NICE National Institute for Health and Care Excellence

NICE guidance

Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation

Technology appraisal guidance
Published: 25 January 2017

www.nice.org.uk/guidance/ta429

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ibrutinib alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults:

- who have had at least 1 prior therapy or
- who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable and
- only when the company provides ibrutinib with the discount agreed in the patient access scheme.

2 The technology

Description of the technology

2.1 Ibrutinib (Imbruvica, Janssen) is a covalent inhibitor of Bruton's tyrosine kinase.

Marketing authorisation

2.2 Ibrutinib 'as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)' and 'as a single agent or in combination with bendamustine and rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy'.

2.3 This appraisal was started before ibrutinib received a license extension to include all 'adult patients with previously untreated chronic lymphocytic leukaemia'. It therefore only includes consideration of the second-line use of ibrutinib in adults with CLL and the first-line use of ibrutinib in patients with a 17p deletion or TP53 mutation when chemo-immunotherapy is unsuitable.

Adverse reactions

2.4 The most common adverse reactions included diarrhoea, neutropenia, haemorrhage (for example, bruising), musculoskeletal pain, nausea, rash and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

2.5 Ibrutinib is administered orally at a daily dose of 420 mg (3 tablets) until disease progression or intolerance.

Price

2.6 The list price for a single tablet of ibrutinib (140 mg) is £51.10 (excluding VAT; 'British national formulary' [BNF] online, accessed October 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 considered evidence submitted by Janssen and a review of this submission by the evidence review group. See the committee papers for full details of the evidence.

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

Symptoms and management of chronic lymphocytic leukaemia

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. The committee understood that people with CLL risk infection, 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 can shorten 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 that not all people can have these treatments. The clinical experts also stated that, once treatment is stopped because of disease progression, if no other treatment is available, survival is poor and so additional treatment options are very valuable. A patient expert described the fatigue and illness she had experienced with chemotherapy, and said that repeat chemotherapy had resulted in only a short period of remission. The committee understood the importance of having different treatment options available for treating CLL.

Generalisability of clinical trial results

4.2 The committee discussed the generalisability of the clinical trial results to the

2 populations in the appraisal:

- patients with relapsed or refractory CLL who have had at least 1 previous treatment and
- patients with untreated CLL who have a 17p deletion or TP53 mutation.

4.3 The committee considered the population who have had at least 1 therapy. It was aware that the key trial (RESONATE, n=391, open label) only included patients who were not eligible for treatment with a purine analogue-based therapy, but that the marketing authorisation does 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 committee concluded that RESONATE was generalisable to patients who had previously had treatment in clinical practice.

4.4 The committee considered the untreated population with a 17p deletion or TP53 mutation. It noted that RESONATE had not included patients who had not had previous treatment. The company stated that the treatment effect in patients with a 17p deletion in the RESONATE trial who had previously had treatment (33% of patients) could be generalised to patients who had not had treatment. The committee agreed that, without any evidence, it was unclear how generalisable this was. It 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 also 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 agreed that, in the absence of any evidence, the data from the previously treated population could be taken into account, but recognised this was associated with uncertainty.

4.5 The committee noted that there were no data available specifically for people with a TP53 mutation. It 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 occur together in the same people. The

committee heard that the clinical experts expected the untreated natural history would be similar in both populations, as would the response from ibrutinib. The committee concluded that it was reasonable to extrapolate data from people with a 17p deletion to people with a TP53 mutation.

Cancer Drugs Fund proposal to address the uncertainty in the untreated 17p deletion or TP53 mutation population

4.6 To improve evidence related to people with the 17p deletion or TP53 mutation, the committee had invited the company to submit a proposal for its use in the Cancer Drugs Fund (CDF). The committee understood that the company chose not to apply to the CDF. The company stated that there were already observational data available for this group, and collecting further data through the CDF would not address the uncertainty in this population. In support of this, the company submitted data that showed both median progression-free survival and overall survival were not met at 30-month follow-up, from a study of 243 patients with 17p deletion (both those who had not had previous treatment and those whose disease had relapsed or was refractory). The committee agreed with the company that data collection through the CDF would not resolve this uncertainty.

