until 24 weeks, or until progression, whichever occurs sooner.	Implemented as per SmPC
HDMP (Subsequent treatment)	Methylprednisolone: 1 g/m^2 daily for day 1 to day 5 days of each 3 week treatment cycle up to 6 cycles	Pileckyte (2011)	Treatment should continue until disease progression, or no longer tolerated by the patient or maximum treatment duration.	Treatment should continue until disease progression, or maximum treatment duration.	Implemented as per Pileckyte trial

5.2.5 If a treatment continuation rule has been assumed for the intervention and comparator(s), provide the rationale for the continuation rule and where it is referenced (for example, [draft] SmPC, European public assessment report, comparator use, clinical practice, or clinical trial protocols). Please note that this refers to clinical continuation rules and not patient access schemes. If a treatment continuation rule is included in the model that is not stated in the (draft) SmPC or information for use (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 implementing the continuation rule (for example, any additional monitoring required)
- the robustness and plausibility of the end point 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 people for whom the technology is particularly cost effective
- issues about withdrawal of treatment for people whose disease does not respond and other equity considerations.

No continuation or stopping rules were applied to the intervention technology or comparators in the economic model other than those described in Table 49 above.

5.3 *Clinical parameters and variables*

5.3.1 Describe how the clinical data were incorporated into the model, also commenting on the following factors:

- Whether intermediate outcome measures were linked to final outcomes (for example, if a change in a surrogate outcome was linked to a final clinical outcome). If so, explain how the relationship was estimated, what sources of evidence were used, and what other evidence there is to support it.
- Whether costs and clinical outcomes are extrapolated beyond the trial follow-up period(s). If so, explain and justify the assumptions that underpin this extrapolation, particularly the assumption that was used about the longer-term difference in effectiveness between the intervention and its comparator. For the extrapolation of clinical outcomes, present graphs of any curve fittings to patient-level data or Kaplan–Meier plots and the methods and results of any internal and external validation exercises. The NICE Decision Support Unit[3] has published technical support document 14, which provides additional information on the implementation of methods and reporting standards for extrapolation with patient level data.

Table 50 summarises the key sources of clinical evidence that were used to populate the model.

Table 50: Summary of clinical evidence and approach for modelling

Clinical evidence	Brief description	Use in the model
RESONATE (18) (28)	Pivotal Phase III, double-blinded RCT in R/R CLL investigating the efficacy of ibrutinib (n=195) vs. ofatumumab (n=196)	• Patient population baseline characteristics • PFS and OS KM data for all patients were projected beyond the trial period to inform PFS and OS outcomes for ibrutinib; projections were used as a reference curve to which HRs were applied to derive the PFS and OS for comparators • PFS KM data were projected beyond the trial period to inform PFS for ofatumumab; a crossover-adjusted OS HR was derived and applied to ibrutinib OS projection to estimate OS of ofatumumab. • Treatment discontinuation for ibrutinib was based on KM data from RESONATE, which accounted for discontinuation due to adverse events • Proportion of patients receiving subsequent treatment based

[3] Although the Decision Support Unit is funded by NICE, technical support documents are not formal NICE guidance or policy.

		on data reported for ofatumumab was used as proxy for all comparators. The ofatumumab arm provides the best data source, given that few patients in the ibrutinib arm had progressed and started receiving subsequent treatment. This assumption was validated by clinical experts (1). • Death during the PFS health state was derived from the entire RESONATE trial population and used as proxy for all comparators. • AE data for ibrutinib and ofatumumab • EQ-5D trial data informed baseline utility and utility during PFS
Study OMB114242 (Österborg,, 2014) (37) (38)	Phase III, open-label RCT in bulky fludarabine-refractory CLL investigating the efficacy of ofatumumab (n=79) vs. PC (n=43)	• ITC conducted via common ofatumumab arm to derive relative treatment effect of ibrutinib vs. PC on PFS and OS • AE data for PC
CLL2M GCLLSG (Fischer, 2011) (29)	Phase II, single-arm trial in patients with relapsed and/or refractory CLL investigating the efficacy of BR (n=78)	• MAIC conducted to derive relative treatment effect of ibrutinib vs. BR on PFS and OS • AE data for BR and proxy for physician's choice
HELIOS (Akmal, 2015) (95)	Phase III RCT in patients with R/R CLL or SLL investigating the efficacy of ibrutinib + BR (n=289) vs. BR + placebo (n=289)	• Pooled analysis conducted to derive relative treatment effect of ibrutinib vs. BR on PFS and OS
Study 119 (Jones, 2014) (39)	Phase III RCT in R/R CLL investigating the efficacy of IO (N=174) vs. ofatumumab (N=84)	• ITC conducted via common ofatumumab arm to derive relative treatment effect of ibrutinib vs. IO on PFS and OS, used to inform relative efficacy of ibrutinib vs. IO (proxy for IR) • AE data for idelalisib + ofatumumab (proxy for IR)
Study 116 (Furman, 2014) (30)	Phase III RCT in R/R CLL investigating the efficacy of IR (N=110) vs. rituximab (N=110)	• Rituximab PFS is used as proxy for the PFS of subsequent treatment
Karolinksa Institute (15)	Real world evidence from Sweden	• Pooled analysis conducted to derive relative treatment effect of ibrutinib vs. PC on PFS and OS; used as alternative efficacy source to validate and triangulate results of comparison vs. OMB114242.

Overview of clinical data used in the model

Clinical trials do not tend to fully capture PFS or OS in R/R CLL. This is especially true in the case of ibrutinib, which was demonstrated to significantly prolong PFS and OS compared to ofatumumab in the RESONATE trial (18). At a median of 16-months follow up, only 17.9% of patients in the ibrutinib arm had progressed and only 8.2% had died (28). Outcomes for the 17p

deletion subgroup were similar. Therefore, extrapolation of PFS and OS data beyond the trial period was necessary.

To extrapolate patient-level data from RESONATE, the 16-month data were analysed and fitted with commonly used distributions such as exponential, Weibull, log-normal, and log-logistic (143) (144). Goodness of fit was tested using statistical criteria (Akaike information criteria [AIC] and Bayesian information criteria [BIC]). Additionally, observed curves were visually compared to the predicted distributions, and the long-term projections were assessed for clinical plausibility. The resulting curve fittings were used to inform outcomes in the model (in place of KM data).

Area under the PFS and OS curve were used to calculate the proportion of patients in health states at given time points (see Section 5.3.2), which drove clinical and QALY outcomes in the model.

For comparisons with non-trial comparators (PC, BR, and IR proxied by IO), projections of ibrutinib PFS and OS curves were used as reference curves to which comparator HRs were applied. Projection of the ofatumumab PFS curve was used to inform the ofatumumab PFS in the model. However, due to the fact that a significant number of ofatumumab patients had progressed and subsequently crossed over to the ibrutinib arm (n=116, 59%) the OS from the ofatumumab arm was contaminated by crossover. Therefore, the ofatumumab OS was estimated by applying a crossover-adjusted HR to the ibrutinib OS curve (see Section 4.4 for a detailed description of the RESONATE crossover adjustment).

More details on the parametric fitting process and results are provided below.

Extrapolation of PFS (ibrutinib and ofatumumab)

All patients

The AIC/BIC from the parametric fittings for the PFS of ibrutinib and ofatumumab suggest that Weibull is the best fit for both the joint fit with treatment as a covariate and the separate fit (Table 51). It should be noted, however, that the AIC/BIC are very similar across the distributions for thhe ibrutinib arm separate fit. A visual assessment of the long-term projection of different parametric functions shows that a significant number of ibrutinib patients remain in PFS at 5 years with exponential, log normal and log logistic distributions (Figure 28). For this reason, a Weibull distribution may provide the most plausible projection.

Visual assessment indicated that the ofatumumab and ibrutinib arms had different progression trends and, accordingly, when Weibull functions were fit separately to each arm (instead of using a combined fit), the resulting shape parameters differed considerably (1.30 [SE 0.19] for ibrutinib vs. 1.77 [SE 0.12] for ofatumumab). Therefore, Weibull with a separate fit for each treatment arm was used for the projection of PFS as the base case, which provides a conservative but reasonable long-term projection. Given that most patients had progressed in the ofatumumab arm, the projection has a greater level of certainty. In the ibrutinib arm, an exponential fit is used in a sensitivity analysis based on BIC, which provides a less conservative long-term projection of the possible impact of ibrutinib on PFS.

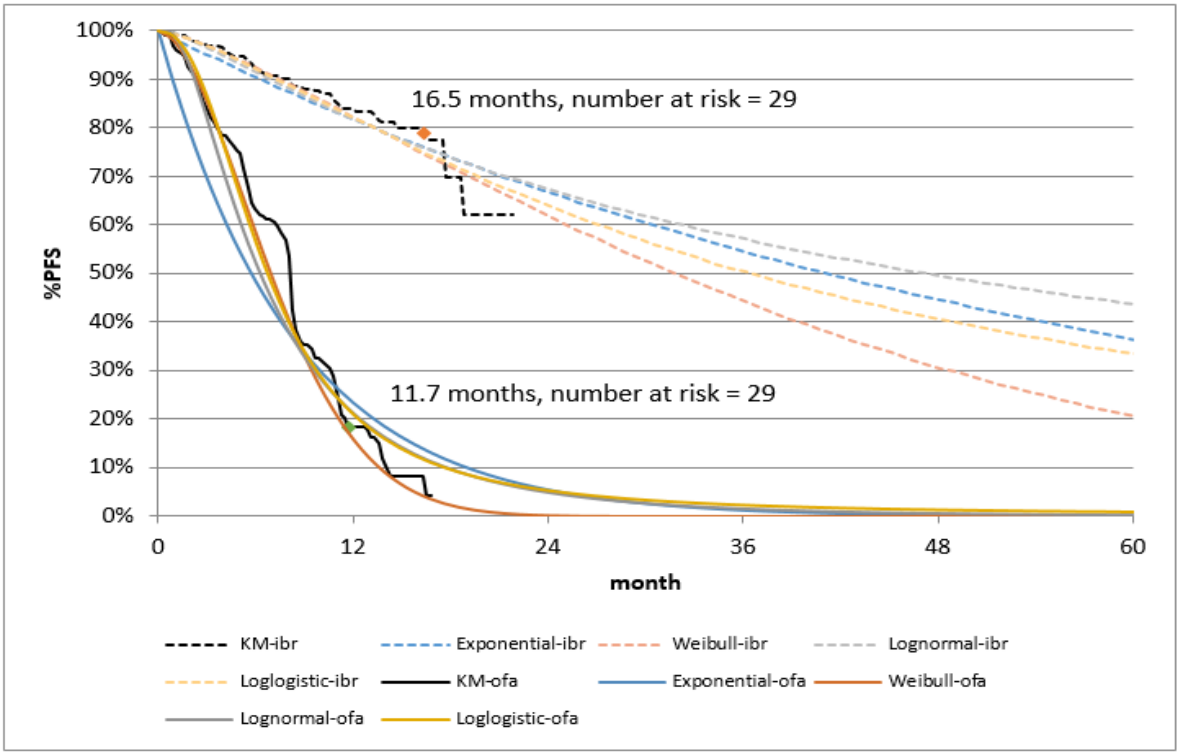
Table 51: AIC and BIC for PFS parametric fitting – all patients*

	Ibrutinib (Separate)		Ofatumumab (Separate)		Joint Fit	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	**267.64**	**274.19**	**411.93**	**418.49**	**681.51**	**693.42**
Lognormal	269.31	275.86	447.36	453.92	738.56	750.46
Log logistic	267.85	274.39	434.04	440.6	711.43	723.34
Exponential	268.43	271.71	469.98	473.25	738.41	746.35

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

*lower AIC or BIC value indicate better statistical fit

Figure 28: Comparison of PFS long-term projection with different parametric functions (separate fit) – all patients



17p deletion subgroup

For the 17p deletion subgroup, the AIC/BIC (Table 52) again are very similar across the distributions for fit to the ibrutinib arm. A visual assessment of the long-term projection of different parametric functions shows that a significant number of ibrutinib patients remain in PFS at 5 years with exponential, log normal and log logistic distributions (Figure 29). For this reason, a Weibull distribution provides the most clinically plausible projection.

The AIC/BIC for the ofatumumab arm shows that Weibull is the best fit. Given that most patients had progressed in the ofatumumab arm, the projection has a greater level of certainty.

Table 52: AIC and BIC for PFS parametric fitting – 17p deletion subgroup*

	Ibrutinib		Ofatumumab	
	AIC	BIC	AIC	BIC
Weibull	268.78	278.60	**409.99**	**419.82**
Lognormal	269.09	278.91	441.88	451.72
Log logistic	**268.70**	278.52	427.69	437.53
Exponential	269.52	**276.07**	469.15	475.70

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

*lower AIC or BIC value indicate better statistical fit

Figure 29: Comparison of PFS long-term projection with different parametric functions– Ibrutinib 17p deletion subgroup

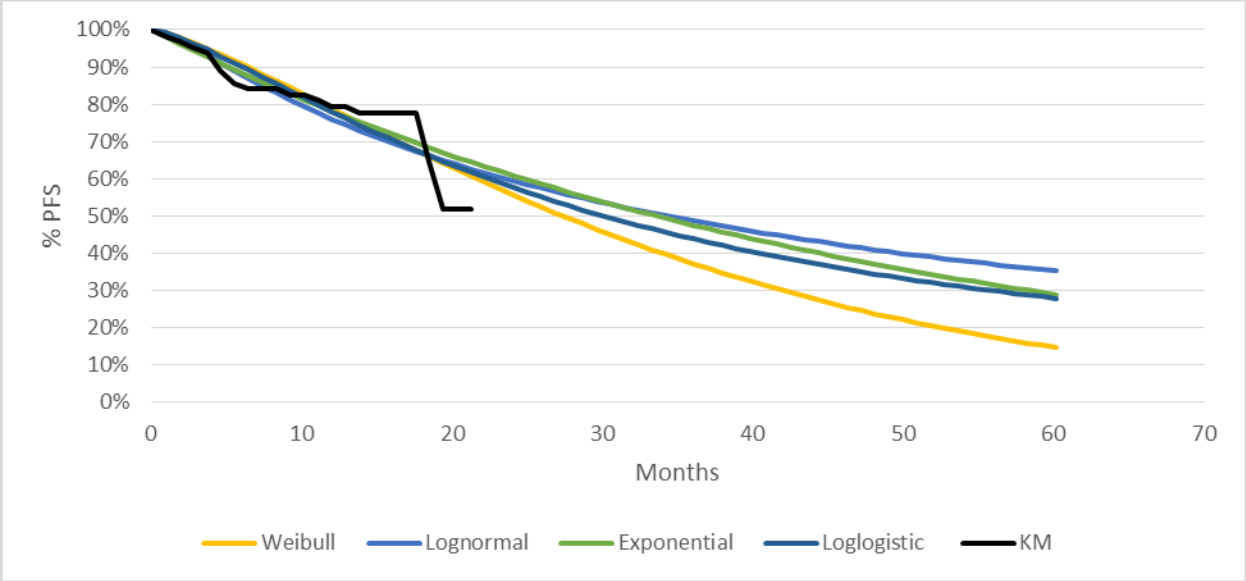
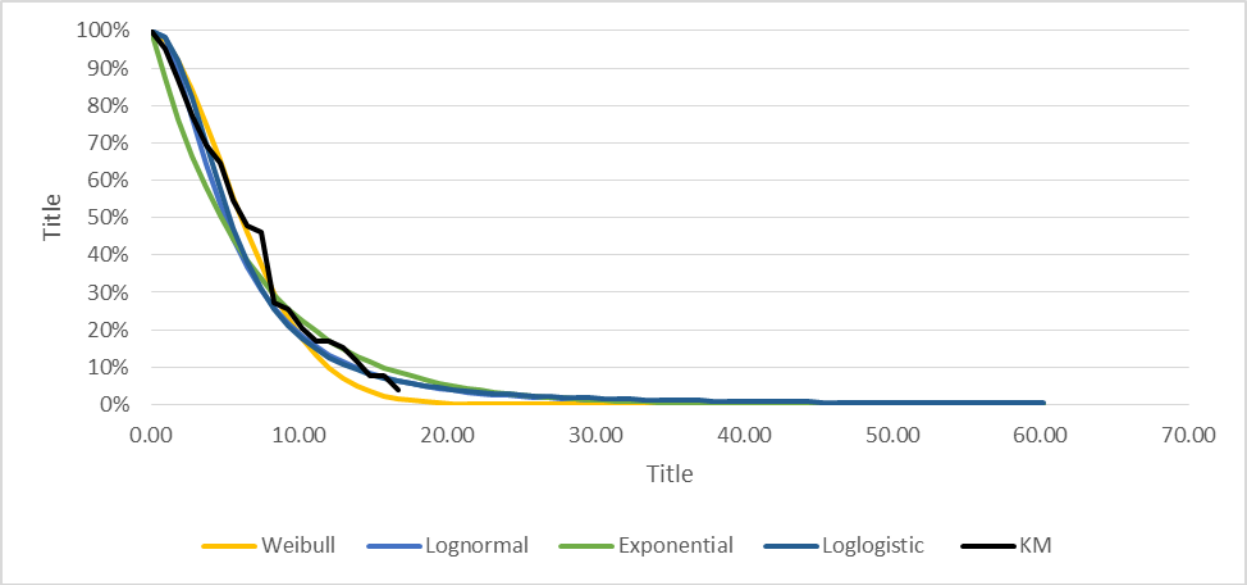


Figure 30: Comparison of PFS long-term projection with different parametric functions– ofatumumab 17p deletion subgroup



Extrapolation of OS (ibrutinib)

All patients

Goodness of fit was tested using AIC and BIC statistical criteria. Additionally, observed curves were graphically compared to the predicted distributions, and the long-term projections were assessed for clinical plausibility. As the AIC/BIC statistics of parametric functions fitted to the observed OS of the ibrutinib arm showed small differences across distributions (Table 53), visual inspection was also used to determine which functional forum best fit the observed data during the trial period.

Given the uncertainty associated with the long-term projection of OS beyond the clinical trial period, two different options for projecting OS were included in the model:

1. Lognormal fit for the first 3 years + exponential fit thereafter (base case)

OS data for R/R CLL patients from the ibrutinib 1102/1103 trial, which had a similar patient population as RESONATE but provided longer follow up (44 months) (22) (23), were used to help determine the appropriate parametric functions for the ibrutinib arm. The OS of ibrutinib from the RESONATE trial is similar to the OS from the 1102/1103 trial (Figure 31) and the lognormal prediction from RESONATE matches the KM curve of OS from the ibrutinib 1102/1103 trial. However, long-term projection of lognormal may not be clinically plausible, given that this distribution has a decreasing hazard in the long-term. Therefore, lognormal was used to inform outcomes only for 3 years based on observations from the 1102/1103 trial. After that time point, the exponential distribution, which has the lowest AIC/BIC was used for the remaining projection of OS. It is important to note that exponential and Weibull distributions provide similar projection in both the short term and long term.

2. Weibull (sensitivity scenario)

A Weibull function is commonly used in oncology for the projections of survival. Due to similar AIC/BIC across different parametric functions, Weibull is tested in a scenario analysis.

Table 53: AIC and BIC for ibrutinib OS parametric fitting

	AIC	BIC
Weibull	214.63	221.18
Lognormal	214.21	220.76
Log logistic	214.46	221.01
Exponential	**212.66**	**215.93**

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Lower AIC or BIC value indicates better statistical fit

Figure 31: Comparison of OS projection with different parametric functions - ibrutinib

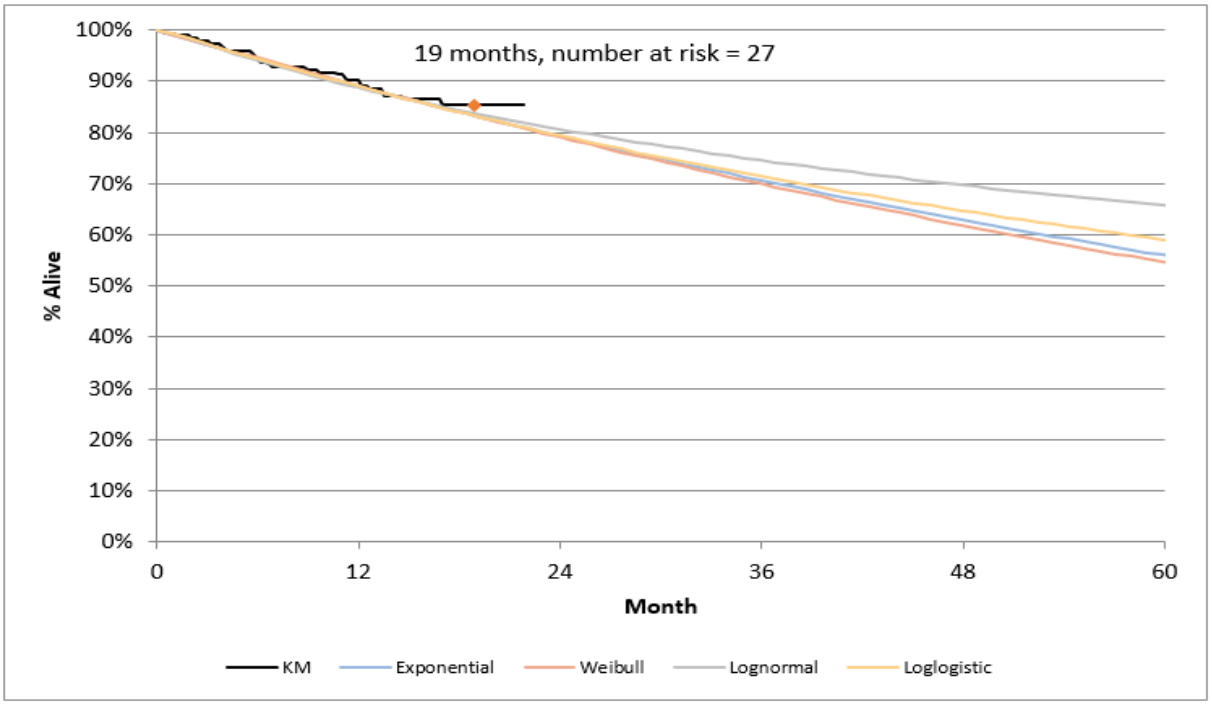
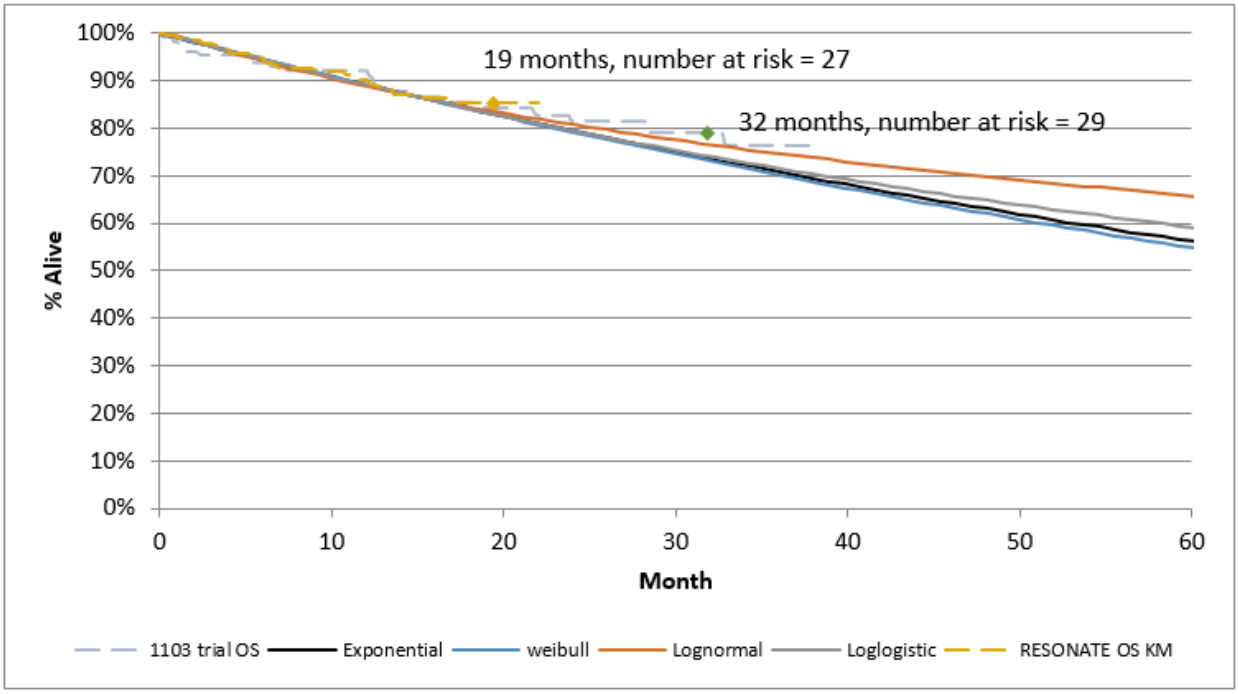


Figure 32: Comparison of ibrutinib OS projection from RESONATE Trial with KM data from 1102/1103 trial



17p deletion subgroup

For the ibrutinib 17p deletion subgroup survival, the AIC/BIC statistics of parametric functions fitted to the observed OS of the ibrutinib arm again showed small differences across distributions (Table 54). Visual inspection was also used to determine which functional form best fit the observed data during the trial period. An exponential function is used in the model analysis as it provides the lowest AIC/BIC and is a reasonable and conservative projection in the long-term.

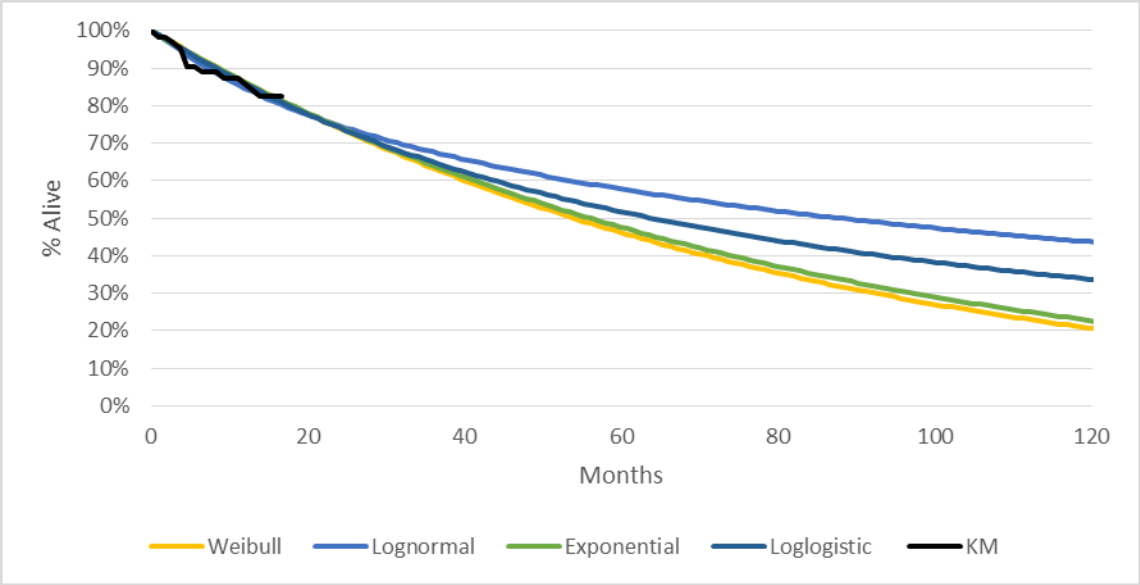
Table 54: AIC and BIC for Ibrutinib OS parametric fitting – 17p deletion subgroup

	AIC	BIC
Weibull	215.68	225.50
Lognormal	214.43	224.25
Log logistic	215.33	225.15
Exponential	**213.70**	**220.25**

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

Lower AIC or BIC value indicates better statistical fit

Figure 33: Comparison of OS projection with different parametric functions ibrutinib – 17p deletion subgroup



Summary of clinical inputs

Table 55 summarises the clinical inputs and data sources used in the economic model. Further details regarding the implementation of each data input are provided in the text below.

Table 55: Summary of clinical input values

	Value (95% CI)	Reference	Reference in submission (section and page number)
PFS Ibrutinib, Weibull			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
PFS 17p deletion Ibrutinib, Weibull			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
PFS ofatumumab Weibull			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
PFS 17p deletion ofatumumab Weibull			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
PFS HRs (ibrutinib vs. comparator)			
PC	[redacted]	ITC based on Osterborg, 2014	Section 4.10

BR	[redacted]	MAIC based on Fischer, 2011	Section 4.10
IO (proxy for IR)	[redacted]	ITC based on Jones, 2014	Section 4.10
OS Ibrutinib Lognormal			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
OS Ibrutinib Exponential			
Intercept	[redacted]	RESONATE	Section 5.3.1
OS 17p deletion Ibrutinib Lognormal			
Intercept	[redacted]	RESONATE	Section 5.3.1
Scale	[redacted]	RESONATE	Section 5.3.1
OS 17p deletion Ibrutinib Exponential			
Intercept	[redacted]	RESONATE	Section 5.3.1
OS HRs (ibrutinib vs. comparator)			
Ofatumumab	[redacted]	RESONATE, adjusted for crossover	Section 4.4
PC	[redacted]	ITC based on Osterborg, 2014	Section 4.10
BR	[redacted]	MAIC based on Fischer, 2011	Section 4.10
IO (proxy for IR)	[redacted]	ITC based on Jones, 2014	Section 4.10
OS HR Del 17p (ibrutinib vs ofatumumab	[redacted]	RESONATE, adjusted for crossover	Section 5.3.1
Subsequent Line of Treatment			
% receiving subsequent treatment	41.9%	Ofatumumab arm of RESONATE (18)	Section 5.3.1
Probability of death during PFS	0.57% per 4 weeks cycle	Estimated from RESONATE (28)	Section 5.3.1

In addition to PFS and OS, the following clinical data were used in the model.

Probability of death during PFS

Probability of death was calculated based on data from the ibrutinib RESONATE trial (combined ibrutinib and ofatumumab patients), resulting in a 0.57% probability of death for every 4 week cycle for all patients in the model. The probabilities of death during the progression-free phase for the comparators were assumed to be the same as those in the RESONATE patients. This parameter was used only to track patients as they moved from PFS into the PPS (i.e. incident progressed patients) in order to assign subsequent treatment, but did not impact overall survival calculations (see section 5.3.2).

Subsequent line of treatment

The model allowed patients to receive a subsequent line of treatment after failure on initial treatment. In UK clinical practice, not all patients will go on to receive subsequent treatment.

The probability of receiving a subsequent line of treatment was based on evidence from the RESONATE trial and validated by UK clinicians (1). Ibrutinib patients in RESONATE went on to subsequent therapy at a lower rate compared with ofatumumab; however, the lower percentage is likely due to fewer patients having progressed on ibrutinib at the time of the trial analysis. More ofatumumab patients experienced PFS events and were thus eligible for subsequent treatment. Nine-month data was used instead of 16-month data, because most ofatumumab patients had crossed over in the 16 month data, which would bias the probability of receiving subsequent treatment for the ofatumumab arm. The proportion of patients who were modelled to receive a subsequent line of treatment is 41.9% (86)**.**

Subsequent line of treatment was modelled to include R+HDMP (50%) and HDMP (50%), informed by UK clinicians (1). Of note, UK clinicians indicated the IR was not likely to be used as a subsequent line of treatment for patients entering PPS in the model.

Patients receiving a subsequent line of treatment were at risk of experiencing a progression event (after which they were modelled to receive BSC). TTP while on subsequent line of treatment was assumed to be the same as the PFS of rituximab from the Furman 2014 trial (30). The Furman trial was selected because its patient population most closely resembles the population included in the RESONATE trial. UK clinical experts indicated that the PFS of the rituximab arm was a reasonable approximation of the duration of time in PFS for patients on subsequent line of treatment (1).

Grade 3 and 4 AEs

AEs affect both costs associated with a drug regimen as well as the health-related quality of life of patients receiving treatment. Grade 3 and 4 AEs were collected from published clinical trial studies for each of the comparator treatment. The AEs that were reported in clinical trials as occurring in ≥5% of patients in at least one of the comparator treatments were considered in the model. UK clinical experts indicated that this inclusion rule was appropriate (1). AEs that were not reported in some trial publications were conservatively assumed to be 0% for calculation purposes.

An important factor to consider when comparing AEs across lines of treatment is time on treatment. Patients treated with ofatumumab in RESONATE had a median duration of treatment of 5.3 months. Accordingly, AEs rarely occurred in ofatumumab patients after this point as patients were not exposed to active treatment. The percentage of patients experiencing AEs while on treatment with ibrutinib is greater than for those receiving ofatumumab due to the fact that ibrutinib's treatment exposure was much longer. An analysis of EAIR of AE was performed and showed that, [redacted]. Similar to ofatumumab, physician's choice is composed of regimens with fixed treatment duration, as is BR. The shorter periods of exposure to drug for these regimens contribute to the relatively low percentage of patients who experienced AEs in comparator trials.

Table 56 below presents the AE data used in the model, with AEs that were not reported marked as "NR".

Table 56: Percentage of patients experiencing AEs by comparator

	Ibrutinib	**Physician's Choice**	**IO** (proxy for IR)	**BR**	**Ofatumumab**
Anaemia	5.6%	3.7%	3.7%	12.0%	7.3%
Diarrhoea	4.6%	NR	NR	20.2%	1.6%
Pneumonia	10.8%	NR	NR	12.7%	5.8%
Hypertension	6.2%	NR	NR	NR	0.5%
Neutropenia	18.5%	8.2%	8.2%	34.1%	13.6%
Thrombocytopenia	5.6%	6.5%	6.5%	13.3%	4.2%
Sepsis	1.5%	NR	NR	NR	1.0%
Reference:	RESONATE trial (18) (28)	Assumed to be the same as BR (Fischer, 2011) (29)	Jones, 2014 (39)	Fischer, 2011 (29)	RESONATE trial (18) (28)
Note: percentage of patients experiencing AEs are not adjusted to account for time on treatment or duration of exposure to drug.					

Abbreviations: AE, adverse event; BR, bendamustine+rituximab; NR, not reported

5.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.

The model uses a survival partition approach to assign patients to different health states; therefore transition probabilities (TPs) were not necessary. The area under the survival curves at each cycle was calculated and used to define the distribution of the patient cohort in each health state.

The partition model approach has been used extensively in oncology since it is particularly suited to conditions in which ongoing risks exist, although the size of these risks may vary over time. Slightly different from the traditional three health-states survival partition model, the PPS state is further stratified to account for the cost implication of subsequent treatment.

PFS state

The overall PFS health state was directly informed by the PFS curves. Incidence of progression in each model cycle was tracked to allow for monitoring of subsequent line of treatment and PFS with subsequent line of treatment. As patients could die directly from the PFS state, death during PFS was incorporated to estimate the incidence of progression. The incidence of progression was calculated as:

$$PFS_{T(n-1)} - PFS_{T(n)} - Death\ during\ PFS_{T(n-1)}$$

In other words, incidence of progression was calculated by subtracting death events during PFS from the PFS events. A constant hazard of death was applied for each 4-week model cycle for patients in the progression-free health states. This calculation was used only to track patients as they moved from the PFS state into the PPS state (i.e. incident progressed patients), but did not impact OS calculations, given that OS was based directly upon OS data collected in trials which would have already accounted for deaths during PFS.

PPS state

The post-progression state is defined by all patients surviving (OS) less those who remain progression free (PFS); thus, the calculation to determine the patients in the progressed state is OS-PFS. OS is informed directly by OS curves projected based on the parametric fitting to RESONATE trial data and HRs for comparators.

During the post-progression stage, a proportion of patients who progress in the model would receive a subsequent line of treatment. The PFS of subsequent treatment is tracked for each incident progressed cohort. Subsequent treatment is included to impact on costs only and is assumed not to impact survival, as survival is estimated based on OS projection using the RESONATE trial and relative treatment effect through ITCs and MAIC.

Patients who did not receive a subsequent line of treatment received BSC immediately after disease progression. The patients who received the subsequent line of treatment switched to

BSC once they experienced further disease progression. The proportion of patients in this health state is calculated with the following equation:

PPS – PFS of subsequent treatment

Death

Death was calculated as:

Death = 1 – OS

To ensure that the survival projected by the parametric function did not exceed that of the general population, age-dependent general population mortality was incorporated into the model. Within each model cycle, the probability of death experienced by CLL patients could not be less than the probability of death of the general population. In cases where the survival projection of the CLL population exceeded that of the general population (e.g., survival extrapolations using functions with long tails), the general population's estimates were used.

5.3.3 If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has 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.

TPs were not used in the economic model. Clinical outcomes were based on time-to-event data, which takes into account changes over time in treatment effect, condition, or disease. See Section 5.3.2 for further details.

5.3.4 If clinical experts have assessed the applicability of the clinical parameters or approximated any of the clinical parameters, provide the following details:

- 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 whose opinion was sought
- the background information provided and its consistency with all 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 experts were consulted to validate a number of clinical assumptions including extrapolation of the clinical parameters to ensure clinical plausibility from the UK clinical practice perspective.

The expert opinions were obtained as follows:

- Eight clinicians were invited to participate; four were available and able to attend.
- Clinicians with no conflict of interest were approached to ask for their attendance at an advisory board hosted by Janssen.
- One advisory board was held in September 2015 with the objective of validating (a) clinical assumptions proposed for inclusion within the cost-effectiveness model presented in this appraisal and (b) the strategy for a CLL treatment submission.

The Advisory Board was conducted in accordance with the ABPI guidelines (145). The clinical experts declared that they had no conflict of interest but were contracted and paid for their time. At the consensus meeting, the panel were presented with suggested approaches of addressing uncertainties within the economic modelling to provide a foundation for discussion. This process involved individuals voicing their opinion on each value sequentially, then if there was discrepancy, a discussion followed. After discussion, the consensus panel was then asked to state their opinion. This process continued until the panel agreed.

The advisory board sought opinion from the clinical experts on the following points:

- The CLL population
- Ibrutinib's position within the CLL treatment landscape
- Validation of extrapolated clinical data
- Relevant comparators for assessment within this appraisal and the most robust clinical evidence to demonstrate comparative efficacy
- Indirect comparisons
- Assumptions on subsequent therapy used in patients who may eventually fail ibrutinib
- AEs in CLL and their management within UK clinical practice

5.4 *Measurement and valuation of health effects*

Health-related quality-of-life data from clinical trials

5.4.1 In a table, summarise the utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6. Justify the choice of utility values, giving consideration to the reference case. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed. See below for a suggested table format.

Table 57 summarises all utility values used and provides justification for their selection and use in the model.

The baseline utility for patients in the PFS state ([redacted]) was informed by an analysis of EQ-5D-5L data collected in RESONATE and represents the weighted average EQ-5D-5L score for patients who remained in the PFS health state from weeks 4 to 60. The utility value is not age-adjusted as it was collected from the RESONATE trial directly, representing the median age of an R/R CLL patient population. After progressing and entering the PPS health state, patients in the model were assigned a utility value informed by the baseline EQ-5D-5L score of patients entering the RESONATE trial ([redacted]) minus a utility decrement associated with progression (0.098), resulting in a utility value of [redacted] for the PPS health state. Utility decrements associated with AEs (ranging from 0.123 to 0.195) were applied to patients as they experienced adverse events in the model. The utility decrements associated with progression and adverse events were based on published literature, as analysis of RESONATE EQ-5D-5L data did not identify differences for these events.

A summary of the RESONATE EQ-5D-5L analysis is presented in Section 5.4.1, with further details provided in Appendix 12. A summary of the SLR to identify utility data from clinical trials and published studies is presented in Section 5.4.3 and Appendix 8 and Appendix 11, with relevant results summarised in Section 5.4.4 and compared in Section 5.5.5.

In a sensitivity analysis, utility increments associated with CR and PR were assigned to patients in PFS depending on their best eventual response to treatment. Utility increments for response were based on published studies and discussed in Section 5.4.11.

Table 57: Summary of utility inputs in economic model

State	Utility increment, decrement, or disutility from baseline: mean (SE)	Utility value for health state: mean (SE)	Reference	Reference in submission	Justification
Health States					
Baseline utility for patients in PFS	Not applicable	[redacted]	RESONATE (18) (86)	Section 5.4.1	Based on RESONATE EQ-5D-5L, consistent with NICE reference case and reflective of RESONATE trial population
Baseline utility for patients in PPS	-0.098	[redacted]	Beusterien, 2010 (146)	Section 5.4.9	Based on standard gamble, which is consistent with NICE reference case; utilities elicited from UK general population with reference to CLL-specific health states
	Decrement subtracted from baseline utility value of [redacted]		RESONATE	Section 5.4.1	Based on RESONATE EQ-5D-5L, consistent with NICE reference case and reflective of RESONATE trial population
Adverse Events					
Anaemia	-0.088 (0.009)	Not applicable	Beusterien, 2010 (146)	Section 5.4.6	Based on standard gamble, which is consistent with NICE reference case; utilities elicited from UK general population with reference to CLL-specific health states
Diarrhoea	-0.195 (0.020)	Not applicable	Assumption		Decrements for these AEs were not available in published literature; assumed to incur the highest utility decrement
Pneumonia	-0.195 (0.020)	Not applicable	Assumption		
Hypertension	-0.195 (0.020)	Not applicable	Assumption		
Neutropenia	-0.185 (0.019)	Not applicable	Tolley, 2013 (147)		Based on TTO, which is consistent with NICE reference case; utilities elicited from UK general population with reference to late-stage CLL-specific health states
Thrombocytopenia	-0.123 (0.012)	Not applicable	Tolley, 2013 (147)		
Sepsis	-0.195 (0.020)	Not applicable	Tolley, 2013 (147)		
Utility values for sensitivity analysis					
Utility increment due to CR*	0.127 (0.013)	0.890 (SE TBD)	Beusterien, 2010 (146)	5.4.11	Based on standard gamble, which is consistent with NICE reference case; utilities elicited from UK general population with reference to CLL-specific health states
Utility increment due to PR*	0.059 (0.006)	0.822 (SE TBD)	Beusterien, 2010 (146)		

HS, health state; AR, adverse reaction
*Used only insensitivity analysis; applied to baseline utility from RESONATE of [redacted]

5.4.2 If health-related quality-of-life (HRQL) data were collected in the clinical trials identified in section 4, comment on whether the data are consistent with the reference case. Consider the following points, but note that this 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.

EQ-5D-5L data was collected in RESONATE at baseline, every 4 weeks until week 24, and every 12 weeks thereafter. A total of 165 patients in the 195 patient ITT-population completed the baseline EQ-5D-5L survey. These data were analysed to derive utility inputs that could be used to inform utilities in the economic model (see Appendix 12 for the full analysis). Results from the analysis were used to inform baseline utility and utility during PFS in the model.

Baseline utility and utility during PFS

Analysis of RESONATE EQ-5D-5L data demonstrated that at baseline, as patients entered the RESONATE trial, patients had an average utility of [redacted]. However, utility for patients who remained in PFS was found to fluctuate over time, which may reflect the fact that patients who were sicker would tend to progress more quickly and would no longer contribute to the average utility of the PFS cohort in later cycles of data collection. In order to account for this dynamic movement of patients, a weighted average of the utility scores for patients remaining in PFS between week 4 and week 60 was calculated to be [redacted] and used as the utility value for all patients for the duration of the time patients spent in PFS.

The utility for patients at baseline in the RESONATE trial [redacted] was used to inform the baseline utility for patients after the PPS health state, in combination with a utility decrement associated with progression.

Changes in utility due to response, AEs and progression

The analysis of the RESONATE EQ-5D-5L data did not identify utility benefit associated with response, disutility associated with AEs or disutility associated with progression. Potential reasons for this are described below. More generally, EQ-5D-

5L may not be sensitive enough to capture certain utility changes, especially in this population (148). For example, fatigue is a common treatment-related AE in CLL and the analysis of PROs from the RESONATE trial suggests that ibrutinib patients experienced a significant reduction in fatigue compared to the ofatumumab arm. However, the EQ-5D is not able to capture the impact of fatigue on patients' utility.

Utility increments due to response

The high rate of response to ibrutinib demonstrated in RESONATE and the fact that non-responders tend to progress more quickly may have contributed to the lack of a signal associated with response. Some of the benefits of response may have been captured in the background utility scores of patients remaining in PFS, as patients who respond to treatment are likely to remain in PFS longer than non-responders.

Utility decrements due to AEs

EQ-5D-5L measurements were not scheduled to coincide with occurrence of adverse events and, therefore, disutility associated with AEs may be partially reflected in the background utility scores. Furthermore, many Grade 3 and 4 AEs occurred relatively rarely in the RESONATE trial.

Utility decrement due to progression

Little EQ-5D-5L data were collected in RESONATE after patients experienced disease progression.

Accordingly, decrements associated with utility and disease progression were sourced from published trials (see Sections 5.4.3, 5.4.5, and 5.4.9). In the base case, utility increments associated with response were not incorporated, but instead the weighted average utility score of patients remaining in PFS informed utility for the PFS health state, which likely captured some benefit of response. Published utility increments associated with response were tested in a sensitivity analysis.

Details of the analysis of RESONATE EQ-5D-5L data are presented in Appendix 12

Mapping

5.4.3 If applicable, describe the mapping methods used to estimate health state utility values from the quality-of-life data collected in clinical trials. Please include the following information:

- which tool was mapped from and onto which other tool (for example, SF-36 to EQ-5D)
- details of the methodology used
- details of validation of the mapping technique

- if the mapping technique is published or has been used in other NICE technology appraisals for similar diseases or health conditions.

Mapping has not been used to estimate HRQOL as EQ-5D utility data were collected in the clinical trial.

Health-related quality-of-life studies

5.4.4 Describe how systematic searches for relevant HRQL data were done. Consider published and unpublished studies, including any original research commissioned for the 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 an appendix.

A SLR was conducted in accordance with CRD standards based on a pre-approved protocol in literature databases (listed below) to identify HRQOL outcomes related to the treatment of R/R CLL patients with any chemotherapeutic, biologic or investigational pharmaceutical agents. The databases searched include:

- MEDLINE (via PubMed) and MEDLINE (R) In-process (via PubMed),
- Embase, and Embase In-process
- CENTRAL
- Database of Abstracts of Reviews of Effects (DARE)
- National Health Service Economic Evaluation Database (NHS EED)
- National Health Services Health Technology assessment (HTA) database,
- EconLit

The search algorithms used in these databases were generated using the PICOS framework (Population, Intervention, Comparators, Outcomes, Study design) in line with the research questions. Search algorithms were tailored to identify studies published as of 03 June 2015. All searches were run without limitations (e.g. no date or language limits). Non-relevant designs (i.e., comments or editorials) were removed from the search hits prior to review of the abstracts.

Additional searches were conducted via the Cochrane Library and the above databases for high-quality, recently conducted systematic reviews (published from 2011 to 2015) to serve as supplemental data sources.

Finally, bibliographies of relevant systematic review articles published since 2011 and the bibliographies of accepted studies were also reviewed to obtain any additional, relevant references.

In addition to the above searches within key databases, 'grey' literature (i.e., material that can be referenced but is not typically published in peer-reviewed, database-indexed medical journals) was also searched for relevant meeting abstracts or posters.. Proceedings from the past three years (as available) for the follow key conferences were reviewed:

- ASCO (2013–2015): http://am.asco.org/
- ASH (2012–2014): http://www.hematology.org/Annual-Meeting/
- EHA (2013–2015): http://www.ehaweb.org/
- ESMO (2012–2013): http://www.esmo.org/Conferences/ESMO-2014-Congress
- ISPOR (2013–2015): http://www.ispor.org/

Search strategies were developed in line with the NICE Methods Guide and are provided in Appendix 8.

Records identified from the searches underwent two rounds of screening according to pre-specified inclusion/exclusion criteria (see Appendix 8). In the first round, two independent investigators evaluated the title/abstracts of all unique records. In the second round, full-texts/publications of all records that met in the inclusion criteria during the title/abstract screening were retrieved and reviewed by two independent investigators. None of the exclusion criteria and all of the protocol-specified inclusion criteria had to be met for a record to have passed this level. During both rounds of the screening process, discrepancies were resolved through consensus by a third investigator.

Relevant data elements were extracted by one investigator, and validated by a second independent investigator. All discrepancies were resolved in discussion with a third investigator. A number of control measures were put in place to ensure the quality and consistency of data extraction. These include pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcomes measures to be extracted from the full papers. The results of this process are presented in the section that follows, Section 5.4.4.

5.4.5 Tabulate the details of the studies in which HRQL was measured.

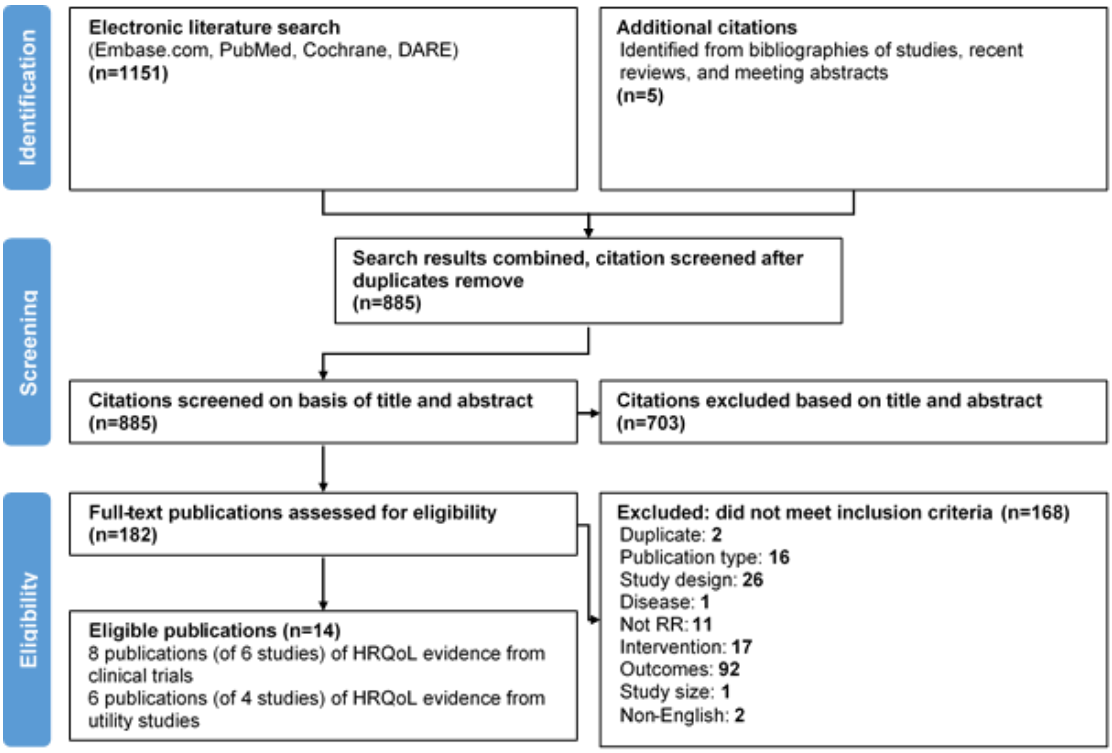
Include the following, but note that this list is not exhaustive:

- population in which health effects were measured
- information on recruitment (for example, participants of a clinical trial, approximations from clinical experts, utility elicitation exercises including members of the general public or patients)
- interventions and comparators
- sample size
- response rates
- description of health states
- adverse reactions

- appropriateness of health states given the 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.

Eight hundred and eighty-five publications were reviewed to identify studies that reported utility and HRQL data after the removal of duplicate citations. Studies were examined for the inclusion of utility or utility input values, patient-reported outcomes (PROs), and HRQL outcomes (including the measures, values, or changes in values of PRO/HRQL scores). Of the 182 citations accepted during abstract screening, 14 met all inclusion and no exclusion criteria. Six studies (represented in eight publications) reported HRQOL data collected in clinical trials, and four studies (represented in six publications) reported utilities based on HRQL data. Figure 34 below illustrates the process of eliminating references based on the protocol.

Figure 34: PRISMA flow diagram HRQOL analyses studies



A total of 10 studies (eight publications of six clinical trials identified in Section 5.1 and six publications of four utility studies) (146, 147, 149-157) were identified that reported HRQOL evidence in a R/R CLL population.

Only one clinical trial publication (153) reported data appropriate for use in cost-effectiveness analysis (using EQ-5D as a method of valuation); other clinical trials used disease-specific measures, such as Functional Assessment of Cancer Therapy questionnaires (151, 152, 154); Quality-Adjusted Time Without Symptoms of disease and Toxicity (Q-TWiST) (149) and EORTC QLQ-C30 (151), and no mapping was used to derive utility values from trial data.

Five publications of utility studies were identified, two of which reported results from the same study (146, 155). One study reported data relevant to a US population, which was not relevant to the current decision analysis (156); the other four publications reported data based on UK-specific populations based on generic, validated methods of utility valuation consistent with the NICE reference case (146, 147, 155, 157).

Appendix 12 presents the EQ-5D data extracted from the Perard et al. 2015 publication; it also presents data extracted from the four utility publications relevant to the UK and NICE reference case.

5.4.6 Highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Clinical trial utility data were available only from RESONATE (86) (18) and Perard, 2015 (153). From RESONATE, a baseline utility of [redacted] and a utility for patients in PFS of [redacted] could be derived. Perard, 2015 (153) reported an on-treatment utility of 0.748 (SE 0.159) for rituximab and an on-treatment utility of 0.8127 for IR. While it is not possible to compare these utilities directly, as the RESONATE utilities are not treatment specific while the Perard utilities are, generally the utility scores are consistent for R/R CLL patients on-treatment.

Utility data corresponding to similar health states (e.g. utility during PFS, utility while "on treatment") were available from Beusterien et al., 2010 (146), Davies, et al., 2013 (155), and Kosmas, et al., 2015 (157). Beusterien et al., 2010 and Davies 2013 reported a second-line treatment utility of 0.71 (SE 0.17). This value is lower than those from clinical trials, which may reflect the trend that utilities elicited from members of the general population tend to be lower than those generated by patients in oncology trials (148). Kosmas et al., 2015 reported utility scores of 0.71 (SD 0.23) and 0.55 (SD 0.25) for PFS without second-line therapy and PFS on second-line therapy. Given that data from both RESONATE and Perard, et al., indicate higher utility while patients are on treatment, the health states used to elicit utilities in the Kosmas study may not be comparable to the "on treatment" experience of patients in clinical trials. The Kosmas paper does not provide details on the "on treatment" vs. "off treatment" health state descriptions.. Utility values reported in Tolley et al., 2013 (147) were based on health states representing a double refractory population, which represents a qualitatively less fit population than RESONATE. Accordingly, the absolute values from Tolley 2013 were not considered for the current analysis.

Adverse reactions

5.4.7 Describe how adverse reactions affect HRQL. The effect of adverse reactions on HRQL should be explored regardless of whether they are included in a cost-effectiveness analysis in the base case analysis. Any exclusion of the effect of adverse reactions on HRQL in the cost-effectiveness analysis should be fully justified.

As discussed, utility decrements associated with AEs were not identified in an analysis of RESONATE EQ-5D-5L data. Published sources of data to inform disutilities associated with AE were therefore sought for each of the AEs included in the economic model (see Section 5.3.1. Publications identified by the SLR of HRQOL studies (see Sections 5.4.3 and 5.4.4) were reviewed to identify inputs that could be used in the model. Both Beusterien, 2010 (146) and Tolley, 2013 (147) elicited utilities from the UK general population using generic, validated methods consistent with the NICE reference case, the health states used in both studies were specific to CLL, and both reported decrements for AEs relevant to the current analysis. Tolley, 2013 (147) elicited utility values for a double refractory CLL population, which makes its absolute utility values less relevant to the current analysis. However, the relative disutility of an AE vs. baseline utility based on Tolley utility values was considered for use in the economic model. No data were available to inform disutilities for diarrhoea, pneumonia and hypertension. It was assumed that diarrhoea would incur the same disutility as infection (the highest utility decrement) and febrile neutropenia and leukopenia would incur the same disutility as thrombocytopenia.

Given that the RESONATE-derived baseline utility differed from the baseline utility reported in published studies, the model implements proportional (rather than absolute) decrements based on the relationship between the baseline and disutility values in published studies. Disutilities were applied as one-time decrements in a patient's current utility value at the time they experienced the AE for a duration of 14 days based on clinical expert opinion solicited from the September 2015 advisory board (1).

As the utility during PFS was collected directly from the RESONATE trial, disutility associated with AEs may be partially reflected in the background utility scores. Applying additional utility decrements for AEs to patients on ibrutinib or ofatumumab in the model may result in double counting of the AE disutility effect. In the base case, utility decrements associated with AEs are applied, which is a conservative approach. In a sensitivity analysis, the duration of AE disutility is reduced to 0 (i.e. no AE disutility).

Table 58: Utility decrement for AEs

AE	Mean	SE	Source
Anaemia	-0.088	0.009	Beusterien (2010) (146)
Diarrhoea	-0.195	0.020	No data; assumed to be the

Pneumonia	-0.195	0.020	same as severe infection (AE with the highest utility decrement)
Hypertension	-0.195	0.020	
Neutropenia	-0.185	0.019	Tolley 2013 (147)
Thrombocytopenia	-0.123	0.012	Tolley 2013 (147)
Sepsis	-0.195	0.020	Tolley 2013 (147) (utility decrement for severe infection)

Abbreviations: AE, Adverse event; SE, Standard error

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.8 Define what a patient experiences in the health states in terms of HRQL in the cost-effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients' quality of life.

Overall, patients in a progression-free health state tend to have a better standard of QOL than patients in post-progression. This has been demonstrated in numerous utility studies, in which progressive disease has been rated much lower than PFS health states by both patients and the UK general population (147) (157) (146). While there is some evidence to suggest that HRQOL within PFS may depend on a patients response status (146) (147) or their specific treatment type (153), analysis of RESONATE EQ-5D-5L did not identify a statistically significant impact of either factor, potentially due to a lack of sensitivity of the EQ-5D-5L tool to this condition. Furthermore, differences in utility according to type of treatment may reflect differences in occurrences of AEs, which are taken into account separately in the economic analysis. To be consistent with the RESONATE EQ-5D-5L data analysis and avoid potential double-counting of treatment-related AEs, all patients were modelled to have the same utility during the PFS health state.

In the progressed health state, it is possible that patients might experience a significant drop in HRQOL in the final few weeks of life during terminal care. However, there were no published utility data or clinical trial data to inform such an input for the model. Furthermore, since most patients will experience the terminal care stage in the model by the end of the time horizon, this drop in HRQOL would not be a differentiating factor between treatment arms. Therefore, the model does not account for any HRQOL changes incurred during terminal care.

5.4.9 Clarify whether HRQL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition.

QOL is modelled to remain constant over time within a health state. Statistical analysis of RESONATE EQ-5D-5L indicated that utility for patients who remained in PFS was higher than at baseline. Instead of trying to model this as a dynamic factor

over time, a single, constant utility value was derived from the PFS utility data using a weighted average approach (see Section 5.4.1). As patients progress and move from the PFS health state to the PPS health state, utility is modelled to decrease.

Progression is a key event in the CLL clinical pathway (see Section 3.1) and indicates the failure of therapy and recurrence of symptomatic disease. Accordingly, utility is expected to be adversely impacted by progression. The utility decrement applied in the model at the point of progression is described in Section 5.4.9.

5.4.10 If appropriate, describe whether the baseline HRQL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline.

Patients entered the model with a baseline utility of 0.799, which reflects the weighted average utility for patients in the RESONATE trial who remain in PFS over time. Patients who experienced disease progression and left the PFS health state were assigned a new baseline utility of [redacted], based on the average baseline utility score for patients in the RESONATE trial, to which a utility decrement of 0.098 [redacted] was applied to give a utility of [redacted]. This utility decrement was derived from Beusterien, 2010 (146), because RESONATE EQ-5D-5L data were not sufficient to derive a post-progression utility decrement. Because baseline utility values in Beusterien and RESONATE differed, a relative, rather than absolute, utility decrement for post-progression was applied.

5.4.11 If the health state utility values used in the cost-effectiveness analysis have been adjusted, describe how and why they have been adjusted, including the methodologies used.

Baseline utility was derived from RESONATE EQ-5D-5L data (as described in Section 5.4.1 and Appendix 12). A utility decrement due to disease progression and disutilities due to AEs were taken from published sources. Given that the RESONATE-derived baseline utility differed from the baseline utility reported in published studies, the model uses proportional (rather than absolute) decrements and disutilities based upon the relationship between the baseline and decrement and disutility values in published studies.

5.4.12 Identify any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis and explain their exclusion.

Several QOL studies identified in the SLR reported QOL impacts associated with response status, with complete and/or partial responders having higher utility than

non-responders (146, 147, 155). RESONATE EQ-5D-5L data were analysed to identify a signal associated with response status, but no statistically significant difference in utility was found to be related to response (see Appendix 12.) As discussed above, this may have been due to the fact that there were so many responders in the ibrutinib arm of RESONATE and non-responders tended to progress quickly. Accordingly, response-based utility was not considered in the base case of the economic evaluation. A sensitivity analysis was included in which utility during PFS was informed by response-related utility increments identified in the published literature. In this scenario, relative utility increments associated with complete and partial response based on Beusterien, 2010 (146) are applied to a baseline utility of 0.763 for patients in PFS, based on the baseline utility for patients as they entered the RESONATE trial.

5.4.13 If clinical experts assessed the applicability of the health state utility values available or approximated any of values, provide the details (see 5.5 Cost and healthcare resource use identification, measurement and valuation

Not applicable.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 All parameters used to estimate cost effectiveness should be presented clearly in a table with 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.

Drug acquisition and administration, unit costs are presented in Section 5.5.5; the unit costs and schedule of use for each health states are summarised in Table 49.

Resource identification, measurement and valuation studies

5.5.2 Describe how relevant cost and healthcare resource use data for England were identified. Include the search strategy and inclusion criteria, and consider published and unpublished studies to demonstrate how relevant cost and healthcare resource use data for England were identified. The search strategy used should be provided in an appendix. If the systematic search yields limited data

for England, the search strategy may be extended to capture data from other countries. Please give the following details of included studies:

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

A combined search for full economic evaluations and resource studies was carried out (previously reported in Section 5.1.1). The search strategy used has been reported in Appendix 8. Of the 11 studies that met inclusion criteria and did not meet exclusion criteria (121-130), only one study (Cognet, et al., 2014) (122) reported costs relevant to English clinical practice. However, because the publication was only available in abstract form, the reported costs were not described in sufficient detail to be useful to the current analysis.

5.5.3 When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised. Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff. Provide the relevant Healthcare Resource Groups and PbR codes and justify their selection with reference to section 2.

NHS reference costs currently cover a wide variety of conditions in oncology and are the most appropriate for costing purposes. The clinical management of CLL includes routine follow-up care including visits to clinical specialists, tests and monitoring procedures. UK clinical experts indicate that the exact type of visits, tests, and procedures and the frequency of care required depend on a patient's response to treatment (1). The specific types of resources and frequency of use for each response category and health state in the model are detailed in Section 5.5.6 and the appropriate Healthcare Resource Groups (HRG) and PbR codes for each resource are provided.

5.5.4 If clinical experts assessed the applicability of the cost and healthcare resource use values available, or approximated any of

the values used in the cost-effectiveness analysis, provide the details (see section 5.3.4).

To understand UK standard practice for routine follow-up care of patients with R/R CLL, a survey was designed to obtain the types and frequency of medical resource use (MRU) (including visits, procedures, and tests) for an average patient (158). Data was generated via a custom, on-line survey launched in November and December 2014 and 100 actively practicing, NHS haematologists and oncologists were invited to participate. A total of 50 participants (9 oncologists, 24 haematologists and 17 haematologist oncologists) provided complete or partial responses. All participants indicated they actively make treatment decisions about patients with CLL.

The survey presented participants with a brief background of the CLL clinical and treatment pathway, which characterised the major phases of disease (PFS, PPS and OS) and included treatment response, to ensure alignment with the pathway on which the economic model was based. Participants were then asked to complete survey questions with reference to their clinical practice with R/R CLL patients, filling out tables to indicate the types of resources (visits, procedures, and tests) and frequency of resource use in the last 6 months of care for patients in the following stages of disease (consistent with the health states in the model):

- PFS, non-responder/stable disease
- PFS, complete responder
- PFS, partial response
- Post progression on subsequent treatment
- Post progression on BSC

The MRU data collected were analysed to determine what types of resources and with what frequency they are used for patients in different health states. A resource was considered to be relevant to UK clinical practice if more than 50% of clinicians indicated that it was used. To determine the frequency of use mean and median values were calculated for each relevant resource. On certain items, there was a high degree of variation in clinician responses and outlier responses may have introduced bias into the mean values. Therefore, median frequencies were implemented in the model. These values are presented in Section 5.5.6.

Intervention and comparators' costs and resource use

5.5.5 In a table, summarise the cost and associated healthcare resource use of each treatment. A suggested format for a table is provided below. Cross refer to other sections of the submission; for example, drugs costs should be cross-referenced to section 2.3.1. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 5.2.2.

Table 59 presents the drug acquisition costs for ibrutinib and comparator drugs.

Clinical experts were surveyed to assess what types of prophylactic medications are used in combination with each active treatment in the model and whether any additional resources (e.g. monitoring, testing, etc.) specific to treatment type are relevant to UK clinical practice. Feedback indicated that the costs of prophylactic medication and treatment-specific resource use were very minimal and, if anything, would be greater for comparator drugs (1). Due to the minimal impact such costs would have on ICERs and in an effort to reduce complexity, it was conservatively assumed to not consider prophylactic medications or treatment-specific resource use in the economic model.

Table 59: Drug costs

	Concentration	**Tablet or vial size**	**Cost per tablet or vial (£)**
Ibrutinib	140 mg	1	51.10
Bendamustine	25 mg/ml	1 ml	69.45
Rituximab	10 mg/ml	10 ml	174.63
Idelalisib	150 mg	1	51.91
Ofatumumab	20 mg/ml	5 ml	182.00
Chlorambucil	2 mg	25	40.51
Cyclophosphamide	500 mg	1	9.20
Fludarabine	25 mg/ml	2 ml	155.00
Methylprednisolone	2,000 mg/ml	1 ml	32.86
	Value	**Reference**	
Administration cost of IV drug	£265.85 [SE £26.59]	National Schedule of Reference Costs - Year 2013-14- NHS trusts and NHS foundation trusts - Chemotherapy Outpatient (159).	
Mean body surface area (BSA)	1.9 m^2	Clinical trial based value from RESONATE baseline patient characteristics (used for estimating dosing of IV rituximab) as per previous methods used in NICE submissions (135) (160).	

Healthcare resource use associated with routine follow-up care (that is not specific to a given treatment) was considered and is summarised separately in Section 5.5.6.

Drug acquisition costs were calculated for each comparator based on the dosing schedule presented in Table 49. The base case assumes wastage and drug costs

were calculated assuming no vial sharing. Sensitivity analyses around patient weight and level of vial-sharing are described in Section 5.8.9.

Not all patients in the RESONATE trial and other clinical trials received full doses of treatment throughout the duration of the trial. For example, in RESONATE, dose reduction or discontinuation of drug due to tolerability issues resulted in a mean relative dose intensity of 94.8%. To ensure that the doses upon which drug costs were calculated matched the evidence from which clinical inputs were derived, the relative dose intensity from clinical trials was used to calculate ibrutinib and comparator drug costs. The specific inputs and source information for dose intensity are listed in Table 60. Orally administered ibrutinib and idelalisib were modelled to have no administration costs.

Table 60: Dose intensity

	Dosing intensity	**Source**
Ibrutinib	94.8%	RESONATE Trial (86)
PC	95.2%	No data available, assume the same as ofatumumab
IO (proxy for IR)	95.2% for both idelalisib and rituximab	No data available, assume the same as ofatumumab
BR	97% rituximab 97% bendamustine	Fischer et al, 2011 (29) - Rituximab: 30.8% (24.4% + 6.4%) had at least 10% dose reduction. Dosing intensity = 100% - 30.8% * 90% = 97% - Bendamustine: 29.5% (23.1% + 6.4%) had at least 10% dose reduction. Dosing intensity = 100% - 29.5% * 10% = 97%
Ofatumumab	95.2%	RESONATE Trial (86)

Health-state costs and resource use

5.5.6 Summarise and tabulate the costs included in each health state. A suggested format for a table is provided below. Cross refer 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 5.2.2.

Table 61 summarises the routine follow-up resource use associated with the PFS and PPS health states. No costs were applied to the model's "death" health state, but cost associated with terminal care is detailed in Section 5.5.8.

Expert opinion was used to inform the types of resources and frequency of use for each health state (see Section 5.5.4 for details of solicitation of expert opinion.) The costs presented in Table 62 in the "total" rows represent total annual cost for routine follow-up care for patients in a given health state.

Within the PFS health state, costs for routine follow-up care were stratified according to response level achieved by patients in clinical trials. Applying different costs of care according to response level is a common approach in NICE HTAs in similar indications (135), and was used in the recent IR submission for CLL (41).

Table 61 presents the percentage of responders for each comparator and the weighted average cost per year in PFS for each treatment, according to the distribution of response. Ibrutinib's superior response rates translate into lower costs overall for patients in PFS. It is important to note that response rates for PC, IO and BR are based on the relative efficacy of ibrutinib vs. the comparator derived from ITCs, as described in Section 4.10.

Table 61: Cost of MRU (158)

	% complete responder	% partial responder	% non-responder	MRU cost per year in PFS (weighted average of response categories)
Total cost per year	£121	£384	£881	
Ibrutinib	6%	84%	10%	£416
PC	0%	10%	90%	£831
IO (proxy for IR)	0%	85%	15%	£459
BR	4%	29%	67%	£707
Ofatumumab	1%	25%	75%	£756

Table 62: Average, annual per person costs of routine follow-up care by health state

Health states	Category	Resource	Frequency / Duration of use	Unit Cost	Cost reference
PFS – Non-responder/Stable disease	Lab tests and scans	Full blood count	4	£3.00	National Schedule of Reference Costs - Year 2013-14 (161)
		LDH	2	£1.18	
		Blood glucose	0	£1.18	
		Lymphocyte counts	3.5	£3.00	
		Chest X-Ray	2	£29.60	National Schedule of Reference Costs - Year 2013-14 (161)
		Bone marrow exam	1	£338.49	National Schedule of Reference Costs - Year 2013-14 (162)
	Visits	Haematologist visit	4.5	£156.41	National Schedule of Reference Costs - Year 2013-14 (163)
		Inpatient non-surgical/medical visit	2	£1,715.23	National Schedule of Reference Costs - Year 2013-14 (164)
		Nurse Home visit	3	£50.00	Unit Costs of Health and Social Care. PSSRU 2014 (165)
	Procedures	Full blood transfusion	2	£286.83	National Schedule of Reference Costs - Year 2013-14 (164)
		Platelet transfusion	0	£286.83	
		Biopsy	2	£3,103.68	National Schedule of Reference Costs - Year 2013-14 (164)
	Total:			**£881**	
PFS – Complete responders	Lab tests and scans	Full blood count	2	£3.00	National Schedule of Reference Costs - Year 2013-14 (166)
		LDH	2	£1.18	
		Blood glucose	0	£1.18	
		Lymphocyte counts	3.5	£3.00	
		Chest X-Ray	0	£29.60	National Schedule of Reference Costs - Year 2013-14 (161)
		Bone marrow exam	0	£338.49	National Schedule of Reference Costs - Year 2013-14 (162)

	Visits	Haematologist visit	2.26	£156.41	National Schedule of Reference Costs - Year 2013-14 (163)
		Inpatient non-surgical/medical visit	.66	£1,715.23	National Schedule of Reference Costs - Year 2013-14 (164)
		Nurse Home visit	1.5	£50.00	Unit Costs of Health and Social Care. PSSRU 2014 (165)
	Procedures	Full blood transfusion	0	£286.83	National Schedule of Reference Costs - Year 2013-14 (162)
		Platelet transfusion	0	£286.83	
		Biopsy	**0**	**£3,103.68**	National Schedule of Reference Costs - Year 2013-14 (164)
	Total:			**£121**	
PFS – Partial responders	Lab tests and scans	Full blood count	4	£3.00	National Schedule of Reference Costs - Year 2013-14 (166)
		LDH	2.26	£1.18	
		Blood glucose	0	£1.18	
		Lymphocyte counts	7	£3.00	
		Chest X-Ray	1	£29.60	National Schedule of Reference Costs - Year 2013-14 (161)
		Bone marrow exam	1		National Schedule of Reference Costs - Year 2013-14 (162)
	Visits	Haematologist visit	3	£156.41	National Schedule of Reference Costs - Year 2013-14 (163)
		Inpatient non-surgical/medical visit	2	£1,715.23	National Schedule of Reference Costs - Year 2013-14 (164)
		Nurse Home visit	2.64	£50.00	Unit Costs of Health and Social Care. PSSRU 2014 (165)
	Procedures	Full blood transfusion	1	£286.83	National Schedule of Reference Costs - Year 2013-14 (162)
		Platelet transfusion	1	£286.83	
		Biopsy	0	£3,103.68	National Schedule of Reference Costs - Year 2013-14 (164)

	Total:			**£384**	
Subsequent treatment – in PFS	Lab tests and scans	Full blood count	4	£3.00	National Schedule of Reference Costs - Year 2013-14 (166)
		LDH	2	£1.18	
		Blood glucose	0	£1.18	
		Lymphocyte counts	3.2	£3.00	
		Chest X-Ray	2	£29.60	National Schedule of Reference Costs - Year 2013-14 (161)
		Bone marrow exam	0	£38.49	National Schedule of Reference Costs - Year 2013-14 (162)
	Visits	Haematologist visit	4	£156.41	National Schedule of Reference Costs - Year 2013-14 (163)
		Inpatient non-surgical/medical visit	2	£1,715.23	National Schedule of Reference Costs - Year 2013-14 (164)
		Nurse Home visit	2	£50.00	Unit Costs of Health and Social Care. PSSRU 2014 (165)
	Procedures	Full blood transfusion	2	£286.83	National Schedule of Reference Costs - Year 2013-14 (162)
		Platelet transfusion	0	£286.83	
		Biopsy	2	£3,103.68	National Schedule of Reference Costs - Year 2013-14 (164)
	Total:			**£845**	
BSC	Lab tests and scans	Full blood count	4	£3.00	National Schedule of Reference Costs - Year 2013-14 (166)
		LDH	0	£1.18	
		Blood glucose	0	£1.18	
		Lymphocyte counts	0	£3.00	
		Chest X-Ray	0	£29.60	National Schedule of Reference Costs - Year 2013-14 (161)
		Bone marrow exam	0	£338.49	National Schedule of Reference Costs - Year 2013-14 (162)

	Visits	Haematologist visit	4.9	£156.41	National Schedule of Reference Costs - Year 2013-14 (163)
		Inpatient non-surgical/medical visit	1	£1,715.23	National Schedule of Reference Costs - Year 2013-14 (164)
		Nurse Home visit	4	£50.00	Unit Costs of Health and Social Care. PSSRU 2014 (165)
	Procedures	Full blood transfusion	2	£286.83	National Schedule of Reference Costs - Year 2013-14 (162)
		Platelet transfusion	0	£286.83	
		Biopsy	0	£3,103.68	National Schedule of Reference Costs - Year 2013-14 (164)
	Total:			**£250**	

Adverse reaction unit costs and resource use

5.5.7 Summarise and tabulate the costs for each adverse reaction listed in section 4.12 and included in the de novo cost-effectiveness analysis. These should include the costs of therapies identified in section 2.3. A suggested format for a table is provided below. Cross refer to other sections of the submission for the resource costs.

A weighted average per event cost of each adverse event included in the economic model (see Section 5.3.2) were calculated based on NHS reference cost data on the number of resources consumed for an event. Table 63 presents the weighted average cost for each of the seven grade 3 and 4 AEs relevant to the economic model. For a detailed calculation of each weighted average from published NHS costs, refer to Appendix 13.

Table 63: Summary cost of grade 3 and 4 AEs in the economic model

Adverse reactions	Average cost	Cost reference
Anaemia	£3,042.17	Weighted average cost per event based on NHS data (167)
Diarrhoea	£2,153.32	
Pneumonia	£2,733.21	
Neutropenia	£2,386.17	
Thrombocytopenia	£2,191.65	
Sepsis	£2,733.21	
Hypertension	£1,444.31	

The costs of treating grade 3 and 4 AEs were applied to the rates of each event for the intervention and comparators to derive the total cost of AEs associated with each treatment.

