NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ibrutinib for treating chronic lymphocytic leukaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ibrutinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal (see the project documents) and the public. This document should be read along with the evidence base (the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ibrutinib in the NHS in England.

For further details, see the guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 22 March 2016

Second appraisal committee meeting: 6 April 2016

Details of membership of the appraisal committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

1 Recommendations

1.1 Ibrutinib is not recommended within its marketing authorisation for treating chronic lymphocytic leukaemia, that is either:

- for people who have had at least 1 prior therapy or,
- for people with 17p deletion or TP53 mutation in whom chemo-immunotherapy is unsuitable.

1.2 People whose treatment with ibrutinib was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Ibrutinib (Imbruvica, Janssen) is a monoclonal antibody that inhibits B-cell proliferation, and promotes cell death. It is administered orally. It has a marketing authorisation for "the treatment of adult patients with chronic lymphocytic leukaemia 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 administered orally at a daily dose of 420 mg (3 tablets) until disease progression or intolerance.

2.2 The most commonly occurring (in 20% of patients of more) adverse reactions reported in the summary of product characteristics were neutropenia, anaemia, diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea and pyrexia. The most common (in 5% or more) severe adverse reactions were anaemia, neutropenia, pneumonia and thrombocytopenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price for a single tablet of ibrutinib (140 mg) is £51.10 (excluding VAT; British national formulary [BNF] online, accessed February 2016). The cost of a year's course of ibrutinib treatment is £55,954.50 (excluding VAT). The company has agreed a patient access scheme with the Department of Health. If ibrutinib had been recommended, this scheme would provide a simple discount to the list price of ibrutinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG; section 8). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company's submission included the RESONATE trial (n=391). This was an open-label multicentre trial (including the UK) comparing oral ibrutinib with intravenous ofatumumab in people with relapsing or refractory chronic lymphocytic leukaemia (CLL). All 195 patients randomised to ibrutinib and 191 of the 196 people randomised to ofatumumab received the assigned treatment (4 withdrew consent and 1 patient died). The trial included 127 people with 17p deletion mutation who had been previously treated, 63 of whom were randomised to ibrutinib and 64 of whom were randomised to ofatumumab. No people with the TP53 mutation were included in the trial. The trial was stopped early, after a positive interim analysis, at 146 progression-free survival

events and with a median time in the trial of 9.4 months (April 2013).

3.2 The primary outcome in RESONATE was progression-free survival. It was defined according to the criteria of the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL; time from randomisation to first documentation of disease progression or time to death due to any cause). Secondary outcomes included overall survival and overall response rate (based on IWCLL criteria and including complete response, complete response with incomplete haematopoietic recovery, partial response with and without lymphocytosis, stable disease and progressive disease).

3.3 In RESONATE, patients were treated with ibrutinib or ofatumumab until disease progression or adverse events. Patients were treated with ofatumumab for a maximum of 6 months; there was no limit for ibrutinib. The trial protocol permitted patients randomised to ofatumumab to switch to ibrutinib on progression of disease. The trial was open label with a blinded independent research committee assessing disease progression. After randomisation ended at 9.4 months, unblinded investigators assessed outcomes.

3.4 Of the 191 patients randomised to ofatumumab, 116 patients crossed over to ibrutinib after disease progression, as of the September 2014 data cut. The primary analysis censored patients that crossover (mathematically removing them from the survival curve), from the time of their first dose of ibrutinib (see section 3.7). The company also provided a post-hoc sensitivity analysis in which all patients in the ofatumumab arm were included irrespective of whether they went on to have ibrutinib. The company also explored adjusting for crossover by using the rank-preserving structural failure time method, inverse probability of censoring weights method, and the iterative parameter estimation algorithm. Of these,

the company chose the rank-preserving structural failure time method. The approach to censoring has an impact on overall survival results only. The main analysis chosen by the company to reflect the association between ibrutinib and overall survival was a post-hoc analysis done using data from a median follow-up at 16 months, adjusted for crossover using the rank-preserving structural failure time method.

Clinical trial results

3.5 At the interim analysis (median follow up 9.4 months) of the RESONATE trial, the hazard ratio for progression-free survival comparing ibrutinib with ofatumumab was 0.22 (95% confidence interval [CI] 0.15 to 0.32; p<0.001). At a median follow-up of 16 months, progression-free survival was longer with ibrutinib than ofatumumab. The median progression-free survival had not been reached at 16 months with ibrutinib, while the median progression-free survival was 8.1 months for ofatumumab (hazard ratio 0.106, 95% CI 0.073 to 0.153, p<0.0001).

3.6 The results for progression-free survival from the RESONATE trial in patients with 17p deletion, a prespecified subgroup, were not different to that of the whole population based on a test for heterogeneity. At the interim analysis (median follow up 9.4 months), the hazard ratio for ibrutinib compared with ofatumumab was 0.25 (95% CI 0.14 to 0.45, p value not reported). At a median follow-up of 16 months, 79% of people with 17p deletion randomised to ibrutinib had no disease progression for 12 months compared with 17% of people randomised to ofatumumab (hazard ratio not reported, p<0.001).

3.7 The company presented overall survival results from RESONATE. At the time of interim analyses, and after 57 patients in the ofatumumab group had crossed over to receive ibrutinib, the

company analysed the data by censoring patients at the time of crossover. The hazard ratio for death in the ibrutinib group was 0.43 (95% CI: 0.24 to 0.79; p=0.005). The company reanalysed the data at 18 months; and provided an analysis adjusted for cross over (120 of 196 patients crossed over from ofatumumab to ibrutinib). The company presented crossover adjusted hazard ratios using the rank-preserving structural failure time approach for the overall population and for the 17p deletion subgroup, but these were academic-in-confidence.

3.8 The most common adverse event in RESONATE was diarrhoea, occurring in about half of the patients. The adverse events were generally grade 1 or 2 in severity, managed with standard treatment, and resulted in only a few patients stopping treatment (less than15%). In comparison with ofatumumab in the RESONATE trial, overall infection rates were higher with ibrutinib (70% compared with 54%), but rates of grade 3 or above infections were similar. Serious adverse events were reported in 40% to 61% of all patients. Most were infection-related, although there were 10 cases of atrial fibrillation with ibrutinib (7 of which were grade 3 or higher in severity) compared with 1 case with ofatumumab.

Non-randomised evidence

3.9 The company included the results from 4 non-randomised non-controlled studies. Of particular interest was the single-arm study by Farooqui et al. (2014; n=51) because it included patients with untreated (n=35) or relapsed or refractory CLL (n=16) and 17p deletion (n=47) and TP53 mutation (n=4). Medians for progression-free and overall survival were not reached, but the company estimated progression-free survival at 24-months as 82% and overall survival rate at 24 months as 74% for patients who had previously received treatment.

Indirect comparisons

3.10 The scope for this appraisal identified 2 populations and their respective comparators:

- People who have received at least 1 prior therapy (that is, ibrutinib second line or beyond) with the comparators identified as:
  - fludarabine + cyclophosphamide + rituximab
  - idelalisib + rituximab
  - bendamustine +/- rituximab
  - chlorambucil +/- rituximab
  - corticosteroids +/- rituximab
  - rituximab alone for refractory disease
  - best supportive care.

- Patients with 17p deletion or TP53 mutation for which chemo-immunotherapy was not suitable (that is, ibrutinib would be first line) with the comparators identified as:
  - alemtuzumab +/- corticosteroids
  - idelalisib + rituximab
  - best supportive care.

