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 June 2016

Third appraisal committee meeting: 4 August 2016

Details of membership of the appraisal committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

1 Recommendations

1.1 Ibrutinib is not recommended for treating chronic lymphocytic leukaemia in adults without a 17p deletion or TP53 mutation.

1.2 The appraisal committee is minded not to recommend ibrutinib as an option for treating chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation. The committee invites the company to submit a proposal for inclusion in the Cancer Drugs Fund. This proposal should:

- detail any commercial access arrangements
- demonstrate a plausible potential for cost effectiveness
- detail how the proposed data collection will address the key clinical uncertainties described in sections 4 and 6
- state the likelihood that additional research will reduce uncertainty enough to support positive guidance in the future
- state the proposed data collection approach and current status (for example, an on-going randomised controlled trial, an existing registry or a new data collection proposal)
- state the timeframe for availability of the results
- if appropriate data collection is on-going, summarise the study protocol
- if appropriate data collection is not on-going, and therefore data collection would be started to address the key areas of uncertainty
  - summarise the proposed data collection protocol specifying:
    - ◊ methodology
    - ◊ study governance details (information governance, patient consent, ethical approval)
    - ◊ analysis plans
    - ◊ data access and accountability for disseminating results

- ◊ accountability for monitoring and validation
- ◊ any funding arrangements.

1.3 This guidance is not intended to affect the position of patients whose treatment with ibrutinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Ibrutinib (Imbruvica, Janssen) is a covalent inhibitor of Bruton's tyrosine kinase. It has a marketing authorisation to treat "adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo immunotherapy". Ibrutinib is administered orally at a daily dose of 420 mg (3 tablets) until disease progression or intolerance.

2.2 The most common adverse reactions (occurring in 20% of patients of more) 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. 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 8) considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG; section 9). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company's submission included RESONATE (n=391), an open-label multicentre trial 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 died). The trial included 127 people with a 17p deletion who had been previously treated, 63 of whom were randomised to ibrutinib and 64 of whom were randomised to ofatumumab. TP53 mutation was neither an inclusion nor an exclusion criterion. The trial was stopped early, after a positive pre-planned interim analysis, when 146 progression-free survival events had occurred and at a median time in the trial of 9.4 months (April 2013).

3.2 The primary outcome in RESONATE was progression-free survival. Secondary outcomes included overall survival and overall response rate.

3.3 In RESONATE, patients were treated with ibrutinib or ofatumumab until disease progression or adverse events. Patients were treated with ofatumumab for up to 6 months; there was no limit for ibrutinib.

A blinded independent research committee assessed disease progression until the trial was stopped at 9.4 months, after which unblinded investigators assessed outcomes.

3.4 Patients randomised to ofatumumab were permitted to switch to ibrutinib on progression of disease, as defined by a protocol amendment by the independent data monitoring committee. Of the 191 patients randomised to ofatumumab, 116 patients crossed over to receive ibrutinib after disease progression, as of a September 2014 data cut. As its primary analysis, the company submitted censored data from patients who crossed over (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 explored adjusting for crossover using the rank-preserving structural failure time (RPSFT) method, the inverse probability of censoring weights method, and the iterative parameter-estimation algorithm. The main analysis chosen by the company to estimate the association between ibrutinib and overall survival was post-hoc, used data from a median follow-up at 16 months, and adjusted for crossover using the RPSFT method.

RESONATE results

3.5 At the interim analysis (median follow-up 9.4 months), the hazard ratio for progression-free survival comparing ibrutinib with ofatumumab was estimated to be 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 with 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, $p<0.0001$). After consultation, the company

provided data from a 30-month median follow-up; median progression-free survival had still not been reached with ibrutinib.

3.6 In patients with a 17p deletion, a pre-specified subgroup, the results reflecting the effectiveness of ibrutinib compared with ofatumumab for progression-free survival 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 a 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. At the time of interim analyses, and after 57 patients in the ofatumumab group 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 a median follow-up of 18 months; after 120 of 196 patients crossed over from ofatumumab to ibrutinib. The company presented crossover-adjusted hazard ratios using the (RPSFT) approach for the overall population and for the 17p deletion subgroup, but these are academic in confidence.

3.8 The most common adverse event was diarrhoea, occurring in about half of the patients. Adverse events were generally grade 1 or 2 in severity, managed with standard treatment, and resulted in less than 5% of patients stopping treatment.

Non-randomised evidence

3.9 The company included the results from 4 non-randomised non-controlled studies. The single-arm study by Farooqui et al. (2014; n=51) included patients with untreated (n=35) or relapsed or refractory CLL (n=16) and a 17p deletion (n=47) or 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.