Miscellaneous unit costs and resource use

5.5.8 Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere (for example, costs relating to subsequent lines of therapy received after disease progression, personal and social services costs). If none, please state.

Cost of subsequent treatment

A proportion of patients were modelled to receive a subsequent line of active treatment after experiencing progression. Expert clinical opinion was solicited (see Section 5.3.4) regarding:

What types of subsequent treatment patients would receive in UK clinical practice after progression

Of patients who would subsequent treatment, what proportion of patients would receive a given type of subsequent treatment?

Patients modelled to receive subsequent treatment were distributed on the following treatments: 50% of patients received R-HDMP and 50% received rituximab monotherapy. These treatments were informed by clinical expert opinion (1). The drug acquisition and administration costs for these treatments were applied according to the proportion of patients modelled to receive each treatment.

In each model cycle, newly progressed patients leave the PFS state and enter a subsequent line of treatment. Patients in subsequent treatment may progress or die, therefore exiting the subsequent treatment health state. The model is able to capture this dynamic movement of patients by tracking the drug and administration cost of subsequent treatment for each incident cohort of progressed patients. In order to fully capture the costs associated with subsequent lines of treatment, the full cost of each subsequent treatment regimen is applied to the proportion of patients receiving subsequent line of treatment. Subsequent treatments are assumed to be given until (a) death, (b) progression of subsequent treatment or (c) when maximum treatment duration is reached. The PFS of subsequent treatment is assumed to be equivalent to the PFS of the rituximab arm from Furman, 2014 (30) based on clinical expert opinion (1)(see Section 5.3.4).

Terminal care

Terminal care (defined for modelling purposes as the last 3 months of life) can involve specific types of healthcare resource use. The cost of terminal care was applied to all patients who died in the model, regardless of the health state in which death occurs. Terminal care costs were based on a published study of the last 3 months of life care for solid tumour cancer patients (168). Clinical experts suggested that the cost of terminal care would be similar between solid tumour and haematology patients (1). The total cost for terminal care, £7,360 (inflated from 2014), was applied as a one-off cost in the cycle when death occurs.

5.6 *Summary of base case de novo analysis inputs and assumptions*

Summary of base case de novo analysis inputs

5.6.1 Tabulate all variables included in the cost-effectiveness analysis, detailing the values used, range (for example, confidence interval, standard error or distribution) and source. Cross refer to other parts

of the submission. Complete the table below that summarises the variables applied in the economic model.

The table detailing the base case values, range for probabilistic sensitivity analysis (PSA) and source of all variables is presented in Section 5.6.2.

5.6.2 For the base case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible. Describe the rationale if an input chosen in the base case de novo analysis:

- deviates from the NICE reference case or
- is taken from other sources (such as the published literature) rather than data from clinical trials of the technology (when available).

Table 64: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source	Reference to section in submission
Model settings				
Time horizon	20 years	10, 30	Assumption	-
Starting age	67	None	RESONATE trial	Section 4.7
Percentage male	68%	None	RESONATE trial	
Cycle length	4-week cycles to capture treatment cycle of comparator treatments	None		Section 5.2.2
Clinical inputs				
Clinical inputs ibrutinib specific				
Response rate	Ibrutinib: CR:6.2%; ORR: 90.3%	None	RESONATE trial	Section 5.3.1
PFS	Weibull parameters Intercept: [redacted]; Scale: [redacted]; Time unit: week	Variance-covariance tables for the Weibull parametric fitting (using Cholesky decomposition)		Section 5.3, Appendix 10
OS	Lognormal parameters for ibrutinib Intercept: [redacted]; Scale: [redacted]; Time unit: week Exponential parameter for ibrutinib Intercept: [redacted]	Variance-covariance tables (using Cholesky decomposition)		Section 5.3, Appendix 10
Treatment duration of ibrutinib	Treatment discontinuation Kaplan-Meier estimates (ibrutinib arm, RESONATE); PFS projection beyond week 92	Varied with PFS		Section 5.3, Appendix 10
Clinical inputs physician's choice specific				
Odd ratio of complete response	Physician's choice: Assume no CR.	None	Assumption	Section 5.3.1
Odd ratio of overall response	Odd ratio of PC vs. ibrutinib: [redacted]	Lognormal distribution [redacted]	ITC based on RESONATE and Osterborg 2014	Section 5.3.1
HR of PFS	HR ibrutinib vs. PC: [redacted]	Lognormal		Section

		distribution [redacted]		5.3.1
HR of OS	HR ibrutinib vs. PC: [redacted]	Lognormal distribution [redacted]		Section 5.3.1
Clinical inputs IR specific				
Odd ratio of complete response	Idelalisib+rituximab Assume no CR.	None	Assumption	Section 5.3.1
Odd ratio of overall response	Odd ratio of idelalisib+rituximab vs. ibrutinib: [redacted]	Lognormal distribution [redacted]	ITC based on RESONATE and Jones 2015	Section 5.3.1
HR of PFS	HR ibrutinib vs. idelalisib+rituximab: [redacted]	Lognormal distribution [redacted]		
HR of OS	HR ibrutinib vs. idelalisib+rituximab: [redacted]	Lognormal distribution [redacted]		
Clinical inputs BR specific				
Odd ratio of complete response	Odd ratio of BR vs. ibrutinib: [redacted]	Lognormal distribution [redacted]	MAIC based on RESONATE and Fischer 2011	Section 5.3.1
Odd ratio of overall response	Odd ratio of BR vs. ibrutinib: [redacted]	Lognormal distribution [redacted]		
HR of PFS	HR ibrutinib vs. BR: [redacted]	Lognormal distribution BR: [redacted]		
HR of OS	HR ibrutinib vs. BR: [redacted]	Lognormal distribution [redacted]		
Clinical inputs ofatumumab specific				
Response rate	Ofatumumab: CR: 0.5%; PR:24.5%	None	RESONATE trial	Section 5.3.1
Progression free survival	Weibull parameters Intercept: [redacted]; Scale: [redacted]; Time unit: week	Variance-covariance tables for the Weibull parametric fitting (using Cholesky decomposition)		
HR of OS	HR ibrutinib vs. ofatumumab: [redacted]	Lognormal distribution [redacted]		
Other clinical inputs				
Probability of death during PFS per 4-week cycle	0.57%	Standard error assumed 10% of the mean, using beta distribution	RESONATE trial	Section 5.3.1
% receiving	41.9%	Standard error	RESONATE trial	Section

subsequent line of treatment		assumed 10% of the mean, using beta distribution		5.3.1
Subsequent treatment distribution	50% R+HDMP 50% HDMP	Standard error assumed 10% of the mean, using beta distribution	KOL survey	Section 5.3.1
PFS of subsequent treatment	Weibull parameters Intercept: [redacted]; Scale: [redacted]; Time unit: 4 weeks	None	Assume the same as rituximab PFS in Furman 2014	Section 5.3.1
Cost inputs				
Drug and administration cost	See Section 5.5.5 for details	None	BNF	Section 5.5.5
Dosing intensity	Ibrutinib: 94.8% PC: 95.2% IR: 95.2% BR:97% Ofatumumab: 95.2%	None	RESONATE Fischer et al., 2011	Section 5.5.5
Follow up cost and terminal care cost	PFS SD/NR: 881 PFS CR: 121 PFS PR: 384 PPS sub tx: 845 PPS BSC: 250 Terminal care: 7,360	Standard gamma distribution Standard Error assumed 10% of the mean	KOL survey	Section 5.5
Cost of subsequent treatment	See Section 5.5.8 for details	Standard gamma distribution Standard Error assumed 10% of the mean	KOL survey	Section 5.5
Utility inputs				
Utility	PFS: [redacted] Post-progression: [redacted] (= baseline utility [redacted] – utility decrement due to progression 0.098)	Standard error: PFS: 0.005 Baseline utility: 0.012 Beta distribution	RESONATE trial	Section 5.4.5
Utility decrement of AE for ibrutinib	0.003	The total utility decrement associated with AE were varied, instead of the individual AE rate. Varied through the percentage change from baseline of individual AE based on Beta distribution	Beusterien 2010 Tolley 2013	Section 5.4.6
Utility decrement of AE for physician's choice	0.003			
Utility decrement of AE for IR	0.006			
Utility decrement of AE for BR	0.001			

Utility decrement of AE for ofatumumab	0.002			
CI, confidence interval; AE, adverse event				

Assumptions

5.6.3 Provide a list of all assumptions used in the de novo economic model and justify each assumption.

The following assumptions were made in the model:

Assumption	Justification
Clinical assumptions	
Differences in study designs between RESONATE and Österborg trials cannot be accounted for using ITC analyses and may impact outcomes of the analysis. The ITC results are assumed to be applicable to both ibrutinib and PC in the RESONATE CLL population	The data represent the most robust clinical data available.
When MAIC is used for the BR comparison, the MAIC could only adjust for reported patient-level characteristics. The MAIC could not adjust for differences in trial design or non-reported population differences. The MAIC results are assumed to be representative to the ibrutinib and comparators in the RESONATE CLL population	The data represent the most robust clinical data available.
It was assumed that subsequent treatment did not impact on survival, but only impacted on cost	Survival is projected directly from RESONATE trial. Probability of receiving subsequent treatment was assumed the same across all comparators. Clinical experts also confirmed the assumption
For chemoimmunotherapies, all patients discontinued treatment when reaching the maximum treatment duration. Before the maximum treatment duration was reached, it was assumed that disease progression was a proxy for treatment discontinuation	Given the lack of data on treatment discontinuation of comparators, this assumption represents the most robust clinical data available.
The model assumed that all subsequent treatments had the same PFS and used rituximab PFS as a proxy	Clinical expert opinion
Utility assumptions	
Baseline and PFS utility and utility decrement due to disease progression were all independent of comparator treatments.	There was no significant difference by treatment observed in utility based on RESONATE trial data.

It was assumed that the relative utility change from baseline observed in Beusterien et al (146) for AEs applied to the RESONATE population.	The data represent the most robust data available.
AEs were assumed to incur a one-time utility decrement at time 0.	The probabilities of AE were obtained from individual clinical trials. The full treatment durations are captured in comparator trials. No more AEs beyond the trial period are expected. The probabilities of AE for Ibrutinib decreased over time. It is assumed all AEs would occur early at treatment initiation.
Cost assumption	
Medical resource use inputs were obtained from UK KOLs through an on-line survey. The medical resource use of patients in the CR/PR health state was assumed to be the weighted average of CR and PR medical resource use based on the percentage of patients with CR and PR by end of trial.	The data represent the most robust data available.
AEs were assumed to incur a one-time cost at time 0.	The probabilities of AEs were obtained from individual clinical trials. The full treatment durations are captured in comparator trials. No more AEs beyond the trial period are expected. The probabilities of AEs for ibrutinib were decreasing overtime. It is assumed all AEs would occur early at treatment initiation.

5.7 *Base–case results*

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

- the link between clinical- and cost-effectiveness results
- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse reactions, and costs associated with follow-up or subsequent treatment.

Results of the base case analysis demonstrated unprecedented gains in LYs and QALYs comparing ibrutinib to PC. Ibrutinib was associated with an incremental increase of 4.42 LYs and 3.29 QALYs compared to PC, in a population that currently has a median survival of less than 2 years. The base case ICER was £45,486 /QALY compared to the PC arm.

Results were similar when comparing ibrutinib to secondary comparators, with ibrutinib consistently associated with substantial gains in LYs and QALYs versus other comparators used commonly in clinical practice. Resulting ICERs were £44,836/QALY, £42,016/QALY, and £45,525/QALY compared to IR (using IO as proxy for efficacy), BR, and ofatumumab, respectively.

[redacted]

Base case incremental cost effectiveness analysis results

5.7.2 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base case incremental cost-effectiveness analysis with the patient access scheme.

Table 65: Base case results (ibrutinib at list price vs. PC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (Ibrutinib vs. comparator)	Incremental LYG (Ibrutinib vs. comparator)	Incremental QALYs (Ibrutinib vs. comparator)	ICER (£) /QALY (Ibrutinib vs. comparator)	ICER (£) /LY (Ibrutinib vs. comparator)
Physician's Choice	[redacted]	[redacted]	[redacted]					
Ibrutinib	[redacted]	[redacted]	[redacted]	149,589	4.42	3.29	45,486	33,843
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 66: Base case results (ibrutinib at list price vs. IR)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (Ibrutinib vs. IR)	Incremental LYG (Ibrutinib vs. IR)	Incremental QALYs (Ibrutinib vs. IR)	ICER (£) /QALY (Ibrutinib vs. IR)	ICER (£) /LY (Ibrutinib vs. IR)
IR	[redacted]	[redacted]	[redacted]					
Ibrutinib	[redacted]	[redacted]	[redacted]	86,718	2.61	1.93	44,836	33,203
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 67: Base case results (ibrutinib at list price vs. BR)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (Ibrutinib vs. BR)	Incremental LYG (Ibrutinib vs. BR)	Incremental QALYs (Ibrutinib vs. BR)	ICER (£) /QALY (Ibrutinib vs. BR)	ICER (£) /LY (Ibrutinib vs. BR)
BR	[redacted]	[redacted]	[redacted]					
Ibrutinib	[redacted]	[redacted]	[redacted]	151,595	4.92	3.61	42,016	30,828
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 68: Base case results (ibrutinib at list vs. ofatumumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (Ibrutinib vs. Ofatumumab)	Incremental LYG (Ibrutinib vs. Ofatumumab)	Incremental QALYs (Ibrutinib vs. Ofatumumab)	ICER (£) /QALY (Ibrutinib vs. Ofatumumab)	ICER (£) /LY (Ibrutinib vs. Ofatumumab)
Ofatumumab	[redacted]	[redacted]	[redacted]					
Ibrutinib	[redacted]	[redacted]	[redacted]	120,487	3.51	2.65	45,525	34,345
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 69: Base case results (full incremental analysis at ibrutinb list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) /QALY	ICER (£) /LY

BR	[redacted]	[redacted]	[redacted]					
Physician's Choice	[redacted]	[redacted]	[redacted]	-2,007	0.50	0.32	6,283	4,035
Ofatumumab	[redacted]	[redacted]	[redacted]	-29,102	0.91	0.64	45,326	31,913
IO (proxy for IR)	[redacted]	[redacted]	[redacted]	33,769	0.90	0.71	47,397	37,670
Ibrutinib	[redacted]	[redacted]	[redacted]	86,718	2.61	1.93	44,836	33,203
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Clinical outcomes from the model

5.7.3 For the outcomes highlighted in the decision problem (see section 3), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover).

The median PFS and median OS for ibrutinib were not reached in RESONATE (18) (see Section 4.7); therefore projected and actual PFS and OS at 6 months and 12 months were compared. The projected curves and the KM curves matched well. Results of this exercise indicate that the model replicates the trial data very accurately. [redacted].

As discussed in Section 4.10, the population in the Österborg trial (37) (38) was more severe than the RESONATE population. The predicted PFS and OS of PC are based on indirect comparison to the RESONATE population and therefore are not comparable to the Österborg trial results.

The efficacy of IO is used as a proxy for IR (Section 4.10). The predicted PFS of IR matches the PFS KM of IO from Jones et al, 2015 (39) well, whilst the predicted OS of IR was overestimated when compared to Jones et al 2015 due to the fact that the ibrutinib trial is used as a reference.

The model projection of the PFS and OS of BR was based on MAIC adjusting for population differences. The Fischer trial for BR (29) was conducted in a relatively healthy population in comparison to the RESONATE trial. Therefore, as the model was estimated OS and PFS in a sicker population, these do not match the trial data.

The OS of ofatumumab was estimated by applying a crossover-adjusted OS HR to the OS curve of ibrutinib which acted as a reference. As the median OS of ofatumumab reported in the RESONATE trial was contaminated by crossover, comparison of the model-projected OS against the trial-reported OS is not appropriate.

Table 70: Summary of model results compared with clinical data

	Clinical trial result	Model result
Ibrutinib		
PFS	RESONATE 6 mo: **0.92** 12 mo: **0.84** Median: **not reached**	Projected from RESONATE KM [redacted]
OS	RESONATE 6 mo: **0.95**	Projected from RESONATE KM [redacted]

	12 mo: **0.90** Median: **not reached**	[redacted]
PC		
PFS	Osterborg 2014 Median: **3.6 mo**	Projected based on ibrutinib reference curve and HR [redacted]
OS	Osterborg 2014 Median: **14.5 mo**	Projected based on ibrutinib reference curve and HR [redacted]
IR (using IO as proxy for efficacy)		
PFS	Jones 2015 Median: **16.3 mo**	Projected based on ibrutinib reference curve and HR [redacted]
OS	Jones 2015 Median: **20.9 mo**	Projected based on ibrutinib reference curve and HR [redacted]
BR		
PFS	Fischer 2011 Median: **15.2 mo**	Projected based on ibrutinib reference curve and HR [redacted]
OS	Fischer 2011 Median: **33.9 mo**	Projected based on ibrutinib reference curve and HR [redacted]
Ofatumumab		
PFS	RESONATE Median: **8 mo**	Projected based on RESONATE KM [redacted]
OS	RESONATE: not presented as the OS was contaminated by crossover	Projected based on ibrutinib reference curve and HR [redacted]

5.7.4 Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.

The proportion of the cohort in each health state over time is presented in Figure 35 to Figure 39. Appendix 14 contains more detailed tables.

[redacted]

5.7.5 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.

Utilities were assigned to the PFS and PPS health states as described in Section 5.4. Utility decrements associated with AE were applied to the proportion of patients with AE at time 0. Graphs presenting the Markov traces of QALY accrual in the ibrutinib arm and the PC arm are tabulated in Appendix 14.

It is important to note that as utilities were obtained from the RESONATE trial and therefore accurately reflected the trial population, the utilities were not further adjusted for age.

Disaggregated results of the base case incremental cost effectiveness analysis

5.7.6 Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental cost effectiveness analysis by category of cost. The tables that should be completed summarising the disaggregated results (for example, QALY gain by health state, costs by health state, predicted resource use by category of cost) are presented below.

Table 71 and Table 75 and Table 79 summarise the QALY gains and total costs by health state, and the predicted resource use for ibrutinib vs. PC.

[redacted]Ibrutinib was associated with substantially higher PFS QALYs of [redacted]and PPS QALYs of QALYs compared with PC, which was associated with PFS and PPS QALYs of [redacted] and [redacted], respectively, for PC. Ibrutinib was also associated with incremental costs vs. PC. This was largely driven by the fact that patients remain on average more than 3 years longer in the PFS state than PC, thus extending the time on treatment. Ibrutinib, however, was associated with slightly lower costs for other resource use, such as management of AEs, subsequent treatment and terminal care.

Incremental results comparing ibrutinib to PC yielded an incremental QALY benefit of 2.09 for PFS and 1.20 for PPS. The difference in total costs for PFS and PPS was £147,491 and £2,098, respectively.

Similar findings resulted from the comparison of ibrutinib with IO (as a proxy for IR), BR and ofatumumab. Ibrutinib was associated with substantially large QALY benefits during PFS and PPS health states, higher overall costs, and slightly lower costs for subsequent treatment and terminal care. See

Table 72 to Table 74, Table 76 to Table 78 and Table 80 to Table 82.

Table 71: Summary of QALY gain by health state (ibrutinib vs. PC)

Health state	Ibrutinib QALY	PC QALY	Incremental outcome	% of total incremental outcome
PFS	[redacted]	[redacted]	2.09	64%
PPS	[redacted]	[redacted]	1.20	36%
Total	[redacted]	[redacted]	3.29	100%

QALY, quality-adjusted life year; PFS, progression-free survival; PPS, post-progression survival

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 72: Summary of QALY gain by health state (ibrutinib vs. IR)

Health state	Ibrutinib QALY	IR QALY	Incremental outcome	% of total incremental outcome
PFS	[redacted]	[redacted]	1.18	61%
PPS	[redacted]	[redacted]	0.76	39%
Total	[redacted]	[redacted]	1.93	100%

Table 73: Summary of QALY gain by health state (ibrutinib vs. BR)

Health state	Ibrutinib QALY	BR QALY	Incremental outcome	% of total incremental outcome
PFS	[redacted]	[redacted]	2.02	56%
PPS	[redacted]	[redacted]	1.59	44%
Total	[redacted]	[redacted]	3.61	100%

Table 74: Summary of QALY gain by health state (ibrutinib vs. ofatumumab)

Health state	Ibrutinib QALY	Ofatumumab QALY	Incremental outcome	% of total incremental outcome
PFS	[redacted]	[redacted]	1.87	71%
PPS	[redacted]	[redacted]	0.78	29%
Total	[redacted]	[redacted]	2.65	100%

Table 75: Summary of costs by state (ibrutinib at list price vs. PC)

Health state	Cost ibrutinib	Cost PC	Incremental cost	% of total incremental cost
PFS	[redacted]	[redacted]	147,491	98%
PPS	[redacted]	[redacted]	2,098	2%
Total	[redacted]	[redacted]	149,589	100%

Table 76: Summary of costs by health state (ibrutinib at list price vs. IR)

Health state	Cost ibrutinib	Cost IR	Incremental cost	% of total incremental cost
PFS	[redacted]	[redacted]	84,556	98%
PPS	[redacted]	[redacted]	2,162	2%
Total	[redacted]	[redacted]	86,718	100%

Table 77: Summary of costs by health state (ibrutinib at list price vs. BR)

Health state	Cost ibrutinib	Cost BR	Incremental cost	% of total incremental cost
PFS	[redacted]	[redacted]	147,402	97%
PPS	[redacted]	[redacted]	4,194	3%
Total	[redacted]	[redacted]	151,595	100%

Table 78: Summary of costs by health state (ibrutinib at list price vs. ofatumumab)

Health state	Cost ibrutinib	Cost Ofatumumab	Incremental cost	% of total incremental cost
PFS	[redacted]	[redacted]	119,257	99%
PPS	[redacted]	[redacted]	1,230	1%
Total	[redacted]	[redacted]	120,487	100%

Table 79: Summary of predicted resource use by category of cost (ibrutinib at list price vs. PC)

Item	Cost of ibrutinib	Cost of PC	Incremental cost	% of total incremental cost
Drug cost	[redacted]	[redacted]	138,790	93%
Administration cost	[redacted]	[redacted]	-3,552	2%
PFS Routine follow up	[redacted]	[redacted]	12,388	8%
AE cost	[redacted]	[redacted]	-136	0%
Subsequent treatment cost	[redacted]	[redacted]	-1,831	1%
BSC cost	[redacted]	[redacted]	6,061	4%
Subsequent treatment routine follow-up cost	[redacted]	[redacted]	-627	0%
Terminal cost	[redacted]	[redacted]	-1,506	1%
Total costs	[redacted]	[redacted]	149,589	100%

Table 80: Summary of predicted resource use by category of cost (ibrutinib at list price vs. IR)

Item	Cost of ibrutinib	Cost of IR	Incremental cost	% of total incremental cost
Drug Cost	[redacted]	[redacted]	80,421	93%
Administration Cost	[redacted]	[redacted]	-2,013	2%
PFS routine follow up	[redacted]	[redacted]	7,138	8%
AE cost	[redacted]	[redacted]	-990	1%
Subsequent Treatment cost	[redacted]	[redacted]	-323	0%
BSC cost	[redacted]	[redacted]	3,834	4%
Subsequent Treatment routine follow-up cost	[redacted]	[redacted]	-340	0%
Terminal care cost	[redacted]	[redacted]	-1,009	1%
Total	[redacted]	[redacted]	86,718	100%

Table 81: Summary of predicted resource use by category of cost (ibrutinib at list price vs. BR)

Item	Ibrutinib Cost	BR Cost	Incremental cost	% of total incremental cost
Drug Cost	[redacted]	[redacted]	137,100	90%
Administration Cost	[redacted]	[redacted]	-2,602	2%
PFS routine follow up	[redacted]	[redacted]	12,097	8%
AE cost	[redacted]	[redacted]	807	1%
Subsequent Treatment cost	[redacted]	[redacted]	-1,552	1%
BSC cost	[redacted]	[redacted]	7,978	5%
Subsequent Treatment routine follow-up cost	[redacted]	[redacted]	-601	0%
Terminal care cost	[redacted]	[redacted]	-1,632	1%
Total	[redacted]	[redacted]	151,595	100%

Table 82: Summary of predicted resource use by category of cost (ibrutinib at list vs. ofatumumab)

Item	Cost of ibrutinib	Cost of ofatumumab	Incremental cost	% of total incremental cost
Drug Cost	[redacted]	[redacted]	111,898	93%
Administration Cost	[redacted]	[redacted]	-2,977	2%
PFS routine follow up	[redacted]	[redacted]	9,944	8%
AE cost	[redacted]	[redacted]	392	0%
Subsequent Treatment cost	[redacted]	[redacted]	-949	1%
BSC cost	[redacted]	[redacted]	3,987	3%
Subsequent Treatment routine follow-up cost	[redacted]	[redacted]	-540	0%
Terminal care cost	[redacted]	[redacted]	-1,268	1%
Total	[redacted]	[redacted]	120,487	100%

5.8 *Sensitivity analysis*

Probabilistic sensitivity analysis

5.8.1 All inputs used in the analysis will be estimated with a degree of imprecision. As specified in the NICE guide to the methods of technology appraisal, probabilistic sensitivity analysis 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. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions for probabilistic sensitivity analysis should not be arbitrarily chosen, but should represent the available evidence on the parameter of interest, and their use should be justified.

Please see Sections 5.8.2–5.8.4 for details.

5.8.2 The distributions and their sources for each parameter should be clearly stated if different from those presented in section 5.5, including the derivation and value of 'priors'. If any parameters or variables were omitted from the probabilistic sensitivity analysis, please provide the rationale for the omission(s).

In PSA, the uncertainties around parameters were estimated, including utility, PFS, OS, TTP of subsequent lines of treatment and non-drug costs. For each parametric function in the model, the model used the Cholesky decomposition of the covariance matrix to correlate the function parameters. For each parameter, the same random number was used across all treatment arms when PSA variations were drawn to ensure consistency. Distributions used in the PSA along with justification are provided in Table 83.

Table 83: Model parameters varied in PSA with justification

Parameter	PSA Distribution	Justification
PFS	Normal Distribution (Cholesky decomposition)	PFS, OS and time to progression of subsequent line of treatment are projected using parametric distributions fitted to KM trial results. The parametric fittings were conducted using the maximum-likelihood estimation which assumes the error to be normally distributed. Therefore normal distribution was chosen. Cholesky decomposition was used to maintain the correlation between parametric fitting parameters.
OS	Normal Distribution (Cholesky decomposition)	
TTP of subsequent line of treatment	Normal Distribution (Cholesky decomposition)	
AE cost and resource use cost based on weighted average of NHS reference costs	Uniform distribution (to the weighting)	The AE cost, cost of biopsy and cost of inpatient visit are estimated based on the weighted average of a few conditions that match the description of the medical resource use. The weighting of each cost component is varied based on uniform distribution to test for the uncertainty around the composition of each type of medical resource use, and use to generate weighted average cost for PSA.

Follow up cost parameters	Gamma distribution	To test for the uncertainty around the frequency of medical resource use, the follow up costs are varied in PSA at the aggregated level. Published guidance suggests that costs derived from log-scale regression models be varied according to a gamma or lognormal distribution (169)
Utility parameter	*Beta distribution*	Beta distribution was chosen for disutility to ensure the alternative values for PSA were between 0 and 1.

5.8.3 Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals). Include scatter plots and cost-effectiveness acceptability curves showing the probability that the treatment is cost effective if the incremental cost-effectiveness ratio ICER is £20,000 to £30,000 per QALY gained. Describe how the probabilistic ICER(s) were calculated and provide the rationale.

A PSA was run for 1,000 iterations. Figure 40 presents the ICER scatter plot for ibrutinib compared to PC.

The plot indicates that in 100% of the model iterations, ibrutinib yields more QALYs than the PC at higher cost.

Figure 41.presents cost-effectiveness acceptability curves for each model comparator. The probability of ibrutinib being cost-effective at a willingness to pay value of £50,000/QALY is 58%.

In comparison to IR, BR and ofatumumab, the probabilities of ibrutinib being cost-effective at a willingness to pay value of £50,000/QALY are 57%, 70% and 58%, respectively.

Figure 40: ICER scatter plot for ibrutinib at list price vs. PC

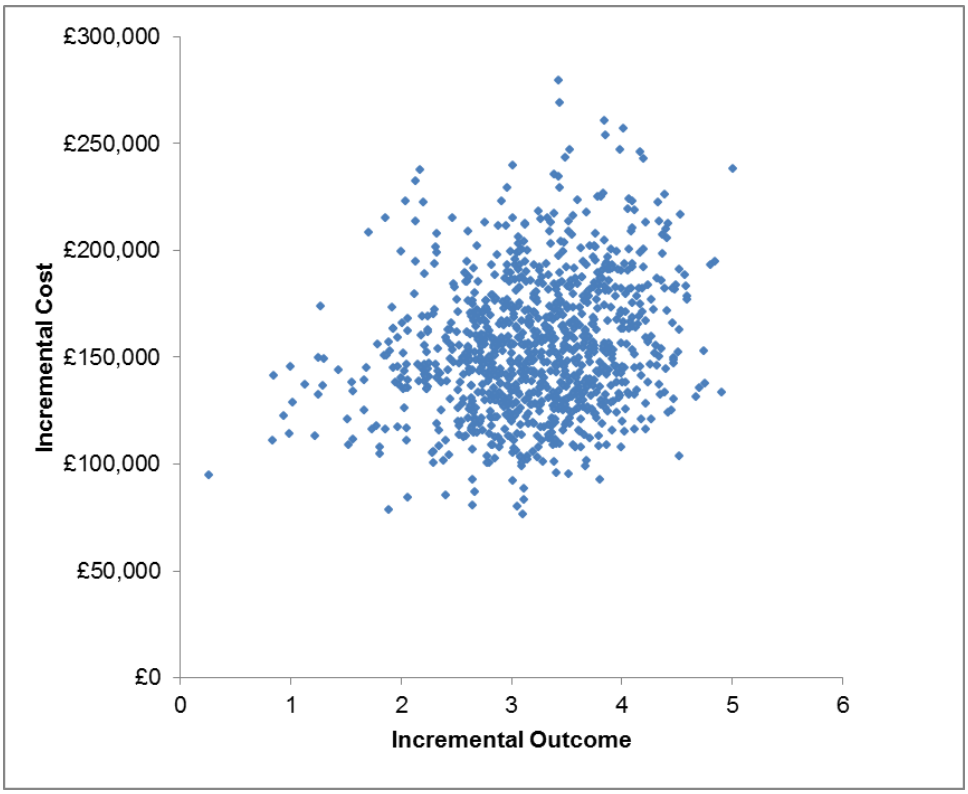


Figure 41: Cost effectiveness acceptability curve for ibrutinib at list price vs. PC

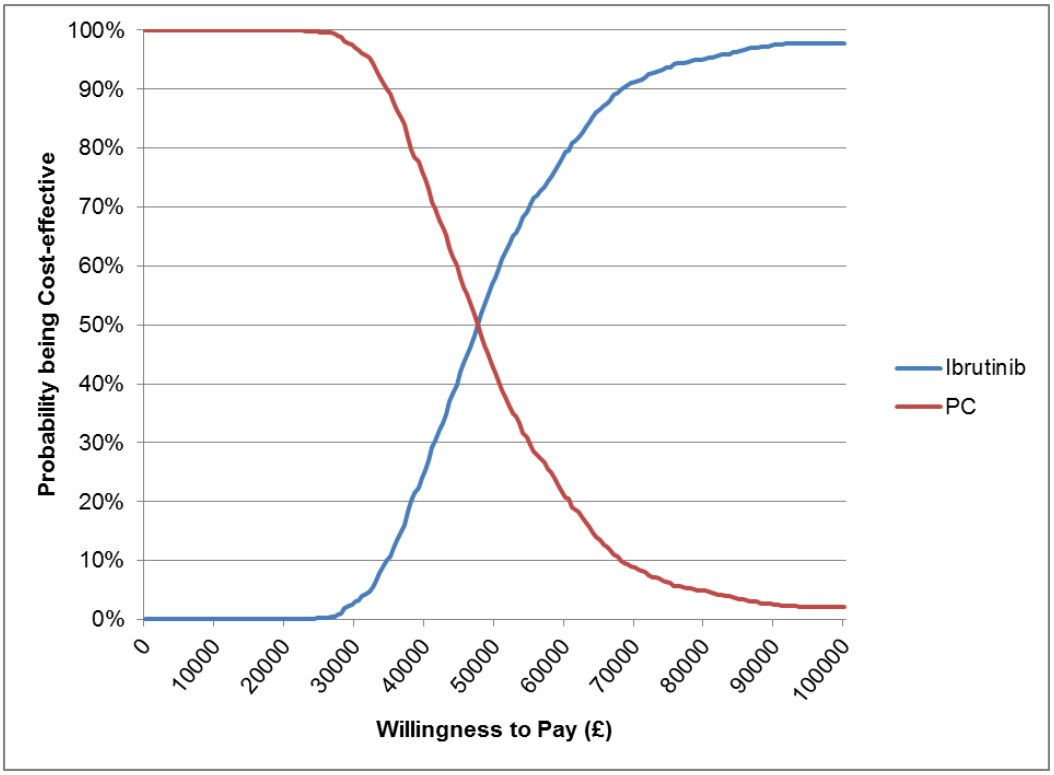


Figure 42: ICER scatter plot for ibrutinib at list price vs. IR

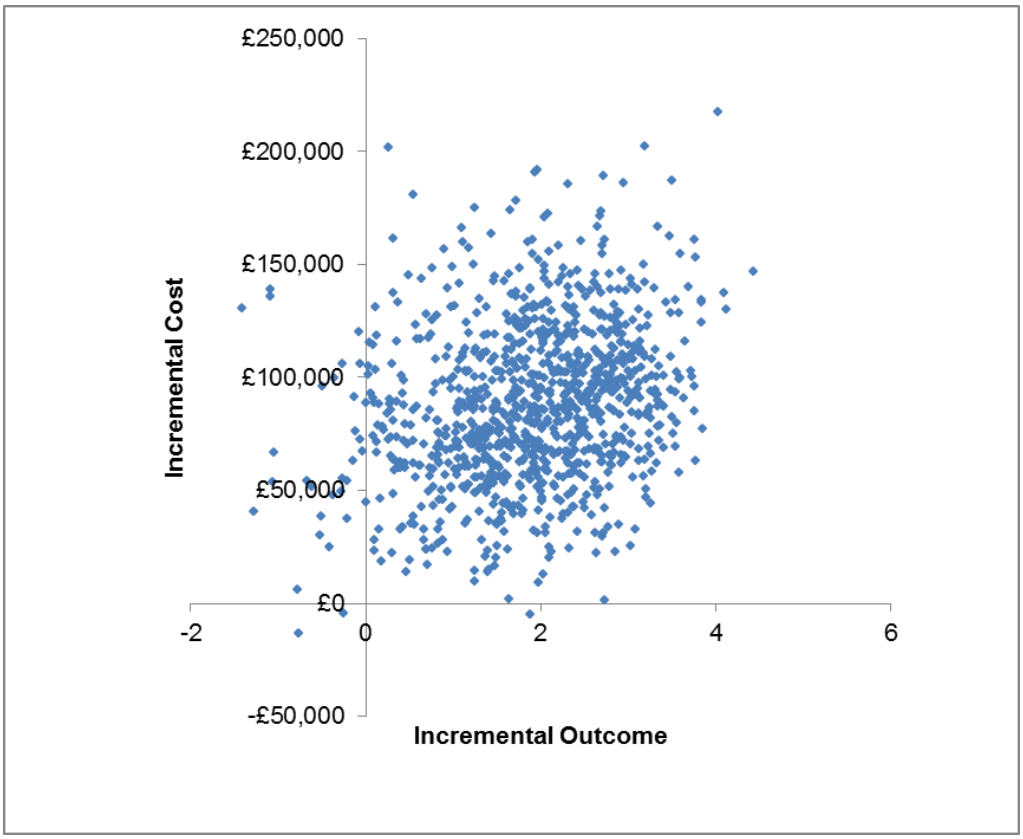


Figure 43: Cost effectiveness acceptability curve for ibrutinib at list price vs. IR

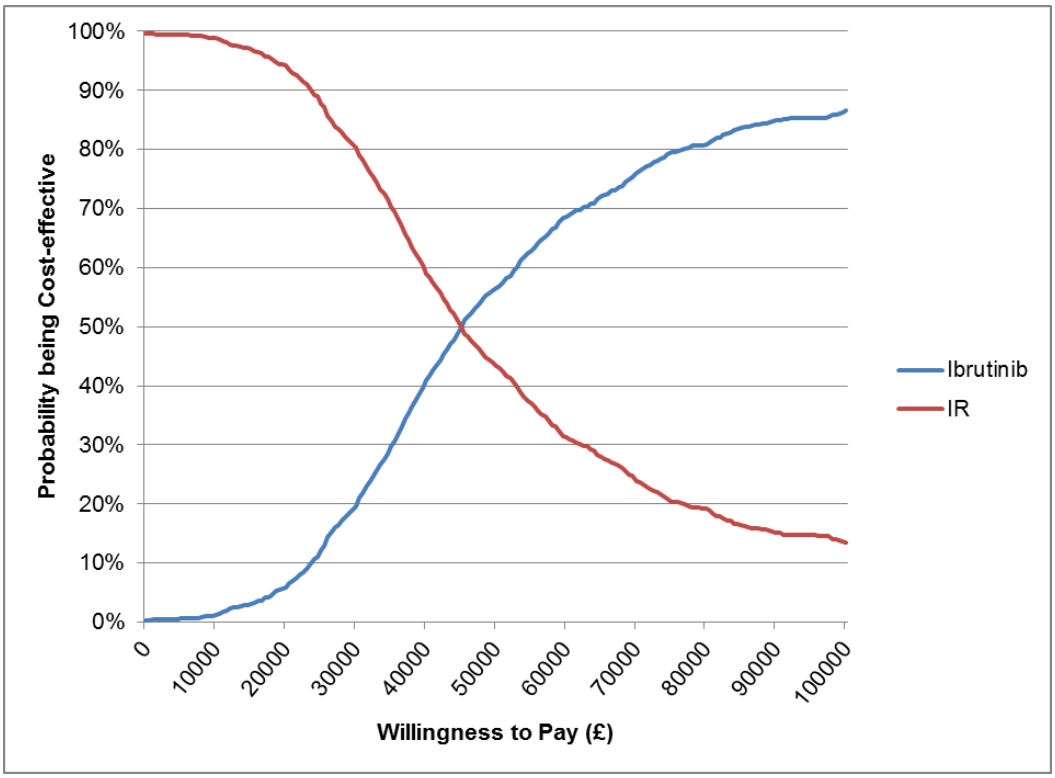


Figure 44: ICER scatter plot for ibrutinib at list price vs. BR

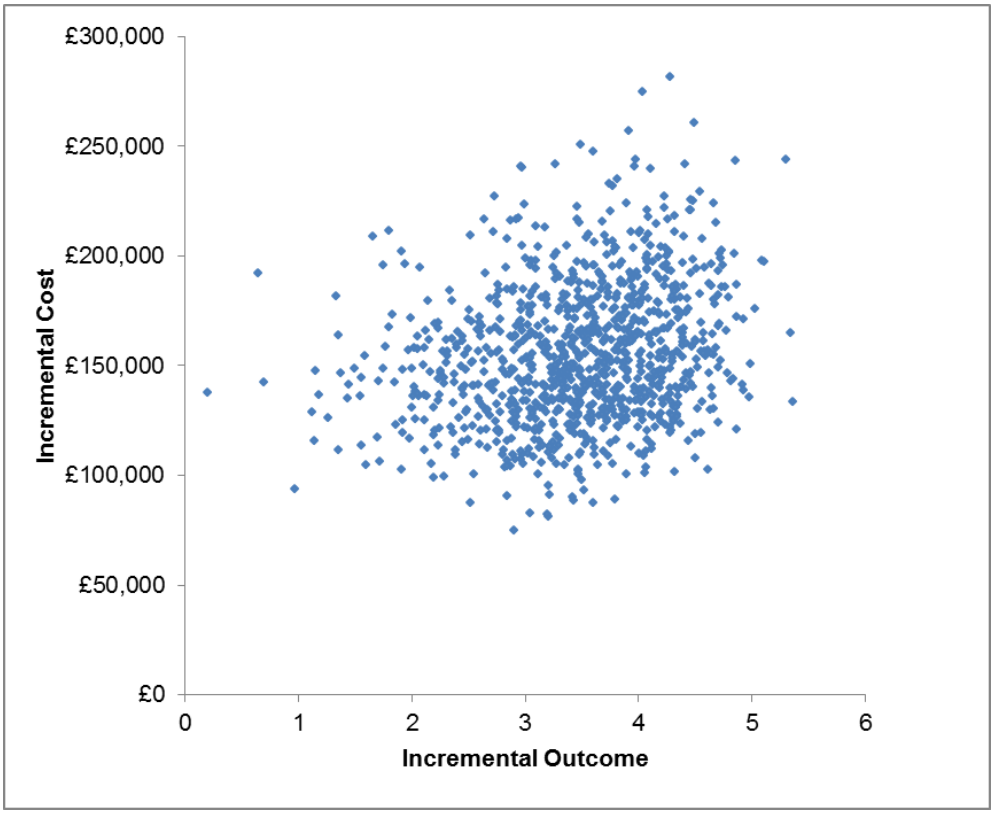


Figure 45: Cost effectiveness acceptability curve for ibrutinib at list price vs. BR

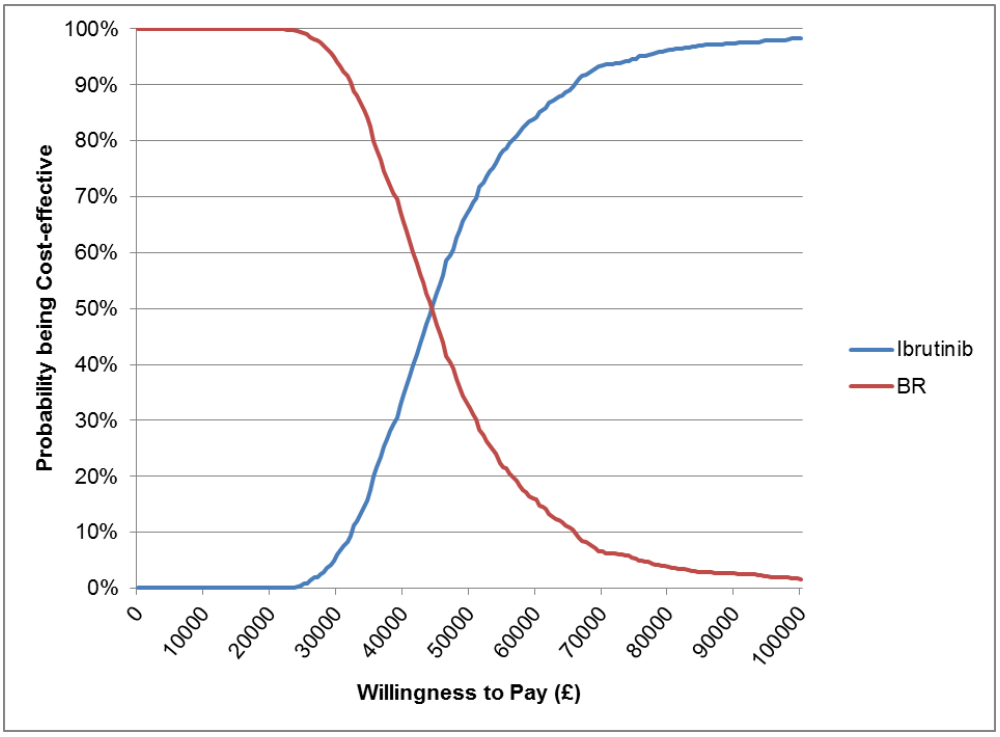


Figure 46: ICER scatter plot for ibrutinib at list price vs. ofatumumab

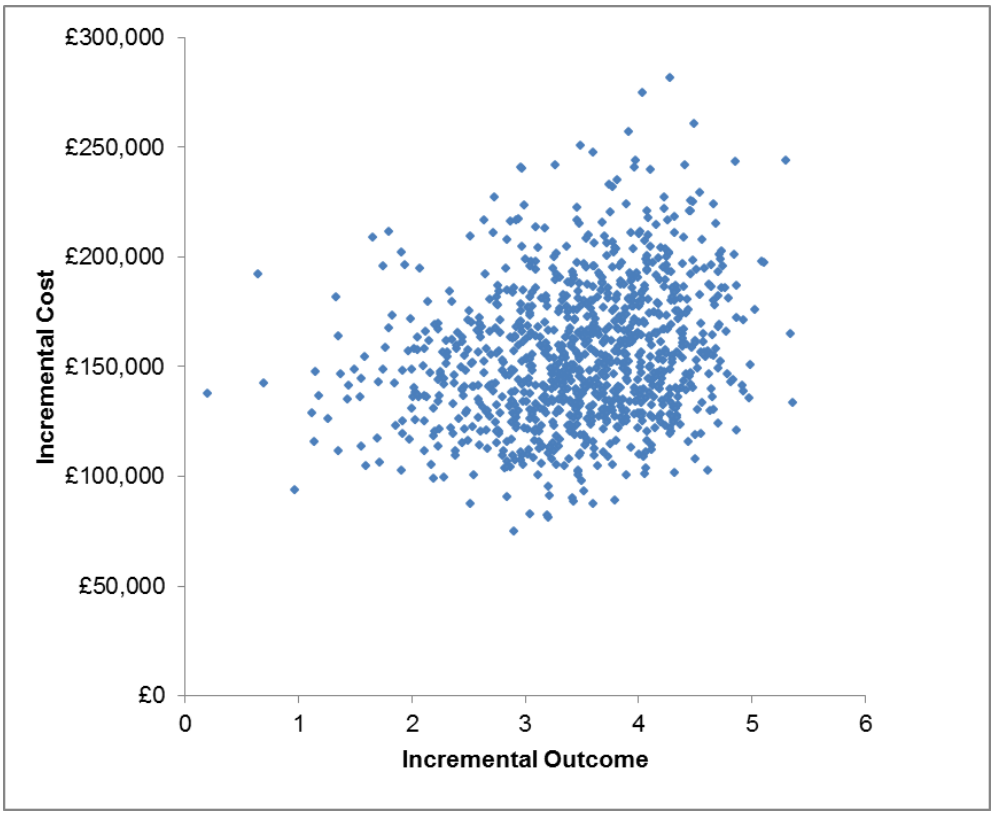
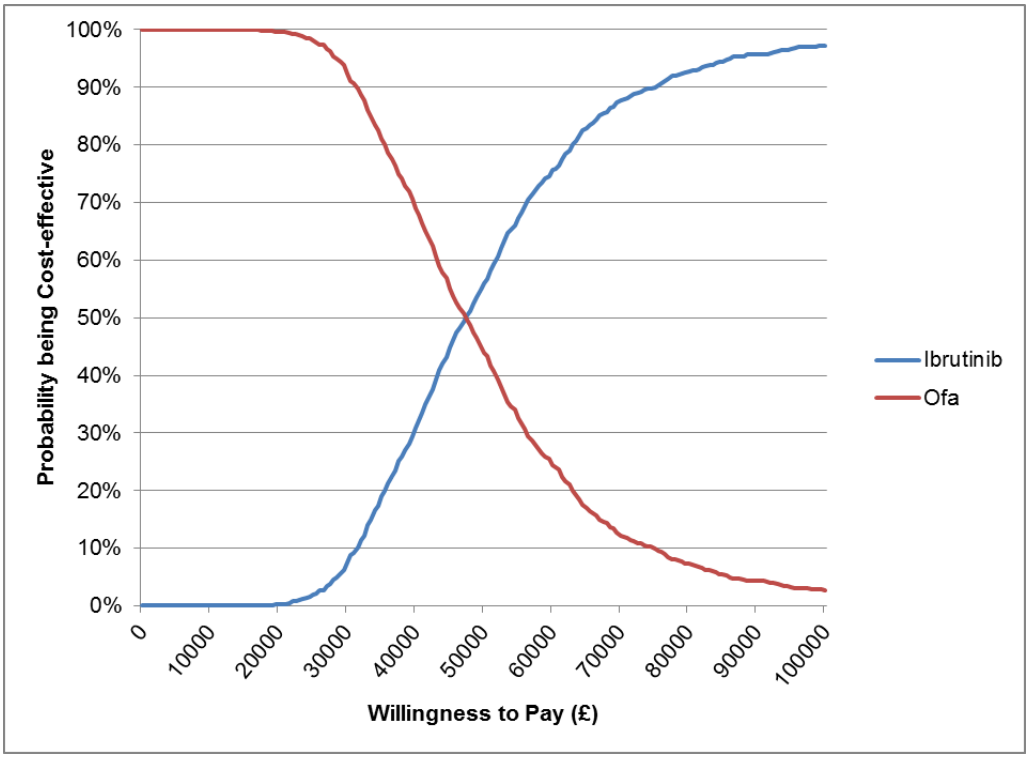


Figure 47: Cost effectiveness acceptability curve for ibrutinib at list price vs. ofatumumab



Deterministic sensitivity analysis

5.8.4 Identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. If any parameters or variables listed in section 5.6.1 were omitted from sensitivity analysis, please provide the rationale.

All major model variables for which values were uncertain were tested in a one-way sensitivity analysis, in order to identify model drivers and examine key areas of uncertainty within the model. Minor variables (e.g. utility decrements for each AE, unit costs and resource use for each resource use item) were incorporated in aggregate form, such as average utility decrement for AEs with each comparator, or follow up costs for each health state. Where possible, confidence intervals or published ranges were used as alternative values. In the absence of confidence intervals or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated as -/+ 20% of the mean, base case value. The parameters were varied as shown in Table 84.

Table 84: Model parameters varied in deterministic sensitivity analysis (ibrutinib vs. PC)

Variable	Base case	Lower	Upper	Rationale
Time horizon	20 years	10 years	30 years	The projected median survival for ibrutinib was approximately 6 years. It is estimated that 10% of patients remain alive at 18 years. A lower time horizon of 10 years has been used to assess the cost-effectiveness of ibrutinib with limited duration of clinical benefit. A longer time horizon of 30 years has been used to assess the cost-effectiveness of ibrutinib over life time horizon.
Health discount	3.5%	1.5%	--	NICE reference case Discounting may significantly impact costs and health benefits when a significant difference in the timing of costs/health benefits exists
Cost discount	3.5%	1.5%	--	
Probability of death during PFS	0.57%	0.46%	0.68%	Extreme value
% of patients receive subsequent treatment for all comparators	41.9%	21.9%	61.9%	Extreme value
Dosing intensity of ibrutinib	94.8%	90%	100%	Extreme value
Dosing intensity of PC	95.2%	90%	100%	Extreme value
Cost of routine care and follow up during PFS	Ibrutinib: £416 PC: £831	Ibrutinib: £333 PC: 665	Ibrutinib: £499 PC: £997	Extreme value
Cost of routine care and follow up for PFS of subsequent treatment	£845	£676	£1,014	Extreme value
Cost of routine care and follow up for BSC	£250	£200	£300	Extreme value
Terminal care cost	£7,360	£5,888	£8,832	Extreme value

Baseline utility and utility during PFS	Baseline utility [redacted] Utility during PFS: [redacted]	Lower 95% CI	Upper 95% CI	95% Confidence interval
Utility decrement due to progression	-0.098	-0.0784	-0.1176	Extreme value
Duration of AE disutility	14 days	0 days	--	Extreme value

5.8.5 Present the results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Results of the one-way sensitivity analysis for ibrutinib vs. PC, in which single parameters were varied one at a time to test impact on model results, are shown in tabular form in Table 85 and in graphical form in

Figure 48.

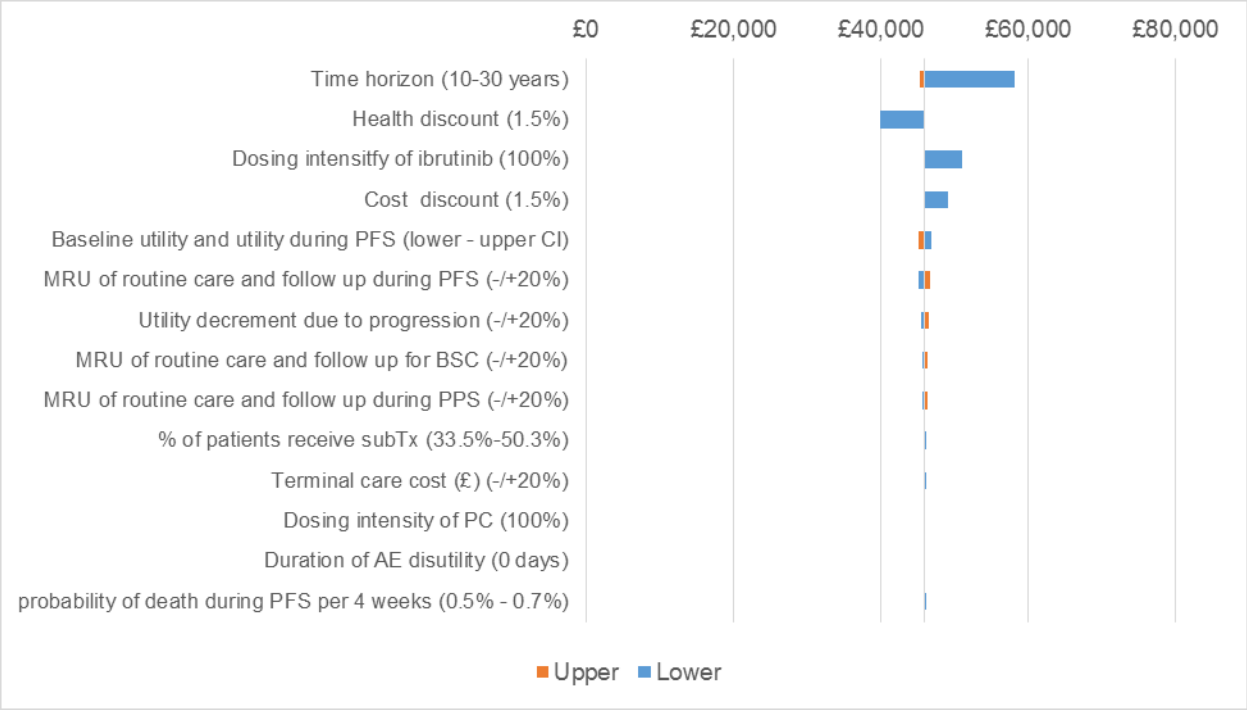
The trend is similar on the ICERs of ibrutinib vs. the other comparators.

Table 85: Sensitivity analysis results for ibrutinib vs. PC

Parameter	Base case value	Alternative value	ICER (£/QALY)
Base case			45,486
Time horizon	20 years	10 years	57,630
		30 years	44,761
Health discount	3.5%	1.5%	39,568
Cost discount	3.5%	1.5%	48,659
Probability of death during PFS per 4 weeks cycle	0.6%	0.5%	45,506
		0.7%	45,466
% of patients receive subsequent treatment for all comparators	41.90%	33.5%	45,625
		50.3%	45,347
Dosing intensity of ibrutinib	94.8%	100%	41,052
		90%	50,550
Dosing intensity of PC	95.2%	100%	45,349
Cost of routine care and follow up during PFS (£)	Ibrutinib: 416 Physician's choice: 831	20% decrease	44,733
		20% increase	46,240
Cost of routine care and follow up during PPS (£)	845	20% decrease	45,156
		20% increase	45,817
Cost of routine care and follow up for BSC(£)	250	20% decrease	45,118
		20% increase	45,855
Terminal care cost (£)	7,360	20% decrease	45,578

		20% increase	45,395
Baseline utility and utility during PFS	Baseline utility: [redacted] Utility during PFS: [redacted]	Baseline utility and utility during PFS Lower 95% CI	46,368
		Baseline utility and utility during PFS Upper 95% CI	44,637
Utility decrement due to progression	-0.098	20% decrease	45,006
		20% increase	45,977
Duration of AE disutility	14 days	0 day	45,486

Figure 48: Tornado diagram of deterministic sensitivity analysis



5.8.6 For technologies whose final price or acquisition cost has not been confirmed, sensitivity analysis should be done over a plausible range of prices. This may also include the price of a comparator that includes a confidential patient access scheme.

Since the net prices of idelalisib and ofatumumab are not publicly available, sensitivity analyses were conducted for ibrutinib vs. IO (as a proxy for IR) and ibrutinib vs. ofatumumab with discount ranging from 5% to 50% in 5% increments applied to idelalisib and ofatumumab. The analysis results are presented in Table 86.

Table 86: Sensitivity analysis results for idelalisib and ofatumumab discount

Variable	Base case	Price discount	ICER (£)
Ibrutinib vs. IO (as a proxy for IR)			
Base case			44,836
Idelalisib price	£51.91 per 150 mg tablet	5% discount	46,260
		10% discount	47,683
		15% discount	49,107
		20% discount	50,531
		25% discount	51,955
		30% discount	53,379
		35% discount	54,803
		40% discount	56,227
		45% discount	57,651
		50% discount	59,074
Ibrutinib vs. ofatumumab			
Base case			45,525
Ofatumumab price	£182 per 20 mg/ml vial of 5 ml	5% discount	46,203
		10% discount	46,880
		15% discount	47,557
		20% discount	48,235
		25% discount	48,912
		30% discount	49,590
		35% discount	50,267
		40% discount	50,944
		45% discount	51,622
		50% discount	52,299

Scenario analysis

5.8.7 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. Present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analyses were conducted for each comparator. The parameters varied for each comparator are shown in Table 87 below.

Table 87: Model parameters varied in scenario analysis for ibrutinib

Variable	Base case	Parameter change	Rationale
PFS projection approach for ibrutinib	PFS fitting using Weibull distribution	PFS of ibrutinib using exponential distribution	Ibrutinib demonstrated significant prolongation of PFS in the RESONATE trial and median PFS was not reached. Amongst all parametric fittings, Weibull and exponential provide clinically plausible long-term projection. Exponential is used in sensitivity analysis as an alternative.
OS projection approach for ibrutinib	OS fitting using lognormal up to 3 years, continue with exponential distribution for long term projection	OS of ibrutinib using Weibull project for entire model time horizon	Lognormal is the best fit according to the AIC BIC. It also matches the OS reported in the 1103 trial long-term follow up for up to 3 years (22) (23). However the long-term projection with lognormal lacks clinical validity. Therefore in sensitivity analysis, Weibull distribution is used for the entire model time horizon.
Duration of ibrutinib treatment benefit	No restriction of ibrutinib treatment benefit	Restrict ibrutinib treatment benefit to 6 years	Due to the lack of long-term follow up, treatment benefit of ibrutinib over the long-term must be extrapolated. This scenario is used to test the impact of restricting ibrutinib treatment benefit to a short time horizon.
		Restrict ibrutinib treatment benefit to 7 years	
Comparative efficacy (PC only)	ITC based on Österborg 2014	MAIC based on Swedish registry data	MAIC based on Swedish registry data is an alternative source for comparative efficacy of PC
Comparative efficacy (BR only)	MAIC based on Fischer 2011	MAIC based on HELIOS	MAIC based on HELIOS is an alternative source for comparative efficacy of BR

Treatment duration of ibrutinib	Time to treatment discontinuation up to the end of trial period; project with PFS for long term	Same as PFS	Ibrutinib is indicated as treat-to-progression in CLL. This analysis reflects the indication.
BSA	Based on RESONATE trial	Based on UK general population	The UK general population has slightly different BSA.
Vial sharing	Excluded	Included	Though vial sharing is not common in the UK, it is tested in this scenario
Impact of response on cost	Cost impact of response are captured based on the distribution of response	Assume no cost benefit due to response	Alternative scenario for estimation of cost benefit due to response.
		Assume cost benefit due to response of comparators to be the same as that for ibrutinib	
Impact of response on utility during PFS	Not considered	Considered. Utility during PFS is estimated based on the baseline utility and the weighted average utility increment due to response for each comparator	Published utility studies have shown that response is associated with better utility.
Percent of AE	Percentage of AE based on trial report	Exclude the AEs with percent reported to be lower than 5%	The list of AEs reported in the RESONATE trial was comprehensive, whereas AEs reported in the comparator trials were restricted to only certain rules, such as only reporting AEs occurred in greater than 5% of patients. This scenario is included to test for the impact of difference in the reporting of AEs.

Table 88: Scenario analysis results for ibrutinib at list price vs. PC

Variable	Base case	Parameter change	ICER (£)
Base case			45,486

PFS projection approach for ibrutinib	PFS fitting using Weibull distribution	PFS of ibrutinib using exponential distribution	62,296
OS projection approach for ibrutinib	OS fitting using lognormal up to 3 years, continue with Weibull distribution for long term projection	OS of ibrutinib using Weibull project for entire model time horizon	46,280
Duration of ibrutinib treatment benefit	No restriction of ibrutinib treatment benefit	Restrict ibrutinib treatment benefit to 6 years	62,128
Comparative efficacy (PC only)	ITC based on Osterborg 2014	Restrict ibrutinib treatment benefit to 7 years	59,128
		Indirect comparison based on multivariate modelling of pooled patient level trial data based on Swedish registry data from Karolinksa institute	54,330
Treatment duration of ibrutinib	Time to treatment discontinuation up to the end of trial period; project with PFS for long term	Same as PFS	45,761
BSA	Based on RESONATE trial 1.9 m2	Based on UK general population 1.79 m2	45,737
Vial sharing	Excluded	Included	45,772
Impact of response on cost	Cost impact of response is captured based on the distribution of response	Assume no cost benefit due to response	50,873
		Assume cost benefit due to response of comparators to be the same as that for ibrutinib	46,039
Impact of response on utility during PFS	Not considered	Considered	44,523
Percent of AE	Percentage of AE based on trial report	Exclude the AEs with percent reported to be lower than 5%	45,443

Table 89: Scenario analysis results for ibrutinib at list price vs. IR

Variable	**Base case**	**Parameter change**	**ICER (£)**
Base case			44,836
PFS projection approach for ibrutinib	PFS fitting using Weibull distribution	PFS of ibrutinib using exponential distribution	67,635

OS projection approach for ibrutinib	OS fitting using lognormal up to 3 years, continue with Weibull distribution for long term projection	OS of ibrutinib using Weibull project for entire model time horizon	45,038
Duration of ibrutinib treatment benefit	No restriction of ibrutinib treatment benefit	Restrict ibrutinib treatment benefit to 6 years	60,050
		Restrict ibrutinib treatment benefit to 7 years	57,183
Treatment duration of ibrutinib	Time to treatment discontinuation up to the end of trial period; project with PFS for long term	Same as PFS	45,303
BSA	Based on RESONATE trial 1.9 m^2	Based on UK general population 1.79 m^2	45,494
Vial sharing	Excluded	Included	45,198
Impact of response on cost	Cost impact of response is captured based on the distribution of response	Assume no cost benefit due to response	49,877
		Assume cost benefit due to response of comparators to be the same as that for ibrutinib	45,266
Impact of response on utility during PFS	Not considered	Considered	43,900
Percent of AE	Percentage of AE based on trial report	Exclude the AEs with percent reported to be lower than 5%	44,763

Table 90: Scenario analysis results for ibrutinib at list price vs. BR

Variable	**Base case**	**Parameter change**	**ICER (£)**
Base case			42,016
PFS projection approach for ibrutinib	PFS fitting using Weibull distribution	PFS of ibrutinib using exponential distribution	57,552
OS projection approach for ibrutinib	OS fitting using lognormal up to 3 years, continue with Weibull distribution for long term projection	OS of ibrutinib using Weibull project for entire model time horizon	42,957
Duration of ibrutinib treatment benefit	No restriction of ibrutinib treatment benefit	Restrict ibrutinib treatment benefit to 6 years	57,831
		Restrict ibrutinib treatment benefit to 7 years	54,986

Comparative efficacy	OR and HR based on MAIC with Fischer 2011	Indirect comparison based on multivariate modelling of pooled patient level trial data based on HELIOS	68,008
Treatment duration of ibrutinib	Time to treatment discontinuation up to the end of trial period; project with PFS for long term	Same as PFS	42,267
BSA	Based on RESONATE trial 1.9 m^2	Based on UK general population 1.79 m^2	42,242
Vial sharing	Excluded	Included	42,261
Impact of response on cost	Cost impact of response is captured based on the distribution of response	Assume no cost benefit due to response	46,719
		Assume cost benefit due to response of comparators to be the same as that for ibrutinib	42,465
Impact of response on utility during PFS	Not considered	Considered	41,250
Percent of AE	Percentage of AE based on trial report	Exclude the AEs with percent reported to be lower than 5%	42,008

Table 91: Scenario analysis results for ibrutinib at list price vs. ofatumumab

Variable	Base case	Parameter change	ICER (£)
Base case			45,525
PFS projection approach for ibrutinib	PFS fitting using Weibull distribution	PFS of ibrutinib using exponential distribution	65,575
OS projection approach for ibrutinib	OS fitting using lognormal up to 3 years, continue with Weibull distribution for long term projection	OS of ibrutinib using Weibull project for entire model time horizon	45,998
Duration of ibrutinib treatment benefit	No restriction of ibrutinib treatment benefit	Restrict ibrutinib treatment benefit to 6 years	60,174

		Restrict ibrutinib treatment benefit to 7 years	57,787
Treatment duration of ibrutinib	Time to treatment discontinuation up to the end of trial period; project with PFS for long term	Same as PFS	45,867
BSA	Based on RESONATE trial 1.9 m^2	Based on UK general population 1.79 m^2	45,542
Vial sharing	Excluded	Included	45,536
Impact of response on cost	Cost impact of response is captured based on the distribution of response	Assume no cost benefit due to response	51,920
		Assume cost benefit due to response of comparators to be the same as that for ibrutinib	46,559
Impact of response on utility during PFS	Not considered	Considered	44,284
Percent of AE	Percentage of AE based on trial report	Exclude the AEs with percent reported to be lower than 5%	45,533

Summary of sensitivity analyses results

5.8.8 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.

Results of the one-way sensitivity analysis demonstrated that model results were relatively stable across variations in inputs and parameters. Time horizon was shown to be the biggest model driver, with a ten-year time horizon increasing ibrutinib's ICER versus PC to £57,630/QALY. When the analysis is restricted to a 10 year time horizon, the benefits of ibrutinib's prolongation of OS cannot be adequately captured, and thus the advantages of treatment with ibrutinib are truncated while the drug costs associated with PFS for ibrutinib still accrue.

Overall, cost and utility inputs had a relatively small impact on the model result except for ibrutinib's dose intensity of ibrutinib. Assuming a dose intensity of 100% for ibrutinib leads to an ICER of £50,550/QALY for ibrutinib vs PC. However, it is extremely unlikely that perfect compliance would ever be achieved in the real world and, if anything, dose intensity of treatments are likely to be lower, rather than greater, than in clinical trials where courses of treatment are more closely monitored. The remainder of the sensitivity analyses have minimal impact on the ICER outcome (+/- 2% of base case ICER).

Among all scenario analyses, 10-year time horizon and 100% dosing intensity of ibrutinib are the only two scenarios with ICER greater than £50,000/QALY. The majority of the sensitivity analyses result in ICERs that remain lower than £50,000/QALY. The same trend is observed for all comparators.

In scenario analysis, the scenarios with alternative OS projection approach, alternative estimation for ibrutinib treatment duration, BSA and vial sharing, and impact of response on utility during PFS result in ICER below £50,000/QALY as well.

Results of scenario analyses indicated that model results were sensitive to the parametric distribution used for PFS projection, which an exponential distribution leading to a higher ICER (37% increase in ICER). This is due to the fact that an exponential fit leads to a longer projection of PFS, which results in longer time accruing the cost of ibrutinib treatment. Given the AIC and BIC, a Weibull distribution used in the current model base case is the best fit. Exponential distribution tested in sensitivity analysis offers a conservative scenario.

HRs for PFS and OS based on the Karolinksa Institute real world evidence were used in a scenario as alternative inputs for the efficacy of ibrutinib vs. PC. In this case, the ICERs [redacted]. Given that there can be significant differences in the design of an RCT versus a registry study, the ITC of RESONATE vs. Österborg, 2015 is preferable, as both data sources were RCTs.

Restriction of ibrutinib's treatment benefit resulted in an increased ICER, due to truncation of ibrutinib's long-term survival benefit. An extreme scenario assuming the follow up cost for the PFS health state to be the same as the follow up of stable disease for all comparators, and removing the cost benefit associated with high response rate resulted in ICER slightly beyond £50,000/QALY.

[redacted]

Summary of sensitivity analyses results

5.9 *Subgroup analysis*

The cost-effectiveness of ibrutinib in R/R CLL patients with 17p deletion was considered.

It was not possible to conduct an economic evaluation of ibrutinib in the treatment-naïve 17p deletion population due to a lack of robust relevant clinical trial data. The cost-effectiveness of ibrutinib for treatment of R/R CLL in the presence of 17p deletion (based on the subgroup data from RESONATE) provides the best available estimate of efficacy associated with ibrutinib in treatment-naïve CLL patients with 17p deletion.

In this scenario, ibrutinib was evaluated against ofatumumab, using the same settings that were used in the base case analysis. This analysis of the R/R CLL 17p deletion population yields an overall ICER of £38,145/QALY compared to ofatumumab, as summarised in Table 92, demonstrating that ibrutinib remains highly cost-effective in the 17p deletion subgroup.

Table 92: Subgroup 17p deletion population results (ibrutinib vs. ofatumumab)

Technology	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/LY)	ICER (£/QALY
Ibrutinib	[redacted]	[redacted]	[redacted]					
Ofatumumab	[redacted]	[redacted]	[redacted]	102,596	3.63	2.69	28,252	38,145

Analysis against other comparators (PC, IR and BR) in this subgroup is not feasible due to lack of data. Specifically, these comparator trials did not report PFS and OS outcomes associated with the 17p deletion subgroup. However, given that few treatments in current practice are effective for patients with 17p deletion, the ICERs of ibrutinib vs. other comparators, especially PC and BR in this subgroup, are likely to be lower than the ICERs for overall R/R CLL patients. IR has a similar license to ibrutinib and has recently gained a positive final appraisal determination from NICE for the use in frontline 17p deletion and TP53 patients due to the acknowledged high level of clinical need in this patient population (40, 41)

5.10 *Validation*

5.10.1 When describing the methods used to validate and quality assure the model, provide:

- the rationale for using the chosen methods
- references to the results produced and cross-references to the evidence identified in the clinical evidence, measurement and valuation of health effects, and cost and healthcare resource sections.

The structure and programming of the Microsoft Excel model was validated by two modelling experts not involved in this study and a variety of stress tests were performed to ensure that the model results reflected the inputs entered. For example, both extreme values and equal values across treatment arms were input and actual results compared against expected results. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy discrepancies. The model was also thoroughly examined by an external vendor (BresMed) who produced a report on clinical assumptions, data sources, and any programming inconsistencies.

Statistical fittings for PFS and OS were validated by comparing of observed PFS and OS KM data for ibrutinib to the curves derived from the predictions. The PFS and OS extrapolated data matched well against the KM curves from the trial. Predicted OS and PFS survival curves for ibrutinib and for comparators (see Section 5.6.3), as well as major model assumptions, were validated by clinical experts practicing in the UK (1).

5.11 *Interpretation and conclusions of economic evidence*

5.11.1 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?

No other published cost-effectiveness analyses of ibrutinib were identified in the SLR and, therefore, results of the current analysis cannot be directly compared to and validated by an external source. Results of the current analysis are in line with other published cost-effectiveness analyses of other treatments of R/R CLL. Specifically, in its recent NICE

submission, IR demonstrated an incremental QALY gain of 1.92 over both rituximab and ofatumumab (41). In the current analysis, ibrutinib demonstrated an incremental QALY gain of 2.06 over ofatumumab.

5.11.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

The current analysis provides estimates of the cost-effectiveness of ibrutinib in all relevant patient groups based on the best available data. In the base case, cost-effectiveness is assessed for treatment of all R/R CLL patients. In a subgroup analysis, cost-effectiveness is evaluated for treatment of R/R CLL patients with 17p deletion, which serves as the best proxy for treatment-naïve CLL patients with 17p deletion or TP53, for which ibrutinib is licensed. Clinical experts agreed that in the absence of data for first-line use of ibrutinib in patients with 17p deletion, data for ibrutinib in R/R patients with 17p deletion constitute a strong argument to support first-line use in the 17p deletion population (1). Relative outcomes in the R/R population with 17p deletion compared to current treatments are expected to be similar, if not better, to relative outcomes R/R patients without 17p deletion, based on clinical experience that chemo-immunotherapeutic regimens perform poorly in 17p deletion patients). It should be noted that IR has recently gained a positive final appraisal determination from NICE for the use in frontline 17p deletion and TP53 patients due to the acknowledged high level of clinical need in this patient population (40, 41)

5.11.3 How relevant (generalizable) is the analysis to clinical practice in England?

To ensure results of this analysis are generalizable to clinical practice in England and Wales, clinical experts currently practicing in England and Wales were interviewed to confirm clinical assumptions and model inputs. Specifically, local experts provided input on:

- Relevant comparators, including composition of PC and subsequent lines of treatment
- Clinical assumptions, including:
    - That ofatumumab time to response KM data was a reasonable proxy for time to response for all comparators
    - That the PFS of rituximab (Furman, 2014) (30) was a reasonable proxy for the duration of PFS on subsequent line of treatment
    - That the proportion of ofatumumab patients who received subsequent treatment in RESONATE was a reasonable proxy for all patients with R/R CLL
    - The exchangeability of efficacy for IR and IO
- MRU associated with each health state, including differences in resource use depending on response status; treatment of AEs and terminal care

Furthermore, where utility values could not be derived from RESONATE EQ-5D data, model inputs were based on published studies based on the UK general population. Finally, projected model survival outcomes were visually graphed to ensure they did not exceed UK general population mortality.

5.11.4 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The economic analysis was based on a de novo economic decision model designed to best capture the unique aspects of the disease and treatment pathway in question, and to make the best use of clinical trial data in order to capture the benefits and costs associated with ibrutinib and its comparator treatments. The structure of the model is consistent with previous published models in this disease area, which have been well accepted by NICE in the same or similar indications (34) (35).

The analysis used the most recent interim data cut (16 months of follow-up) from the RESONATE trial, which represents the most mature data available, to inform inputs for ibrutinib and ofatumumab. The impact of crossover from the ofatumumab arm was adjusted for, to remove bias from survival outcomes. Comparative data to inform the relative treatment effect of ibrutinib vs. comparators of relevance to UK clinical practice were very limited. The analysis made the best use of the available data by conducting an ITC comparing ibrutinib with PC and using the MAIC technique to adjust for population differences between RESONATE and single-arm comparator trials, to limit the bias that naïve comparison of clinical trial results would have introduced.

The economic analysis was limited in certain respects, largely due to the availability of data. However, extensive sensitivity analyses and scenario analyses were conducted to test the impact of uncertainty around data inputs. With 86% of ibrutinib patients still alive at a median of 16 months in RESONATE, OS outcomes had to be extrapolated in the economic model and predicted outcomes cannot be well validated by trial data. To minimise uncertainty related to survival projections, alternative parametric fittings for survival were tested in the scenario analysis. Furthermore, a scenario in which ibrutinib's treatment benefit was restricted to 5 years was tested and results remained within the cost-effective range.

Ibrutinib has the potential to provide additional benefits to patients not captured in this analysis. Ibrutinib is an orally-administrated treatment, which reduces patient burden in comparison to standard infused treatments. The potential utility benefit of ibrutinib's oral administration was not captured in this economic analysis. Additionally, long-term results from ibrutinib's phase II trial (PCYC-1102/1103) indicate that ibrutinib's long-term tolerability profile is very favourable (32). By prolonging time in PFS, ibrutinib may delay time until the use of more toxic, infusion-based treatments which can lead to costly and taxing outcomes such as bone marrow depletion.

In summary, ibrutinib addresses a high unmet need, dramatically prolonging PFS and OS where current treatment options are suboptimal. Ibrutinib's manageable tolerability profile allows patients to stay on treatment longer, delaying the use of other more toxic treatments.

5.11.5 What further analyses could be carried out to enhance the robustness or completeness of the results?

Median PFS and OS for patients treated with ibrutinib have not been reached in RESONATE or PCYC112/1103. These trials are ongoing and will continue to provide evidence of ibrutinib's treatment benefits.