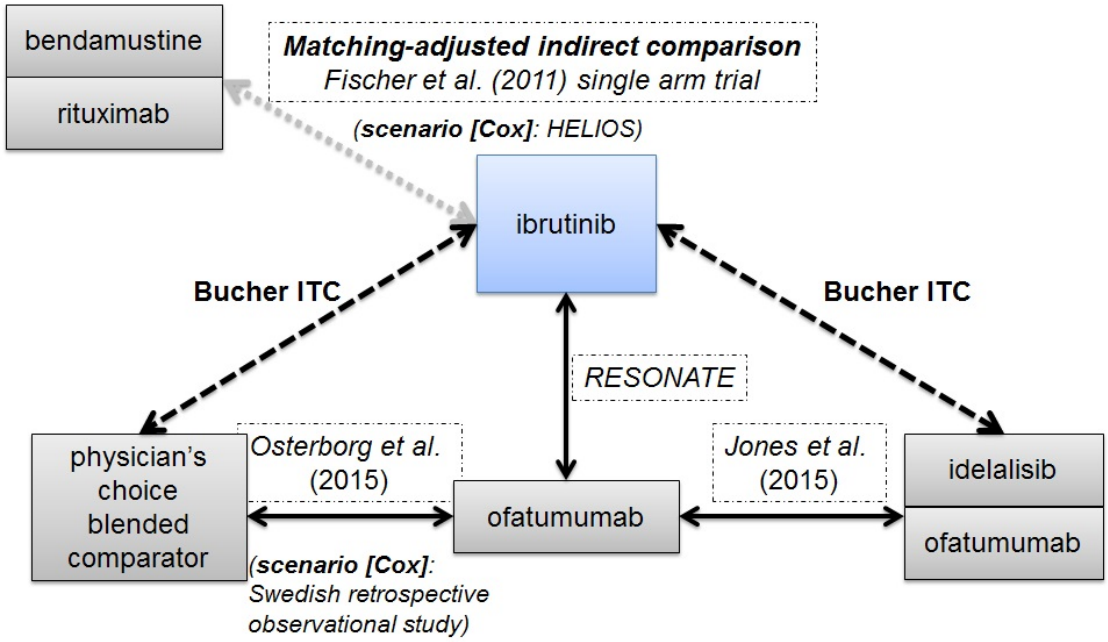
3.11 The company redefined the first population as patients having received at least 1 prior therapy, but for whom fludarabine-containing therapy in the next line of therapy was not appropriate. For this population, the company chose different comparators than those listed in the scope: ofatumumab, idelalisib plus ofatumumab, bendamustine plus rituximab and 'physician's choice' (a blended comparator reflecting multiple treatments). The company compared these using a network (see figure 1 below), using 3 methods to compare treatments within the network:

- an indirect treatment comparison

- a matching-adjusted indirect comparison (MAIC) using individual patient data from RESONATE matching it to pooled patient data from patients in the comparator study
- an indirect comparison based on multivariate Cox model using pooled individual patient level data from 2 studies, adjusted for population differences.

A summary of the trial network used by the company is shown in **Error! Reference source not found.** below.

Figure 1 Network of trials used by the company (trials in network in boxes, with indirect comparison method in brackets)



3.12 The company presented pairwise indirect treatment comparisons based on Bucher et al. (1997) comparing ibrutinib (using RESONATE, which compared ibrutinib with ofatumumab) with physician's choice (using Osterborg et al. 2014, which compared ofatumumab with physician's choice) and with idelalisib plus ofatumumab (using Jones et al. 2015, which compared ofatumumab with idelalisib plus ofatumumab). To make this comparison, the company had assumed that idelalisib plus

ofatumumab was as effective as idelalisib plus rituximab, the comparator in the scope. This was based on clinical advice given to the company. The company also stated that there were no data directly comparing rituximab and ofatumumab in patients with CLL. However, 1 trial (the ORCHARRD study) in a different population (patients with relapsed or refractory diffuse large B-cell lymphoma) compared ofatumumab with rituximab, both in combination with cisplatin, cytarabine, and dexamethasone, and showed no difference in efficacy between the 2 treatments.

3.13 For the comparison of ibrutinib with bendamustine plus rituximab, the company conducted an MAIC to compare patient level data from RESONATE with a single arm trial (Fischer et al. 2011) of bendamustine plus rituximab in people with relapsing or refractory CLL. The company matched 22 parameters using the MAIC methodology, which limited the sample size to 30 patients (from 156). The company also used a Cox multivariable model with individual patient level data from both RESONATE and HELIOS, an unpublished trial that compared ibrutinib plus bendamustine and rituximab with bendamustine plus rituximab.

3.14 The indirect analyses comparing ibrutinib with idelalisib plus ofatumumab resulted in a progression-free survival hazard ratio of 0.39 (95% CI 0.23 to 0.66) and overall survival hazard ratio of 0.50 (95% CI 0.24 to1.04).

3.15 For patients with 17p deletion who had not received previous treatment, the company provided no estimate of the effect of ibrutinib compared with any of the identified comparators. Instead, the company used the efficacy estimates from RESONATE from the 17p deletion population who had previously received treatment as a proxy for those who had not been previously treated (see section 3.6).

Evidence review group comments

3.16 The ERG consider that RESONATE was a well-conducted trial and that the RESONATE trial population is representative of the UK population. However, the ERG noted that the control treatment, ofatumumab, was not a relevant comparator for English NHS practice because it is not recommended for relapsed or refractory CLL and has been removed from the Cancer Drugs Fund.

3.17 The ERG commented on the company's adjustment for overall survival taking into account crossover in the full relapsed-refractory population using the rank-preserving structural failure time (RPSFT) model. The ERG was satisfied that the company's test for a 'common treatment effect' was appropriate. However, it considered that residual confounding remained possible, even though the company had controlled for, among others, the presence of absence of refractory disease, 17p deletion, prior lines of therapy, Eastern Cooperative Oncology Group status, age at baseline, gender and ethnicity. The ERG also noted that the only information about the Jones trial came from an abstract, and that the company only adjusted the RESONATE trial, used to compare overall survival for ibrutinib compared with idelalisib, for cross-over. The ERG stated that it would be more consistent to use the intention-to-treat estimates from all studies, including RESONATE, for the network meta-analysis.

3.18 The ERG noted that, in the Osterborg et al. (2014) trial (comparing ofatumumab with physician's choice), physician's choice did not reflect the composition of treatments offered in the UK to patients with relapsed or refractory or refractory CLL. In addition, the ERG (and the company) noted that the patients in the Osterborg trial included patients with a poorer prognosis than those in RESONATE. The ERG noted the Osterborg trial was not supported by a peer-reviewed publication. The ERG noted that the company's

analysis which restricted the RESONATE population to a population similar to Osterborg (the Bucher indirect comparison), was the most reliable approach possible with the data available for the comparison between ibrutinib and physician's choice. The ERG commented that, although the indirect treatment comparisons suggested that ibrutinib is more clinically effective than physician's choice, the sensitivity analyses done by the company confirmed that there was significant uncertainty about the magnitude of the difference between ibrutinib and these comparators.

3.19 For the comparison of ibrutinib with idelalisib, the ERG noted that the company did not adjust the patient data from RESONATE to match for patient characteristics of Jones et al. (2015; which compared idelalisib plus ofatumumab with ofatumumab plus placebo). The ERG noted the differences in populations between the trials, particularly in the proportion of patients with 17p deletion in each trial, which is associated with poorer outcomes (32.3% of people randomised to ibrutinib and 32.7% randomised to ofatumumab in RESONATE, compared with 26.4% of people randomised to idelalisib plus ofatumumab and 21.8% of people randomised to ofatumumab plus placebo in Jones et al.). The ERG also noted that, because the company had chosen an MAIC as its preferred approach to comparing ibrutinib with bendamustine plus rituximab, it may also have been possible for the company to have done an MAIC analysis to compare ibrutinib with idelalisib using the Jones et al. trial.

3.20 For the company's comparison of ibrutinib with bendamustine plus rituximab in the relapsed and refractory population, the ERG noted that the company did not justify how it had selected Fischer et al. (2011) for its base-case comparison using the matching-adjusted indirect comparison method or the HELIOS study for its sensitivity analysis using the multivariate Cox model, and queried whether

other studies may have been available. The ERG noted that the HELIOS trial included patients whose disease was not as severe as those in RESONATE. The ERG commented that it preferred the multivariate Cox model sensitivity analysis for the comparison of ibrutinib with bendamustine plus rituximab as individual patient data from both studies could be used and adjusted for patient level confounders.