Comparators for the previously treated population

4.7 The committee discussed the relevant comparators, in the context of current clinical practice in the UK. It 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 CDF and, wherever possible, treatment with ibrutinib is preferred because of its effectiveness and because of the adverse effects associated with idelalisib. However, the experts agreed that, in the absence of ibrutinib, clinicians would offer idelalisib plus rituximab. The committee agreed that idelalisib plus rituximab is a comparator.

4.8 The committee discussed the other comparators included in the scope and the

company submission:

- **Bendamustine:** the committee heard from the clinical experts that bendamustine is no longer available through the CDF and noted comments during the course of the appraisal that it is not available in NHS practice. The committee noted that the company's marketing data indicated that bendamustine is still being used in practice, but agreed that these estimates were based on small numbers and could reflect exceptional individual funding requests. The committee, at its third meeting, was satisfied that bendamustine is not routinely available and is therefore not an appropriate comparator.

- **Fludarabine plus cyclophosphamide and rituximab:** the clinical experts stated that retreating with fludarabine plus cyclophosphamide and rituximab would be an option only 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 4.3).

- **Chlorambucil (with or without rituximab) and rituximab monotherapy:** the committee heard that these were rarely used in clinical practice and concluded they were not comparators.

- **Corticosteroids (with or without rituximab):** the committee heard that corticosteroids were considered a palliative option, and did not consider them a comparator.

- **Ofatumumab:** the committee was aware that ofatumumab was the treatment in the control arm of the main ibrutinib trial and that the company included ofatumumab in the decision problem. However, NICE had previously not recommended ofatumumab because ofatumumab was not proven to be clinically or cost effective. Additionally, ofatumumab 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 from consultees that ibrutinib replaced ofatumumab in the CDF and ofatumumab should therefore be considered an appropriate comparator in this appraisal. 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 clinically effective or 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.

- **'Physician's choice':** 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 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 (Osterborg et al. 2016) rather than individual datasets, physician's choice was not a blended comparator as such. 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. By contrast, physician's choice included treatments that, although included in the scope, were not considered to be comparators by the committee based on advice from the clinical experts, for example, methylprednisolone plus rituximab (25%), or fludarabine plus cyclophosphamide and rituximab (10%). 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 physician's choice was not an appropriate comparator.

- **Best supportive care:** before the committee's second meeting of this appraisal, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) published safety concerns for idelalisib. The committee recognised that for some people, idelalisib plus rituximab may not be a treatment option. With no other treatment options available, the committee considered that comparing ibrutinib with best supportive care (which was listed in the scope) would be useful. The company explained that

clinicians aim to offer active treatments, and that no standard definition of best supportive care is available.

The committee concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years, and for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator.

Comparators for the untreated 17p deletion or TP53 mutation population

4.9 The committee heard that alemtuzumab was previously offered to people with a 17p deletion or TP53 mutation, but is difficult to obtain because the company for alemtuzumab has limited the marketing authorisation to multiple sclerosis. The committee concluded that this was not an appropriate comparator.

4.10 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 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. At its third meeting, the committee noted that the EMA's Committee for Medicinal Products for Human Use had confirmed that the benefits of idelalisib outweigh the risk of side effects and had now concluded that idelalisib 'can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed'. The committee was aware that, in the absence of idelalisib, people with untreated CLL and a 17p deletion or TP53 mutation have no treatment options, and recognised the unmet need in this population. The committee therefore agreed that the relevant comparators for this group were idelalisib plus rituximab or best supportive care.