6 Assessment of factors relevant to the NHS and other parties

There are two patient groups addressed within this appraisal, both of which are within ibrutinib's license:

- treatment-naïve CLL patients with 17p deletion or TP53 mutation
- CLL patients who have received one prior therapy and for whom fludarabine-containing regimens are inappropriate

The incidence of CLL is estimated to be 7 per 100,000 in England (8) and is assumed to remain constant for the time horizon of the budget impact model. Of these patients, 67% would be expected to require treatment based upon Dighiero 2003 (9) which reports: a third of patients have an initial indolent disease followed by progression of the disease; a third of patients have aggressive disease at the onset and require early treatment; and the remaining third never require treatment, have a long survival and die of causes unrelated to CLL.

Dohner et al (2000) (58) report 7% of people diagnosed with CLL have 17p deletion or TP53 mutation, aligning with the NICE Final Scope (6) which states 5-10%. Therefore, 7% is used within the budget impact model to estimate patients with 17p deletion or TP53 mutation. Based upon this, 189 patients are expected to be eligible for treatment in the treatment-naïve patient group with CLL associated with 17p deletion or TP53 mutation in England and Wales.

In a recent audit conducted by HMRN, it has been estimated that the proportion of patients who fail first-line therapy would be 32% (170). Of these patients, it is assumed that fludarabine-containing regimen will be inappropriate for 75% of them. Based upon this, 645 patients are expected to be eligible for treatment in the prior therapy patient group.

The acquisition cost and administration cost of treatment were added together to give the total treatment cost for patients in each of these patient groups. Unit costs have been sourced from the British National Formulary online (53) and NHS Reference Costs 2013-2014 (159, 161-164, 166) and are described in more detail in section 5.5. Details of the budget impact incorporating the PAS are provided in Appendix 14.

Table 93 summarises the market share in the "world without ibrutinib" scenario and the "world with ibrutinib" scenario.

The total market share of ibrutinib for both the patient group who have received one prior therapy and the treatment-naïve patient group with 17p deletion or TP53 mutation was estimated according to Janssen internal forecasts as [redacted] in year 1 and [redacted] in years 2 to 5.

Table 94 and Table 95 shows the total budget impact of ibrutinib across both populations. In year 1 the budget impact is expected to be £[redacted] million rising to £[redacted] million thereafter with increased uptake.

Table 93: Market share of relevant treatment options before the introduction of ibrutinib

	Treatment-naïve 17p deletion CLL (%)	R/R CLL (%)
BR	0%	21%
FCR	0%	6%
R-CHOP	0%	6%
R+HDMP	50%	15%
Chlorambucil	0%	12%
IR	50%	35%
Ofatumumab	0%	4%
Total	100%	100%

Key: BR, bendamustine+rituximab; FCR, fludarabine, cyclophosphamide+rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-HDMP, rituximab+high dose methylprednisolone; IR, idelalisib+rituximab.

Table 94: Budget impact of ibrutinib in NHS England (total treatment costs)

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
TN 17p patients	179	180	182	183	185
R/R CLL patients	610	615	620	625	630
Total number of patients eligible for treatment	789	796	802	808	815
Patients expected to receive ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs without ibrutinib					
Total cost of current treatments	£25,810,409	£26,977,573	£27,240,168	£27,458,089	£27,725,280
Costs with ibrutinib					
Cost of ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of future treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: TN, treatment-naïve; R/R, relapsed or refractory

Table 95: Budget impact of ibrutinib in NHS Wales (total treatment costs)

	Year 1	Year 2	Year 3	Year 4	Year 5
TN 17p patients	10	10	10	10	11
R/R CLL patients	35	35	35	36	36
Total number of patients eligible for treatment	45	45	46	46	46
Patients expected to receive ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs without ibrutinib					
Total cost of current treatments	£1,469,271	£1,535,712	£1,550,660	£1,563,066	£1,578,276
Costs with ibrutinib					
Cost of ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of future treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	£300,955	£441,626	£528,293	£532,923	£534,481
Key: TN, treatment-naïve; R/R, relapsed or refractory					

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8 Appendices

1	European public assessment report and Summary of Product Characteristics (Section 2.2)
2	Search strategy for relevant clinical studies (Section 4.1, Section 4.10, and Section 4.12)
3	Availability and comparability of data for relevant treatments in the UK (Section 4.1)
4	Cross-over adjustment analysis for RESONATE trial (Section 4.4)
5	Quality assessment of relevant clinical studies (Section 4.6, Section 4.10, Section 4.11, and Section 4.12) (Excel spreadsheet)
6	Details on methods and results of ITCs, MAIC, and indirect comparison using multivariate Cox model (Section 4.10)
7	Additional details of non-randomised phase II studies (Section 4.11 and Section 4.12)
8	Search strategy for cost-effectiveness studies and for measurement and valuation of health effects (Section 5.1 and Section 5.4)
9	Quality assessment of cost-effectiveness studies (Section 5.1) (Excel spreadsheet)
10	Parametric fitting methods (Section 5.3, Section 5.6.2)
11	Health-related quality of life studies identified by SLR (Section 5.4)
12	Utility data analysis based on RESONATE trial (Section 5.4)
13	Calculation of weighted average costs per adverse event (Section 5.5)
14	Patient access scheme and related cost-effectiveness results (Section 5.7)
15	Parameters varied in the PSA (Section 5.8)
16	Checklist of confidential information

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Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID749]

Dear [redacted],

The Evidence Review Group, Aberdeen HTA Group], and the technical team at NICE have now had an opportunity to take a look at the submission received on the 22 October 2015 by Janssen. The ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **27 November 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via the link provided.

If you have any further queries on the technical issues raised in this letter then please contact Richard Diaz, Technical Lead (richard.diaz@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION**. The number of studies evaluated for inclusion in the flow diagram (Figure7) (15 RCTs + 26 non-RCTS) and the number of studies listed in Appendix 3 (Availability and comparability of data for relevant treatments in the UK) (N=33) are inconsistent. Please provide a list of all included and excluded studies, along with bibliographic details.

A2. **PRIORITY QUESTION**. Are there established definitions of "relapsed" disease and "refractory" disease used in the UK? Please provide a definition of "relapsed" disease and "refractive" disease used for this submission. Please comment on whether comparators differ for each group.

Survival Analyses

A3. **PRIORITY QUESTION** Please present the unadjusted OS Kaplan-Meier data for both arms separately without censoring for crossover. For the ofatumumab arm, please include patients who have crossed over and remain at risk in the number of patients remaining at risk. Please present the data in the table format included below. Please note that for a given time point not all columns may require data entries.

Please also present this data for the 17p subgroup.

			N at risk		
Time	N events	N censored	N	N cross-over	S(t)
0	0	0	???	0	100%
???	???	???	???	???	???
etc.	???	???	???	???	???

For the ofatumumab arm, please also present the RPSFT Kaplan-Meier estimator S(t) and the IPCW Kaplan Meier estimator S(t) at the corresponding time points. Please present the data in the table format included below. As above, not all columns may require data entries.

Please also present this data for the 17p subgroup.

Time	N events	N censored	N at risk	S(t)	RPSFT S(t)	IPCW S(t)
0	0	0	???	100%	100%	100%
???	???	???	???	???	???	???
etc.	???	???	???	???	???	???

A4. **PRIORITY QUESTION** Please describe what constitutes a PFS event within the PFS analysis? What constitutes a censoring event within the PFS analysis?

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A5. **PRIORITY QUESTION** Please present the independent review committee (IRC)-assessed PFS Kaplan Meier data for both arms using the table format provided below. If available, please present the same for the 17p subgroup.

Time	N events	N censored	N at risk	PFS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A6. **PRIORITY QUESTION** Please present the investigator assessed PFS Kaplan Meier data for both arms using the table format provided below. If available, please present the same for the 17p subgroup.

Time	N events	N censored	N at risk	PFS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A7. **PRIORITY QUESTION** Please present the Kaplan Meier data for Figures 21, 22 and 23 (pages 85-6).

Time	N events	N censored	N at risk	PFS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A8. According to the EPAR for ibrutinib (page 98/140), the RESONATE trial was stopped early at 146 progression free survival (PFS) events due to a positive interim analysis. Are the data in the submission based on the interim analysis of RESONATE? Were further data collected beyond that stage?

A9. Were proportionate hazards tested for within the RESONATE trial PFS data? If so, please describe how this was done and the relevant results.

A10. Was data collected on the mean response durations by arm, or median response durations if means are not available, for complete response (CR), CR with incomplete hematopoietic recovery (CRi) and partial response (PR) in RESONATE (1112), PCY1102 and PCY1103? If so, please present this data.

A11. According to the RESONATE CONSORT diagram (figure 9, page 59), 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm discontinued treatment in the RESONATE trial due to reasons other than progression or death.

- Was progression monitored after discontinuation and, if so, how was it treated in the PFS Kaplan-Meier curves?
- How many of those 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm were lost to follow up in terms of progression? How was this treated within the PFS Kaplan-Meier curves?

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- How many of the 24 patients in the ofatumumab arm that this applies to discontinued treatment without having crossed over to ibrutinib?
- How many of those 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm were lost to follow up due to death? How was this treated within the overall survival (OS) Kaplan-Meier curves?

A12. Table 64 (pages 154-5) suggests that section 5.3 and appendix 10 provide details of the Kaplan Meier time to treatment discontinuation curve for ibrutinib, but these data are not in the sections referenced. Please direct us to the Kaplan Meier curves if included in the submission. Otherwise, please provide the Kaplan-Meier time to treatment discontinuation data curves and tabulate the Kaplan Meier time to treatment discontinuation data for ibrutinib treatment in the ibrutinib arm and for ofatumumab treatment in the ofatumumab arm for all patients using the table format provided below.

Please also present these data for the 17p subgroup.

Time	N events	N censored	N at risk	TTD S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

Parametric fitting

A13. **PRIORITY QUESTION** Page 5 of appendix 4 states that the results from the IPCW model are nearly identical to the RPSFT model, but the details of the IPCW results are not included. Please provide the IPCW results for the intention-to-treat (ITT) analysis and for the early ITT analysis when only 47 patients had crossed over. Also, please explain the rationale for choosing the cut-off of 47 patients crossing over for the early ITT analysis.

A14. The ERG has been unable to replicate the log logistic curves included in Appendix 10 of the submission despite using several functional forms using the intercept and scale parameters. Please specify the correct functional form.

A15. Parameterised curves appear to be used with the exception of the time to treatment discontinuation curve for ibrutinib. What is the rationale for this approach? If possible, please provide a corresponding time to treatment discontinuation curve for ofatumumab.

A16. Does the post-progression survival analysis include patients in the ofatumumab arm who progressed and subsequently crossed over to receive ibrutinib? Please present the Kaplan Meier data using the table formats below, split by arm for all patients that underlies figure 10 (page 8 of appendix 10). Please present this assuming that time zero is the time of progression as in figure 10 of appendix 10.

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Please also present this data to the extent that it is available for the 17p subgroup.

Ibrutinib arm			
Time	N events	N censored	N at risk
0	0	0	???
???	???	???	???
etc.	???	???	???

Ofatumumab arm			
Time	N events	N censored	N at risk
0	0	0	???
???	???	???	???
etc.	???	???	???

RESONATE arms combined				
Time	N events	N censored	N at risk	PPS S(t)
0	0	0	???	100%
???	???	???	???	???
etc.	???	???	???	???

A17. Both the RPSFT and the IPCW analyses appear to assume proportionate hazards. Hazard ratios are applied to the ibrutinib OS curve to derive the OS curves for the other comparators. However, the base case assumes a 3 year lognormal OS curve for ibrutinib. The ERG understands that the lognormal function is incompatible with proportional hazards. Please clarify the justification of the lognormal function being used for the base case, when the AIC and the BIC for the Weibull function are only marginally different from those of the lognormal with the Weibull more naturally fitting an assumption of proportional hazards.

Health-related quality of life

A18. Please clarify the patient group for whom EQ-5D-5L VAS data underlying figure 14 (page 66 of submission) was collected for. How would patients crossing over to ibrutinib contribute to this EQ-5D data? Please clarify whether figure 14 for the EQ-5D was measured by the UK social tariff and if not, please clarify which tariff was used and provide a version of figure 14 using the UK social tariff.

Adverse events

A19. **PRIORITY QUESTION** Please present in the table format below the number of patients who have not discontinued ibrutinib treatment in the ibrutinib arm at the end of each assessment time point and the total ibrutinib dose administered during the preceding period using the table format provided below. Please similarly present the number of patients who have not discontinued or completed ofatumumab treatment in the ofatumumab arm and the total ofatumumab dose administered during the preceding period. If this data is only readily available for the ibrutinib arm, please present this.

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	Ibrutinib arm		Ofatumumab arm	
Time	N not discontinued	Total drug admin (mg)	N not discontinued	Total drug admin (mg)
Wk1	???	???	???	???
Wk2	???	???	???	???
…	???	???	???	???
Wk8	???	???	???	???
Wk12	???	???	???	???
Etc.	???	???	???	???

A20. Adverse events (AE) and serious adverse events (SAEs) were reported as being higher in the ibrutinib arm. To what extent were the AE rates in the ofatumumab arm adjusted for cross-over? If it is not possible to present this, please state what number of the 191 patients in the ofatumumab arm at 6 months had crossed over. Please tabulate the values underlying table 44 (page 89 of submission), and if possible provide a similar tabulation of SAE rates by 6 month bands.

A21. Please explain the rationale for using the matching adjusted indirect comparison (MAIC) which matches 22 factors and therefore has the smallest effective sample size. What are the additional 3 factors to the 19 which are listed in Appendix 6?

A22. The hazard rate for overall survival has a baseline general population mortality rate. Considering that that Kaplan Meier PFS events are likely to include both progression and death, should the PFS hazards rates have had a similar baseline mortality rate?

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY QUESTION** Please provide the mean EQ-5D value at baseline and the mean EQ-5D value subsequent to baseline among the 17p depleted subgroup?

B2. **PRIORITY QUESTION** For the ibrutinib arm intention-to-treat population, please calculate the number of patients for whom EQ-5D values are available and the mean (and standard deviation) EQ-5D value using the UK social tariff. If possible, please detail how many of these patients have only partial data for model 1 or alternatively please include some measurement of the extent of missing data. Please also present in the table format below the number reporting EQ-5D with progressive disease and their mean (s.d.) EQ-5D using the investigator assessment of progression, and the parallel data using the independent research committee assessment of progression.

If the evidence allows, please provide the same analysis for the 17p depletion subgroup.

Please present the same data for the ofatumumab arm and for the ofatumumab arm among those who have not crossed over.

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	Patients reporting EQ-5D			Patients reporting EQ-5D with PD			
	Total	Mean QoL	Partial data	Inv. assessed PD		IRC assessed PD	
Time	N	EQ-5D μ (s.d.)	N	N	EQ-5D μ (s.d.)	N	EQ-5D μ (s.d.)
Baseline	???	???	???	???	???	???	???
Wk 4	???	???	???	???	???	???	???
Wk 8	???	???	???	???	???	???	???
etc.	???	???	???	???	???	???	???

B3. Please provide a copy of the QoL analysis report for appendix 12.

- The submission provides little detail on when the EQ-5D data was collected but it appears that EQ-5D data was collected subsequent to progression given the progressive disease element within the response category. Is this correct? Please clarify why progressive disease and stable disease were grouped together. Table A.3 (page 5 in appendix 12) only includes parameters for 1 responder variable rather than the 2 measures of responder status that are outlined on page 2 of appendix 12 (progressive disease + stable disease and progressive disease + stable disease + and partial response). Please state which predictor of responder status was used in the analyses summarised in table A.3. Please also provide another version of table A.3 using the alternative responder status definition.

- Appendix 12 states that a time covariate was included within the models and retained if it was statistically significant. Please provide the central estimates of their time covariates, their P value., the model values when the time covariates were included and whether the time covariate were included in the final models separately for each model as in table A.3 (on page 5 of appendix 12). .

- Please detail how the QoL values and the time covariates are calculated using the central parameter values of Table A.3 (page 5 of appendix 12) for a patient responding at week 12 with a baseline EQ-5D QoL of 0.7, treated with ibrutinib and who had experienced a grade 3 adverse event. Please provide the detail, separately for each of the 3 models.

B4. Please detail how missing data was handled within the EQ-5D analyses?

B5. It was unclear whether EQ-5D data was collected only up to the point of progression or whether any data after progression was collected. Is the last cycle of table A.4 (page 6 of appendix 12) the same as the cycle data collection point immediately after progression? If these are not the same please present a version of table A.4 for the cycle immediately after progression.

B6. The model only included SAEs that occurred in at least 5% of 1 arm of the RESONATE trial. Is this 5% specified within the protocol for the trial? Please provide the reasons given by the clinical experts for the use of this inclusion rule? Please present table 56 (page 125) for ibrutinib and for ofatumumab, and for the other

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comparators to the extent that data is available, for all grade 3 and grade 4 SAEs regardless of their incidence.

B7. The submission notes that the comparator physician choice was based upon Osterborg et al. adjusted to reflect UK practice. Please clarify what adjustments were made.

Section C: Textual clarifications and additional points

C1. Please clarify if the definition of progression that underlies the curves of appendix 10 was based upon the independent research committee assessed progression or investigator assessed progression.

C2. Table 25 (page 53) of the submission states that treatment was until disease progression. Was this progression assessed by the investigator or assessed by the independent research committee?

C3. Table 25 states that the duration of PFS as assessed by the independent research committee was the primary outcome. What was the time cut-off for this analysis?

C4. Please clarify the time cut-off for figure 9 (page 59) of the submission.

C5. Please clarify whether the OS for figure 17 (page 70 of submission) is intention-to-treat, censored for cross-over, RPSFT or something else.

C6. In the model treatment is assumed to stop at progression. How is progression measured?

C7. Please provide the data specific to the 51 patients receiving 420mg in PCY1102. Or explain why the data is unavailable.

C8. Appendix 12 states that “each dimension had three levels of severity” but the submission refers to the EQ-5D-5L VAS. Did RESONATE collect EQ-5D-3L or EQ-5D-5L?

C9. In the EQ-5D analysis did complete response (CR) include complete response with incomplete haematopoietic recovery (CRi)?

C10. Please provide a definition of INV responder in table A.2 (page 3-4) of appendix 12?

C11. What measures of response were applied within the EQ-5D analyses reported in appendix 12: investigator assessed, or IRC assessed or a mixture of both?

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C12. What measures of progression were applied within the EQ-5D analyses: investigator assessed, or IRC assessed, or a mixture of both?

C13. What is the definition of “censored” within table A.4 (page 6 of appendix 12)?

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID749]

The following notation is used: information submitted under 'commercial in confidence (CIC)' is highlighted in turquoise, and all information submitted under 'academic in confidence (AIC)' in yellow.

Encl. checklist for in confidence information
Encl. Excel file of commercial in confidence data: There is an accompanying Excel file to this document that contains requested Kaplan-Meier data. Each worksheet is labelled with the question number the data pertain to. Please consider this Excel file as CIC.

Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION**. The number of studies evaluated for inclusion in the flow diagram (Figure7) (15 RCTs + 26 non-RCTS) and the number of studies listed in Appendix 3 (Availability and comparability of data for relevant treatments in the UK) (N=33) are inconsistent. Please provide a list of all included and excluded studies, along with bibliographic details.

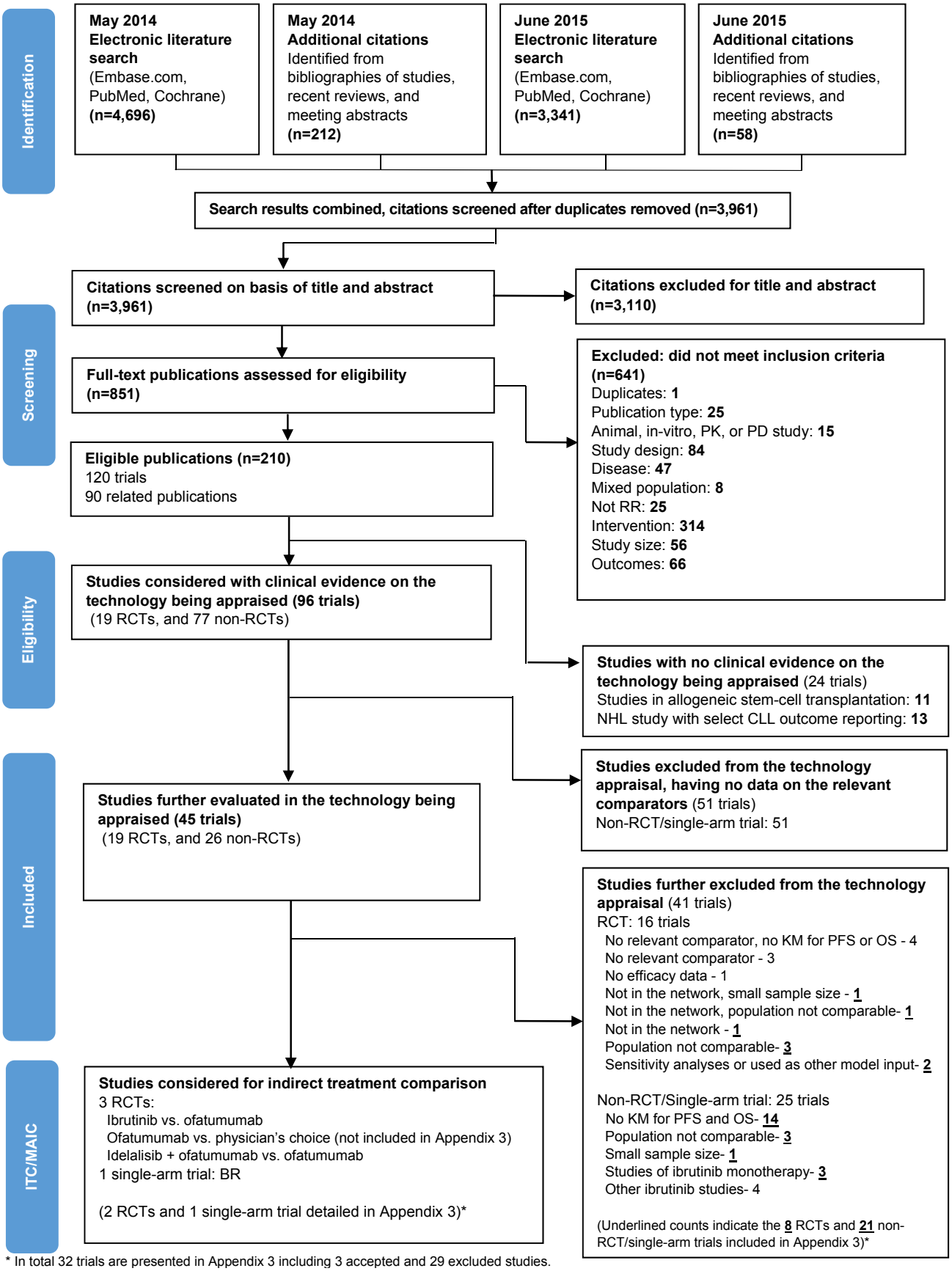
Figure 1 is a revised PRISMA diagram to provide further clarity. The revised diagram shows that 45 studies (19 RCTs + 26 non-RCTs) were 'further evaluated for consideration of relevant evidence'. This is updated from the initial 41 studies (15 RCTs + 26 non-RCTs) shown in Figure 7 of the submission; the update is due to reasons explained below.

The aim of Appendix 3 (*Availability and comparability of data for relevant treatments in the UK*) was to provide the Committee and the ERG with transparency around the level of assessment carried out on the studies which were identified by the SLR for further evaluation (i.e. to gauge whether they contained relevant evidence). Appendix 3 correctly provided a summary of the 33 studies evaluated but the reasoning behind the discrepancy between n = 33 and n = 45 was not explained clearly in the submission and therefore we provide further details here:

- 41 of the 45 studies were excluded (16 RCTs + 25 non-RCTs):
    - 8 of the 16 RCTs were included in Appendix 3; the other 8 RCTs did not require further detailed assessment as they did not include a relevant comparator and/or and KM data for PFS or OS (it was clear they did not provide relevant data which would help establish relative efficacy).
    - 21 of the 25 non-RCTs were included in Appendix; the other 4 non-RCTs were other ibrutinib studies which were appraised as part of the submission.

- 4 of the 45 studies were included (3 RCTs + 1 non-RCT):
    - 2 of the 3 RCTs were included in Appendix 3; 1 RCT (Österborg et al., 2014) was included separately by the SLR as a study which assessed comparators (ofatumumab and Physician's Choice, PC) not listed in the NICE Final Scope. Due to its relevance in allowing for indirect treatment comparisons (ITC) to be conducted in order to establish the relative efficacy of ibrutinib compared to comparators listed in the NICE Final Scope, it was included and was separately assessed as part of the ITC methodology (see Section 4.10 of the submission).
    - The non-RCT was included in Appendix 3.

Figure 1: Revised PRISMA diagram with further details added for clarity



* In total 32 trials are presented in Appendix 3 including 3 accepted and 29 excluded studies.

A2. **PRIORITY QUESTION**. Are there established definitions of “relapsed” disease and “refractory” disease used in the UK? Please provide a definition of “relapsed” disease and “refractive” disease used for this submission. Please comment on whether comparators differ for each group.

The British Committee for Standards in Haematology (BCSH) guidelines for CLL (BCHS, 2013) reference the International Workshop on Chronic Lymphocytic Leukemia (iWCLL) definitions of relapsed and refractory disease:

- Relapse: disease progression at least 6 months after achieving a complete response (CR) or partial response (PR).
- Refractory: treatment failure or disease progression within 6 months of anti-leukaemic therapy.

The guidelines further note that the duration of response that should influence the choice of second line therapy remains an area of continued debate.

The RESONATE trial defined relapsed and refractory disease as follows:

- Relapse: a patient who met criteria for CR or PR, but progressed beyond 12 months post-treatment.
- Refractory: treatment failure or disease progression within 12 months of anti-leukaemic therapy; furthermore, the refractory subgroup analysis conducted in RESONATE is more strictly for “purine-analogue refractory” patients.

The RESONATE definitions were used for this submission to align with the most robust clinical data available. It is not possible to retrospectively align the RESONATE subgroups to the definitions used by BCSH as these subgroups were pre-specified and required information would have had to be collected in a specific manner at patient enrolment in the trial.

With respect to comparators, clinical advice provided at an advisory board conducted by Janssen on 4th September 2015 (a full description of which can be found in the submission) suggested that treatment options are selected based on a number of factors and the most relevant comparator would likely change with the population under consideration, for example by the patients’ level of fitness and/or risk (i.e. the presence of 17p deletion or TP53 mutation). Figure 2 and Figure 6 in the submission shows the proposed therapies by fitness and risk group; these being:

- ***Unfit, low risk patients***: Ibrutinib, physician’s choice, idelalisib with rituximab (IR), bendamustine with rituximab (BR), and chlorambucil.

- ***Unfit, high risk patients***: Ibrutinib, IR, ofatumumab, and best supportive care (BSC)
- ***Fit, high risk patients***: Ibrutinib and IR
- ***Fit, low risk patients***: chemo-immunotherapy (e.g. FCR)

Survival Analyses

A3. **PRIORITY QUESTION** Please present the unadjusted OS Kaplan-Meier data for both arms separately without censoring for crossover. For the ofatumumab arm, please include patients who have crossed over and remain at risk in the number of patients remaining at risk. Please present the data in the table format included below. Please note that for a given time point not all columns may require data entries.

Please also present this data for the 17p subgroup.

The unadjusted Overall Survival (OS) data for both arms of RESONATE separately without censoring for crossover are provided in the accompanying Excel file entitled "ID749 ibrutinib - clarification letter – Janssen Response", sheet "A3a". Data for the 17p subgroup are also provided in sheet "A3b".

For the ofatumumab arm, please also present the RPSFT Kaplan-Meier estimator S(t) and the IPCW Kaplan Meier estimator S(t) at the corresponding time points. Please present the data in the table format included below. As above, not all columns may require data entries.

Please also present this data for the 17p subgroup.

For the ofatumumab arm, the Rank-preserving structural failure time (RPSFT) KM estimator S(t) and the Inverse probability of censoring weights (IPCW) estimator S(t) are also presented in the accompanying Excel file, sheet "A3c". Data for the 17p subgroup are also provided in sheet "A3d".

As RPSFTM results are only valid under the assumption of completely balanced treatment arms within a trial, and randomisation is only expected to create perfect balance across treatment arms on average, the RPSFTM-analysis was implemented, including baseline covariates known to have an important influence on the primary outcome, in order to compensate for any lack of balance between treatment arms and to improve precision. The following baseline covariates were included in the analysis: refractory disease, del17p and del11q, prior lines of therapy, ECOG status, age at baseline, gender, ethnicity, region, RAI disease stage, bulky disease, and β2-microglobulin.

As the cross-over adjusted HR is based on a multivariate cox proportional hazards regression model, it is not possible to simply create a Kaplan-Meier estimate of the counterfactual survival times for the ofatumumab arm that fully represents the full cross-over correction.

A similar problem exists for the IPCW method: the crossover adjusted HR is calculated based on a weighted repeated logistic regression model which serves an approximation for the time-dependent weighted cox model. Again, it is not trivial to create a KM curve that properly represents this cross-over adjustment.

To graphically illustrate the impact of the cross-over adjustment, the RPSFTM and IPCW adjusted survival curves for the ofatumumab arm, as presented in figure 1, were generated by applying the adjusted HR obtained from the RPFSTM ([redacted]) and IPCW ([redacted]) -models to ibrutinib arm. This is done by using the following formula:

$$S_{ofa}(t)=[S_{ibrut}(t)]^{(1/HR)},$$

Figure 2 illustrates that during the first 10 months of the follow-up, the simulated survival curves for both models fit very well the observed survival curve for the ofatumumab arm. After month 10, the observed survival of ofatumumab starts to flatten; this illustrates the survival benefit for the ofatumumab patients who have crossed-over to ibrutinib. The observed survival of ofatumumab then starts to diverge from the cross-over adjusted survival curves of ofatumumab, which simulate survival when cross-over would not have happened (the cross-over adjusted survival).

Figure 2: Overall survival by treatment arm: observed versus cross-over corrected survival curves

A4. **PRIORITY QUESTION** Please describe what constitutes a PFS event within the PFS analysis? What constitutes a censoring event within the PFS analysis?

Progression free survival (PFS) was defined as the time from the date of randomisation until disease progression or death from any cause, whichever occurred first.

A PFS event was defined as follows: a CT scan was required to evaluate all cases of suspected progressive disease regardless of the modality of disease progression (e.g. lymph node, lymphocytosis, or transformation). Progressive disease required at least ONE of the following:

- New enlarged nodes >1.5cm, new hepatomegaly or splenomegaly; or other organ infiltrates
- ≥50% increase from nadir in existing lymph node (must reach >1.5cm in the longest diameter) or ≥50% increase from nadir in sum of product of diameters of multiple nodes
- ≥50% increase from nadir in enlargement of liver or spleen
- ≥50% increase from baseline in lymphocyte count (and to ≥5 $x10^9$/L) unless considered treatment-related lymphocytosis
- New cytopenia (haemoglobin or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia, drugs, or bleeding), as documented by a decrease of Hgb levels from baseline by more than 20 g/L (2g/dL) or to less than 100 g/L (10g/dL) and lower than baseline, or by a decrease of platelet counts from baseline by ≥50% or to less than 100 × 10^9/L (100,000/µL) and lower than baseline in the presence of active CLL, defines disease progression; a marrow biopsy must demonstrate an infiltrate of clonal CLL cells if no other evidence of disease progression is present on CT scan.
- Transformation to a more aggressive histology (e.g., Richter's Transformation). Whenever possible, this diagnosis should be established by biopsy.

Suspected progressive disease had to be confirmed by a serial exam at least 2 weeks later and required Independent Review Committee (IRC) confirmation. PFS was assessed by IRC as well as investigators (INV) for the first 9.4 months (interim analysis); after that, PFS was only assessed by the investigators.

Patients who withdrew from the study or who were considered lost to follow-up without prior documentation of disease progression were censored on the date of the last adequate disease assessment. For patients without an adequate post-baseline disease assessment, PFS were censored on the date of randomisation.

A5. **PRIORITY QUESTION** Please present the independent review committee (IRC)-assessed PFS Kaplan Meier data for both arms using the table format provided below. If available, please present the same for the 17p subgroup.

The IRC-assessed PFS KM data for both arms are presented in the accompanying Excel file, sheet “A5a”. Data for the 17p subgroup are also provided in sheet “A5b”. These data are from the interim analysis (9.4 month data cut).

As stated above, following the 9.4 month interim analysis, PFS was only assessed by the investigators. Therefore, only 9.4 months of data are available for IRC-assessed PFS. It is therefore important to bear in mind that this submission used the 16-month data cut from RESONATE within the cost-effectiveness analysis and as such, used the INV-assessed PFS. The updated analysis (16-month data cut) was used because these data represent the longest follow-up available for the pivotal phase III study, providing greater certainty. Furthermore, INV assessment is more representative of clinical practice because within a real world setting, independent blinded review is not applicable.

A6. **PRIORITY QUESTION** Please present the investigator assessed PFS Kaplan Meier data for both arms using the table format provided below. If available, please present the same for the 17p subgroup.

The INV-assessed PFS KM data for both arms are presented in the accompanying Excel file, sheet “A6a”. Data for the 17p subgroup are also provided in sheet “A6b”. These data are from the updated analysis (16 month data cut).

A7. **PRIORITY QUESTION** Please present the Kaplan Meier data for Figures 21, 22 and 23 (pages 85-6).

The KM data are presented in the accompanying Excel file, sheet “A7” for the following:

- Figure 21: PCYC1102 PFS for all patients based on 26 month data cut
- Figure 22: PCYC1102 OS for all patients based on 26 month data cut

With respect to Figure 23, it refers to the PCYC1102/1103 PFS for patients given 420 mg based on 30 month data cut (n = 67). These data are summarised in Table 1 and the full data can be found in the accompanying Excel file, sheet “A7”.

Table 1: PFS by Investigator Assessment, Relapsed/Refractory Patients, Study 1102 + 1103 Long Term Follow-up

	RR420 mg (N=67)	RR840 mg (N=34)	RR Total (N=101)
[redacted]			

PD = Progressive disease, N = Number of subjects who achieved PR or better, n = number of subjects within the subset, CI = Confidence Interval, K-M = Kaplan-Meier, NR = Not reached, NE= Not estimable, PR = Partial Response.
[1] Subjects that have not been assessed as disease progression by investigators or died are included as 'censored'.
[2] Progression-free time is calculated as the number of months from first dose date of study treatment to disease progression or death or date of censoring. Months are derived as days x 12/365.25.

A8. According to the EPAR for ibrutinib (page 98/140), the RESONATE trial was stopped early at 146 progression free survival (PFS) events due to a positive interim analysis. Are the data in the submission based on the interim analysis of RESONATE? Were further data collected beyond that stage?

The interim analysis for RESONATE comprised of 9.4 months of trial data (interim analysis). Further data were collected beyond the interim analysis - an additional data cut at median follow-up of 16 months provides additional data (updated analysis).

As stated within the submission, the data presented in the clinical sections are from the interim analysis drawn from the published paper (Byrd et al., 2014) and from the trial CSR (Pharmacyclics, 2014). Data from the updated analysis (available from a poster and abstract presented at ASH in December 2014 (Brown et al., 2014)) are also presented to further supplement the results of the interim analysis.

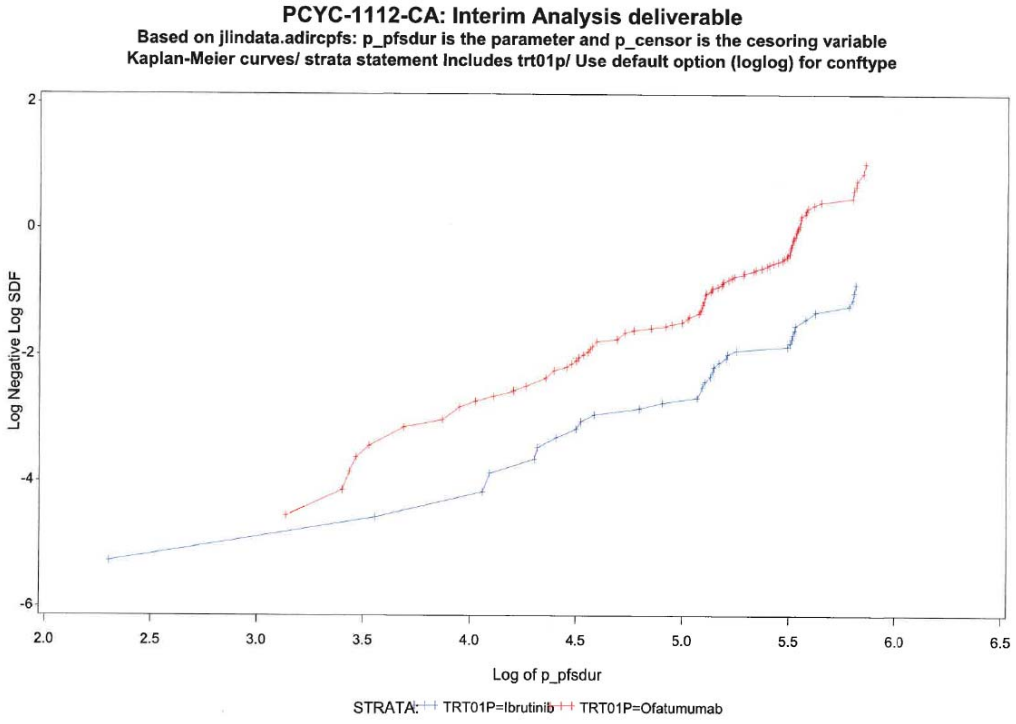
The cost-effectiveness analysis uses the updated analysis (16 month data) wherever possible as the updated analysis represents the longest follow-up, providing further certainty and robustness to the RESONATE data.

A9. Were proportionate hazards tested for within the RESONATE trial PFS data? If so, please describe how this was done and the relevant results.

The proportional hazards assumption was tested for within the RESONATE trial PFS data at interim analysis. If hazards are proportional, then log(-log(survival) versus log(time) plot will show parallel curves. The null hypothesis to test for treatment*time interaction (hazards are proportional) was also performed.

Results show no evidence that hazards are not proportional (see Figure 3 below).

Figure 3: Test for proportional hazards assumption



A10. Was data collected on the mean response durations by arm, or median response durations if means are not available, for complete response (CR), CR with incomplete hematopoietic recovery (CRi) and partial response (PR) in RESONATE (1112), PCY1102 and PCY1103? If so, please present this data.

The data collected on response from RESONATE (1112) are presented in Table 32 of the submission.

The data collected on response from PCYC1102 are presented below in Table 2.

Table 2: Response to treatment in PCYC1102

	RR 420 mg dose (n=21)	**RR High Risk 420 mg dose (n=17)**
Time to initial response (months) n Mean (SD) Median (min, max)		
Time to best response (months) n Mean (SD) Median (min, max)		
Time to complete response (months) n		

Mean (SD) Median (min, max)	[redacted]	
RR – relapsed or refractory; SD – standard deviation Source: Pharmacyclics, 2013		

The data collected on response from PCYC1103 are presented below in Table 3.

Table 3: Response to treatment in PCYC1103

	RR 420 mg dose (n=61)
Median time to initial response, months	1.8
Median time to best response, months	7.4
Median time to complete response, months	19.9
Median DOR, months (95% CI) 30-month DOR (95% CI)	NR (35.9 to NE) 82.2% (68.5 to 90.4)
RR – relapsed or refractory; CI – confidence interval; DOR – duration of response; NR – not reached; NE – not estimated. Source: Coutre et al., 2015	

A11. According to the RESONATE CONSORT diagram (figure 9, page 59), 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm discontinued treatment in the RESONATE trial due to reasons other than progression or death.

- Was progression monitored after discontinuation and, if so, how was it treated in the PFS Kaplan-Meier curves?
- How many of those 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm were lost to follow up in terms of progression? How was this treated within the PFS Kaplan-Meier curves?
- How many of the 24 patients in the ofatumumab arm that this applies to discontinued treatment without having crossed over to ibrutinib?
- How many of those 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm were lost to follow up due to death? How was this treated within the overall survival (OS) Kaplan-Meier curves?

All patients were followed for disease assessment until progressed disease, irrespective of treatment discontinuation. If a patient had progressed disease, it was counted as progression; otherwise, the patient was censored at the last disease assessment.

There were 10 patients (11 patients are erroneously quoted in question A11) in the ibrutinib arm and 24 patients in the ofatumumab arm who discontinued treatment due to reasons other than progression or death.

Of the 10 patients in the ibrutinib arm:

- 5 had PFS during post-end of treatment follow-up (1 death, 4 progressed disease, PD).

- 5 were censored; 4 at the last adequate disease assessment date and 1 at the randomization date (no post-baseline disease assessment); 2 of the 5 censored subjects withdrew from the study after treatment discontinuation, and 3 were being followed at the clinical cut-off.

Of the 24 patients in the ofatumumab arm:

- 13 had PFS during post-end of treatment follow-up (6 deaths, 7 PD).
- 11 were censored; 9 at the last adequate disease assessment date and 2 at the randomisation date (no post-baseline disease assessment); 2 of the 11 censored subjects withdrew from the study after treatment discontinuation, and 9 were being followed at the clinical cut-off.

These data are summarised in Table 4.

Lastly, 19 of the 24 patients in the ofatumumab arm did not cross over to ibrutinib.

Table 4: Summary of details associated with RESONATE CONSORT diagram

		Ibrutinib N	Ofatumumab N
PFS Event during follow-up	Death	1	6
	PD	4	7
	Total	***5***	***13***
Censored	***Time of censoring***		
	At last adequate assessment date	4	9
	At randomization date (no post-baseline assessment)	1	2
	Total	***5***	***11***
	Disposition after treatment discontinuation		
	Withdrew from study	2	2
	In follow-up at clinical cut-off	3	9
	Total	***5***	***11***
	Grand total	***10***	***24***

A12. Table 64 (pages 154-5) suggests that section 5.3 and appendix 10 provide details of the Kaplan Meier time to treatment discontinuation curve for ibrutinib, but these data are not in the sections referenced. Please direct us to the Kaplan Meier curves if included in the submission. Otherwise, please provide the Kaplan-Meier time to treatment discontinuation data curves and tabulate the Kaplan Meier time to treatment discontinuation data for ibrutinib treatment in the ibrutinib arm and for ofatumumab treatment in the ofatumumab arm for all patients using the table format provided below.

Please also present these data for the 17p subgroup.

The omission of the time to treatment discontinuation (TTD) KM curve from the referenced section within the submission was by error. The time to treatment

discontinuation KM data (and curves) for both arms are presented in the accompanying Excel file, sheet “A12a”. Data for the 17p subgroup are also provided in sheet “A12b”. These data are from the interim analysis (16 month data cut).

Parametric fitting

A13. **PRIORITY QUESTION** Page 5 of appendix 4 states that the results from the IPCW model are nearly identical to the RPSFT model, but the details of the IPCW results are not included. Please provide the IPCW results for the intention-to-treat (ITT) analysis and for the early ITT analysis when only 47 patients had crossed over. Also, please explain the rationale for choosing the cut-off of 47 patients crossing over for the early ITT analysis.

The IPCW results are presented in Appendix 4 and are replicated here for ease of reference:

[redacted]

The corresponding results from the RPSFT model resulted in an estimate of [redacted]. Thus, the IPCW results further corroborate the RPSFT results.

The early ITT analysis was based on a pre-specified interim analysis for both superiority and futility performed after approximately 117 PFS events were reported in RESONATE; 117 PFS events correspond to 50% of the required number of 234 PFS events for the final analysis. At the time of this early ITT analysis, 47 patients had crossed over.

A14. The ERG has been unable to replicate the log logistic curves included in Appendix 10 of the submission despite using several functional forms using the intercept and scale parameters. Please specify the correct functional form.

The log logistic parameters presented in Appendix 10 were verified against the RESONATE trial data analysis results. Log logistic curves in Appendix 10 are derived based on the following functional form where the time unit is per 4-week cycle:

$$S(t) = \frac{1}{\left(1 + e^{\frac{-\text{Intercept}}{\text{Scale}}} * t^{\frac{1}{\text{Scale}}}\right)}$$

A15. Parameterised curves appear to be used with the exception of the time to treatment discontinuation curve for ibrutinib. What is the rationale for this approach? If possible, please provide a corresponding time to treatment discontinuation curve for ofatumumab.

Treatment discontinuation KM data for ibrutinib as reported in the RESONATE trial are used directly to inform the treatment discontinuation during the trial period. Following the

trial period, long-term projection of treatment discontinuation is assumed to be the same as the long-term projection of PFS. The reasons for this approach are described below.

Parametric fitting was carried out on the treatment discontinuation KM data for ibrutinib. Using parameterised curves and extrapolating the trial treatment discontinuation curve over the full time horizon of the cost-effectiveness analysis, however, introduces challenges in terms of clinical validity:

- A log-logistic fitting was found to be the best fit based on AIC and BIC statistics; however, the long-term projection using log-logistic showed that over 30% of patients remained on treatment at 10 years, which is not considered clinically plausible.

- A lognormal fitting was also found to lack clinical plausibility as the long term projection showed that more than 30% of patients remained on treatment at 10 years.

- Exponential and Weibull fittings provided long-term projections that were more clinically plausible; however, both projected curves cross with the long-term projection of PFS (Figure 4). This is inconsistent with the trend shown by the comparison of the PFS and treatment discontinuation KM data and ibrutinib's treat-to-progression indication.

Because long-term projections of treatment discontinuation either were not clinically plausible or intersected with PFS projections (which contradicts the observed relationship between treatment discontinuation and PFS in the trial and ibrutinib's treat-to-progression indication), the parameterised curves were not applied. The base case uses the direct KM data for the trial duration and then assumes the same long-term projection of PFS for the remainder of the modelled time horizon. In scenario analyses, the full treatment discontinuation curve is set equal to the projected PFS curve. Considering the relationship of treatment discontinuation and PFS seen within the trial, using PFS as a proxy for treatment discontinuation is a conservative approach both in part (as in the base case) and in full (as in the scenario analyses), as this assumption may in fact overestimate ibrutinib time-on-treatment.

With respect to ofatumumab treatment discontinuation, it is assumed to be the same as the ofatumumab PFS up to the maximum treatment duration. This is not a conservative assumption given that the RESONATE trial data demonstrated a small portion of ofatumumab-treated patient discontinue treatment prior to disease progression (Figure 5). As ofatumumab is a fixed treatment duration drug, however, the impact of this assumption on model results is small. The ICER for ibrutinib vs. ofatumumab changes from £45,525 in the current base case to £46,148 by using the RESONATE trial reported ofatumumab treatment discontinuation KM curve.

Table 5 below summarises the data used to estimate the parameterised treatment discontinuation curves for ibrutinib.

Table 5: Parametric fittings of ibrutinib treatment discontinuation

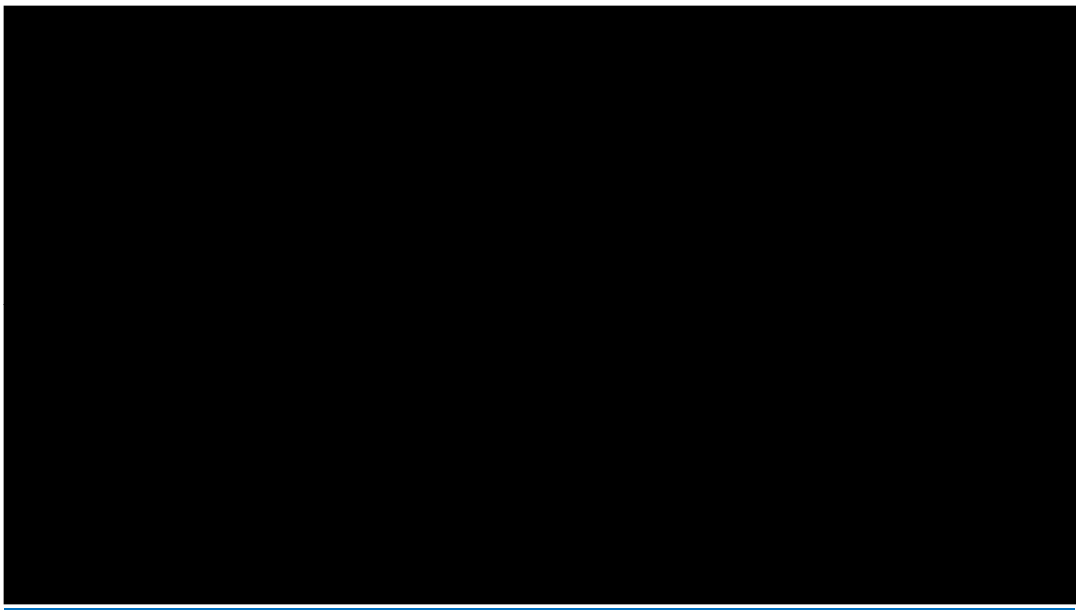
	Param 1	s.e.	Param 2	s.e.	Param 3	s.e.	AIC	BIC
	Intercept		Scale		Shape			
Weibull	4.115	0.239	1.003	0.140	0.997	0.140	318.99	325.54
Lognormal	4.129	0.273	1.848	0.223			318.58	325.13
Loglogistic	4.111	0.146	1.000	NA	1.000	NA	316.99	320.27
Exponential	3.901	0.228	0.940	0.128			318.92	325.46

AIC; Akaike information criterion; BIC: Bayesian information criterion; Param: parameter; s.e.: standard error

Figure 4: Comparison of Treatment Discontinuation and PFS of Ibrutinib

KM: Kaplan Meier; PFS: progression-free survival; TTD: time to treatment discontinuation

Figure 5: Comparison of Treatment Discontinuation and PFS of Ofatumumab



PFS: progression-free survival; TTD: time to treatment discontinuation

A16. Does the post-progression survival analysis include patients in the ofatumumab arm who progressed and subsequently crossed over to receive ibrutinib? Please present the Kaplan Meier data using the table formats below, split by arm for all patients that underlies figure 10 (page 8 of appendix 10). Please present this assuming that time zero is the time of progression as in figure 10 of appendix 10.

Please also present this data to the extent that it is available for the 17p subgroup.

OS in the cost-effectiveness model was estimated based on projections of the empirical OS KM data from RESONATE directly. Therefore, no analysis of post-progression survival data was explicitly incorporated.

Figure 10 of Appendix 10 shows the PFS of subsequent treatment, which is considered in the post progression health state (PPS). In PPS, some patients may still receive a subsequent treatment which is assumed to lead to an additional progression-free period (associated with the subsequent treatment) for the patients in the post-progression health state.

Time in progression free survival of subsequent treatment within the PPS state was based on the PFS of rituximab from the Furman, et al. publication of Study 116, as illustrated in Figure 10 of Appendix 10. The PFS of rituximab from Study 116 was used as proxy to inform subsequent treatment PFS, which impacted routine follow-up costs and subsequent treatment duration, but did not impact any health outcomes, such as OS or QALYs.

The same approach and data were used for the del17p subgroup.

A17. Both the RPSFT and the IPCW analyses appear to assume proportionate hazards. Hazard ratios are applied to the ibrutinib OS curve to derive the OS curves for the other comparators. However, the base case assumes a 3 year lognormal OS curve for ibrutinib. The ERG understands that the lognormal function is incompatible with proportional hazards. Please clarify the justification of the lognormal function being used for the base case, when the AIC and the BIC for the Weibull function are only marginally different from those of the lognormal with the Weibull more naturally fitting an assumption of proportional hazards.

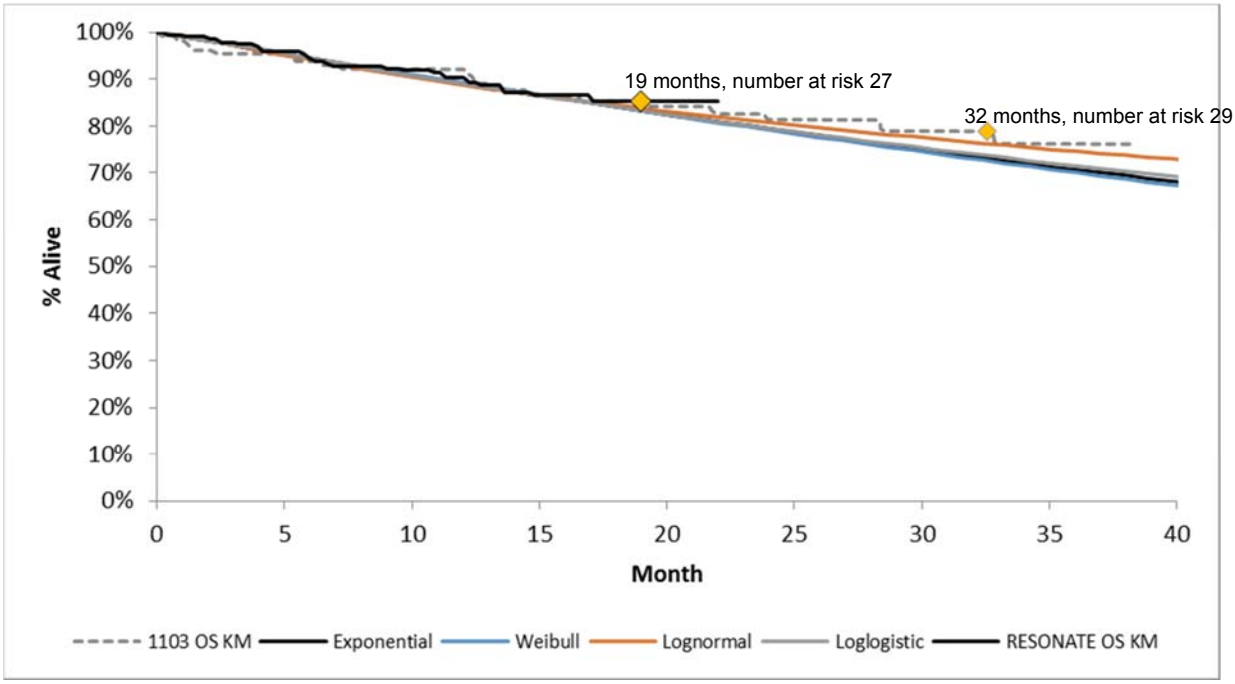
As the ERG notes, goodness of fit statistics were similar across parametric fittings of RESONATE KM data. OS data for R/R CLL patients from the ibrutinib PCYC1102/1103 trial, which had a similar patient population to RESONATE but provided longer follow up (44 months), were also used to help determine the appropriate parametric functions for the ibrutinib arm. The OS of ibrutinib from the RESONATE trial is similar to the OS from the PCYC1102/1103 trial and the lognormal prediction from RESONATE best matched the KM curve of OS from the ibrutinib PCYC1102/1103 trial (Figure 6).Long-term projection of lognormal may not be clinically plausible, however, given that this distribution has a decreasing hazard in the long-term. Therefore, lognormal is used to inform outcomes only for three years based on observations from the PCYC1102/1103 trial; Weibull is used for the remainder of the modelled time horizon.

When using the lognormal fitting, the hazard rate of the reference curve was calculated for each model cycle. The mean hazard rate of comparators for a given cycle is calculated by multiplying the hazard rate of the reference curve with a hazard ratio. The OS curves for comparators are calculated from the hazard rates. Hazard ratios were not directly applied to the scale parameter lambda. Table 6 below illustrates the calculation steps.

Table 6: Derivation of OS for Comparators

Cycle	OS (reference curve)	Hazard rate (reference curve)	Hazard rate (comparator)	OS (comparator)
N	Sref(n)			
n+1	Sref(n+1)	Hazard rate ref(n)= [Sref(n)-Sref(n+1)]/Sref(n)	Hazard rate comp(n)= Hazard rate ref(n) * HR of comp vs. ref	Scomp(n+1)= Scomp(n)*[1-Hazard rate comp(n)]
HR: hazard rate; OS: overall survival Sref(n): % of patients remain alive at time n according to the reference curve. Scomp(n): % of patients remain alive at time n according to the comparator curve. Hazard rate ref(n): the mean hazard rate between time n and time n+1 for the reference curve. Hazard rate comp(n): the mean hazard rate between time n and time n+1 for the comparator curve.				

Figure 6: (Original submission Figure 32): Comparison of ibrutinib OS projection from RESONATE Trial with KM data from 1102/1103 trial



KM: Kaplan Meier; OS: overall survival

Health-related quality of life

A18. Please clarify the patient group for whom EQ-5D-5L VAS data underlying figure 14 (page 66 of submission) was collected for. How would patients crossing over to ibrutinib contribute to this EQ-5D data? Please clarify whether figure 14 for the EQ-5D was measured by the UK social tariff and if not, please clarify which tariff was used and provide a version of figure 14 using the UK social tariff.

The EQ-5D data within RESONATE was measured by the UK social tariff. As a full list of the UK social tariff (i.e. index values) is not yet available for EQ-5D-5L, the cross-walk approach, which establishes a link or "bridge" between the EQ-5D-3L and EQ-5D-5L descriptive systems, was used. As such, the complete list of UK index values associated with EQ-5D-3L was used. The full description of this methodology can be found in Section 4 (“Converting EQ-5D-5L states to an index value”) of the EQ-5D-5L User Guide (Rabin et al., 2011 and van Reenen et al., 2015).

Adverse events

A19. **PRIORITY QUESTION** Please present in the table format below the number of patients who have not discontinued ibrutinib treatment in the ibrutinib arm at the end of each assessment time point and the total ibrutinib dose administered during the preceding period using the table format provided below. Please similarly present the number of patients who have not discontinued or completed ofatumumab treatment in the ofatumumab arm and the total ofatumumab dose administered during the preceding period. If this data is only readily available for the ibrutinib arm, please present this.

Table 6 provides a summary of the number of patients who have not discontinued and the total dose administered, by RESONATE treatment arm. The data are outputs of analyses based on study drug exposure as reported in the CSR (Pharmacyclics, 2014).

Table 7: Summary of Exposure Over Time; Safety Population (Study PCYC-1112-CA)

A20. Adverse events (AE) and serious adverse events (SAEs) were reported as being higher in the ibrutinib arm. To what extent were the AE rates in the ofatumumab arm adjusted for cross-over? If it is not possible to present this, please state what number of the 191 patients in the ofatumumab arm at 6 months had crossed over. Please tabulate the values underlying table 44 (page 89 of submission), and if possible provide a similar tabulation of SAE rates by 6 month bands.

AEs and SAEs associated with patients who crossed over were collected separately and were not considered as part of the AE data collected from patients who had initially started on either ibrutinib or ofatumumab and had not crossed over. Essentially, AE and SAE data were collected for 'three' patient groups:

1. The AE data associated with the ibrutinib arm consisted only of data from patients who initiated ibrutinib and did not include those who had crossed over to ibrutinib from ofatumumab.

2. The AE data associated with the ofatumumab are consisted only of data from patients who initiated ofatumumab until the point they crossed over to ibrutinib

3. The AE data associated with the cross-over patients were collected and recorded separately from the above two patient groups.

A21. Please explain the rationale for using the matching adjusted indirect comparison (MAIC) which matches 22 factors and therefore has the smallest effective sample size. What are the additional 3 factors to the 19 which are listed in Appendix 6?

The list of 19 characteristics provided in Appendix 6 is the overall list of key variables for appraisal in any study selected from an MAIC. Not all of these variables were captured from the Fischer et al., 2011 publication (e.g. RAI, bulky disease, ECOG status, race, DEL13q, Trisomy12, and white blood cell count were not captured) which was the study used for the MAIC to establish relative efficacy of ibrutinib compared with bendamustine and rituximab (BR).

The 22 variables are those which are listed in Table 1 and Table 2 of Appendix 6. There are often more variables per characteristic and as such, there are 22 variables pertaining to only 12 characteristics from the overall list of 19 characteristics initially introduced.

A22. The hazard rate for overall survival has a baseline general population mortality rate. Considering that that Kaplan Meier PFS events are likely to include both progression and death, should the PFS hazards rates have had a similar baseline mortality rate?

To ensure clinical face validity, the PFS projection is capped to be no higher than the OS projection (Col R in model engine). Thus, a baseline mortality rate is indirectly applied to PFS through this capping approach.

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY QUESTION** Please provide the mean EQ-5D value at baseline and the mean EQ-5D value subsequent to baseline among the 17p depleted subgroup?

Table 8 and Table 9 present the EQ-5D values for ibrutinib and ofatumumab, respectively, the 17p deletion subgroup. These data are based on the interim analysis (9.4 month data cut).

While the subgroup analysis of EQ-5D data were considered in developing the submission, due to the small sample size of the 17p deletion subpopulation, it was decided that such an analysis would not generate meaningful utility values and as such, it was a more robust approach to use the EQ-5D data from the overall R/R CLL population. Incorporating the EQ-5D data for the 17p deletion subgroup into the model as an additional scenario analysis for the comparison versus PC would result in an ICER of £40,295 at list price (versus £38,124 at list price in the base case using the overall R/R utility data).

Table 8: Summary of EQ-5D-5L Utility Score Over Time for Subjects Randomised to Ibrutinib with Presence of 17p Deletion

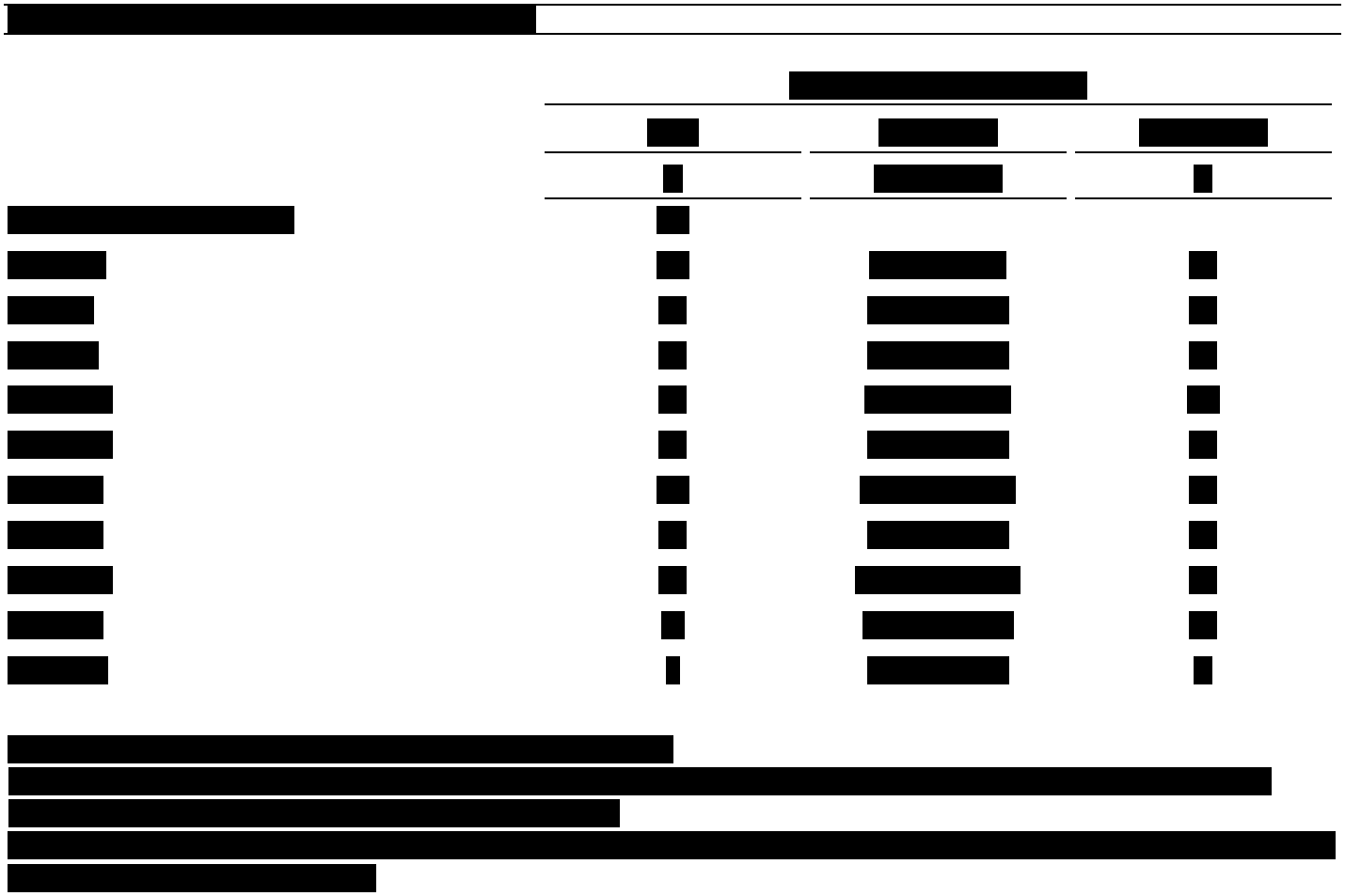
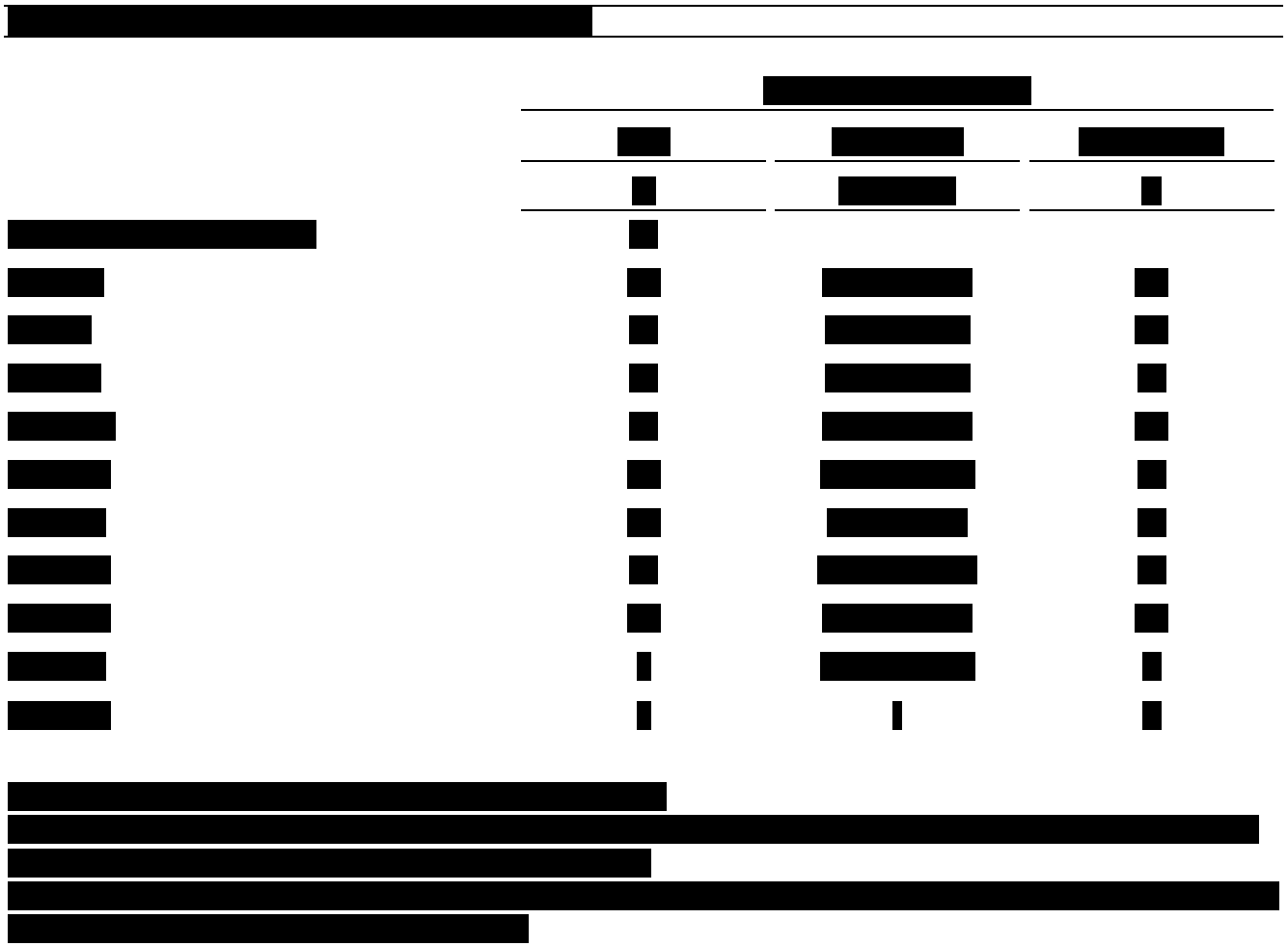


Table 9: Summary of EQ-5D-5L Utility Score Over Time for Subjects Randomised to Ofatumumab with Presence of 17p Deletion



B2. **PRIORITY QUESTION** For the ibrutinib arm intention-to-treat population, please calculate the number of patients for whom EQ-5D values are available and the mean (and standard deviation) EQ-5D value using the UK social tariff. If possible, please detail how many of these patients have only partial data for model 1 or alternatively please include some measurement of the extent of missing data. Please also present in the table format below the number reporting EQ-5D with progressive disease and their mean (s.d.) EQ-5D using the investigator assessment of progression, and the parallel data using the independent research committee assessment of progression.

If the evidence allows, please provide the same analysis for the 17p depletion subgroup.

Please present the same data for the ofatumumab arm and for the ofatumumab arm among those who have not crossed over.

Table 10 and Table 11 present the EQ-5D values for ibrutinib and ofatumumab, respectively. These data are based on the interim analysis (9.4 month data cut) and are consistent with the data presented in Appendix 12 from which utility at baseline and utility during PFS were derived.

An analysis of post-progression utility data from RESONATE was conducted but was not found to be meaningful. EQ-5D data were collected in the RESONATE trial at screening/week1 (baseline), every 4 weeks in the first 24 weeks, every 12 weeks starting from the week 24 visit until disease progression was confirmed by IRC, and at the last treatment visit before treatment discontinuation. The only opportunity to collect EQ-5D data for patients with progressive disease therefore occurred at the last treatment visit before discontinuation. This visit may or may not have been proximate enough to the progression event itself to capture a change in QoL associated with progression. Accordingly, trial data on QoL at progression were not used in the economic model. Instead, utility associated with post-progression was based on published sources.

We have not presented data for the ofatumumab arm excluding those patients who had crossed over to ibrutinib because crossover occurred only after progression (it is important to note here that the 4 patients who did cross over prior to progression were protocol violations). Therefore, censoring patients who crossed over would only impact post-progression utility which, as discussed above, was not found to be meaningful.

Table 10: Summary of EQ-5D-5L Utility Score Over Time for Subjects Randomised to Ibrutinib

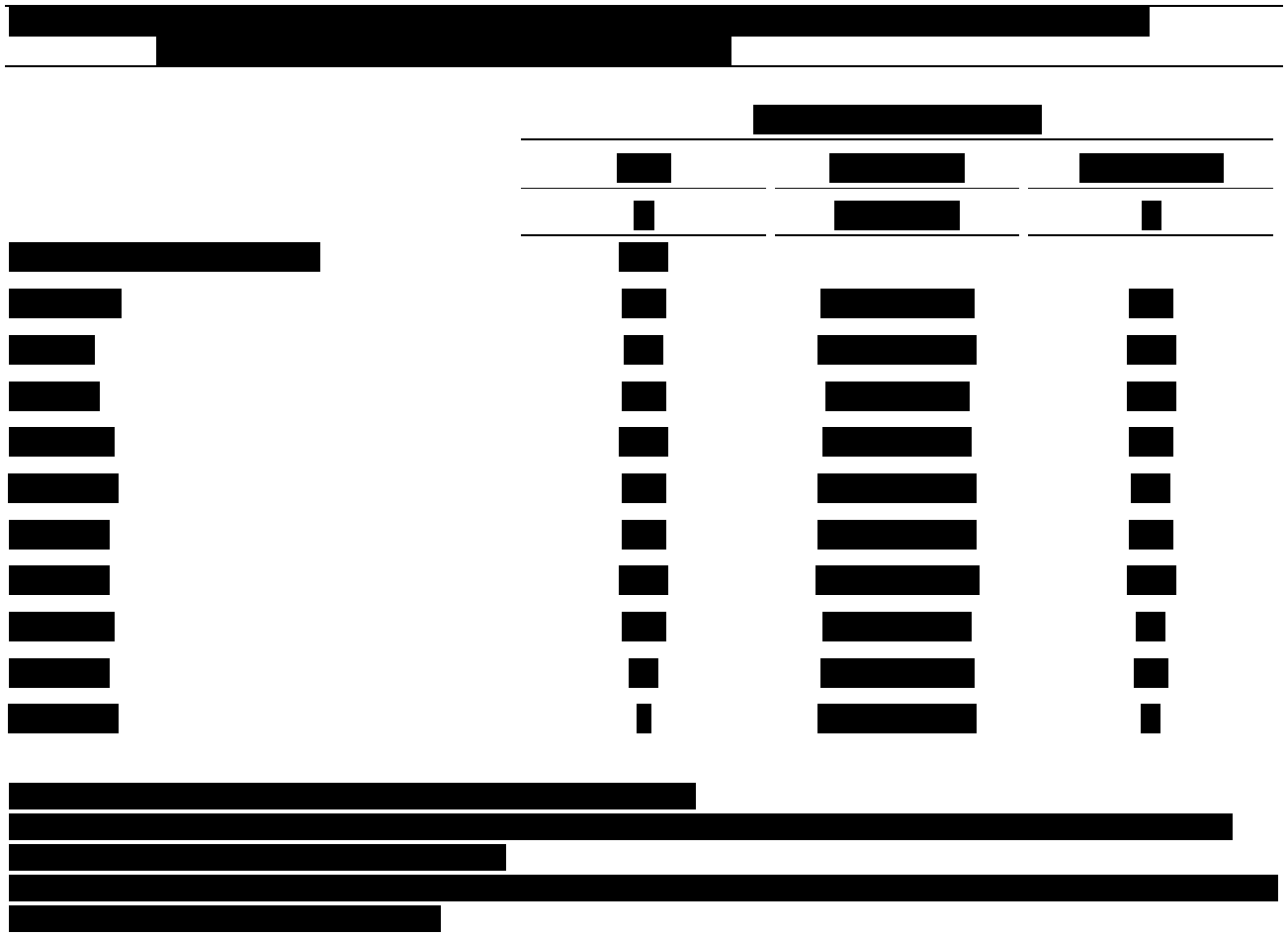


Table 11: Summary of EQ-5D-5L Utility Score Over Time for Subjects Randomised to Ofatumumab

B3. Please provide a copy of the QoL analysis report for appendix 12.

Appendix 12 presents a full report of the RESONATE QoL analysis which was conducted specifically to inform the economic model. It should be noted that only two utility values from the RESONATE QoL analysis presented in Appendix 12 were ultimately implemented in the economic model: a value of 0.799 to inform utility for patients in PFS and a value of 0.763 (from which a decrement of 0.098 was subtracted, based on the relationship between baseline and post-progression survival utility values in Beusterien, 2010) to inform utility for patients in PPS.

The RESONATE QoL analysis presented in Appendix 12 was based on the interim analysis (9.4 month data cut). In the trial, EQ-5D data were collected at screening/week1 (baseline), every 4 weeks in the first 24 weeks, every 12 weeks starting from the week 24 visit until disease progression was confirmed by IRC, and at the last treatment visit before treatment discontinuation. The 9.4 month data cut was used to inform utility data because reporting of IRC-assessment of PFS discontinued after the 9-month data cut. One limitation of these data is that the model extrapolates PFS outcomes based on INV-assessed PFS, but by necessity had to rely on EQ-5D data assessed at the time of IRC confirmation of PFS. These data reflect the best available evidence of QoL for the relevant population.

- The submission provides little detail on when the EQ-5D data was collected but it appears that EQ-5D data was collected subsequent to progression given the progressive disease element within the response category. Is this correct? Please clarify why progressive disease and stable disease were grouped together. Table A.3 (page 5 in appendix 12) only includes parameters for 1 responder variable rather than the 2 measures of responder status that are outlined on page 2 of appendix 12 (progressive disease + stable disease and progressive disease + stable disease + and partial response). Please state which predictor of responder status was used in the analyses summarised in table A.3. Please also provide another version of table A.3 using the alternative responder status definition.

  In the RESONATE trial, EQ-5D data were collected at screening/week1 (baseline), every 4 weeks in the first 24 weeks, every 12 weeks starting from the week 24 visit until disease progression was confirmed by IRC, and at the last treatment visit before treatment discontinuation. The regression analyses for the results presented in Appendix 12, Table A.3 only included EQ-5D assessments collected during the PFS period assessed by IRC, but did not include the assessment at the last treatment visit.