Cost effectiveness

3.21 The company's submission included a de novo economic model. The company's base case included adults with relapsed or refractory disease who had received at least 1 previous treatment, and whose disease was not suitable for repeat treatment with a fludarabine-containing compound. The company did a scenario analysis based on the previously treated 17p deletion subgroup. The company chose comparators that differed from those identified in the NICE scope, and excluded comparators that were listed in the scope. The base-case analysis modelled the following comparisons in people with CLL:

- ibrutinib compared with idelalisib plus rituximab
- ibrutinib compared with ofatumumab (not in the scope)
- ibrutinib compared with physician's choice (the company's base-case comparator, not in the scope)
- ibrutinib compared with bendamustine plus rituximab

Physician's choice included: rituximab plus cyclophosphamide, doxorubicin, and prednisolone (also known as R-CHOP); bendamustine plus rituximab; fludarabine plus cyclophosphamide and rituximab; rituximab plus high dose methylprednisolone; and chlorambucil. This choice reflects the therapies in the physician's choice arm of the Osterborg et al (2014) trial (which compared it against ofatumumab).The company adjusted the proportion of

these treatments, using their costs, to reflect treatments in the UK, based on expert opinion sought by the company.

3.22 The company developed a survival partition model to assign patients to different health states. It used 4-week cycle lengths (with half-cycle corrections) and a time horizon of 20 years. The starting age of patients entering the model was 67 years. 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.

3.23 The model consisted of 3 health states, 'progression free', 'post progression', and 'death'. In the model, the company:

- used the progression-free survival curves based on fitting parametric curves to RESONATE trial data to estimate time in the progression-free health state
  - selecting the Weibull parametric function for its base case, and using the exponential function in a sensitivity analysis
- estimated the number of people in the post-progression health state as all surviving patients minus those who remained progression free
- estimated average time to death by extrapolating overall survival curves based on parametric fitting to RESONATE trial data
  - using the log-normal function for the first 3 years of the data and then the exponential function
- estimated hazard ratios for the association between ibrutinib and comparators using data from the network of indirect comparisons, except for the comparison with ofatumumab, in which the company used extrapolated results from RESONATE
- used the area under the progression-free and overall survival curves to calculate the proportion of patients in health states at given time points

- incorporated into the model the death rate of the age-matched general population so that, within each model cycle, the death rate for people with CLL was always higher than the general population.

3.24 To model the therapies patients would receive after disease progression, the company assumed that a proportion of patients in the post-progression health state would receive a subsequent line of active treatment. The company assumed that the remainder would receive best supportive care (symptom management without active intervention) immediately on entering the post-progression health state. Once patients progressed on their subsequent line of therapy, they then receive best supportive care until death.

3.25 For treatment duration, the company assumed that people take ibrutinib and idelalisib until disease progression. The average time on treatment in the company's model for ibrutinib was 2.6 years (as calculated by the NICE technical team). The company assumed that bendamustine plus rituximab or ofatumumab treatments were given for a maximum of 5 model cycles. The company applied a half cycle correction and discounting from the first cycle to the ibrutinib arm, but not to the comparator arm, which resulted in lower treatment costs for ibrutinib.

3.26 The company's base-case results included the list prices for ibrutinib and the comparators. The company did not model drug administration costs because it assumed ibrutinib is self-administered, but did include these costs for all comparators. Costs in the progression-free health state were assigned according to the distribution of response. The company based drug costs on the British National Formulary (August 2015). The company included a confidential discount for ibrutinib as part of a patient access scheme. To determine the costs for ibrutinib and its comparators,

and because not all patients in RESONATE and other clinical trials received full doses of treatment throughout the trials, the company calculated the relative dose 'intensity' from the trials. The company used these values to ensure that the doses in the model matched the trials. The company assumed that serious adverse events generate costs, and assumed that they last for 14 days. The company determined the costs of routine follow-up for progression-free survival based on the proportions of patients whose disease responded completely or partially, and whose disease was stable in each treatment group in RESONATE. The company applied the costs of terminal care when modelled patients reached the death health state.

3.27 The company used the results of the RESONATE trial, adjusted for crossover, to inform its model to compare ibrutinib with ofatumumab. It used the results of the indirect treatment comparisons to inform the model for the comparisons of ibrutinib with physician's choice, the company's base-case comparator, and with idelalisib plus ofatumumab, which the company assumed is equivalent to idelalisib plus rituximab. The company used the results of the MAIC to compare ibrutinib with bendamustine plus rituximab.

3.28 The baseline utility for patients in the progression-free health state was informed by an analysis of EQ-5D-5L data collected in RESONATE. It represented the weighted average EQ-5D-5L score for patients who remained progression-free from weeks 4 to 60 during the trial (value cannot be reported as it is academic in confidence). The utility value was not age-adjusted, having been collected from the RESONATE trial directly. After progression, patients moved into the post-progression health state, where they were assigned a utility value calculated using the baseline EQ-5D-5L score of patients entering the RESONATE trial minus a

utility decrement associated with progression (0.098; values cannot be reported as they were provided academic in confidence). Published utility increments associated with response were tested in a sensitivity analysis.

3.29 The model included utility decrements associated with adverse effects of treatment (ranging from 0.123 to 0.195). The utility decrements associated with adverse events were based on published literature (because an analysis of RESONATE EQ-5D-5L data did not identify differences for these events) and 'assumptions' for diarrhoea, pneumonia and hypertension. Serious adverse events were modelled as having quality-of-life impacts, which the company assumed lasted for 14 days.

3.30 The company presented deterministic pairwise ICERs for ibrutinib against the comparators in its decision problem for both the overall and 17p deletion population using list prices for all treatments (see table 1). Because some of the comparator treatments (idelalisib and ofatumumab) have patient access schemes, the ERG used the company's model and prices with the confidential patient access scheme discounts for ibrutinib, idelalisib and ofatumumab applied. Those results are commercial in confidence. Unless otherwise stated, all the ICERs in this document are based on list prices for all treatments.

Table 1 Company's base-case deterministic economic results, pairwise ICERs for ibrutinib compared with comparators (using list prices)

	Incremental cost	Incremental undiscounted LYs	Incremental QALYs	ICER
All patients				
Ibrutinib	..	..	..	..
Physician's choice	£149,589	5.78	3.29	£45,486

Ofatumumab	£120,487	4.69	2.65	£45,525
Idelalisib+ rituximab	£86,718	3.56	1.93	£44,836
Bendamustine + rituximab	£151,595	6.35	3.61	£42,016
17p deletion subgroup				
Ibrutinib				
Physician's choice	£128,939	4.727	2.8	£46,045
Ofatumumab	£102,596	4.592	2.69	£38,145
Idelalisib+ rituximab	£73,989	3.051	1.722	£42,967
Bendamustine + rituximab	£130,618	5.133	3.036	£43,028
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.				

3.31 The results of the one-way sensitivity analysis showed that the time horizon was the biggest driver of results. When the time horizon was reduced from 20 years to 10 years, the ICER for ibrutinib compared with physician's choice increased from £45,486 per quality-adjusted life year (QALY) gained to £57,630 per QALY gained without any of the patient access schemes applied. The remainder of the sensitivity analyses had a smaller impact on the ICER (+/- 2% of base case ICER).

3.32 The company also conducted a scenario analysis that varied the parametric distribution used for extrapolating progression-free survival. When the company used an exponential distribution, it led to a higher ICER than the base case (£67,635 vs. £44,836 per QALY gained for ibrutinib compared with idelalisib plus rituximab). The company explained that, because an exponential fit leads to a

longer projection of progression-free survival, and because people take ibrutinib until disease progression, this results in higher cost of ibrutinib treatment. The company stated that, based on the Akaike information criterion and Bayesian information criterion, it considered the Weibull distribution used in the analysis to be the best fit.

3.33 The company explored another scenario in which ibrutinib's treatment benefit was maintained for 5 years instead of indefinitely; this increased the ICER compared with the base-case (£60,050 vs. £44,836 per QALY gained for ibrutinib compared with idelalisib plus rituximab). The company also explored a scenario in which the follow-up costs for the progression-free health state (which were determined by the proportions of patients whose disease responded completely or partially, and whose disease was stable; and therefore differed across treatments) equalled the follow-up costs of stable disease for all comparator. Therefore all treatments were associated with the same cost irrespective of response rate, which removed the benefit for treatments associated with high response rates. This resulted in an ICER of about £49,877 vs. £44,836 per QALY gained for ibrutinib compared with idelalisib plus rituximab.

3.34 A scenario was conducted for the subgroup of patients with 17p deletion using data from patients in RESONATE who had the 17p deletion, to estimate the effect on the progression-free survival and overall survival associated with ibrutinib in this group. Patients with the 17p deletion in RESONATE had all received treatments before, however these data were used to represent people with the 17p deletion who have not had treatment. In this scenario, ibrutinib was compared with ofatumumab using the same assumptions that were used in the company's base-case analysis. This resulted in an

ICER of approximately £38,145 per QALY gained for ibrutinib compared with ofatumumab.