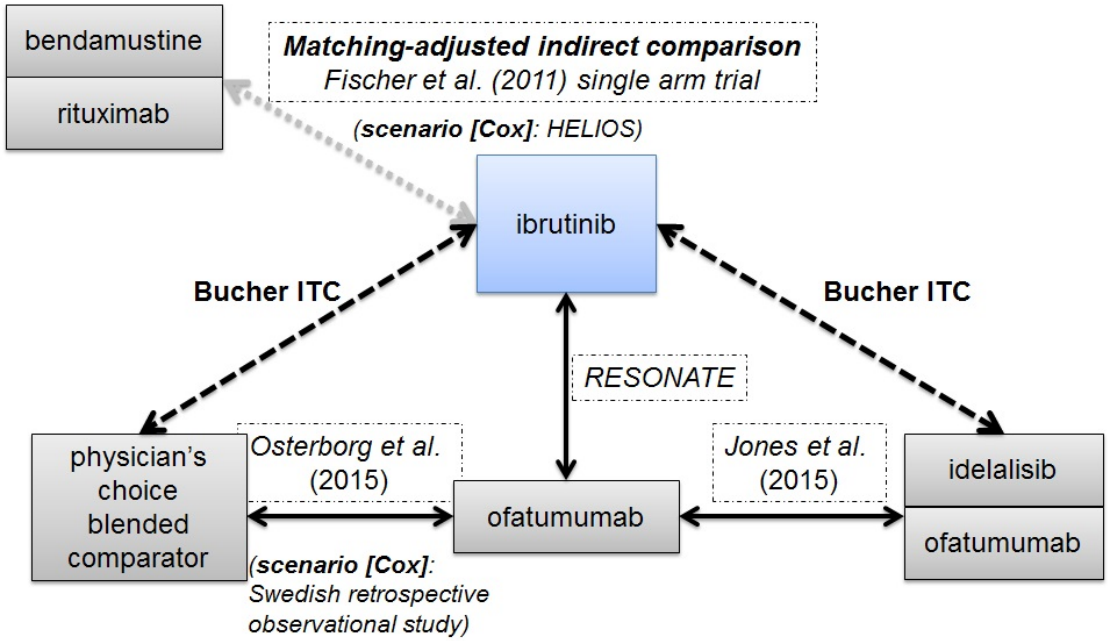
- Patients with a 17p deletion or TP53 mutation for which chemo-immunotherapy was not suitable (that is, ibrutinib would be first line) with the comparators identified as:
  - alemtuzumab +/- corticosteroids
  - idelalisib + rituximab
  - best supportive care.

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 3 comparators not listed in the scope: ofatumumab, idelalisib plus ofatumumab, and 'physician's choice' (a blended comparator reflecting multiple treatments listed separately within the scope); and 1 comparator listed in the scope: bendamustine plus rituximab. The company compared these using a network that used 3 methods to compare treatments indirectly within the network:

- Bucher method
- matching-adjusted indirect comparison (MAIC)
- multivariate Cox proportional hazards modelling.

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

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



Abbreviation: ITC, indirect treatment comparison.

3.12 The company presented pairwise indirect treatment comparisons based on Bucher et al. (1997) to compare ibrutinib with each of physician's choice and idelalisib plus ofatumumab. The company compared ibrutinib (using RESONATE, which compared ibrutinib with ofatumumab) to physician's choice (using Osterborg et al. 2014, which compared physician's choice with ofatumumab) and to idelalisib plus ofatumumab (using Jones et al. 2015, which compared idelalisib plus ofatumumab with ofatumumab alone). Acknowledging that the scope included the comparator idelalisib plus rituximab but not idelalisib plus ofatumumab, the company assumed that the 2 combinations were equally effective based on clinical advice. The company 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 (relapsed or refractory diffuse large B-cell lymphoma) compared ofatumumab with rituximab, both combined with cisplatin, cytarabine, and dexamethasone, and showed no difference in efficacy between the 2 treatments.

3.13 To compare ibrutinib with bendamustine plus rituximab, the company conducted an MAIC matching patient-level data from RESONATE with study-level characteristics from 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, with an effective sample size of 30 patients (from 156). As an alternative, the company used a Cox multivariate model with individual patient-level data from both RESONATE and HELIOS, which compared ibrutinib plus bendamustine plus 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). Using the MAIC to compare ibrutinib with bendamustine plus rituximab resulted in a progression-free survival hazard ratio of 0.08 (95% CI 0.04 to 0.18) and overall survival hazard ratio of 0.19 (95% CI 0.07 to 0.51). Using the Cox model resulted in a progression-free survival hazard ratio of 0.20 (95% CI 0.15 to 0.28) and overall survival hazard ratio of 0.33 (95% CI 0.39 to 1.02).

3.15 For patients with a 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 considered that RESONATE was a well-conducted trial and that the trial population was representative of the UK population. However, the ERG noted that the control treatment, ofatumumab, is not a relevant comparator for English NHS practice because NICE did not recommend it for relapsed or refractory CLL and it has been removed from the Cancer Drugs Fund.

3.17 The ERG commented on the company's adjustment for overall survival in the full relapsed-refractory population, taking into account crossover using the 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 other things, the presence or absence of refractory disease, 17p deletion, prior lines of therapy, Eastern Cooperative Oncology Group status, age at baseline, sex and ethnicity. The ERG noted

that the only information about the Jones et al. (2015) trial came from an abstract, and that the company adjusted only the RESONATE trial for crossover, but not the Jones et al. study. The ERG stated that it would be consistent to use the intention-to-treat estimates from all studies, including RESONATE, for the network meta-analysis.

3.18 The ERG further noted that, for the comparison of ibrutinib with idelalisib, the company did not adjust the patient-level 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 a 17p deletion in each trial (32.3% randomised to ibrutinib and 32.7% randomised to ofatumumab in RESONATE, compared with 26.4% randomised to idelalisib plus ofatumumab and 21.8% randomised to ofatumumab plus placebo in Jones et al.). The ERG also noted that, because the company chose an MAIC as its preferred approach when comparing ibrutinib with bendamustine plus rituximab, it may also have been possible for the company to do an MAIC analysis to compare ibrutinib with idelalisib using the Jones et al. trial.

3.19 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, which used the MAIC method or for its sensitivity analysis the HELIOS study 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 sensitivity analysis using the multivariate Cox model to compare ibrutinib with bendamustine

plus rituximab, because it used individual patient data from both studies and adjusted for patient-level confounders.

3.20 For the comparison of ibrutinib to physician's choice, 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. The ERG and the company both noted that 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, was the most reliable approach possible with the data available. 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.

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 partitioned survival analysis 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 fitting parametric curves 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 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 estimate treatment duration, the company assumed that people have ibrutinib and idelalisib until disease progression. 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.

3.25 The company's base-case results included the list (rather than discounted) prices for ibrutinib and the comparators using the British National Formulary (August 2015). Separately, the company provided analyses with the confidential discount for ibrutinib. The costs of treating grade 3 and 4 adverse events were applied to the rates of each event for the intervention and comparators to derive the total cost of adverse events associated with each treatment. The company did not model drug administration costs because it assumed that, being oral, ibrutinib is self-administered, but did include these costs for all comparators. The company determined

the costs of routine follow-up during the progression-free survival health state based on the proportions of patients whose disease responded completely or partially, and whose disease was stable from RESONATE. The company applied the costs of terminal care in the death state.