  The analysis was conducted to initially also consider the impact of response in the model. For this reason the analyses were stratified to capture potential differences in PFS utility according to response status. This is the reason that EQ-5D analysis results reported in Appendix 12 Table A.2 were stratified by response status (responder vs. non-responder). The response category included patients who achieved either a partial or complete response to treatment. Given that no statistically significant differences were identified in PFS utility according to response status, utility stratified by response status is not used in the model. Instead, a weighted average utility for all patients who remain in PFS from week 4 to week 60 is used.

  At the 9-month data cut, no complete responses (CR, CRi, or nPR) were reported for IRC assessed response; all responders in both ibrutinib and ofatumumab arms had

achieved only a PR. Therefore, regression analysis further stratifying response by CR, PR and SD was not conducted with the 9-month data cut.

- Appendix 12 states that a time covariate was included within the models and retained if it was statistically significant. Please provide the central estimates of their time covariates, their P value., the model values when the time covariates were included and whether the time covariate were included in the final models separately for each model as in table A.3 (on page 5 of appendix 12). .

  Time covariate was found to be statistically insignificant, and thus was not included in the final model. Time (in weeks) was tested as a continuous variable in the preliminary regression analysis. Given that the time covariate was found to be statistically insignificant in all regression models, it was not included in the final regression model. The preliminary analysis results are not available for reporting.

- Please detail how the QoL values and the time covariates are calculated using the central parameter values of Table A.3 (page 5 of appendix 12) for a patient responding at week 12 with a baseline EQ-5D QoL of 0.7, treated with ibrutinib and who had experienced a grade 3 adverse event. Please provide the detail, separately for each of the 3 models.

  As described in Appendix 12, because there was no statistical significance identified for time dependent variable of response and AE, the regression analysis results were not included in the model. The calculation steps for the utility estimate of the sample patient below are only used to illustrate how the variables were defined in the regression analysis.

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Table 12: Derivation of utility of sample patient (Note: not used in the model)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
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B4. Please detail how missing data was handled within the EQ-5D analyses?

Compliance rates for EQ-5D measures at baseline were [redacted] for ibrutinib and ofatumumab, respectively. From week 4 to week 24, compliance rates ranged from [redacted] for ibrutinib and [redacted] for ofatumumab.

Analyses for EQ-5D index scores were performed using mixed-model repeated measures (MMRM) with an unstructured covariance matrix. In this event of non-convergence, the compound symmetry covariance structure could be used. Alternative analyses use imputation methods such as worst observation carried forward (WOCF) and last observation carried forward (LOCF) were also explored.

B5. It was unclear whether EQ-5D data was collected only up to the point of progression or whether any data after progression was collected. Is the last cycle of table A.4 (page 6 of appendix 12) the same as the cycle data collection point immediately after progression? If these are not the same please present a version of table A.4 for the cycle immediately after progression.

EQ-5D was collected up to the cycle when disease progression was confirmed by IRC, and at the "end of treatment" visit. The data presented in table A.4 of Appendix 12 for the cohort labelled as progression (baseline n=116, last cycle n=123) reflect the data collected immediately after progression. As described in the response to question B2, the only opportunity to collect EQ-5D data for patients with progressive disease occurred at the last treatment visit before discontinuation. This visit may or may not have been proximate enough to the progression event itself to capture a change in QoL associated with progression.

B6. The model only included SAEs that occurred in at least 5% of 1 arm of the RESONATE trial. Is this 5% specified within the protocol for the trial? Please provide the reasons given by the clinical experts for the use of this inclusion rule? Please present table 56 (page 125) for ibrutinib and for ofatumumab, and for the other comparators to the extent that data is available, for all grade 3 and grade 4 SAEs regardless of their incidence.

The list of SAEs included in the model was determined based on the occurrence of SAE reported for all comparators and not just based on the ibrutinib arm of the RESONATE trial alone. SAE that occurred in at least 5% in at least 1 comparator trial were included. The 5% cut-off was considered by clinical experts to be sufficient to capture SAEs that would impact patients with any consistency and to have validity in a real-world setting, where SAEs are monitored in a less strict manner compared with a clinical trial setting.

Analyses would be biased against ibrutinib if all AEs that occurred in any frequency in patients receiving ibrutinib were considered because reporting of AEs varies between trials publications. The Österborg et al., 2014 study reported serious AE which occurred in ≥ 5% of the trial population. The Jones et al. study reported AE (all grade) which occurred in ≥ 15% patients in the idelalisib in combination with ofatumumab

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(IO) group. The Fischer et al. study reported 'most common' AEs without mention of which AEs were excluded or how the exclusion was applied. The 5% cut-off is used to minimise the impact of the inconsistency in reporting.

Please also note that the information presented in Table 56 of the submission document was mislabelled for physician's choice, IO and BR. For ease, the correct version has been reproduced here as Table 13, presenting the percentage of patients experiencing serious AEs included in the model by comparator based on the 5% inclusion rule. Table 14 below presents a summary of all serious AEs reported in the relevant clinical trials.

Table 13: Percentage of patients experiencing SAEs by comparators (AEs that occurred in at least 5% of patients in one treatment arm)

	Ibrutinib	Physician's Choice	IO (proxy for IR)	BR	Ofatumumab
Anaemia	5.6%	9.3%	12.0%	3.7%	7.3%
Diarrhoea	4.6%	NR	20.2%	NR	1.6%
Pneumonia	10.8%	18.6%	12.7%	NR	5.8%
Hypertension	6.2%	NR	NR	NR	0.5%
Neutropenia	18.5%	9.3%	34.1%	8.2%	13.6%
Thrombocytopenia	5.6%	NR	13.3%	6.5%	4.2%
Sepsis	1.5%	14.0%	NR	NR	1.0%
Reference	RESONATE trial	Österborg, 2014	Jones, 2014	Fischer, 2011	RESONATE trial

AE: adverse events; BR: bendamustine with rituximab; IR: idelalisib in combination with rituximab; IO: idelalisib in combination with ofatumumab; NR: not reported; SAE: severe adverse events

Table 14: Percentage of patients experiencing SAEs by comparators (all AEs reported in clinical trials)

	Ibrutinib*	Physician's Choice	IO (proxy for IR)	BR	Ofatumumab*
Anaemia	5.6%	9.3%	12.0%	3.7%	7.3%
Diarrhoea	4.6%	NR	20.2%	NR	1.6%
Pneumonia	10.8%	18.6%	12.7%	NR	5.8%
Hypertension	6.2%	NR	NR	NR	0.5%
Neutropenia	18.5%	9.3%	34.1%	8.2%	13.6%
Thrombocytopenia	5.6%	NR	13.3%	6.5%	4.2%
Sepsis	1.5%	14.0%	NR	NR	1.0%
Haemolysis	NR	4.7%	NR	0.6%	NR
Leukopenia	2.6%	NR	NR	4.8%	0%
Allergic reaction	NR	NR	NR	0.6%	NR
Infection	NR	NR	NR	3.4%	NR
Fatigue	2.6%	NR	3.5%	NR	1.6%

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Cough	NR	NR	0.6%	NR	NR
Nausea	NR	NR	0.6%	NR	NR
Infusion reaction	NR	NR	2.3%	NR	NR
Constipation	NR	NR	0%	NR	NR
Decreased appetite	NR	NR	0.6%	NR	NR
Dyspnea	2.6%	NR	4.1%	NR	0.5%
Rash	2.1%	NR	4.1%	NR	0%
Upper respiratory infection	NR	NR	0%	NR	NR
Peripheral oedema	NR	NR	0%	NR	NR
Abdominal pain	NR	NR	2.9%	NR	NR
Febrile neutropenia	4.1%	NR	NR	NR	2.6%
Urinary tract infection	4.1%	NR	NR	NR	0.5%
Atrial fibrillation	3.6%	NR	NR	NR	0%
Lung infection	3.1%	NR	NR	NR	0%
Cellulitis	2.1%	NR	NR	NR	0.5%
Hyponatraemia	2.1%	NR	NR	NR	0.5%
Reference	RESONATE trial	Österborg, 2014	Jones, 2014	Fischer, 2011	RESONATE trial
* SAEs reported in at least 2% of patients for either ibrutinib arm or ofatumumab arm in RESONATE were included.					

AE: adverse events; BR: bendamustine with rituximab; IR: idelalisib in combination with rituximab; IO: idelalisib in combination with ofatumumab; NR: not reported; SAE: severe adverse events

B7. The submission notes that the comparator physician choice was based upon Österborg et al. adjusted to reflect UK practice. Please clarify what adjustments were made.

In the Österborg et al., 2014 trial, the most common regimens used as part of physician's choice were: alkylator-based therapies in combination with rituximab (R), such as R-CVP (28%); alemtuzumab monotherapy or combination with steroids (26%); fludarabine-based therapies, such as FCR, FC, FR (14%); and bendamustine or BR (12%). These proportions total to 80% (the remaining 20% were not reported); therefore a full picture of the composition of PC is not available from the Österborg publication.

The UK advisory board suggests that R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone) is more commonly used in the UK while R-CVP is less commonly used. Additionally, UK clinicians indicated the R+HDMP and chlorambucil are also used.

Based on these expert opinions, the physician's choice treatment composition is adjusted as presented in Table 15 below. This composition was used to calculate the cost of the PC regimen in the cost-effectiveness model. The efficacy of PC was

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informed by the ITC comparing ibrutinib vs. PC grounded on UK clinical expert opinion that the efficacy of PC from Österborg et al., 2014 could be used to approximate the efficacy of PC based on the revised composition.

Table 15: Adjusted composition of physician's choice

Regimen	Composition in Österborg	Composition in submission
R-CVP	28%	
Alemtuzumab	26%	
BR	12%	
FCR	14%	
R-CHOP	-	
R-HDMP	-	
Chlorambucil	-	
Total	**80%**	

BR: Bendamustine and rituximab; FCR: Fludarabine and cyclophosphamide and rituximab; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, and prednisolone; R-CVP: Rituximab plus cyclophosphamide, vincristine, and prednisolone R-HDMP: Rituximab plus high dose methylprednisolone

Section C: Textual clarifications and additional points

C1. Please clarify if the definition of progression that underlies the curves of appendix 10 was based upon the independent research committee assessed progression or investigator assessed progression.

The definition of progression that underlines the curves in appendix 10 was based on investigator-assessed PFS.

C2. Table 25 (page 53) of the submission states that treatment was until disease progression. Was this progression assessed by the investigator or assessed by the independent research committee?

This was investigator-assessed.

C3. Table 25 states that the duration of PFS as assessed by the independent research committee was the primary outcome. What was the time cut-off for this analysis?

The time cut-off for this analysis was 9.4 months (the interim analysis).

C4. Please clarify the time cut-off for figure 9 (page 59) of the submission.

The time cut-off for this analysis was 9.4 months (the interim analysis).

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C5. Please clarify whether the OS for figure 17 (page 70 of submission) is intention-to-treat, censored for cross-over, RPSFT or something else.

The OS is based on the ITT population.

C6. In the model treatment is assumed to stop at progression. How is progression measured?

Progression was investigator-assessed.

C7. Please provide the data specific to the 51 patients receiving 420mg in PCY1102. Or explain why the data is unavailable.

Data specific to the 51 patients receiving 420mg in PCYC1102 are provided in Table 16. These data are stratified by risk status.

Table 16: Patient characteristics at baseline for PCYC1102 R/R patients (420mg) – by risk status

	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]

C8. Appendix 12 states that “each dimension had three levels of severity” but the submission refers to the EQ-5D-5L VAS. Did RESONATE collect EQ-5D-3L or EQ-5D-5L?

The RESONATE trial collected EQ-5D-5L.

C9. In the EQ-5D analysis did complete response (CR) include complete response with incomplete haematopoietic recovery (CRi)?

At the 9.4-month data cut, no complete responses (CR, Cri, or nPR) were reported for IRC assessed response; all responders in both ibrutinib and ofatumumab arms had achieved only a PR. Therefore, regression analysis further stratifying response by CR, PR and SD was not conducted with the 9-month data cut.

C10. Please provide a definition of INV responder in table A.2 (page 3-4) of appendix 12?

INV responder is defined based on the response status of the patient at the end of interim analysis (9.4 month follow-up) as assessed by the respective investigator.

C11. What measures of response were applied within the EQ-5D analyses reported in appendix 12: investigator assessed, or IRC assessed or a mixture of both?

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Investigator assessed measures of response were applied within the EQ-5D analysis reported in appendix12.

C12. What measures of progression were applied within the EQ-5D analyses: investigator assessed, or IRC assessed, or a mixture of both?

Investigator assessed measures of progression were applied within the EQ-5D analysis.

C13. What is the definition of “censored” within table A.4 (page 6 of appendix 12)?

EQ-5D was collected up to the IRC-confirmed progression. As some patients had not progressed yet by the end of the interim analysis (9.5 month follow-up), the last cycle of EQ-5D data collected for those patients was during the PFS stage. Those patients who stopped contributing to EQ-5D data due to reasons other than progression (i.e. were lost to follow-up) are considered censored.

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Patient/carer organisation submission (STA)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: CLL Support Association

Your position in the organisation: [redacted]

Brief description of the organisation:

The CLL Support Association (CLLSA) is national patient led charity run by volunteers and was formed in 2005; it is the only UK Chronic Lymphocytic Leukaemia (CLL) specific support charity. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments.

CLLSA provides support to the UK CLL community and CLLSA membership of 1500+ association members who live with CLL or are carers and 2400+ CLLSA on-line community members. CLLSA provide 3 to 4 regional patient meetings/conferences a year. CLLSA support patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and https://healthunlocked.com/cllsupport . The association is funded by member's donations, legacies, members' fund raisers and unrestricted educational grants

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

2. Living with the condition

CLL is a heterogeneous condition, the disease type and path will be very different for each patient. Following diagnosis, the great majority of patients live on "watch and wait" for a variable length of time and live with a varying degree of symptom burden. This ranges from asymptomatic patients with no adverse effects, to patients with crushing fatigue and B symptoms of sweats and weight loss and patients experiencing many constitutional symptoms requiring treatment. Recurrent infections, some of which will require hospital admission, are a common symptom as the immune system does not work effectively. A high lymphocyte count is typically accompanied by generalised large lymphadenopathy, liver and spleen enlargement which fill the abdomen and the development of anaemia, neutropaenia and low platelets as the marrow fills up

with CLL cells and leaves no room for the production of normal, essential blood cell components.

Some patients will have a particularly poor prognosis, will require early treatment and relapse quickly after treatment. Some of these patients will have poor prognostic genetic markers such as 17p and will not respond well to currently available treatments such as Fludarabine.

CLL is currently incurable (with the exception of the very few who qualify for a high risk treatment such as stem cell transplantation) Treatment with current therapies available will end with eventual relapse. The wait/treat/relapse cycle is repeated and continues until death. The uncertainty of living with CLL brings with it serious psychological and emotional issues combined with other physical issues that impact negatively on a patient's quality of life. Treatment for CLL is only initiated when the CLL patient's disease has progressed to the point where it has to be treated. Patients wait whilst there is a decline in their wellbeing and clinical assessments, uncertain of what may happen next and often live for years with these negative quality of life issues waiting for treatment or progression.

Patients treated using immunochemotherapies will achieve remissions ranging from the durable for some (median 4 years remission) to those who do not respond to treatment or relapse quickly in less than 2 years. There is a real need for effective options to be approved by NICE which are suitable for both relapsed and hard to treat patients.

The average age of CLL patients at diagnosis is 72 and current, more toxic treatments are not generally well tolerated by the majority diagnosed over the age of 60. Also, treatment with immunochemotherapy regimens often result in a variable but significant incidence of infectious complications. Regimens like FCR result in serious infectious complications ranging from 35% at 3 months to 12% at 9 months and this regime is poorly tolerated in patients older than 65-70 years. Many of our members fear the consequences of toxic side effects and complications caused by repeated myelotoxic therapies and live knowing relapse and further treatment is inevitable and likely to further impact negatively on quality of life.

Patients with 17p deletion know that their life expectancy is likely to be short and that any treatments they do have are unlikely to be effective thereby resulting in a short lasting remission.

Patients with CLL have a higher risk and rate of infection even if they have the earliest stage of disease as their immune system is compromised by the disease. This is true even if they do not require specific treatment for their CLL yet. These recurrent infections impact negatively on the quality of life for CLL

patients, their carers and their relationships with extended family and friends. During the winter, a long period of social isolation may be necessary in order to protect against infection. It often takes longer for CLL patients to recover from infections and infection is the cause of death in up to 50% of CLL patients, and such statistics mean that patients live in fear of complication from infections.

A diagnosis of CLL and living with the effects of CLL is not easy and impacts on the whole family. Patients live with significant emotional, psychological and physical issues that impact negatively on quality of life and ability to carry out tasks of day to day living, making personal/family relationships difficult, preventing patients from enjoying a normal life, reducing the ability to contribute to society and ultimately it may considerably shorten life expectancy although some patients will never require treatment.

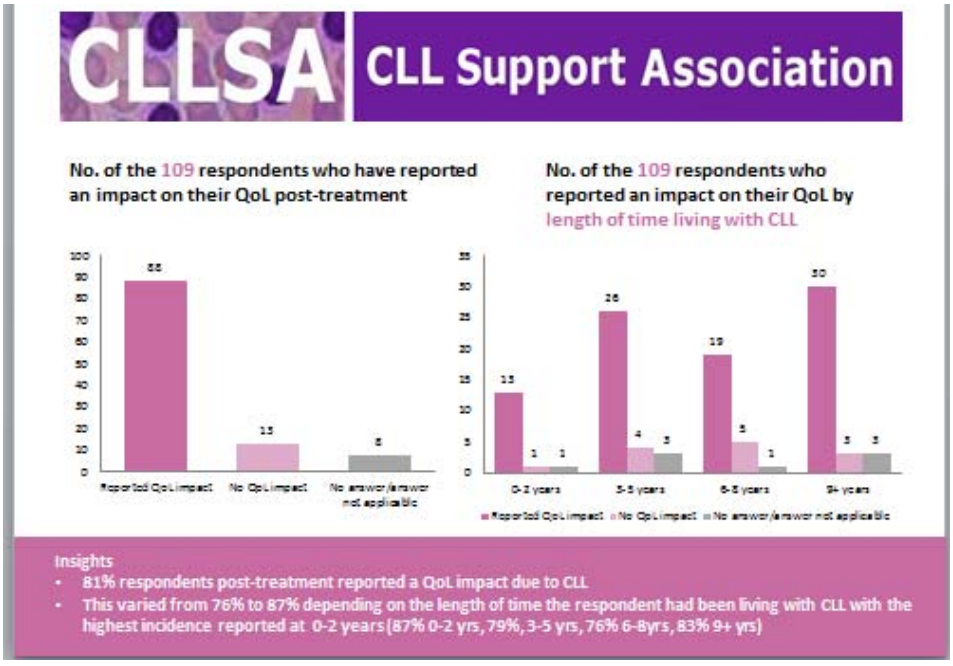
In our CLLSA survey below; members identified the range of symptoms normally associated with CLL which affect quality of life.

One of these observations of particular note is*:*

Many patients, particularly post treatment, said that their compromised immune system had affected their quality of life and had resulted in an increase in infections and allergies

Quantitate analysis results from the quality of life survey among 282 CLLSA members September 2014

Sample:



Results from the quality of life survey among CLLSA members
http://www.ukcllforum.org/downloads/2017%5E ***What is it like to live with the condition or what do carers experience when caring for someone with the condition?***

Report http://www.ukcllforum.org/downloads/2015%5E

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

In the absence of a cure, patients living with CLL want treatments that:

- Provide as deep and lengthy a remission as is possible in order to extend life with minimum side effects and long term toxicity.
- Eliminate the need for repeated conventional toxic treatments which are always followed by relapse and reduced responses in subsequent treatments.
- Are effective in treating all groups, including 17p-/TP53 mutated CLL. The average age of the CLL community is 72, many people suffer with comorbidities, are less fit and need access to tolerable treatments that are effective.
- Improve their quality of life - to be able to live and enjoy as normal a life as is possible. CLL is a chronic and incurable condition; patients spend considerable time living with a symptom burden or the complications of disease progression and treatment.
- Reduce risk of complications caused by treatment. Current treatments carry significant short and long term risk to the patient due to their toxicity. This includes infections, myelodysplasia, other leukaemias.
- Reduce admissions to hospital for treatment or supportive care
- Reduce the number of prophylactics required with conventional therapies and associated complications.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

CLL is currently an incurable condition with the exception of the very few who qualify for a high risk treatment such as stem cell transplantation.

All patients who require treatment know that, at some point, their CLL will relapse and they will need further treatment. In addition, patients know that any future treatments are less likely to be effective, with less likelihood of a response and a shorter time before CLL progression and yet further treatment is required. Their lives are punctuated by frequent infections, some requiring hospital admission, caused partly by the disease and partly by the treatment regimes.

CLL is a heterogeneous disease and there will be a small number of patients who have high risk, poor prognosis disease which is unlikely to respond to available therapies. If a match can be found, those that are considered fit enough, will have an allogenic stem cell transplant. Treatments suitable for the younger fitter patient such as FCR and BR have significant toxicity. The less toxic, more tolerable regimens, which may be suitable for patients unable to tolerate the stronger therapies, do not provide significant remissions. In addition, the older less fit patient group may be unable to tolerate, or be unsuitable for further chemotherapy based treatment following relapse. Subsequent treatment courses available using monoclonal antibodies and steroids provide short remissions of only a few months until they are eventually ineffective.

Following relapse any further responses to treatment courses tend to provide shorter remission periods with increasing complications and side effects until no options remain. Those with refractory and hard to treat CLL such as 17p, TP53 mutated CLL who are unsuitable for transplant have very few options available to them.

We welcome the news that NICE is due to publish guidance on 28th October for use of idelalisib plus rituximab following the positive Final Appraisal Determination (FAD). That will offer untreated patients with a 17p deletion or TP53 mutation or adults who have been treated but have relapsed within 24 months a new treatment.. This is an important step forward but it is not the only step required it is essential that clinicians have a range of treatment options available to suit individual patient need and provide clinical choice

The potential impact of the CDF prioritization process and decision to delist Bendamustine as a treatment option in England for treating relapsed patients will substantially restrict patient's & clinician's choice when considering

treatment options. NICE has an opportunity here to increase effective CLL therapies available to treat relapsed CLL.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Patients consider Ibrutinib to be a paradigm shift in the treatment of CLL providing high response rates and extended remissions in all sub sets of CLL including those with poor prognostic features with significantly less side effects than current conventional treatments.

Preliminary studies, including the Phase III RESONATE study of 391 patients and a paper by Byrde et al in Blood April 2015 with a follow up of 3 years showed low levels of myelosuppression and reduced infections. The PCYC-1102 study confirmed the reduced infection rate and showed evidence of recovery of the humoral immunity in patients with increases in levels of immunoglobulins in the blood.

Patients consider reduced infections and thereby fewer hospital admissions to be very important, particularly with the increase in antibiotic resistance now occurring.

In some studies the data is relatively immature but Ibrutinib produced responses with the median progression free survival interval not yet reached compared to months for other treatments.

Relapsed refractory patients and those in difficult to treat groups are expecting this treatment to provide them an effective treatment, a strong response, eliminate physical symptoms and provide an enduring remission. Some may currently have few options and we expect the treatment to be easier to tolerate and more effective than chemo based alternatives.

Patients are aware of the challenges and risks involved with the repeated use of Chemo based regimes. The benefit of Ibrutinib lies in the reduced risk of treatment mediated complications and damage to an already compromised immune system, and reduced hospital visits for treatment of complications.

Patients expect to experience an improvement in quality of life as individuals and a family and become better able to perform activities involved in daily living and therefore be able to contribute to society. Younger patients are likely to be able to return to work.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

The advantage of Ibrutinib over other NHS treatments in England lies in its key characteristics as an orally administered, molecular targeted therapy. It is a radical departure from chemoimmunotherapy. Ibrutinib's targeting of the B-Cell receptor pathway represents one of the most important milestones in the current treatment of CLL. Patients are genuinely hopeful for the first time that there will be a transformation in the effective long-term treatment of their CLL. This applies to all subsets of relapsed CLL patients and in addition it represents a real step change for treatment-naive patients with 17p- or TP53 mutation/deletion who have no currently approved therapies. Ibrutinib produces durable remissions using an easily administered oral drug which offers convenience, reduced travel to hospital, no need for infusions with the potential for infusion reactions, less hospital time and most importantly, promotes patient independence. All these benefits lead to improvements in quality of life including less anxiety, in addition to the physiological benefits induced by the drug itself.

Ibrutinib produces high response rates which improve over time, and because of its modest toxicity profile compared to chemoimmunotherapies, patients can

remain on the drug for an extended period of time. A gradual decrease in infectious complications is seen during treatment, this is reverse of the situation in chemoimmunotherapy treatment.

The effectiveness of targeted Ibrutinib therapy is in line with the medical, political and social demands of the day and can open the door to even more effective therapies in the future. It is vital that it is given the chance to demonstrate these benefit within the NHS.

We welcome the news that Idelalisib with Rituximab will soon be available through NHS England for certain indications. However Ibrutinib has the advantage of being an exclusively oral therapy and its toxicity profile is more suitable for patients with gastrointestinal, hepatic and lung issues. As well as convenience benefits there are cost benefits for use of ibrutinib a monotherapy oral agent compared to the dual therapy of Idelalisib plus rituximab. In the dual Idelalisib rituximab therapy there may be an increased infection risk from rituximab use which may be short and long term, In addition, patients requiring treatment following relapse are more at risk than treatment naive 17p- patients due to previous toxicity and possible comorbidities if elderly/frail . Ibrutinib as a single agent may be more beneficial .

Ibrutinib offers clinicians and patients a necessary alternative to Idelalisib/Rituximab.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.
None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Currently available treatments require hospital administration during treatment cycles and often require infusion and are accompanied with risk or reactions as well as associated costs and inconvenience for patients, their families, having to journey to and spend time at the hospital. This can have knock on effects negatively impacting on employment and associated costs for support needed to attend the clinic.

The limited effectiveness and toxicity of currently available treatments for high risk groups may result in short remissions and more frequent treatments and a reduced quality of life. Symptoms and increased risk of treatment related complications, in particular infections, result in hospitalisation and sickness. Patients are also concerned about the long term effect of the toxicity of current treatments on their health and the risks associated with their use; the potential for disease evolution, long term cytopenias and a negative impact on an already damaged immune system. 50% of CLL patient deaths arise from complications related to infection.

For groups unable to tolerate, or who are relapsed /refractory or unlikely to respond to effective immunochemotherapy there are few options available that extend life and provide a good quality of life

The forthcoming inclusion of Idelalisib with Rituximab into the CLL treatment portfolio is a welcomed addition but with the use of a monoclonal antibody the patient will have to make frequent hospital visits for infusions with all the disadvantages already listed above. With rituximab there is also the risk of potential infusion reactions and increased risk of infection both short and long

term, patients requiring treatment following relapse are more at risk than treatment naive 17p- patients due to previous treatment toxicity and possibly comorbidities if elderly/frail

Please list any concerns patients or carers have about the treatment being appraised.

There are very few concerns. There is evidence of atrial fibrillation and patients understand the need for clinical monitoring, also evidence of potential bleeding events require clinicians consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies. Patients will balance evidenced low grade adverse events against the significant benefits of the technology and be willing to accept them.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

People who have received at least 1 therapy, those in hard to treat groups who are relapsed/refractory or unfit for chemo immunotherapy based regimens. or considered unlikely to respond to conventional chemo based therapy including those with 17p-/TP53 deletion/mutation appear to respond to this treatment..

Less fit relapsed patients living with treatment related complications and comorbidities have few suitable tolerable treatment options and may be limited to current milder less effective therapies that provide short remissions and require repeating, thereby increasing complications until they are eventually ineffective and no options remain. Best supportive care does not extend life. It appears that the treatment offers opportunities for achieving enduring remissions for even the most frail with an improved quality of life..

The few treatment options available for fitter relapsed patients may have been further reduced by CDF delisting of bendamustine..Resulting in increased benefits for this group for the treatment with ibrutinib.

Untreated people with a high risk 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable respond to the treatment offering an

alternative to campath and corticosteroid therapy and associated myelotoxic complications and side effects. The treatment also offers an effective alternative to recently approved idelalisib plus rituximab and its toxicity profile is more suitable for patients with gastrointestinal, hepatic and lung issues. And may be more suitable for the frailer patient.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

All will benefit from this treatment significantly more than with current chemotherapy.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The treatment has recently been made available to NHS through CDF but there has been insufficient time for comparison. However, following review and consultation, Ibrutinib is due to be withdrawn from the CDF from 4th November 2015. This is of great concern to CLL patients. Anecdotal patient comments from those who have been fortunate enough to receive Ibrutinib via CDF and the Patient Access Scheme are overwhelmingly positive.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, the trials have shown high levels of response rates with very little toxicity and durable responses. Ibrutinib appears to be a highly effective treatment.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not aware of any due to limited use outside clinical trials.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

- 2015 - Bloodwise formerly Leukaemia & Lymphoma Research, have published their phase 1 report following thier prioritization of patient needs surveys. Many CLL patients contributed their experienceces as part of the unmet needs surveys, CLL is listed in the report findings as one of the top five blood cancers that are early early killers . PDF Download of report : https://leukaemialymphomaresearch.org.uk/sites/default/files/block_images/patient_need_report_web.pdf

- 2014 - CLLSA quality of life survey of 282 patients

  Results from the quality of life survey among CLLSA members *http://www.ukcllforum.org/downloads/2017%5E What is it like to live with the condition or what do carers experience when caring for someone with the condition?*

  Report http://www.ukcllforum.org/downloads/2015%5E

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

New technology drugs have been adopted in other disease groups. Ibrutinib offers a first in class technology which will offer durable remissions and reduced toxicities. Not to offer it to CLL patients will discriminate against a group with protected characteristics of age and disability.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

It is unlikely that there are any patients who would have difficulty using the treatment but there are groups of patients who currently cannot tolerate the existing treatment options.

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Ibrutinib is a first in class compound, targeting Bruton's tyrosine kinase (BTK). This treatment has demonstrated high efficacy at treating CLL with durable remissions despite a very low toxicity profile and has proved to be effective in hard to treat groups who are relapsed/refractory/unfit for conventional treatments or considered unlikely to respond to conventional chemo based therapy including those with 17p-/TP53 deletion/mutation.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- An innovative, orally administered, molecular targeted therapy producing high response rates which improve over time, modest toxicity with infectious complications decreasing over time and providing superior effectiveness over conventional chemotherapy in every important measure
- A new option in the treatment portfolio which will allow clinicians to select the most appropriate treatment for patients in this heterogenous population and would help to close some of the current gap between NHS England and the US and Europe in the adoption of new technologies for CLL patients
- An effective treatment for patients who have few treatment options and a poor prognosis, including the less fit, relapsed/refractory and high risk patient including those with 17p-/TP53 deleted/mutated CLL
- A treatment offering improved quality of life and a longer life with an improvement in immunity leading to reduced treatment related complications and risk of infection which is the greatest cause of morbidity in CLL patients.
- The Value Based Pricing system should result in better access for patients to innovative drugs as it allows higher QALY costs for drugs that show greater therapeutic innovation or improvements compared with other products and it tackles a disease with a ‘high burden of illness’

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. We support people affected by leukaemia, lymphoma; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; myelodysplastic syndrome; myeloproliferative disorders and aplastic anaemia.

Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception over 25 years ago our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes emotional effects of a blood cancer and help for those caring for a patient. Our focus is purely on information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia, with approximately 3,200 people diagnosed in the UK each year. It is more common in men than women and it is most prevalent in older people, with over 85% people over the age of 60 at diagnosis.

Whilst CLL is the most common form of leukaemia, it is still a rare condition. Being diagnosed with CLL can be extremely "scary", particularly when you've never even heard of it. Because of this patients may experience a range of complex thoughts and emotions following diagnosis and require emotional support.

> "The thoughts that rushed through my mind when I was diagnosed were bizarre. I wondered how long I'd have left to live, how I'd tell my family and if I'd get through this."

Following diagnosis some patients may experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Many of these feelings can have a profound impact on both their physical and psychological wellbeing.

Common symptoms of patients with CLL include severe fatigue, breathlessness, paleness, headaches, frequent/persistent infections, fever, unexplained weight loss, night sweats, unexplained bleeding and bruising and enlarged lymph nodes. Many patients have no symptoms at the time when they are diagnosed and are often diagnosed following a routine blood test for something else. However, most patients will experience some or all of these symptoms as their disease progresses.

Patients with CLL are more susceptible to infections and have to be "extremely careful" to avoid picking up infections. Common symptoms in infection include fever, aching muscles, diarrhoea, headaches and excessive tiredness. The effort of avoiding infection and infection itself can have a huge impact your daily life. For example, avoiding family and friends who have been

unwell, avoiding public transport (or other crowded public places) and changes in diet.

Living with a chronic cancer, such as CLL, does not affect a patient in isolation but instead creates a "ripple effect". Family, friends and colleagues of a patient may all be affected by the diagnosis. As such, improvements in a patients' treatment and quality of life will have a wider impact on the lives of their family and friends.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The most important considerations from the patient perspective will include survival (both progression free and overall), improved response rates and a better quality of life (e.g. improved symptom control or reduced side effects).

Another consideration for patients, their carers, friends and family is the knowledge that there may be access to further effective treatment options, should their current treatments fail. As such, access to ibrutinib in this setting would not only benefit patients who may be treated with it, but also offers a sense of security to those who may or may not require it in the future. Access to ibrutinib would act as a "safety net" to many CLL patients.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Although there are several treatment options available to patients, CLL is currently incurable for the vast majority of patients.

Aggressive treatment options such as fludarabine and cyclophosphamide with rituximab (FCR) or bendamustine with rituximab (BR) are considered to be effective therapies, offering high response rates. However, these treatments are only suitable for younger/fitter patients who can tolerate the high toxicity of these treatments. Due to the average age of a patient diagnosed with CLL, many patients with the condition will not be suited to such aggressive

treatment options and the remaining, less aggressive options are not always as effective. For patients unable to tolerate the more aggressive treatment regimens, their available options potentially include treatment with chlorambucil, corticosteroids or idelalisib (with or without rituximab). These treatment options, although tolerable for many patients, are considered to be less effective providing shorter periods of remission, until they eventually become ineffective.

Patients with hard to treat CLL (such as those with 17p deletion/TP53 mutation) currently have few treatment options available to them. These mutations usually respond less well to standard treatments (such as FCR). As such, there is a clear need for further effective treatment options.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

- Extended progression-free survival
- Improved overall survival
- Increased overall response rates

- Enhanced patient experience and quality of life

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

- Oral treatment - reduces the number of trips to hospital for treatment
- New mechanism of action
- Lower toxicity
- Effective therapy in hard to treat patients

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please see above comments.

Please list any concerns patients or carers have about the treatment being appraised.

- Long duration of treatment
- Higher frequency of certain adverse events (as per the clinical trial data) – including bleeding-related AEs and atrial fibrillation

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

At present patients with adverse cytogenetic risk factors (such as 17p deletion and TP53 mutation) have limited effective treatment options. Specifically, patients with 17p deletion have reasonably poor prognosis and lower survival rates when treated with conventional therapy options. Clinical trial data suggests that ibrutinib remains an effective treatment option for these patients, so may be of greater benefit for these patients (compared to existing treatments).

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

- New mechanism of action – first in class Bruton's tyrosine kinase inhibitor

Are there any other issues that you would like the Appraisal Committee to consider?

N/A

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- CLL is a chronic and incurable condition which impacts greatly on both the physical and emotional health of patients and their families. Patients spend considerable time living with a symptom burden or the complications of disease progression and treatment.

- Common symptoms of CLL include: severe fatigue, breathlessness, paleness, headaches, frequent/persistent infections, fever, unexplained weight loss, unexplained bleeding and bruising, night sweats and enlarged lymph nodes.

- There is a clear need for new tolerable therapies that prolong survival for CLL patients. Patients with 17p del / TP53 have a particularly poor prognosis and represents an area of high unmet need.

- Ibrutinib offers an effective, tolerable alternative to currently available treatments that appears to improve patients' survival (PFS and OS), response rates, experience of treatment and quality of life.

- Ibrutinib is an oral treatment, necessitating less frequent hospital visits with reduced travel for patients and carers, a lower risk of infection and the opportunity to self-care and maintain their independence.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Dr G Follows

Name of your organisation

UK CLL Forum

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?
How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The treatment of patients with relapsed / refractory (R/R) CLL in the NHS has typically relied on chemotherapy drugs such as fludarabine / cyclophosphamide / chlorambucil with or without rituximab antibody infusions. However, since the Cancer Drugs Fund (nCDF) made idelalisib / rituximab and ibrutinib available to patients in England, there has been a radical change in the way R/R CLL has been managed. Idelalisib / rituximab has now been made available on the NHS via NICE.

There is a universal consensus that patients who relapse early (less than 3 years) post immunochemotherapy are best served by treatment with either ibrutinib or idelalisib / rituximab. Patients who relapse late after a prolonged first remission were potentially excluded from the major phase 3 licensing trials of either drug, and therefore uncertainty remains, particularly for fitter younger patients, as to how this group of patients are optimally managed. There is therefore a lack of consensus as to how these patients should be managed.

The major competing technology for ibrutinib for R/R CLL is idelalisib / rituximab. The drugs have quite different side effect profiles, but the general consensus amongst clinicians treating patients with CLL is that ibrutinib is a better tolerated drug with a more predictable toxicity profile. There is also a belief amongst most CLL clinicians in the UK that ibrutinib is a more effective therapy than idelalisib. There are comparative datasets that support this view.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

A large body of data indicates that CLL patients with 17p deletion / TP53 mutation (collectively referred to as TP53 disruption) and patients with unmutated IgvH genes have poorer prognosis CLL. These patients progress more rapidly, respond less well to immunochemotherapy, relapse early and have a worse overall survival. These data are consistent across many immunochemotherapy trials. However, when treated with ibrutinib, the survival of these poorer risk patients is similar to patients without these adverse genetic features, i.e. while ibrutinib appears to benefit all subgroups of CLL, the traditionally poor risk patients appear to derive disproportionately more benefit.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

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Single Technology Appraisal (STA)

Ibrutinib would need to be prescribed and supervised by a specialist haematology consultant. This could be delivered in any secondary care clinic with standard oncology/ chemotherapy capacity (e.g. specialist nurse, pharmacist etc)

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Ibrutinib is currently available via the nCDF for R/R CLL. Patients need to meet key criteria that are based on the inclusion criteria for the RESONATE trial. Broadly, patients must have received prior immunochemotherapy and have relapsed but are not suitable for re-treatment with purine analogues due to a range of criteria.

The licensed indications for ibrutinib in CLL are broader than the nCDF indications. I am not aware of any NHS use of ibrutinib us in CLL outside its current licensed indications. I am aware that there is a huge interest in using ibrutinib for other indications such as R/R Waldenstroms macroglobulinaemia, but I am unaware of any agreed funding stream within the NHS that makes this possible.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

In my role as the UK CLL Forum chairman, I also chair the BCSH CLL Guidelines Panel. To date, the only guideline we have published to address the use of ibrutinib / idelalisib has been an on-line interim guideline (http://www.bcshguidelines.com/documents/Interim_statement_CLL_guidelines_version6.pdf). The definitive re-writing of the BCSH guidelines is not complete. The evidence sourced for this guideline has been primarily based on the RESONATE trial data.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

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Single Technology Appraisal (STA)

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I have extensive clinical experience with using ibrutinib in CLL and mantle cell lymphoma. Currently I manage over 35 patients who currently take ibrutinib (on and off trial) as the main therapy for their blood cancer. Furthermore, in my role as chair of the UK CLL Forum, I have collated real-world data ibrutinib on over 280 patients treated in over 50 hospitals in the UK and Ireland. I have submitted the data on the first 270 patients to the British Society for Haematology Annual Scientific Meeting. The abstract is below:

Ibrutinib for Relapsed / Refractory CLL: A UK and Ireland Survival Analysis

UK CLL Forum

In 2014, a compassionate scheme made ibrutinib available for relapsed/refractory CLL patients who broadly matched RESONATE trial entry criteria. 501 UK/Ireland patients were registered by October 2014 and following scheme closure, the UK CLL Forum initiated a service evaluation of data from patients with a minimum 1 year follow-up. The pre-planned primary end-points were the two most objective measures; number still on therapy at 1 year and 1 year absolute overall survival (aOS). Data with >1 year follow-up were returned on 270 patients from 50 hospitals. Median age:69 (range:41-92) and median prior lines:2 (range:1-14; 48%>=3). TP53 was disrupted in 77/247(31.2%) (74=17p-; 3=TP53 mutated).

Clinician-assessed ORR was 86% with 74.4%(201/270) of patients still on therapy at 1 year and aOS of 82.6% (223/270). With 15 months median follow-up, OS was 77.8%(210/270). 1 year aOS was no different +/- TP53 disruption (81.8% vs 82.9%;p=0.76) or 1 vs 2 vs 3+ prior lines (82.2% vs 82.1% vs 82.9%;p=0.94). Nearly all surviving patients who stopped ibrutinib before 1 year had stopped due to AE rather than PD (13/15). Patients with dose reductions for any reason (125/270=46%) had a 2.52 fold higher risk of death (OS: 66.6% vs 86.8%; p<0.0001). AEs were reported in 56.7% with an expected profile, including AF (5.6%). 17.4% stopped ibrutinib permanently due to an AE. 25/270 (9.3%) had clinical suspicion of Richter's with 16/25 biopsy proven, 21/25 have died.

This is the largest real-world ibrutinib R/R CLL evaluation with individual patient-level data so far presented. Objective outcomes such as aOS appear inferior to the RESONATE trial (1 year OS; 90%:PFS;84%), despite similar patient characteristics. Although a direct causal link between dose reductions and OS cannot be made from this data, it is noteworthy that nearly half the patients in this evaluation were dose reduced which strongly associated with poorer OS.

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My personal clinical experience reflects the 'real-world' data summarised above. The clear majority of my patients have continued therapy to and beyond one year. Many have reported a marked improvement in quality of life on the medication and those of working age have continued to work, indeed, some have increased their hours of work since starting ibrutinib. As expected, many of my patients have reported low grade side effects such as diarrhoea, bruising, rash, arthralgia etc, but it remains a minority who stop the medication due to side effects. Certain side effects do remain a concern, such as haemorrhage (due to an effect on platelet function), atrial fibrillation (around 5 to 7% at one year, likely with an increasing risk with each year on therapy), rare but more serious cardiac dysfunction, and occasionally, significant myalgias that can be disabling. A number of patients raise the concern that treatment is open ended, but there is no data to support any stopping criteria based on response assessments. Another concern raised by clinicians and patient groups is the risk of Richter's high grade transformation (RT) while on ibrutinib therapy. Our UK real-world data has found an incidence of around 6% (biopsy-proven RT) which is in line with published data. It remains a much debated issue as to whether this level of RT, which appears higher than experienced pre-ibrutinib, is a reflection of the natural history of CLL in patients who would otherwise have died of end-stage CLL, or whether RT is more likely in R/R patients treated with ibrutinib. From the UK dataset, we have not collected toxicity data in a rigorous way, although I am not aware of any firm data identifying any new or unexpected toxicities observed in patients treated off trial.

Compared with the pre-ibrutinib era, the number of very poor risk patients who survive to one year and beyond is striking. The real-world and trial data both demonstrate very high one year survivals with ibrutinib which contrast markedly with historical data when the median survival was 9 months for fludarabine refractory patients treated with alemtuzumab.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I am not aware of any equality and diversity issues with this treatment

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

If required, I am happy to share the raw data used to prepare the UK CLL Forum abstract submitted to the BSH meeting.

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Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The use of ibrutinib is already very widespread in England via nCDF access. I do not think any additional training would be required to implement this technology within the NHS

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: molly fletcher wilkinson
Name of your nominating organisation: cllsa
Do you know if your nominating organisation has submitted a statement?

□ Yes □

Do you wish to agree with your nominating organisation's statement?

□ Yes □

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

□ Yes □

- a carer of a patient with the condition?

□ Yes □

- a patient organisation employee or volunteer?

□ Yes □

Do you have experience of the treatment being appraised?

□ Yes □

If you wrote the organisation submission and do not have anything to add, tick here (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is your experience of living with the condition as a patient or carer? Dx with CLL in 2006 disease progression in 2008 6 months of FC chemo achieved CR. Further disease progression in 2014 7 months FCR including overdose of F finishing in June 2015. Disease progression within 6 months. Started Ibrutinib 20th October 2015

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would like to have quality of life, not constant illness and more energy to be able to do live fully. I would also like to not have to live apart from others in constant fear of contracting illnesses.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I was extremely ill with both chemo treatments and will not be doing any more in the future. I feel they damaged my health and my short term memory permanently.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)

- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

I might be able to live with the CII indefinitely

Ibrutinib gave me much more energy, I felt turbo charged

More energy made me feel as if I could do anything I wanted

Family and friends noticed a difference in my energy and demeanour

Please explain any advantages that you think this treatment has over other NHS treatments in England.

There is no comparison with taking a KID drug over enduring chemo. It is extremely effective with few side effects so far

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Others have side effects such as muscle pain and tiredness

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)

- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Taking a pill three times a day every day for ever is quite a commitment. Also having to drink 2 lt water every day is difficult for me as I have urge incontinence so it is especially difficult drinking so much. I find the pills give me a feeling of bloating and indigestion that is quite uncomfortable.

Please list any concerns you have about the treatment being appraised.

I wish I had been given it as a front line therapy as I don't think I benefitted from doing chemo.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

others have side effects

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I think younger patients would benefit as they are more likely to have disease progression and chemo treatment is horrible and the disease always comes back.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

People on Watch and Wait who don't have symptoms

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

□ Yes □

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I dont think I have been on the drug long enough but generally people talk about Ibrutinib as a 'wonder' drug that has given them their life back. I would concur with this.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, it is good to know how long the drug is effective for and generally how well it is tolerated in other patients when CLL is such an individual disease.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

I contracted my third episode of shingles after one month of Ibrutinib as I was inadvertently taken off the anti viral drug Aciclovir so from now on I will be taking it alongside the Ibrutinib and will vigorously question any attempt to take me off it.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐

If yes, please provide references to the relevant studies.

Postings on HealthUnlocked by Dr John Byrd in USA

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

The expense involved in this drug probably means it will have limitations as to how many people will get this amazing drug.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐

If yes, please explain what makes it significantly different from other treatments for the condition.

It is very effective without the horrible side effects of chemo. I started to feel different within two hours of taking the first Ibrutinib pill. I can now walk briskly up hills or stairs without help or puffing and panting as before.

Is there anything else that you would like the Appraisal Committee to consider?

I think this drug should be considered as a front line treatment in younger patients and also it would be worth finding other cheaper sources of this drug so it can be available to everyone with CLL.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Ibrutinib is an amazing new drug
- very few side effects
- Chemotherapy is not effective long term
- Other KID drugs are available for after Ibrutinib if needed
- Ibrutinib should be considered as a front line treatment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Tricia Gardom

Name of your nominating organisation: CLLSA

Do you know if your nominating organisation has submitted a statement?

X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X No

- a patient organisation employee or volunteer?

X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes X No

If you wrote the organisation submission and do not have anything to add, tick here (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NO

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnose with both CLL and breast cancer in 2006 and they were both treated effectively with 4 chemotherapy drugs, Epirubicin, Cyclophosphamide, Methotrexate and 5-FU together with G-CSF with each cycle. My CLL started to progress again in 2010 and since then I have experienced reduced quality of life due to repeated shingles, multiple sinus and chest infections and emergency hospitalization for viral encephalitis. My immune system is severely compromised and I administer SCIG weekly at home, and take daily prophylactic antibiotics and antivirals. These issues lead to social isolation from family and friends, fatigue which requires constant management and reduced flexibility with work and studying. In July 2015 after extensive spleen and lymph node enlargement, significant weight loss, anaemia, thrombocytopenia and increased lymphocytosis, it was decided to commence treatment. I was considered treatment-naïve for CLL and my prognostic profile is 17p-, Unmutated and Trisomy 12. The treatment options were limited to alemtuzumab or Best Supportive Care, but I was fortunate to be granted access to Gilead's patient access scheme for Idelalisib/Rituximab. Whilst I would have preferred an oral only regimen, there was nothing either UK approved or available in a trial at the time when treatment became necessary.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

There is no cure for CLL and treatment goals are essentially palliative. Therefore realistic goals would be increased survival, a reduction in suffering and improved quality of life. Treatments should be effective in treating all sub-groups of patients. A long remission with minimal short term and long term

toxicity and a short treatment cycle would be the ideal. It is important to minimise infections and lengthy stays in hospital in order to increase quality of life for the patient, their family and carers.

It is also important that treatments do not contribute to secondary malignancies, neutropenia, sepsis, clonal evolution, transformation and autoimmunity.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

My initial chemotherapy in 2006/7 was extremely toxic and delivered intravenously in a production-line environment with little care. My current Idelalisib/Rituximab treatment combines a daily oral drug with an intravenous infusion and is a different experience. Although the long day in the Oncology Day Ward is arduous with long wait times, proximity to very poorly patients and the overall unhealthy environment, the expert staff manage to create a positive and caring environment which is invaluable. The side effect profile of Idelalisib/Rituximab, as targeted therapy, compares very favourably with chemotherapy, leading to an improved feeling of wellness and absence of crushing fatigue, nausea and 'brain fog/chemo brain'. These issues are very important to patients who are on long term treatment which may need to be continuous or repeated with another targeted agent.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)

- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Ibrutinib is considered to be a significant new therapy providing high response rates and extended remissions is all sub sets of CLL patients, including those with poor prognostic markers and who have relapsed from previous therapies. It is effective in reducing physical symptoms and therefore increases quality of life. When it is delivered orally it provides convenience and does not necessitate so many visits to the hospital, thereby saving NHS staff time. This is appreciated by both the patient and their family/carers.

Some early data indicates lower levels of myelosuppression and reduced infections when compared to chemo immunotherapy, hence requiring fewer hospital admissions.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Lower toxicity profile than chemo immunotherapy.

A valuable addition for the less fit patients, those with p53/17p deletion/mutation. Early data indicates that this could apply to those with 11q- and Unmutated prognostic markers.

Ibrutinib has a different adverse effect profile to Idelalisib so it provides an alternative for clinicians to consider in this patient population, particularly those who are frail and elderly or with co-morbidities, or who cannot tolerate a monoclonal antibody. If offers a valuable forward path for patients who may have become resistant to other kinase inhibitor therapies or who are unable to tolerate their toxicity.

It appears to offer the option of a maintenance therapy until improved options or a cure can be found.

If you know of any differences in opinion between you and other

patients or carers about the benefits of the treatment being appraised, please tell us about them.

NO

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Patients who relapse early from chemo immunotherapy such as FCR, BR or Chlorambucil/monoclonal antibody have few viable options for subsequent treatment. They are less likely to gain a meaningful response and are unlikely to gain an extended life or regain a good quality of life. Bendamustine is no longer available in England for the treatment of relapsed CLL through the Cancer Drugs Fund. Currently available chemo immunotherapy treatments require hospital administration for infusion and are accompanied with risks and reactions as well as associated costs and inconvenience for patients and their families, having to spend long periods of time at the hospital. This can impact negatively on employment and additional costs to attend clinic.

Patients with high risk disease have only one viable option, the recently approved Idelalisib/Rituximab. The inclusion of the monoclonal brings disadvantages as outlined above, such as potential infusions reactions and increased risk of infection in both the short and long term. The toxicity profile of idelalisib may not be suitable for all patients and therefore new alternatives are required.

Please list any concerns you have about the treatment being appraised.
There are 3 adverse effects that give rise to concern for patients, hypertension, atrial fibrillation and bleeding. Bleeding issues are particularly important in patients who need surgery and can be challenging for them when they are taken off the drug for even a short while. Bleeding issues are compounded in young fertile women who become anaemic very quickly.

Now that Ibrutinib has been used more widely in the patient community, there is evidence from several patients than arthralgia and myalgia are areas of significant concern, particularly in the first year of treatment. This can lead to lower QOL, reduction in dose of Ibrutinib and in some cases requires a change of drug. It would be fair to say that expectations of this drug have been very high amongst patients and some find it difficult to cope with these new and unexpected random pains.

Neutropenia can be a persistent issue especially in patients who have been treated with several chemo immunotherapy regimens, and complication from infection is the most frequent cause of death in CLL.

Some patients have needed to cease treatment due to disease progression or unacceptable toxicity. In these cases it will be a challenge to safely manage the transition to a new therapy. I am not aware of any data that indicates that Ibrutinib therapy can be safely stopped so there is a need for continuous treatment, certainly when it is delivered as a single therapy.

Responsibility for taking Ibrutinib lies with the patient and the treatment schedule must be adhered to.

If you know of any differences in opinion between you and other

patients or carers about the disadvantages of the treatment being appraised, please tell us about them

QOL experience is very different between patients who have no adverse effects, and there are many, and those who have numerous adverse effects particularly in the first year. This can affect their attitude to therapy and create low mood, less hope and increased anxiety. This can affect treatment adherence

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who cannot tolerate existing chemo immunotherapy regimens.

Patients who are frail and elderly

Less fit patients with co-morbidities

Patients with p53/17p deletion/mutation

Patients who relapse early for whatever reason.

Patients who are unsuitable for Idelalisib/Rituximab due to its toxicity profile which appears not to overlap with the toxicity profile of Ibrutinib.

Patients being treated with Idelalisib/Rituximab who experience unacceptable toxicity or disease progression.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not according to currently available data.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

X☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I have not used this treatment.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, the trials have shown high levels of response rates with very little toxicity and durable responses. Ibrutinib appears to be a highly effective treatment.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not aware of any but see answer to point 5 above about concerns.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes X No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

N/A

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Ibrutinib is a first in class compound, targeting Bruton's Tyrosine Kinase (BTK) and can be delivered orally. This treatment has demonstrated efficacy at treating CLL with durable remissions despite a very low toxicity profile and has proved to be effective in hard to treat groups who are relapsed/refractory/unfit for conventional treatments or considered unlikely to respond to conventional chemo based therapy including those with p53/17p deletion/mutation.

Is there anything else that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- An innovative, orally administered, molecular targeted therapy producing high response rates which improve over time, modest toxicity with infectious complications decreasing over time and providing superior effectiveness over conventional chemotherapy in every important measure.
- A new option in the treatment portfolio which will allow clinicians to select the most appropriate treatment for patients in this heterogeneous population and would help close some of the current gap between NHS England and the US and Europe in the adoption of new technology drugs for CLL patients.
- An effective treatment for patients who have few treatment options and a poor prognosis, including the less fit, relapsed/refractory and high risk patient including those with p53/17p deleted/mutated CLL.
- A treatment offering an improved quality of life and a longer life with an improvement in immunity leading to reduced treatment related

complications and risk of infection which is the greatest cause of morbidity in CLL patients.

- The Value Based Pricing system should result in better access for patients to innovative drugs as it allows higher QALY costs for drugs like Ibrutinib that show greater therapeutic innovation or improvements compared with other products and it tackles disease with a ‘high burden of illness’.

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID 749]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

None

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Ewen Cummings acted as health economist; critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and rebuilt the economic model, and carried out further sensitivity analyses. David Cooper acted as statistician; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Clare Robertson acted as systematic reviewer; critiqued the clinical effectiveness methods. Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. Dominic Culligan acted as clinical expert; provided clinical advice and general guidance. Craig Ramsay acted as project lead for this appraisal; contributed to the critique and review of the clinical effectiveness methods, and supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

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List of abbreviations

AE	Adverse effects
BCSH	British Committee for Standards in Haematology
BR	Bendamustine and rituximab
BSC	Best supportive care
CAP	cyclophosphamide, doxorubicin and prednisolone
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisolone
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CVP	cyclophosphamide vincristine and prednisolone
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol-5D
ERG	Evidence review group
FACIT	Functional Assessment of Chronic Illness Therapy
FCR	Fludarabine plus cyclophosphamide plus rituximab
HRQOL	Health-related quality of life
IR	Idealisib and rituximab
IRC	Independent research committee
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
NICE	National Institute for Health and Clinical Excellence
ORR	Overall response rate
OS	Overall survival
PC	Physician's choice
PFS	Progression free survival
PR	Partial response
QALY	Quality adjusted life year
QoL	Quality of life
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, and prednisolone
RCT	Randomised controlled trial

R-CVP	Rituximab plus cyclophosphamide, vincristine, and prednisolone
R-HDMP	Rituximab plus high dose methylprednisolone
RPSFT	rank-preserving structural failure time
RR	Relapsed or refractory

1 Summary

1.1 Critique of the decision problem in the company's submission

The ERG agree that the population, intervention and outcomes are in line with those in the NICE scope.

The ERG notes that ofatumumab is now withdrawn from the cancer drug fund and does not appear in the NICE final scope; however, the company argues that it should remain as a relevant comparator for their submission. The company state their rationale for their argument as follows:

- Ofatumumab is the comparator within the pivotal phase III trial for ibrutinib (RESONATE), as it was the only licensed treatment for R/R CLL at the time of trial initiation.
- Ofatumumab remains licensed for use in Europe for R/R CLL.
- Rituximab monotherapy is not licensed and not widely used in UK clinical practice; however, it remains within the NICE final scope.
- Clinical advisors for the company suggests that it remains a relevant comparator in the UK for R/R CLL.

Whilst the ERG recognises that ofatumumab will be needed to connect the network of trials to address the other comparators in the company submission, it is the ERG's opinion that ofatumumab is not a valid comparator for ibrutinib given it is no longer available in the cancer drug fund

1.2 Summary of clinical effectiveness evidence submitted by the company

The company presented the results of the single RCT (RESONATE) comparing ibrutinib with ofatumumab in patients with CLL who have received at least one prior treatment. In addition there were four non randomised and non-controlled studies of ibrutinib included within the submission.

All included studies provided information to directly address the first population of interest:

- Adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate

Only one non-RCT study provided data to directly address the second population of interest:

- Adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation.

Efficacy

Data from the 16-month median follow-up analysis of RESONATE trial revealed 12-month PFS of 79% for patients with 17p deletion receiving ibrutinib vs. 17% in those receiving ofatumumab, p<0.001.

OS was significantly prolonged with ibrutinib vs. ofatumumab: hazard ratio for death in the ibrutinib group was 0.43 (95% CI: 0.24 to 0.79; p=0.005). Adjusting for crossover increased the effect to [redacted].

The overall response rate (ORR) was significantly higher in the ibrutinib group vs. the ofatumumab group, 43% vs. 4% (odds ratio, 17.4; 95% CI, 8.1 to 37.3; p<0.0001).

In the 17p deletion subgroup of the RESONATE population, the OS HR comparing ibrutinib vs. ofatumumab adjusting for crossover was [redacted].

[redacted]

A clinically meaningful improvement in EORTC QLQ-C30 global health scores was observed in both arms, although more patients had a clinically meaningful improvement in the ibrutinib arm, 47% vs. 40%, OR:1.3, p=0.2049

The non-randomised studies showed similar efficacy profile for PFS, OS and response rates compared to the ibtrutinib treatment arm in RESONATE.

Adverse events

The most common AE in each study was diarrhoea, occurring in approximately half of the patients. The cases were generally grade 1 or 2 in severity, managed with standard treatment and resulted in very few discontinuations (<15% across the studies). In comparison with ofatumumab in the RESONATE trial, infection rates were higher with ibrutinib (70% v 54%), but rates of grade 3 or above infections was similar. Serious adverse events were reported in 40-61% of patients, most were infection-related although there were a small number of cases of atrial fibrillation. The majority of serious AE were described as not related to ibrutinib.

Evidence for adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation.

Only one investigator initiated study in patients with untreated or R/R CLL and TP53 mutation conducted in one site in the US was identified. The study included 35 patients with untreated disease and 16 that were previously treated.

In patients with previously untreated disease, 84% remained alive at 24 month follow-up. In comparison, for those with R/R disease the estimated OS was 74% at 24 months. Median PFS was not reached and 24 month estimated PFS was 82%. Data were not provided on PFS by prior treatment status.

Indirect treatment comparisons

Also provided were abstract and poster details on two trials involving ofatumumab which was used as a comparator to form a network for indirect treatment comparisons and a single arm study of bendamustine and rituximab .

The company uses indirect treatment comparisons and matched adjusting indirect comparisons to compare ibrutinib to the other comparators of physician's choice, a combination of idelalisib and ofatumumab and a combination of bendamustine and rituximab to estimate the comparative effect of ibrutinib in in patients with relapsed or

refractory chronic lymphocytic leukaemia. In these comparisons ibrutinib was again superior in terms of PFS and OS to all included comparators:

Ibrutinib versus physician choice
ORR OR [redacted]; PFS HR [redacted]; OS HR [redacted]

Ibrutinib versus idelalisib and ofatumumab
ORR OR 1.65 (95% CI: 0.66, 4.10); PFS HR 0.39 (95% CI: 0.23-0.66); OS HR 0.50 (95% CI: 0.24-1.04)

Ibrutinib versus bendamustine plus rituximab
ORR OR [redacted]; PFS HR [redacted]; OS HR [redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG opinion is that the data for efficacy of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia is consistent and impressive. When compared with ofatumumab PFS and OS were highly statistically significantly improved. The OS benefit appeared to be consistent across all subgroups reflecting good outcome across severity of risk (e.g. older patients, advanced disease, multiple pre-treatments) including patients with 17p deletion. The ERG opinion is that ibrutinib also demonstrates a good safety profile.

The ERG note caution with the magnitude of the estimates in the ITC and MAIC analyses given only single trials were used in each comparison, the differences between trial populations and the sensitivity analyses undertaken by the company. The ERG also note that if the multivariate cox model or the MAIC was the preferred approach, then it is unclear to the ERG in the selection of studies from the evidence review whether some other comparators could have been included in the network.

The data provided on treatment-naïve patients only comes from 33 cases in a single non-RCT, non- comparative study. It is therefore difficult to make any definitive statement on treatment efficacy. However the ERG note that a benefit of ibrutinib use

has been demonstrated within the single study. The data presented on relapsed or refractory disease patients with 17p deletion or TP53 mutation within the non-RCT and RESONATE trial do provide evidence that the ibrutinib treatment effect is comparable to those without 17p deletion or TP53 mutation. The ERG opinion is that data are limited, though promising, of the efficacy and safety of ibrutinib for use in treatment-naïve patients with 17p deletion or TP53 mutation.

1.4 Summary of cost effectiveness submitted evidence by the company

The company compares ibrutinib with:

- Physician choice which is a mixture of treatments as drawn from Osterborg et al (2014) with the company having adjusted the costs of this mixture to better reflect UK practise:
  - [redacted]: Bendamustine plus rituximab
  - [redacted]: Methylprednisolone plus rituximab (R-HDMP)
  - [redacted]: Chlorambucil
  - [redacted]: Fludarabine and cyclophosphamide plus rituximab (FCR)
  - [redacted]: Cyclophosamide, doxorubicin, vincristine and prednisolone plus rituximab (R-CHOP)
- Ofatumumab
- Ibrutinib plus rituximab
- Bendamustine plus rituximab

The company has submitted a markov model with a 20 year time horizon and a four week cycle. The four main health states of the model are:

- Progression free survival on 1st line active treatment (PFS)
- Post-progression survival on 2nd line active treatment (PPS)
- Post-progression survival receiving only best supportive care (BSC)
- Dead

Patients start in progression free survival with a mean age of 67 years and with 68% being male. Upon progression, as assessed by the investigator and not by the IRC, a proportion of patients receive a second active treatment. Those who do not receive a

second active treatment and those who further progress while on a second active treatment move onto best supportive care.

The total number of deaths is determined by the overall survival curve. A constant percentage of patients in progression free survival are assumed to die. The residual number of deaths implied by the overall survival curve and the number dying while remaining in progression free survival are among those on best supportive care. This latter forms the majority of deaths.
To model overall survival parameterised curves are estimated from the RESONATE trial data for ibrutinib. For the all patients modelling the lognormal is selected for the first three years, despite the goodness of fit statistics, with this being followed by the exponential thereafter. For the 17p depleted subgroup the exponential is used throughout.

For ofatumumab a hazard ratio derived from the RPSFT adjusted RESONATE data is applied to the ibrutinib parameterised overall survival curve. Similarly, for the other comparators the hazard ratios of the ITC are applied.

A similar approach is undertaken to model progression free survival. But since cross over is not a problem parameterised curves are fitted to the RESONATE data for both ibrutinib and ofatumumab. The company chooses the Weibull parameterisations. For the other comparators the hazard ratios of the ITC are applied.

The quality of life value for progression free survival is based upon post baseline EQ-5D data collected during the RESONATE trial. The quality of life values for post progression survival and best supportive care are estimated by applying a percentage quality of life reduction associated with progression as drawn from the literature to the baseline EQ-5D average of the RESONATE trial.

Serious adverse events are also modelled as having cost and quality of life impacts, and are assumed to last for 14 days.

Ibrutinib and idelalisib are assumed to be taken for the entire period of progression free survival. The other 1st line treatments are administered to a given schedule for a

maximum of up to five model cycles. Treatment specific drug utilisation percentages are applied to account for dose reductions and treatment holidays.

The routine follow-up costs while in progression free survival are determined by treatment specific company estimates of the proportions of patients achieving complete response, partial response and being in stable disease.

A proportion of patients are assumed to go on to receive 2nd line treatment but this only affects costs within the model.

Terminal care costs are applied when patients die.

The company model estimates are that ibrutinib more than trebles overall survival compared to physician choice, more than doubles it compared to ofatumumab and somewhat more than quadruples it compared to bendamustine plus rituximab. The gains compared to idelalisib plus rituximab are less but ibrutinib is still anticipated to result in a survival gain of more than three quarters.

These gains, coupled with longer progression free survival result in net gains of 3.289 QALYs compared to physician choice, 2,647 QALYs compared to ofatumumab, 1.934 QALYs compared to idelalisib plus rituximab and 3.608 QALYs compared to bendamustine plus rituximab. The longer survival results in considerably greater drug costs and so quite high net total costs. At list prices the net total costs are £149,589 compared to physician choice, £120,487 compared to ofatumumab, £86,718 compared to idelalisib plus rituximab and £151,595 compared to bendamustine plus rituximab.

The deterministic cost effectiveness estimates are consequently £45,486 per QALY compared to physician choice, £45,525 per QALY compared to ofatumumab, £44,836 compared to idelalisib plus rituximab and £42,016 compared to bendamustine plus rituximab.

The probabilistic cost effectiveness estimates are slightly worse, at £47,200 per QALY compared to physician choice, £47657 per QALY compared to ofatumumab,

£47,754 compared to idelalisib plus rituximab and £43,559 compared to bendamustine plus rituximab.

The company results are sensitive to the time horizon, the ibrutinib drug utilisation proportion, whether ongoing costs should be differentiated by the company treatment specific response rate estimates, whether the Weibull or the exponential should be used for PFS, the duration of benefit from ibrutinib and, for the comparisons with physician choice and bendamustine plus rituximab, which of the company ITCs is applied.

The company also presents a comparison of ibrutinib and ofatumumab for the 17p depleted population. This applies subgroup specific overall survival and progression free survival curves estimated from the RESONATE trial. The net gain from ibrutinib is estimated to be 2.690 QALY but at a net cost of £102,596, resulting in a cost effectiveness estimate of £38,145 per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

Results for the comparisons with physician choice and bendamustine plus rituximab are sensitive to whether the company base case ITC is applied or its alternative ITC. The impact of the alternative company ITC upon the comparison with bendamustine plus rituximab is a major worsening of the cost effectiveness estimate, increasing the company estimate by around 50%.

The ERG prefers the unadjusted ITT RESONATE ofatumumab data in part due to the ITC having to use the unadjusted ITT ofatumumab data of the comparator trials. The ERG has revised the model to apply the ITT OS hazard ratios for the comparisons with physician choice and idelalisib plus rituximab.

There are uncertainties around the response rates, their definitions across the trials of the ITC and how the rates have been derived for the comparator treatments. ERG expert opinion also suggests that patients will not receive ongoing biopsies as part of routine follow-up, and that routine follow-up will not typically be much differentiated by response status. In the light of this the ERG prefers to not differentiate non-drug routine follow up costs by treatment.

The EQ-5D regression analysis is poorly documented, with prior analyses conducted by the company having been discarded and not being available for reporting. It also concentrates upon the IRC assessment of response, with only partial responses being categorised within this. The quality of life values of the model are taken from a simple averaging of post baseline values which may be subject to bias given missing data. It may be questionable to assume that quality of life for a given health state will be constant over the 20 year time horizon of the model.

The modelling of 2nd line therapy, which assumes a 50:50 balance between R-HDMP and HDMP may not reflect current practise. The PFS curve for these is also derived from the rituximab arm of the idelalisib plus rituximab trial.

The company model includes treatment specific estimates for reductions in the proportion of patients receiving treatment due to dose reductions and possibly also to treatment holidays while on treatment. The derivation of the drug utilisation proportions is unclear and does not particularly distinguish between dose reductions and treatment holidays. It is not obviously reasonable for the company to have assumed that idelalisib drug utilisation would more reflect that of ofatumumab than that of ibrutinib. For bendamustine plus rituximab it appears that only dose reductions have been considered and not treatment holidays, or the number of completed cycles.

The company model applies the drug utilisation proportions twice for ibrutinib but only once for the comparator treatments. Given the model structure the ERG finds it difficult to imagine how this double discount for ibrutinib can be accidental so it appears to be the intended company model structure.

There are other asymmetries in company modelling of the direct drug costs where ibrutinib has been treated in a different manner than the other comparators. The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis. It seems reasonable to conclude that some and perhaps all of these are deliberate choices made by the company. If so this may raise questions about other company choices, both seen and unseen.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

A high quality RCT (RESONATE) underpins the evidence for safety and efficacy of ibrutinib.

The model structure has been cross checked by a full ERG model rebuild. These correspond, though the rebuild also highlight certain assumptions within the model which are not highlighted within the submission.

The model approach, perspective and discounting is in line with the NICE TAPS methods guide, with the exception of the 17p depleted subgroup modelling not being implemented probabilistically.

A good range of sensitivity analyses are conducted for the all patient modelling.

1.6.2 Weaknesses and areas of uncertainty

The robustness and magnitude of the ITC and MAIC analyses is difficult to assess given only single trials were used in each comparison, the differences between trial populations and the sensitivity analyses undertaken by the company.

An unavoidable weakness given the length of the RESONATE trial and the impressive clinical effectiveness of ibrutinib during the RESONATE trial is the degree of extrapolation which is required for both overall survival and progression free survival. The numbers at risk in RESONATE drop off sharply around the 20th month. In the ibrutinib arm there are still around 85% surviving and around 60% remaining progression free. The parameterise curves are little different from one another during this period. It is only during the period of extrapolation that they diverge, in some cases quite dramatically.

The comparison with bendamustine plus rituximab is limited by the bendamustine trial identified by the company being a single arm trial.

To the ERG there is no obvious reason to apply the lognormal overall for three years followed by the exponential. The goodness of fit statistics also tend to favour the

exponential. The ERG may consequently have misunderstood the company arguments.

A key determinant of costs is the progression free survival curve. The goodness of fit statistics do not provide any clear guidance as to which curve should be preferred, but the company prefers the Weibull. ERG expert opinion suggests that the Weibull models too small a proportion of patients remaining progression free in the medium term for the anticipated overall survival. Of the parameterised curves ERG expert opinion suggests that the exponential provides a more credible proportion of patients remaining progression free given the anticipated survival.

The degree of extrapolation that is required, with around 10% of ibrutinib patients being modelled as still surviving at twenty years, is the largest that the ERG has seen during its STA reviewing. As a consequence, in the opinion of the ERG alongside the formal statistical tests and parameterised curves there is a greater need than usual for expert opinion as to the reasonableness of the extrapolations and the anticipated gains.

ERG expert opinion suggests that anticipating 10% remaining alive with ibrutinib after twenty years may be reasonable. But it is also of the opinion that the survival benefits from ibrutinib compared to idelalisib plus rituximab are likely to be exaggerated. ERG expert opinion also does not find it credible for bendamustine plus rituximab to be estimated to have such an inferior survival compared to ofatumumab, at least among the non 17p depleted patient population.

But turning to the papers of the ITC suggests that the model may overestimate survival for physician choice and for idelalisib plus rituximab, while somewhat underestimating it for bendamustine plus rituximab. It is difficult to align the various data sources with the model survival estimates.

The 17p depleted subgroup cannot be modelled probabilistically within the submitted model. Probabilistic estimates for the all patient modelling were a bit worse than the corresponding deterministic estimates.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

ERG revisions to the company base case are quite extensive. But the main changes are to:

- Apply the ITT OS hazard ratios for physician choice and idelalisib plus rituximab.
- Apply exponential OS and exponential PFS curves.
- Remove the asymmetries in the treatment of ibrutinib drug and administration costs.
- Not differentiate the non-drug routine costs of care by treatment.
- Remove the costs of ongoing biopsies from the non-drug routine costs of care.

The other model revisions have only a limited impact.

ERG revisions to the company base case are quite extensive. But the main changes are to:

- Apply the ITT OS hazard ratios for physician choice and idelalisib plus rituximab.
- Apply exponential OS and exponential PFS curves.
- Remove the asymmetries in the treatment of ibrutinib drug and administration costs.
- Not differentiate the non-drug routine costs of care by treatment.
- Remove the costs of ongoing biopsies from the non-drug routine costs of care.

The other model revisions have only a limited impact.

The ERG model revisions worsen the deterministic cost effectiveness estimates quite considerably.

- £71,812 per QALY vs physician choice
- £72,336 per QALY vs ofatumumab
- £88,484 per QALY vs idelalisib plus rituximab
- £62,756 per QALY vs bendamustine plus rituximab

The central probabilistic cost effectiveness estimates are slightly worse.

- £74,253 per QALY vs physician choice
- £73,789 per QALY vs ofatumumab

- £92,562 per QALY vs idelalisib plus rituximab
- £64,962 per QALY vs bendamustine plus rituximab

Reverting to the company hazard ratios improves the cost effectiveness estimates for the comparisons with physician choice and idelalisib plus rituximab.

- £67,907 per QALY vs physician choice
- £74,842 per QALY vs idelalisib plus rituximab

Applying the company alternative ITC hazard ratios for physician choice and bendamustine plus rituximab worsens the cost effectiveness estimates.

- £81,169 per QALY vs physician choice
- £99,620 per QALY vs bendamustine plus rituximab

Reverting to the Weibull PFS curves for ibrutinib and ofatumumab, with this flowing through to the PFS curves for idelalisib plus rituximab and bendamustine plus rituximab via the hazard ratios, has a major impact. The deterministic cost effectiveness estimates improve markedly.

- £53,976 per QALY vs physician choice
- £50,545 per QALY vs ofatumumab
- £61,171 per QALY vs idelalisib plus rituximab
- £46,892 per QALY vs bendamustine plus rituximab

Patients receiving ibrutinib and idelalisib long term may tend to be those who tolerate it well and may have a higher drug utilisation than estimated from the RESONATE trial. Applying a 100% utilisation rate from week 32 worsens the cost effectiveness estimates.

- £75,109 per QALY vs physician choice
- £76,147 per QALY vs ofatumumab
- £93,156 per QALY vs idelalisib plus rituximab
- £65,617 per QALY vs bendamustine plus rituximab

For the 17p depleted subgroup the cost effectiveness estimates for ibrutinib compared to physician choice, idelalisib plus rituximab and bendamustine plus rituximab if the

all patient hazard ratios can be applied to the ibrutinib 17p depleted OS and PFS curves are similar to the all patient estimates. The sensitivity of these estimates also mirrors the sensitivity of the all patient estimates.

For the 17p depleted subgroup the cost effectiveness estimate for ibrutinib compared to ofatumumab is £62,624 per QALY. If the Weibull PFS curves are used this improves to £44,745 per QALY.

The ERG has undertaken a range of other sensitivity analyses but these have only limited impacts upon results.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of chronic lymphocytic leukaemia (CLL) in terms of prevalence, symptoms and complications is accurate and appropriate to the decision problem. The company describes CLL as an incurable, often life-threatening cancer of the blood that arises from monoclonal expansion of mature malignant B lymphocytes in bone marrow and eventually streams into the lymphatic system and other bodily organs,[1] and prevents the development of normal white and red blood cells, and platelets. CLL is the most common form of leukaemia in adults. Incidence increases with age and the disease is more common in men than women.[2] The company states that the annual incidence of CLL is 3.7 to 7 new cases per 100,000[3] with 2712 new cases reported[2, 4] in England for 2011;[4, 5] however, the ERG believes this refers to newly diagnosed CLL and not R/R patients, who are the population of interest for this appraisal. Symptoms of CLL include anaemia, bleeding, tendency to prolonged and recurrent infection, enlarged lymph nodes and "B symptoms" (night sweats, fever, rapid and unexplained weight loss). The company provides a description of the clinical characteristics of CLL as described in Table 1.