Evidence review group comments

3.35 The ERG considered that the only relevant comparators to include in the incremental analysis are bendamustine plus rituximab and idelalisib plus rituximab because ofatumumab is no longer available through the Cancer Drugs Fund and physician's choice is problematic as a blended comparator.

3.36 The ERG recognised that the immature trial data meant that the company had to extrapolate both progression-free survival and overall survival to a greater degree than is usual for cancer drugs, which increased uncertainty. The ERG observed that there was little difference between parametric curves during the trial period but, during the extrapolation period they diverged, in some cases 'quite dramatically'. For overall survival, the ERG did not agree with the company's use of the log-normal function for 3 years followed by the exponential function because the goodness-of-fit statistics favoured the exponential distribution. For progression-free survival, a key determinant of costs, the ERG acknowledged that the goodness-of-fit statistics did not provide any clear guidance as to which curve was best, but the ERG preferred an exponential curve while the company preferred a Weibull curve. The ERG interpreted the Weibull curve as predicting that too many people live for too long between disease progression and dying. ERG expert opinion suggested that the exponential curve provided a more credible proportion of patients remaining progression free given the anticipated survival. The ERG observed that using the exponential function to extrapolate progression-free survival from RESONATE was a key driver of the cost-effectiveness of ibrutinib.

3.37 The ERG found that the company had not included all the details on how it had done its regression analysis of EQ-5D, which did not allow the ERG to critique its methodology. The ERG was concerned that the definition of response focused only on the independent review committee's assessment of response, and not on response defined through the trial period. The ERG was concerned that the quality-of-life values in the model, having been taken from a simple averaging of post baseline values, may have been subject to bias because of missing data. The ERG queried the company's assumption that patients maintained the same quality of life for a given health state over the 20-year time horizon of the model.

3.38 The ERG had other concerns about the company's model.

- The ERG identified uncertainties around the response rates used in the model, including their definitions across the trials and how the rates have been derived. The ERG noted these were important in determining model costs.
- The ERG noted further differences in the modelling of direct drug costs in which the company had treated ibrutinib in a more favourable manner than the comparators, namely:
  - the use of the time to treatment discontinuation curve only in the ibrutinib arm, but not in the ofatumumab arm
  - assuming that the minimum of the time to treatment discontinuation curve and progression-free survival 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.

- The ERG disagreed that patients would receive ongoing biopsies as part of routine follow-up, and that routine follow-up would differ by response status.

3.39 The ERG stated that the modelling of second-line therapy, which assumed a 50:50 balance between rituximab plus high dose methylprednisolone and high dose methylprednisolone alone may not reflect current practice. The progression-free survival curve for these treatments was also derived from the rituximab arm of the idelalisib plus rituximab trial, which does not account for second-line therapy with high dose methylprednisolone alone.

3.40 The ERG conducted exploratory analyses. The main changes in its preferred analyses were:

- applying hazard ratios for overall survival from intention-to-treat analyses (rather than adjusted for crossover) for the comparison of ibrutinib with physician's choice and idelalisib plus rituximab (see section 3.17)
- extrapolating overall survival using an exponential curve, rather than log-normal for the first 3 years (see section 3.36)
- extrapolating progression-free survival using an exponential curve, rather than Weibull (see section 3.36)
- removing differences in drug and administration costs between ibrutinib and comparators(section 3.38)
- removing the costs of ongoing biopsies from the non-drug routine costs of care (section 3.38).

Adjusting for the above, the ICER for ibrutinib compared with idelalisib plus rituximab for the overall population rose to £88,484 per QALY gained and £62,756 per QALY gained for ibrutinib compared with bendamustine plus rituximab, using list prices.

3.41 The ERG calculated the ICERs using its preferred assumptions for the subgroup with 17p deletion for ibrutinib compared with: physician's choice; idelalisib plus rituximab; and bendamustine plus rituximab. The ERG was aware that subgroup analyses in the RESONATE showed no interaction by subgroup, one of which was defined by the presence or absence of 17p deletion. It therefore applied the 'all patient' hazard ratios for ibrutinib to the 17p deletion subgroup, and to overall survival and progression-free survival curves. Also applying the ERG's preferred adjustments (see section 3.40), the ICER for ibrutinib compared with idelalisib plus rituximab for the 17p deletion population was £86,942 per QALY gained using the list prices.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of chronic lymphocytic leukaemia (CLL) and the value placed on the benefits of ibrutinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The committee considered the impact of CLL on patients and their families and carers. The committee heard from patient experts that the uncertainty associated with living with CLL greatly affected their quality of life, both psychologically and emotionally. The committee understood that there is a risk of infection in patients with CLL even

at earliest stages of the disease, and that recurrent infections are common. The patient experts described how people become isolated from family and friends to protect themselves from infection, which stops patients from living a normal life, reduces their contribution to society and shortens life expectancy. The committee heard from clinical and patient experts that current treatment options are associated with significant adverse effects that are often life threatening, which means not all patients can have these treatments. The clinical experts also stated that once treatment is stopped because of progression, if no other treatment is available, survival is poor and therefore additional treatment options are very valuable. A patient expert described the fatigue and illness they had experienced with chemotherapy, and that repeat chemotherapy had resulted in only a short period of remission. The committee understood the importance of the availability of different treatment options for treating CLL.

4.2 The committee discussed the population relevant to this appraisal. The committee was aware that the key trial (RESONATE) included only people who were not eligible for treatment with fludarabine (because they had experienced a short progression-free interval after fludarabine-containing chemo-immunotherapy), but that the marketing authorisation did not include this restriction. The committee heard from clinical experts that they would wish to offer ibrutinib to patients who had had at least 1 round of fludarabine containing chemo-immunotherapy. The clinical experts also explained that, in practice, clinicians would not offer patients another round of fludarabine-containing chemo-immunotherapy because of significant adverse effects, and because it was unlikely to work well; so, RESONATE was reflective of clinical practice. The committee also noted that ibrutinib has a marketing authorisation for the first-line treatment of CLL in the presence of 17p deletion or

TP53 mutation in patients in whom chemo-immunotherapy is unsuitable. The committee agreed that the 2 populations relevant to the appraisal are:

- patients with CLL (without the 17p deletion or TP53 mutation) who have had at least 1 round of previous treatment, and
- patients with CLL who have the 17p deletion or TP53 mutation.

4.3 The committee discussed the relevant comparators, in the context of current clinical practice in the UK, for each of the 2 populations. The committee first discussed patients with CLL that has previously been treated and that has relapsed or is refractory. The committee noted that NICE's technology appraisal on idelalisib for treating chronic lymphocytic leukaemia recommends idelalisib plus rituximab for CLL in adults with treated disease that has relapsed within 24 months. The clinical experts stated that both ibrutinib and idelalisib have been available on the Cancer Drugs Fund (CDF) and, wherever possible, treatment with ibrutinib is preferred because of the unpredictable adverse effects associated with idelalisib. However, the experts agreed that, in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab. The committee discussed the other comparators included in the scope and the company submission:

- The committee heard from the clinical experts that bendamustine is no longer available through the CDF. It has therefore become more difficult to obtain, but it is still offered alongside rituximab for some patients, particularly those whose disease had been treated but relapsed after 24 months.
- The clinical experts stated that retreating with fludarabine plus cyclophosphamide and rituximab would only be a treatment option after a very long remission, and the committee had

agreed that the population relevant for this appraisal would not be eligible for fludarabine (see section 4.2).

- The committee heard that chlorambucil (with or without rituximab) and rituximab monotherapy were rarely used in clinical practice, and that corticosteroids (with or without rituximab) were considered a palliative option.
- The committee was aware that ofatumumab was the control treatment in the main ibrutinib trial and that the company included ofatumumab in the decision problem, even though it had not been recommended by NICE and is no longer available on the CDF. The clinical experts confirmed that since the availability of idelalisib and ibrutinib, clinicians no longer offer ofatumumab monotherapy to patients.
- The committee was aware the company had presented a comparison with physician's choice, which is a blended comparator. The committee recognised the comments from the clinical experts and the ERG that the composition presented by the company did not reflect the treatments offered in the UK (see section 3.18). The committee also had concerns about using a blended comparator because this approach averages the cost effectiveness of the treatments included, masking the cost effectiveness of the individual treatments. Therefore there is a risk of displacing effective and cost effective treatment options that are included within the blended comparator. The committee agreed that where there are several treatment options incremental cost effectiveness analysis, as preferred in the Guide to the methods of technology appraisal 2013, is a more appropriate approach. The committee concluded that the blended comparator physician's choice was not an appropriate comparator.