3.26 The company used the results from RESONATE, adjusted for crossover, to model ibrutinib compared with ofatumumab. It used the results of the indirect treatment comparisons to model ibrutinib compared with physician's choice, the company's base-case comparator, and with idelalisib plus ofatumumab, which the company equated to idelalisib plus rituximab. The company used the results of the MAIC to compare ibrutinib with bendamustine plus rituximab.

3.27 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 because 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, in which the company assigned a utility value it calculated using EQ-5D-5L score of patients entering the RESONATE trial minus a utility decrement associated with progression (0.098; values cannot be reported because they were provided academic in confidence). Published utility increments associated with response were tested in a sensitivity analysis.

3.28 The company chose to model utility decrements associated with adverse events (ranging from 0.123 to 0.195 from the published literature) because it noted that an analysis of RESONATE

EQ-5D-5L data did not identify differences. The company made assumptions about the value of disutility for diarrhoea, pneumonia and hypertension, for which it did not provide published values. The company modelled disutility for serious adverse events, which the company assumed lasted for 14 days.

3.29 The company presented deterministic pairwise incremental cost-effectiveness ratios (ICERs) for ibrutinib against the comparators in its decision problem for both the overall and 17p deletion population using list prices for all treatments. The ICERs for ibrutinib compared with idelalisib plus rituximab and bendamustine plus rituximab were £44,836 and £42,016 per quality-adjusted life year (QALY) gained respectively. The ICER for the 17p deletion and TP53 mutation population was £42,967 per QALY gained compared with idelalisib plus rituximab. Because the comparator treatments idelalisib and ofatumumab have patient access schemes, the ERG used the company's model and applied discounted prices for ibrutinib, idelalisib and ofatumumab. Those results are commercial in confidence. Unless otherwise stated, all the ICERs in this document are based on list prices for all treatments.

3.30 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 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).

3.31 The company also conducted a scenario analysis in which it varied the parametric distribution for extrapolating progression-free

survival. When the company chose an exponential distribution, the ICER increased (£67,635 versus £44,836 per QALY gained for ibrutinib compared with idelalisib plus rituximab). The company explained that the exponential distribution increased progression-free survival and, because people have ibrutinib until disease progression, this resulted in higher costs of ibrutinib treatment. The company stated that it chose the Weibull distribution for the base case, based on the information criteria (Akaike and Bayesian).

3.32 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 versus £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 generated 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 versus £44,836 per QALY gained for ibrutinib compared with idelalisib plus rituximab.

3.33 The company did a scenario using data from patients in RESONATE who had a 17p deletion, to estimate ibrutinib's effect on the progression-free survival and overall survival. Patients with a 17p deletion in RESONATE had all received treatments first line, and the company generalised these data to patients with a 17p deletion who had not had any treatments. In this scenario, ibrutinib was compared with ofatumumab using the same modelling parameters 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.

3.34 After consultation, the company presented a revised base-case analysis addressing some of the committee's preferred assumptions. These included:

- using the exponential function to extrapolate overall survival
- removing differences in drug and administration costs (see section 3.40)
- removing the costs of repeated biopsies
- age-adjusting utility values

3.35 The company did not include the following changes preferred by the committee in its revised base case:

- applying the hazard ratio for overall survival from the intention-to-treat analysis from RESONATE to the indirect comparison with idelalisib plus ofatumumab
- using the exponential function to extrapolate progression-free survival
- using the Cox method, rather than the MAIC, to compare ibrutinib with bendamustine plus rituximab
- not differentiating costs by response status.

3.36 Based on list prices, the company's revised base-case ICERs for ibrutinib compared with idelalisib plus rituximab and bendamustine plus rituximab were £53,644 and £49,023 per QALY gained respectively. The ICER for the 17p deletion and TP53 mutation population was £51,464 per QALY gained compared with idelalisib plus rituximab.

Evidence review group comments

3.37 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.

3.38 The ERG recognised that the immaturity of the RESONATE data meant that the company had to extrapolate both progression-free survival and overall survival considerably, which increased uncertainty. The ERG observed that there was little difference between parametric curves during the trial period. However, during the extrapolation period the curves diverged, in some cases 'quite dramatically'. 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. However, the ERG preferred an exponential curve, while the company preferred a Weibull curve. The ERG interpreted the Weibull curve as predicting that, between disease progression and dying, too many people live for too long. Expert clinical opinion sought by the ERG suggested that the exponential curve provided a more credible estimate of the proportion of patients remaining progression free, given the anticipated survival, and so a more credible estimate of patients in the post-progression state. 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. 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 of the goodness-of-fit statistics, and instead favoured the exponential distribution.

3.39 The ERG had other concerns about the company's model:

- It identified uncertainties around the response rates used in the model, noting that the definition of response differed across the trials of ibrutinib and comparators, querying how the company had derived the rates and noting these were important in determining model costs.
- It noted differences in the modelling of drug costs in which the company treated ibrutinib more favourably than the comparators, namely, the company:
  - used the time to treatment discontinuation curve only in the ibrutinib arm, but not in the ofatumumab arm
  - assumed that the proportion eligible for treatment is the minimum of the value of the time to treatment discontinuation Kaplan Meier curve or the value of the parameterised progression free survival curve
  - applied the discount for drug utilisation twice in the ibrutinib arm, but only once in the comparator arms
  - did not apply the drug utilisation proportions to drug administration costs, which would have reduced the costs of comparators but not ibrutinib because the company assumed that ibrutinib has zero administration costs
  - applied half-cycle correction and immediate discounting to the ibrutinib drug costs, but not to the comparator drug costs.
- It disagreed that patients would receive repeated biopsies as part of routine follow-up.
- It disagreed that routine follow-up would differ by response status.