Table 1 Clinical characteristics of CLL patients[6, 7 8]

Non-specific symptoms may include:	**Clinical signs may include:**	**In advanced disease patients may experience:**
Weakness Fatigue Abdominal discomfort Night sweats Fever	Abnormal enlargement of lymph nodes (lymphadenopathy) Abnormal enlargement of organs (organomegaly), e.g. spleen (splenomegaly) or liver enlargement (hepatomegaly) Ecchymoses (bruising) Swelling and redness of joints	Weight loss Recurrent infections Bleeding secondary to thrombocytopenia Symptomatic anaemia

The company states that CLL is a debilitating condition that has major negative impact on quality of life, especially patients' emotional wellbeing and levels of fatigue,[9] with patients showing significantly poorer quality of life compared with the general population[9] and patients within working age require significantly more leave from work, thus impacting on worker productivity.[10] Quality of life (QoL) is poorest in patients aged over 70 years[11] and the negative impact of CLL increases during active treatment.[9, 12] The diagnosis of an incurable disease, with added uncertainty around timing and impact of disease progression and treatment, can also negatively affect the QoL for patients and their carers.[13]

A majority of CLL patients who come to treatment will eventually relapse and prognosis is poor for those who relapse within 24 months of first-line therapy. The disease is genetically heterogeneous and becomes more difficult to treat as mutations accumulate with time.[14] High-risk disease is characterised by relapsed or refractory (R/R) disease and/or the presence of cytogenetic mutations or abnormalities (e.g. 17p deletion or TP53 mutation).[15] In most cases (approximately 80%), 17p deletion and TP53 mutations will occur concomitantly.[16]

The British Committee for Standards in Haematology (BCSH) guidelines for CLL[7] refer to the following definitions of relapsed and refractory disease:[17]

- Relapse: disease progression at least 6 months after achieving a complete response (CR) or partial response (PR).
- Refractory: treatment failure or disease progression within 6 months of anti-leukaemic therapy.

At clarification, the company informed the ERG that their submission refers to the definitions of relapsed and refractory disease as used in the RESONATE trial:

- Relapse: a patient who met criteria for CR or PR, but progressed beyond 12 months post-treatment.
- Refractory: treatment failure or disease progression within 12 months of anti-leukaemic therapy; furthermore, the refractory subgroup analysis conducted in RESONATE is more strictly for "purine-analogue refractory" patients.

The company stated in their response to clarification that:

> "The RESONATE definitions were used for this submission to align with the most robust clinical data available. It is not possible to retrospectively align the RESONATE subgroups to the definitions used by BCSH as these subgroups were pre-specified and required information would have had to be collected in a specific manner at patient enrolment in the trial.

The ERG comments that the differences between company used and BCSH definitions of relapsed and refractory disease were unlikely to cause any substantive bias in results.

Approximately, one third of CLL patients have aggressive, high-risk disease at presentation and will have a poor response to treatment. The company states that these patients present with more advanced disease at diagnosis[18] and are more likely to be resistant to conventional chemotherapy. Consequently, these patients have particularly poor outcomes and short survival.[16] The company states median overall survival associated with current treatment is less than 2 years in this patient group.

2.2 Critique of company's overview of current service provision

CLL is a disease of repeated relapses. The primary aim of treatment is to improve survival and QoL, although these aims are driven by individual patient characteristics, depending on whether the patient is physically fit/unfit and whether they have low/high risk disease. In Europe, the Binet system is commonly used to evaluate a patient to determine their prognosis and choice of therapy. Treatment options range from chemotherapy using single agents and combination regimens consisting of chemotherapy and monoclonal antibodies (immuno-chemotherapy) and targetted therapies (see Table 2).[19]

Table 2 Therapies for CLL

Drug class	Drug therapy	Mechanism of action
Cytotoxic therapies	Chlorambucil	Alkylating agent
	Fludarabine	Purine analogue
	Bendamustine	Alkylating agent, purine analogue
Monoclonal antibodies	Rituximab	Anti-CD20 monoclonal antibody
	Ofatumumab	Anti-CD20 monoclonal antibody
	Obinutuzumab	Anti-CD20 monoclonal antibody
	Alemtuzumab	Anti-CD52 monoclonal antibody
Targeted therapies	Ibrutinib	BTK inhibitor
	Idelalisib	PI3Kδ inhibitor

The NICE Final Scope recommended the following comparator treatments for ibrutinib: FCR; bendamustine (with or without rituximab); chlorambucil (with or without rituximab); corticosteroids (with or without rituximab); Idelalisib and rituximab (IR); and best supportive care (BSC). To provide further information on the current state of guidance for CLL, the information provided in the scope has been updated by the ERG to include recommendations for IR use that were issued as an interim statement by the BSCH Guidelines Panel for CLL[20] (see Table 3). Please note Table 3 is not intended to represent all actual comparators for this appraisal. The company state that, following clinical guidelines and advice received from an advisory board of UK haematologists, that there is no established standard of care for treating R/R CLL patients in the UK. The ERG agrees with the company's assertion. This is because treatment options depend on a number of factors, including whether genetic abnormalities are present, the type of previous treatment received and whether the patient responded to that treatment, and the duration of the response.[21]

NICE recommends fludarabine, cyclophosphamide and rituximamb (FCR) as an initial therapy for treatment naïve patients who are able to tolerate fludarabine. Bendamustine is recommended for patients who are unsuitable for fludarabine.[22] Guidance for R/R CLL patients is limited, however. NICE recommends repeat administration of FCR, unless the patient is refractory to fludarabine or has received previous rituximamb treatment. For those patients unsuitable for repeat FCR, NICE

recommends oral fludarabine for patients who have failed on, or are intolerant to, first-line chemotherapy who would otherwise have received standard combination chemotherapy (i.e. cyclophosphamide, doxorubicin, vincristine and prednisolone [CHOP], cyclophosphamide, doxorubicin and prednisolone [CAP] or cyclophosphamide vincristine and prednisolone [CVP]).

NICE, currently, does not provide any specific treatment pathways for patients with 17p deletion or TP53 mutation; therefore, these patients are treated using the same guidance as the wider CLL patient population, although response to immune-chemotherapy is poor for these patients.

Table 3 Treatments considered in the NICE CLL treatment pathway and their technology appraisals

Agent	NICE Guidance
Initial treatment	
Rituximab (given as FCR) TA174, July 2009[23]	Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of CLL.
Bendamustine TA216 February 2011[22]	Bendamustine is recommended 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.
Obinutuzumab, in combination with chlorambucil TA343 June 2015[24]	Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • Bendamustine-based therapy is not suitable and • the company provides obinutuzumab with the discount agreed in the patient access scheme •
Ofatumumab, in combination with chlorambucil TA344 June 2015[25]	Ofatumumab in combination with chlorambucil is recommended as an option for untreated CLL only if: • the person is ineligible for fludarabine-based therapy and • bendamustine is not suitable and

Agent	NICE Guidance
Initial treatment	
	• the company provides ofatumumab with the discount agreed in the patient access scheme
Fludarabine monotherapy TA119 February 2007[26]	Fludarabine monotherapy, within its licensed indication, is not recommended for the first-line treatment of CLL.
R/R treatment	
Rituximab (given as FCR) TA193 July2010[21]	Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with R/R CLL except when the condition: • is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or • has previously been treated with rituximab, unless: o in the context of a clinical trial, at a dose lower than the dose currently licensed for CLL or o in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide.
Fludarabine monotherapy TA29 September 2001[27]	Oral fludarabine is recommended as second line therapy for B-cell CLL for patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either: • CHOP • CAP • CVP
Ofatumumab TA202 October 2010[28]	Ofatumumab is not recommended for the treatment of CLL that is refractory to fludarabine and alemtuzumab.
Idelalisib, in combination with rituximab TA359 October 2015[29]	NICE [FAD September 2015 (TAG pending)] Idelalisib, in combination with rituximab, is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed within 24 months.

The BCSH have also issued UK-specific guidance (see Table 4).[7, 20]

Table 4 Summary of BCSH guidelines for the management of CLL

Patient population	Summary of guidance
First-line treatment of patients without TP53 abnormality who are fit enough to receive fludarabine	• FCR is recommended • Bendamustine plus rituximab is an alternative option in patients in whom FCR is contraindicated
First-line treatment of patients without TP53 abnormality who are not fit enough to receive fludarabine	• Chlorambucil in combination with ofatumumab or obinutuzumab • Chlorambucil in combination with rituximab is an alternative treatment if access to ofatumumab or obinutuzumab is restricted. • In particularly frail patients, chlorambucil is the treatment of choice for palliating frail patients, but bendamustine monotherapy is an option
First-line treatment of patients with TP53 abnormality	• idelalisib + rituximab or ibrutinib. If either idelalisib + rituximab or ibrutinib are not available then treatment with alemtuzumab +/- corticosteroids remains preferable to chemotherapy
R/R CLL	• Idelalisib + rituximab or ibrutinib is the treatment of choice for patients with relapsed CLL who meet specific criteria (trial entry eligibility criteria)[30, 31] Patients with relapsed CLL who do not meet the treatment criteria for either idelalisib + rituximab or ibrutinib should be treated with chemotherapy+/- rituximab, most likely BR or FCR although the quality of data to support this choice is limited. CBL is an option where a more palliative approach is required.
High risk (TP53 mutation/17p deletion or failing fludarabine combination therapy within 2 years) patients	• Ibrutinib monotherapy or IR. • If not available, alemtuzumab with or without corticosteroids are preferable to chemotherapy
CLL with autoimmune cytopenias as a complication	• Steroids as first-line treatment • cyclosporine, intravenous immunoglobulin, thrombopoietin

Patient population	Summary of guidance
	mimetic agents, low-dose cyclophosphamide, rituximab, alemtuzumab and splenectomy for patients unable to take steroids
CLL with infections as a complication	• Anti-microbial prophylaxis in patients at high risk of infection • Immunoglobulin replacement therapy may be considered to reduce bacterial infections in patients with a low serum IgG level with previous infection despite prophylaxis

The company states that, despite the existence of UK recommendations, these are not wholly reflective of current clinical practice. The company state that clinical advisors from their Advisory panel suggest a number of clinical issues regarding use of the guidance in clinical practice (see Table 5).

Table 5 Therapies in NICE final scope for relapsed CLL and their use in clinical practice

Drug class	Treatment in scope	Patients who receive treatment	Use in clinical practice	Issues
Cytotoxic therapies for patients fit enough to receive fludarabine	FCR	Patients relapsing after fludarabine or chlorambucil within 2 years who are fit enough to receive fludarabine	Most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset	Clinical experts suggested that FCR would not be used to treat patients who relapse early and it is not an option in older patients and those with significant comorbidities. Experts agreed that chemo-immunotherapy regimens such as this would not be suitable for relapsed patients with a 17p deletion or TP53 mutation..
Cytotoxic therapies for patients unable to receive fludarabine	Chlorambucil (with or without rituximab)	Patients relapsing after chlorambucil treatment, with or without an anti-CD20 antibody	Chlorambucil monotherapy is the third most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset. Chlorambucil in combination with rituximab is also used.	Clinical experts agreed that chlorambucil±R is used sparingly in R/R CLL. Furthermore, data are limited in the R/R setting making it difficult to estimate relative efficacy. The experts also noted that using chlorambucil±R in relapsed patients with a 17p deletion or TP53 mutation would be unlikely.

Drug class	Treatment in scope	Patients who receive treatment	Use in clinical practice	Issues
	Bendamustine (with or without rituximab)	Patients relapsing after chlorambucil treatment, with or without an anti-CD20 antibody	BR is the second most commonly used regimen in England, over all lines of treatment combined, as reported in the Systemic Anti-Cancer Therapy Dataset. Bendamustine monotherapy is also used.	Clinical experts agreed that B±R is an appropriate option in R/R CLL. However, data are limited in the R/R setting making it difficult to estimate relative efficacy. The experts also noted that using B±R in relapsed patients with a 17p deletion or TP53 mutation would be unlikely.
Anti-CD20 antibodies	Rituximab monotherapy	Not recommended as monotherapy	Clinical advice suggests this is not used as single agent in current practice Clinical advice further suggests rituximab would be expected to have a similar efficacy to ofatumumab, the seventh most commonly used regimen in England as reported in the Systemic Anti-Cancer Therapy Dataset	Not assessed by NICE in this population and not licensed for use as monotherapy in this population.
Targeted therapies	Idelalisib in combination with rituximab (IR)	Patients relapsed within 24 months	Based on the therapies available through the Cancer Drug Fund (CDF) for CLL in the R/R setting, IR is the second most commonly used regimen (49 or 17% of notifications) behind ibrutinib (178 or 62%) as reported by the CDF for the first quarter of	NICE have recently completed appraisal of this therapy and issued a FAD recommending use in untreated CLL in adults with a 17p deletion or TP53 mutation or for CLL in adults when the disease has been treated but has relapsed

Drug class	Treatment in scope	Patients who receive treatment	Use in clinical practice	Issues
			2015. The other funded CLL therapies are bendamustine (48; 17%) and ofatumumab (13; 5%)	within 24 months. The final TAG expected in November 2015 at the earliest.
Supportive therapies	Corticosteroids (with or without rituximab)	Patients refractory to chlorambucil and unable to tolerate myelosuppressive therapy	Steroid use is not certain and not captured in the Systemic Anti-Cancer Therapy Dataset	Not assessed by NICE in this population.
	Best supportive care (BSC) (including but not limited to regular monitoring, blood transfusions, infection control and psychological support)	In patients not fit enough to receive any of the above treatments, or where all other treatment options have been exhausted.	BSC consists of a wide range of therapies. Recent NICE appraisal documents reported that BSC would be comprised of outpatient review, blood/red cell transfusion for anaemia, inpatient stays, platelet transfusion for thrombocytopenia, immunoglobulin replacement, and plasmaphoresis. Additionally, there would be high use of anti-infective agents (e.g. antimicrobial, antifungals, and antivirals).	Not assessed by NICE in this population.

The ERG notes that is a fast-changing clinical area and that the above seems to be a reasonable representation of current service provision in the UK.

3 Critique of company's definition of decision problem

Differences between the company submission and the NICE final scope are summarised in Table 6 and described in sections 3.1 to 3.5.

Table 6 Differences between the final scope issued by NICE and the decision problem addressed in the company submission

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	As per the final scope: • Adults with CLL who have received at least one therapy • Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable		
Intervention	As per the final scope: • Ibrutinib		
Comparator (s)	<u>For adults with CLL who have received at least one prior therapy:</u> • Fludarabine in combination with cyclophosphamide and rituximab (FCR) • Bendamustine with or without rituximab (BR or B) • Chlorambucil with or without rituximab • Corticosteroids with or without rituximab • Idelalisib in combination with rituximab (IR) • Rituximab alone for refractory disease • Best supportive care (BSC)	<u>For adults with CLL who have received at least one prior therapy:</u> • Physician's Choice (PC) • BR • IR • Ofatumumab	<u>For adults with CLL who have received at least one prior therapy:</u> PC aims to accurately reflect the fact that there is currently no clear standard of care for patients with R/R CLL. It is comprised of the comparators listed within the final NICE scope except for (a) IR which is compared to independently and (b) rituximab monotherapy which is not licensed and not widely used in UK clinical practice. Ofatumumab is an important comparator as it is licensed for use in Europe for R/R CLL (while rituximab is not), it is the comparator within the pivotal phase III trial for ibrutinib (RESONATE), as it was the only licensed treatment within R/R CLL at the time of trial initiation, and most importantly, clinical opinion strongly suggests that it remains a relevant comparator in the UK for R/R CLL

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
	<u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable:</u> • Alemtuzumab with or without corticosteroids • IR • BSC	<u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable:</u> • Alemtuzumab with or without corticosteroids • IR • BSC	<u>For adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable:</u> As scope.
Outcomes	As per the final scope: Overall survival (OS), progression-free survival (PFS), response rates, adverse effects (AE) of treatment, health-related quality of life (HRQOL)		
Economic analysis	As per the final scope: the reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY); 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 (PSS) perspective; if appropriate, the appraisal should include consideration of the costs and implications of additional testing for genetic markers, but will not make recommendations on specific diagnostic tests or devices; and the availability of any patient access schemes (PAS) for the intervention or comparator technologies should be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered for adults with untreated CLL: Presence or absence of 17p deletion. Presence or absence of TP53 mutation.	Presence or absence of 17p deletion in untreated CLL. Presence or absence of 17p deletion in R/R CLL.	Clinical data are limited and disparate for these subgroups. The ibrutinib pivotal trial collected 17p deletion but not TP53 mutation status and thus analyses can be performed for 17p deletion only. However, as these mutations have the same impact on the cell biology, disease prognosis and treatment outcomes, ibrutinib data in patients with 17p deletion are used as a proxy for ibrutinib's efficacy in TP53

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			mutation. Where cost-effectiveness is demonstrated in the 17p deletion subgroup, it can be assumed to apply equally to the patient subgroup with TP53 mutation. This assumption is reflected in the BCSH interim guidelines which make no distinction in treatment recommendations between the two cytogenetic abnormalities, and use the encompassing term 'TP53 disruption' Data for other comparators as above are limited and thus subgroup comparisons against PC, BR and IR are not feasible.
Special considerations including issues related to equity or equality	The current, most effective therapies available for the treatment of CLL are most suited to young and fit patients. However, ibrutinib is suitable for a wider patient population, including high-risk and older patients. The addition of ibrutinib into the treatment pathway will likely address equality issues regarding the availability of suitable treatments for an older, frailer population.		Introduction of ibrutinib may alleviate a potential equality issue within the current treatment pathway of CLL.
Key: CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; BR, bendamustine plus rituximab; IR, Idelalisib in combination with rituximab; BSC, best supportive care; PC, physicians' choice; R+HDMP, rituximab plus high dose methylprednisolone; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin and prednisolone; PFS, progression free survival; OS, overall survival; AE, adverse event; HRQOL, health related quality of life; QALY, quality adjusted life year.			

3.1 Population

The company submission addresses the following two patient populations, both of which are included within ibrutinib's marketing authorisation:

- Adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate
- Adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation.

The ERG agrees that the population presented in the company submission is appropriate and in line with the NICE final scope.

3.2 Intervention

Ibrutinib is a first-in-class inhibitor of Bruton's tyrosine kinase (BTK), which is a critical signalling kinase in the B cell receptor (BCR) pathway for tumour cell survival and proliferation. It produces sustained inhibition of enzymatic activity by forming a stable covalent bond within BTK's active site Cys-48. By blocking BTK, ibrutinib disrupts the BCR signalling pathway and prevents proliferation and survival of B cells.

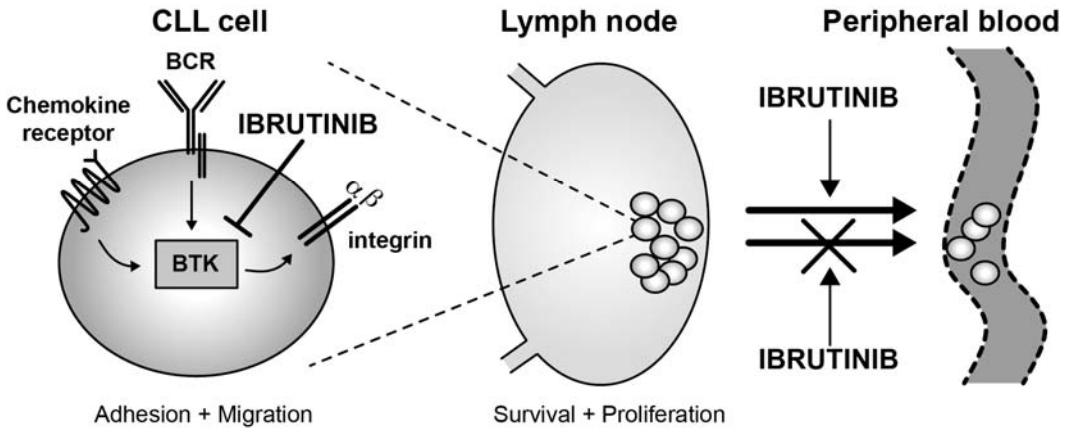


Figure 1 Mechanism of action of ibrutinib in CLL[32]

Ibrutinib is a rapidly absorbed, non-cytotoxic agent, administered orally as a hard gel capsule containing 140mg of the drug substance[33]. The recommended dose is 3 capsules once a day, taken at the same time each day, swallowed whole with water.

The dose should be reduced to 140 mg once daily (one capsule) or withheld for up to7 days when it is used concomitantly with moderate or strong CYP3A4 inhibitors and patients should be monitored for toxicity. A dose reduction is also recommended in patients with mildly or moderately reduced liver function. Ibrutinib is not recommended in patients with severely reduced liver function.[33]

Patients should avoid consumption of grapefruit and Seville oranges during treatment, as these contain moderate inhibitors of CYP3A4. Similarly, concomitant use of St John's Wort and proton pump inhibitors should be avoided as this can reduce the efficacy of ibrutinib.[34]

Ibrutinib should be continued until disease progression or until the side effects become intolerable.[33]

Ibrutinib is also used to treat mantle cell lymphoma and Waldenström's macroglobulinaemia.[35]

3.2.1 Special populations

Renal impairment

While, no specific studies on renal impairment have been conducted, patients with mild/moderate renal impairment (greater than 30 mL/min creatinine clearance) were treated with ibrutinib in clinical trials. There are no data for patients with severe impairment or dialysis patients, and ibrutinib should only be administered to these patients when benefits are thought to outweigh associated risks.[33]

Hepatic impairment

Ibrutinib is metabolised in the liver. It is, therefore, not recommended for use in patients with severe hepatic impairment and dosage should be reduced in patients with mild/moderate impairment.[33]

Severe cardiac disease

Patients with severe cardiac disease were excluded from ibrutinib clinical trials.[33]

Pregnancy

Ibrutinib may cause harm to the unborn foetus. Ibrutinib should, therefore, not be used in pregnant women, and women using ibrutinib should avoid pregnancy during treatment and for up to three months after treatment has ended. It is unknown whether ibrutinib reduces the effectiveness of hormonal contraceptives, therefore, women advised to use additional barrier methods of contraception. It is also unknown whether ibrutinib is excreted in breast milk, thus, breastfeeding should be discontinued during treatment.

Paediatric population

No data are available for children aged 0-18 years[33].

3.2.2 Known adverse effects

Haemorrhagic events have occurred in patients treated with ibrutinib, both with and without thrombocytopenia. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib and supplements such as fish oil and vitamin E. Other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding. Other known adverse events include: leukostasis, infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections), cytopenias, atrial fibrillation/flutter, tumour lysis syndrome and mild decrease in the QTcF interval.[33]

A tabulated list of treatment-emergent adverse reactions is presented in Table 7.

Table 7 Treatment-emergent adverse reactions in patients treated with ibrutinib for mantle cell lymphoma (MCL), chronic lymphocytic leukaemia (CLL) or Waldenstrőm's macroglobulinaemia (WM) (N = 420) and post-marketing adverse reactions[33]

System organ class	Frequency (All grades)	Adverse reactions
Infections and infestations	Very common	Pneumonia* Upper respiratory tract infection Urinary tract infection Sinusitis* Skin infection*
	Common	Sepsis*
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia Anaemia
	Common	Febrile neutropenia Leukocytosis Lymphocytosis
Metabolism and nutrition disorders	Common	Dehydration Hyperuricaemia
	Uncommon	Tumour lysis syndrome
Nervous system disorders	Very common	Dizziness Headache
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage* Epistaxis Bruising* Petechiae
	Common	Subdural haematoma

System organ class	Frequency (All grades)	Adverse reactions
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation
	Common	Dry mouth
Skin and subcutaneous tissue disorders	Very common	Rash*
	Uncommon	Angioedema Urticaria
	Not known	Erythema
Musculoskeletal and connective tissue Disorders	Very common	Arthralgia Musculoskeletal pain*
General disorders and administration site Conditions	Very common	Pyrexia Oedema peripheral

* Includes multiple adverse drug reaction terms.

3.3 Comparators

The company states that their clinical advisors suggest that treatment options are selected based on a number of factors and the most relevant comparator would likely change with the population under consideration, for example by the patients' level of fitness and/or risk (i.e. the presence of 17p deletion or TP53 mutation). The company response at clarification states:

"*With respect to comparators, clinical advice provided at an advisory board conducted by the company on 4th September 2015 (a full description of which can be found in the submission) suggested that treatment options are selected based on a number of factors and the most relevant comparator would likely change with the population under consideration, for example by the patients' level of fitness and/or*

risk (i.e. the presence of 17p deletion or TP53 mutation). Figure 2 and Figure 6 in the submission shows the proposed therapies by fitness and risk group; these being:

- *Unfit, low risk patients: Ibrutinib, physician's choice, idelalisib with rituximab (IR), bendamustine with rituximab (BR), and chlorambucil.*
- *Unfit, high risk patients: Ibrutinib, IR, ofatumumab, and best supportive care (BSC)*
- *Fit, high risk patients: Ibrutinib and IR*
- *Fit, low risk patients: chemo-immunotherapy (e.g. FCR)*"

Figure 2, replicates Figures 2 and 6 of the company submission and shows the proposed therapies by fitness and risk group. The company asserts that ibrutinib is suitable for treating all patients, except those who are physically fit with low risk disease. The ERG agrees with that assertion.

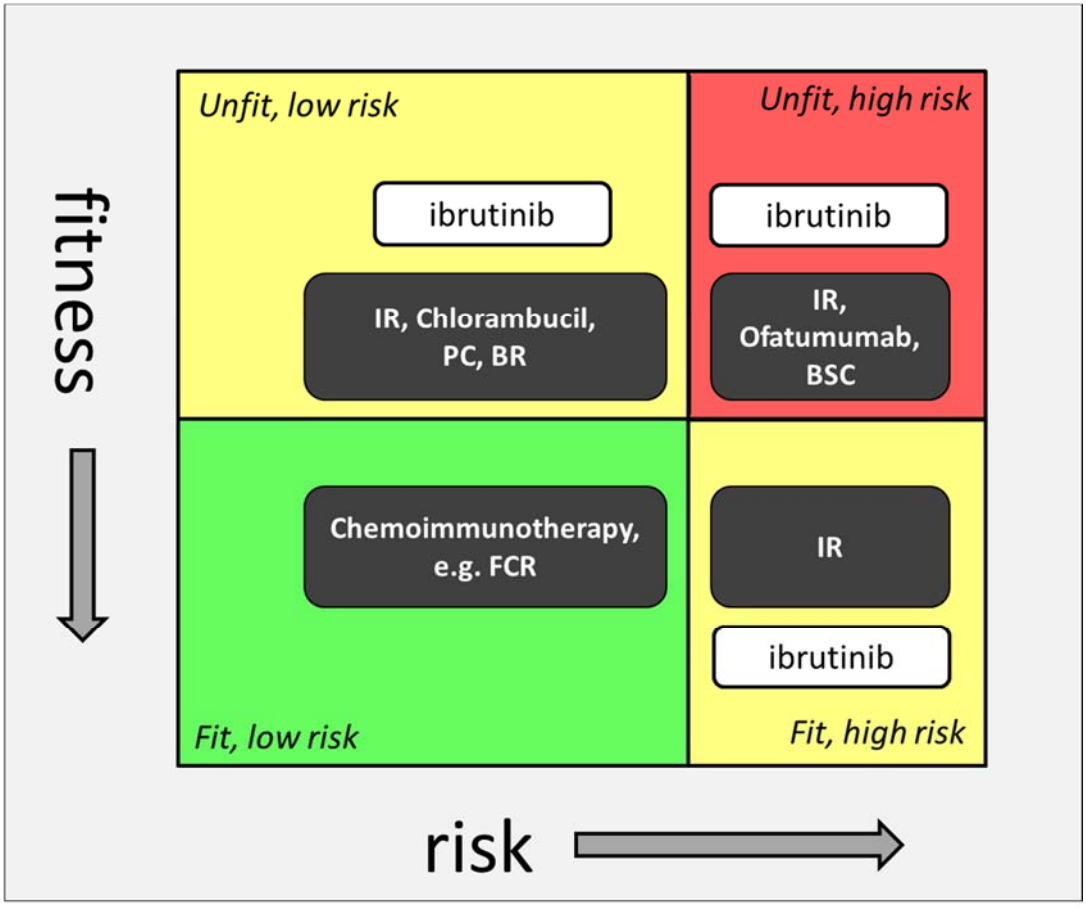


Figure 2 Place in therapy for ibrutinib

The company submission considers four comparators: Physician's choice (PC), Idelalisib in combination with rituximab (IR), bendamustine in combination with rituximab (BR) and ofatumumab. The company state that PC is the main comparator for ibrutinib in their submission and is based on a phase III RCT comparing PC with ofatumumab that was adjusted to be relevant to UK practice.[36] At clarification, the company reported that their advisory board suggested that rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone (R-CHOP) is more commonly used in the UK while Rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP) is less commonly used. Additionally, UK clinicians indicated rituximab plus high dose methylprednisolone (R-HDMP) and chlorambucil are also used. Based on these expert opinions, the physician's choice treatment composition was adjusted as presented in Table 8 below.

Table 8 Adjusted composition of physician's choice for economic modelling

Regimen	Composition in Österborg	Composition in submission
R-CVP	28%	[redacted]
Alemtuzumab	26%	[redacted]
BR	12%	[redacted]
FCR	14%	[redacted]
R-CHOP	-	[redacted]
R-HDMP	-	[redacted]
Chlorambucil	-	[redacted]
Total	**80%**	[redacted]

BR: Bendamustine and rituximab; FCR: Fludarabine and cyclophosphamide and rituximab; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, and prednisolone; R-CVP: Rituximab plus cyclophosphamide, vincristine, and prednisolone R-HDMP: Rituximab plus high dose methylprednisolone

The ERG notes that ofatumumab is now withdrawn from the cancer drug fund and does not appear in the NICE final scope; however, the company argues that it should remain as a relevant comparator for their submission. The company state their rationale for their argument as follows:

- Ofatumumab is the comparator within the pivotal phase III trial for ibrutinib (RESONATE), as it was the only licensed treatment for R/R CLL at the time of trial initiation.[30]
- Ofatumumab remains licensed for use in Europe for R/R CLL.
- Rituximab monotherapy is not licensed and not widely used in UK clinical practice; however, it remains within the NICE final scope.
- Clinical advisors for the company suggests that it remains a relevant comparator in the UK for R/R CLL.

Whilst the ERG recognises that ofatumumab will be needed to connect the network of trials to address the other comparators in the company submission, it is the ERG's opinion that ofatumumab is not a valid comparator for ibrutinib given it is no longer available in the cancer drug fund.

3.4 Outcomes

The outcomes considered in the company submission are in line with those detailed in the NICE final scope. The considered outcomes are: overall survival (OS), progression-free survival (PFS), response rates, adverse effects (AE) of treatment and health-related quality of life (HRQOL).

3.5 Other relevant factors

3.5.1 Subgroup analysis

The NICE final scope detailed two patient subgroups to be considered for adults with untreated CLL, if the evidence allowed: presence/absence of 17p deletion, and presence/absence of TP53 mutation. The company state that clinical data for these subgroups are limited and that the pivotal trial for ibrutinib did not collect data for TP53 mutation, thus analyses could be performed for 17p deletion only. The company further states that these mutations have the same impact on cell biology, disease prognosis and treatment options; therefore, ibrutinib data for patients with 17p

deletion are used as a proxy for ibrutinib's efficacy in TP53 mutation patients. ERG clinical opinion agrees in general that disease prognosis and treatment options for TP53 mutation and 17p deletion would have the same impact, though ERG are unclear that the impact on cell biology would be the same.

3.5.2 Equality

The company assert that the introduction of ibrutinb may alleviate a potential equality issue within the current CLL treatment pathway. The company state that the current, most effective therapies available for treatment of CLL are most suited to young and fit patients,(BresMed, unpublished summary report from Advisory Board, 2015) whereas ibrutinib is suitable for a wider population, including older and high-risk patients. The company, therefore, states that the addition of ibrutinib into the treatment pathway would address equality issues regarding the availability of suitable treatments for an older, frailer population. The ERG believes there are currently other combinations of treatments available in the UK for older, frailer populations such as idelalisib in combination with rituximab.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases: MEDLINE (Pubmed), EMBASE (Embase.com) and CENTRAL (Cochrane Library) were searched initially in May 2014 and updated on 3rd June 2015 without date limits. However, the start date from which the databases were searched is unclear. In addition, the three most recent years' conference proceedings of five relevant conferences were screened (ASCO, ASH, EHA,ESMO, ISPOR). Reference lists of identified studies and recently published reviews were also screened.

The search strategies are documented in full in Appendix 2 of the company submission and are reproducible. The PUBMED and EMBASE searches combined three search facets using the Boolean operator AND: the patient population (chronic lymphocytic leukaemia); intervention or comparator (salvage treatment or refractory disease or second/third line treatment); and study design (RCTs). The search in the Cochrane Library for CENTRAL excluded the RCT facet which was appropriate. A comprehensive selection of phrases relating to the disease were used to search the conference proceedings.

Appropriate controlled vocabulary terms and a comprehensive range of text terms were used for the defined search facets. The ERG believes however that ibrutinib and the specific drug comparators as detailed in the decision problem should have also been included in the intervention facet of the search to ensure a comprehensive search. However, the ERG undertook a scoping search and found no additional publications of relevant trials involving ibrutinib.

The company did not provide any details of searching registers for ongoing trials, stating only that there were no relevant company-sponsored trials.

4.1.2 Inclusion criteria

The company's systematic review focussed on R/R CLL patients reporting efficacy outcomes and safety outcomes.

Table 9 Inclusion and exclusion criteria for clinical studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
Population	R/R CLL patients	Less than 85% R/R CLL patients (i.e., studies involving treatment- naïve CLL patients, other lymphoma subtypes, or patients receiving first-/front-line therapies)	In order to align with the population section of the remit/appraisal objective of this STA the population chosen were **adults with CLL** who have received at least one therapy. Studies with less than 85% R/R CLL patients were excluded because were unlikely to provide results data adequately statistically powered for the R/R CLL sub-population.
Intervention	**Interventions of interest:** • Ibrutinib monotherapy • Ibrutinib combination therapy • Bendamustine ± rituximab (BR) • Rituximab + high-dose methyl prednisone/steroids (R + HDMP) • Rituximab + cyclophosphamide + doxorubicin (hydroxydaunomycin) + vincristine + prednisolone (R-CHOP) • Rituximab + cyclophosphamide + vincristine + prednisone (RCVP) • Fludarabine + cyclophosphamide ± mitoxantrone (FC ± M) ± rituximab • Fludarabine ± rituximab • Ofatumumab + cyclophosphamide	No treatment of interest (e.g., radioimmunotherapy, "watch and wait"/no treatment, prophylactic or palliative care alone)	Studies investigating ibrutinib were included in order to identify clinical evidence on ibrutinib. Studies that investigated interventions without investigating ibrutinib monotherapy were initially included because the review was initially designed with a comprehensive scope including the identification of studies that could provide data for indirect analyses to compare ibrutinib to relevant comparators to ibrutinib that may be used in place of ibrutinib in NHS England (including the comparators listed as part of the scope for the current appraisal).

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
	+ fludarabine • Ofatumumab monotherapy • Lenalidomide ± rituximab • Chlorambucil ± rituximab • Chlorambucil + ofatumumab • Rituximab monotherapy • Alemtuzumab monotherapy • Idelalisib ± rituximab • Idelalisib + ofatumumab • Allogeneic stem cell transplant (ASCT)		
Comparators	Any of the interventions listed above or placebo.	None of the interventions of interest or placebo.	
Outcomes	**Efficacy:** • Overall response (OR): number of patients • Complete response (CR): number of patients • Partial response (PR): number of patients • Stable disease (SD): number of patients • Progressive disease (PD): number of patients • Unconfirmed complete response (uCR) or nodular partial response (nPR): number of patients • Minimal residual disease • Response duration: in months • Time to first response: in weeks	• Publications that did not report safety or efficacy outcomes for relapsed or refractory CLL patients. • Articles investigating *in vitro*, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/ pharmacodynamic outcomes without outcomes of interest reported.	These are the most clinically relevant efficacy/safety outcomes for the indication being appraised and align with those listed in the outcomes section of the remit/appraisal objective of this STA.

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
	• TTP: in weeks • PFS: in months • OS: in months • Treatment-related death: number of patients • Overall death: number of patients		
	• EFS: in months • TTF: in months **Safety:** • Grade 3, 4, or 3/4 safety endpoints (each outcome definition was captured as reported; the number of patients was captured or calculated from a percent for each outcome unless otherwise specified) • Infusion-related complications • Neutropenia • Febrile neutropenia • Thrombocytopenia • Leukopenia • Anaemia • Infection • Hypertension • Dehydration/hypotension • Dyspnoea • Hyperbilirubinemia		

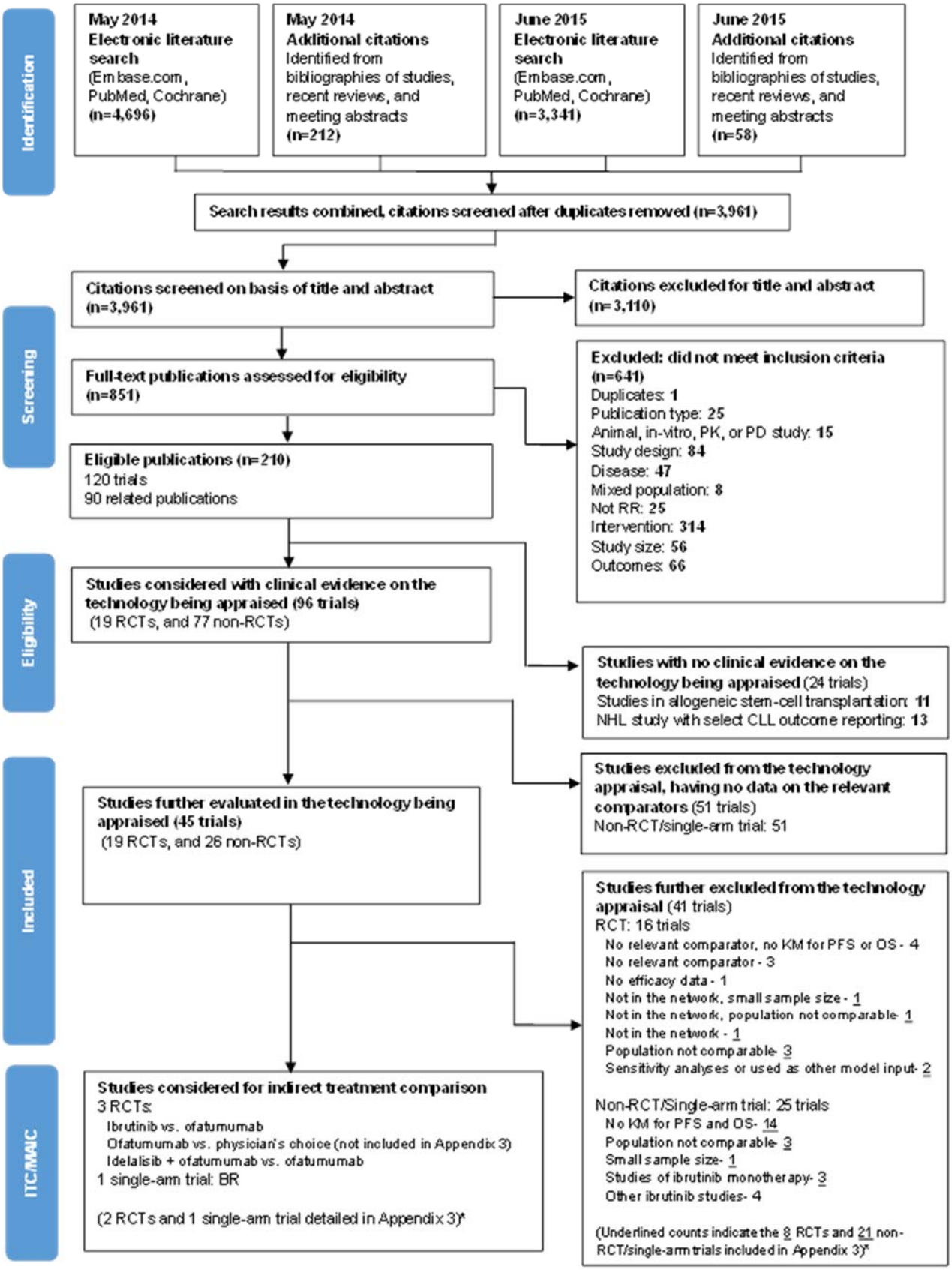
Clinical effectiveness	**Inclusion criteria**	**Exclusion criteria**	**Rationale**
Study design	Prospective, interventional trials	• Narrative publications, non- systematic reviews, case studies, case reports, and editorials. • Non-English, full-text articles or articles without an abstract published in English. • Comparative studies with fewer than 10 patients per treatment group in at least two treatment arms or single-arm studies with fewer than 10 patients.	In order to identify relevant randomised clinical trials and relevant non-randomised/non-controlled studies that may provide clinical evidence to be used in this section of the submission. Systematic reviews were also initially included in order to identify and include relevant potentially relevant clinical trials in their bibliographic lists.
Language restrictions	English-language publications	Publications without English full- text	In line with CRD guidance, non-English language articles were identified and rejected for "Non-English". Significant/major randomised clinical trials and relevant non-randomised/non-controlled studies on the clinical effectiveness of ibrutinib have been published in English.

The ERG considers that as there is no single drug for the spectrum of the disease the company's approach of considering a range of interventions is correct. The list of inclusion interventions covers all of those on the final scope issued by NICE.

The number of studies evaluated for inclusion in the flow diagram presented as Figure 7 of the company submission is inconsistent with the number of studies listed in Appendix 3 of the company submission. The ERG requested at clarification a full list of all included and excluded studies from the company, along with their bibliographic details, to allow cross-checking of the included and excluded studies. In response to the ERG's request for clarification, the company provided a revised PRISMA flow diagram (see Figure 3) and provided the following explanation:

> *"The revised diagram shows that 45 studies (19 RCTs + 26 non-RCTs) were 'further evaluated for consideration of relevant evidence'. This is updated from the initial 41 studies (15 RCTs + 26 non-RCTs) shown in Figure 7 of the submission; the update is due to reasons explained below.*
>
> *The aim of Appendix 3 (Availability and comparability of data for relevant treatments in the UK) was to provide the Committee and the ERG with transparency around the level of assessment carried out on the studies which were identified by the SLR for further evaluation (i.e. to gauge whether they contained relevant evidence). Appendix 3 correctly provided a summary of the 33 studies evaluated but the reasoning behind the discrepancy between n = 33 and n = 45 was not explained clearly in the submission and therefore we provide further details here:*
>
> - *41 of the 45 studies were excluded (16 RCTs + 25 non-RCTs):*
>   - *8 of the 16 RCTs were included in Appendix 3; the other 8 RCTs did not require further detailed assessment as they did not include a relevant comparator and/or KM data for PFS or OS (it was clear they did not provide relevant data which would help establish relative efficacy).*
>   - *21 of the 25 non-RCTs were included in Appendix; the other 4 non-RCTs were other ibrutinib studies which were appraised as part of the submission.*

- *4 of the 45 studies were included (3 RCTs + 1 non-RCT):*
    - *2 of the 3 RCTs were included in Appendix 3; 1 RCT (Österborg et al., 2014) was included separately by the SLR as a study which assessed comparators (ofatumumab and Physician's Choice, PC) not listed in the NICE Final Scope. Due to its relevance in allowing for indirect treatment comparisons (ITC) to be conducted in order to establish the relative efficacy of ibrutinib compared to comparators listed in the NICE Final Scope, it was included and was separately assessed as part of the ITC methodology (see Section 4.10 of the submission).*
    - *The non-RCT was included in Appendix 3."*



* In total 32 trials are presented in Appendix 3 including 3 accepted and 29 excluded studies.

Figure 3 Company's revised PRISMA diagram with further details added for clarity

The company did not provide bibliographic details of the studies. It has, therefore, not been possible for the ERG to cross-check the company's list of included and excluded studies and their response remains unclear.

4.1.3 Critique of data extraction

The methods used to identify and data extract current evidence are considered appropriate. Two independent reviewers screened the abstracts identified by the literature searches. Any disagreements were resolved by a third reviewer. One reviewer screened full-text articles for eligibility, and all rejected articles were independently verified by a second, senior-level investigator. Accepted full-text articles were further validated for inclusion during data extraction. It is unclear how many reviewers conducted data extraction. The company followed NICE STA guidance to conduct the risk of bias assessment. The company submission details the information and data extracted from the included study and are considered to be generally accurate by the ERG.

Data are drawn from the published RESONATE paper,[30] a poster and abstract presented at ASH in December 2014[37] and from the clinical study report (CSR) (Pharmacyclics Inc., Clinical Study Report, 2014)..

4.1.4 Quality assessment

The ERG performed a quality assessment of the company's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 10). The quality of the systematic review was generally good apart from the aforementioned difficulty with identifying included/excluded studies.

Table 10 Quality assessment of the company's review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Unclear
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The company did not conduct any meta-analyses as only one RCT was identified.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company identified one RCT comparing ibrutinib with a comparator considered by the company to be relevant to their submission. The company presented the results of the single RCT (RESONATE) comparing ibrutinib with ofatumumab in patients with CLL who have received at least one prior treatment.[30] In addition there were four non randomised and non-controlled studies of ibrutinib included within the submission[38-40] (Pharmacyclic Int, PSYC1117 Clinical Study Report, 2014). All included studies provided information to directly address the first population of interest:

- Adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate.

Only the investigator led Farooqui study[40] provided any data to directly address the second population of interest:

- Adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation.

Reflecting this split in the evidence, section 4.2.1 describes a critique of the RESONATE,[30] PCYC1102,[39] PCYC1103[38] and PCYC117 studies and section 4.2.2

describes the Farooqui study[40] and implications for the treatment-naïve patients that have 17p deletion or TP53 mutation.

4.2.1 Critique of studies involving adult patients with CLL who have received at least one prior therapy and for whom fludarabine-based regimens are inappropriate

Critique of RESONATE trial methodology

RESONATE enrolled patients from June 2012 to April 2013. The trial recruited 391 patients (ibrutinib, n=195; ofatumumab, n=196) at 67 sites. RESONATE also includes a subgroup of patients with 17p deletion, 63 of whom received ibrutinib and 46 received ofatumumab.

The primary outcome of RESONATE was progression free survival (PFS) according to the criteria of the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL),[17] which require CT scans to evaluate response. The company notes that treatment-related lymphocytosis was not considered as progressive disease. PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression or death due to any cause, whichever occurred first. At clarification, the company provided further detail about their definition of what constituted a PFS event and what constituted a censoring event within their analysis as follows:

"A PFS event was defined as follows: a CT scan was required to evaluate all cases of suspected progressive disease regardless of the modality of disease progression (e.g. lymph node, lymphocytosis, or transformation). Progressive disease required at least ONE of the following:

- *New enlarged nodes >1.5cm, new hepatomegaly or splenomegaly; or other organ infiltrates*
- *≥50% increase from nadir in existing lymph node (must reach >1.5cm in the longest diameter) or ≥50% increase from nadir in sum of product of diameters of multiple nodes*
- *≥50% increase from nadir in enlargement of liver or spleen*
- *≥50% increase from baseline in lymphocyte count (and to ≥5 x109/L) unless considered treatment-related lymphocytosis*

- *New cytopenia (haemoglobin or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia, drugs, or bleeding), as documented by a decrease of Hgb levels from baseline by more than 20 g/L (2g/dL) or to less than 100 g/L (10g/dL) and lower than baseline, or by a decrease of platelet counts from baseline by ≥50% or to less than 100 × 109/L (100,000/μL) and lower than baseline in the presence of active CLL, defines disease progression; a marrow biopsy must demonstrate an infiltrate of clonal CLL cells if no other evidence of disease progression is present on CT scan.*
- *Transformation to a more aggressive histology (e.g., Richter's Transformation). Whenever possible, this diagnosis should be established by biopsy. Suspected progressive disease had to be confirmed by a serial exam at least 2 weeks later and required Independent Review Committee (IRC) confirmation. PFS was assessed by IRC as well as investigators (INV) for the first 9.4 months (interim analysis); after that, PFS was only assessed by the investigators. "*

Patients who withdrew from the study or who were considered lost to follow-up without prior documentation of disease progression were censored on the date of the last adequate disease assessment. For patients without an adequate post-baseline disease assessment, PFS were censored on the date of randomisation."

RESONATE pre-planned sample size required a minimum of 176 PFS events to provide 90% power to detect the target HR of 0.6 based on a log-rank test and a 2-sided overall significance level of 0.05 adjusting for 1 interim analysis. The interim analysis was planned for approximately 117 PFS events and the final analysis was planned for 176 PFS events. The interim analysis was actually conducted with 146 PFS events, representing 83% of the planned total events. RESONATE was terminated early, at 146 PFS events, due to a positive interim analysis, with a median time on study at 9.4 months. PFS was assessed by both the independent research committee (IRC) and RESONATE investigators for the first 9.4 months, after which time PFS was only assessed by the investigators.

At clarification, the company provided details of data collected beyond the interim analysis:

"*The interim analysis for RESONATE comprised of 9.4 months of trial data (interim analysis). Further data were collected beyond the interim analysis - an additional data cut at median follow-up of 16 months provides additional data (updated analysis).*

As stated within the submission, the data presented in the clinical sections are from the interim analysis drawn from the published paper[30] and from the trial CSR (Pharmacyclics Inc., Clinical Study Report, 2014). Data from the updated analysis (available from a poster and abstract presented at ASH in December 2014[37] are also presented to further supplement the results of the interim analysis.

The cost-effectiveness analysis uses the updated analysis (16 month data) wherever possible as the updated analysis represents the longest follow-up, providing further certainty and robustness to the RESONATE data."

It is the ERG's opinion that use of the updated data based on only investigator assessed PFS could theoretically introduce a small risk of bias on the PFS outcome due to knowledge of the RESONATE trial result. RESONATE investigators would, consequently, be aware of trial treatment effect when assessing trial outcomes on individual participants and marginal decisions on whether progression occurred in the ofatumumab trial group may have favoured use of ibrutinib. The ERG note however that rigorous following of the trial protocol for assessing progression would likely negate this risk.

Secondary outcomes included: duration of overall survival (OS) and overall response rate (ORR). OS was defined as the time from the date of randomisation to the date of death from any cause. CT scans were also used to evaluate response and persistent improvement for at least two months to confirm the response. The criteria for ORR were based on those of the IWCLL and included complete response (CR) and partial response (PR). The company provide definitions of the various levels of response in Table 26 of the company submission and the ERG replicates these in Table 11.

Table 11 Explanation of the various levels of response

Level of response	Explanation
CR	All of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow aspiration is required to confirm CR
Cri	Defined as CR with incomplete hematopoietic recovery (patients who fulfil all the criteria for a CR but who have persistent anaemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity)
PR	Requires two criteria from Group A, if abnormal at baseline to respond plus 1 of the criteria from Group B must be met. Improvement in Group B criteria must be in absence of growth factor or transfusion support. If all group B criteria normal at baseline, criteria must continue to remain within these limits. Note if all PR criteria with the exception of ALC are met this is consistent with a PR with lymphocytosis.
SD	The absence of PD and the failure to achieve a CR, CRi, nPR, PR, or PR with lymphocytosis.
PD	At least one of the above criteria from Group A or B are met or development of transformation to a more aggressive histology

Other considered outcomes include patient-reported outcomes (assessed by FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D) and drug adherence.

A summary of the RESONATE trial methodology is presented in Table 25 of the company submission and replicated here as Table 12. The ERG agrees with the company's quality assessment of the RESONATE trial that it is a high quality study.

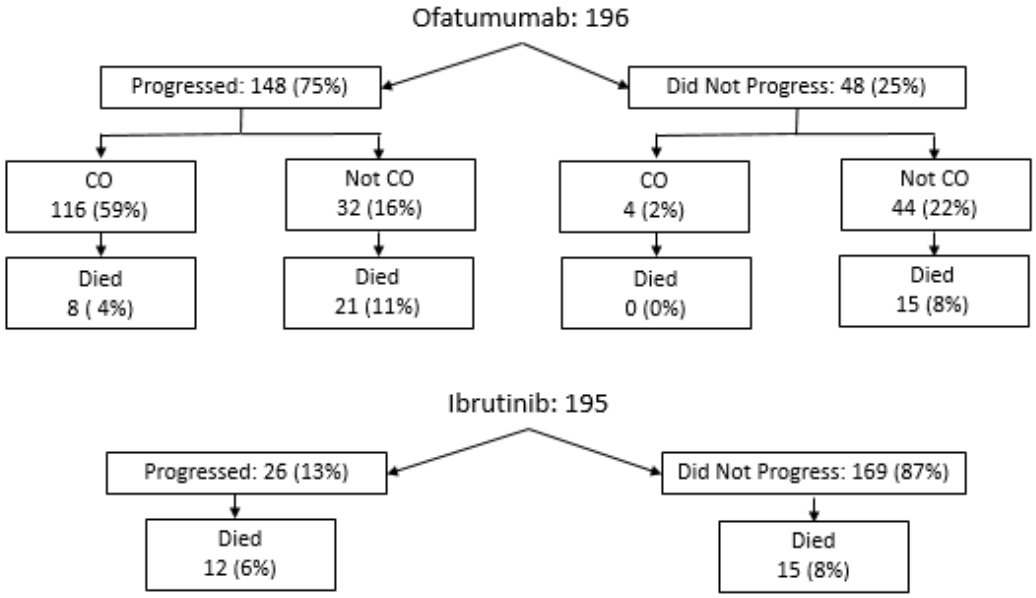
Table 12 Summary of methodology of RESONATE

	RESONATE
Location	Europe (UK, France, Ireland, Italy, Poland, Spain, Austria), the US and Australia US, Germany, Denmark, The Netherlands
UK patients	73 patients from the UK from 12 units; 34 patients were randomised to ibrutinib and 39 were randomised to ofatumumab.
Trial design	Multicentre open label controlled study
Enrolment	From June 2012 to April 2013, 391 patients were enrolled at 67 sites
Randomisation and blinding	Randomisation was via an interactive web response system (IWRS). Two randomisation schemes were generated: one for each geographical region (US vs. non-US). Under each scheme, patients were stratified according to resistance to purine analogue chemo-immunotherapy within 12 months of the last dose of a purine analogue and the presence/absence of 17p13.1. Given that the study was open-label in design, neither the subjects nor the investigators were blinded to treatment. However, it is important to note that progressive disease for the primary end-point and responses were assessed by the Independent Review Committee (IRC), members of which were blinded to both study treatment and absolute lymphocyte count. In addition, access to data was controlled so that the sponsor did not have access to aggregated efficacy data by treatment arm until unblinding
Eligibility criteria	• Patients with CLL or SLL with R/R disease • Patients with CLL or SLL who had received at least one prior therapy and were considered inappropriate candidates for purine analogue treatment (e.g. fludarabine), due to a short PFS after immunochemotherapy, were aged 70 years or more or with a chromosome 17p13.1 deletion. • ECOG performance score of less than 2 (ECOG scores from 0 for least disability to 5 for greatest disability). • Absolute neutrophil count of at least 750 cells/µl. • Platelet count of at least 3,000 cells/µl. • Adequate liver and kidney function.
Exclusion criteria	• Patients receiving warfarin or strong CYP3A4/5 inhibitors
Trial drugs	Patients were randomised in a 1:1 ratio to receive oral ibrutinib (420 mg od) until disease progression or unacceptable toxicity (n=195) or IV ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by 2,000 mg weekly for 7 weeks, and then every 4 weeks for 16 weeks (n=196). Promising data from a phase II study [41] resulted in a revision in the study protocol which allowed patients on ofatumumab with disease progression to crossover to the ibrutinib arm see **Accounting for crossover in RESONATE** later in this section.

	RESONATE
Monitoring	Patients were monitored each week for the first 8 weeks, then every 4 weeks until month 6 and then every 12 weeks.
Primary outcome	Duration of PFS, as assessed by the IRC
Secondary outcomes	Duration of OS Overall response rate (defined as the proportion of patients achieving a best overall response of either CR, CRi (CR with incomplete haematopoietic recovery), nPR or PR) CT scans were used to evaluate response and persistent improvement for at least 2 months to confirm response.
PRO outcomes	Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) EORTC QlQ-C30 EQ-5D
Adherence	Adherence to ibrutinib was assessed by the site pharmacist or designee at each visit using direct questioning, examination of patient diaries and capsule counts. Ofatumumab was administered at the clinical site, and adherence was checked by the site pharmacist or designee.
Pre-planned subgroups for PFS	• Age (<65 vs. ≥65) • Gender (Male, Female) • Race (White, Non-White) • Geographical region (US, Other) • Rai Stage at screening (Stage 0-II, III-IV) • ECOG at randomisation (0, 1) • Bulky disease (<5 cm, ≥5 cm) • Number of prior treatment lines (<3, ≥3) • Refractory disease to purine analogues as recorded in IWRS (Yes, No) • 17p deletion as recorded in IWRS (Yes, No) • 11q deletion (Yes, No) • β2-microglobulin at baseline (≤3.5 mg/l, >3.5 mg/l)
Pre-planned subgroups for OS and ORR	Age, gender, race, region, 17p deletion, and disease refractory to purine analogues

RESONATE allowed patients treated with Ofatumumab to crossover or start receiving treatment with ibrutinib once they had developed progressive disease. Figure 8 in the company submission provides details of the 116 (59%) ofatumumab

patients who had progressed and crossed over to ibrutinib at the time of the data-cut at 7 September 2014. These details are provided by the ERG as Figure 4. The company notes that four patients who had not progressed but crossed from ofatumuab to ibrutinib were protocol violations.



CO = crossover

Figure 4 Diagram of RESONATE crossover

The baseline characteristics of the RESONATE participants are provided in Table 13. The characteristics of the patients were generally well balanced between the two arms with no statistically significant differences, with the exception of presence of bulky disease (64% in ibrutinib arm vs. 52% in the ofatumumab arm, p=0.04) and median time from last therapy (8 months vs. 12 months, p=0.02), both of which confer a poor prognosis. Patients in the ibrutinib arm had received treatment with a median of three prior treatments vs. two treatments in the ofatumumab arm. The ERG believes that the RESONATE trial population are representative of the UK population.

Table 13 Patient characteristics at baseline in RESONATE

Characteristic	Ibrutinib (n=195)	Ofatumumab (n=196)
Patients with SLL, number (%)	10 (5%)	8 (4%)
Median age (range), year	67 (30–86)	67 (37–88)
Male sex, number (%)	129 (66%)	137 (70%)
Cumulative Illness Rating Scale score >6, number (%)	38 (32%)	39 (32%)
Creatinine clearance <60 ml/min, number (%)	62 (32%)	61 (31%)
Median haemoglobin (range) g/l	110 (70–160)	110 (60–160)
Median platelet count (range), per mm^3	116,500 (20,000–441,000)	122,000 (23,000–345,000)
Median lymphocyte count (range), per mm^3	29,470 (90–467,700)	29,930 (290–551,030)
ECOG performance status 0, number (%)	79 (41%)	80 (41%)
ECOG performance status 1, number (%)	116 (59%)	116 (59%)
Bulky disease ≥5 cm, number (%)	124 (64%)	101 (52%)
Interphase cytogenetic abnormalities, number (%)		
Chromosome 11q22.3 deletion	63 (32%)	59 (30%)
Chromosome 17p13.1 deletion	63 (32%)	64 (33%)
β2-microglobulin >3.5 mg/l, number (%)	153 (78%)	145 (74%)
Previous therapies		
Median number (range)	3 (1–12)	2 (1–13)
≥3, number (%)	103 (53%)	90 (46%)
Type of therapy, number (%)		
Alkylator	181 (93%)	173 (88%)
Bendamustine	84 (43%)	73 (37%)
Purine analogue	166 (85%)	151 (77%)
Anti-CD20	183 (94%)	176 (90%)
Alemtuzumab	40 (21%)	33 (17%)
Allogeneic transplantation	3 (2)	1 (1)
Median time from last therapy (range), months	8 (1–140)	12 (0–184)
Resistance to purine analogues, number (%)	87 (45)	88 (45)

The ERG note that, according to the RESONATE CONSORT diagram, 11 patients in the ibrutinib arm and 24 patients in the ofatumumab arm discontinued treatment in the RESONATE trial due to reasons other than progression or death (see Figure 5).

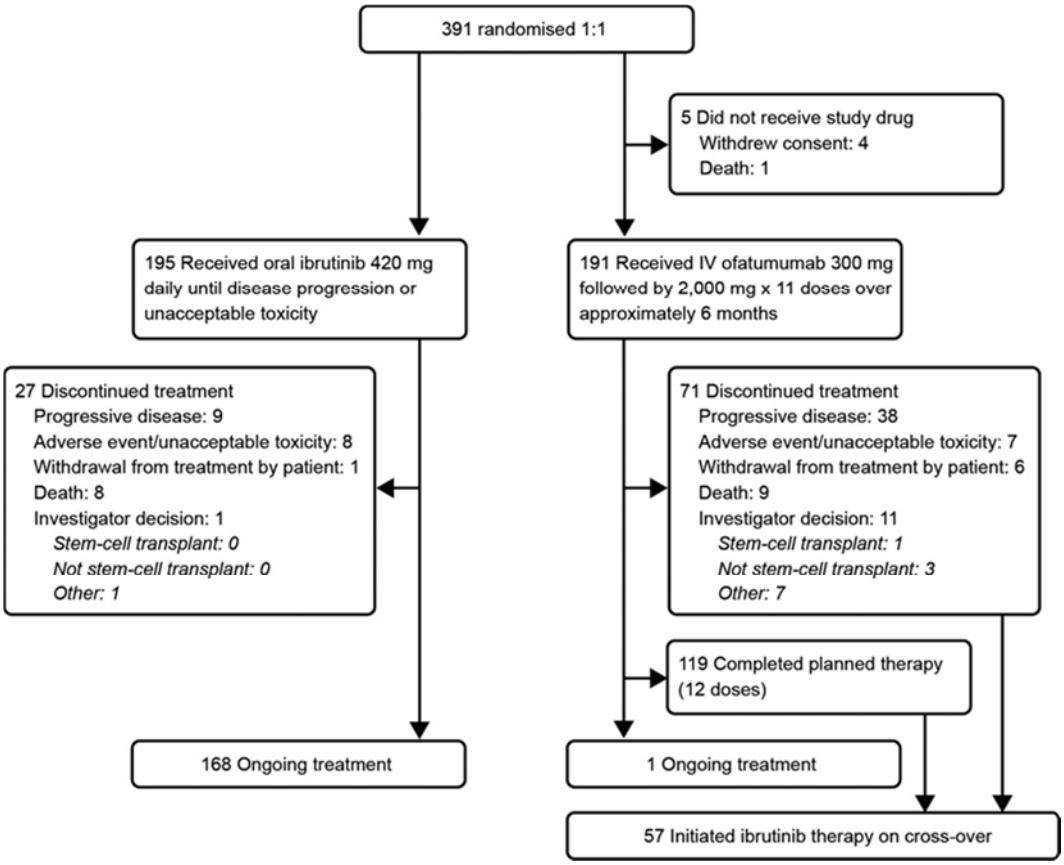


Figure 5 RESONATE CONSORT diagram

At clarification, the company responded that:

> *"All patients were followed for disease assessment until progressed disease, irrespective of treatment discontinuation. If a patient had progressed disease, it was counted as progression; otherwise, the patient was censored at the last disease assessment.*
>
> *There were 10 patients (11 patients are erroneously quoted in question A11) in the ibrutinib arm and 24 patients in the ofatumumab arm who discontinued treatment due to reasons other than progression or death.*
>
> *Of the 10 patients in the ibrutinib arm:*
>
> - *5 had PFS during post-end of treatment follow-up (1 death, 4 progressed disease, PD).*
> - *5 were censored; 4 at the last adequate disease assessment date and 1 at the randomization date (no post-baseline disease assessment); 2 of*

the 5 censored subjects withdrew from the study after treatment discontinuation, and 3 were being followed at the clinical cut-off.

Of the 24 patients in the ofatumumab arm:

- *13 had PFS during post-end of treatment follow-up (6 deaths, 7 PD).*
- *11 were censored; 9 at the last adequate disease assessment date and 2 at the randomisation date (no post-baseline disease assessment); 2 of the 11 censored subjects withdrew from the study after treatment discontinuation, and 9 were being followed at the clinical cut-off.*

Lastly, 19 of the 24 patients in the ofatumumab arm did not cross over to ibrutinib.

These data are summarised in Table 14.

Table 14 Summary of details associated with RESONATE CONSORT diagram

		Ibrutinib	**Ofatumumab**
		N	N
PFS Event during follow-up	Death	1	6
	PD	4	7
	Total	**5**	**13**
Censored	**Time of censoring**		
	At last adequate assessment date	4	9
	At randomization date (no post-baseline assessment)	1	2
	Total	**5**	**11**
	Disposition after treatment discontinuation		
	Withdrew from study	2	2
	In follow-up at clinical cut-off	3	9
	Total	**5**	**11**
Grand total		**10**	**24**

RESONATE median follow-up was 9.4 months (range 0.1-16.6) and 86% of patients were still receiving ibrutinib at the time of the published analysis.[30] Updated data with median follow-up of 16 months are presented in a poster at ASH 2014.[37]

Critique of the methods used in the non-RCT studies

The following describes a critique of the PCYC1102, PCYC1103 and PCYC117 studies.

PCYC1102/ PCYC1103[38, 39]

PCYC1102 was an open label phase II study of 85 patients conducted at eight sites in the US. PCYC1103 was a long-term extension study to PCYC1102. A description of the trial methodologies was given in Table 1 of Appendix 7 of the company submission and is replicated in Table 15 below.

Table 15 Methodology of PCYC1102/ PCYC1103

	PCYC1102 (1)	PCYC1103 (2)
Study type	PCYC1102 was an open label phase II study conducted at eight sites in the US.	PCYC1103 was a long-term extension study to study 1102.
Eligible patients	Patients with R/R CLL or SLL were eligible for treatment. The first two cohorts were required to have received at least two previous therapies, including a purine analogue. On the basis of positive outcomes from cohort 1, a third cohort was added which included patients with high risk disease that did not respond to a chemo-immunotherapy regimen or that progressed within 24 months of completion of treatment.	Patients without disease progression were able to enrol in PCYC1103 after a minimum of 12 cycles of treatment or at the closure of PCYC1102.
Inclusion criteria	Diagnosis of R/R CLL or SLL. Cohorts 1 and 2 were required to have had at least two prior treatments, including a purine analogue. Cohort 3 included patients with high risk disease that did not respond to a chemo-immunotherapy regimen or that progressed within 24 months of completion of treatment Absolute neutrophil count of at least 750 cells/m^3 Platelet count of at least 50,000 cells/m^3. An amendment to the protocol allowed 22 patients to enrol with any degree of cytopenia as long as it was due to bone marrow involvement. Adequate liver and kidney function. Absence of infection. ECOG status 0-2. Patients of reproductive age to use highly effective contraception for the duration of the study and for 30 days after the last dose of study drug.	As per PCYC1102

	PCYC1102 (1)	PCYC1103 (2)
Exclusion criteria	Any type of cancer which limited survival to <2 years excluding adequately treated basal cell carcinoma, squamous skin cancer or in situ cervical cancer.	As per PCYC1102
	• Life threatening illness which could compromise the patient's safety, interfere with the metabolism or absorption of ibrutinib or put study outcomes at undue risk. • Significant cardiovascular disease or ECG abnormalities. • Prior chemotherapy, immunotherapy, radiotherapy or experimental therapy within 4 weeks of first dose of study drug. • Gastro-intestinal disease which might inhibit ibrutinib absorption. • Medicines associated with torsades de pointes. • Previous exposure to ibrutinib. • Central nervous system involvement by lymphoma. • Grade 2 or higher toxicity (excluding alopecia) continuing from prior anti-cancer treatment. • Any active systemic infection including HIV, hepatitis C and hepatitis B. • Major surgery within 4 weeks of first dose of study drug. • Pregnant or breast-feeding women. • Concomitant use of warfarin. • History of Richter's transformation or prolymphocytic leukaemia.	
Study design	Patients were enrolled without randomisation.	Patients were enrolled without randomisation.
Treatment	Two cohorts (cohort 1 and cohort 3) received 420 mg/day of ibrutinib and one cohort (cohort 2) received 840 mg/day. Both doses were given orally until disease progression or unacceptable toxicity.	420 mg/day or 840 mg/day ibrutinib, given orally until disease progression or unacceptable toxicity

	PCYC1102 (1)	PCYC1103 (2)
Number of patients	85 51 received 420 mg dose and 34 received 840 mg dose	101
Primary end-point	The primary end-point was safety of the two fixed dose regimens. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Haematological toxic effects were graded according to the International Workshop on Chronic Lymphocytic Leukaemia.	The primary end-point was safety, as assessed by the frequency and severity of grade ≥3 adverse events (AEs), serious AEs, and AEs requiring dose reduction or discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v4.0
Secondary end-points	Secondary end-points included overall response rate, PFS, pharmacokinetics and pharmacodynamics as assessed by the investigators.	Secondary end-points included overall response rate, CR, PFS and OS as assessed by the investigators.
Assessments	Safety monitoring which included clinical history, physical examination and laboratory tests was carried out every week for the first month, every other week for the second month and monthly thereafter.	Long-term follow-up patients were seen by the investigator every 3 months, at which time routine blood counts with differential, chemistries including liver function tests, physical examination, and

The ERG notes that in PCYC1102 there were two cohorts of patients receiving different doses of ibrutinib - 51 patients received 420 mg/day and 34 received 840 mg/day dose. The patients enrolled in PCYC1102 had higher risk disease than the RESONATE trial and had received a median of 4 previous treatments, 65% had advanced stage disease, 33% had 17p13.1 deletions and 36% had 11q22.3 deletions.

Patients in PCYC1102 without progression were able to enrol in PCYC1103 after a minimum of 12 cycles of treatment or at the closure of PCYC1102. 101 patients were enrolled in PCYC1103 and at 45 months followup, 60% (n=40) were still receiving ibrutinib.

PCYC117

PCYC117 was a 144 patient multicentre, international, open label, single arm, phase II study carried out in the US, UK, Germany, Turkey, Sweden, Australia, Belgium, Canada and New Zealand. Fourteen patients (9.7%) were enrolled from the UK. The included patients all had 17p deletion, were refractive or relapsed, and had received at least one line of systemic therapy. The patients received 420 mg of ibrutinib. In PCYC117, patients had high risk disease, a median of two previous treatments (range 1-7) and 39% had three or more previous treatments. 33% of patients were female. A full description of the study patient characteristics is given in Table 6 of Appendix 7 in the company submission. This study has not yet been published and data are drawn from the CSR, the unpublished protocol and data presented at ASH 2014 which provides data with a 13 month median follow-up.[42]

The following sections now describe the results of the RESONATE trial and the non-RCTs.

4.2.2 Progression free survival

RESONATE trial

Ibrutinib significantly extended the duration of PFS compared with ofatumumab. With ibrutinib the median PFS was not reached after a median follow-up of 9.4 months vs. a median duration of PFS of 8.1 months with ofatumumab, see Figure 6.

The HR for progression or death in the ibrutinib group was 0.22 (95% CI, 0.15 to 0.32; p<0.001). This represents a 78% reduction in the risk of progression or death among patients treated with ibrutinib vs. ofatumumab.

At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression vs. 65% in the ofatumumab group.

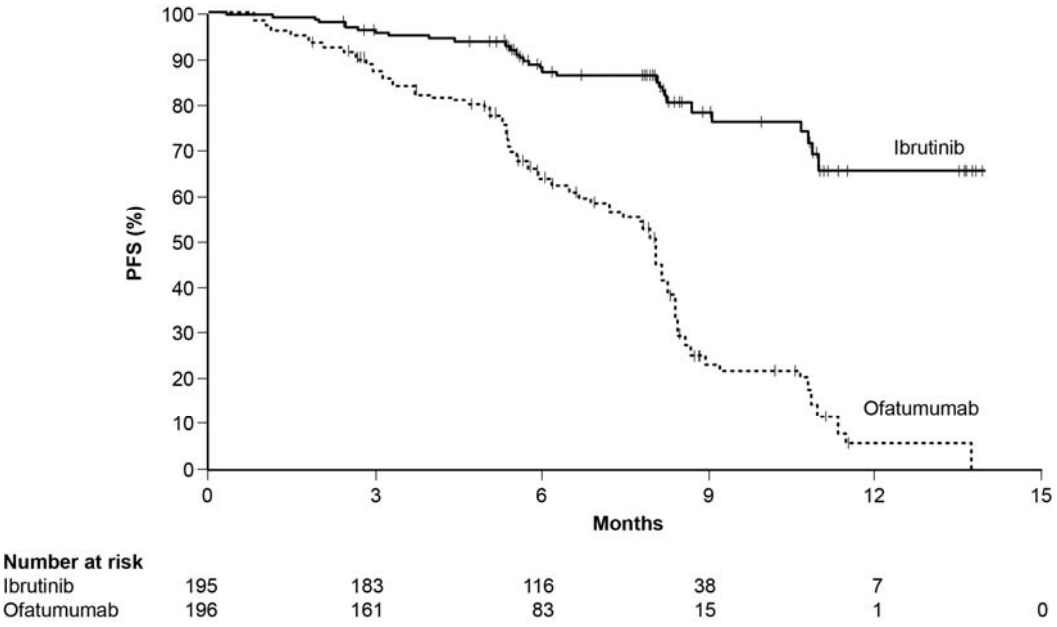


Figure 6 KM curve of PFS in RESONATE, IRC assessment (ITT analysis)

Investigator-assessed PFS was significantly longer for ibrutinib vs. ofatumumab; median PFS had not been reached with ibrutinib vs. 8.1 months with ofatumumab, HR 0.106, 95%CI 0.073-0.153, p<0.0001, see Figure 7.

The 12-month investigator-assessed PFS rates were 84% for ibrutinib and 19% for ofatumumab.