The committee concluded that for the population relevant to the decision problem, idelalisib plus rituximab was the most relevant comparator in clinical practice. It further concluded that for those for whom idelalisib was not appropriate (the population outside of the NICE recommendation), bendamustine was most likely to be used.

4.4 The committee noted that in clinical practice ibrutinib could be used after idelalisib. It heard from clinical experts that they would be keen to offer ibrutinib if idelalisib failed, or if patients had stopped idelalisib because of adverse events. The committee heard that it was important to have a range of treatment options because the disease tends to respond less well with each subsequent therapy, and is associated with shorter remissions. The committee, however, was not presented with any data for using ibrutinib after idelalisib, and considered that the data available could not be generalised to this setting. The committee concluded that ibrutinib could not be considered for this setting.

4.5 The committee then discussed the relevant comparator treatments for untreated CLL in patients with 17p deletion or TP53 mutation. The committee noted that NICE's technology appraisal on idelalisib for treating chronic lymphocytic leukaemia recommends idelalisib plus rituximab for untreated CLL in adults with 17p deletion or TP53 mutation. The committee heard that alemtuzumab used to be offered to people with 17p deletion or TP53 mutation, but is difficult to obtain since the company for alemtuzumab limited the marketing authorisation to multiple sclerosis, and so it is rarely used in clinical practice. The committee concluded the only comparator for this population was idelalisib plus rituximab.

4.6 The committee concluded that the comparators for this appraisal are:

- Idelalisib plus rituximab:
  - for patients with refractory or relapsed CLL whose disease progresses within 24 months after the end of previous treatment and in whom further treatment with a fludarabine-containing compound is not appropriate
  - patients with untreated CLL who have 17p deletion or TP53 mutation.
- Bendamustine plus rituximab for patients with refractory or relapsed CLL whose disease progresses 24 months after the end of previous treatment and in whom further treatment with a fludarabine containing compound is inappropriate.

4.7 The committee considered the evidence from the RESONATE trial comparing ibrutinib with ofatumumab. The committee noted that after a positive interim analysis the trial terminated early, when the median time on-trial was 9.4 months. The committee acknowledged that the company had re-analysed the data at 16 months in November 2014 (approximately 11 months before the company submitted its evidence to NICE). The committee appreciated that in RESONATE the comparison was with ofatumumab, which is neither recommended at this position in the treatment pathway by NICE, nor used in UK clinical practice (see section 4.3). The committee agreed that the trial showed ibrutinib extended progression free survival compared with ofatumumab. The committee concluded that the results from RESONATE were immature and uncertain and that the comparison with ofatumumab was not directly relevant to UK clinical practice.

4.8 The committee was aware that no data were available for untreated patients with CLL who have 17p deletion or TP53 mutation. The company stated that the treatment effect in people with 17p deletion in the RESONATE trial who had previously been treated could be generalised to people who had not received

treatment. The committee noted comments from clinical experts that treating patients with 17p deletion with fludarabine plus cyclophosphamide and rituximab worsens their disease and prognosis. The committee questioned whether the results from RESONATE could therefore be considered a conservative estimate of the treatment effect in patients who would receive ibrutinib as first-line treatment; however, without any evidence, the committee deemed this to be uncertain. The committee noted that the single-arm Farooqui et al. (2014) trial of ibrutinib presented by the company included a few patients with untreated CLL with 17p deletion, but that the company did not use this to estimate clinical efficacy. The committee concluded that there was considerable uncertainty when generalising the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with 17p deletion to the previously untreated population with 17p deletion.

4.9 The committee noted that there were no data available for people with TP53 mutation and discussed whether the results from the previously treated 17p deletion population from RESONATE could be extrapolated to patients with TP53 mutation. The clinical experts stated that, while 17p deletion was routinely tested for in the NHS, TP53 mutation was not, but that this was likely because both were on the same gene locus and tended to appear together in the same patients. The committee heard that the clinical experts expected the response would be similar in both populations. The committee concluded that it was reasonable to extrapolate data from people with 17p deletion to people with TP53 mutation.

4.10 The committee considered the indirect treatment comparisons conducted by the company, and specifically the comparison of overall survival between ibrutinib with idelalisib. The committee noted that the company adjusted the trial results of RESONATE

(which compared ibrutinib with ofatumumab) to account for cross over, but did not similarly adjust the hazard ratio from the Jones et al. (2015) trial (which compared idelalisib plus ofatumumab with ofatumumab). The committee heard from the company that this was because the Jones trial did not allow cross-over to idelalisib. However, it heard from clinical experts that they considered it very likely that, after progression, patients leaving the trial would go on to receive other life-extending therapies. The committee appreciated that adjusting one trial, but not the other, would exaggerate the benefit of ibrutinib over idelalisib plus ofatumumab. Furthermore, the company did not justify its use of the rank-preserving structural failure time method for adjusting for cross-over over other methods, for example, the inverse probability of censoring weighted method. The evidence review group (ERG) commented, and the committee agreed, that this was inconsistent and that it would have been more appropriate for the company to use the intention-to-treat analysis from RESONATE to conduct its indirect comparisons. The committee concluded that adjusting for the effect of treatment crossover on overall survival was appropriate, but it was not appropriate to do so for only 1 trial in the indirect comparison network.

4.11 The committee further discussed the comparison of ibrutinib with idelalisib. It noted that the scope included idelalisib plus rituximab as a comparator, but that the company presented results for ibrutinib compared with idelalisib plus ofatumumab (not rituximab).

- The committee was aware that a trial comparing idelalisib plus rituximab with rituximab was available (Study 116), and questioned why the company had not included this in its network of studies. The company stated in the meeting that it had attempted a matching-adjusted indirect comparison (MAIC) but did not detail or describe it in the submission. The company

stated it did not include the MAIC because it had substantial limitations including differences in trial design and follow-up and, in the company's opinion, an indirect comparison of ibrutinib with idelalisib plus ofatumumab provided more robust results. The committee, however, considered the details and results of the MAIC for idelalisib plus rituximab would have been valuable in its decision making.

- The committee understood that the company had taken this approach because it considered that idelalisib plus ofatumumab was an appropriate proxy for idelalisib plus rituximab. The committee from the company and clinical experts that idelalisib plus ofatumumab and idelalisib plus rituximab could be considered equivalent in terms of efficacy. The company also stated that in the appraisal of idelalisib, the committee had accepted that rituximab and ofatumumab were interchangeable in terms of efficacy. However, the committee noted that in the idelalisib appraisal, it was rituximab and ofatumumab monotherapy that were accepted as having equal efficacy, due to a lack of available evidence, rather than each in combination with idelalisib.

The committee considered that there are uncertainties around the assumptions applied to the comparison of ibrutinib with idelalisib plus rituximab. It concluded that it had not been presented with a clear exploration of the evidence available that would enable it to determine whether idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab for the purposes of the comparison with ibrutinib.

4.12 The committee considered the company's comparison of ibrutinib with bendamustine plus rituximab using an MAIC to match the RESONATE population to the Fischer et al (2011) trial population. The company chose to match 22 parameters using the MAIC methodology, and this limited the sample size to 30 patients,

reduced from 156 available in the ibrutinib arm of RESONATE. The ERG observed that the more covariates the company chose, the smaller the numbers in the analysis, and the more favourable the hazard ratio for ibrutinib (see section 3.13). By comparison, the alternative Cox multivariate analyses (see section 3.13), using data from the HELIOS trial presented by the company, had the advantage of being able to use individual patient data from both trials, allowing for adjustment of potential confounders. Although the company stated that disease severity in the RESONATE trial population was greater than in the HELIOS trial, the committee concluded that the Cox multivariate analysis provided a statistically more robust analysis with which to compare ibrutinib with bendamustine plus rituximab. The committee further concluded that, based on the Cox multivariate analysis, ibrutinib improves progression-free and overall survival compared with bendamustine plus rituximab.