Clinical effectiveness of ibrutinib compared with ofatumumab

(randomised controlled trial evidence)

4.11 The committee considered the clinical evidence that came from the randomised controlled RESONATE trial which compared ibrutinib with ofatumumab. The committee noted that after a positive interim analysis the trial terminated early, when the median time in the trial was 9.4 months. The committee acknowledged that the company had re-analysed the data at a median 16-month follow-up and at a median of 30 months of follow-up. After a median of 16 months, the median progression-free survival had not been reached with ibrutinib; that is, fewer than half of the people randomised to ibrutinib had progressed disease, while for patients randomised to ofatumumab the median progression-free survival was 8.1 months (hazard ratio 0.106, 95% confidence interval 0.073 to 0.153, p<0.0001). 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 agreed that the results from RESONATE showed that ibrutinib was a very effective therapy, a conclusion that the clinical experts supported. It was clear that the 'immaturity' of the data reflected the effectiveness of ibrutinib and viewed this positively. However, the committee was mindful 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.

Clinical effectiveness of ibrutinib compared with idelalisib plus ofatumumab (indirect treatment comparison)

4.12 The committee considered the indirect treatment comparisons conducted by the company, and specifically the comparison of overall survival between ibrutinib with idelalisib plus ofatumumab. The common comparator was ofatumumab. The committee noted that the company adjusted the trial results of RESONATE (which compared ibrutinib with ofatumumab) to account for crossover at disease progression. It agreed that this was appropriate, recognising that the unadjusted hazard ratio for death from the RESONATE trial would underestimate ibrutinib's effectiveness relative to ofatumumab. However, the committee noted that the company did not adjust the hazard ratio from the Jones et al. (2015) trial (also known as the 119 trial, and 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 for crossover in the 119 trial because this trial did not allow crossover 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 of a compassionate-use programme for ibrutinib in place at the time.
- The company stated that this treatment switching was not within the trial period and so it did not believe that adjusting was appropriate. However, distinguishing between crossover to the intervention within a trial and switching treatments, the committee considered that adjusting for treatment switching within the idelalisib trial was appropriate because, based on what it had heard and read in the consultation comments, it was likely that more patients randomised to placebo (compared with idelalisib) in the 119 trial received treatments that both extended life and were not part of standard NHS practice.
- The committee was aware of the NICE Decision Support Unit document on treatment switching, which supports adjusting for post-study therapies that do not reflect routine care.

  The committee agreed that the treatment switching to ibrutinib that occurred after the 119 trial was relevant when determining the relative effectiveness of ibrutinib and idelalisib.

4.13 The committee discussed how to account for the effect of the treatment switching that occurred after the 119 trial on the relative effectiveness of ibrutinib and idelalisib. It recognised that the company did not have access to the data from the 119 trial, so could not adjust this data. The committee considered the options available, which were either to adjust the data from the RESONATE trial only, or to adjust neither trial's data. The committee noted that it had not seen any data to quantify the extent to which switching to ibrutinib occurred after the 119 trial. The committee concluded that the true estimates of the clinical benefit of ibrutinib compared with idelalisib plus rituximab would likely be weaker than, but closer to, the company's estimates of clinical effectiveness when adjusting only the RESONATE data for crossover, compared with estimates based on not adjusting data from either trial.

4.14 The committee considered the clinical benefits of treatment with ibrutinib compared with idelalisib. The committee noted 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 but are manageable, and are less severe than those seen with other treatments for CLL. It heard from clinicians that, because of the risks associated with idelalisib (see section 4.8), their preference would be to offer ibrutinib. The committee concluded that ibrutinib offered a more preferable toxicity profile, and was likely to offer progression-free and overall survival benefits compared with idelalisib plus rituximab, but was mindful that the extent of this benefit was uncertain.

Idelalisib plus ofatumumab as a proxy for idelalisib plus rituximab

4.15 The committee noted that the scope included idelalisib plus rituximab as a comparator, but that the company presented results for idelalisib plus ofatumumab rather than idelalisib plus rituximab.