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

- applying hazard ratios for overall survival from intention-to-treat analyses (rather than adjusted for crossover) to compare

ibrutinib with physician's choice and with 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 3.38)
- extrapolating progression-free survival using an exponential curve, rather than Weibull (see section 3.38)
- removing differences in drug and administration costs between ibrutinib and comparators (section 3.39)
- removing the costs of repeated biopsies from the non-drug routine costs of care (section 3.39).

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

3.41 The ERG, using its own assumptions (see section 3.39), calculated the ICERs for the subgroup with a 17p deletion for ibrutinib compared with physician's choice, with idelalisib plus rituximab, and with bendamustine plus rituximab. The ERG was aware that subgroup analyses of the effectiveness of ibrutinib compared with ofatumumab in RESONATE showed no interaction by subgroup, one of which was defined by the presence or absence of 17p deletion. The ERG therefore applied the 'all patient' hazard ratios to the curves for overall survival and progression-free survival for the subgroup. The ICER for ibrutinib compared with idelalisib plus rituximab for the 17p deletion population was £86,942 per QALY gained using the list prices.

3.42 After consultation, the ERG critiqued the company's revised analyses (see section 3.35) and presented its own revised base-case and exploratory analyses. In its revised base case, the ERG

applied the following changes that differed from its previous assumptions:

- the hazard ratio for overall survival from the crossover adjusted analysis (rather than intention-to-treat) from RESONATE for the indirect comparison with idelalisib plus ofatumumab
- ongoing costs of partial disease rather than of stable disease during progression-free survival
- age-adjusted utilities
- a body surface area of 1.85m^2 to account for sex differences.

3.43 Based on list prices, the ERG's revised base-case ICERs for ibrutinib compared with idelalisib plus rituximab was £78,936 per QALY gained and for bendamustine plus rituximab was £105,000 per QALY gained. The ICER for ibrutinib in the 17p deletion and TP53 mutation population was £78,140 per QALY gained compared with idelalisib plus rituximab.

3.44 The ERG provided sensitivity analyses. A key scenario incorporated the committee's preferred assumption of applying the hazard ratio for overall survival from the intention-to-treat analysis from RESONATE to the indirect comparison with idelalisib plus ofatumumab. This resulted in an ICER of £93,293 per QALY gained compared with idelalisib plus rituximab. The ICER for ibrutinib in the 17p deletion and TP53 mutation population was £91,251 per QALY gained compared with idelalisib plus rituximab.

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 people 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 people 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 people 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 said 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 a purine analogue-based therapy, 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 or who otherwise reflected the population in RESONATE. 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 first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients in whom chemo-immunotherapy is unsuitable, and who were excluded from RESONATE. The committee agreed that the 2 populations relevant to the appraisal are:

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

4.3 The committee discussed the relevant comparators, in the context of current clinical practice in the UK, and for each of the 2 populations. The committee first discussed patients with previously treated CLL 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. 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 was unlikely to 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. However, it was not 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 heard that ibrutinib 'replaced' ofatumumab in the Cancer Drug Fund. However, the committee was clear that, in line with NICE's Guide to the methods of technology appraisal 2013, ofatumumab was not an appropriate comparator because it was not considered a cost-effective use of NHS resources in NICE's technology appraisal guidance on ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab.
- The committee was aware the company had presented a comparison with physician's choice, which is a blended comparator. The committee appreciated that the components of

the blended comparator included treatments within the NICE scope. The committee recognised comments from the clinical experts and the evidence review group (ERG) that the composition presented by the company did not reflect the treatments offered in the UK. 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 clinically-effective and cost-effective treatment options that are included within the blended comparator. The committee noted comments from the company that, because the data were taken from a single trial, rather than individual datasets, physician's choice was not a blended comparator. The committee was aware that the 'blending' referred to the mix of therapies, and not to a mix of trials contributing to the evidence. The ERG highlighted that bendamustine plus rituximab comprises 35% of physician's choice in the company's submission. The committee agreed that this was problematic, because bendamustine plus rituximab was a separate comparator in this appraisal. The committee also considered that, where different comparators can be identified for identifiable patient groups, these should be discussed as separate subgroups. 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 for patients who had relapsed within 2 years. It further concluded that, for patients for whom idelalisib was not an option (those who relapsed beyond 2 years, or those for

whom idelalisib was not appropriate), bendamustine plus rituximab 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. 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 people with a 17p deletion or TP53 mutation. The committee heard that alemtuzumab was previously offered to people with a17p deletion or TP53 mutation, but is difficult to obtain because the company for alemtuzumab has limited the marketing authorisation to multiple sclerosis. 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 a 17p deletion or TP53 mutation. At its second meeting, the committee was made aware of recent provisional advice by the European Medicines Agency (EMA) on idelalisib following a number of serious adverse events in some post-marketing trials. The committee noted that the advice included not starting treatment in people with a 17p deletion or TP53 mutation who had not had previous treatment. The committee was aware that, in the absence of idelalisib, people with untreated CLL and 17p deletion or TP53 mutation have no treatment options, and recognised the unmet need in this population. The committee concluded that, because the EMA advice was provisional, and

because no other appropriate comparisons had been presented, the only comparator that the committee could currently consider for this population was idelalisib plus rituximab. The Committee however agreed that in a comparison against best supportive care would be valuable.

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

- for patients with refractory or relapsed CLL
  - Idelalisib plus rituximab (for those whose disease progresses within 2 years after the end of previous treatment)
  - Bendamustine plus rituximab (for those whose disease progresses 24 months after the end of previous treatment)
- for patients with untreated CLL who have a 17p deletion or TP53 mutation.
  - Idelalisib plus rituximab

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 a median16 month follow-up in November 2014 (approximately 11 months before the company submitted its evidence to NICE). At its second meeting, the committee noted that the company presented data from a median 30-month follow-up that supported the results in its submission. The committee considered that the results from RESONATE were immature and uncertain in the longer term, and that the comparison with ofatumumab was not directly relevant to UK clinical practice as this is not used in UK clinical practice. The committee appreciated that the immaturity of the data related to the

trial stopping early because ibrutinib was shown to be effective, but that it did mean that a greater proportion of the modelled time horizon depended on extrapolations. The committee agreed that the trial showed ibrutinib extended progression-free survival compared with ofatumumab.