4.13 The committee considered the clinical benefits of treatment with ibrutinib compared with idelalisib. The committee reiterated its concerns about the RESONATE trial, and the uncertainty around the company's indirect comparisons, but took note of the promising results associated with ibrutinib. The committee heard from the patient experts about how ibrutinib changed their lives, and provides long-lasting progression-free survival for many patients. The committee heard from clinical experts that ibrutinib is very well tolerated in most patients. It noted that some adverse reactions can be serious (such as atrial fibrillation), but that these are manageable and less severe than those seen with other treatments for CLL. It noted, however, that idelalisib is associated with colitis, and it is not possible for clinicians to identify in advance which patients might develop colitis. It heard from clinicians that, because of the risks associated with idelalisib, their preference would be to

offer ibrutinib. The committee concluded that there was considerable uncertainty around the progression free and overall survival benefits of ibrutinib compared idelalisib plus rituximab, but agreed ibrutinib was likely to offer a more preferable toxicity profile.

Cost effectiveness

4.14 The committee considered the effectiveness of treatment over time in the company's model. The committee noted that the company had assumed constant benefits from ibrutinib over the entire course of the model. The committee heard from clinical experts that the benefits of ibrutinib were likely to decrease over time. The committee noted that a scenario analysis done by the company (see section 3.33), which reduced the duration of benefits with ibrutinib to 5 years increased the ICER for ibrutinib compared with idelalisib plus rituximab. The committee agreed that this analysis should be considered as part of its decision making.

4.15 The committee considered the company's extrapolation of data from the RESONATE trial over the time horizon of the model for progression-free survival and overall survival. The committee and the ERG noted that data were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of RESONATE), which led to uncertainty. The committee noted that the company chose a Weibull curve to calculate progression-free survival although the exponential curve provided a better fit. The committee noted that for overall survival the company chose the log-normal function for the first 3 years and then the exponential function, but the rationale for this was not clear considering that the exponential function provided a better fit to the Kaplan-Meier overall survival data. The committee noted that the model predicted that some patients live with progressed disease for an improbably long time before dying, recalling that the

clinicians observed that patient do not live long periods with progressed disease. The committee noted that the ERG used the exponential function to extrapolate both progression-free survival and overall survival, which provided a more credible period of time in progressed disease. The committee noted that using the exponential function to extrapolate progression-free survival from RESONATE was a key driver of the cost-effectiveness results. The committee concluded that there was considerable uncertainty around the extrapolations over 20 years in the company's model, but it preferred the exponential distributions.

4.16 The committee considered the face validity of the extrapolation of overall survival results when comparing ibrutinib with idelalisib. The committee noted that the company's model predicted that 10 times as many patients who take ibrutinib would be alive at 20 years compared with patients taking idelalisib plus rituximab. The committee considered this improbable and could be due to the indirect comparison generating biased results. The committee concluded that the degree of benefit estimated by the company's model was not supported by the data or clinical experience.

4.17 The committee considered the model inputs for the 17p deletion and TP53 populations. The committee noted that the company only compared ibrutinib with ofatumumab in the 17p deletion population. The ERG had, however, explored the cost effectiveness of ibrutinib compared with idelalisib plus rituximab and bendamustine plus rituximab in this subgroup. However, most of the comparator data in the economic model were not specific to the 17p deletion population. This included the hazard ratios for progression-free and overall survival, which were based on the overall population. Additionally, the committee remained unsure of whether the results could be extended to people with previously untreated CLL, or the TP53 population (see section 4.9). The committee took note of the

unmet need for treatment options in these populations. It was aware of the lack of evidence available for these subgroups and agreed this data was the best available and could be used to support decision making in the untreated and TP53 population. The committee concluded that, because the data for the 17p deletion or TP53 mutation populations were uncertain and that the data did not include evidence for the untreated 17p deletion population or the TP53 mutation population, the results from the model were associated with uncertainty.

4.18 The committee considered the time horizon used by the company in its modelling. The committee noted that the company used a 20-year horizon in its base case, and conducted sensitivity analyses varying this to 10 year and 30 years. The committee noted that incremental cost-effectiveness ratios (ICERs) were sensitive to the time horizon chosen, and the ICER increased when the horizon was shortened. The ERG commented that 20 years may be too short a time horizon because a proportion of the population treated with ibrutinib modelled by the company were still alive at the end of this time period. However, the committee heard from clinical experts that, with a median age of 70 years, a time horizon of 20 years might be too long and that the modelling of progression-free survival and overall survival seemed to be unrealistic (see section 4.19). The committee concluded that, although there was some uncertainty about the most appropriate time horizon, it accepted that the 20-year time horizon was suitable for decision-making.

4.19 The committee understood that time to progression determined treatment duration, which in turn determined the cost of treatment. Having heard that clinicians in the NHS may continue to offer ibrutinib after disease progression, the committee considered that this could contribute to costs beyond those modelled by the

company. The committee concluded that, while there may be continued benefit from treatment with ibrutinib post progression, it was uncertain what impact this would have on the cost effectiveness of ibrutinib.

4.20 The committee considered the company's assumptions around the cost of routine follow-up. The committee noted that, for patients before disease progression (in the progression-free health state), costs of routine follow-up were determined by disease response to treatment as measured in RESONATE. The company included costs of repeat bone marrow biopsies every 2 years as part of these costs. The committee heard from clinical experts that patients whose disease has responded to treatment would not be followed up differently depending on the level of response to treatment. The committee also heard that doctors in the UK would not routinely and repeatedly biopsy patients. The committee was aware that the ERG had corrected for both these assumptions in its exploratory analyses, and the committee concluded that this was appropriate.

4.21 The committee considered the health-related quality-of life-evidence presented by the company. The committee noted that EQ-5D data were collected during the RESONATE trial. The committee noted that the quality-of-life values collected at baseline before treatment did not differ much from those collected during treatment in both arms of RESONATE. The clinical experts commented that this did not reflect their clinical experience, stating that symptoms improve immediately with ibrutinib and patients have a very good quality of life unless they have an adverse event. Having heard the positive experience of patients with ibrutinib, particularly with regard to energy levels and lack of side effects, the committee was concerned that the quality-of-life benefits may not have been appropriately captured, noting that the EQ-5D does not directly measure fatigue. The committee concluded that the EQ-5D

may not have fully captured the experience of patients with CLL, and the quality of life benefit with ibrutinib may have been underestimated in the model.

4.22 The committee considered the utility values applied in the company's model. The committee heard from the clinical experts that they would not expect the utility values in the post-progression health state to be as high as the company has predicted them to be (see section 3.28). The committee noted that the values used by the company did not reflect the reality described by the clinical experts. The committee was also aware that the utilities had not been age adjusted. The committee concluded that the company's choice of utilities in the post-progression health state were likely to be overestimated and should have been age adjusted.

4.23 The committee considered the most plausible ICERs based on the evidence available. The committee noted the changes made by the ERG in its exploratory analyses and agreed that these reflected the committee's preferred assumptions. These included:

- applying the hazard ratio for overall survival from the intention-to-treat analysis from RESONATE to the indirect comparison with idelalisib plus ofatumumab (see section 3.17)
- using the exponential function to extrapolate the overall survival and progression-free Kaplan-Meier survival curves from RESONATE (see section 3.36)
- removing the further differences in drug and administration costs (section 3.38)
- removing the costs of ongoing biopsies (section 3.38).

4.24 The committee noted that with these changes made, the ICERs with patient access schemes included were all substantially greater

than £30,000 per quality adjusted life-year (QALY). For reference, the ICERs based on list prices were:

- For patients with refractory or relapsed CLL whose disease progresses within 24 months of previous treatment, the most plausible ICER was £88,500 per QALY gained for ibrutinib compared with idelalisib plus rituximab.
- For patients with refractory or relapsed CLL whose disease progresses after 24 months of previous treatment, the most plausible ICER was £62,800 per QALY gained for ibrutinib compared with bendamustine plus rituximab.
- For patients with CLL who have 17p deletion or TP53 mutation, the most plausible ICER was £87,000 per QALY gained for ibrutinib compared with idelalisib plus rituximab.