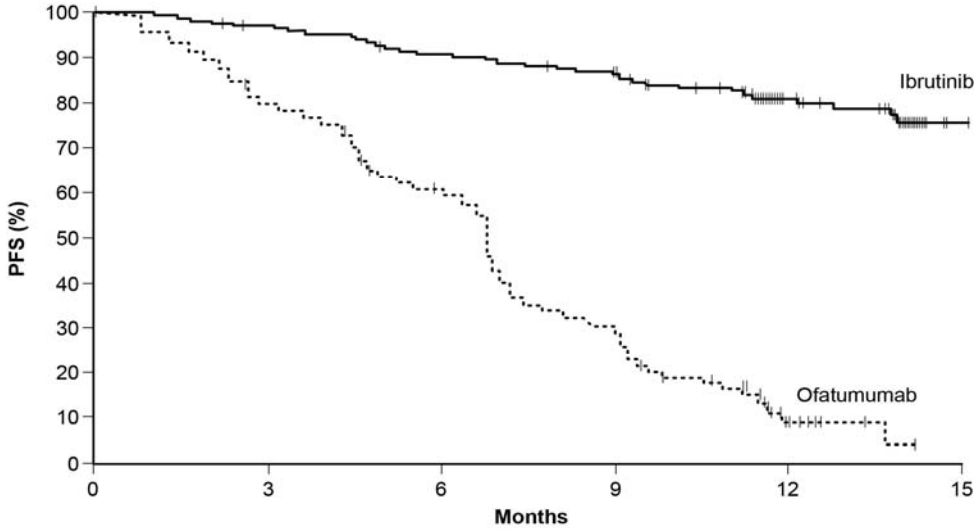


Figure 7 KM curve of PFS in RESONATE (ITT analysis): 16 month follow-up

Subgroup analysis for progression free survival

The company conducted pre-planned subgroups for PFS included the following potential prognostic variables at screening or baseline:

- Age (<65 vs. ≥65)
- Gender (Male, Female)
- Race (White, Non-White)
- Geographical region (US, Other)
- Rai Stage at screening (Stage 0-II, III-IV)
- ECOG at randomisation (0, 1)
- Bulky disease (<5 cm, ≥5 cm)
- Number of prior treatment lines (<3, ≥3)
- Refractory disease to purine analogues as recorded in IWRS (Yes, No)
- 17p deletion as recorded in IWRS (Yes, No)
- 11q deletion (Yes, No)
- β2-microglobulin at baseline (≤3.5 mg/l, >3.5 mg/l)

The effect of ibrutinib on PFS was consistent regardless of baseline clinical characteristics or molecular features - see Figure 8. The company state that the only significant test for heterogeneity was geographical region (p=0.02). In order to address this, the company employed a multivariate Cox proportional hazard analysis, using a comprehensive list of baseline prognostic variables as covariates. After adjustment for the baseline covariates, the HR was 0.22 (0.085, 0.564) for US and 0.20 (0.092, 0.451) for Europe/other. The company state the selected covariates were considered clinically appropriate and there is no reason to anticipate major differences between the regions.[35] The benefit was maintained after 16 month follow-up, rates of 12-month PFS were significantly better with ibrutinib than ofatumumab regardless of lymphocytosis, number of prior lines of therapy, presence of 17p deletion or other adverse cytogenetics.[37]

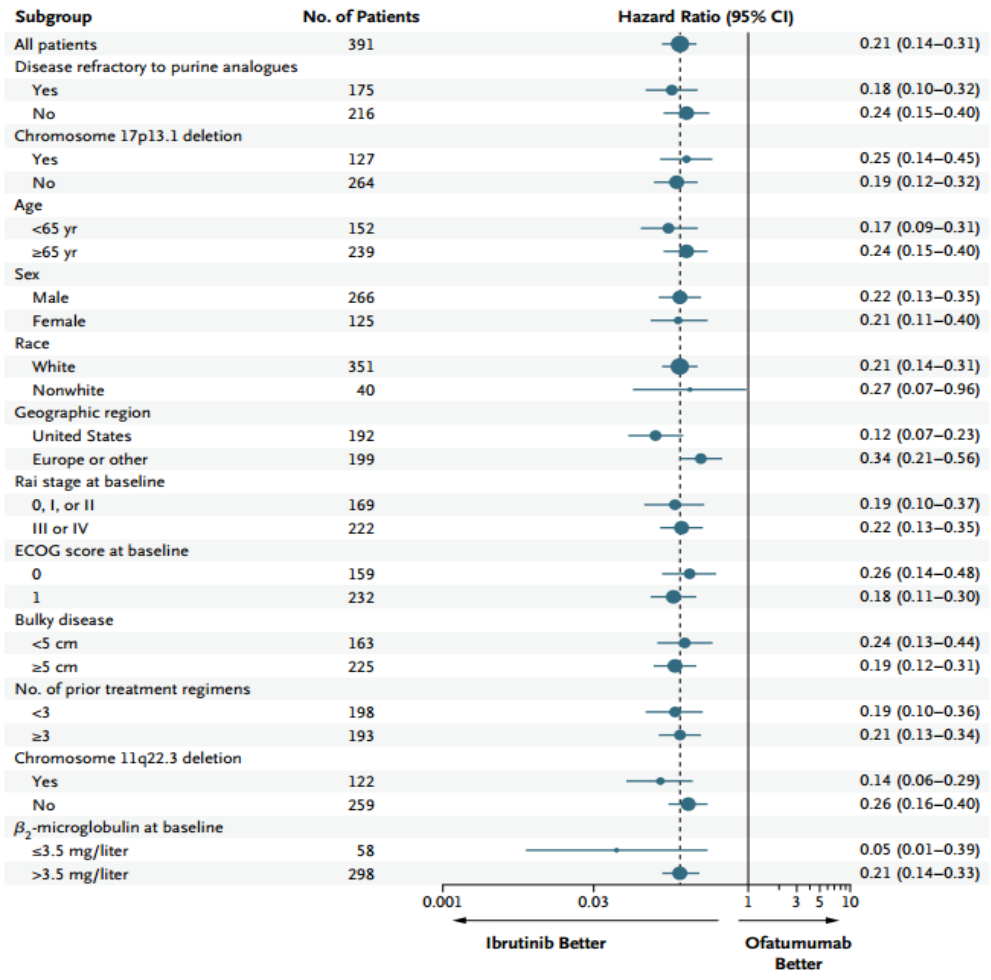
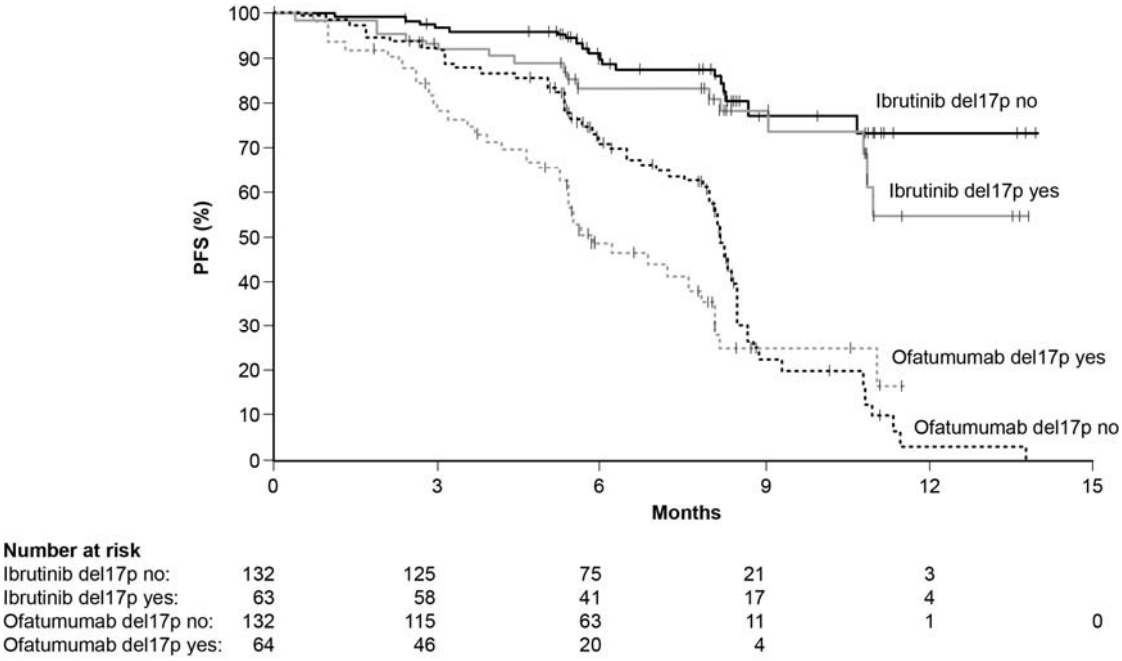


Figure 8 Subgroup analyses of PFS in RESONATE

Further data were presented for patients with the 17p deletion; median PFS was not reached in the ibrutinib arm vs. a median PFS of 5.8 months in the ofatumumab arm (HR for progression or death, 0.25; 95% CI 0.14-0.45). At 6 months, 83% of patients in the ibrutinib arm were alive with no disease progression vs. 49% of those in the ofatumumab arm. Figure 9 shows the KM curves for PFS for patients with and without 17p deletion.



Number at risk						
Ibrutinib del17p no:	132	125	75	21	3	
Ibrutinib del17p yes:	63	58	41	17	4	
Ofatumumab del17p no:	132	115	63	11	1	0
Ofatumumab del17p yes:	64	46	20	4		

Figure 9 KM curves for PFS for patients with and without 17p13.1 deletion in RESONATE

Data from the 16-month median follow-up analysis revealed 12-month PFS of 79% for patients with 17p deletion receiving ibrutinib vs. 17% in those receiving ofatumumab, $p<0.001$.[37]

4.2.3 Non-RCT data PFS

PCYC1102/1103[38, 39]

For PCYC1102, PFS results were not given by each dosage (420 mg or 840 mg) of ibrutinib and the overall (all patients combined) PFS at 26-month follow-up was 75%. In PCYC1103, median PFS was not reach at 45 month follow-up. For patients receiving 420 mg in PCYC1103, the 30-month PFS was 76% (95%CI 62.5%-85.1%). The KM curve of PFS in PCYC1103 was given in Figure 23 of the company submission and replicated in Figure 10 below.

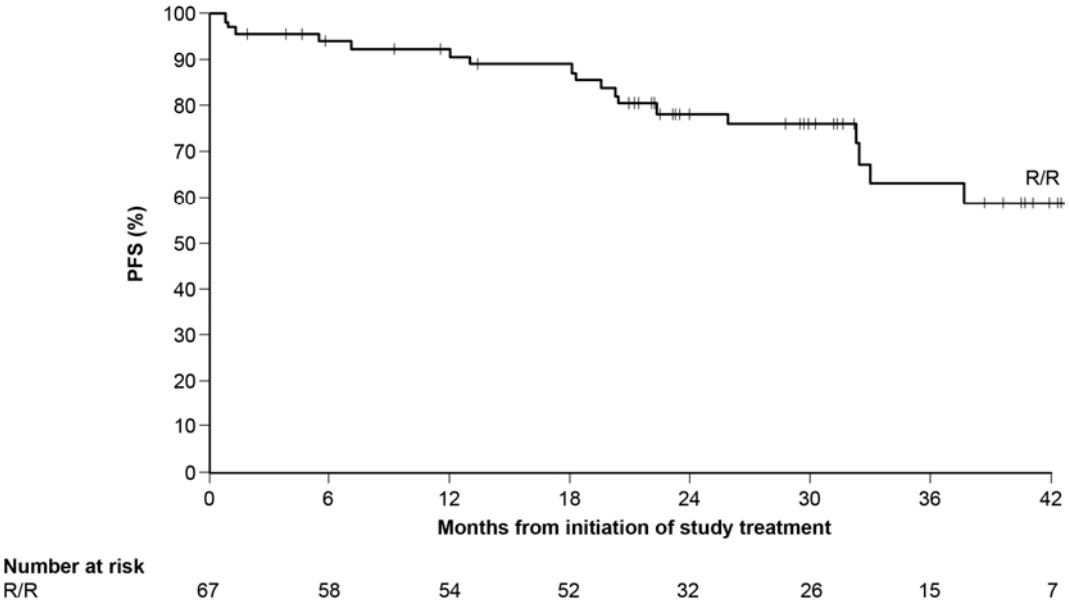


Figure 10 KM curve of PFS in PCYC1103[43]

PCYC1117

At median of 13 month follow-up (range 0.5-16.7), the estimated PFS at 12 months was 79.3%. The KM curve of PFS in PCYC1117 was given in Figure 4 of Appendix 7 of the company submission and replicated in Figure 11 below.

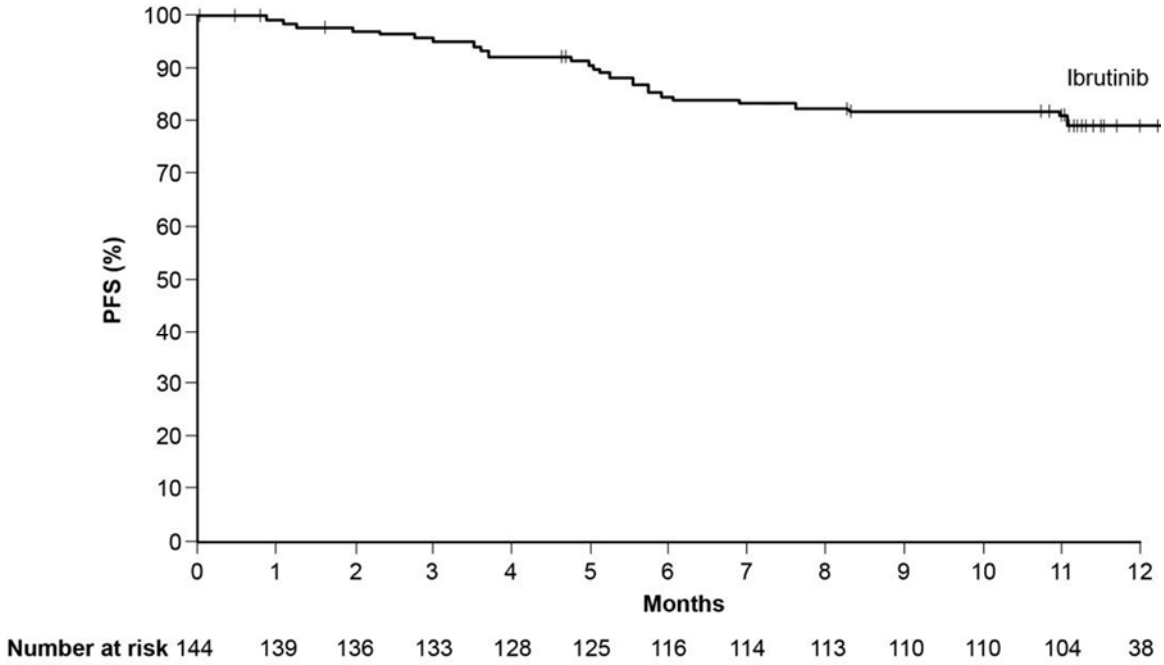


Figure 11 KM curve of PFS in PCYC1117[42]

ERG comment on PFS data

The ERG believes the non-RCT data and the RESONATE data demonstrate a relatively consistent PFS profile across the overall population and across the pre-specified subgroup of patients with R/R disease. The results are impressively better for those receiving ibrutinib

4.2.4 Overall survival

RESONATE trial

At the time of the first published analysis, 57 patients in the ofatumumab group had crossed over to receive ibrutinib after confirmed disease progression. The survival effect was based on an analysis in which data were censored at the time of crossover. OS was significantly prolonged with ibrutinib vs. ofatumumab: hazard ratio for death in the ibrutinib group was 0.43 (95% CI: 0.24 to 0.79; p=0.005), with the risk of death reduced by 57%, see Figure 12.

At 12 months, the OS rate was 90% in the ibrutinib group vs. 81% in the ofatumumab group. The uncensored sensitivity analysis showed similar results: hazard ratio for death of 0.39 (p=0.001), OS rate 90% vs. 79%.

After 16 months follow-up, OS remained significantly superior for ibrutinib vs. ofatumumab with 18-month OS rates of 85% and 78% respectively, despite crossover

of 120 patients (61%) from ofatumumab to ibrutinib, who were censored at crossover.[37]

The company acknowledges, and the ERG agrees, that crossover can cause bias in OS analyses because survival in the ofatumumab arm reflects the mixed effects of standard care and after crossover to ibrutinib. The company, therefore, rejected a traditional intention-to-treat analysis as they state this would underestimate ibrutinib's relative treatment effect on OS. The company, instead, chose to conduct a rank-preserving structural failure time (RPSFT) model to adjust for crossover. The company acknowledge that the key assumption of the RPSFT model is "common treatment effect of the active treatment" i.e. patients who crossed over to ibrutinib after having progressed after ofatumumab-initiation, still benefit equally from ibrutinib compared to patients who originally were assigned to the ibrutinib arm" and that RPSFT also assumes balanced treatment arms within a trial. The company test the "common treatment effect" assumption through post hoc analyses which show similar survival for those who crossover from the ofatumumab arm and those who were randomized to ibrutinb. To compensate for any lack of balance between treatment arms, the company include a number of baseline covariates in the model. These covariates are refractory disease, del17p, del11q, prior lines of therapy, ECOG status, age at baseline, gender, ethnicity, region, RAI disease stage, bulky disease and B2M. The ERG considers that the inclusion of these should balance the treatment arms, though as with any non-randomised study the bias associated with unmeasured confounders remains.

The resulting HR comparing ibrutinib vs. ofatumumab OS outcomes in the overall R/R CLL RESONATE population was [redacted].

Figure 13 below presents the 16 month KM data for ibrutinib and ofatumumab for the overall R/R CLL population, in which the ofatumumab curve has been adjusted for crossover using an OS HR (ibrutinib vs. ofatumumab) of [redacted].

[redacted]

[redacted]

Subgroup analysis for overall survival

Subgroup analysis for OS included age, gender, race, region, 17p deletion, and refractory disease to purine analogues (Pharmacyclics Inc., Clinical Study Report, 2014).In line with PFS, the difference in OS was preserved in all subgroups, see Figure 14. The benefit was maintained at 16 months. In the 17p deletion subgroup of the RESONATE population, the OS HR comparing ibrutinib vs. ofatumumab adjusting for crossover was [redacted].

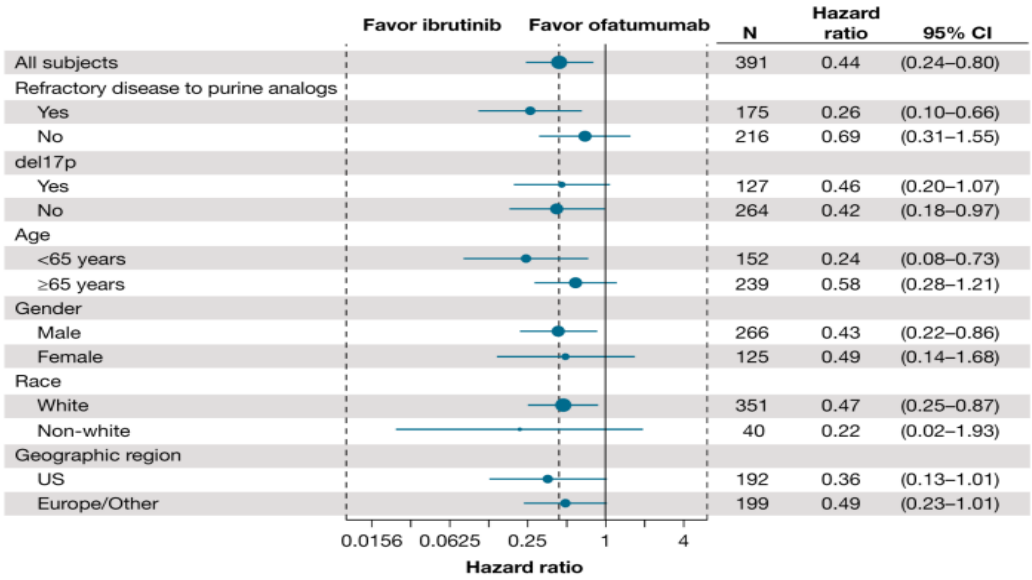


Figure 14 Subgroup analyses of OS in RESONATE

4.2.5 Non-RCT data OS

PCYC1102/1103

For PCYC1102, OS results were not given by each dosage (420 mg or 840 mg) of ibrutinib and the overall (all patients combined) OS at 26-month follow-up was 83%. For patients receiving 420 mg in PCYC1103, the 30-month OS was 87% (95%CI 75.8%-93.3%).

PCYC1117

The estimated OS at 12 months was 83.5%.

ERG comment on OS data

The ERG believes the non-RCT data and the RESONATE data demonstrate a relatively consistent OS profile and that there is a marked, statistically significant, improvement in survival for patients receiving ibrutinib that were maintained whether crossover was or was not adjusted for.

4.2.6 Response

RESONATE trial

The company state that response rates were consistently higher in the ibrutinib arm compared to the ofatumumab arm, regardless of whether they were independently assessed or investigator assessed, see Table 16.

The ORR was significantly higher in the ibrutinib group vs. the ofatumumab group, 43% vs. 4% (odds ratio, 17.4; 95% CI, 8.1 to 37.3; $p<0.0001$). In addition, 20% of the patients receiving ibrutinib had a PR with lymphocytosis (resulting in a 63% ORR with lymphocytosis). The ORR by investigator assessment was significantly higher in the ibrutinib group vs. the ofatumumab group, 70% vs. 21%, $p<0.0001$.

Lymphocytosis was observed in 69% of patients treated with ibrutinib and was not considered to be disease progression according to the study protocol. Lymphocytosis resolved in 77% of these patients during follow-up.

Lymphocytosis is observed in the majority of patients receiving ibrutinib. It tends to resolve within 8 months of treatment; however, a minority of patients have

lymphocytosis lasting >12 months.[44] Lymphocytosis does not have an impact on clinical outcomes and resolves completely once treatment with ibrutinib is stopped.[45]

Table 16 Best response to treatment in RESONATE

	Ibrutinib (n=195)	**Ofatumumab (n=196)**	**Ibrutinib (n=195)**	**Ofatumumab (n=196)**
	Independent assessment, n(%)		**Investigator assessment, n(%)**	
ORR	83 (43%)	8 (4%)	136 (70%)	42 (21%)
ORR with PR with lymphocytosis	122 (63%)	8 (4%)	162 (83%)	46 (23%)
CR or CR with incomplete haemoglobin Recovery			4 (2%)	1 (1%)
PR	83 (43%)	8 (4%)	132 (68%)	41 (21%)
PR with lymphocytosis	39 (20%)	0	30 (15%)	4 (2%)
Stable disease	63 (32%)	153 (78%)	22 (11%)	106 (54%)
Progressive disease	5 (3%)	20 (10%)	2 (1%)	27 (14%)

Subgroup analysis for overall response rate

The company state that the subgroup analysis for ORR included age, gender, race, region, 17p deletion, and refractory disease to purine analogues(Pharmacyclics Inc., Clinical Study Report, 2014). The company state that the consistent benefit in all subgroups was maintained after 16 month follow-up

4.2.7 Non-RCT data ORR

PCYC1102/1103

For PCYC1102, ORR was 71% for the 51 ibrutinib 420 mg patients (CR was 4%; PR was 67%). For patients receiving 420 mg in PCYC1103, the ORR by investigator assessment was 92% (n=61).

PCYC1117

The ORR per IRC assessment was [redacted].

ERG comment on Response data

In line with both the PFS and OS findings, the ERG believes the non-RCT data and the RESONATE data demonstrate a marked, statistically significant, improvement in response for patients receiving ibrutinib. The ERG also agrees with the company that the investigator assessment may more accurately reflect real practice.

4.2.8 Patient reported outcomes (PROs)

The company presented data on PROs taken from a poster and abstract presented at ASH 2014 provides information on PROs[46] data on EQ-5D is sourced from the RESONATE clinical study report (Pharmacyclics Inc., Clinical Study Report, 2014). No PRO data was available from the non-RCT studies.

EORTC QLQ-C30

A clinically meaningful improvement in EORTC QLQ-C30 global health scores was observed in both arms, although more patients had a clinically meaningful improvement in the ibrutinib arm, 47% vs. 40%, OR:1.3, p=0.2049[46]

EQ-5D

[redacted]

(Pharmacyclics Inc. Clinical Study report PCYC-1102-CA, 2013).

RESONATE EQ-5D data regression analysis

The EQ-5D was collected at baseline, every 4 weeks during the first 24 months and every twelve weeks subsequently until disease progression was confirmed by IRC assessment and at the last treatment visit before discontinuation.

The interim data cut of 9.4 months was chosen by the company for its analysis of the EQ-5D data due to IRC assessment of progression stopping after the interim data cut. At this point no IRC complete responses had been reported. As a consequence, all IRC responders were only partial responders and it was not possible to further stratify IRC response status.

It should be borne in mind that the investigator assessed measure of progression is what underlies all the cost effectiveness modelling. The EQ-5D data within Appendix 12, Table A.2 is also split by investigator response status and not by IRC response status. As a consequence it is unclear to the ERG why the interim data cut was applied by the company and why it was the IRC assessment of response rather than the investigator assessment of response that was used for the analysis.

Note also that prior to the presentation of Appendix 12 of the submission at least one interim analysis was conducted which eliminated some statistically insignificant time variables. Apparently the preliminary analysis results are not available for reporting. It

is unknown whether any further analyses were conducted prior to the presentation of Appendix 12. The company describes Appendix 12 as a full report of the RESONATE QoL analysis which was conducted specifically to inform the economic model.

A repeated measures regression analysis of the data estimated three models:

- Model 1: Treatment arm, baseline utility, responder status and SAE status
- Model 2: Baseline utility, responder status and SAE status
- Model 3: Baseline utility and responder status

With the following results for the estimated changes from baseline.

Table 17 RESONATE EQ-5D repeated measures analysis

	Model 1		Model 2		Model 3	
	Estimate	**P value**	**Estimate**	**P value**	**Estimate**	**P value**
Intercept	0.294	<.0001	0.292	<.0001	0.299	<.0001
Ibrutinib treatment	0.022	0.895				
Baseline Utility	-0.402	<.0001	-0.403	<.0001	-0.391	<.0001
Responder status	-0.056	0.655	-0.042	0.656	-0.052	0.581
SAE	0.023	0.051	0.024	0.040		

Only the parameters for the intercept and the baseline utility were statistically significant. Despite having eliminated statistically insignificant time parameters in an interim analysis, apparently no further analyses were conducted that eliminated the statistically insignificant responder status variable.

What is striking is that given the mean baseline quality of life value of the model of 0.763 the baseline utility coefficients suggest small quality of life reductions of -0.013 and -0.015 for models 1 and 2, and only a very small gain of less than 0.001 for model 3. This contrasts with a gain of 0.037 within the company model.

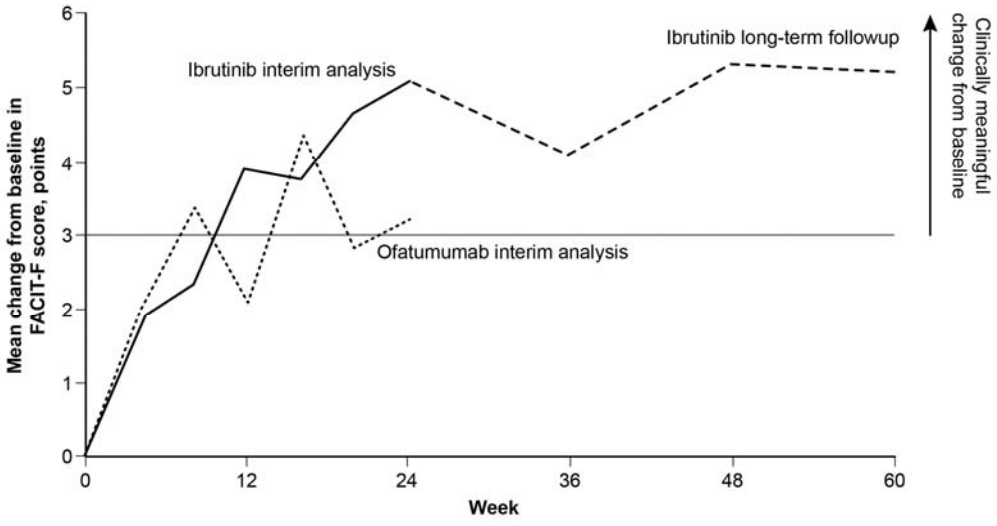
The ERG is surprised that the analysis concentrated upon the IRC responder status and as a consequence curtailed the analysis at the interim data cut. It is also surprised that no further process of the elimination of statistically insignificant variables was undertaken given the interim analysis elimination of the statistically insignificant time

variable. In the absence of this, it seems reasonable to conduct an analysis that assumes no quality of life increase from baseline for those remaining on treatment.

FACIT-Fatigue

More patients achieved a clinically meaningful improvement in FACIT-Fatigue score (increase of ≥3 points) with ibrutinib than with ofatumumab (56% vs. 43%, OR: 1.69, p=0.0101). Clinically meaningful deterioration was reported by 14% vs. 24% respectively, p=0.08, see Figure[46]

A clinically meaningful improvement in fatigue (≥10 points) was also observed on the EORTC Fatigue Subscale Score from baseline to week 24: mean -11 vs. 0 observed.



Number at risk										
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**60**
Ibrutinib	165	121	131	122	116	112	115	97	53	23
Ofatumumab	154	101	102	97	91	80	87			

Figure 16 Improvement in FACIT-Fatigue by treatment arm in RESONATE

The company did not present data for subgroup analyses of patient reported outcomes.

4.2.9 Adverse events

Adverse events reported in RESONATE trial

Due to ibrutinib being taken until disease progression or unacceptable toxicity while ofatumumab is administered for a set course, the company noted that exposure to treatment was longer in patients receiving ibrutinib than in patients receiving ofatumumab (8.6 months vs. 5.3 months). Analysis of exposure-adjusted incidence

rates (EAIR) of adverse events (AE) was performed and showed that [redacted] Discontinuation of treatment due to AE occurred in 4% of patients in each arm, a low discontinuation rate. Dose reduction due to AE occurred in 4% of ibrutinib patients and 0.5% of ofatumumab patients. The most common AEs in the ibrutinib group were diarrhoea, fatigue, pyrexia and anaemia. The most common AEs in the ofatumumab group were fatigue, infusion site reactions and cough, see Table 18.

Table 18 Adverse events in the RESONATE study reported in at least 10% of patients in either arm of the study

AE	Ibrutinib (n=195)	Ofatumumab (n=191)	Relative risk (95% CI)
Any AE occurring during treatment	194 (99%)	187 (98%)	1.02 (0.99-1.04)
Diarrhoea	93 (48%)	34 (18%)	2.68 (1.91-3.76)
Fatigue	54 (28%)	57 (30%)	0.93 (0.68-1.27)
Nausea	51 (26%)	35 (18%)	1.43 (0.97-2.09)
Pyrexia	46 (24%)	28 (15%)	1.61 (1.05-2.46)
Anaemia	44 (23%)	33 (17%)	1.31 (0.87-1.96)
Neutropenia	42 (22%)	28 (15%)	1.47 (0.95-2.27)
Cough	38 (19%)	44 (23%)	0.85 (0.58-1.24)
Thrombocytopenia	33 (17%)	22 (12%)	1.47 (0.89-2.43)
Arthralgia	34 (17%)	13 (7%)	2.56 (1.40-4.70)
Upper respiratory tract infection	31 (16%)	20 (10%)	1.52 (0.90-2.57)
Constipation	30 (15%)	18 (9%)	1.63 (0.94-2.83)
Vomiting	28 (14%)	12 (6%)	2.29 (1.20-4.36)
Headache	27 (14%)	11 (6%)	2.40 (1.23-4.71)
Petechiae	27 (14%)	2 (1%)	13.22 (3.19-54.84)
Muscle spasm	25 (13%)	16 (8%)	1.53 (0.84-2.77)
Dysponea	23 (12%)	20 (10%)	1.13 (0.64-1.98)
Peripheral oedema	22 (11%)	15 (8%)	1.44 (0.77-2.68)
Back pain	22 (11%)	12 (6%)	1.80 (0.91-3.53)
Sinusitis	21 (11%)	12 (6%)	1.71 (0.87-3.39)
Dizziness	22 (11%)	10 (5%)	2.15 (1.05-4.43)
Contusion	21 (11%)	6 (3%)	3.43 (1.41-8.31)
Stomatitis	21 (11%)	4 (2%)	5.14 (1.80-14.70)
Pain in limb	20 (10%)	8 (4%)	2.45 (1.11-5.42)
Pneumonia	19 (10%)	13 (7%)	1.43 (0.73-2.82)
Urinary tract infection	19 (10%)	10 (5%)	1.86 (0.89-3.90)
Myalgia	19 (10%)	7 (4%)	2.66 (1.14-6.18)
Blurred vision	19 (10%)	6 (3%)	3.10 (1.27-7.60)
Night sweats	10 (5%)	24 (13%)	0.41 (0.20-0.83)
Peripheral sensory neuropathy	8 (4%)	24 (13%)	0.33 (0.15-0.71)
Infusion-related reaction	0	53 (28%)	Not calculated

The company noted that ofatumumab was only administered for 24 weeks and therefore AE after 6 months in the ofatumumab arm were rare as patients were not receiving treatment at that point. A similar picture was observed with AE ≥ grade 3, the most common of which were cytopenias and pneumonia in both arms. Data from long-term follow-up[46] reveal that most AEs in patients treated with ibrutinib occurred early in treatment, mostly within the first year, see Figure 17.

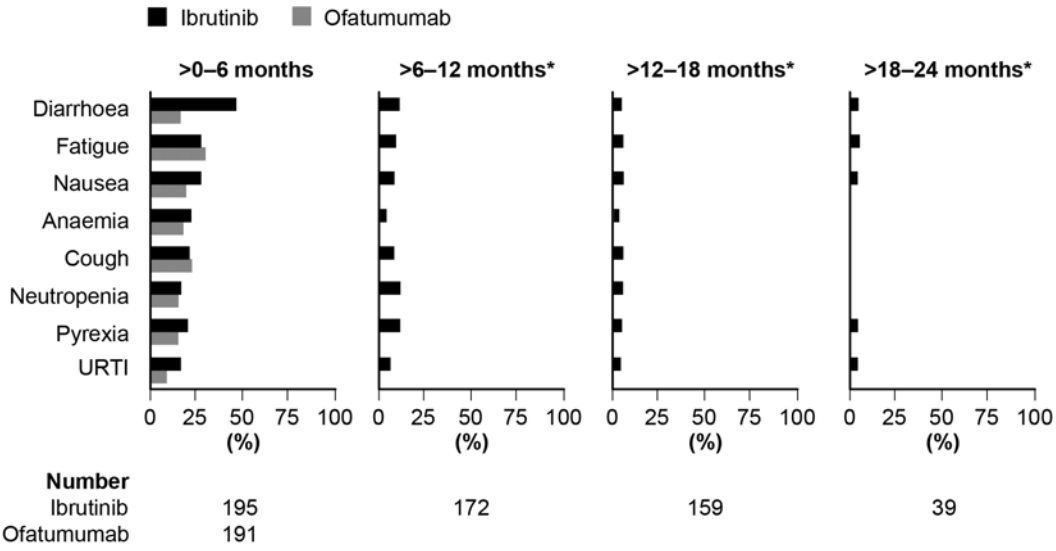


Figure 17 AE (all grades) by time to event onset in RESONATE[46]

AE of grade 3 or higher severity were observed in 57% of ibrutinib patients and 47% of ofatumumab patients. Rates of grade 3 or higher diarrhoea and atrial fibrillation (AF) were higher with ibrutinib than with ofatumumab (4% vs. 2% and 3% vs. 0%). AF was observed in 10 (5%) patients receiving ibrutinib vs. one (0.5%) patient receiving ofatumumab. AF was severe or grade 3 or higher in seven patients.

However, only one case was considered to be treatment related and only one patient discontinued treatment due to AF. Most of the patients who experienced AF were older (aged over 70 years) and all of them had risk factors for AF (including a prior history in three patients). The company note that the ibrutinib summary of product characteristics advises periodically monitoring all patients clinically for AF and to perform an ECG for those who develop arrhythmic symptoms or new onset of dyspnoea.[35]

In RESONATE, 50% of patients were receiving anticoagulants or antiplatelet agents in the ibrutinib arm. Bleeding-related AE were more common in the ibrutinib arm (44% vs. 12%), major haemorrhage (defined as any haemorrhagic event grade 3 or higher requiring hospitalisation or blood transfusion) was observed in two (1%) ibrutinib patients and three (2%) ofatumumab patients.

Other AE which were more common with ibrutinib than ofatumumab were rash (8% vs. 4%), pyrexia (24% vs. 15%) and blurred vision (10% vs. 3%). Most of these events were grade 1 or 2 in severity. The incidence of cataracts was 3% vs. 1%. Infection of any grade was more common in the ibrutinib group (70% vs. 54%), however, rates of grade 3 or above infection were similar (24% vs. 22%). Infusion site reactions, peripheral sensory neuropathy, urticaria, night sweats and pruritus were all more common with ofatumumab than ibrutinib.

Of the patients enrolled in the study, 63% had some form of cytopenia at baseline (45% were anaemic, 35% had thrombocytopenia and 20% neutropenia). There was a sustained improvement in cytopenia(s) in both arms, although the improvement was significantly greater in the ibrutinib arm vs. the ofatumumab arm (69% of patients vs. 43%, $p<0.0001$).[46]

There were eight deaths (4%) in the ibrutinib group and nine (5%) in the ofatumumab group. Most deaths were due to infection (pneumonia or sepsis) or disease progression.

Data from the updated analysis[37] revealed that AEs were consistent with those reported above. In an updated analysis with a median follow up period of 16 months, the majority of patients were still receiving ibrutinib. Discontinuation rates remained relatively low, with 11% of patients (n=47) discontinuing ibrutinib due to adverse events. There were two additional deaths in the ibrutinib arm, making a total of ten deaths at median 16 month follow-up.

Adverse events from non-RCT

The adverse events from the non-RCT were described in Appendix 7 of the company submission and summarised below.

PCYC1102/1103

AE reported in at least 15% of patients is given in Table 10 of Appendix 7 in the company submission and copied below in Table 19 for information. All patients had at least one AE but most were grade 1 or 2 in severity. Serious adverse events were reported in 61% (n=52) of patients though only nine were thought related to ibrutinib. The majority of the serious AEs were due to infection, though three patients experienced atrial fibrillation.

Additional AE data at 3-year follow-up was provided[38]. Most discontinuations due to AEs were observed in the first year of treatment (11/132 patients, 8%) falling to (4/103, 4%) and (2/71, 2%) at years 2 and 3 respectively. Only four of the discontinuations were possibly related to ibrutinib treatment. Diarrhoea, observed in 55% of R/R patients, was the most frequent any- grade AE.

Table 19 AE in PCYC1102 reported in at least 15% patients

AE	Grade 1-2	Grade 3-4	Total
Diarrhoea	40 (47%)	2 (2%)	42 (49%)
Upper respiratory tract infection	28 (33%)	0	28 (33%)
Fatigue	24 (28%)	3 (4%)	27 (32%)
Cough	26 (31%)	0	26 (31%)
Arthralgia	23 (27%)	0	23 (27%)
Rash	23 (27%)	0	23 (27%)
Pyrexia	19 (22%)	4 (5%)	23 (27%)
Oedema, peripheral	18 (21%)	0	18 (21%)
Muscle spasms	16 (19%)	1 (1%)	17 (20%)
Constipation	14 (16%)	1 (1%)	15 (18%)
Dizziness	14 (16%)	1 (1%)	15 (18%)
Headaches	14 (16%)	1 (1%)	15 (18%)
Hypertension	11 (13%)	4 (5%)	15 (18%)
Nausea	14 (16%)	1 (1%)	15 (18%)
Sinusitis	11 (13%)	4 (5%)	15 (18%)
Contusion	14 (16%)	0	14 (16%0
Vomiting	13 (15%)	1 (1%)	14 (16%)
Neutropenia	0	13 (15%)	13 (15%)
Oropharyngeal pain	13 (15%)	0	13 (15%)

PCYC1117

All patients experienced at least one AE. The most common AE were diarrhoea (36%), fatigue (30%) and cough (24%). Serious AEs were reported in 58 (40%) patients. Pneumonia (11.8%) and atrial fibrillation (4.2%) were the most common serious AEs. The AE considered related to ibrutinib with incidence of at least 10% were given in Table 11 in Appendix 7 of the company submission and copied below in Table 20

Table 20 AE [in PCYC1117] related to ibrutinib with incidence ≥ 10%

	All grades	Grade 3-4
Any AE related to ibrutinib	117 (81%)	43 (30%)
Diarrhoea	35 (24%)	0
Neutropenia	18 (12.5%)	15 (10%)
Arthralgia	16 (11%)	1 (<1%)
Fatigue	15 (10%)	1 (<1%)
Increased bruising	15 (10%)	0

Farooqui study

Adverse events reported in the farooqui study did not differentiate between those patients previously untreated and those that were R/R. Nevertheless most AE were grade 1 or 2 in severity with arthralgia (59%), diarrhoea (51%) and rash (47%) the most common. The AE in the Farooqui study[40] with incidence of at least 5% of patients were given in Table 12 in Appendix 7 of the company submission and copied below in Table 21.

Table 21 AE in the Farooqui study with incidence of at least 5% of patients

AE	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia	24 (47%)	6 (12%)	..	..
Diarrhoea	25 (49%)	1 (2%)	..	..
Rash	23 (45%)	..	1 (2%)	..
Nail ridging	22 (43%)	..	..	..
Bruising	17 (33%)	..	..	..
Muscle spasm or cramps	15 (29%)	1 (2%)	..	..
Neutropenia	1 (2%)	2 (4%)	11 (22%)	1 (2%)
Fatigue	13 (25%)	..	..	..
Bilirubin increase	10 (20%)	..	..	..
Lung infection (pneumonia)	..	6 (12%)	3 (6%)	..
Anaemia	2 (4%)	..	7 (14%)	..
Alkaline phosphatase increase	6 (12%)	2 (4%)	..	..
Alanine aminotransferase increase	7 (14%)	1 (2%)	..	..
Aspartate aminotransferase increase	7 (14%)	1 (2%)	..	..
Dyspepsia	8 (16%)	..	..	..
Mucositis	8 (16 %)	..	..	..
Thrombocytopenia	3 (6%)	..	4 (8%)	1 (2%)
Hair texture changes	7 (14%)	..	..	..
Oedema in limbs	3 (6%)	1 (2%)	..	..
Epistaxis	3 (6%)	1 (2%)	..	..
Skin ulceration	4 (8%)	..	..	..
Dry skin	3 (6%)	..	..	..
Nausea	3 (6%)	..	..	..
Myalgia	2 (4%)	1 (2%)	..	..
Subconjunctival haemorrhage	2 (4%)	1 (2%)	..	..

ERG summary of adverse event data

The most common AE in each study was diarrhoea, occurring in approximately half of the patients. The cases were generally grade 1 or 2 in severity, managed with standard treatment and resulted in very few discontinuations (<15% across the studies). In comparison with ofatumumab in the RESONATE trial, infection rates were higher with ibrutinib (70% v 54%), but rates of grade 3 or above infections was similar. Serious adverse events were reported in 40-61% of patients, most were

infection-related although there were a small number of cases of atrial fibrillation. The majority of serious AE were described as not related to ibrutinib. The ERG opinion is that ibrutinib demonstrates a good safety profile.

4.2.10 Critique of evidence for adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation

There was only one study, Farooqui study, that provided interpretable data on this cohort of patients who were treatment naïve[40] (PCYC1102 did have two patients that had 17p deletion and no previous treatment, but the ERG could not find details of the outcome of those two patients.

The Farooqui study was an investigator initiated study in patients with untreated or R/R CLL and TP53 mutation conducted in one site in the US. The study included 35 patients with untreated disease (though only 33 had evaluable data) and 16 that were previously treated. Patients received ibrutinib 420 mg. Full details of the methodology were summarised in Table 2 of Appendix 7 in the company submission. Median follow-up for the previously untreated cohort was 15 months (IQR 12·5–25·7) and for the relapsed or refractory cohort was 26 months (25·4–28·3). The patient characteristics of the study are taken from Table 6 in Appendix 7 and replicated in Table 22 below.

Table 22 Patient characteristics at baseline for the Farooqui study[40]

	Farooqui	
	Previously untreated CLL (n=35)	**R/R CLL(n=16)**
Age (years), median (range)	62 (33-82)	62 (56-79)
Sex		
Female	12 (34%)	8 (50%)
Male	23 (66%)	8 (50%)
Rai stage III/IV	22 (63%)	12 (75%)
Bulky adenopathy (≥5 cm)	8 (23%)	8 (50%)
Splenomegaly (≥315 mL)	30 (86%)	14 (88%)
IGHV unmutated	22 (63%)	12 (75%)
% CLL cells with deletion 17p13.1 (median, range)	61% (13-97%)	42% (12-94%)
β 2 microglobulin ≥3 mg/dl	25 (71%)	13 (81%)
β 2 microglobulin ≥3.5 mg/dl	25 (71%)	13 (81%)

The patients in the study had higher risk disease in comparison to the RESONATE trial.

PFS outcomes

Median PFS was not reached and 24 month estimated PFS was 82%. Data were not provided by prior treatment status. The KM curve of PFS was provided in Figure 7 of Appendix 7 of the company submission and copied below in Figure 18.

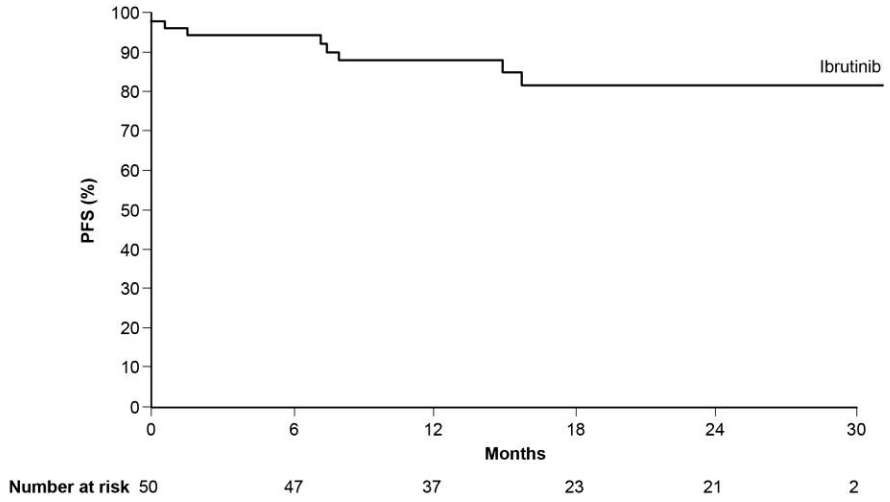


Figure 18 KM curve of PFS in Farooqui study[40]

Overall survival

In patients with previously untreated disease, 84% remained alive at 24 month follow-up. In comparison, for those with R/R disease the estimated OS was 74% at 24 months. The KM curve of OS was provided in Figure 8 of Appendix 7 of the company submission and copied below in Figure 19.

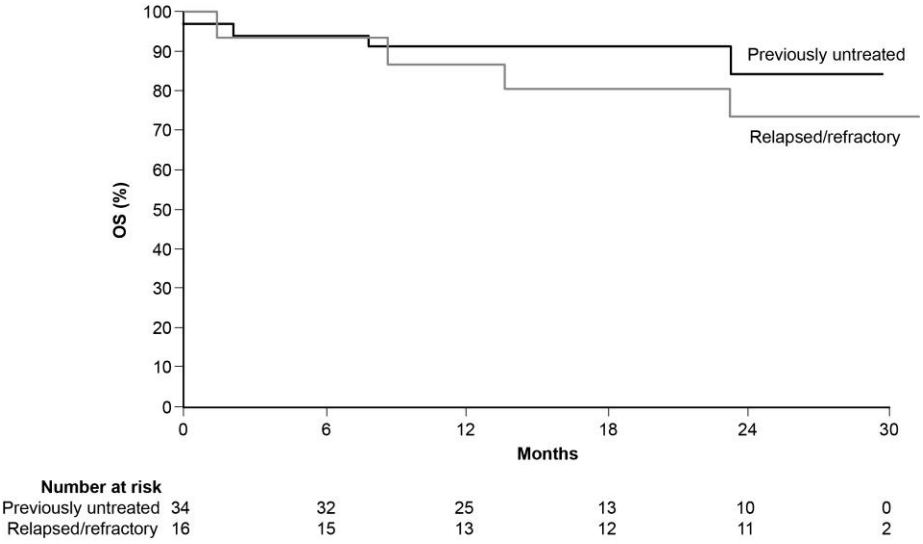


Figure 19 KM curve of OS in Farooqui study

ERG comment on evidence provided for adult patients with CLL who are treatment-naïve and have 17p deletion or TP53 mutation

The data provided on treatment-naïve patients only comes from 33 cases in the Farooqui study. It is therefore difficult to make any definitive statement on treatment

efficacy. However it is the case that a clear benefit of ibrutinib use has been demonstrated within the Farooqui study. The data presented earlier on R/R disease patients with 17p deletion or TP53 mutation within the non-RCT and RESONATE trial do provide evidence that the ibrutinib treatment effect is maintained compared to those without 17p deletion or TP53 mutation.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

There are 4 trials included in the analysis.[30, 36, 47, 48] Only one of these compares ibrutinib to one of the listed comparators, ofatumumab.[30, 37] Two of the trials involve ofatumumab and can therefore be compared with ibrutinib through indirect treatment comparisons.[36, 48] The other is a single arm trial which uses matched adjusted indirect comparison to include it in the network.[47] The network is shown in Figure 20.

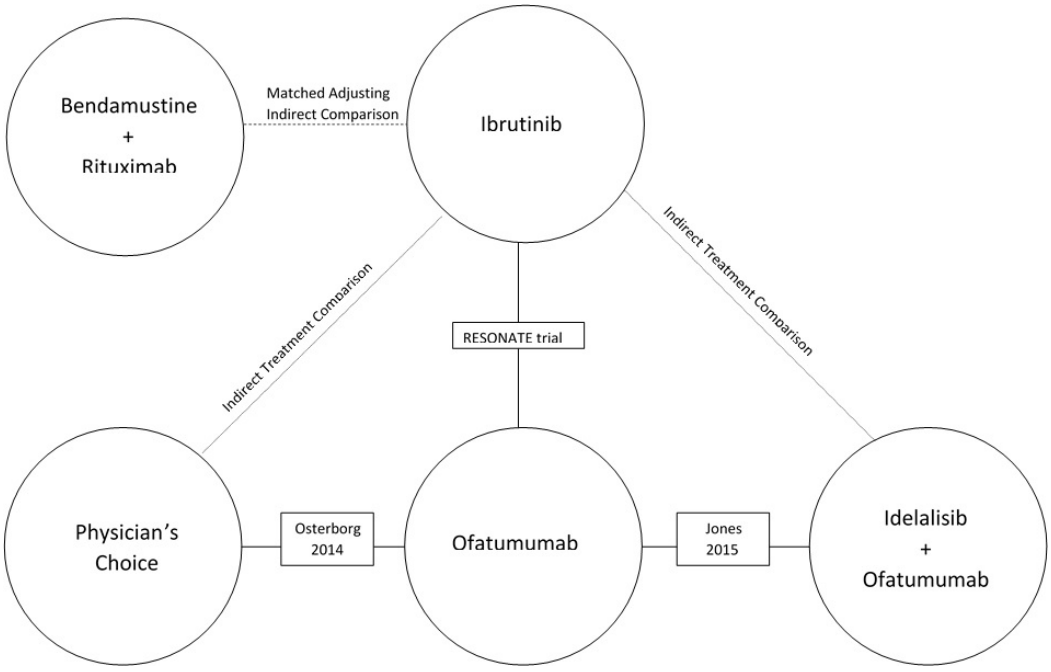


Figure 20 Network diagram

Ibrutinib and ofatumumab are compared in RESONATE trial. Full discussion of the methodology of the trial was given previously in section 4.2, but the study was assessed by the ERG to be of low risk of bias.

The two trials of ofatumumab v physician's choice[36] and ofatumumab v idelalisib + ofatumumab[48] are not reported in full but only by abstract and poster. In neither were the participants or investigators blinded. There is generally insufficient information to fully assess the risk of bias.

The single arm trial is of bendamustine and rituximab and does not have to deal with blinding or allocation concealment issues. While responses and disease progression were assessed by the investigators, these were validated by independent medical review.

The Jones study[48] is an RCT comparing a combination of idelalisib and ofatumumab with ofatumumab in patients with relapsed CLL. Patients had received at least 2 cycles of purine analogue or bendamustine and had progressed within 24 months of their last therapy. Patients were stratified for relapsed versus refractory CLL, 17p deletion and / or tp53 mutation. The first endpoint was PFS and the 2nd endpoint confirmed ORR.
The hazard ratio of 0.27 shows a 73% reduction in the risk of progressing for patients receiving idelalsib, while the odds ratio indicates those receiving idelalisib are considerably more likely to respond to their treatment.

Table 23 Results of PICOS: ibrutinib vs. idelalisib + anti-CD20 monoclonal antibody

PICOS Factor	Parameter	RESONATE[30, 37]		Study 119[48]	
		Ibrutinib	Ofatumumab	IO	Ofatumumab
Population	Median age (range)	67 (30–86)	67(37-88)	68 (40-85)	67 (36-84)
	≥65, n (%)	118 (60.5%)	121 (61.7%)	107 (61.5%)	60 (69%)
	Del 17p	63 (32.3%)	64 (32.7%)	48 (26.4%)	19 (21.8%)
	Median # of prior therapies (range)	3 (1–12)	3 (1 to 13)	3 (1-11)	3 (1-11)
	IGVH unmutated	98 (73%)	83 (63%)	137 (78.7%)	68 (78.2%)
	% male	66%	70%	71.3	71.3
	Refractory disease	87 (45%)*	88 (45%)*	82 (47%)	47 (54%)
	Rai Stage				
	II	30 (15.4%)	39 (19.9%)	15%	24%
	III	23 (11.8%)	35 (17.9%)	14%	12%
	IV	86 (44.1%)	78 (39.8%)	53%	45%
Interventions		Ibrutinib, 420 mg daily		Idelalisib: 150 mg bd Ofatumumab: 300 mg Week 1; then 1,000 mg weekly x7 and then every 4 weeks x 4 (total 12 doses; finishing Week 24)	
Comparators			Ofatumumab, 300 mg at week 1, followed by a dose of 2,000 mg weekly for 7 weeks and then		Ofatumumab: 300 mg Week 1; then 2,000 mg weekly x 7 and then every 4 weeks x 4

PICOS Factor	Parameter	RESONATE[30, 37]		Study 119[48]	
		Ibrutinib	**Ofatumumab**	**IO**	**Ofatumumab**
			every 4 weeks for 16 weeks		(total 12 doses; finishing Week 24)
Outcomes	**Median PFS**	Not reached+	8.1 months+	16.3 months^	8.0 months^
	Median OS	Not reached (90% at 12 months)	Not reached (81% at 12 months)	20.9 months	19.4 months
Study design	**Sample size**	195	196	174	87
	Trial design	RCT, phase III		RCT, phase III	
	Eligibility criteria	**Inclusion criteria** • Active CLL requiring therapy with at least one previous therapy • Inappropriate for purine analogue therapy (due to short progression-free interval after chemo-immunotherapy or coexisting illnesses, age ≥70, or del 17p) • ECOG score PS <2 • Absolute neutrophil count ≥750 cells per microliter • Platelet count ≥30,000 cells per microliter • Adequate liver and kidney function. **Exclusion criteria** • Patients requiring warfarin or strong CYP3A4/5 inhibitors		**Inclusion criteria** • Diagnosis of B-cell CLL and requiring treatment, per International • Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria2 • CLL progression <24 months from completion of last therapy • Prior therapy: ≥2 cycles of a purine analogue or bendamustine • Karnofsky score ≥60 • Complete blood count: any values • Estimated creatinine clearance (eCrCl) >30 mL/min (Cockcroft-Gault) **Exclusion criteria** • Prior therapy with inhibitor of AKT, BTK, JAK, mTOR, PI3K, or SYK • Prior allogeneic stem cell or solid organ transplantation • Progression within 6 months of last ofatumumab dose	

*Purine analogue-refractory

~del17p and/or TP53 mutation

+Investigator-assessed outcome

^Independent review committee-assessed outcome

The company comment that due to RESONATE and Jones[48] enrolling similar patient populations no adjustment for patient characteristics was necessary and therefore the two trials can be used for indirect treatment comparison. The ERG have some observations to make on this comment.

Both studies measure the objective response rate, progression free survival and overall survival and so the ERG are happy that the same outcomes are being measured. The indirect treatment comparison is using the ofatumumab arm in both trials as the common comparator. In RESONATE those receiving ofatumumab receive 300mg at week 1, followed by 2000mg weekly for 7 weeks and then every 4 weeks for the remaining 16 weeks.
In Jones, the ofatumumab patients receive 300mg in week 1, then 2000mg weekly for 7 weeks and then a dose every 4 weeks for the next 16 weeks. In both trial 12 doses are received in total and the ERG are satisfied that the comparator arms are receiving the same doses.

The patient populations are similar but the ERG think it is important to highlight the difference in del17p (the deletion of the area of chromosome 17 where the TP53 tumour suppressor gene is located). In the resonate trial the patient populations receiving ibrutinib and ofatumumab have 32.3% and 32.7% while in Jones the proportions are 26.4% for idelasib with ofatumumab and 21.8% for ofatumumab. It is the view of the ERG that there is a poorer prognosis for those enrolled in the RESONATE trial and therefore the effect of ibrutinib may appear greater.

The ERG also observe that whilst ibrutinib and idelalisib in combination with ofatumumab have beneficial effects on PFS and ORR it is only ibrutinib which has a significant effect on overall survival and it is therefore possible that the two interventions do not function in exactly the same way. The ERG also highlight that there is no adjustment for crossover in the analysis of the comparison between the combination of idelalisib and ofatumumab and ofatumumab on its own.

Österborg[36] was a randomised trial comparing ofatumumab with physician's choice in patients with bulky fludarabine refractory CLL. Physician's choice (PC) included all well established and approved treatments for CLL but not experimental drugs. The

most frequently used were combinations with rituximab, alemtuzumab monotherapy or combination with steroids, fludarabine-based therapies and bendamustine or bendamustine and rituximab. Primary efficacy was measured using PFS with ORR, OS and time to next therapy (TNT) used to measure secondary efficacy.

The primary objective of the study was to evaluate progression-free survival and the hazard ratio of 0.56 indicates that patients were 44% less likely to progress if they were receiving ofatumumab. The authors do not present a hazard ratio for time to next treatment nor do they present an odds ratio for response but the tests performed show significant differences in favour of ofatumumab. In the study patients receiving physician's choice were able to receive ofatumumab salvage at the point of progressive disease. There was no adjustment in the trial for crossover.

Table 24 PICOS results comparing Byrd (2014)[30] and Österborg (2014)[36]

PICOS Factor	Parameter	RESONATE[30, 37]		Österborg 2014[36]	
		Ibrutinib	**Ofatumumab**	**Ofatumumab**	**Physician's choice**
Population	**Median age (range)**	67 (30–86)	67(37-88)	61.5 (46 to 82)	63.0 (40 to76)
	≥65, n (%)	118 (60.5%)	121 (61.7%)	Not reported	Not reported
	Del 17p	63 (32.3%)	64 (32.7%)	15 (18.9%)	9 (20.9%)
	Del 11q	63 (32.3%)	59 (30.1%)	21 (27%)	12 (28%)
	Median # of prior therapies (range)	3 (1–12)	3 (1 to 13)	4 (2 to 16)	3 (2 to 11)
	≥3	103 (52.8%)	90 (45.9%)	NR	NR
	Bulky disease (≥5cm)	124 (63.6%)	101 (51.5%)	NR (assumed 100% according to eligibility criteria)	NR (assumed 100% according to eligibility criteria)
	Refractory disease	87 (45%)*	88 (45%)*	NR (assumed 100% according to eligibility criteria)~	NR (assumed 100% according to eligibility criteria)~
	Rai Stage				
	0,I, or II	86 (44.1%)	83 (42.3%)	33 (42%)	18 (42%)
	III or IV	109 (55.9%)	113 (57.7%)	43 (54%)	24 (56%)
Interventions		Ibrutinib, 420 mg daily		Ofatumumab, 300 mg week 1; 2000 mg week 2,3,4,5,6,7,8,12, 16,20,24	
Comparators			Ofatumumab, 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4		Physician's choice; dosing details not reported

PICOS Factor	Parameter	RESONATE[30, 37]		Österborg 2014[36]	
		Ibrutinib	**Ofatumumab**	**Ofatumumab**	**Physician's choice**
			weeks for 16 weeks		
Outcomes	**Median PFS**	Not reached	8.1 months	7.0 months	4.5 months
	Median OS	Not reached (90% at 12 months)	Not reached (81% at 12 months)	11.5 months	6.5 months
Study design	**Sample size**	195	196	79	43
	Trial design	RCT, phase II		RCT, phase III	
	Eligibility criteria	**Inclusion criteria** • Active CLL • At least one previous therapy • Inappropriate for purine analogue therapy (due to short progression-free interval after chemo-immunotherapy or coexisting illnesses, age ≥70, or del 17p) • ECOG score PS <2 • Absolute neutrophil count ≥750 cells per microliter • Platelet count ≥30,000 cells per microliter • Adequate liver and kidney function. **Exclusion criteria** • Patients requiring warfarin or strong CYP3A4/5 inhibitors		**Inclusion criteria** • Active fludarabine-refractory CLL requiring therapy • At least 2 prior therapies • Bulky (>5 cm) lymph nodes • ECOG PS 0-2 **Exclusion criteria** • Prior allogeneic stem cell transplantation • Known Richter's transformation • Prolymphocytic leukemia • Autoimmune haemolytic anaemia unless with PD • Active infection	
*Purine analogue-refractory ~Fludarabine-refractory					

On inspection of the above table the ERG believes that the patient population for Österborg contains patients with more severe conditions and therefore there is the possibility for the relative treatment effects to be higher for those with the more severe condition. The analysis undertaken by the company to restrict the RESONATE population to a similar population to Österborg will produce a more relevant comparison and thus the

[redacted] are the more relevant for the comparison between ibrutinib and PC.

Fischer was a trial of bendamustine combined with rituximab in patients with chronic lymphocytic leukaemia. Patients had either relapsed or refractory disease and had received between one or three previous treatments. The primary end-point of the trial was ORR with progression free survival and overall survival included as secondary end-points. A comparison of the patient populations was given in Table 38 of the company submission. The ERG highlight the difference in 17p deletion which suggests that the population in Fischer had less severe disease than in RESONATE. The study shows an ORR of 59% when using all patients. The marked difference in trial populations led the company to conduct a Matched adjusted indirect comparison (MAIC).

Matched adjusted indirect comparisons leverage the IPD (in the company's submission it is the ibrutinib data from the RESONATE trial which is used) to re-weight patients so that the average baselines match those in the comparator trial (in this case it is the single arm trial of bendamustine and rituximab[47])

Trials need to have similar inclusion and exclusion criteria. The comparator trial needs to be more exclusive than the IPD trial so that in theory the IPD trial could encompass the comparator trial population. The company decided that Fischer's definition of event free survival as "the date of first treatment with BR to the date of progressive disease, the beginning of new treatment for any hematologic malignancy, or death as a result of any cause" was close enough to the RESONATE definition of PFS and therefore the EFS data was a proxy for PFS.

The first stage in the MAIC process is to align the inclusion and exclusion criteria so that patients excluded from one study would also be excluded from the other study. The next step re-weights patients in the RESONATE trial so that their baseline characteristics match those in Fischer. The effective sample size (the ratio of the square of the summed weights to the sum of the squared weights) indicates the impact of re-weighting. The effective sample size is maximised when all patients have the same weight. A small sample size indicates "some patients are receiving extreme

weights, and there may be little statistical power to detect differences between treatments."

The company used a matching process starting with as many available baseline characteristics as possible and then dropped these one at a time until only one was left.

Based on clinical input, variables were ranked in the following order (from most important to least important for prognosis) and preserved in the matching analysis accordingly. These 19 are the overall list of key variables but not all were captured in Fischer and so there are at most 12 characteristics included in the model.

1. 17p deletion status
2. Number of prior lines of therapy
3. Purine refractory status
4. Age
5. Binet/RAI
6. Unmutated immunoglobulin variable region heavy chain (IGVH) status
7. Bulky disease
8. Serum beta2-microglobulin (>3.5mg/L)
9. Del 11q status
10. ECOG score 0 versus 1
11. Creatinine clearance
12. Platelets
13. Race
14. Percent male
15. Del 13q
16. Hemoglobin
17. Absolute lymphocyte count
18. Trisomy 12
19. White blood cell count

Table 25 is an extract from the company's analysis of dropping each available characteristic until there is only one remaining in the model.

Table 25 MAIC analysis

Variables matched	Effective sample size	Odds Ratio (95% CI)		HR (95% CI)	
		ORR	CR	PFS	OS
22	30	[redacted]	[redacted]	[redacted]	[redacted]
7	91	[redacted]	[redacted]	[redacted]	[redacted]
1	169	[redacted]	[redacted]	[redacted]	[redacted]

The result which appears in the submission is for matching 22 factors (these were 1-6, 8-9, 11-12, 14, 16 and 17 from the above list). Some of these factors required more than one variable to be included in the model. The company were asked at clarification "Please explain the rationale for using the matching adjusted indirect comparison (MAIC) which matches 22 factors and therefore has the smallest effective sample size" but did not provide any justification apart from their earlier statement of 17p deletion status being the most important variable based on clinical input. The ERG are therefore unclear on which model should be used and there are marked differences in the HR.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

The company presents indirect treatment comparisons using the Bucher methodology in order to compare ibrutinib to the other treatments which have been trial interventions. The company states "with such limited RCT data available, all of which are further confounded by differences in trial designs and patient populations, a network meta-analysis was not possible." Having examined the references provided by the company the ERG agree with their statement regarding not conducting a network meta-analysis due to limited trial data and differences in patients and trial design.

The outcomes considered for the indirect comparisons of ibrutinib and physician's choice and the combination of idelalisib and ofatumumab and also the MAIC of ibrutinib and bendamustine and rituximab are objective response rate, progression free survival and overall survival.

Table 26 summarises the results of the ITC and MAIC. The company presents the odds ratio for objective response rates and hazard ratios for the progression free survival and overall survival. The outputs for the table come from Table 27.

Table 26 Summary of results of ITCs and MAICs

Comparison	Analysis type	Data sources	OR ORR (95% CI)	HR PFS (95% CI)	HR OS (95% CI)
Ibrutinib vs. PC	ITC, Bucher method	RESONATE[30] vs. Osterborg, 2014[36]	[redacted]	[redacted]	[redacted]
Ibrutinib vs. IO	ITC, Bucher method	RESONATE[30 49] vs. Jones, 2015[48]	1.65 (0.66, 4.10)	0.39 (0.23-0.66)	0.50 (0.24-1.04)
Ibrutinib vs. BR	MAIC	RESONATE[30] vs. Fischer, 2011[47]	[redacted]	[redacted]	[redacted]

Table 27 Data inputs

	OR ORR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
Ibrutinib vs. ofatumumab	26.25 (14.93-46.16)	0.106 (0.07-0.15) p<0.0001	[redacted]
Ofatumumab vs. PC	3.15 (1.24-7.97)	0.56 (0.38-0.82) p=0.003	0.68 (0.41-1.15) p = 0.1295
IO vs. ofatumumab	15.94 (7.80-32.58)	0.27 (0.19-0.39) p<0.0001	0.74 (0.44-1.25) p=0.27

The analyses show significant effects in favour of ibrutinib in comparison to ofatumumab, physician's choice and the combination of bendamustine and rituximab. These can be seen for all of objective response rate, progression free survival and overall survival. The effect size and confidence intervals for the objective response rate indicate small numbers of events are being observed for the various interventions.

In comparison the effect sizes for ibrutinib versus idelalisib and ofatumumab are reduced for the objective response rate, progression free survival and overall survival and it is only progression free survival where there is a statistically significant effect.

For sensitivity analysis, the company presented an alternative indirect comparison based upon a multivariate Cox model of pooled patient-level trial data for ibrutinib versus bendamustine and rituximab using data from the HELIOS trial.[50] The HELIOS trial compared ibrutinib plus bendamustine and rituximab to bendamustine and rituximab. The Cox model compared data from the bendamustine and rituximab arm of the trial with the RESONATE trial data. The HR PFS for ibrutinib versus bendamustine and rituximab was [redacted] and the HR OS was [redacted]. The key advantage of the approach is the use of IPD and the ability to adjust for patient level confounders. The HELIOS study however included less severe patients then RESONATE and so may be biasing in favour of bendamustine and rituximab.

The company also presented an alternative indirect comparison based upon a multivariate Cox model of pooled patient-level trial data for ibrutinib versus physician choice using data from a retrospective observational study of 148 consecutive patients conducted in Stockholm by the Karolinska Institute (Unpublished data, Karolinksa Institute, 2015) The HR PFS for ibrutinib versus physician choice was [redacted] and the HR OS was [redacted].

The ERG were unable to identify a clear reason in the company submission for the selection of the two studies used in the sensitivity analyses and therefore whether other studies may have been available. The ERG also note that if the multivariate cox model or the MAIC was the preferred approach, then it is unclear to the ERG in the selection of studies from the evidence synthesis whether some other comparators could have been included. For example, the ERG note that it may have been possible for the company to have performed an MAIC analysis using the idelalisib plus rituxumab versus rituximab plus placebo trial.[31] Such an analysis could provide reassurance that the current estimate of benefit of ibrutinib compared to idelalisib in the network is robust.

The ERG agree that the ITC of ibrutinib versus physician choice and ibrutinib versus bendamustine and rituximab does demonstrate improved efficacy of ibrutinib, but the sensitivity analyses undertaken by the company demonstrate that there is significant uncertainty over the magnitude of the differences.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG do not agree with the company that the adjusted for crossover HR of overall survival from the RESONATE trial should be used as the data input in the indirect treatment comparisons. Given that the data inputs from the other trials in the network were not adjusted for crossover, the ERG believe it would be more consistent methodology to use the ITT estimates from all studies, including RESONATE. The ERG revised estimates are shown in Table 28. All data inputs are the same as the company estimates apart from the ibrutinib versus ofatumumab HR OS intention to treat estimate of 0.43 (95%CI 0.24-0.79) is used instead of [redacted]. Given the need for IPD, the ERG was unable to make any amendments to the ibrutinib versus BR estimate.

The table illustrates that the ERG estimates increased the HR for OS using the Bucher method.

Table 28 Summary of ERG reanalysis of HR overall survival ITCs and MAICs

Comparison	Analysis type	Data sources	Company HR OS (95% CI)	ERG HR OS (95% CI)
Ibrutinib vs. PC	ITC, Bucher method	RESONATE[30] vs. Osterborg, 2014[36]	[redacted]	[redacted]
Ibrutinib vs. IO	ITC, Bucher method	RESONATE[30] vs. Jones, 2015[48]	0.50 (0.24-1.04)	0.58 (0.26-1.30)
Ibrutinib vs. BR	MAIC	RESONATE[30] vs. Fischer, 2011[47]	[redacted]	[redacted]

4.6 Conclusions of the clinical effectiveness section

In summary the company providing detail on one randomised controlled trial, RESONATE comparing ibrutinib with ofatumumab in patients with relapsed or

refractory chronic lymphocytic leukaemia. A further four non-RCT, non-comparative studies of ibrutinib were included.

The ERG opinion is that the data for efficacy of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia is consistent and impressive. When compared with ofatumumab PFS and OS were highly statistically significantly improved. The OS benefit appeared to be consistent across all subgroups reflecting good outcome across severity of risk (e.g. older patients, advanced disease, multiple pre-treatments).

The most common AE in each study was diarrhoea, occurring in approximately half of the patients. The cases were generally grade 1 or 2 in severity, managed with standard treatment and resulted in very few discontinuations (<15% across the studies). In comparison with ofatumumab in the RESONATE trial, infection rates were higher with ibrutinib (70% v 54%), but rates of grade 3 or above infections was similar. Serious adverse events were reported in 40-61% of patients, most were infection-related although there were a small number of cases of atrial fibrillation. The majority of serious AE were described as not related to ibrutinib. The ERG opinion is that ibrutinib demonstrates a good safety profile.

Also provided were abstract and poster details on two trials involving ofatumumab which was used as a comparator to form a network for indirect treatment comparisons and a single arm study of bendamustine and rituximab.

The company uses indirect treatment comparisons and matched adjusting indirect comparisons to compare ibrutinib to the other comparators of physician's choice, a combination of idelalisib and ofatumumab and a combination of bendamustine and rituximab to estimate the comparative effect of ibrutinib in in patients with relapsed or refractory chronic lymphocytic leukaemia. In these comparisons ibrutinib was again superior in terms of PFS and OS to all included comparators. The ERG note some caution with the magnitude of the estimates given only single trials were used in each comparison, the differences between trial populations and the sensitivity analyses undertaken by the company. The ERG also note that if the multivariate cox model or the MAIC was the preferred approach, then it is unclear to the ERG in the selection of

studies from the evidence synthesis whether some other comparators could have been included in the network.

The data provided on treatment-naïve patients only comes from 33 cases in a single non-RCT, non- comparative study. It is therefore difficult to make any definitive statement on treatment efficacy. However it is the case that a clear benefit of ibrutinib use has been demonstrated within the single study. The data presented on R/R disease patients with 17p deletion or TP53 mutation within the non-RCT and RESONATE trial do provide evidence that the ibrutinib treatment effect is maintained compared to those without 17p deletion or TP53 mutation. The ERG opinion is that data are limited, though promising, of the efficacy and safety of ibrutinib for use in treatment-naïve patients with 17p deletion or TP53 mutation.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

Reports of cost effectiveness were sought by searching MEDLINE (Pubmed), EMBASE (Embase.com), NHS Economics Evaluation Database (NHS EED), Health Technology Assessment (HTA) database and EconLit on 3rd June 2015. However, the start date from which the databases were searched is unclear. In addition CENTRAL and the Database of Abstracts of Review of Effects (DARE) were searched although these databases are unlikely to identify any economic evaluations. The three most recent years' conference proceedings of five relevant conferences were screened (ASCO, ASH, EHA,ESMO, ISPOR) were also searched. Reference lists of identified studies and recently published reviews were also screened. The search strategies are documented in full in Appendix 8.

The PUBMED and EMBASE searches combined three search facets using the Boolean operator AND: the patient population (chronic lymphocytic leukaemia); intervention or comparator (salvage treatment or refractory disease or second/third line treatment) ; and outomes (economics or costs). The search in the NHS EED and HTA Database also included economic terms which seemed unnecessary since these are databases of economic evaluations and HTA reports respectively. Appropriate controlled vocabulary terms and a comprehensive range of text terms were used for the defined search facets. The ERG believes however that ibrutinib and the specific drug comparators as detailed in the decision problem should have also been included in the intervention facet of the search to ensure a comprehensive search.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

Although the company submission states the criteria were provided in Appendix 8, the ERG could not identify the criteria in the Appendix.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies

The company states that 673 citations were identified and, of these, 531 citations were excluded at the abstract level. Among the 142 citations remaining, 116 were rejected following further application of the inclusion/exclusion criteria to full-text citations and 25 citations were finally accepted into the review: 11 cost-effectiveness studies[51-61] and 11 resource identification studies.[62-72] Additionally, two cost-minimisation studies[73, 74] and one health-state simulation model[75] were identified. The cost-minimisation studies were excluded from this discussion due to the fact that no health or QOL outcomes were analysed and the health-state simulation model study did not report any cost. The PRISMA Economic Analyses Flow Diagram is detailed in Figure 25 of the company submission.

Four of the 11 cost-effectiveness analyses took the perspective of the UK. However, no full-text publications were available for these 11 studies (only abstracts) with the exception of Hoyle et al[55] therefore, very limited information was available regarding the studies' methods and inputs. Details on the model, patient populations, and results of the four studies relevant to the UK are presented in Table xx of the company submission. The remaining seven cost-effectiveness studies, three of which were only available as abstracts, took the perspectives of non-UK countries, which limits their relevance to decision-making in England and Wales and the company, therefore, excluded these from the review. The ERG agrees with this decision.

Table 29 Summary list of published cost-effectiveness studies

Study	Country	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Almond et al. 2013[52] (abstract only)	UK	Cost-effectiveness model from TA202 (comparing ofatumumab with BSC) was reproduced and populated with alternative survival data from the perspective of the UK NHS. Individual patient-level data were reconstructed from KM curves using a published algorithm. Plausible survivor functions were fitted to the data using Markov chain Monte-Carlo simulation.	NR	NR	NR	ICER comparing ofatumumab vs. BSC: £52,400 (compared to £49,252 reported in TA202).
Batty et al. 2010[53] (abstract only) [76]	UK	Cost-effectiveness of ofatumumab vs. BSC was evaluated in the UK national healthcare setting using a partitioned survival analysis model. PFS and OS for ofatumumab were estimated by fitting a Weibull curve to trial data; no similar data could be identified for BSC, therefore Cox regression models were fit to non-responder data vs. all fludarabine-refractory patients. Costs and	Not listed.	BSC patients (approximated by non-responders): 0.50 QALYs Ofatumumab patients: 0.77 QALYs	BSC: £4,876 Ofatumumab: £43,828	Ofatumumab vs. BSC: £144,266.66/ QALY

Study	Country	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		utilities were taken from published and unpublished sources.				
Hoyle et al. 2011[77]	UK	An 'area under the curve' or 'partitioned-survival' model was used to project expected clinical and economic outcomes for patients with DR CLL who were assumed to receive ofatumumab or BSC. The model had a three-state structure: 'alive pre-progression', 'alive post progression' and 'dead'.	NR	No QALYs reported	NR	£38,241 per QALY
Dretzke et al. 2010[54 78]	UK	The objective of the model was to assess the cost per QALY of R-FC compared to FC based on clinical parameters taken from the REACH trial. The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.	CLL (median age: 63 years)	No QALYs reported	NR	Base case - £15,593/QALY
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); BSC, BSC; DR, double refractory						

A brief summary of the quality of life assessment of the included studies is provided in Appendix 9 of the company submission. The ERG believes the methods used for this assessment are appropriate and that the results are transparent.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The company submission does not detail any conclusions arising from the data available to the cost effectiveness review. The ERG agrees that data are insufficient to make any robust conclusions.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 30 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	For the all patients modelling the company considers: - Physician choice, which is a basket of treatments - Ofatumumab - Idelalisib plus rituximab - Bendamustine plus rituximab For the 17p depleted population the company considers: - Ofatumumab.
Patient group	As per NICE scope. "*Adults with CLL who have received at least 1 therapy and untreated adults with CLL with 17p depletion or TP53 mutation for whom chemo-immunotherapy is not suitable*"	The RESONATE all patient modelling reflects the CLL patient population who have received at least 1 therapy. The RESONATE 17p depleted population modelling is taken as a proxy for treatment naïve patients with 17p depletion who are not suitable for chemo-immunotherapy.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis
Time horizon	Sufficient to capture differences in costs and outcomes	20 years. Within the ibrutinib arm at 20 years there is a reasonable proportion modelled as still surviving. If this is reasonable patient benefits have been truncated.
Synthesis of evidence on outcomes	Systematic review	The overall survival and progression free survival hazard ratios are based upon an ITC which is in turn based upon a systematic review.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		Response rates have some impact upon costs within the company modelling. Their derivation is less clear.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The progression free survival quality of life is based upon EQ-5D-5L data collected during RESONATE. The quality of life decrement for progression is based upon a TTO study among 93 members of the UK general public.
Benefit valuation	Time-trade off or standard gamble	TTO
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes for the EQ-5D data. The decrement for progression is based upon a sample of the UK public, but quite a small one.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	The all patient modelling presents deterministic and probabilistic results. The 17p depletion subgroup modelling only presents deterministic results.
Sensitivity analysis		A range of sensitivity analyses are presented for the all patient modelling. No sensitivity analyses are presented for the 17p depletion subgroup modelling.