4.8 The committee was aware that no data were available for patients with a 17p deletion or TP53 mutation who have not had treatment. The company stated that the treatment effect in people with a 17p deletion in the RESONATE trial who had previously had treatment could be generalised to people who had not received treatment. The committee noted comments from clinical experts that treating CLL in patients with a 17p deletion with fludarabine plus cyclophosphamide and rituximab may worsen their disease and prognosis. The committee noted that the single-arm Farooqui et al. (2014) study of ibrutinib presented by the company included a few patients with untreated CLL with a 17p deletion, but that the company did not use this to estimate clinical efficacy. The committee noted that without any evidence it was unclear how generalisable the treatment effect of ibrutinib in the RESONATE trial from the previously treated population with a 17p deletion was to the previously untreated population with a 17p deletion. The Committee agreed that in the absence of this evidence, the data from the previously treated population could be taken into account, but recognised this was associated with a lot of uncertainty. The Committee agreed that data collection to support the generalisability of the results to the previously untreated population would be valuable.

4.9 The committee noted that there were no data available specifically for people with a TP53 mutation and discussed whether the results from the previously treated 17p deletion population from RESONATE could be generalised to people with a TP53 mutation.

The clinical experts stated that, while 17p deletion was routinely tested for in the NHS, TP53 mutation was not, but that both were on the same gene locus and tended to appear together in the same people. 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 a 17p deletion to people with a 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 adjust the hazard ratio from the Jones et al. (2015) trial (which compared idelalisib plus ofatumumab with ofatumumab) to account for treatment switching to ibrutinib.

- The committee heard from the company that it did not adjust the Jones et al. trial for cross over because the 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, including ibrutinib because a compassionate-use programme was available.
- The company stated that this treatment switching was not within the trial period and so adjusting was not appropriate. The committee, however, considered that adjusting for treatment switching was appropriate because more patients randomised to placebo (compared with idelalisib) in Jones et al. were likely to receive treatments that both extended life and were not part of standard NHS practice.

- The committee was aware that the NICE Decision Support Unit document on treatment switching supports adjusting for post-study therapies when they do not reflect routine care.

The Committee agreed that the treatment switching to ibrutinib following the Jones et al. study was relevant when determining the relative effectiveness of ibrutinib and idelalisib.

4.11 The committee discussed how best to account for the effect of treatment switching, following the Jones et al trial, on the relative effectiveness of ibrutinib and idelalisib. The Committee recognised the company did not have access to the data from Jones et al, and therefore could not adjust this trial. The Committee therefore considered the options available, which were to either adjust the RESONATE trial only, or adjust neither trial. The Committee recognised that adjusting 1 trial, but not the other, would exaggerate the benefit of ibrutinib over idelalisib plus ofatumumab. It recognised that if crossover and treatment switching occurred more often in RESONATE than in Jones et al, then adjusting neither trial would underestimate the treatment effect of ibrutinib. Similarly, if the crossover or treatment switching occurred more often in Jones et al, this would overestimate the treatment effect of ibrutinib. The committee agreed that, of the options available, adjusting neither trial would be the most appropriate approach.

4.12 The committee noted that the scope included idelalisib plus rituximab as a comparator, but that the company presented results for idelalisib plus ofatumumab (not rituximab).

- The committee was aware that a trial comparing rituximab with idelalisib plus rituximab (Sharman et al. 2014) formed the key evidence for NICE's decision on idelalisib, and questioned why

the company had not included this in its network of studies. The company stated it did not include this within a matching-adjusted indirect comparison (MAIC) because it had substantial limitations, including differences in trial design follow-up and crossover and, in the company's opinion, an indirect comparison of ibrutinib with idelalisib plus ofatumumab provided more robust results. The committee noted that, after consultation, the company presented results from a MAIC including Sharman et al. for progression-free survival, but the ERG was unable to verify the results because of a lack of statistical details.

- The committee understood that the company had taken this approach because it considered that idelalisib plus ofatumumab was a proxy for idelalisib plus rituximab. The committee heard from the 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, rather than each in combination with idelalisib. The company stated that it was not clinically plausible that the efficacy would differ in combination, but the committee did not see any evidence to support this. Moreover, the committee heard during consultation that the company should not use evidence of rituximab with ofatumumab in diffuse large B-cell lymphoma as evidence to indicate comparability between the 2 drugs when used in CLL.

The committee agreed there were uncertainties around the assumptions when comparing ibrutinib with idelalisib plus rituximab. It concluded that it was unable to establish whether idelalisib plus

rituximab is equivalent to idelalisib plus ofatumumab for the purposes of the comparison with ibrutinib.

4.13 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. By comparison, the alternative Cox multivariate analyses, 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. The company stated that disease severity in the RESONATE trial population was greater than in the HELIOS trial. The company also stated that the data from the HELIOS study was not adjusted for crossover and so the efficacy of bendamustine plus rituximab may be overestimated; the committee was unclear why the company had not adjusted for crossover because it had access to the individual patient data. The committee recognised that both approaches were associated with limitations, but 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.

4.14 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 had 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 also heard during consultation about on-going regulatory inquiry into idelalisib. 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

4.15 The committee considered the assumptions in the company's economic model. The committee noted that a key assumption made by the company was a constant benefit from ibrutinib over the entire course of the model. It 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 ibrutinib's benefits to 5 years, increased the incremental cost-effectiveness ratio (ICER) for ibrutinib compared with idelalisib plus rituximab. The committee agreed to consider this analysis as part of its decision-making.