The committee was aware that these ICERs did not include the ERG exploration of limiting duration of benefit with ibrutinib to 5 years. The committee recalled that this would increase the committee's preferred ICERs (see section 3.33). The committee also reiterated that these ICERs were associated with substantial uncertainty relating to efficacy estimates, utility values and long term outcomes.

4.25 The committee recognised that idelalisib plus rituximab has only recently become available and therefore differences between idelalisib plus rituximab and ibrutinib in efficacy estimates, utility values and long-term outcomes are unknown. In the absence of robust data to support a difference between the treatments, as proposed by the company, the committee agreed that some consideration should be given to their relative acquisition costs. The committee agreed that the uncertain benefits of ibrutinib compared with idelalisib plus rituximab did not warrant the significant additional acquisition cost of ibrutinib compared with

idelalisib plus rituximab (when patient access schemes were applied).

Innovation

4.26 The committee considered whether ibrutinib could be considered an innovative treatment. The committee heard from both the patient representatives and clinical experts that ibrutinib was an important new technology in the treatment of CLL. The committee heard that patients appreciated how well the treatment worked and how easy it was to take as an oral treatment. The committee heard from the company that ibrutinib is a 'first-in-class' treatment and that it fulfils an unmet need, particularly in people with 17p deletion and TP53 mutation, in which there are few treatment options. The committee also heard that some of the benefits of ibrutinib may not have been captured in the modelling, such as the impact on fatigue (see section 4.20). The committee concluded that ibrutinib could be considered an innovative treatment.

End of life

4.27 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.28 The committee considered the populations in the appraisal separately to determine whether the end-of-life criteria applied. The committee was aware that before idelalisib had been recommended as a treatment option, patients lived for a shorter length of time. In the current treatment landscape, the committee was unsure whether the life expectancy for patients with CLL would be less than 24 months. The committee noted that the company's evidence about life expectancy for people who had previously been treated with fludarabine plus cyclophosphamide and rituximab was from a cohort of Swedish patients on therapies comprising physician's choice, which the committee noted did not represent the treatments in the NHS. The committee noted that the source of this life-expectancy estimate was unpublished data held by the company. During the meeting, the committee queried how many patients had died in the cohort, which the company could not provide. One clinical expert commented that several CLL registries exist, and the committee was aware that the company itself manages a CLL registry. The committee noted that this evidence had not been included in the company's submission. The committee also noted that no evidence was provided about the life expectancy of patients with the 17p deletion or TP53 mutation. The company had not provided sufficient evidence to confirm the first criteria, and therefore the committee did not discuss end of life further. The committee concluded that the end-of-life criteria had not been met, mainly because the company did not provide sufficient evidence to support it being applied.

4.29 The committee considered all the evidence before it and agreed that ibrutinib represented an important treatment in CLL, but because of the numerous uncertainties in the evidence base and economic modelling presented by the company, and because of the incremental cost effectiveness ratios, it could not recommend ibrutinib for CLL as a cost effective use of NHS resources.

4.30 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Ibrutinib for treating CLL**	**Section**
Key conclusion		
Ibrutinib is not recommended within its marketing authorisation for treating chronic lymphocytic leukaemia, that is either: • for people who have had at least 1 prior therapy or, • for people with 17p deletion or TP53 mutation in whom chemo-immunotherapy is unsuitable. The committee considered all the evidence before it and agreed that ibrutinib represented an important treatment in CLL, but because of the numerous uncertainties in the evidence base and economic		1.1, 4.29

modelling presented by the company, and because of the incremental cost effectiveness ratios, it could not recommend ibrutinib for CLL as a cost effective use of NHS resources.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard from clinical and patient experts that current treatment options are associated with significant adverse effects that are often life-threatening. The committee understood the importance of the availability of different treatment options for treating CLL. The treatment options currently used in England in the NHS for CLL are: • Idelalisib plus rituximab: o for patients with refractory or relapsed CLL whose disease progresses within 24 months after the end of previous treatment and who are not appropriate for further treatment with a fludarabine-containing compound o as first-line treatment for patients with CLL who have 17p deletion or TP53 mutation. • Bendamustine plus rituximab for patients with refractory or relapsed CLL whose disease progresses 24 months after the end of previous treatment and in whom further treatment with a fludarabine containing compound is inappropriate.	4.1, 4.7

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee concluded that ibrutinib improves progression-free and overall survival compared with bendamustine plus rituximab. The committee concluded that there was considerable uncertainty around the progression free and overall survival benefits of ibrutinib compared idelalisib plus rituximab, but agreed ibrutinib was likely to offer a more preferable toxicity profile. The committee heard from both the patient representatives and clinical experts that ibrutinib is an important new technology in the treatment of CLL and that patients appreciate how well the treatment works and how easy it is to take as an oral treatment. The committee heard from the company that ibrutinib is a 'first-in-class' treatment and that it fulfils an unmet need, particularly in people with 17p deletion and TP53 mutation, in which there are few treatment options. The committee concluded that ibrutinib could be considered an innovative treatment.	4.12, 4.13 4.26
What is the position of the treatment in the pathway of care for the condition?	Ibrutinib has a marketing authorisation for the treatment of adult patients with CLL who have received at least 1 prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo immunotherapy. The committee heard from clinical experts that they would wish to	4.2

	offer ibrutinib to patients with CLL who have received at least 1 prior therapy with fludarabine, and as first line therapy for people with the 17p deletion or TP53 mutation.	
Adverse reactions	The committee concluded that ibrutinib was likely to offer a more preferable toxicity profile.	4.13
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that after a positive interim analysis the trial terminated the RESONATE trial early when the median time on-trial was 9.4 months. The committee acknowledged that the company had re-analysed the data at 16 months in November 2014 (approximately 11 months before the company submitted its evidence to NICE). The committee appreciated that in RESONATE the comparison was with ofatumumab, which is neither recommended at this position in the treatment pathway by NICE, nor used in UK clinical practice. The committee was aware that no data were available for untreated patients with CLL who have 17p deletion or TP53 mutation. The committee noted comments from clinical experts that treating patients with 17p deletion with fludarabine plus cyclophosphamide and rituximab worsened their disease and prognosis. The committee concluded that there was considerable uncertainty when	4.7, 4.8, 4.9, 4.4

	generalising the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with 17p deletion to the previously untreated population with 17p deletion. The committee noted that there were no data available for people with TP53 mutation but concluded that it was reasonable to extrapolate data from people with 17p deletion to people with TP53 mutation. The committee noted that in clinical practice ibrutinib could be used after idelalisib. The committee was not presented with any data for using ibrutinib after idelalisib, and considered that the data available could not be generalised to this setting. The committee concluded that ibrutinib could not be considered for this setting.	
Relevance to general clinical practice in the NHS	The committee concluded that the comparators for this appraisal are: • Idelalisib plus rituximab: – for patients with refractory or relapsed CLL whose disease progresses within 24 months after the end of previous treatment and in whom further treatment with a fludarabine-containing compound is not appropriate – patients with untreated CLL who have 17p deletion or TP53 mutation.	4.6

	• Bendamustine plus rituximab for patients with refractory or relapsed CLL whose disease progresses 24 months after the end of previous treatment and in whom further treatment with a fludarabine containing compound is inappropriate.	
Uncertainties generated by the evidence	The committee concluded that the results from RESONATE were immature and uncertain and that the comparison with ofatumumab was not directly relevant to UK clinical practice. The committee concluded that there was considerable uncertainty when generalising the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with 17p deletion to the previously untreated population with 17p deletion. The committee concluded that, while adjusting for the effect of treatment crossover on overall survival was appropriate, with methods sufficiently justified, it was not appropriate to do so for only 1 trial in the indirect comparison network. The committee considered that there are uncertainties around the assumptions applied to the comparison of ibrutinib with idelalisib plus rituximab. It concluded that it had not been presented with a clear exploration of the evidence available that would enable it to	4.7, 4.8, 4.10, 4.11

	determine whether idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab for the purposes of the comparison with ibrutinib.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee was aware that no data were available for untreated patients with CLL who have 17p deletion or TP53 mutation. The company stated that the treatment effect in people with 17p deletion in the RESONATE trial who had previously been treated could be generalised to people who had not received treatment. The committee noted comments from clinical experts that treating patients with 17p deletion with fludarabine plus cyclophosphamide and rituximab worsens their disease and prognosis. The committee questioned whether the results from RESONATE could therefore be considered a conservative estimate of the treatment effect in patients who would receive ibrutinib as first-line treatment; however, without any evidence, the committee deemed this to be uncertain. The committee concluded that there was considerable uncertainty when generalising the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with 17p deletion to the previously untreated population with 17p deletion. Although no data were available for people with the TP53 mutation, the committee heard from clinical experts that both the 17p and	4.8, 4.9