5.2.2 Model structure

The company has submitted a markov model with a 20 year time horizon and a four week cycle. The four main health states of the model are:

- Progression free survival on 1st line active treatment (PFS)
- Post-progression survival on 2nd line active treatment (PPS)
- Post-progression survival receiving only best supportive care (BSC)
- Dead

Patients start in progression free survival. Upon progression, as assessed by the investigator and not by the IRC, a proportion of patients receive a second active treatment. Those who do not receive a second active treatment and those who further progress while on a second active treatment move onto best supportive care.

The total number of deaths is determined by the overall survival curve. A constant percentage of patients in progression free survival are assumed to die. The residual number of deaths implied by the overall survival curve and the number dying while remaining in progression free survival are among those on best supportive care. This latter forms the majority of deaths.

The quality of life value for progression free survival is based upon post baseline EQ-5D-5L data collected during the RESONATE trial. The quality of life value for post progression survival and best supportive care is estimated by applying a percentage quality of life reduction associated with progression, drawn from the literature, to the baseline EQ-5D-5L average of the RESONATE trial.

Serious adverse events are also modelled as having cost and quality of life impacts, and are assumed to last for 14 days.
Ibrutinib and idelalisib are assumed to be taken for the entire period of progression free survival. The other 1st line treatments are administered to a given schedule for a maximum of up to five model cycles.

The routine follow-up costs while in progression free survival are determined by treatment specific proportions of patients achieving complete response, partial response and being in stable disease.

Terminal care costs are applied when patients die.

5.2.3 Population

The patient population is based upon the RESONATE trial, with a mean age of 67 years with 68% being male, and an average height and weight of 1.71m and 77.3kg apparently implying a body surface area of $1.9m^2$.

A subgroup analysis of the RESONATE 17p depleted population is also presented for the comparison of ibrutinib with ofatumumab.

5.2.4 Interventions and comparators

Ibrutinib is compared with:

- Physician choice which is a mixture of treatments as drawn from Osterborg et al (2014) with the company having adjusted the costs of this mixture to better reflect UK practise:
  - [redacted]: Bendamustine plus rituximab
  - [redacted]: Methylprednisolone plus rituximab (R-HDMP)
  - [redacted]: Chlorambucil
  - [redacted]: Fludarabine and cyclophosphamide plus rituximab (FCR)
  - [redacted]: Cyclophosamide, doxorubicin, vincristine and prednisolone plus rituximab (R-CHOP)
- Ofatumumab
- Ibrutinib plus rituximab
- Bendamustine plus rituximab

5.2.5 Perspective, time horizon and discounting

The perspective for benefits is that of the patient and for costs is that of the NHS/PSS. The time horizon is 20 years. Costs and benefits are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Overall survival: ibrutinib

Parameterised curves were fitted to the ibrutinib Kaplan Meier data. The company applies the lognormal curve for the first three years of the model followed by the exponential. The goodness of fit parameters are as below.

Table 31 OS: Ibrutinib RESONATE parameterisations goodness of fit

	All patients		17p depleted	
	AIC	**BIC**	**AIC**	**BIC**
Weibull	214.63	221.18	215.68	225.50
Log-Normal	214.21	220.76	214.43	224.25
Log-Logistic	214.46	221.01	215.33	225.15
Exponential	**212.66**	**215.93**	**213.70**	**220.25**

The parameterised curves mapped against the Kaplan Meier curve and the number at risk across all patients is as below, the left hand graph being for 40 four week cycles in order to provide more detail and the right hand graph being for 100 four week cycles to outline the effects of the extrapolation assumptions.

The left hand graph for both all patients and 17p depleted patients shows that by around the 20th cycle very few remain at risk to contribute data to the Kaplan Meier curve. Up to this point the parameterised curves are effectively indistinguishable, though for the 17p depleted patients there may be a suggestion of the lognormal curve lying slightly below the other curves. It is only during the extrapolation beyond this point that the parameterised curves start to diverge with the lognormal curve rising above the other curves.

The company submission states that the lognormal curve for ibrutinib derived from RESONATE matches the KM curve of the ibrutinib 1102/1103 trial. The company has supplied the Kaplan Meier data for overall survival in the 1102 trial[a]. Note that this data includes both the 51 patient on the 420mg dose and the 34 patients on the 840 mg dose.

[a] Note that the 1102 data is reported as months which the ERG has taken to be equivalent to the four week cycle of the model. This might be the source of the slight visual discrepancy between the figure and figure 31 of the company submission, with the latter suggesting that very slightly more of the 1102 Kaplan Meier curve lies above the parameterised curves.

As with the RESONATE trial the numbers at risk in the 1102 trial are quite small by around the 20th cycle. Note that the above Kaplan Meier data was supplied at clarification and does not appear to be in line with Figure 31 of the submission which states that at 19 months the number at risk is 27 when the above suggests that at 19 months the number at risk is 37, which may suggest that the ERG has misinterpreted the 1102 Kaplan Meier data supplied at clarification. It is not obvious to the ERG that the above figure or Figure 31 of the company submission provides any additional support for the lognormal survival curve being chosen for the modelling over the other parameterised curves.

Despite the goodness of fit statistics for the all patients modelling the company applies the lognormal curve due to visual inspection of the curves. But the company states that extrapolation using the lognormal curve results in an infeasible proportion surviving at 20 years, around [redacted]. In the light of the above, the company has chosen to apply the hazard from the exponential curve after three years. As can be seen from the right hand graph, for the all patients modelling this results in the modelled overall survival following the lognormal curve for three years and then having a faster rate of decline as the hazard of the exponential is applied. Throughout the time horizon of the model the overall survival curve of the model remains above those of the exponential and the weibull parameterisations, though there is a slow convergence. This extrapolation results in the model suggesting that around [redacted] survive at 20 years. The exponential and the Weibull would if applied suggest 20 year survival rates of [redacted] and [redacted] respectively.

For the 17p depleted subgroup modelling the company applies the exponential curve throughout.

Overall survival: comparator treatments

The company adjusted the ofatumumab overall survival curve for cross-over using the RPSFT and the IPCW methods. Applying the resulting RPSFT and IPCW hazard ratios to the ibrutinib Kaplan Meier curve results in adjusted Kaplan Meier curves as below. The numbers at risk are the total number who remain at risk and the total number who remain at risk who have crossed over.

The Kaplan Meier curves remain reasonably aligned until around the 11th 4 week cycle after which they start to diverge as the total number who remain at risk who have crossed over climbs. After around the 18th 4 week cycle the vast majority of the total number who remain at risk have crossed over, though the total number at risk is falling quite steeply beyond this point.

Hazard ratios relative to ibrutinib are also estimated for physician choice, idelalisib plus rituximab and bendamustine plus rituximab as summarised below. The company also supplied a hazard ratio for an early analysis which was based on a pre-specified data cut when approximately 117 PFS events had occurred, at which point only 47 patients had crossed over in the ofatumumab arm. For ofatumumab the company prefers the RPSFT hazard ratios, as reviewed above in the clinical effectiveness section.

Table 32 OS: Hazard ratios for comparators

	All patients				17p
	Ofat.	**Phys. chc**	**Idel.+R**	**Bend.+R**	**Ofat.**
ITC	[redacted]	[redacted]	0.499	[redacted]	[redacted]
ITT	[redacted]	[redacted]	..	[redacted]	[redacted]
EarlyITT	[redacted]	[redacted]	..	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	..	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	..	[redacted]	[redacted]

Unfortunately, due to rewording of the ERG clarification question some values for the ITT analysis and the IPCW analysis for the 17p depleted subgroup are not available.

Scenario analyses which used Swedish registry data to estimate a hazard ratio of 0.370 for physician choice and the HELIOS data to estimate a hazard ratio of 0.488 for bendamustine plus rituximab were also explored.

This results in the following overall survival curves for the base case.

[redacted]

By the end of the 20 year time horizon patients are 87 years of age. UK life table data suggests a little more than one third of 67 year olds will survive to be 87 years old. For all patients the model projects that [redacted] will survive after 20 years under ibrutinib, physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab.

For 17p depleted patients the model predicts that [redacted] will survive after 20 years under ibrutinib, physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab.

Progression free survival: ibrutinib and ofatumumab

Parameterised curves are separately fitted to the RESONATE investigator assessed progression free survival data for ibrutinib and for ofatumumab as outlined below.

[redacted]

[redacted]

[redacted]

[redacted]

The goodness of fit statistics for this for the all patient data analysis is as below.

Table 33 PFS: RESONATE parameterisations goodness of fit statistics

	All patients				17p depleted patients			
	Ibrutinib		Ofatumumab		Ibrutinib		Ofatumumab	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	**267.64**	274.19	**411.93**	**418.49**	**268.78**	278.60	**409.99**	**419.82**
Log-Normal	269.31	275.86	447.36	453.92	269.09	278.91	441.88	451.72
Log-Logistic	267.85	274.39	434.04	440.60	268.70	278.52	427.69	437.53
Exponential	268.43	**271.71**	469.98	473.25	269.52	**276.07**	469.15	475.70

The company notes that the information criteria for the ibrutinib curves are all reasonably similar. The company also notes that a significant number of patients in the ibrutinib arm remained in PFS under the lognormal, loglogistic and exponential and as a consequence the company prefers the Weibull projection.

Note that since:

- the PFS curves are used to partition the space under the overall survival curve;
- those in PFS incur the quite considerable drug costs of ibrutinib; and,
- the quality of life decrement for progressing is relatively small,

a worse PFS curve for ibrutinib improves its cost effectiveness estimate.

Progression free survival: comparator treatments

PFS curves for the other comparators are based upon applying a hazard ratio to the hazard of ibrutinib PFS curve.

Table 34 PFS: hazard ratios for comparators

	All patients and 17p depleted patients			
	Ofat.	Phys. chc	Idel.+R	Bend.+R
ITC	[redacted]	[redacted]	0.393	[redacted]
Alt. ITC	[redacted]	[redacted]	..	[redacted]
ITT	[redacted]	[redacted]	..	[redacted]

While a hazard ratio is available for the comparison with ofatumumab the base case uses the Weibull parameterised curve for ofatumumab PFS estimated from RESONATE data.

Alternative hazard ratios from alternative ITCs are also estimated for physician choice based upon Swedish registry data and for bendamustine plus rituximab based upon the application of the HELIOS data.

This results in the following PFS survival curves.

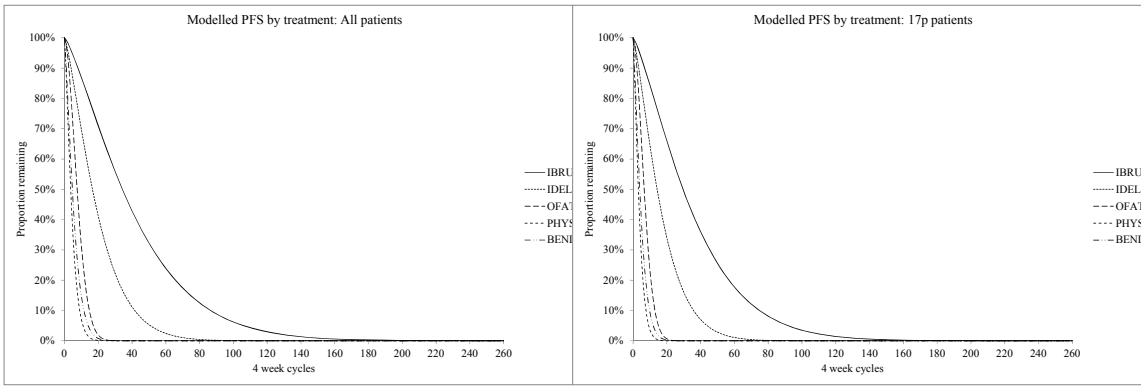


Figure 28 Company base case PFS curves

Response rates

Response rates are used to condition costs within the model, and to condition quality of life values in a scenario analysis.

The company derives peak response rates from the RESONATE trial for ibrutinib and ofatumumab. Response rates for physician choice are taken from Osterborg et al[36] for idelalisib plus rituximab from Jones et al[48] and for bendamustine plus rituximab from Fischer et al.[47]

Table 35 Response rates: all patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
Complete response	6%	0%	1%	0%	4%
Partial response	84%	10%	25%	85%	29%
Stable disease	10%	90%	75%	15%	67%

Reported response rates for physician choice and idelalisib plus rituximab appear to have been assumed to be only partial responses with there being no peak response of complete response for these treatments.

Response rates specific to 17p depleted patients for ibrutinib and ofatumumab were not derived from RESONATE but were rather assumed to be the same as the all patient data. Due to a lack of data the response rates for 17p depleted patients for the other comparators were assumed to be the same as the all patient data.

Serious adverse event rates

The company model derives the following SAE rates from the same clinical sources as above. Where none were reported in a trial the rate is assumed to be zero.

Table 36 Company model serious adverse event rates

	Anaemia	Diarrhoea	Pneum.	Hypertens.	Neutropen.	Thromb.enia	Sepsis
Ibrutinib	5.6%	4.6%	10.8%	6.2%	18.5%	5.6%	1.5%
Phys Chce	9.3%	NR	18.6%	NR	9.3%	NR	14.0%
Ofat.	7.3%	1.6%	5.8%	0.5%	13.6%	4.2%	1.0%
Idel + R	12.0%	20.2%	12.7%	NR	34.1%	13.3%	NR
Bend + R	3.7%	NR	NR	NR	8.2%	6.5%	NR

These rates are applied only once within the modelling and it is assumed that there are no further ongoing serious adverse events during the subsequent period of ongoing treatment for either ibrutinib or for idelalisib plus rituximab. Figure 24 of the submission provides support for this assumption.

Idelalisib plus rituximab is estimated to have a somewhat worse adverse event profile compared to ibrutinib, while that for bendamustine plus rituximab is slightly better.

Second line treatment

Based upon the ofatumumab arm of the RESONATE trial it is assumed that 42% of those progressing go on to receive 2nd line treatment, with 50% of these patients receiving R-HDMP and 50% receiving HDMP. This only affects costs and there are no quality of life impacts from being on 2nd line treatment. The intention of the model is that the proportion remaining on treatment is conditioned by a PPS PFS curve. The company applies a Weibull curve for this estimated from the rituximab arm of the Furman et al trial[31] of idelalisib plus rituximab against rituximab.

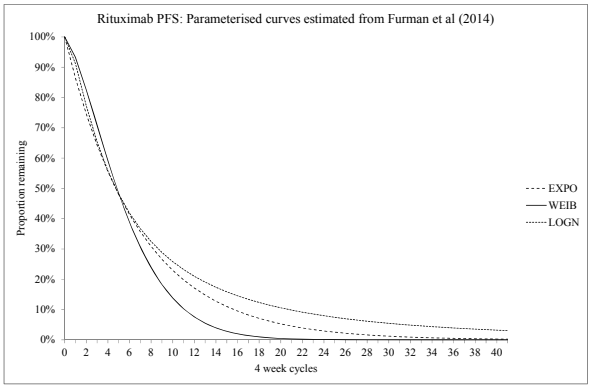


Figure 29 PPS Tx PFS curve

Note that in the above the first cycle does not correspond to the first cycle of the model but to the point at which patients progress and become eligible for 2nd line treatment; i.e. the curve is applied to incident patients in each cycle of the model.

5.2.7 Health related quality of life

EQ-5D data was collected during the RESONATE trial.

Table 37 RESONATE EQ-5D mean QoL by time point

	All patients				17p depleted patients			
	Ibrutinib		Ofatumumab		Ibrutinib		Ofatumumab	
	EQ-5D	N	EQ-5D	N	EQ-5D	N	EQ-5D	N
Baseline	[redacted]							
Week 4								
Week 8								
Week 12								
Week 16								
Week 20								
Week 24								
Week 36								
Week 48								
Week 60								

The above data for all patients suggests a mean baseline value of [redacted]. Post baseline means are [redacted] for ibrutinib and [redacted] for ofatumumab, and [redacted] when averaged across both arms. For the 17p depleted subgroup the mean baseline value is somewhat

less at [redacted]. The post baseline mean values are also less at [redacted] for ibrutinib and [redacted] for ofatumumab, and [redacted] when averaged across the arms.

Given the apparent improvement in quality of life while on treatment compared to baseline, progression free survival was assumed to have a quality of life value of [redacted].

A repeated measures regression analysis of the RESONATE EQ-5D data is presented in Appendix 12 of the submission but is not used for the modelling.

The quality of life value for those progressing is assumed to be the baseline mean EQ-5D [redacted] value, taken to be the value for stable disease, with this being further reduced by 12.8% as drawn from Beusterein et al,[79] resulting in a quality of life value for post progression survival while on 2nd line treatment and BSC of [redacted].

An 11.5% reduction in quality of life due to anaemia is also drawn from Beusterein et al.[79] Reductions of 24.3%, 16.1% and 25.6% for neutropenia, thrombocytopenia and sepsis are drawn from Tolley et al.[80] These reductions are applied to the RESONATE mean baseline quality of life value of [redacted]. Due to a lack of other data the absolute quality of life decrements for diarrhoea, pneumonia and hypertension are assumed to be equal to that of the worst of the other adverse events.

When coupled with the treatment specific adverse event rates and an assumed SAE duration of 14 days this results in total losses due to SAEs of:

- [redacted] QALYs for ibrutinib;
- [redacted] QALYs for physician choice;
- [redacted] QALYs for ofatumumab;
- [redacted] QALYs for idelalisib plus rituximab; and
- [redacted] QALYs for bendamustine plus rituximab.

5.2.8 Resources and costs

1st line dosing and administration

The weekly dosing and infusion visits for the first line treatments are assumed to be as below.

Table 38 1st line drug dosing and infusion visit schedules: single regime comparators

Regime	Dose	Infusions visit
Ibrutinib	420mg per day ongoing	None
Ofatumumab	1 dose of 300mg, then 1 doses each week, 7 times, of 2,000mg, then 1doses every 4 weeks, 4 times, of 2,000mg	1 per ofatumumab dose
Idelalisib + Rituximab	300mg per day ongoing + 1 dose of 375mg/m^2, then 1 dose every 2 weeks, 4 times, of 500mg/m^2, then 1 dose every 4 weeks, 3 times, of 500mg/m^2	None + 1 per rituximab dose
Bendamustine + Rituximab	2 doses per week every 4 weeks, 6 times, of 70mg/m^2 1 dose of 375mg/m^2, then 1 dose every 4 weeks, 5 times, of 500mg/m^2	1 per bendamustine dose 1 for the 1st dose of rituximab

Treatment with both ibrutinib and idelalisib is ongoing for those remaining in PFS, with an annual ongoing cost at list prices and 100% dosing of £55,955 for ibrutinib and £37,896 for idelalisib.

Physician choice is assumed to be:

- [redacted]: bendamustine plus rituximab
- [redacted]: R-HDMP
- [redacted] chlorambucil
- [redacted] FCR
- [redacted] R-CHOP

The dosing and infusion visit schedule for bendamustine plus rituximab is as per the table above. The dosing and infusion visit schedule for the other regimes is as below.

Table 39 1st line drug dosing and infusion visit schedules: physician choice

Regime	Dose	Infusions visit
FCR		
Fludarabine + Cyclophos. + Rituximab	25mg/m^2 days 2-4 every 4 weeks for 6 cycles 250mg/m^2 days 1-3 every 4 weeks for 6 cycles 375mg/m^2 day 0 then 500mg/m2 day 1 every 4 weeks for 6 cycles	4 in total each treatment week
R-HDMP		
Methpred. + Rituximab	1g/m^2 days 1-5 every 3 weeks for 6 cycles 375mg/m^2 day 0 then 500mg/m2 day 1 every 3 weeks for 6 cycles	5 in total each treatment week
R-CHOP		
Cyclophos. + Doxorubicin + Vincristine + Prednisolone + Rituximab	750mg/m^2 on day 1 every 3 weeks for 8 cycles 50mg/m^2 on day 1 every 3 weeks for 8 cycles 1.4mg/m^2 on day 1 every 3 weeks for 8 cycles 40mg/m^2 days 1-5 every 3 weeks for 8 cycles 375mg/m^2 day 0 then 500mg/m2 day 1 every 3 weeks for 8 cycles	5 in total each treatment week
Chlorambucil		
Chlorambucil	12mg/m^2 days 1-7 every 4 weeks for 3 cycles	None

All 1st line treatments are assumed to stop at progression.

Drug unit costs were sourced from the BNF with the base case allowing for vial drug wastage. All infusions were costed using the 2013-14 reference cost for *Chemotherapy Outpatient: SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance* at a cost of £266.

Proportion of PFS patients receiving treatment

The direct drug and administration costs of the 1st line treatments are major determinants of total costs within the modelling. These are driven by unit costs, the proportion of patients in PFS and the proportion of patients in PFS that are assumed to receive treatment.

For the ibrutinib arm for the first 24 cycles of the model the proportion eligible for treatment is assumed to be the minimum of:

- the value of the time to treatment discontinuation Kaplan Meier curve
- the value of the parameterised PFS curve

After the first 24 cycles of the model for which there is no TTD Kaplan Meier data within the model, the value of the parameterised PFS curve is used. Taking the minimum of the TTD Kaplan Meier and the parameterised PFS curve reduces costs in the ibrutinib arm.

The RESONATE trial yields data on time to treatment discontinuation (TTD) for both ibrutinib and for ofatumumab as outlined below for all patients.

For ibrutinib the proportion being treated and incurring drug costs is whichever is the lesser of the Kaplan Meier TTD curve and the PFS curve. As a consequence, the proportion of ibrutinib patients on treatment initially follows the Kaplan Meier TTD up to the 14th cycle of the model. After this point the Kaplan Meier TTD curve rises above the PFS curve so the company uses the lower proportion given by the PFS curve.

For ofatumumab the Kaplan Meier TTD curve is ignored, despite always being below the PFS curve. The company uses the higher proportion implied by the PFS curve throughout during the first seven cycles of the model when ofatumumab is administered.

The situation is similar for the 17p depleted subgroup. The proportion of ibrutinib patients on treatment initially follows the Kaplan Meier TTD up to the 12th cycle of the model. After this point the Kaplan Meier TTD curve rises above the PFS curve and as a consequence the company uses the lower proportion given by the PFS curve thereafter. This is with the exception of the 21st cycle when the Kaplan Meier TTD curve again briefly dips below the PFS curve, so at this point the company chooses to use the TTD curve.

For ofatumumab the Kaplan Meier TTD curve is again ignored, despite always being below the PFS curve. The company uses the higher proportion implied by the PFS curve throughout during the first seven cycles of the model when ofatumumab is administered.

For the other comparators no TTD Kaplan Meier curves are considered. The values of the parameterised PFS curve are used throughout.

The proportions of PFS patients eligible for treatment are further conditioned by treatment specific estimates of the percentages dose utilisation to reflect dose reductions and treatment holidays. It is unclear to the ERG whether for ibrutinib there is some double counting here, given the application of te ibrutinib TTD curves.

These drug utilisation proportions were estimated from the RESONATE trial for ibrutinib, 94.8%, and for ofatumumab, 95.2%. The corresponding proportions for both physician choice and idelalisib were assumed to be the same as ofatumumab. The 97.0% value for bendamustine was calculated from Fischer et al[47] which the company report as suggesting 29.5% of those receiving bendamustine have a dose reduction of at least 10% and 30.8% of those receiving rituximab have a dose reduction of at least 10%.

For the ibrutinib arm the company model applies the 94.8% proportion twice to arrive at a proportion of only 89.9% of PFS patients receiving ibrutinib, so reducing the ibrutinib drug costs by around a further 5%. For the other comparators the company model does not apply these proportions twice.

The company model does not apply these proportions when calculating the drug administration costs. Only ibrutinib is associated with zero drug administration costs. The other comparators are all associated with drug administration costs. The application of these proportions within the modelling to administration costs would reduce the costs of the comparators but not the cost of ibrutinib.

For the ibrutinib arm the company model applies half cycle correction to the proportion receiving treatment. Discounting of this proportion is also applied from the first cycle that ibrutinib drug costs are modelled as occurring. Rather oddly the ibrutinib administration costs calculation in the column immediately to the right of the column containing the ibrutinib drug costs calculation correctly refers to the PFS curve without half cycle correction. But since administration costs are zero in the ibrutinib arm applying half cycle correction to them would not have further reduce the ibrutinib treatment and administration costs.

For the drug costs of the comparators the company model does not apply half cycle correction. Discounting is also not applied from the first cycle that comparator drug costs are modelled as occurring.

The selective application of half cycle correction and discounting to the ibrutinib drug costs but not to the comparator drug costs or to the ibrutinib administration costs strongly suggests that the half cycle correction to the ibrutinib drug costs was a later model revision by the company.

The half cycle correction and discounting reduces the treatment costs in the ibrutinib arm. For the comparators there are no cost reductions through the application of half cycle correction and discounting.

Routine follow-up costs

For those in progression free survival the routine follow-up resource use is differentiated by patients' responses. For those who have progressed the routine follow-up resource use is differentiated by whether patients are are receiving a 2nd line treatment or are receiving BSC. Resource use estimates are drawn from a company expert survey.

Table 40 Routine annual follow-up resource use: tests

	FBC	**LDH**	**X-ray**	**Lymph. Count**	**Bone marrow exam**	**Biopsy**	
Annual resource use							
Complete response	2	2	..	3.5	..	..	
Partial response	4	2.26	1	7	1	..	
Stable disease	4	2	2	3.5	1	2	
SubTx	4	2	2	3.2	..	2	
Post-progression	4	..	..	..	..	..	
Unit costs	£3	£1	£30	£3	£338	£3,104	
Annual cost							Total
Complete response	£6	£2	£0	£11	£0	£0	£19
Partial response	£12	£3	£30	£21	£338	£0	£404
Stable disease	£12	£2	£59	£11	£338	£6,207	£6,630
PPS 2nd line Tx	£12	£2	£59	£10	£0	£6,207	£6,291

Post-progression	£12	£0	£0	£0	£0	£0	£12

The main determinant of the total annual costs is biopsy. It is assumed that these are only required for those in stable disease and for those receiving post progression 2nd line treatment who each require an ongoing two biopsies per year at a cost of £6,207.

Table 41 Routine annual follow-up resource use: visits and transfusions

	Haematol. OP	IP stay	Nurse home visit	Full blood transf.	Platelet transf.	
Annual resource use						
Complete response	2.26	0.66	1.5			
Partial response	3	2	2.64	1	1	
Stable disease	4.5	2	3.18	2		
SubTx	4	2	2	2		
Post-progression	4.9	1	4	2		
Unit costs	£156	£1,715	£50	£287	£287	
Annual cost						Total
Complete response	£353	£1,132	£75			£1,561
Partial response	£469	£3,430	£132	£287	£287	£4,605
Stable disease	£704	£3,430	£159	£574		£4,867
SubTx	£626	£3,430	£100	£574		£4,730
Post-progression	£766	£1,715	£200	£574		£3,255

For those who are progression free the main determinant of the visit and transfusion costs is the rate of hospital inpatient stays. For those whose in complete response it is assumed that only two thirds require an inpatient stay on average, whereas other patients are assumed to require two inpatient stays. But outpatient visits to haematology and nurse home visits also contribute to this differentiation.

For those in progression free survival these resource use estimates are differentiated by treatment by conditioning the resource use by response status by the company estimates of response rates for each treatment.

Table 42 Company model routine follow up annual costs by treatment

	Cost	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
Complete response	£1,579	6%	0%	1%	0%	4%
Partial response	£5,009	84%	10%	25%	85%	29%
Stable disease	£11,497	10%	90%	75%	15%	67%
Mean annual cost		£5,426	£10,840	£9,858	£5,986	£9,228

Ibrutinib is estimated to have half the routine follow up costs of physician choice due to the company estimating a much lower proportion of patients experiencing a

response of only stable disease. These mean annual costs are assumed to apply for the entire period that a patient remains on a given treatment.

SAE costs

Serious adverse event costs were derived by averaging a variety of non-elective inpatient reference costs with the average unit costs being as below.

Table 43 Adverse event unit costs

	Cost
Anaemia	£3,042
Diarrhoea	£2,153
Pneumonia	£2,733
Hypertension	£1,444
Neutropenia	£2,386
Thrombocytopenia	£2,192
Sepsis	£2,733

When coupled with the adverse event rates this led to one of costs for SAEs of:

- £1,259 QALYs for ibrutinib;
- £1,396 QALYs for physician choice;
- £866 QALYs for ofatumumab;
- £2,252 QALYs for idelalisib plus rituximab; and
- £451 QALYs for bendamustine plus rituximab.

Terminal care costs

Those who are modelled as dying within the 20 year time horizon of the model have terminal care costs of £7,360 applied as drawn from Round et al[81] and uprated for inflation.

5.2.9 Cost effectiveness results

Company base case results

The company deterministic base case results are as below. All quantities are discounted at 3.5% with the exception of life years which are presented as undiscounted quantities.

Table 44 Company deterministic modelling results: all patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
PFS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin. cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	..	£149,589	£120,487	£86,718	£151,595
Total undisc. LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc. LY	..	5.783	4.693	3.561	6.350
net PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALYs	..	3.289	2.647	1.934	3.608
ICER	..	£45,486	£45,525	£44,836	£42,016

Examining the life years first, ibrutinib is estimated to have a total undiscounted survival of [redacted]. The overall survival estimates for the comparator treatments are very much lower and more heavily weighted towards post progression survival. Despite this a great deal of the gain in survival from ibrutinib is modelled as occurring post progression, and the majority of the survival gains for the comparisons with physician choice, idelalisib plus rituximab and bendamustine plus rituximab occur in the post progression health state when all patients have ceased their 1st line.

Overall survival gains of [redacted] life years, [redacted] life years, [redacted] life years and [redacted] life years are anticipated compared to physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab. Ibrutinib is anticipated to more than

triple life expectancy compared to physician choice, more than double it compared to ofatumumab and more than quadruple it compared to bendamustine plus rituximab. The overall survival gain estimated for ibrutinib relative to idelalisib plus rituximab is to not quite double it, but is still a major increase of around a three quarters increase in life expectancy.

This increase in overall survival is reflected in the discounted total QALYs of [redacted] for ibrutinib. This is more than triple the total for physician choice of [redacted] QALYs, more than double the total for ofatumumab of [redacted] QALYs and more than four times the total for bendamustine plus rituximab of [redacted] QALYs. Only idelalisib plus rituximab with a total of [redacted] QALYs is estimated to yield anything even approaching that of ibrutinib, but this is still only 60% of the ibrutinib total.

Costs are very much higher in the ibrutinib arm, mainly driven by the costs of ibrutinib itself. Net costs of £150k per patient compared to physician choice, £120k per patient compared to ofatumumab and £152k per patient compared to bendamustine plus rituximab result in cost effectiveness estimates of £45,486 per QALY, £45,525 per QALY and £42,016 per QALY respectively.

For the comparison with idelalisib plus rituximab, despite idelalisib plus rituximab yielding more QALYs than the other comparators there are corresponding increases in costs due to the costs of idelalisib and rituximab. As a consequence, the costs effectiveness estimate for ibrutinib compared to idelalisib plus rituximab is similar to those of the other comparators at £44,836 per QALY.

The company probabilistic modelling results in the following estimates.

Table 45 Company probabilistic modelling mean estimates: all patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER vs comparator		£47,200	£47,657	£47,754	£43,559

The mean probabilistic cost effectiveness estimates are all slightly worse than those of the deterministic modelling. The CEACs and the probabilities of ibrutinib being cost effective at various willingness to pay values are presented below.

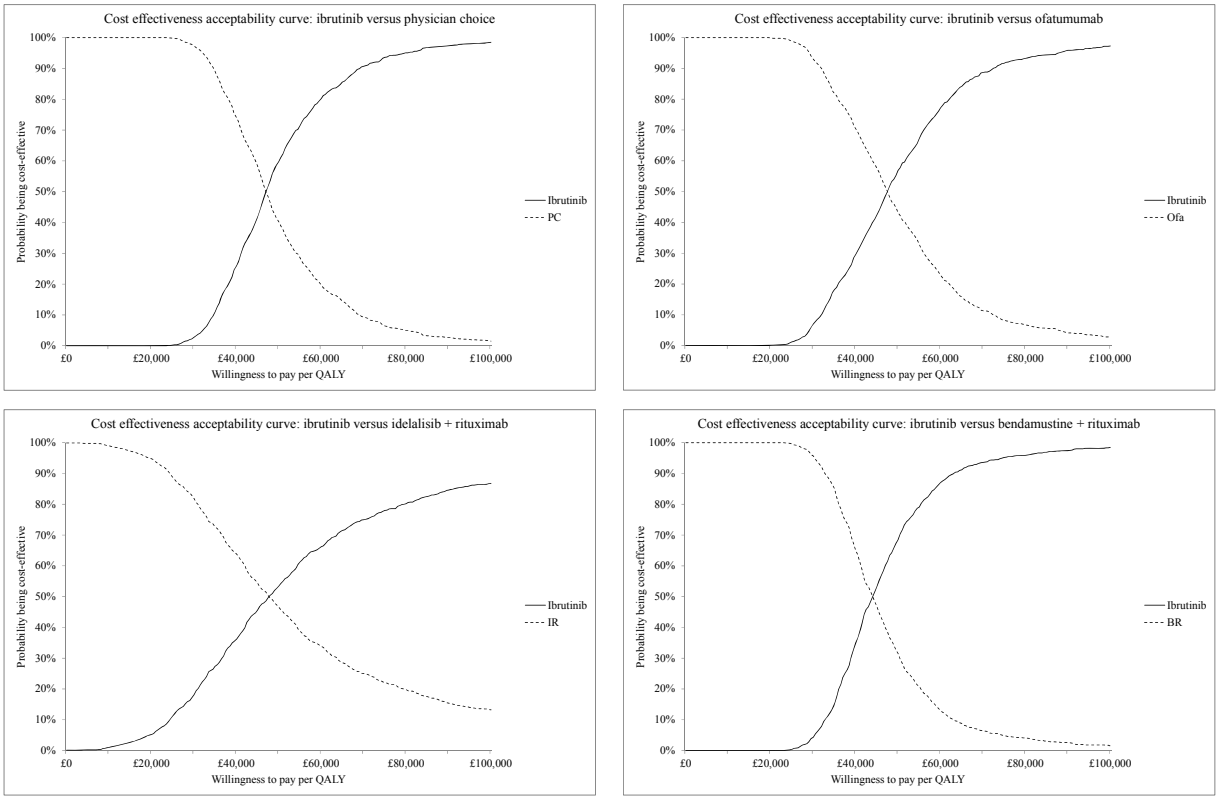


Figure 32 Company pairwise CEACs: all patients

Table 46 Pairwise probabilities of ibrutinib being cost effective: all patients

WTP per QALY	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
£0	0%	0%	0%	0%
£10,000	0%	0%	1%	0%
£20,000	0%	0%	5%	0%
£30,000	3%	7%	18%	4%
£50,000	60%	57%	53%	69%
£100,000	99%	97%	87%	99%

The probabilistic modelling results can also be combined into a single analysis that encompasses all the comparators, as undertaken by the ERG and presented below. Due to physician choice being a combination of treatments, including bendamustine

plus rituximab, it may be better to exclude it from this analysis as per the right hand diagram of Figure 33 below[b].

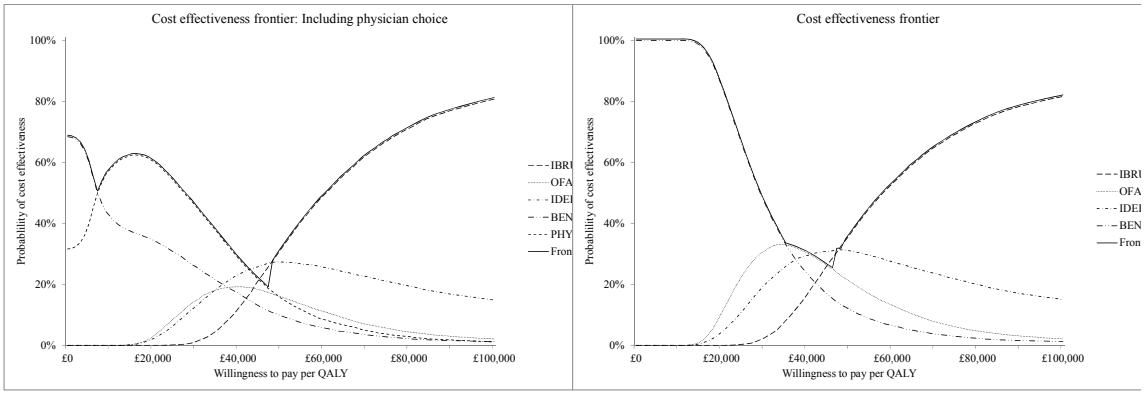


Figure 33 Company model base case CEAFs: all patients

If physician choice is included, the CEAF[c] suggests that at willingness to pay values up to around £8k per QALY bendamustine plus rituximab has best expected cost effectiveness. For willingness to pay values between around £8k per QALY and around £48k per QALY physician choice has the best expected cost effectiveness. For willingness to pay values above around £48k per QALY ibrutinib has the best expected cost effectiveness.

If physician choice is excluded, the CEAF suggests that at willingness to pay values of up to around £34k per QALY bendamustine plus rituximab has the best expected cost effectiveness. For willingness to pay values between around £34k per QALY and around £48k per QALY ofatumumab is estimated to have the best cost effectiveness estimate, though the picture is quite mixed within this range between ofatumumab and idelalisib plus rituximab. For willingness to pay values above around £48k per QALY ibrutinib has the best expected cost effectiveness.

5.2.10 Sensitivity analyses

The company submission presents a range of univariate sensitivity analyses for the comparison with physician choice, and states that the impacts upon the cost

[b] In restrospect, given the sources of the clinical effectiveness data it might have been better for the ERG to have excluded bendamustine plus rituximab and to have retained physician choice.
[c] Note that the CEAF has throughout had an arbitrary 0.5% added to the correct value in order to ease the identification of the treatment curve it corresponds to; i.e. the depicted frontier lies 0.5% above the treatment curve that corresponds to the true frontier.

effectiveness estimates for ibrutinib versus the other comparators were similar. The full set of values is presented below.

Table 47 Company model deterministic sensitivity analyses: all patients

	Parameter values		ICERs			
	Base	**SA**	**PhysChce**	**Ofat**	**Idel+R**	**Bend+R**
Base case	..	..	£45,486	£45,525	£44,836	£42,016
Time horizon	20 years	10 years	£57,630	£60,393	£62,832	£51,918
		30 years	£44,761	£44,243	£42,840	£41,577
Benefits discount	3.50%	1.5%	£39,568	£39,186	£38,109	£36,750
Costs discount	3.50%	1.5%	£48,659	£49,274	£49,021	£44,955
PFS prob. Death		0.46%	£45,506	£45,545	£44,853	£42,033
		0.68%	£45,466	£45,504	£44,818	£41,999
% subs. treatment	42%	34%	£45,625	£45,626	£44,894	£42,126
		50%	£45,347	£45,425	£44,780	£41,906
Ibrutinib dosing	95%	90%	£41,052	£40,015	£37,295	£37,974
		100%	£50,550	£51,818	£53,446	£46,632
Comparator dosing	95% (97% BR)	100%	£45,349	£44,842	£43,080	£41,925
MRU during PFS	Various by Tx	-20%	£44,733	£44,774	£44,098	£41,345
		+20%	£46,240	£46,277	£45,574	£42,687
MRU during PPS Tx	£845	-20%	£45,156	£45,265	£44,474	£41,607
		+20%	£45,817	£45,786	£45,197	£42,425
MRU during BSC	£250	-20%	£45,118	£45,224	£44,439	£41,574
		+20%	£45,855	£45,826	£45,232	£42,458
Terminal care	£7,360	-20%	£45,578	£45,621	£44,940	£42,106
		+20%	£45,395	£45,429	£44,731	£41,926
Base and PFS QoL	0.762, 0.799	Lower 95% CI	£46,368	£46,347	£45,730	£42,893
		Upper 95% CI	£44,637	£44,732	£43,975	£41,175
Prog. QoL decrement	-0.098	-20%	£45,006	£45,135	£44,324	£41,480
		+20%	£45,977	£45,922	£45,359	£42,566
AE days per event	14	0	£45,486	£45,523	£44,840	£42,014

Results are quite sensitive to the time horizon that is assumed. In the ibrutinib arm, around [redacted] are modelled as surviving at 10 years, 20 years and 30 years respectively.

Results are also reasonably sensitive to the proportion of PFS ibrutinib patients who are assumed to receive it. Results show less sensitivity to the proportion of PFS patients in the comparator arms who are assumed to receive treatment.

The other sensitivity analyses are less dramatic, though it should be borne in mind that the sensitivity analyses that vary the medical resource use during progression free survival do so equally for all comparators.

A variety of scenarios were also considered:

- Scenario01: For the costs during progression free survival apply the costs of stable disease across all treatments.
- Scenario02: For the costs during progression free survival apply the ibrutinib cost across all treatments.
- Scenario03: Apply the exponential curve for ibrutinib progression free survival.
- Scenario04: Apply the Weibull curve for ibrutinib overall survival
- Scenario05: Restrict the overall survival and progression free survival benefits from ibrutinib in terms of lower hazards toonly six years[d].
- Scenario06: Restrict the overall survival and progression free survival benefits from ibrutinib to only seven years.
- Scenario07: Base the indirect treatment comparison upon Swedish registry data rather than Osterborg et al (2014) for the comparison with physician choice and from MAIC with HELIOS for the comparison with bendamustine plus rituximab.
- Scenario08: Time to treatment discontinuation for ibrutinib based solely upon the PFS curve.
- Scenario09: A mean patient BSA of 1.79m^2 as per the UK average rather than the 1.90m^2 of RESONATE.
- Scenario10: Assume vial sharing.
- Scenario11: Apply treatment specific PFS quality of life values based upon response rates of [redacted] for ibrutinib, [redacted] for physician choice, [redacted] for

[d] The ERG has based this interpretation upon an examination of the markov worksheets of the model and the only apparent restriction of clinical benefits being to cells J10:J410

ofatumumab, [redacted] for idelalisib plus rituximab and [redacted] for bendamustine plus rituximab[e].

- Scenario 12: Exclude SAEs with less than 5% incidence.

Table 48 Company model deterministic scenario analyses: all patients

		ICERs			
	Scenario description	**PhysChce**	**Ofat**	**Idel+R**	**Bend+R**
Base case	..	£45,486	£45,525	£44,836	£42,016
Scenario 01	All PFS costs = SD costs	£50,873	£51,920	£49,877	£46,719
Scenario 02	All PFS costs = Ibrutinib PFS costs	£46,039	£46,559	£45,266	£42,465
Scenario 03	Ibrutinib PFS exponential	£62,296	£65,575	£67,635	£57,552
Scenario 04	Ibrutinib OS Weibull	£46,280	£45,998	£45,038	£42,957
Scenario 05	Ibrutinib OS benefit 6 years	£62,128	£60,174	£60,050	£57,831
Scenario 06	Ibrutinib OS benefit 7 years	£59,128	£57,787	£57,183	£54,986
Scenario 07	Revised ITCs	£54,330	..	..	£68,008
Scenario 08	Ibrutinib TTD based upon PFS curve	£45,761	£45,867	£45,303	£42,267
Scenario 09	Mean patient BSA 1.79m^2	£45,737	£45,542	£45,494	£42,242
Scenario 10	Vials sharing	£45,772	£45,536	£45,198	£42,261
Scenario 11	Tx specific PFS QoL values	£44,523	£44,284	£43,900	£41,250
Scenario 12	Only SAEs with 5%+ incidence	£45,443	£45,533	£44,763	£42,008

With the exception of scenario 11, the company explored scenarios all worsen the cost effectiveness of ibrutinib.

Equalising the costs of progression free survival across treatments worsens the cost effectiveness estimates due to ibrutinib having previously benefitted from an assumption of lower costs due to a higher response rate. Equalising these costs at the value for stable disease has a larger effect due to this cost being higher and applying for longer in the ibrutinib arm than in the comparator arms.

Applying an exponential curve rather than the Weibull for ibrutinib progression free survival significantly worsens the cost effectiveness estimates. Changing the overall survival projection after the first three year's log-normal projection to be a Weibull curve rather than an exponential curve has little impact.

[e] These values have been calculated by the ERG and have not been cross checked with the company at clarification.

Restricting the overall survival and progression free survival benefits to around double that of the duration of RESONATE somewhat worsens the cost effectiveness estimates.

The alternative ITCs also significantly worsen the cost effectiveness estimates for ibrutinib compared to physician choice and bendamustine plus rituximab.
The other company scenario analyses do not particularly affect the ICERs.

The company also submitted an analysis for the 17p depleted subgroup with the following results.

Table 49 Company deterministic modelling results: 17p depleted patients

	Ibrutinib	**Ofatumumab**
PFS costs	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]
Admin. cost	[redacted]	[redacted]
Follow up	[redacted]	[redacted]
AE cost	[redacted]	[redacted]
PPS costs	[redacted]	[redacted]
SubTx Tx cost	[redacted]	[redacted]
BSC cost	[redacted]	[redacted]
SubTx Follow up	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]
Net cost		£102,596
Total undisc. LY	[redacted]	[redacted]
PFS LY	[redacted]	[redacted]
PPS LY	[redacted]	[redacted]
Net undisc. LY	..	4.592
net PFS LY	[redacted]	[redacted]
net PPS LY	[redacted]	[redacted]
PFS QALYs	[redacted]	[redacted]
PPS QALYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Net QALYs	..	2.690
ICER		£38,145

5.2.11 Model validation and face validity check

Model validation: OS curves

The company model suggests that by 20 years a little over [redacted] of those in the ibrutinib arm would still survive, but only around [redacted] in the idelalisib plus rituximab arm and effectively none in the other comparator arms. ERG expert opinion does not find the estimate of around [redacted] for ibrutinib unreasonable to expect, but it does find the [redacted] estimate for idelalisib plus rituximab unreasonably low in the light of this. ERG expert opinion is that few would survive with the other comparators at 20 years.

The company base case suggests mean undiscounted overall survival over the 20 year time horizon of the model of [redacted] years, [redacted] years, [redacted] years, [redacted] years and [redacted] years for ibrutinib, physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab.

ERG expert opinion is that the overall survival estimate for idelalisib plus rituximab is too low when compared with the estimate for ibrutinib, and that it is questionable whether ibrutinib would close to double life expectancy compared to idelalisib plus rituximab.

ERG expert opinion is also that bendamustine plus rituximab being estimated to have a much lower life expectancy than ofatumumab is questionable, particularly for the majority of patients who do not have 17p depletion. Rather than bendamustine plus rituximab having half the life expectancy of ofatumumab it would be more reasonable to expect them to have similar life expectancies, certainly for those without 17p depletion.

Model validation: PFS curves

The cost effectiveness results are sensitive to whether the Weibull or the exponential form is used for the PFS curve for ibrutinib. This is because the costs of ibrutinib are determined by the PFS curve and the costs of ibrutinib form the great majority of the total costs in the ibrutinib arm.

The company suggests that the goodness of fit statistics for the ibrutinib PFS curves are generally similar. As a consequence, the judgement about which if either curve is

reasonable to apply comes down to a visual inspection of the curves and expert opinion. The company notes that the exponential suggests a much higher proportion of patients remaining in PFS, deems this to be clinically implausible and so prefers the ibrutinib Weibull PFS curve.

In the opinion of the ERG, the plausibility of the PFS curves can only be decided when viewed alongside the associated OS curve. The correct OS curve first needs to be decided upon. The proportion surviving will then help inform the clinical plausibility of the PFS curve.

As previously noted, the number at risk drops off considerably between the 18th and the 20th 4 week cycle, and by the 20th cycle there are few patients that remain at risk. The Weibull and the exponential curves for OS are virtually indistinguishable up to the 20th cycle, and much the same can be said of the PFS curves. It is only during the period of extrapolation that the Weibull and the exponential curves begin to diverge. This divergence becomes quite dramatic for the PFS curves for the extrapolation period of the model.

The above figure can be made more explicit below by tabulating the values for the various curves.

Table 50 Ibrutinib: OS and PFS: all patients

		OS			PFS	
Cycle	**Years**	**Exponential**	**Weibull**	**Model**	**Exponential**	**Weibull**
20	1.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	3.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	4.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	7.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	9.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
261	20.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

While arbitrary, for illustrative purposes the 100th cycle can be selected which corresponds to around 7.7 years from baseline and so is when those surviving have reached 75 years of age. [redacted] of ibrutinib CLL patients are modelled as surviving to be 75 years of age. The ibrutinib OS curve further suggests that over the remaining 12.3 years of the 20 year time horizon the average additional survival among these patients is [redacted] years. This compares to 9.8 years additional survival for the general public based upon the UK life tables of the model.

The ibrutinib Weibull PFS curve suggests that only [redacted] of the original patient cohort will remain progression free at the 100th cycle. In other words, among those still surviving age 75 the Weibull PFS curve suggests that only [redacted] will still be progression free and that [redacted] will have progressed at this point.

The ibrutinib exponential PFS curve suggests that [redacted] of the original patient cohort will remain progression free at the 100th cycle. In other words, among those still surviving age 75 the exponential PFS curve suggests that [redacted] will still be progression free and that [redacted] will have progressed at this point.

Given the [redacted] who are modelled as surviving to age 75 with these patients being modelled as having on average another [redacted] years survival over the next 12.3 years, to the ERG the question seems to be what PFS proportion would be required to achieve this. The ibrutinib Weibull PFS curve suggests a proportion of [redacted], while the ibrutinib exponential PFS curve suggests a proportion of [redacted]. One or the other may be

preferred, or neither may be plausible and it may be felt more reasonable to extrapolate PFS as a proportion of the remaining OS.

The exponential and Weibull PFS curves derived from RESONATE can be presented alongside Kaplan Meier data for trials 1102 and 1103[f] as below as a further means of model validation. Due to 1103 being an extension of 1102 the ERG assumption is that the 1103 baseline is the same as the 1102 baseline, rather than being the end of the 1102 trial.

Due to longer follow up, despite the original sample size of 1103 being only 67 patients compared to the 85 of 1102, the numbers of patients at risk crosses over at around the 14th 4 week cycle. There appears to be the suggestion in the above that the Kaplan Meier curves of 1102 and 1103 provide more support for the exponential than for the Weibull and that perhaps even the exponential might be an underestimate. It should be noted that towards the end of the 1103 Kaplan Meier curve the absolute number of patients remaining at risk becomes quite small. But the above curve may support the exponential over the Weibull.

Turning to the 17p depleted subgroup much the same presentation can be made.

[f] PFS for patients given 420 mg

Due to the ibrutinib OS exponential curve being used throughout for the 17p depleted subgroup, the OS curve of the model overlies the ibrutinib OS exponential curve. The values for the various curves are as below.

Table 51 Ibrutinib: OS and PFS: 17p depleted patients

		OS			PFS	
Cycle	**Years**	**Exponential**	**Weibull**	**Model**	**Exponential**	**Weibull**
20	1.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	3.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	4.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	7.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	9.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
261	20.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the 17p depleted subgroup, the OS curve suggests that [redacted] still survive after 7.7 years, aged 75. The ibrutinib OS curve further suggests that over the remaining 12.3 years of the model time horizon the average additional life expectancy of these patients is [redacted] years.

The ibrutinib Weibull PFS curve suggests that only [redacted] of the original patient cohort will remain progression free at the 100th cycle. In other words, among those still surviving age 75 the Weibull PFS curve suggests that only [redacted] will still be progression free while [redacted] will have progressed.

The ibrutinib exponential PFS curve suggests that [redacted] of the original patient cohort will remain progression free at the 100th cycle. In other words, among those still surviving age 75 the exponential PFS curve suggests that [redacted] will still be progression free while [redacted] will have progressed.

Given the [redacted] who are modelled as surviving to age 75 with these patients being modelled as having on average another [redacted] years survival over the next 12.3 years, as for the all patients modelling the question seems to be what PFS proportion would be reasonable to achieve this. The ibrutinib Weibull PFS curve suggests a proportion of [redacted], while the ibrutinib exponential PFS curve suggests a proportion of [redacted].

ERG expert opinion is that given the OS curves the more plausible of the two parameterised PFS curves is the exponential. The Weibull is seen as projecting too low a proportion of patients remaining in PFS for the OS curve to be credible.
The above figures are likely to be important to the Assessment Committee discussion about which PFS curve should be used. The ERG has cross-checked them but it is always possible that error has slipped in. The ERG urges the company to cross check these figures given their possible centrality to the discussion and the sensitivity of the cost effectiveness estimates to the choice of the ibrutinib PFS curve.

Model validation against cited studies
Osterborg et al[36] report a median investigator assessed PFS of 4.5 months and median overall survival of 14.5 months for physician choice. The model suggests medians of between [redacted] months for investigator assessed PFS and of between [redacted] months for overall survival. As a consequence the model appears to underestimate the PFS slightly, but to exaggerate the overall survival by quite a lot. If the overall survival hazard ratio is correct this may suggest that the ibrutinib overall survival curve is too optimistic, but it might also suggest that the overall survival hazard ratio is too pessimistic

Jones et al[48] report a median PFS of 16.3 months, though it is not clear whether this is IRC assessed or investigator assessed, and a median overall survival of 20.9 months for idelalisib plus ofatumumab. The model suggests medians of between [redacted]

months for PFS and of between [redacted] months for overall survival. The PFS medians are in line, but the model somewhat exaggerates the median overall survival for idelalisib plus rituximab if idelalisib plus ofatumumab is seen as a reasonable proxy. Again, if the overall survival hazard ratio is correct this may suggest that the ibrutinib overall survival curve is too optimistic, but it might also suggest that the overall survival hazard ratio is too pessimistic.

Fischer et al[47] report a median event free survival (EFS) of 14.7 months, though it is not clear whether this is IRC assessed or investigator assessed, and a median overall survival of around 33 months for bendamustine plus rituximab though it appears that very few patients remain at risk at this point. The model suggests medians of between [redacted] months for PFS and of between [redacted] months for overall survival. The model appears to somewhat underestimate the benefits of bendamustine plus rituximab.

It is not clear whether the overall survival curve for ibrutinib is too optimistic. Or if the company hazard ratios are only short term estimates with it being reasonable to anticipate a greater relative efficacy in the medium term compared to physician choice and compared to idelalisib plus rituximab. But the model validation against the median overall survivals for the comparators is poor. The model also appears to underestimate the benefits of bendamustine plus rituximab.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has attempted to rebuild the company model replicating all the company assumptions, and gets a good correspondence with the cost effectiveness estimates of the company model. For reasons that are unclear the ERG rebuild estimates for total QALYs are around 0.003 QALYs less than those of the company model. But this applies to all the comparators, and the ERG model rebuild ICERs are in line with those of the company model.

Table 52 ERG model rebuild compared to company base case: all patients

	ERG model rebuild			Company base case		
	Costs	QALYs	ICER vs.	Costs	QALYs	ICER vs.
Irbutinib	[redacted]	[redacted]		[redacted]	[redacted]	
Phys. Chce.	[redacted]	[redacted]	£45,493	[redacted]	[redacted]	£45,486
Ofatumumab	[redacted]	[redacted]	£45,546	[redacted]	[redacted]	£45,525
Idelalisib + R	[redacted]	[redacted]	£44,782	[redacted]	[redacted]	£44,836
Bend. + R	[redacted]	[redacted]	£42,042	[redacted]	[redacted]	£42,016

Table 53 ERG model rebuild compared to company base case: 17p patients

	ERG model rebuild			Company base case		
	Costs	QALYs	ICER vs.	Costs	QALYs	ICER vs.
Irbutinib	[redacted]	[redacted]		[redacted]	[redacted]	
Ofatumumab	[redacted]	[redacted]	£38,098	[redacted]	[redacted]	£38,145

5.3.2 Data inputs: correspondence between written submission and sources cited

Quality of life post progression

Beusterein et al study[79] was sponsored and co-authored by Napp Pharmaceutical, the manufacturer of duvelisib for relapsed/refractory CLL. This interviewed 93 members of the UK general public using the time trade-off (TTO) to estimate quality of life values for a number of health states associated with CLL.

The responses of four respondents were excluded due to them preferring at least one worse health states compared to a better health state. This appears to be error on the part of these respondents, but it should be borne in mind that there may be equal errors on the part of the other respondents akin to trembling hand error in standard gamble assessments. Excluding respondents for not understanding the questions and apparently illogical responses may bias the analysis. Other respondents with responses which are deemed logical may have had a similarly poor understanding of the questions.

The company summary of the Beusterein TTO quality of life values is incomplete as it chooses not to mention a quality of life value for 2nd line treatment of 0.71. This appears to be directly relevant to the health states of the company model structure so it

is surprising that the company chose to omit this value from its summary of Beusterein et al and from its modelling.

Table 54 Beusterein et al TTO quality of life values[79]

			Difference vs stable disease	
	Mean	**95% CI**	**Absolute**	**Relative**
Complete response	0.91	(0.88, 0.93)	0.13	16.7%
Partial response	0.84	(0.81, 0.87)	0.06	7.7%
Stable disease	0.78	(0.75, 0.82)	..	..
2nd line treatment	0.71	(0.68, 0.75)	-0.07	-9.0%
Progressive disease	0.68	(0.64, 0.72)	-0.10	-12.8%
SAE Anaemia	-0.09	(-0.12, -0.05)		
SAE Pyrexia	-0.11	(-0.14, -0.07)		
SAE Pneumonia	-0.20	(-0.23, -0.16)		

It would have been more reasonable of the company to have applied the 2nd line treatment quality of life decrement to the RESONATE baseline quality of life value for the post progression survival health state. But this has little impact upon the ICERs.

Barring the omission of the 2nd line therapy quality of life value of Beusterein et al, the company approach of applying the proportionate reduction in quality of life at progression seems reasonable. It may be more questionable to have assumed that quality of life does not decline further thereafter.

But since the Beusterein et al[79] quality of life values are from a single source it seems sensible to apply these, though whether these are more appropriate for the base case is less clear. Applying the Beusterein et al quality of life values[g] worsen the company base case ex PAS ICERs for ibrutinib relative to physician choice, ofatumumab, idelalisib and bendamustine from £45,486 per QALY, £45,525 per QALY, £44,836 per QALY and £42,016 per QALY to £45,814 per QALY, £46,003 per QALY, £45,097 per QALY and £42,168 per QALY respectively. The effects are relatively muted, only worsening the ICERs by between £152 per QALY and £478 per QALY.

[g] Implemented in the *Parameters* worksheet by setting cell F73=0.78 and cell F84=0.68.

Quality of life: idelalisib STA

The company submission for idelalisib in the same indication summarised the trial as collecting EQ-5D data at baseline, every 2 weeks until week 8, then every 4 weeks until week 24, then every 8 weeks until week 48 and then every 12 weeks until progression. Completion rates among those remaining progression free were reasonably high, typically above 80% and often above 90% with a total 1,667 observations. A generalised estimating equation (GEE) analysis yielded a post baseline quality of life for progression free survival with rituximab of 0.7475 and for idelalisib plus rituximab of 0.8127.

The ERG expressed some concerns about the imbalance at baseline, with the EQ-5D responses in the idelalisib plus rituximab arm being somewhat better than those in the rituximab arm, and questioned whether the GEE analysis would or could have sufficiently adjusted for this.

The idelalisib company submission also identified the Dretzke et al report[54] for the STA of rituximab for relapsed/refractory CLL from which it took the post progression quality of life value. The ERG preferred this source for all quality of life values due to it providing a single source for quality of life estimates rather than the company base case which drew quality of life estimates from disparate sources. The quality of life estimates were 0.8 for progression free survival and 0.6 for survival with progression, suggesting a lower quality of life for post progression survival than that used in the current submission. Tracing these back through the references eventually arrives at Hancock et al,[82] a West Midlands Health Technology Assessment Report for fludarabine for 1st line treatment of CLL. This estimated quality of life values from either EORTC-QLQ-C30 data or FACT-G data from 81 CLL patients as reported in Holzner et al 2001[83]. But in Holzner et al the current ERG has only been able to identify data relating to a pooled CLL group of patients, and nothing regarding subgroups that were pre-progression and post-progression. It appears that some elements of the quality of life values in the West Midlands fludarabine report may have been by assumption.

Following some corrections to the EQ-5D utility values by the company the assessment committee concluded that the values from the trial were suitable for the

progression free health state of the model. The current ERG has not been able to find these revised values within the publicly available documents, though this may have been more a modelling revision that revised which quality of life values applied to which health states than any revision of the actual quality of life values that were estimated from the EQ-5D data.

The Dretzke et al[54] quality of life values worsen the company base case ex PAS ICERs for ibrutinib relative to physician choice, ofatumumab, idelalisib and bendamustine from £45,486 per QALY, £45,525 per QALY, £44,836 per QALY and £42,016 per QALY to £47,135 per QALY, £46,843 per QALY, £46,600 per QALY and £43,882 per QALY respectively.

Physician choice dosing regimen: Osterborg et al[36]

Osterborg et al randomised 43 patients to physician choice, the most common treatments of which consisted of alkylator based therapies in combination with rituximab for 12 (28%) patients, alemtuzumab monotherapy or in combination with steroids for 11 (26%) patients, fludarabine based therapies such as FCR, FC and FR for 6 (14%) patients and bendamustine or bendamustine plus rituximab for 5 (12%) patients. Treatments for the remaining 8 (20%) patients were not itemised. In total 16 (37%) patients in the physician choice arm received rituximab. This is not obviously in line with that assumed within the modelling which was based upon a company expert survey:

- [redacted]: bendamustine plus rituximab
- [redacted]: R-HDMP
- [redacted]: chlorambucil
- [redacted]: FCR
- [redacted]: R-CHOP

ERG expert opinion suggests that R-CHOP is not much used as 1st line among relapsed refractory patients. The proportion applied by the company for R-HDMP may also be too high. ERG expert opinion indicates that the balance in their clinic between bendamustine plus rituximab and chlorambucil is perhaps around 2:1, but that idelalisib plus rituximab is rapidly increasing, currently stands at around 30% of patients and is likely to quite quickly increase further.

This introduces some difficulties in terms of costing the physician choice basket of treatments. If idelalisib plus rituximab is ignored on grounds of it being somewhat newer and different than the treatments in Osterborg et al and also being evaluated in its own right, the most appropriate balance might be to set R-CHOP and equal to zero. R=HDMP might also be reduced.

Reference costs for chemotherapy administrations

The NHS reference costs for 2013-14 outline the following costs for chemotherapy administered in the outpatient setting.

Table 55 Chemotherapy outpatient administration reference costs 2013-14

Code	Currency description	Reference cost guidance	Cost
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance	30 minutes nurse time and 30 to 60 minutes chair time for complete cycle	£165
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	60 minutes nurse time and up to 2 hours chair time for complete cycle	£219
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at first Attendance	60 minutes nurse time and more than two hours chair time	£266
SB15Z	Deliver subsequent elements of a chemotherapy cycle	..	£314
SB97Z	Same Day Chemotherapy Admission or Attendance	..	£0

The ERG interpretation of the above is that the chemotherapy administration costs include all the costs for chemotherapy administration on a given day. If more than one chemotherapy drug is given during the same day only one reference cost should be applied to the chemotherapy administrations for that day. ERG expert opinion suggests that with the exception of R-CHOP and R-HDMP the regimes under consideration should have the SB14Z cost applied. The ERG has revised the base case to exclude R-CHOP from the basket of treatments making up physician choice and the company model appropriately costs the first infusions.

But the reference costs also suggest a common subsequent cost for chemotherapy given during any one day of £314 which is somewhat higher than the company base case of £266.

Drug and administration costs for bendamustine plus rituximab

The company correctly summarise the proportion of patients who had dose reductions reported in Fischer et al.[47] But it seems that these dose reductions were among patients who continued to receive the cycle of treatment for which the dose was being reduced. The company does not present the Fischer et al data on the numbers of completed cycles. As a consequence, it appears that it is not treating bendamustine plus rituximab in a parallel manner to ibrutinib, for which the calculation appears to be based upon the total number of administrations divided by the time spent in progression free survival.

Fischer et al[47] report that up to six 28 day cycles were administered, with an interim assessment after three cycles permitting patients who had achieved at least stable disease to continue for the remaining three cycles. The number of patients competing all six cycles was 44 (56.4%), while 60 (76.9%) patients completed at least three cycles.

Based upon Figure A of Fischer et al,[47] progression free survival at three months was around 88% and at six months was around 75%. Fischer et al also note that during the course of the study 34 (43.6%) patients out of the 78 within the study had treatment withdrawn with this being due to progressive disease for 8 (10.2%) patients, loss of consent of 9 (11.5%) patients, toxicity for 15 (19.2%) patients and for other reasons for 2 (2.5%) patients. So it appears that the withdrawal of treatment due to progression was in line with the progression free survival curve, but that there were a further 33.3% of patients who did not complete the course of six cycles for reasons other than progression, most notably the 19.2% of patients who did not complete the six cycle course due to toxicity. But it is not stated when these withdrawals occurred and as a consequence the mean number of administrations among those who are progression free cannot be calculated from this.

Fischer et al[47] state that 353 cycles were administered, which is an average of 4.52 cycles per patient. Assuming a linear progression free survival curve between baseline and six months with the value of the curve at six months being 75% as seems reasonable to assume from Figure A of Fischer et al suggests a total possible number of administrations among those remaining progression free of 5.38. This would seem to suggest an average of 84.2% of patients who are progression free being treated. It is possible that there may be some concerns around those withdrawing from treatment being lost to follow-up, though it appears that the trial intention was to follow-up all the ITT patients which was presumably also the case for RESONATE and the ibrutinib average administered dose calculation.

So it may be most reasonable to apply this 84.2% average proportion of PFS patients on bendamustine plus rituximab treatment as the natural corollary of the 94.8% company estimate for the average proportion of PFS patients on ibrutinib treatment. This would be applied to both the drug costs and the infusion costs. This would be in addition to the company estimate of 97.0% dosing for bendamustine plus rituximab, with this 97% only being applied to the drug costs for bendamustine plus rituximab.

Applying this 84.2% to the drug and administration costs of bendamustine in addition to the 97.0% allowance for dose reduction worsens the company base case ICER for ibrutinib compared to bendamustine plus rituximab from £42,016 per QALY to £42,597 per QALY. This will also affect the cost effectiveness estimate for the comparison with physician choice, but to a lesser extent unless all the treatments within physician choice are affected to a similar degree.

Dose intensity: idelalisib

The company submission for idelalisib in the same indication estimated a dose intensity of 93.2%. No further details appear to be available in the idelalisib company submission.

The idelalisib STA dose intensity of 93.2% worsens the company base case ex PAS ICERs for ibrutinib relative to idelalisib £44,836 per QALY to £46,600 per QALY.

Terminal care costs

Round et al[81] is a literature survey, citing both the Nuffield report[84] on the costs of cancer in the 90 days prior to death and the Guest study[85] of the costs of cancer from the start of strong opioid use until death. There is no obvious reason for the company preferring one over the other. The Nuffield costs per cancer death of £7,287 are somewhat higher than the costs of Guest which range between £1.75k for breast cancer to £4.79k for cancer of the ovaries. The Guest unweighted average of £2.90k would rise to around £3.60k when uprated for inflation since 2006.

Results are not particularly sensitive to terminal care costs. Applying the £3.6k of Guest et al worsens the company base case ex PAS ICERs for ibrutinib relative to physician choice, ofatumumab, idelalisib and bendamustine from £45,486 per QALY, £45,525 per QALY, £44,836 per QALY and £42,016 per QALY to £45,720 per QALY, £45,770 per QALY, £45,102 per QALY and £42,247 per QALY respectively[h]. All the ICERs worsen by around £250.

5.3.3 Data inputs: correspondence between written submission and electronic model

The data inputs of the written submission correspond with the electronic model. There are elements of the electronic model that have not been brought out in the written submission. The ERG summary of the company model in sections 5.2.1 through to 5.2.8 above attempts to address this and to provide a fuller picture of the model.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Overall survival extrapolation: ibrutinib

The use of the lognormal for the first three years of the ibrutinib overall survival modelling is not obviously justified by the RESONATE data or the 1102 data. During the period of the trial the OS curves are extremely similar. The information criteria, while also similar, favour the exponential extrapolation. The ERG prefers applying the exponential throughout, this getting rid of the need for the ad hoc adjustment at the three year point.

[h] Implemented in the *Parameter* worksheet by setting F184=£3,600

Progression free survival extrapolation: ibrutinib

During the period of the trial the curves are similar as are the information criteria, with the AIC slightly favouring the Weibull and the BIC favouring the exponential. The company prefers the Weibull extrapolation as it simulates fewer patients remaining progression free within the ibrutinib arm.

The ERG is of the opinion that the reasonableness of the PFS curve can only be judged against the associated overall survival curve. ERG expert opinion as summarised in section 5.2.11 above suggests that the Weibull projects too small a proportion of ibrutinib patients as being progression free given the anticipated overall survival. Of the Weibull and the exponential the ERG consequently prefers the exponential.

Progression free survival extrapolation: ofatumumab

The submitted model only permits the Weibull curve to be used for the PFS for ofatumumab. As a consequence, it seems likely that sensitivity analyses that apply the exponential curve for PFS for the comparison of ibrutinib with ofatumumab apply the exponential for ibrutinib but the Weibull for ofatumumab. The ERG has revised the model to permit the exponential curve to be applied for ofatumumab[i].

Response rates and resource use

It appears that the response rates which are used for differentiating ongoing resource use are peak response rates for ibrutinib and ofatumumab.

The ERG asked at clarification about time to response data and duration of response data. The company responded that the data collected on response in RESONATE is presented in table 32 of the submission, but this only outlines peak response rates and nothing on the time to response or response duration. Data was supplied at clarification for trial 1102 which suggested mean times to initial response and to best

[i] Implemented in the *Raw_clinical_inputs* worksheet by setting X17=[redacted], Y17=[redacted], X18=1, Y18=1, F18=CHOOSE(ind_subgrp,X17,Y17), F19=1, F28=NORMINV(RAND(),F18,[redacted]), F29=1, F39=IF(Psa_on,F28,F18), F40=1, and in the *Model(ibrutinib_vs_ofa)* worksheet setting cell N416 ='Raw clinical inputs'!F39, N417=1, N418=EXP(-N416/N417), N419=1/N417, N421= EXP(-N418*$A421^$N$419), M421=MIN(L421,CHOOSE(O5,M421,N421)), P422= IF(O421<=0.1^10,1,(O421-O422)/O421) and with the cells below N421, M421 and P422 being of the same form.

response of [redacted] months and [redacted] months respectively. Data from trial 1103 was similar, with the median duration of response not having been reached but with [redacted] of responders achieving a 30 month duration of response. It is unclear whether the duration of response data is duration of response or duration of peak response. The ERG assumption is that it is duration of response.

The extent to which the response rate estimates for the comparator treatments have taken into account the ITC is unclear, and the methods of estimation do not appear to have been presented in the clinical effectiveness section.

ERG expert opinion is also that repeated biopsies are unlikely to occur, and it may even be the case of biopsies being used to confirm complete response rather than being more frequent during stable disease. As a consequence, the ERG views it as reasonable to remove the costs of ongoing biopsies from the analysis.

In the light of the above and the uncertainties around the time to peak response, the duration of peak response and the response rates which have been assumed for the comparator treatments is unclear to the ERG how sensible it is to differentiate treatments by the company estimated response rates. ERG expert opinion is also that routine follow-up is unlikely to be differentiated by response status. Consequently the ERG thinks that the base case should not differentiate routine follow-up by response status and treatment arm.

If the response rate estimates are viewed as being acceptable there may be an argument for differentiating inpatient visits by response status, but this is the lesser element of the differentiation of costs by treatment.

Equalising the ongoing resource use across the treatments worsens the cost effectiveness estimates for ibrutinib. But eliminating the costs of ongoing biopsies tends to improve them due to the longer survival associated with ibrutinib. As a consequence, these two changes tend to offset one another and the overall impact is relatively muted with a worsening of the ICERs of around £500 to £1,000 per QALY.

Adverse events

Unfortunately, due to time pressures the ERG has not reviewed the adverse event rates, costs and quality of life impacts. They are not central to the modelling results. The model applies one off costs and quality of life impacts from these. There may be some concerns about adverse events continuing throughout progression free survival for ibrutinib and idelalisib plus rituximab, but Figure 24 of the submission provides reassurance on this.

Quality of life: RESONATE EQ-5D data regression analysis

(Note the following critique of the EQ-5D regression analysis is a repeat of the text in the clinical effectiveness section 4.2.8, replicated here for the context of the modelling)

The EQ-5D was collected at baseline, every 4 weeks during the first 24 months and every twelve weeks subsequently until disease progression was confirmed by IRC assessment and at the last treatment visit before discontinuation.

The interim data cut of 9.4 months was chosen by the company for its analysis of the EQ-5D data due to IRC assessment of progression stopping after the interim data cut. At this point no IRC complete responses had been reported. As a consequence, all IRC responders were only partial responders and it was not possible to further stratify IRC response status.

It should be borne in mind that the investigator assessed measure of progression is what underlies all the cost effectiveness modelling. The EQ-5D data within Appendix 12, Table A.2 is also split by investigator response status and not by IRC response status. As a consequence it is unclear to the ERG why the interim data cut was applied by the company and why it was the IRC assessment of response rather than the investigator assessment of response that was used for the analysis.

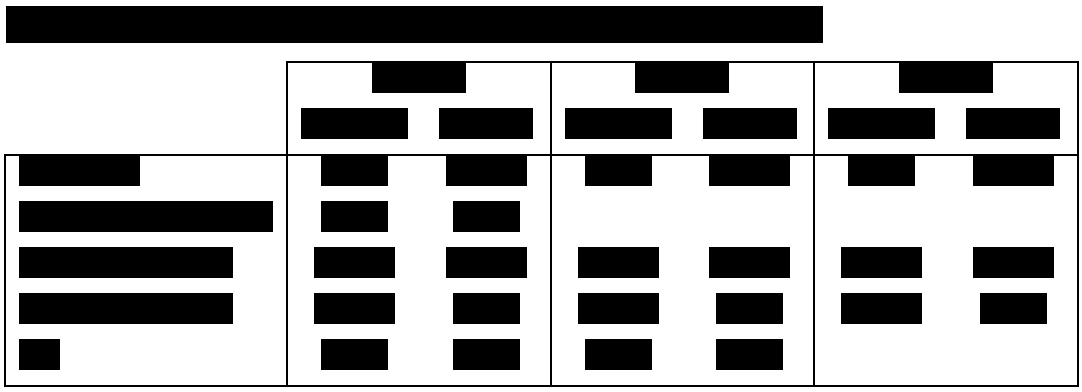
Note also that prior to the presentation of Appendix 12 of the submission at least one interim analysis was conducted which eliminated some statistically insignificant time variables. Apparently the preliminary analysis results are not available for reporting. It seems a pity that no information about the values, signs and p-values for these time

variables was retained. It is unknown whether any further analyses were conducted prior to the presentation of Appendix 12. The company in response to ERG clarification question B3 quite precisely states that "*Appendix 12 presents a full report of the RESONATE QoL analysis which was conducted specifically to inform the economic model*".