4.16 The committee considered the company's extrapolation of data from RESONATE for progression-free survival and overall survival over the 20-year time horizon of the model. 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 the committee acknowledged may reflect a successful treatment effect, but which led to uncertainty.

- The committee considered how overall survival was modelled. It recognised that during consultation the company had agreed with the committee that Weibull function provided the best fit of the options presented.
- The committee considered how progression-free survival was modelled. 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 patients do not live for long periods with progressed disease. It recognised that progression free survival extrapolation contributed to this. The committee noted that the ERG suggested the exponential function provided a more credible period of time in progressed disease, whereas the company suggested the weibull function provided a better for to the data.

The committee noted that the extrapolation of progression-free survival from RESONATE was a key driver of the cost-effectiveness results. The ERG stated that addressing clinical face validity of the curves was even more important than usual given the large degree of extrapolation. The committee agreed that the Weibull function resulted in implausibly long survival after progression (estimates marked commercial in confidence by the company). The committee concluded that there was considerable

uncertainty around the company's post-trial extrapolations, and that it preferred the exponential distributions.

4.17 The committee considered the face validity of the extrapolation of overall survival results for ibrutinib relative to idelalisib. The committee noted that the company's model predicted that 10 times as many patients who have ibrutinib would be alive after 20 years compared with patients having idelalisib plus rituximab. The committee considered this improbable. The committee concluded that the degree of benefit estimated by the company was not supported by data or clinical experience.

4.18 The committee considered the model inputs for the 17p deletion and TP53 populations. The committee noted that 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 untreated CLL (see section 4.8).The committee noted the unmet need for treatment options in the 17p deletion and TP53 populations. It was aware of the lack of evidence in these subgroups, and agreed that data from the overall population was the best available and could be used to support decision-making in the untreated 17p deletion and TP53 mutation populations. The committee also recalled that, given the provisional advice on the safety of idelalisib from the EMA, there was uncertainty around the appropriate comparator for this population (see section 4.5). The committee considered that the results from the model were associated with uncertainty. The committee concluded that availability of data specific to the 17p deletion and TP53 mutation populations, in the previously treated and untreated settings, would reduce the uncertainty associated with the results.

4.19 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 the incremental ICERs were sensitive to the time horizon chosen, and the ICER increased with shorter time horizons. The ERG commented that 20 years may be too short a time horizon because people treated with ibrutinib modelled by the company were still alive at the end of this time period. By contrast, the committee heard from clinical experts that, a time horizon of 20 years might be too long because the population had a mean starting age of 67 years. 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.

4.20 The committee understood that time to progression determines treatment duration, which in turn determines 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 higher than those modelled by the company. The committee considered that it might also contribute to greater benefits than stopping treatment at disease progression, but did not see any evidence to support this. The committee concluded that any continued benefit from treatment with ibrutinib post progression generated an uncertain impact on the cost effectiveness of ibrutinib.

4.21 The committee noted that for patients in the progression-free health state, costs of routine follow-up were determined by disease response to treatment as measured in RESONATE. The committee heard from clinical experts that patients (whose disease has responded to treatment) would not be followed up at different

intervals depending on the level of response to treatment. After consultation, the company maintained that routine follow-up and inpatient costs should be determined by response level. The ERG agreed with the company that it may be more reasonable to equalise costs at the partial response level, but stated that the company had not proven that rates of admission to hospital differ by response status. The committee noted that this was not a driver of the cost-effectiveness results. The committee concluded that, after consultation, the company had corrected most imbalances in the costs (see section 3.34), and that the costs of routine follow-up had a negligible impact on the ICERs.

4.22 The committee considered the health-related quality-of life-evidence presented by the company. The committee noted that the company had collected EQ-5D data in RESONATE. The committee noted that the quality-of-life values collected at baseline before treatment did not differ much from those collected during either treatment. The clinical experts commented that this did not reflect their clinical experience, stating that symptoms improve immediately with ibrutinib and patients usually 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 few side effects, the committee was concerned that benefits may not have been appropriately captured, noting that the EQ-5D does not directly measure fatigue. After consultation, the company applied a utility increment for ibrutinib. The committee heard from the ERG that this increment was derived from EQ-5D data, so did not resolve the committee's concerns about the sensitivity of the EQ-5D. Also, this increment was based on the quality-of-life difference between idelalisib and rituximab treatment. The ERG noted that it was not appropriate to apply this as an additional increment to the EQ-5D quality-of-life estimate for

ibrutinib. The committee was aware that this had a minor impact on the results. The committee concluded that the EQ-5D may not have captured the experience of people with CLL, and the base case may have underestimated the quality-of-life benefit with ibrutinib.

4.23 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 assumed (see section 3.27). 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 company did not age-adjust the utilities. After consultation, the company provided age-adjusted utility values, and chose a lower utility value in the post-progression state (0.60). The committee noted that this had a small impact on the ICERs. The committee agreed with these 2 changes.

4.24 The committee considered the cost effectiveness of ibrutinib based on the evidence available. The committee noted that the company's results did not reflect all its preferred assumptions, but was aware that exploratory analyses conducted by the ERG addressing these assumptions were available. 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 (that is, not adjusting for crossover or treatment switching in either trial; see section 3.17).
- using the exponential function to extrapolate the overall survival and progression-free Kaplan-Meier survival curves from RESONATE (see section 3.38)
- removing the differences in drug and administration costs between intervention and comparator arms (section 3.39)
- removing the costs of repeated biopsies (section 3.39).

4.25 The committee noted that, with these changes, the ICERs including patient access schemes were all substantially greater than £20,000 to £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 above £93,293 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 £105,000 per QALY gained for ibrutinib compared with bendamustine plus rituximab.
- For patients with CLL who have a 17p deletion or TP53 mutation, the most plausible ICER was £91,000 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. The committee also reiterated that these ICERs were associated with substantial uncertainty relating to efficacy estimates, utility values and long- term outcomes. The committee acknowledged that, following recent advice from the EMA on idelalisib, the costs associated with idelalisib were likely to increase. However, the committee considered that this was unlikely to improve the cost effectiveness of ibrutinib compared with idelalisib substantially.