- The committee was aware that a double-blind randomised controlled trial comparing rituximab with idelalisib plus rituximab (Sharman et al. 2014, also known as the 116 trial) formed the key evidence for NICE's decision on idelalisib. It questioned why the company had not included this in its network of studies. The company stated that it did not include the 116 trial within a matching-adjusted indirect comparison (MAIC) because the trial had substantial limitations, including differences to RESONATE in trial design, follow-up and crossover and, in its 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 an MAIC including the 116 trial for progression-free survival, but the ERG was unable to verify the results because the analyses lacked statistical details.
- The committee understood that the company did not include a comparison between ibrutinib and idelalisib plus rituximab because it considered that idelalisib plus ofatumumab was a proxy for idelalisib plus rituximab. The company also stated that, in the appraisal of idelalisib, the committee had

accepted that rituximab and ofatumumab were equally effective. However, the committee noted that, in the idelalisib appraisal, it was rituximab and ofatumumab monotherapy that were accepted as being equal, rather than each in combination with idelalisib. The company stated that it was not plausible that the efficacy would differ in combination. The committee heard from the clinical experts that idelalisib plus ofatumumab and idelalisib plus rituximab could be considered equivalent in terms of effectiveness.

The committee agreed there were uncertainties around the company's assumptions when comparing ibrutinib with idelalisib plus rituximab. On balance, the committee concluded that the company's assumption that idelalisib plus rituximab is equivalent to idelalisib plus ofatumumab was reasonable.

Clinical effectiveness of ibrutinib compared with best supportive care (using physician's choice as a proxy for best supportive care)

4.16 The committee was aware the company had not compared ibrutinib with best supportive care for people who cannot take idelalisib plus rituximab. The committee discussed whether physician's choice could be considered a proxy for best supportive care in people who cannot have idelalisib plus rituximab. However, the committee considered that this was problematic because bendamustine plus rituximab comprises 35% of physician's choice. The committee noted that taking bendamustine out of the mix would lower the cost, but also the effectiveness, of physician's choice. Without formal analyses, it concluded that it could not judge the impact this would have on clinical and cost effectiveness. The committee discussed whether ofatumumab would be a proxy for best supportive care. It noted that, in the Osterborg et al. trial, in the intention-to-treat analyses, patients randomised to ofatumumab lived longer than patients randomised to physician's choice (despite patients crossing over from the physician's choice arm) and therefore ofatumumab was unlikely to reflect best supportive care. The committee concluded that it was not presented with any evidence which compared ibrutinib with best supportive care. However, it concluded that it was likely that ibrutinib would be more effective compared with best supportive care than when compared with idelalisib plus rituximab.

Using ibrutinib after idelalisib in the treatment pathway

4.17 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, however, was not presented with any data for using ibrutinib after idelalisib. The committee concluded that it could not consider ibrutinib for this setting.

Cost effectiveness

4.18 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 ERG, 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.

4.19 The committee considered the company's extrapolations 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 (see section 4.11) 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 the 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 the choice of statistical model for extrapolating progression-free survival determined this. The committee noted that the ERG suggested that the exponential function provided a more

credible period of time in progressed disease, whereas the company suggested the Weibull function provided a better fit for the data.

The committee noted that the choice of model to extrapolate progression-free survival from RESONATE was a key driver of the cost-effectiveness results. The committee agreed that the Weibull function resulted in implausibly long survival after disease progression (estimates marked commercial in confidence by the company). The committee concluded that it preferred the exponential distributions.

4.20 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 this population. This included the hazard ratios for progression-free and overall survival, which were based on the overall population. 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.

Time horizon

4.21 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 years and 30 years. The committee noted that the 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, according to the company model, people treated with ibrutinib would still be 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.

Treatment duration

4.22 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 noted that the summary of product characteristic states that treatment should continue only until disease progression or when it is no longer tolerated by the patient. The committee therefore concluded to consider only the costs and benefits of treatment until progression in the modelling.