A repeated measures regression analysis of the data estimated three models:

- Model 1: Treatment arm, baseline utility, responder status and SAE status
- Model 2: Baseline utility, responder status and SAE status
- Model 3: Baseline utility and responder status

With the following results for the estimated changes from baseline.



Only the parameters for the intercept and the baseline utility were statistically significant. Despite having eliminated statistically insignificant time parameters in an interim analysis, apparently no further analyses were conducted that eliminated the statistically insignificant responder status variable.

What is striking is that given the mean baseline quality of life value of the model of [redacted] the statistically significant coefficients suggest small quality of life reductions of [redacted] and [redacted] for models 1 and 2, and only a very small gain of less than [redacted] for model 3. This contrasts with a gain of [redacted] within the company model. This has to be read against the possibility of those reporting EQ-5D values later in the trial tending to have a better baseline quality of life value, but there is no information about this.

The ERG is surprised that the analysis concentrated upon the IRC responder status and as a consequence curtailed the analysis at the interim data cut. It is also surprised that no further process of the elimination of statistically insignificant variables was undertaken given the interim analysis elimination of the statistically insignificant time variable and the signs on the statistically insignificant variables. In the absence of this, it seems reasonable to conduct an analysis that assumes no quality of life increase from baseline for those remaining on treatment.

1st line drug and administration costs

As outlined in the model summary the drug and administration costs are treated asymmetrically in order to reduce costs in the ibrutinib arm:

- Use of the TTD curve in only the ibrutinib arm but no consideration of this in the ofatumumab arm, and no attempt to provide a similar analysis for the other comparators even if only be assumption.
- Assuming that the minimum of the TTD curve and the PFS curve is the proportion eligible for treatment in the ibrutinib arm.
- Applying the drug utilisation proportion twice in the ibrutinib arm but only once in the comparator arms.
- Not applying the drug utilisation proportions to drug administration costs, which would reduce the costs of comparators but not ibrutinib due to ibrutinib having zero administration costs.
- Applying half cycle correction and immediate discounting to the ibrutinib drug costs but not to the comparator drug costs.

As outlined in greater detail in Appendix 1 the double discount given to ibrutinib appears to be the model structure that the company intended to submit. As a consequence, the ERG may have misunderstood the company model structure and may be wrong to highlight this as biasing the analysis. The ERG urges the company to review this and to provide an account of its chosen model structure.

There may be an argument around not applying the drug utilisation percentages to administration costs if it could be demonstrated that the drug utilisation percentages

are only due to dose reductions rather than treatment holidays. But nothing has been presented on this.

In the opinion of the ERG these modelling choices made by the company bias the cost effectiveness estimates.

Ibrutinib drug utilisation

The company supplied the number who had not discontinued treatment and the total ibrutinib dose that had been administered in response to ERG clarification question A19. The company also supplied the Kaplan Meier data for the time to treatment discontinuation curve in response to ERG clarification question A12. It had been the ERG intention to review this data to assess the mean dose of ibrutinib among those remaining on treatment. But as can be seen in the following table the numbers at risk diverge and as a consequence it appears that the data is only congruent up to week 28. The ERG is unclear why there should be this discrepancy. Restricting attention to just the first 28 weeks the Kaplan Meier of the TTD curve suggests the following days spent TTD which in turn implies the mean dose and utilisation. Note that week 12 through to week 28 are 28 day periods.

Table 57 Number not discontinued, ibrutinib dosing and TTD number at risk

Week	N not disc.	Total dose(mg)	TTD KM N at risk	Days TTD	Mean dose	Utilisation
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.4%
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.3%
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.2%
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95.6%
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.2%
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.4%
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95.4%
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.7%
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	96.6%
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	94.1%
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95.3%
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	94.7%
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95.4%
32	[redacted]	[redacted]	[redacted]			
36	[redacted]	[redacted]	[redacted]			
40	[redacted]	[redacted]	[redacted]			
44	[redacted]	[redacted]	[redacted]			
48	[redacted]	[redacted]	[redacted]			
52	[redacted]	[redacted]	[redacted]			
56	[redacted]	[redacted]	[redacted]			
60	[redacted]	[redacted]	[redacted]			
64	[redacted]	[redacted]	[redacted]			
68	[redacted]	[redacted]	[redacted]			
72	[redacted]	[redacted]	[redacted]			

The ERG had been concerned that if adverse events were concentrated during the early period of the trial that the ibrutinib utilisation among those remaining on treatment would pick up again once the adverse events had washed through. There is no evidence of this in the above though whether the 28 weeks is sufficient to assess this is a moot point. Figure 24 of the submission suggests that the vast majority of adverse events were during the first 28 weeks of the trial, with very few adverse events thereafter. Over the first 28 weeks of the TTD curve the mean ibrutinib utilisation based upon the above is 95.6%. The ERG is unclear how the company has calculated the 94.8% but the figures are similar.

Given Figure 24 of the submission, it seems reasonable to conduct a sensitivity analysis where the ibrutinib reduced dosing of 94.8% is not applied from model cycle 32. While slightly arbitrary, for this sensitivity analysis it seems most reasonable to also apply this assumption to idelalisib plus rituximab.

Idelalisib drug utilisation

To the ERG, idelalisib appears to be more similar to ibrutinib than to ofatumumab. The ERG finds it surprising that the company should have assumed that the drug utilisation for idelalisib plus rituximab would be more akin to that of ofatumumab than ibrutinib. ERG opinion is that for the base case it is more reasonable to apply the ibrutinib drug utilisation percentage to idelalisib plus rituximab than the ofatumumab drug utilisation percentage.

Infusion visits

ERG expert opinion suggests that the first dose of rituximab is often given on day 1 rather than day 0 of the first cycle and that prednisolone is administered orally. In the light of this it appears that the number of infusion visits during each week of treatment should be:

- 2 for bendamustine plus rituximab
- 1 for R-CHOP

The rituximab SmPC does however specify intravenous administration of prednisolone and as a consequence the above will only be explored as a sensitivity analysis. The main effect is upon R-CHOP which the ERG has removed from the basket of treatments for physician choice based upon ERG expert opinion. As a consequence, the impact upon the ERG revised base case is limited.

PPS 2nd line treatment PFS curve

It is not obvious that the PPS PFS curve derived from the rituximab arm of the idelalisib plus rituximab trial is appropriate. Beyond this comment the ERG has not reviewed the PPS PFS curve due to time constraints. The importance of this to the model results is explored through a sensitivity analysis that excludes 2nd line treatment.

PPS 2nd line treatments

ERG expert opinion suggests that assuming that 2nd line treatment would be equally balanced between HDMP and R-HDMP is likely to be dated and to not reflect current practise. For instance, it is likely that those failing on bendamustine plus rituximab would now tend to receive idelalisib plus rituximab, while those failing on idelalisib plus rituximab would now tend to receive bendamustine plus rituximab.

There is no obvious means of incorporating this ERG opinion into the model structure. As a consequence it can only really be explored by setting the proportion receiving 2nd line treatment to zero and examining how much this affects results.

PPS 2nd line treatment percentage

The PPS treatment percentage of 42% is based upon the ofatumumab arm of the RESONATE trial at the nine month data cut prior to many ofatumumab patients having crossed over. The reason for the company selecting only the data from the ofatumumab arm is apparently due to fewer having progressed in the ibrutinib arm. The company does note that the proportion receiving 2nd line treatment among those discontinuing from ibrutinib was lower than that of the ofatumumab arm, but supplies no data on this.

The ERG remains unclear why the ibrutinib data was ignored. It might suggest a lower overall rate for 2nd line treatment, which would slightly worsen the cost effectiveness estimates. But it might suggest a lower rate for ibrutinib compared to ofatumumab which would tend to improve the cost effectiveness estimate for this pairwise comparison.

PPS 2nd line treatment and administration costs

The PPS treatment and administration cost only apply the costs relevant to the first model cycle to the incident number of PPS patients. These costs are also further qualified by the PPS PFS curve. But this qualification is by the model cycle and not by the PPS incident cycle. In other words in, say, the tenth cycle of the model the incident number of PPS patients is qualified by the PPS PFS curve 40 week proportion, around [redacted] despite these PPS patients being newly incident.

In the opinion of the ERG it would have been better to calculate a total mean present value cost per incident patient by conditioning the per cycle PPS costs by:

- the PPS proportion that receive treatment
- the PPS proportion in PFS curve and
- the benefit discount factor

and then summing these over the cycles of PPS PFS when treatment occurs. This total present value cost per incident patient could then have been applied to each cycle's incident PPS cases and also discounted for the cycle in which the PPS incidence occurred. This exaggerates the impact of PPS PFS treatment as in effect it assumes that none die while on PPS PFS treatment, but given the steepness of the PPS PFS curve this exaggeration seems likely to be slight. The resulting estimated present value cost of [redacted] is quite large.

Correcting this improves the company base case ex PAS ICERs for ibrutinib relative to physician choice, ofatumumab, idelalisib and bendamustine from £45,486 per QALY, £45,525 per QALY, £44,836 per QALY and £42,016 per QALY to £45,420 per QALY, £45,193 per QALY, £44,408 per QALY and £41,897 per QALY respectively[j]. The effects are minor.

Subcutaneous rituximab

Roche has developed subcutaneous rituximab. On the assumption that it is as effective as rituximab infusions, this would quite dramatically affect administration costs for the comparators were it to be permitted in CLL. The current rituximab EPAR permits subcutaneous rituximab for non-Hodgkin's lymphoma but still envisages only intravenous administration for CLL.

[j] Implemented by calculating a present value for the total costs per incident PPS patient receiving treatment based upon the costs in cells AF10:AJ18 of the *Subtx_drug_cost* worksheet being conditioned by the PPS PFS survival curve in cells S10:S17 of the markov worksheets and discounted by cells AZ10:AZ17 of the markov worksheets, and modifying the cells in column AU of the markov worksheets to be of the form BT11*prob_subtx*PV where PV is the present value of the PPS treatment costs which the ERG calculates to be £17,193.

Minor issue: physician choice infusion costs

There is a minor referencing error which if corrected marginally improves the company base case ex PAS ICER for ibrutinib relative to physician choice from £45,486 per QALY to £45,475 per QALY[k].

17p depleted patient population: other comparators

The company model contains the facility to apply the all patient hazard ratios to the 17p depleted patient population modelling. In the absence of other data, this may be the most reasonable assumption that can be made if the other comparators are to be considered. Consideration of the RESONATE trial data and the similarity of results between the all patients analysis and the 17p depleted subgroup may qualify this.

Applying the all patients hazard ratios for the other comparators within the 17p depleted patient population modelling results in the following base case deterministic cost effectiveness estimates.

[k] Implemented within the *PC_cost_summary* worksheet cell G15 by revising the reference to *'PC drug cost'!CG13* to be to *'PC drug cost'!CG12*

Table 58 17p depleted patients results: all comparators

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
PFS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin. Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost		£128,939	£102,596	£73,989	£130,618
Total undisc. LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc. LY		4.727	4.592	3.051	5.133
net PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALYs		2.800	2.690	1.722	3.036
ICER		£46,045	£38,145	£42,967	£43,028

Unfortunately, as far as the ERG can ascertain the clinical parameters for the 17p depleted subgroup have not been implemented probabilistically within the submitted model and the required variance-covariance matrices are not available. As a consequence, the ERG has not run the model probabilistically for the 17p depleted subgroup.

Cost effectiveness estimate: 17p subgroup

There is no data on the treatment naïve 17p depleted patient population. There is only the data from RESONATE for the 17p depleted subgroup.

The company states that clinical opinion suggests that "*the cost effectiveness estimates in the R/R 17p depletion population should provide a plausible, although conservative, estimate of ibrutinib's value for money in a first line 17p depletion subgroup*". When assessing this assertion the annual cost of ibrutinib of £55,954 or [redacted] including the PAS should be borne in mind, and weighed against the company cost effectiveness estimates compared to ofatumumab in the R/R 17p depletion subgroup of £38,145 per QALY excluding the PAS and [redacted] per QALY including the PAS. Presumably those with 17p depletion who are treatment naïve will be anticipated to survive for longer and receive ibrutinib for longer compared to the treatment experienced 17p depletion subgroup of the RESONATE trial. The proportion of overall survival which is anticipated to be in the progression free health state might also be anticipated to be larger.

In the light of this it is unclear to the ERG why it should be anticipated that the cost effectiveness of ibrutinib among treatment naïve 17p depleted patients will be superior to that among treatment experienced 17p depleted patients. The cost effectiveness estimates for ibrutinib among treatment experienced 17p depleted patients may be a poor guide to cost effectiveness of ibrutinib among treatment naïve 17p depleted patients.

In the opinion of the ERG, a major determinant of this will be the proportion of overall survival that patients spend progression free and on ibrutinib treatment when being treated with ibrutinib. If this is likely to higher among treatment naïve 17p depleted patients than among treatment experienced 17p depleted patients, the cost effectiveness estimates for ibrutinib among treatment experienced 17p depleted patients are likely to be too optimistic. The cost effectiveness among treatment naïve patients is likely to be worse than among treatment experience patients, other things being equal. But if the proportion of survival that patients spend progression free when being treated with ibrutinib is likely to be lower among treatment naïve 17p

depleted patients than among treatment experienced 17p depleted patients the reverse is likely to be the case.

The recent Farooki et al (2015) abstract may provide some guidance on this. Whether there is sufficient data within Farooki et al to reliably estimate parameterised OS and PFS curves for ibrutinib is a moot point. If there is and the application of the all patients hazard ratios is of interest in the absence of 17p patient specific data, these two elements could be coupled to provide scenario analyses that estimate the cost effectiveness of ibrutinib in the treatment naive 17p depleted patient population.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the company model along the following lines:

- Apply the exponential OS curves and the exponential PFS curves[l].
- Assume that the time on treatment for ibrutinib is synonymous with the PFS curve[m].
- Apply a hazard ratio for OS for idelalisib plus rituximab of [redacted][n].
- Apply a hazard ratio for OS for physician choice of [redacted][o].
- Remove the half cycle correction from the ibrutinib direct drug costs[p].
- Not apply the 94.8% utilisation reduction to ibrutinib twice[q].
- Apply the same utilisation rate for idelalisib as for ibrutinib[r].
- Apply the Beusterein et al[79] quality of life decrement for being on 2nd line treatment[s].
- Apply the stable disease routine follow-up costs for those remaining progression free[t].

[l] Implemented in the *Options* worksheet by setting C62=3 and C60=2
[m] Implemented in the *Options* worksheet by setting C70=1
[n] Implemented in the *Options* worksheet by setting [redacted]
[o] Implemented in the *Options* worksheet by setting [redacted]
[p] Implemented in the markov worksheets by having cells AQ10:AQ410 be multiplied by cells AB10:AB410 rather than by cells AI10:AI410
[q] Implemented in the *Parameter* worksheet in cells F118 by deleting the reference to *C_compliance_Ibr*
[r] Implemented in the Parameter worksheet by setting cell F112=F110
[s] Implemented in the markov worksheets in column AN by adding AE*U_BL*3.8% to cells AN11:AN410 and to AN422:AN821
[t] Implemented in the *Micro_Cost* worksheet by setting cells L42:l46 equal to cell S35

- Apply the utilisation percentages to both the direct drug costs and the administration costs[u].
- Apply the 84.2% treatment holiday proportion to bendamustine plus rituximab[v].
- Revise the physician choice treatments to not include R-CHOP[w].
- Revise the physician choice administration costs[x].
- Revise the 1st cycle FCR cost[y].
- Revise the mean BSA to 1.79m^2 [z].
- Increase the cost for subsequent infusions to £314[aa].
- Remove the costs of ongoing biopsies[bb].
- Revise the PPS treatment costs to be a survival conditioned present value that is applied to the PPS incident patients who are assumed to receive 2nd line treatment[cc].
- Revise the PPS 1st cycle half cycle adjustment[dd].
- Revise the PPS administration cost for R-HDMP[ee].
- Include terminal care costs for those alive at the end of the time horizon[ff].

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[u] Implemented in the *Drug_Costs* worksheet by conditioning columns AY:BC by the relevant percentages

[v] Implemented in the *Drug_Cost* worksheet by multiplying cells AU10:AU410 and, with the exclusion of the *C_admin_IV_d1extra* element, cells BA10:BA18 by 0.842 and similarly conditioning cells BZ12:BZ412 and CF12:CF412 of the *PC_drug_cost* worksheet. Note that this also removes the conditioning of cells BA10:BA18 of the *Drug_cost* worksheet and CF12:CF412 of the *PC_drug_cost* worksheet *C_compliance_br.*

[w] Implemented in the PC_cost_summary worksheet by setting F7=0and F11=1-SUM(F7:F10)

[x] Implemented in the *PC_cost_summary* worksheet by having cell G15 refer to 'PC drug cost'!CG12 rather than 'PC drug cost'!CG13, with similar revisions to cells G16:G415

[y] Implemented within the *PC_drug_cost* worksheet by revising cell CA12 to be IF($BY12<=32,SUM(OFFSET(BK$12,$BY12,0):OFFSET(BK$12,$BY12+3,2)),SUM(BK$44:BM$47))

[z] Implemented in the *Parameter* worksheet by setting cell F128=1.79.

[aa] Implemented in the *Cost_Inputs* worksheet by setting cell G43=314

[bb] Implemented in the *Micro_costs* worksheet by setting I28=0

[cc] Implemented in the markov worksheet by setting cell AU11=BT11*prob_sub_tx*PV_PPS_Tx where PV_PPS_Tx is the present value calculated over the four model cycles in *Subtx_drug_cost* worksheet by averaging (AF10+AI10) and (AG10+AJ10) and likewise for the subsequent three cycles, conditioning these by the PPS PFS curve percentages of 'Model (ibrutinib vs PC)'!S10:S13, discounting them by 'Model (ibrutinib vs PC)'!AZ10:AZ13 and summing the resulting four values to give an average PPS Tx present value cost of £17,192.

[dd] Implemented within the markov worksheets by amending cells AE11, AF11, AE422 and AF422 to be of the form (X+Y)/2 rather than AVERAGE(X:Y)

[ee] Implemented within the *Subtx_drug_cost* cells AI10:AI18 by amending them to be of the form SUM(OFFSET(N$10,$AE10,0):OFFSET(N$10,$AE10+3,0))

[ff] Implemented within the markov worksheets by adding OFFSET(L10,Timehorizon+1,0)*OFFSET(BH10,Timehorizon+1,0)*C_terminal to cell BQ9 and OFFSET(L421,Timehorizon+1,0)*OFFSET(BH421,Timehorizon+1,0)*C_terminal to cell BQ420

In order to aid cross checking by the company the analyses of the confidential appendix that include the ibrutinib PAS and those of its competitors has been implemented along the following lines in the *Parameters* worksheet.

- Cell D118 = IF(ISBLANK(E118),F118,E118)*(1-ERG_PAS_IBRU)
- Cell D119 = IF(ISBLANK(E119),F119,E119)*(1-ERG_PAS_BEND)
- Cell D123 = IF(ISBLANK(E123),F123,E123)*(1-ERG_PAS_OFAT)
- Cell D126 = IF(ISBLANK(E126),F126,E126)*(1-ERG_PAS_IDEL)

where the ERG_PAS_ variables are the relevant PAS percentages.

The ERG revised company model, with the competitor PAS percentages removed, is available upon request[gg]. The ERG encourages the company to request this in order to not only check the quite extensive ERG model revisions to what is a quite involved model structure, but also to check the ERG implementation of the CEAFs since it seems possible that these rather than the pairwise CEACs will be what the Assessment Committee will concentrate upon.

The ERG has also undertaken a range of sensitivity analyses:

- SA01 of reverting to the company base case hazard ratios.
- SA02 of applying the alternative ITC hazard ratio estimates of the company for physician choice and for bendamustine plus rituximab.
- SA03 of applying the lognormal extrapolation for ibrutinib OS for the first three years.
- SA04 of applying the Weibull extrapolations for PFS.
- SA05 that combines SA04 and SA05 above
- SA06 of limiting the hazard ratio benefits of ibrutinib to the first 20 4-week cycles given the numbers at risk and the NICE TAPs methods guide, and to the first 3, 6 and 7 years[hh].
- SA07 of no quality of life increment subsequent to baseline for those on treatment[ii].

[gg] To generate the with PAS ICERs of the confidential appendix the ERG has generated each of the ex PAS ICERs as reported in the tables in section 5.4 and then in the *ERG_Assump* worksheet set cell C18="Yes" before moving on to generate another ex PAS ICER.

[hh] Implemented in the *Clinical_Inputs* worksheet by setting cells G16 and G17 equal to 1.5, 3, 6 and 7

- SA08 of applying the all patient QoL values to the 17p depletion subgroup modelling.
- SA09 of 100% ibrutinib and idelalisib utilisation from week 32[jj].
- SA10 of removing the 84.2% bendamustine plus rituximab on treatment holiday.
- SA11 of no 2nd line treatment[kk].
- SA12 of +50% on PFS death rate[ll].
- SA13 of no serious adverse events[mm].
- SA14 revising the number of infusion visits to 2 for bendamustine plus rituximab and to 1 for R-CHOP[nn].

For the all patients modelling the ERG revised base case is as follows.

Table 59 Deterministic ERG revised model: all patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
PFS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin. Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost		£230,089	£200,563	£151,597	£231,760
Total undisc. LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[ii] Implemented in the *Utility_inputs* worksheet by setting cell L12=L10
[jj] Implemented in the *Drug_costs* worksheet by not conditioning cells AS18:AS410 by *C_compliance_ibr* and not conditioning cells AV18:AV410 by *C_compliance_ir*
[kk] Implemented in the *Clinical_inputs* worksheet by setting H81=0
[ll] Implemented in the *Clinical_inputs* worksheet by conditioning cell H45 by the relevant percentage
[mm] Implemented in the *Clinical_inputs* worksheet by setting cells H97:N101=0
[nn] Implemented in the Drug_costs worksheet by setting cell P10=2 and in the PC_drug_cost worksheet by setting cell AB12=2 and AF12=AF15=AF18=AF21=AF24=AF27=AF30=AF33=1

PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc. LY		5.295	4.616	2.874	6.161
net PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALYs		3.204	2.773	1.713	3.693
ICER		£71,812	£72,336	£88,484	£62,756

The overall survival gains are slightly less than those of the company base case, but are broadly similar. As a consequence, the ERG expert opinion concerns about the modelled survival gains as summarised in the validation section, particularly for ibrutinib compared to idelalisib plus rituximab where a gain of around 60% is still anticipated despite the ERG revision to the hazard ratio, largely remain. But most of the gains are now modelled as occurring during progression free survival rather than a large part of the survival gains being anticipated to occur after progression when treatment has ceased.

There is a slight oddity in the comparison with idelalisib plus rituximab where all the gains are anticipated during progression free survival with none being anticipated post progression, the net figure for the latter actually turning a little negative. But given the survival gains, the net QALYs are not too dissimilar to those of the company base cases.

Given the greater survival during PFS, as would be anticipated the direct drug costs for ibrutinib increase somewhat compared to the company base cases. The ibrutinib drug costs also increase due to the ERG having removed the company asymmetric treatment of drug costs.

This results in cost effectiveness estimates of:

- £71,812 per QALY compared to physician choice, rather than the £45,486 per QALY of the company

- £72,336 per QALY compared to ofatumumab, rather than the £45,525 per QALY of the company
- £88,484 per QALY compared to idelalisib plus rituximab, rather than the £44,836 per QALY of the company
- £62,756 per QALY compared to bendamustine plus rituximab, rather than the £42,016 per QALY of the company

For the all patient modelling the central probabilistic estimates are as follows.

Table 60 Probabilistic ERG revised model: all patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		£74,253	£73,789	£92,562	£64,962

The central probabilistic estimates are slightly worse than the deterministic estimates. This is most marked for the comparison with idelalisib plus rituximab for which the deterministic estimate is £88,484 per QALY and the central probabilistic estimate is £92,562 per QALY.

Note that the ERG has excluded ofatumumab from the calculation of the following CEAFs on the grounds of it not being a comparator specified within the scope.

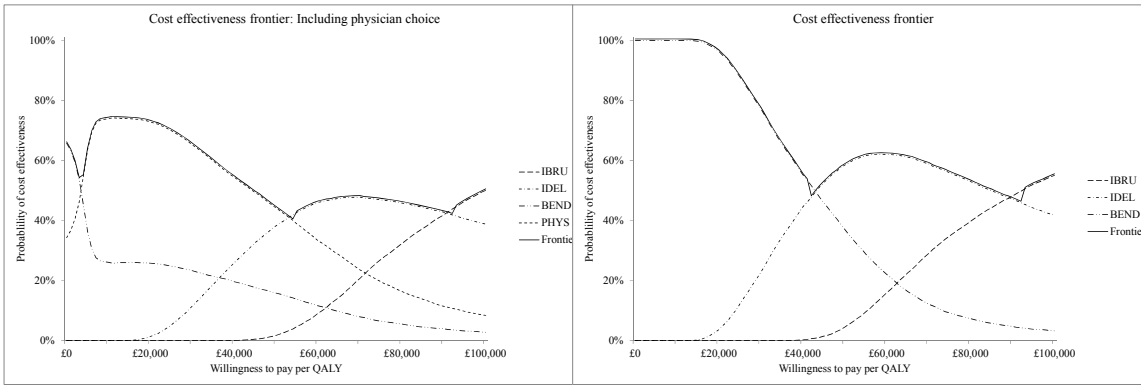

Figure 37 ERG revised model base case CEAFs: all patients

If physician choice is included in the CEAF up to a willingness to pay of £3k per QALY bendamustine plus rituximab is estimated to have the greatest cost effectiveness. Physician choice has the greatest cost effectiveness between £4k per QALY and £54k per QALY, with idelalisib plus rituximab thereafter up to £92k per QALY. Ibrutinib is estimated to have the greatest cost effectiveness for a willingness to pay of £93k per QALY and above.

If physician choice is excluded from the CEAF up to a willingness to pay of £41k per QALY bendamustine plus rituximab is estimated to have the greatest cost effectiveness, with idelalisib plus rituximab thereafter up to £92k per QALY. Ibrutinib

is estimated to have the greatest cost effectiveness for a willingness to pay of £93k per QALY and above.

The pairwise probabilities of being ibrutinib being cost effective at the various willingness to pay per QALY values are as below.

Table 61 Pairwise probabilities of ibrutinib cost effectiveness: all patients

WTP per QALY	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
£0	0%	0%	0%	0%
£10,000	0%	0%	0%	0%
£20,000	0%	0%	0%	0%
£30,000	0%	0%	0%	0%
£50,000	4%	6%	11%	10%
£100,000	83%	82%	57%	93%

The sensitivity analyses for the all patients modelling using the ERG revised model are as follows.

Table 62 Sensitivity analyses: ERG revised model: all patients

		ICERs			
	Description	**PhysChce**	**Ofat**	**Idel+R**	**Bend+R**
Base case	..	£71,812	£72,336	£88,484	£62,756
SA01	Company base case HRs	£67,907	..	£74,842	..
SA02	Company alternative ITC HRs	£81,169	..	..	£99,620
SA03	Ibrutinib OS 3 years lognormal	£70,853	£71,686	£88,373	£61,435
SA04	Ibrutinib PFS Weibull extrapolation	£53,976	£50,545	£61,171	£46,892
SA05	SA04 and SA05 combined	£53,217	£50,039	£61,076	£45,872
SA06a	1.5 years ibrutinib HR benefit	£99,425	£94,590	£140,909	£88,645
SA06b	3 years ibrutinib HR benefit	£91,352	£89,304	£117,599	£81,875
SA06c	6 years ibrutinib HR benefit	£83,288	£82,690	£102,670	£74,097
SA06d	7 years ibrutinib HR benefit	£81,410	£81,010	£99,884	£72,282
SA07	PFS QoL = baseline QoL	£75,166	£75,834	£93,212	£65,218
SA08	All patient QoL applied	..	..	..	..
SA09	100% drug utilisation from week 32	£75,109	£76,147	£93,156	£65,617
SA10	Remove 84.2% Bend+R Tx holiday	£71,662	..	..	£62,306
SA11	No 2nd line Tx	£72,596	£73,149	£89,373	£63,426
SA12	50% higher PFS death rate	£71,549	£72,065	£88,190	£62,531
SA13	No SAEs	£71,853	£72,192	£89,071	£62,534
SA14	Revised number of infusion visits	£71,840	..	..	£62,827

The ERG revision to the overall survival hazard ratios slightly worsens the cost effectiveness estimate for ibrutinib compared to physician choice. The impact is more dramatic impact upon the comparison of ibrutinib with idelalisib plus rituximab, where reverting to the company hazard ratio improves the cost effectiveness estimate from £88,484 per QALY to £74,842 per QALY.

As in the company modelling, the company alternative hazard ratios have quite a dramatic effect. The cost effectiveness estimate for ibrutinib compared to physician choice worsens from £71,812 per QALY to £81,169 per QALY while that for the comparison with bendamustine plus rituximab worsens from £62,756 per QALY to £99,620 per QALY.

The lognormal overall survival curve has only a limited impact. Reverting to the Weibull PFS curves for ibrutinib and ofatumumab, with this flowing through to the PFS curves for idelalisib plus rituximab and bendamustine plus rituximab via the

hazard ratios, has a major impact. The cost effectiveness estimates improve markedly: from £71,812 per QALY to £53,976 per QALY for the comparison with physician choice; from £72,336 per QALY to £50,545 per QALY for the comparison with ofatumumab; from £88,484 per QALY to £61,171 per QALY for the comparison with idelalisib plus rituximab and from £62,756 per QALY to £46,892 per QALY for the comparison with bendamustine plus rituximab.

As would be anticipated, restricting the duration of benefits has a major impact upon results. But it should be borne in mind that while these sensitivity analyses restrict the duration of benefits in terms of the hazard ratios for overall survival and PFS, those in PFS in the ibrutinib arm are still modelled as receiving ibrutinib even after the period of benefits has ended.

Assuming that there is no quality of life increase from baseline for those in progression free survival worsens the cost effectiveness estimates, but the effects are not particularly dramatic with the possible exception of the comparison with idelalisib plus rituximab where the effect is larger. For this comparison the cost effectiveness estimate worsens from £88,484 per QALY to £93,212 per QALY.

Tolerability may tend to improve among those remaining on ibrutinib and idelalisib plus rituximab in the longer term and as a consequence the drug utilisation proportions for these may tend to increase. Assuming a 100% drug utilisation from week 32 worsens the cost effectiveness estimates, and again the effect is most marked for the comparison with idelalisib plus rituximab for which the cost effectiveness estimate worsens from £88,484 per QALY to £93,156 per QALY.

The effects of the other sensitivity analyses are relatively minor.

The deterministic estimates for the 17p depleted patient population where the modelling for the comparisons with physician choice, idelalisib plus rituximab and bendamustine plus rituximab applies the all patients hazard ratios are as follows.

Table 63 Deterministic ERG revised model: 17p depleted patients

	Ibrutinib	Phys. Chce.	Ofatumumab	Idelalisib+R	Bend.+R
PFS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin. Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Tx cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SubTx Follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost	[redacted]	£194,522	£167,552	£127,923	£195,942
Total undisc. LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net undisc. LY	[redacted]	4.456	4.592	2.517	5.133
net PFS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
net PPS LY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALYs	[redacted]	2.652	2.676	1.471	3.017
ICER	[redacted]	£73,345	£62,624	£86,942	£64,952

The base case cost effectiveness estimates for the comparisons with physician choice, idelalisib plus rituximab and bendamustine plus rituximab when the all patients hazard ratios are applied to the ibrutinib 17p OS and PFS curves are similar to the all patient modelling. But the cost effectiveness estimate for the comparison with ofatumumab of £62,624 per QALY is somewhat better than the £72,736 per QALY estimate of the all patient modelling. This may raise questions about the validity of applying the all patients hazard ratios within the 17p subgroup modelling, and what if anything might be more reasonable to apply instead.

The deterministic sensitivity analyses for the 17p depleted patients modelling using the ERG revised model are as follows.

Table 64 Sensitivity analyses: ERG revised model: 17p depleted patients

		ICERs			
	Description	**PhysChce**	**Ofat**	**Idel+R**	**Bend+R**
Base case	..	£73,345	£62,624	£86,942	£64,952
SA01	Company base case HRs	£69,714	..	£74,449	..
SA02	Company alternative ITC HRs	£81,870	£62,624	£86,942	£98,817
SA03	Ibrutinib OS 3 years lognormal	..	..	..	..
SA04	Ibrutinib PFS Weibull extrapolation	£56,915	£44,745	£61,734	£50,096
SA05	SA04 and SA05 combined	..	..	..	..
SA06a	1.5 years ibrutinib HR benefit	£98,978	£77,918	£129,917	£89,186
SA06b	3 years ibrutinib HR benefit	£91,637	£75,941	£111,943	£82,728
SA06c	6 years ibrutinib HR benefit	£83,856	£71,098	£99,320	£75,133
SA06d	7 years ibrutinib HR benefit	£82,052	£69,751	£96,865	£73,393
SA07	PFS QoL = baseline QoL	£78,647	£66,605	£93,974	£68,940
SA08	All patient QoL applied	£70,021	£59,614	£83,235	£61,785
SA09	100% drug utilisation from week 32	£76,626	£65,876	£91,514	£67,836
SA10	Remove 84.2% Bend+R Tx holiday	£73,186	..	..	£64,453
SA11	No 2nd line Tx	£74,155	£63,343	£87,847	£65,647
SA12	50% higher PFS death rate	£73,070	£62,380	£86,637	£64,716
SA13	No SAEs	£73,395	£62,475	£87,625	£64,680
SA14	Revised number of infusion visits	£73,380	..	..	£65,039

Given the similarity of the base case cost effectiveness estimates for the comparisons with physician choice, idelalisib plus rituximab and bendamustine plus rituximab when the all patients hazard ratios are applied to the ibrutinib 17p OS and PFS curves, the sensitivity analyses for these comparison parallel those of the all patient modelling.

For the comparison with ofatumumab, the main sensitivities are to the restriction of the durations of benefit and the Weibull being used for the PFS extrapolation. The latter improves the cost effectiveness estimate from £62,624 per QALY to £44,745 per QALY.

5.5 Conclusions of the cost effectiveness section

The company submission appears to not present the derivation of the treatment specific response rates and how these are aligned with the ITC and the response rate definitions for the treatments in the ITC.

There are biases in the modelling of the direct drug costs that benefit ibrutinib.

The company concludes that the cost effectiveness estimate for the treatment naïve 17p depleted patient population which is based upon the RESONATE treatment experienced 17p depleted patient subgroup is biased and is conservative. The reason for concluding this is not obvious to the ERG.

Given the incompleteness of the RESONATE OS and PFS curves for ibrutinib there are considerable uncertainties around the extrapolations out to 20 years. The parameterised curves are little different from one another during the period of the RESONATE trial before the numbers at risk drop off, and the statistical information criteria do not particularly distinguish between them.

Results will be sensitive to the overall survival that is modelled for ibrutinib, but this is not reflected in the formal sensitivity analyses due to the available parameterised curves within the model projecting similar overall survivals.

Results are very sensitive to the progression free survival that is applied for ibrutinib because this determines the total ibrutinib drug costs.

There are corresponding uncertainties as to the reasonableness of applying the hazard ratios for the comparators over the period of extrapolation.

For the all patients modelling ofatumumab is considered as a comparator despite it not being in the scope. Comparators that are in the scope but are not considered are FCR, chlorambucil, corticosteroids, rituximab in isolation and BSC.

For the 17p subgroup modelling ofatumumab is considered as a comparator despite it not being in the scope. Comparators that are in the scope but are not considered are alemtuzumab and BSC.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

ERG revisions to the company base case are quite extensive. But the main changes are to:

- Apply the ITT OS hazard ratios for physician choice and idelalisib plus rituximab.
- Apply exponential OS and exponential PFS curves.
- Remove the asymmetries in the treatment of ibrutinib drug and administration costs.
- Not differentiate the non-drug routine costs of care by treatment.
- Remove the costs of ongoing biopsies from the non-drug routine costs of care.

The other model revisions have only a limited impact.

The ERG model revisions worsen the deterministic cost effectiveness estimates quite considerably.

- £71,812 per QALY vs physician choice
- £72,336 per QALY vs ofatumumab
- £88,484 per QALY vs idelalisib plus rituximab
- £62,756 per QALY vs bendamustine plus rituximab

The central probabilistic cost effectiveness estimates are slightly worse.

- £74,253 per QALY vs physician choice
- £73,789 per QALY vs ofatumumab
- £92,562 per QALY vs idelalisib plus rituximab
- £64,962 per QALY vs bendamustine plus rituximab

Reverting to the company hazard ratios improves the cost effectiveness estimates for the comparisons with physician choice and idelalisib plus rituximab.

- £67,907 per QALY vs physician choice
- £74,842 per QALY vs idelalisib plus rituximab

Applying the company alternative ITC hazard ratios for physician choice and bendamustine plus rituximab worsens the cost effectiveness estimates.

- £81,169 per QALY vs physician choice
- £99,620 per QALY vs bendamustine plus rituximab

Results will be sensitive to the overall survival that is modelled for ibrutinib, but the curves available within the model all project reasonably similar overall survivals and the model results are not particularly sensitive to which is chosen.

Reverting to the Weibull PFS curves for ibrutinib and ofatumumab, with this flowing through to the PFS curves for idelalisib plus rituximab and bendamustine plus rituximab via the hazard ratios, has a major impact. The deterministic cost effectiveness estimates improve markedly:

- £53,976 per QALY vs physician choice
- £50,545 per QALY vs ofatumumab
- £61,171 per QALY vs idelalisib plus rituximab
- £46,892 per QALY vs bendamustine plus rituximab

Patients receiving ibrutinib and idelalisib long term may tend to be those who tolerate it well and may have a higher drug utilisation than estimated from the RESONATE trial. Applying a 100% utilisation rate from week 32 worsens the cost effectiveness estimates.

- £75,109 per QALY vs physician choice
- £76,147 per QALY vs ofatumumab
- £93,156 per QALY vs idelalisib plus rituximab
- £65,617 per QALY vs bendamustine plus rituximab

For the 17p depleted subgroup the cost effectiveness estimates for ibrutinib compared to physician choice, idelalisib plus rituximab and bendamustine plus rituximab if the all patient hazard ratios can be applied to the ibrutinib 17p depleted OS and PFS curves are similar to the all patient estimates. The sensitivity of these estimates also mirrors the sensitivity of the all patient estimates.

For the 17p depleted subgroup the cost effectiveness estimate for ibrutinib compared to ofatumumab is £62,624 per QALY. If the Weibull PFS curves are used this improves to £44,745 per QALY.

The 17p depleted subgroup modelling was not implemented probabilistically.

7 End of life

The company notes that for the recent STA of idelalisib it was judged to meet the end of life criteria. It also notes that observed a median overall survival of [redacted] months, with Brown et al[86] providing supportive evidence that median survival is less than two years. Note that the NICE TAPS methods guide is ambiguous as to whether median or mean survival should be less than 24 months.

The base case company modelling estimates median survivals of [redacted] for ibrutinib, physician choice, ofatumumab, idelalisib plus rituximab and bendamustine plus rituximab respectively. The mean survival estimates are [redacted]. The means are somewhat higher than the medians due to the long tails of the parameterised curves. Which estimate is to be preferred is beyond the scope of the ERG but with regards the [redacted] year median and [redacted] year mean for idelalisib plus rituximab ERG expert opinion notes its rapidly increasing use since its recent approval, with its FAD being dated Sep 2015.

8 Overall conclusions

The ERG opinion is that the data for efficacy of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia is consistent and impressive. When compared with ofatumumab PFS and OS were highly statistically significantly improved. The OS benefit appeared to be consistent across all subgroups reflecting good outcome across severity of risk (e.g. older patients, advanced disease, multiple pre-treatments). The ERG opinion is that ibrutinib also demonstrates a good safety profile.

The company uses indirect treatment comparisons and matched adjusting indirect comparisons to compare ibrutinib to the other comparators of physician's choice, a combination of idelalisib and ofatumumab and a combination of bendamustine and rituximab to estimate the comparative effect of ibrutinib in in patients with relapsed or refractory chronic lymphocytic leukaemia. In these comparisons ibrutinib was superior in terms of PFS and OS to all included comparators. The ERG note some caution with using the estimates given only single trials were used in each comparison and the differences between trial populations.

The data provided on treatment-naïve patients only comes from 33 cases in a single non-RCT, non- comparative study. It is therefore difficult to make any definitive statement on treatment efficacy. However it is the case that a benefit of ibrutinib use was demonstrated within the single study. The data presented on R/R disease patients with 17p deletion or TP53 mutation within the non-RCT and RESONATE trial do provide evidence that the ibrutinib treatment effect is maintained compared to those without 17p deletion or TP53 mutation. The ERG opinion is that data are very limited, though promising, of good efficacy and safety of ibrutinib for use in treatment-naïve patients with 17p deletion or TP53 mutation.

A key area of uncertainty relates to the degree of extrapolation that is required for the ibrutinib overall survival and progression free survival curves. This is an unavoidable outcome of the trial duration and the impressive clinical effectiveness of ibrutinib. This also then follows through to the reasonableness of applying the hazard ratios of the ITC for the duration of the extrapolation and the resulting estimates for the

survival gains that ibrutinib will yield over its comparators. ERG expert opinion is concerned that these may be exaggerated, particularly for the comparison of ibrutinib with idelalisib plus rituximab. The company model estimates a gain of more than 75% and even the ERG revised model estimates a gain of around 60%.

If the survival curves of the model are reasonable by the end of the 20 year time horizon it is estimated that around 10% of ibrutinib patients will remain alive. The 20 year time horizon of the model may consequently truncate the patient gains from ibrutinib. But the impact upon cost effectiveness is less clear since cost effectiveness is also determined by the proportion of these patients who remain on treatment and incur the quite considerable costs of ibrutinib.

Results for the comparisons with physician choice and bendamustine plus rituximab are sensitive to whether the company base case ITC is applied or its alternative ITC. The impact of the alternative company ITC upon the comparison with bendamustine plus rituximab is a major worsening of the cost effectiveness estimate, increasing the company estimate by around 50%.

The company and the ERG disagree whether in the ITC the RESONATE ofatumumab arm should use the unadjusted ITT data or the RPSFT adjusted data. The ERG prefers the unadjusted ITT RESONATE ofatumumab data in part due to the ITC having to use the unadjusted ITT data of the comparator trials.

There is uncertainty about which if any of the ibrutinib PFS parameterised curves which have been estimated from RESONATE data should be applied within the modelling. There is little difference between these in terms of their shape during the period when reasonable numbers of patients remain at risk in RESONATE, and there is little difference between the information criteria. In the opinion of the ERG the only sensible means of choosing which if any of the parameterised PFS curves should be selected is by considering them alongside the associated overall survival curve and coming to a judgement as to which seems reasonable. Due to the Weibull PFS curve suggesting very few ibrutinib patients remain progression free but the overall survival curve suggesting that these patients have a considerable life expectancy which is not

that different from that implied by the UK life tables for the general public, the ERG has a preference for the exponential PFS curve over the Weibull PFS curve.

The company argues that the cost effectiveness estimate for ibrutinib compared to ofatumumab based upon the treatment experienced 17p depleted subgroup of the RESONATE trial is a conservative estimate for the treatment naive 17p depleted patient group who are not suitable for chemo-immunotherapy. It may be possible to argue that the clinical effectiveness estimates are conservative, but it is less obvious why the cost effectiveness estimate should be conservative. The latter in part depends upon the proportion of overall survival that is spent progression free and so incurring the quite considerable costs of ibrutinib. It is not clear why this proportion should be lower for the treatment naive 17p depleted patient group than that estimated from the treatment experienced 17p depleted subgroup of the RESONATE trial.

The company and the ERG disagree upon whether it is appropriate to treat the ibrutinib drug costs differently from the comparator drug costs:

- Use of the TTD curve in only the ibrutinib arm and no consideration of this in the ofatumumab arm, or any attempt to provide a similar analysis for the other comparators even if only be assumption.
- Assuming that the minimum of the TTD curve and the PFS curve is the proportion eligible for treatment in the ibrutinib arm.
- Applying the treatment specific drug utilisation proportion twice in the ibrutinib arm but only once in the comparator arms, which appears to reduce the ibrutinib drug costs by around a further 5%.
- Not applying the drug utilisation proportions to drug administration costs, which would reduce the costs of comparators but not ibrutinib due to ibrutinib having zero administration costs.
- Applying half cycle correction and immediate discounting to the ibrutinib drug costs but not to the comparator drug costs.

The ERG prefers to not differentiate the ongoing non-drug costs of CLL patients who have not progressed by their response status. This is in part due to ERG expert opinion which suggests that routine follow-up will not typically be differentiated by

response status, and which also suggests that patients will not typically receive ongoing repeat biopsies. It is also due to a lack of clarity around the time to peak response, the duration of peak response, quite which response rates have been used for the other comparators, and how the response rates for the other comparators have been derived in the company ITC.

Whether it is reasonable to anticipate no decline in quality of life for a given health state over the 20 year time horizon of the model is a moot point.

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Appendices

Appendix 1 ERG understanding of the double application of treatment specific estimates

The ERG may be making too much of the double application of the treatment specific estimates for reductions in the proportion of patients receiving ibrutinib when the comparator treatments only have this proportion applied once. For those familiar with modelling in excel the following may help clarify the issue.

The model contains named variables for the drug utilisation proportion of patients on treatment:

- *C_compliance_Ibr* for ibrutinib
- *C_compliance_pc* for physician choice
- *C_compliance_ofa* for ofatumumab
- *C_compliance_ir* for idelalisib plus rituximab
- *C_compliance_br* for bendamustine plus rituximab

Within the *Drug_Cost* worksheet of the model the formulae for the drug cost summary are in immediately adjacent cells as below. The column and rows have been transposed for reasons of space but the cells are immediately adjacent to one another and have a common format with a common logic to them. The physician choice costs have been calculated in the separate spreadsheet *PC_Cost_Summary* due to it being a basket of a number of treatments, but the logic of its handling in the *Drug_Cost* worksheet is the same as for the other treatments.

Column	***Drug_Costs* worksheet Row 10**	**Treatment**
AS	=IF($AR10<=32,SUM(OFFSET(AI$10,$AR10,0):OFFSET(AI$10,$AR10+3,0)),SUM(AI$42:AI$45))*C_compliance_Ibr	Ibrutinib
AT	=IF($AR10<=32,SUM(OFFSET(AJ$10,$AR10,0):OFFSET(AJ$10,$AR10+3,0)),SUM(AJ$42:AJ$45))*C_compliance_ofa	Ofatumumab
AU	=IF($AR10<=32,SUM(OFFSET(AK$10,$AR10,0):OFFSET(AK$10,$AR10+3,1)),SUM(AK$42:AL$45))*C_compliance_br	Bend.+R
AV	=IF($AR10<=32,SUM(OFFSET(AM$10,$AR10,0):OFFSET(AM$10,$AR10+3,2)),SUM(AM$42:AN$45))*C_compliance_ir	Idel.+R
AW	='PC cost summary'!F15*C_compliance_pc	Phys. Chce

The above correctly applies the treatment specific estimates for reductions in the proportion of patients receiving treatment appropriately for each treatment.

Within the *Parameter* worksheet the formulae for the drug unit costs are as below. Again, these cells are immediately adjacent to one another.

Row	***Parameter* worksheet Column F**	**Treatment**
118	='Cost Inputs'!L22*C_compliance_Ibr	Ibrutinib
119	='Cost Inputs'!L23	Bendamustine
120	='Cost Inputs'!L24	Chlorambucil
121	='Cost Inputs'!L25	Cyclophosphamide
122	='Cost Inputs'!L26	Fludarabine
123	='Cost Inputs'!L27	Ofatumumab
124	='Cost Inputs'!L28	Methylprednisolone
125	='Cost Inputs'!L29	Rituximab
126	='Cost Inputs'!L30	Idelalisib

The ERG finds it very difficult to imagine how *C_compliance_Ibr* can have been inserted by error into cell F118 without a similar error having been applied to the other treatments. In the opinion of the ERG the most reasonable interpretation of the above is that it is the model structure that the company knowingly intended to submit. The ERG urges the company to provide an account of its submitted model structure in this regard.

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ADDENDUM EXCLUDING PAS

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia

Produced by Aberdeen HTA Group

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Date completed 26 January 2016

Version 1

Additional sensitivity analyses:

ERG revised base case except:

- SA01: Biopsy costs retained
- SA02: PFS treatment costs differentiated by response estimates
- SA03: SA01 and SA02 combined.

		ICERs			
	Description	**PhysChce**	**Ofat**	**Idel+R**	**Bend+R**
All patients: No PAS					
SA01	Retain biopsy costs	£79,213	£79,986	£96,894	£69,018
SA02	Diff. PFS costs by response	£71,209	£71,659	£87,601	£62,253
SA03	SA01 and SA02 combined	£71,383	£71,272	£87,902	£62,396
17p depleted patients: No PAS					
SA01	Retain biopsy costs	£80,930	£69,349	£95,362	£71,460
SA02	Diff. PFS costs by response	£72,730	£62,030	£86,068	£64,431
SA03	SA01 and SA02 combined	£72,935	£61,713	£86,387	£64,600

Incremental analyses

Janssen base case: All comparators: All patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Phys. Choice	[redacted]	[redacted]	£2,007	0.319	£6,283
Ofatumumab	[redacted]	[redacted]	£29,102	0.642	£45,326
Idelalisib + R	[redacted]	[redacted]	£33,769	0.712	£47,397
Ibrutinib	[redacted]	[redacted]	£86,718	1.934	£44,836

Janssen base case: All comparators: 17p patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Phys. Choice	[redacted]	[redacted]	£1,678	0.235	£7,129
Ofatumumab	[redacted]	[redacted]	£26,343	0.111	£238,108
Idelalisib + R	[redacted]	[redacted]	£28,607	0.968	£29,564
Ibrutinib	[redacted]	[redacted]	£73,989	1.722	£42,967

Janssen base case: Three comparators: All patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Idelalisib + R	[redacted]	[redacted]	£64,878	1.674	£38,758
Ibrutinib	[redacted]	[redacted]	£86,718	1.934	£44,836

Janssen base case: Three comparators: 17p patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Idelalisib + R	[redacted]	[redacted]	£56,629	1.314	£43,108
Ibrutinib	[redacted]	[redacted]	£73,989	1.722	£42,967

ERG base case: All comparators: All patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Phys. Choice	[redacted]	[redacted]	£1,671	0.489	£3,418
Ofatumumab	[redacted]	[redacted]	£29,526	0.431	£68,438
Idelalisib + R	[redacted]	[redacted]	£48,966	1.059	£46,222
Ibrutinib	[redacted]	[redacted]	£151,597	1.713	£88,484

ERG base case: All comparators: 17p patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Phys. Choice	[redacted]	[redacted]	£1,420	0.365	£3,896
Ofatumumab	[redacted]	[redacted]	£26,969	-0.023	Dominated
Idelalisib + R	[redacted]	[redacted]	£66,598	1.204	£55,306
Ibrutinib	[redacted]	[redacted]	£127,923	1.471	£86,942

ERG base case: Three comparators: All patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Idelalisib + R	[redacted]	[redacted]	£80,163	1.980	£40,491
Ibrutinib	[redacted]	[redacted]	£151,597	1.713	£88,484

ERG base case: Three comparators: 17p patients: No PAS

	Cost	QALYs	Net Cost	Net QALYs	ICER
Bendamustine + R	[redacted]	[redacted]			
Idelalisib + R	[redacted]	[redacted]	£68,019	1.545	£44,015
Ibrutinib	[redacted]	[redacted]	£127,923	1.471	£86,942

Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia

ERRATUM

This document contains the ERG report errata in response to the manufacturer's factual inaccuracy check.

The following are the pages to be replaced in the original document and the nature of the change:

Page 7

The QALY of *2,647 has been corrected to 2.647*

Page 9

The following sentence:

"The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis. It seems reasonable to conclude that some and perhaps all of these are deliberate choices made by the company. If so this may raise questions about other company choices, both seen and unseen."

has been amended to:

"The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis."

Page 157

The following sentence:

"The company prefers the Weibull extrapolation as it simulates fewer patients remaining progression free within the ibrutinib arm"

has been amended to:

"Based upon expert opinion the company selected the Weibull extrapolation which simulates fewer patients remaining progression free within the ibrutinib arm."

maximum of up to five model cycles. Treatment specific drug utilisation percentages are applied to account for dose reductions and treatment holidays.

The routine follow-up costs while in progression free survival are determined by treatment specific company estimates of the proportions of patients achieving complete response, partial response and being in stable disease.

A proportion of patients are assumed to go on to receive 2nd line treatment but this only affects costs within the model.

Terminal care costs are applied when patients die.

The company model estimates are that ibrutinib more than trebles overall survival compared to physician choice, more than doubles it compared to ofatumumab and somewhat more than quadruples it compared to bendamustine plus rituximab. The gains compared to idelalisib plus rituximab are less but ibrutinib is still anticipated to result in a survival gain of more than three quarters.

These gains, coupled with longer progression free survival result in net gains of 3.289 QALYs compared to physician choice, 2.647 QALYs compared to ofatumumab, 1.934 QALYs compared to idelalisib plus rituximab and 3.608 QALYs compared to bendamustine plus rituximab. The longer survival results in considerably greater drug costs and so quite high net total costs. At list prices the net total costs are £149,589 compared to physician choice, £120,487 compared to ofatumumab, £86,718 compared to idelalisib plus rituximab and £151,595 compared to bendamustine plus rituximab.

The deterministic cost effectiveness estimates are consequently £45,486 per QALY compared to physician choice, £45,525 per QALY compared to ofatumumab, £44,836 compared to idelalisib plus rituximab and £42,016 compared to bendamustine plus rituximab.

The probabilistic cost effectiveness estimates are slightly worse, at £47,200 per QALY compared to physician choice, £47657 per QALY compared to ofatumumab,

The EQ-5D regression analysis is poorly documented, with prior analyses conducted by the company having been discarded and not being available for reporting. It also concentrates upon the IRC assessment of response, with only partial responses being categorised within this. The quality of life values of the model are taken from a simple averaging of post baseline values which may be subject to bias given missing data. It may be questionable to assume that quality of life for a given health state will be constant over the 20 year time horizon of the model.

The modelling of 2nd line therapy, which assumes a 50:50 balance between R-HDMP and HDMP may not reflect current practise. The PFS curve for these is also derived from the rituximab arm of the idelalisib plus rituximab trial.

The company model includes treatment specific estimates for reductions in the proportion of patients receiving treatment due to dose reductions and possibly also to treatment holidays while on treatment. The derivation of the drug utilisation proportions is unclear and does not particularly distinguish between dose reductions and treatment holidays. It is not obviously reasonable for the company to have assumed that idelalisib drug utilisation would more reflect that of ofatumumab than that of ibrutinib. For bendamustine plus rituximab it appears that only dose reductions have been considered and not treatment holidays, or the number of completed cycles.

The company model applies the drug utilisation proportions twice for ibrutinib but only once for the comparator treatments. Given the model structure the ERG finds it difficult to imagine how this double discount for ibrutinib can be accidental so it appears to be the intended company model structure.

There are other asymmetries in company modelling of the direct drug costs where ibrutinib has been treated in a different manner than the other comparators. The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis.

Progression free survival extrapolation: ibrutinib

During the period of the trial the curves are similar as are the information criteria, with the AIC slightly favouring the Weibull and the BIC favouring the exponential. Based upon expert opinion the company selected the Weibull extrapolation which simulates fewer patients remaining progression free within the ibrutinib arm.

The ERG is of the opinion that the reasonableness of the PFS curve can only be judged against the associated overall survival curve. ERG expert opinion as summarised in section 5.2.11 above suggests that the Weibull projects too small a proportion of ibrutinib patients as being progression free given the anticipated overall survival. Of the Weibull and the exponential the ERG consequently prefers the exponential.

Progression free survival extrapolation: ofatumumab

The submitted model only permits the Weibull curve to be used for the PFS for ofatumumab. As a consequence, it seems likely that sensitivity analyses that apply the exponential curve for PFS for the comparison of ibrutinib with ofatumumab apply the exponential for ibrutinib but the Weibull for ofatumumab. The ERG has revised the model to permit the exponential curve to be applied for ofatumumab[1].

Response rates and resource use

It appears that the response rates which are used for differentiating ongoing resource use are peak response rates for ibrutinib and ofatumumab.

The ERG asked at clarification about time to response data and duration of response data. The company responded that the data collected on response in RESONATE is presented in table 32 of the submission, but this only outlines peak response rates and nothing on the time to response or response duration. Data was supplied at clarification for trial 1102 which suggested mean times to initial response and to best

[1] Implemented in the *Raw_clinical_inputs* worksheet by setting X17=[redacted] Y17=[redacted], X18=1, Y18=1, F18=CHOOSE(ind_subgrp,X17,Y17), F19=1, F28=NORMINV(RAND(),F18[redacted]), F29=1, F39=IF(Psa_on,F28,F18), F40=1, and in the *Model(ibrutinib_vs_ofa)* worksheet setting cell N416 ='Raw clinical inputs'!F39, N417=1, N418=EXP(-N416/N417), N419=1/N417, N421= EXP(-N418*$A421^$N$419), M421=MIN(L421,CHOOSE(O5,M421,N421)), P422= IF(O421<=0.1^10,1,(O421-O422)/O421) and with the cells below N421, M421 and P422 being of the same form.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ibrutinib for treating chronic lymphocytic leukaemia [ID749]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 18 January 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Aberdeen HTA group response to Pro-forma Response

26th January 2016

Issue 1 Clarify results are without-PAS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Overall document: wherever the ICER or the cost effectiveness results are reported or discussed, it is unclear whether it is the with-PAS or without-PAS results which are reported.	Amend description of the results wherever they appear in the document to state "without-PAS".	This amendment will provide clarity and factual accuracy to the reader that the results are based on the list price and not with the PAS considered. It will also provide context that with-PAS results are available.	No factual error. No revision required. The ERG report is internally consistent with there being no mention of a PAS in the drug costs section of 5.2.8.

Issue 2 Minor typos

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7: "These gains, coupled with longer progression free survival result in net gains of 3.289 QALYs compared to physician choice, 2,647 QALYs compared to ofatumumab, 1.934 QALYs compared to idelalisib plus rituximab and 3.608 QALYs compared to bendamustine plus rituximab" Page 49: "Reflecting this split in the evidence, section 4.2.1 describes a critique of the RESONATE, PCYC1102, PCYC1103 and PCYC117 studies…" Page 70: "The results are	Amend the statement on page 7: "These gains, coupled with longer progression free survival result in net gains of 3.289 QALYs compared to physician choice, 2.647 QALYs compared to ofatumumab, 1.934 QALYs compared to idelalisib plus rituximab and 3.608 QALYs compared to bendamustine plus rituximab" Amend the statement on page 49: "Reflecting this split in the evidence, section 4.2.1 describes a critique of the RESONATE, PCYC1102, PCYC1103 and PCYC1117 studies…" Amend the statement on page 70: "The results are impressively better for those receiving ofatumumab" Amend the statement on page 133: "When coupled with the adverse event rates this led to	Typos.	The ERG agrees that the figure 2,647 is a typo and will amend accordingly. The ERG does not agree that the sentence "The results are impressively better for those receiving ibrutinib" is a typo and believes this sentence is factually correct. The proposed revision is not accepted. The other typos are minor and do not factually alter the intended meaning. The proposed revision is not

impressively better for those receiving ibrutinib” Page 133: “When coupled with the adverse event rates this led to one of costs for SAEs of…”	one-off costs for SAEs of…”		accepted.

Issue 3 Ofatumumab as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 1 and 37: "Whilst the ERG recognises that ofatumumab will be needed to connect the network of trials to address the other comparators in the company submission, it is the ERG's opinion that ofatumumab is not a valid comparator for ibrutinib given it is no longer available in the cancer drug fund."	Remove this statement entirely as clinical opinion (i.e. the most relevant opinion in this matter) supports ofatumumab as a relevant comparator. Alternatively, rephrase the statement to more accurately present the facts: "~~Whilst~~ The ERG recognises that ofatumumab will be needed to connect the network of trials to address the other comparators in the company submission. It is also important to note ~~it is the ERG's opinion~~ that ofatumumab ~~is not a valid comparator for ibrutinib given it~~ is no longer available in the Cancer Drugs Fund (CDF) as its withdrawal from the CDF list was concomitant and subsequent to the introduction of ibrutinib (Jan 2015), specifically indicating that its place in the treatment pathway is the same as ibrutinib"	If the statement remains, it should at least be amended to reflect factual accuracy: that the withdrawal of ofatumumab from the CDF list was concomitant and subsequent to the introduction of ibrutinib (Jan 2015), specifically indicating that its place in the treatment pathway is the same as ibrutinib and therefore, ofatumumab represents a suitable comparator.	This statement is ERG opinion. The proposed revision is not accepted.

Issue 4 Methods used to select OS parametric extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6: "For the all patients modelling the lognormal is selected for the first three years, despite the goodness of fit statistics, with this being followed by the exponential thereafter." Page 117: "Despite the goodness	Rephrase the statement on page 6: "For the all-patients modelling, the lognormal is selected for the first three years, considering goodness of fit statistics, external data sources, and clinical plausibility of long-term projections, with this being followed by the exponential thereafter." Rephrase the statement on page 117: "In	The amendment is to correct the description of steps taken to select the most appropriate parametric fitting. More specifically, to state "*despite* the goodness of fit statistics" would plainly be a factual inaccuracy as this was not the case	The ERG report is explicit in Table 31 and about the AIC and BIC values being similar but that bit better for the exponential. This is consistent with the company submission tables 53 and 54 which also highlight the exponential. No

of fit statistics for the all patients modelling the company applies the lognormal curve due to visual inspection of the curves."	consideration of goodness of fit statistics for the all-patients modelling, external data sources to validate long-term projections, and the clinical plausibility of projections, the company applies the lognormal curve ~~due to visual inspection of the curves.~~"	at all.	amendment necessary.

Issue 5 Dose intensity of ibrutinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9: "The company model applies the drug utilisation proportions twice for ibrutinib but only once for the comparator treatments. Given the model structure the ERG finds it difficult to imagine how this double discount for ibrutinib can be accidental so it appears to be the intended company model structure."	Remove statement: ~~"Given the model structure the ERG finds it difficult to imagine how this double discount for ibrutinib can be accidental so it appears to be the intended company model structure."~~	The supposition that the dose intensity error was introduced purposefully is speculative and unsound. This was a genuine human error, for which Janssen apologises, and we confirm this should be corrected.	The opinion is clearly stated as being that of the ERG. Appendix 1 of the ERG report clearly outlines the error and the ERG clearly stated that we thought we may have been misreading the model structure because the error was so gross and hence urged the Company to clarify the double discount. Not a factual error. No amendment necessary.

Issue 6 Asymmetries in costing within the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9: "The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis. It seems	Remove the statement: ~~"The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis. It seems reasonable to conclude that some and perhaps all of these are deliberate choices made by the company. If~~	The supposition that asymmetries were included with the intent of biasing analyses is speculative and unsound. The company can provide sound justification for any "asymmetries" noted by the ERG	It is in the opinion of the ERG that it is true that there are asymmetries and the effect of the asymmetries will bias the analysis.

reasonable to conclude that some and perhaps all of these are deliberate choices made by the company. If so this may raise questions about other company choices, both seen and unseen.”	~~so this may raise questions about other company choices, both seen and unseen.”~~	(which are primarily driven by the fact that ibrutinib is the only oral monotherapy treatment option considered in the model).	The ERG will amend the statement as follows: “The effect of each of these asymmetries is to reduce the drug costs of ibrutinib but not those of the comparators, and so bias the analysis.”

Issue 7 Epidemiology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15: "The company states that the annual incidence of CLL is 3.7 to 7 new cases per 100,000 with 2712 new cases reported in England for 2011; however, the ERG believes this refers to newly diagnosed CLL and not R/R patients, who are the population of interest for this appraisal."	We confirm that the 2,712 cases refer to newly diagnosed cases. Further information provided in Section 6 of the submission estimates cases of R/R CLL. Rephrase this statement: "The company states that the annual incidence of CLL is 3.7 to 7 new cases per 100,000 with 2,712 new cases reported in England for 2011. The majority of patients (67%) would be expected to require treatment based on published literature and of those patients, a recent audit estimates that 32% of patients would fail first-line therapy. The population of patients within the scope of this appraisal (the R/R population) is, therefore, relatively small".	These data are provided in the company submission and amending the statement on page 15 provides further factual clarity.	The statement is factually correct. The proposed revision is not accepted.

Issue 8 Probabilistic modelling of 17p deletion patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10: "The model approach, perspective and discounting is in line with the NICE TAPS methods guide, with the exception of the 17p depleted subgroup modelling not being implemented probabilistically."	Amend the statement: "The model approach, perspective and discounting is in line with the NICE TAPS methods guide ~~with the exception of the 17p depleted subgroup modelling not being implemented probabilistically~~."	The modelling has indeed been implemented probabilistically for the 17p depleted subgroup, but results were not provided in the submission for the sake of brevity. The probabilistic subgroup modelling can be provided if desired and the statement can be removed. The company can provide these data which would make this statement moot.	The statement is factually correct. The proposed revision is not accepted.

Issue 9 Comparability of populations in indirect comparisons

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94: "The patient populations are similar but the ERG think it is important to highlight the difference in del17p (the deletion of the area of chromosome 17 where the TP53 tumour suppressor gene is located). In the resonate trial the patient populations receiving ibrutinib and ofatumumab have 32.3% and 32.7% while in Jones the proportions are 26.4% for idelalisib with ofatumumab and 21.8% for ofatumumab. It is the view of the ERG that there is a poorer prognosis for those enrolled in the RESONATE trial and therefore the effect of ibrutinib may appear greater."	Remove this statement: "~~The patient populations are similar but the ERG think it is important to highlight the difference in del17p (the deletion of the area of chromosome 17 where the TP53 tumour suppressor gene is located). In the resonate trial the patient populations receiving ibrutinib and ofatumumab have 32.3% and 32.7% while in Jones the proportions are 26.4% for idelalisib with ofatumumab and 21.8% for ofatumumab. It is the view of the ERG that there is a poorer prognosis for those enrolled in the RESONATE trial and therefore the effect of ibrutinib may appear greater~~."	For it to be true that a greater treatment effect would be seen between ibrutinib and ofatumumab in a patient population with a higher proportion of 17p deletion, a superior HR would be expected in the 17p deletion subgroup compared to non-17- deletion patients. In fact the opposite is the case, as seen in Figures 8 and 14 of the ERG report, and so this supposition by the ERG is technically incorrect and therefore factually inaccurate.	This is the opinion of the ERG and not factually incorrect so no revision. The ERG agree with the Company that in RESONATE the effect of ibrutinib in the 17p deletion subgroup is larger (worse) than those without 17p deletion. This is in line with the expectation that patients with 17p deletion have poorer prognosis. Therefore there is consistent evidence that the prognosis of patients in RESONATE may be poorer compared to the Jones study (which had fewer 17 p deletion patients). The statement in the ERG report however relates to the indirect comparison with Jones study. If indeed the prognosis of patients was worse in RESONATE study then more progression events would be occurring in the ofatumumab arm of RESONATE and hence the effect of ibrutinib compared

			to idelalisib *may* be greater.

Issue 10 Crossover analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94: "The ERG also highlight that there is no adjustment for crossover in the analysis of the comparison between the combination of idelalisib and ofatumumab and ofatumumab on its own."	Amend this statement: "The ERG also highlight that there is no adjustment for crossover in the analysis of the comparison between the combination of idelalisib and ofatumumab and ofatumumab on its own. This is explained by the fact that no crossover has been reported in the publicly available trial data."	The amendment provides factual accuracy and clarifies that crossover adjustment was not applied for idelalisib combination therapy simply because no crossover information has been reported in the public domain. Had crossover been reported, we would have attempted to account for it.	The statement is factually accurate. The proposed revision is not accepted.

Issue 11 MAIC clarification question

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100: "The company were asked at clarification "Please explain the rationale for using the matching adjusted indirect comparison (MAIC) which matches 22 factors and therefore has the smallest effective sample size" but did not provide any justification apart from their earlier statement of 17p deletion status being the most important variable based on clinical input. The ERG is therefore unclear on which model should be used and there are marked differences in the HR."	Remove part of this statement and rephrase: "The company were asked at clarification "Please explain the rationale for using the matching adjusted indirect comparison (MAIC) which matches 22 factors and therefore has the smallest effective sample size" but ~~did not provide any justification apart from their earlier statement of 17p deletion status being the most important variable based on clinical input. The~~ the ERG would like further clarity on which model should be used as there are marked differences in the HR."	We were not aware that our response did not fully clarify the point for the ERG and we can provide further explanation.	The statement is factually accurate. The proposed revision is not accepted.

Issue 12 TTD vs. PFS curves

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 128: "After this point the Kaplan Meier TTD curve rises above the PFS curve so the company uses the lower proportion given by the PFS curve." Page 129: "For the other comparators no TTD Kaplan Meier curves are considered. The values of the parameterised PFS	Amend the statement on page 128: "After this point the Kaplan Meier TTD curve rises above the PFS curve, which contradicts ibrutinib's treat-to-progression, so the company uses the lower proportion given by the PFS curve." Amend the statement on page 129: "For the other comparators no TTD Kaplan Meier curves ~~are considered~~ were available. Accordingly,	The amendments provide clarity and factual accuracy as to why the company took this action (i.e. they were evidence-based). Not including these amendments suggest the company made bias assumptions to favour ibrutinib which was not the case.	The statement is factually accurate. The proposed revision is not accepted.

curve are used throughout."	PFS curves were used to inform time on treatment as the best available proxy. ~~The values of the parameterised PFS curve are used throughout~~."		

Issue 13 Half-cycle correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130: "The selective application of half cycle correction and discounting to the ibrutinib drug costs but not to the comparator drug costs or to the ibrutinib administration costs strongly suggests that the half cycle correction to the ibrutinib drug costs was a later model revision by the company."	Remove the statement: ~~"The selective application of half-cycle correction and discounting to the ibrutinib drug costs but not to the comparator drug costs or to the ibrutinib administration costs strongly suggests that the half-cycle correction to the ibrutinib drug costs was a later model revision by the company."~~	The supposition that half cycle correction was added later in model development is irrelevant and not grounded in evidence; the use of the phrase "selective application" suggests bias where none has been introduced. The company can provide further explanation on this to the ERG as primarily the decision to apply half-cycle correction in the way it appears within the model is based on differences in treatment regimen (e.g. short-course IV vs daily oral monotherapy) of the various treatment options within the model.	The statement is factually accurate. The half cycle correction was used on ibrutinib only (i.e. selectively). The proposed revision is not accepted.

Issue 14 Model validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 148: "But the model validation against the median overall survivals for the comparators is poor."	Amend the statement on page 148: "~~But~~ The model validation against the median overall survivals for the comparators is poor. This is expected due to differences in patient baseline	The amendment provides further factually accurate clarity on why the validation may initially appear poor.	The statement is factually accurate. The proposed revision is not accepted.

	characteristics across the various trials. With respect to the Österborg (PC) trial, the trial population was notably different from RESONATE. With respect to Study 119 (IO), there was a large degree of censoring at median OS and therefore when comparing to RESONATE, it is important to focus on comparisons at earlier data points (e.g. 12 months) and a good match was observed."	If the statement is left as is without amendment to explain the context, it suggests the model is not robust and Janssen believes this is not the case.	

Issue 15 Comparative efficacy of BR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 148: "The model also appears to underestimate the benefits of bendamustine plus rituximab."	Remove or amend this statement: "The model also appears to underestimate the benefits of bendamustine plus rituximab due to the data available (or lack thereof) for establishing comparative efficacy."	While the model may underestimate the benefits of BR (when using the Fischer trial data, while overestimating the benefits of BR when using the HELIOS data as tested in sensitivity analysis), this is driven by the availability of data and not by bias selection of data by the company. The amendment will provide context and add factual accuracy which will limit any bias that the unedited version of the statement may raise.	The statement is factually correct. The proposed revision is not accepted.

Issue 16 Methods used to select PFS parametric extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 157: "The company prefers the Weibull extrapolation as it simulates fewer patients remaining progression free within the ibrutinib arm"	Amend the statement: "The company selected the Weibull extrapolation considering goodness of fit statistics, visual inspection, and clinical plausibility of long-term projections."	To state that the company "*prefers* Weibull extrapolation as it simulates fewer patients remaining progression free within the ibrutinib arm" is speculation and supposition on the part of the ERG. The reasons Janssen selected Weibull are in fact as follow: • Goodness of fit statistics were reviewed as a first step. The AIC/BIC measures were very similar and therefore, selection of the most appropriate extrapolation could not be based solely on AIC/BIC. • Visual inspection found all extrapolations closely matched the RESONATE PFS KM data and therefore, this measure did not provide any further clarity. • Finally, clinical plausibility was reviewed and over the long term (i.e. over 15 years of the 20 year time horizon), Weibull resulted in no patients remaining progression free at 15 years while exponential, log-logistic and log-normal projections suggest 5%, 10%,	The ERG will revise the statement as follows: Based upon expert opinion the company selected the Weibull extrapolation which simulates fewer patients remaining progression free within the ibrutinib arm."

		and 15% of patients remain progression free, respectively. Clinical opinion was sought on this matter and it was deemed that patients would not likely remain progression free after 15 years. Therefore, the company selected the Weibull extrapolation. The exponential extrapolation was tested in a sensitivity analysis and the PFS extrapolation was further tested overall by limiting ibrutinib's treatment benefit.	

Issue 17 Rituximab mode of administration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 166: "Roche has developed subcutaneous rituximab. On the assumption that it is as effective as rituximab infusions, this would quite dramatically affect administration costs for the comparators were it to be permitted in CLL. The current rituximab EPAR permits subcutaneous rituximab for non-Hodgkin's lymphoma but still envisages only intravenous administration for CLL."	Remove this statement: "~~Roche has developed subcutaneous rituximab. On the assumption that it is as effective as rituximab infusions, this would quite dramatically affect administration costs for the comparators were it to be permitted in CLL. The current rituximab EPAR permits subcutaneous rituximab for non-Hodgkin's lymphoma but still envisages only intravenous administration for CLL~~"	This statement is conjecture and introduces confusion/alternatives unnecessarily. This is neither current practice nor is it expected to be future practice in CLL as highlighted by the ERG statement ("The current rituximab EPAR… still envisages only intravenous administration for CLL"). Therefore we suggest that it should be removed.	The statement is ERG comment. The proposed revision is not accepted. The ERG draws attention to this simply in case something changes during the course of the assessment.

Issue 18 Uptake of idelalisib combination therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 185: "…ERG expert opinion notes its rapidly increasing use since its recent approval, with its FAD being dated Sep 2015."	Remove this statement: "…~~ERG expert opinion notes its rapidly increasing use since its recent approval, with its FAD being dated Sep 2015.~~"	Current market research data contradict this statement. Please note that while both ibrutinib monotherapy and idelalisib combination therapy were available on the CDF, the prescription ratio was in the order of 80% in favour of ibrutinib (https://www.england.nhs.uk/wp-content/uploads/2015/11/cdf-quarterly-figures-april-sept-1516.xlsx).	This is the opinion of the ERG and not factually incorrect so no revision.

Additional corrections offered by Janssen	ERG response
1. Page 10: "Although the company submission states the criteria were provided in Appendix 8, the ERG could not identify the criteria in the Appendix". While this is factually accurate, it was an oversight by Janssen and we apologise. We will send this data along so that the ERG have all the information on hand and this statement can be removed. 2. Page 119: "Unfortunately, due to rewording of the ERG clarification question some values for the ITT analysis and the IPCW analysis for the 17p depleted subgroup are not available." Janssen is uncertain, based on how this phrase is written, as to who is responsible for the rewording of the ERG clarification question; if this was Janssen, it was done by mistake. We kindly ask that the ERG clarify what data they need because we are happy to provide it. We did not intentionally re-word any clarification questions.	1. Not a factual error, no change required 2. The rewording was not performed by the Company and the Company bears no responsibility for this.