4.26 The committee recognised that idelalisib plus rituximab has only recently become available, so 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 to consider their relative acquisition costs. The committee was aware that the price of ibrutinib was much higher than idelalisib. The committee agreed that the uncertain benefits of ibrutinib compared with idelalisib plus rituximab was unlikely to warrant the significant additional acquisition cost of ibrutinib compared with idelalisib plus rituximab even when applying the current patient access schemes.

Innovation

4.27 The committee discussed whether it could consider ibrutinib innovative. The committee heard from both the patient and clinical experts that ibrutinib was an important new technology in treating CLL. The committee heard that patients appreciated how well the treatment worked and how easy it was to take being 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 a 17p deletion and TP53 mutation, in which there are few, if any, 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 4.21). The committee concluded that ibrutinib is an innovative treatment.

End of life

4.28 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. For this advice to be applied, both of 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.

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.

4.29 The considered the short life expectancy criteria. The committee was aware that before idelalisib had been recommended as a treatment option, people lived for a shorter length of time. In the current treatment landscape, the committee was unsure whether the life expectancy for people with CLL would be less than 24 months. However, in its second meeting, the committee noted that the mean overall survival associated with idelalisib plus rituximab (and on which the NICE decision on idelalisib plus rituximab was based) was estimated to be 21.6 months. The committee noted that no evidence was provided about the life expectancy of people with a 17p deletion or TP53 mutation, but the committee was aware that this population probably has a worse prognosis. The committee agreed that the criterion for short life expectancy was met.

4.30 The committee discussed the extension to life offered by ibrutinib, first considering the previously treated population. The committee was mindful of the uncertainty around the long-term efficacy results from RESONATE because median overall survival for people having ibrutinib had not been reached at a 30-month data cut; the committee recognised that this pointed to the effectiveness of ibrutinib. The committee also noted the estimates for median survival in the overall population from the model (these are commercial in confidence and so are not presented here). The committee recognised the uncertainty in the economic modelling

but concluded that the level of confounding in the indirect comparisons was unlikely to translate to life extensions less than 3 months. The committee noted that there was far greater uncertainty in the extension to life estimates for people with a 17p deletion or TP53 mutation (see section 4.9). However, the committee was aware of comments from experts that ibrutinib is very effective in this population. On balance, the committee was satisfied that the extension to life criterion was met. The committee concluded that the end-of-life criteria had been met for the populations in this appraisal.

4.31 The committee considered all the evidence it had been presented with. It agreed that ibrutinib represented an important treatment in CLL, but was aware of the numerous uncertainties in the evidence base and in its preferred modelling assumptions. The Committee agreed that, even taking end-of-life criteria into account, the ICERs were above the range considered a cost-effective use of NHS resources.

4.32 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.

4.33 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England. Under the

new arrangements, drugs that appear promising, but for which the evidence is not strong enough for routine use, may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while more data are collected. The committee discussed whether it could recommend ibrutinib for use within the Cancer Drugs Fund. The committee was aware that in considering this, the following criteria must be met:

- The ICERs have the plausible potential for satisfying the criteria for routine use.
- It is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS.
- It is possible that the data will be able to inform a subsequent update of the guidance (normally within 24 months).

4.34 The committee considered the analyses presented for people who have had previous treatment and do not have a 17p deletion or TP53 mutation. It agreed that collecting more data on this group would not rectify the issues related to the company's economic model, and the ICERs did not indicate a plausible potential for cost effectiveness. Therefore, the committee could not recommend ibrutinib for use in the Cancer Drugs Fund for people without a 17p deletion or TP53 mutation.

4.35 The committee discussed ibrutinib for people with CLL who have a 17p deletion or TP53 mutation. The committee recalled the uncertainties in the evidence base for this population, including whether the results for ibrutinib second line could be extended to

people with untreated CLL. The committee was aware of the small observational studies that provided the evidence for this subgroup. The committee was aware that the company, at the second meeting, was not in a position to confirm whether it would offer ibrutinib in the Cancer Drugs Fund. The committee noted that the ICERs currently available for decision-making, compared with idelalisib, were substantial (see section 4.24), and that no ICERs were presented compared with best supportive care. It was concerned about whether the ICERs in this population have the plausible potential for satisfying the criteria for routine use, compared with idelalisib or best supportive care. The committee was reassured that, as part of the process, it would have the opportunity to discuss the data collection arrangements, timeframe, and the commercial access arrangements agreed by the company and NHS England, before providing a final recommendation for use within the Cancer Drugs Fund. The committee considered that, based on the current evidence, it was minded not to recommend ibrutinib, for patients with CLL who have a 17p deletion or TP53 mutation. The committee however invited the company to submit a proposal for inclusion in the Cancer Drugs Fund.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Ibrutinib for treating CLL**	**Section**
Key conclusion		
Ibrutinib is not recommended for treating chronic lymphocytic leukaemia (CLL) in people without a 17p deletion or TP53 mutation. The committee considered that there was considerable uncertainty around the progression-free and overall survival benefits of ibrutinib compared with idelalisib plus rituximab. The incremental cost-effectiveness ratios (ICERs) were above the range considered a cost-		1.1, 4.13, 4.25, 4.32

effective use of NHS resources, and were associated with substantial uncertainty relating to efficacy estimates, utility values and long-term outcomes. The committee also considered that collecting more data on this group through the Cancer Drugs Fund would not rectify the issues related to the company's economic model, and that the ICERs did not indicate a plausible potential to be cost effective. The committee understood the uncertainties in the evidence base for people with CLL who have a 17p deletion or TP53 mutation. These included whether the results for ibrutinib second line could be extended to people with untreated CLL. The committee was also mindful of the unmet need in light of the provisional advice from the European Medicines Agency suggesting that idelalisib should no longer be offered to people with untreated CLL who have these mutations. However, the ICERs, compared with idelalisib, were above the range considered a cost-effective use of NHS resources and no ICERs compared with best supportive care were presented. The committee, based on the current evidence, was minded not to recommend ibrutinib for patients with CLL who have a 17p deletion or TP53 mutation. The committee invited the company to submit a proposal for inclusion in the Cancer Drugs Fund.		
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:	4.1, 4.6