Modelling the level of response to treatment

4.23 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 on the first appraisal consultation document, the company maintained that response level should determine routine follow-up and inpatient costs. The ERG agreed with the company that it may be more reasonable to equalise costs at the level of partial response, but stated that the company had not shown that rates of admission to hospital differ by response status. The committee concluded that, after consultation on the first appraisal consultation document, the company had corrected most imbalances in the costs, and that the costs of routine follow-up had a negligible impact on the ICERs.

Utility values

4.24 The committee considered the evidence on health-related quality of life 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 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 on the first appraisal consultation document, 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.

4.25 The committee considered the utility value for post-progression applied in the company's model. The committee heard from the clinical experts that they would not expect utility in the post-progression health state to be as high as assumed by the company. The committee was also aware that the company did not age-adjust the utilities. After consultation on the first appraisal consultation document, 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.

Cost-effectiveness results

4.26 The committee considered the cost effectiveness of ibrutinib based on the evidence available. The committee reiterated that these ICERs were associated with uncertainty relating to efficacy estimates, utility values and long-term outcomes. 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 many of these assumptions. These included:

- using the exponential function to extrapolate the overall survival and progression-free Kaplan–Meier survival curves from RESONATE
- removing the asymmetries in the modelling where the direct drug costs and administration costs associated with ibrutinib were treated differently from other comparators
- removing the costs of repeated biopsies.

The committee was also aware that these ICERs did not include the ERG's exploration of limiting the duration of benefit with ibrutinib to 5 years. The committee recalled that this would increase the committee's preferred ICERs. The committee acknowledged that, after recent advice from the EMA on idelalisib, the costs associated with the adverse effects from idelalisib were likely to increase, which may improve the cost effectiveness of ibrutinib compared with idelalisib. Additionally, the ERG explored the upper bound of the ICER by not adjusting the results of the RESONATE trial for crossover (see section 4.13). The committee considered that the true ICER was likely to fall between the results of the ERG scenarios that did or did not adjust for crossover in the RESONATE trial.

4.27 The committee considered the ICERs including the updated ibrutinib patient access scheme and the patient access scheme for idelalisib. It noted that the ERG scenario without adjusting for crossover in the RESONATE trial was around £50,000 per quality-adjusted life year (QALY) gained, and the scenario adjusting for crossover was below £50,000 per QALY gained.

Innovation

4.28 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. 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. The

committee concluded that ibrutinib is an innovative treatment.

End of life

4.29 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee considered the short life-expectancy criterion, that is, whether the patient group with CLL included in this appraisal would normally live less than 24 months. The committee was aware that before idelalisib had been recommended as a treatment option, people lived for a shorter length of time. 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. However, it 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 whether ibrutinib extended life by an average of at least 3 additional months, first considering the previously treated population. The committee acknowledged the uncertainty around the long-term efficacy results from RESONATE (see section 4.11). 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, even with confounding in the indirect comparisons, ibrutinib was likely to extend life more than 3 months compared with idelalisib plus rituximab. The committee noted that there was far greater uncertainty in the degree to which ibrutinib extends life for people with a 17p deletion or TP53 mutation. The committee acknowledged comments from experts that ibrutinib is very effective in this population. On balance, the committee was satisfied that ibrutinib met the extension-to-life criterion. The committee concluded that both end-of-life criteria had been met for the populations in this appraisal.

Conclusions

4.31 The committee considered all the evidence presented to it. It agreed that ibrutinib represented an important and effective treatment in CLL. The committee was satisfied that, in both populations of this appraisal and with the patient access scheme offered by the company, the ICERs for ibrutinib fell within the range normally considered as a cost-effective use of NHS resources for a treatment that fulfils the end-of-life criteria.

Pharmaceutical Price Regulation Scheme 2014

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.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that ibrutinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Janssen have agreed that ibrutinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Janssen on 0149 456 7400 or at janssenukcustomerservices@its.jnj.com.

6 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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.

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, Boglarka Mikudina
Technical Lead

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager

ISBN: 978-1-4731-2276-5