	TP53 mutation occur on the same gene locus and tended to appear together in patients. The committee heard that the clinical experts expected the response would be similar in both populations. The committee concluded that it was reasonable to extrapolate data from people with 17p deletion to people with TP53 mutation.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee agreed that RESONATE showed ibrutinib extended progression free survival compared with ofatumumab, although the comparison was with ofatumumab, which is neither recommended at this position in the treatment pathway by NICE, nor used in UK clinical practice. The committee concluded that the Cox multivariate analysis provided a statistically more robust analysis with which to compare ibrutinib with bendamustine plus rituximab. The committee concluded that, based on the Cox multivariate analysis, ibrutinib improves progression-free and overall survival compared with bendamustine plus rituximab. The committee concluded that there was considerable uncertainty around the progression free and overall survival benefits of ibrutinib compared idelalisib plus rituximab, but agreed ibrutinib was likely to offer a more preferable toxicity profile.	4.7, 4.12, 4.13

Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that data from RESONATE were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of the study). The committee noted that the company only compared ibrutinib with ofatumumab in the 17p deletion population. The ERG had, however, explored the cost effectiveness of ibrutinib compared with idelalisib plus rituximab and bendamustine plus rituximab in this subgroup. However, most of the comparator data in the economic model were not specific to the 17p deletion population. This included the hazard ratios for progression-free and overall survival, which were based on the overall population.	4.16, 4.17
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that there was considerable uncertainty around the extrapolations over 20 years in the company's model, but it preferred the exponential distributions. The committee considered the face validity of the extrapolation of overall survival results when comparing ibrutinib with idelalisib noting that the company's model predicted that 10 times as many people who take ibrutinib	4.15, 4.16, 4.17, 4.18, 4.19, 4.24

	would be alive at 20 years compared with those taking idelalisib plus rituximab. The committee considered this improbable and could be due to the indirect comparison generating biased results. The committee noted that data from RESONATE were immature (notably, median progression-free survival and overall survival had not been reached in the ibrutinib arm of RESONATE), which led to considerable uncertainty around the extrapolations of progression-free survival and overall survival over 20 years in the company's model. The committee acknowledged that data are sparse for people with the 17p deletion or TP53 mutation. Nevertheless, the committee concluded that, because the data for the 17p deletion or TP53 mutation populations were uncertain and that the data did not include evidence for the untreated 17p deletion population, the results from the model for these populations were associated with uncertainty. The committee noted the ERG comment that 20 years may be too short a time horizon because a proportion of the population treated with ibrutinib modelled by the company were still alive at the end of this time period. The committee concluded that, although there was some uncertainty about the most appropriate	

	time horizon, it accepted that the 20-year time horizon was suitable for decision-making. The committee concluded that, while there may be benefits from treatment with ibrutinib post progression, it was uncertain what impact this would have on the cost effectiveness of ibrutinib. The committee was aware that these ICERs did not include the ERG exploration of limiting duration of benefit with ibrutinib to 5 years. The committee recalled that this would increase the committee's preferred ICERs (see section 3.33). The committee also reiterated that these ICERs were associated with substantial uncertainty resulting from uncertainty around efficacy estimates, utility values and long term outcomes.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model,	The quality-of-life values collected at baseline before treatment did not differ much from those collected during treatment in both arms of RESONATE. The clinical experts commented that this did not reflect their clinical experience, stating that symptoms improve immediately with ibrutinib and patients have a very good quality of life unless they have an adverse event. Having heard the positive experience of patients with ibrutinib, particularly with regard to energy levels and lack of side effects, the committee was concerned that the quality-of-life benefits may	4.21, 4.22

and how have they been considered?	not have been appropriately captured, noting that the EQ-5D does not directly measure fatigue. The committee concluded that the EQ-5D may not have fully captured the experience of patients with CLL. The clinical experts told committee that they would not expect the utility values in the post-progression health state to be as high as the company has predicted them to be (see section 3.28). The committee was also aware that the utilities had not been age adjusted. The committee concluded that the company's choice of utilities in the post-progression health state were likely to be overestimated and should have been age adjusted..	
Are there specific groups of people for whom the technology is particularly cost effective?	No.	
What are the key drivers of cost effectiveness?	The key drivers of cost effectiveness are the choice of Kaplan-Meier parametric curve, time horizon and length of time of benefit for ibrutinib.	4.14, 4.15, 4.18
Most likely cost-effectiveness estimate (given as	Based on the committee' s preferred assumptions, the committee considered that: • For patients with refractory or relapsed	4.24

an ICER)	CLL whose disease progresses within 24 months of previous treatment, the most plausible ICER was £88,500 per QALY gained for ibrutinib compared with idelalisib plus rituximab. • For patients with refractory or relapsed CLL whose disease progresses after 24 months of previous treatment, the most plausible ICER was £62,800 per QALY gained for ibrutinib compared with bendamustine plus rituximab. • For patients with CLL who have 17p deletion or TP53 mutation, the most plausible ICER was £87,000 per QALY gained for ibrutinib compared with idelalisib plus rituximab. When the confidential patient access schemes were applied, these ICERs remained substantially above £30,000 per QALY gained.	
Additional factors taken into account		
End-of-life considerations	The committee was aware that before idelalisib had been recommended as a treatment option, patients lived for a shorter length of time. In the current treatment landscape, the committee was unsure whether the life expectancy for patients with CLL would be less than 24 months. The	4.28

	committee noted that the company's evidence about life expectancy for people who had previously been treated with fludarabine plus cyclophosphamide and rituximab was from a cohort of Swedish patients on therapies comprising physician's choice, which the committee noted did not represent the treatments in the NHS. The committee also noted that no evidence was provided about the life expectancy of patients with the 17p deletion or TP53 mutation. The company had not provided sufficient evidence to confirm the first criteria, and therefore the committee did not discuss end of life further. The committee concluded that the end-of-life criteria had not been met, mainly because the company did not provide sufficient evidence to support it being applied.	
Equalities considerations and social value judgements	No equality issues were raised during the appraisal.	

5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Idelalisib for treating chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance TA359
- Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance TA344
- Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (2015) NICE technology appraisal guidance TA343
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (2011) NICE technology appraisal guidance TA216
- Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (2010) NICE technology appraisal guidance TA202
- Rituximab for the treatment of relapsed chronic lymphocytic leukaemia (2010) NICE technology appraisal guidance TA193
- Rituximab for the first-line treatment of chronic lymphocytic leukaemia (2009) NICE technology appraisal guidance TA174
- Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (2001) NICE technology appraisal guidance TA29

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda I. Adler

Chair, Appraisal Committee

February 2016

7 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Sanjeev Patel (Vice Chair)
Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Rebecca Kearney

Clinical Lecturer, University of Warwick

Dr Sanjay Kinra

Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne

Professorial Fellow in Public Health, Wessex Institute, University of Southampton

Mr Christopher O'Regan

Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Nigel de Kare Silver

General Practioner

Ms Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Ken Stein

Professor of Public Health, University of Exeter Medical School

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Mr Nigel Westwood

Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz

Technical Lead

Raisa Sidhu

Technical Adviser

Jeremy Powell

Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA:

- Cummins E, Culligan D, Cooper D et al, Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia [ID 749], January 2016

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Janssen

II. Professional/expert and patient/carer groups:

- British Society for Haematology
- Cancer Research UK
- Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Chronic Lymphocytic Leukaemia Forum

- III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

- IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Roche by attending the initial committee discussion and providing a written statement to the committee. They are invited to comment on the ACD.

- Dr George Follows, Consultant Haematologist, Cambridge University Hospitals NHS Foundation Trust, nominated by the UK CLL Forum – clinical expert
- Professor Peter Hillmen, Professor of experimental haematology, University of Leeds, nominated by Janssen – clinical expert
- Molly Fletcher, nominated by the CLL Support Association – patient expert
- Nick York, Trustee of the CLL Support Association, nominated by the CLL – patient expert

D. Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Janssen