	• for patients with refractory or relapsed CLL: o idelalisib plus rituximab (for those whose disease progresses within 2 years after the end of previous treatment) o Bendamustine plus rituximab (for those whose disease progresses 24 months after the end of previous treatment) • for patients with untreated CLL who have a 17p deletion or TP53 mutation: o idelalisib plus rituximab	
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 the patient 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 a	4.12, 4.13 4.26

	17p deletion and TP53 mutation, in which there are few treatment options. The committee concluded that ibrutinib could be considered an innovative treatment.	
What is the position of the treatment in the pathway of care for the condition?	Ibrutinib has a marketing authorisation for the treatment of CLL in adult patients who have had at least 1 prior therapy or, first line, in patients with a 17p deletion or TP53 mutation for whom chemotherapy is unsuitable. The committee heard from clinical experts that they would wish to offer ibrutinib to patients with CLL who have received at least 1 prior treatment with fludarabine, and as first line therapy for people with a 17p deletion or TP53 mutation.	4.2
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 RESONATE trial was stopped early, when the median time on-trial was 9.4 months. At its second meeting, the committee noted that the company presented data from a median 30-month follow-up. 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	4.7, 4.8, 4.9, 4.4

	clinical practice. The committee was aware that no data were available for people with untreated CLL who have a 17p deletion or TP53 mutation. The committee noted comments from clinical experts that treating patients with a 17p deletion with fludarabine plus cyclophosphamide and rituximab worsened their disease and prognosis. The Committee agreed that in the absence of this evidence, the data from the previously treated population could be taken into account, but recognised this was associated with a lot of uncertainty. The committee noted that there were no data available for people with a TP53 mutation, but concluded that it was reasonable to extrapolate data from people with a 17p deletion to people with a 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. 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: The treatment options currently used in	4.6

	England in the NHS for CLL are: • for patients with refractory or relapsed CLL: o idelalisib plus rituximab (for those whose disease progresses within 2 years after the end of previous treatment) o Bendamustine plus rituximab (for those whose disease progresses 24 months after the end of previous treatment) • for patients with untreated CLL who have a 17p deletion or TP53 mutation: o idelalisib plus rituximab	
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 to the previously untreated population with a 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	4.7, 4.8, 4.10, 4.11

	do so for only 1 trial in the indirect comparison network. It concluded that it was unable to establish 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 people with untreated CLL who have a 17p deletion or TP53 mutation. The company stated that the treatment effect in people with a 17p deletion in the RESONATE trial who had previously had treatment could be generalised to people who had not received treatment. The committee noted comments from clinical experts that treating patients with a 17p deletion with fludarabine plus cyclophosphamide and rituximab worsens their disease and prognosis.	4.8
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 neither is recommended at this position in the treatment pathway by NICE, nor used in UK clinical practice. 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	4.7, 4.12, 4.13

	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.	
Evidence for cost effectiveness		
Availability and nature of evidence	The company 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 The company did a scenario analysis based on the previously treated 17p deletion subgroup, only comparing ibrutinib with ofatumumab. The evidence review group had, however, explored the cost effectiveness of ibrutinib compared with idelalisib plus rituximab and bendamustine plus rituximab in this subgroup.	3.21,
Uncertainties around and plausibility of	The committee appreciated that the immaturity of RESONATE data was partly	4.7, 4.16,

assumptions and inputs in the economic model	related to the trial stopping early because ibrutinib was shown to be effective, but that it did mean a greater proportion of the modelled time horizon depended on extrapolations. The committee concluded that there was considerable uncertainty around the extrapolations in the company's model, and 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 have ibrutinib would be alive at 20 years compared with those having idelalisib plus rituximab. The committee considered this improbable. 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. 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 any continued benefit from treatment with ibrutinib post progression generated an uncertain impact on	4.17, 4.18, 4.19

	the cost effectiveness of ibrutinib.	
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, and how have they been considered?	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 clinical experience, stating that symptoms improve immediately with ibrutinib. 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.	4.22
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 with ibrutinib.	4.15, 4.16, 4.19, 4.20
Most likely cost-effectiveness estimate (given as	Based on the committee's preferred assumptions (and based on list prices), the committee considered that:	4.24

an ICER)	• For patients with refractory or relapsed CLL whose disease progresses within 24 months of previous treatment, the most plausible ICER was £93,000 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 £105,000 per QALY gained for ibrutinib compared with bendamustine plus rituximab. • For patients with CLL who have a 17p deletion or TP53 mutation, the most plausible ICER was £91,000 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 concluded that the end-of-life criteria had been met for the populations in this appraisal.	4.29, 4.30
Equalities considerations and social value	No equality issues were raised during the appraisal.	

judgements		

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 Recommendations for research

6.1 To support a proposal to include ibrutinib in the Cancer Drugs Fund for treating chronic lymphocytic leukaemia (CLL) in people with a

17p deletion or TP53 mutation, the company should provide a protocol for data collection to address the uncertainties in the evidence base.

6.2 This should include data collection to support the company's assumption that people with a 17p deletion and TP53 mutation whose CLL has been previously treated is a reasonable proxy for data in people with untreated disease, in terms of overall survival, progression-free survival and quality of life

7 Proposed date for review of guidance

7.1 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 proposal. 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
May 2016

8 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)
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Dr Sanjeev Patel (Vice Chair)
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr Ray Armstrong
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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