NICE National Institute for Health and Care Excellence

NICE guidance

Ibrutinib for treating relapsed or refractory mantle cell lymphoma

Technology appraisal guidance
Published: 31 January 2018

www.nice.org.uk/guidance/ta502

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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.

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1 Recommendations

1.1 Ibrutinib is recommended as an option for treating relapsed or refractory mantle cell lymphoma in adults, only if:

- they have had only 1 previous line of therapy and
- the company provides ibrutinib with the discount agreed in the commercial access agreement with NHS England.

1.2 This recommendation is not intended to affect treatment with ibrutinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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2 Information about ibrutinib

Description of the technology

2.1 Ibrutinib (Imbruvica, Janssen) inhibits a protein called Bruton's tyrosine kinase, stopping B-cell (lymphocyte) proliferation and promoting cell death.

Marketing authorisation

2.2 Ibrutinib has a marketing authorisation in the UK for the treatment of adults 'with relapsed or refractory mantle cell lymphoma'.

Adverse reactions

2.3 The most common adverse reactions associated with ibrutinib include diarrhoea, musculoskeletal pain, upper respiratory tract infection, haemorrhage, bruising, rash, and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

2.4 Ibrutinib is taken orally (4×140-mg capsules) once daily, until the disease progresses or there is unacceptable toxicity.

Price

2.5 Ibrutinib is available at the list price of £4,599.00 for 90×140-mg capsules (£51.10 per capsule) and £6,132.00 for 120×140-mg capsules (£51.10 per capsule; excluding VAT, British national formulary [BNF] June 2016). The pricing

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arrangement considered during guidance development was a patient access scheme agreed with the Department of Health that applied to all indications for ibrutinib. The company subsequently agreed a commercial access agreement with NHS England that replaced the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.

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3 Committee discussion

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

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of relapsed or refractory mantle cell lymphoma 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

Clinical management of relapsed or refractory mantle cell lymphoma

3.1 The committee heard from the clinical expert that the most common first-line options for treating mantle cell lymphoma are rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), or rituximab in combination with bendamustine. These are followed by 2 years of rituximab maintenance treatment. The committee understood that there is no accepted standard of care for treating relapsed or refractory mantle cell lymphoma, and that a range of chemotherapy regimens are used. It heard from the clinical expert that these often contain rituximab, even though many people will have had rituximab as part of first-line and maintenance treatment. The clinical expert highlighted that as many as 22 different treatments are used in the UK for treating relapsed or refractory mantle cell lymphoma. The choice of treatment largely depends on the availability of drugs and clinician's choice, because there is no treatment regimen that has been shown to be the most effective in this setting. The clinical expert also commented that temsirolimus, the comparator in the main ibrutinib study (RAY), is not used in the UK because it is considered to be of low efficacy despite being licensed for this indication. The committee concluded that there is no standard of care for treating relapsed or

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refractory mantle cell lymphoma in England, and that treatment tends to combine rituximab with a range of chemotherapy options. It also concluded that temsirolimus is not relevant to UK clinical practice.

Clinical need of patients with mantle cell lymphoma

3.2 The committee noted that mantle cell lymphoma is an aggressive form of non-Hodgkin's lymphoma and in some cases can be associated with debilitating symptoms. There are very high rates of relapse after initial treatment, and a huge effect on quality of life. The committee heard from the patient and clinical experts that ibrutinib is already widely used in clinical practice because of its previous availability through the Cancer Drugs Fund, and is welcomed by patients because it is highly effective compared with existing treatments and extremely well tolerated with very few adverse reactions. It is taken orally and people value this highly because it can be taken in the privacy of their own home and reduces the need for hospital visits. It can be used by older and frail people and, unlike current chemotherapy options, patients do not usually need additional treatments to counter adverse reactions. For these reasons, the patient experts considered that ibrutinib is a life-transforming drug that results in a step change in the quality of life of patients with relapsed or refractory mantle cell lymphoma and their families and carers, allowing many to participate in general day-to-day activities, and very quickly return to their normal life. The committee concluded that the availability of an effective oral therapy with a manageable adverse-reaction profile is highly valued by patients and addresses a high unmet need among people with relapsed or refractory mantle cell lymphoma.

Overview of ibrutinib studies

3.3 The committee noted that the evidence on the clinical effectiveness of ibrutinib came from 1 randomised controlled trial (RAY) and 2 single-arm studies (SPARK and PCYC-1104). It considered that RAY is not strictly relevant to NHS practice because temsirolimus, the comparator treatment in the trial, is not routinely used in the UK. It noted the absence of any trials comparing ibrutinib with any comparator defined in the NICE scope. It also noted that all 3 studies were open label, which made them potentially prone to bias, although it accepted that the

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studies addressed potential measurement bias by using an independent review committee to evaluate the primary outcome. The committee concluded that the studies were of a reasonable quality but were limited by the lack of a comparison against a treatment used in UK clinical practice.

Clinical evidence – trial results

3.4 The committee noted that at median follow-up of 20 months, median progression-free survival in RAY was statistically significantly longer for ibrutinib compared with temsirolimus (14.6 months compared with 6.2 months; hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.32 to 0.58; p<0.0001). At the time of the first appraisal committee meeting the overall-survival data from RAY were immature and median overall survival had not yet been reached in the ibrutinib arm, indicating that more than 50% of patients were still alive. The committee noted that the crossover of 23% of patients in the temsirolimus arm to the ibrutinib arm could confound the overall-survival results, which could also be confounded by the use of subsequent anticancer systemic therapies in both arms (31.7% of patients in the ibrutinib arm and 58.2% of patients in the temsirolimus arm). Following consultation on the appraisal consultation document, the committee considered updated RAY data submitted by the company, with a median follow-up of 39 months. It noted that the results were consistent with the earlier data and that median overall survival had now been reached (30.3 months for ibrutinib compared with 23.5 months for temsirolimus; HR 0.74; 95% CI 0.54 to 1.02). The committee concluded that the results from RAY suggest that ibrutinib significantly improves progression-free survival compared with temsirolimus. But the overall-survival benefits remain uncertain, despite the availability of more mature data, because of potential confounding from crossover and the use of further anticancer therapies.

3.5 The committee considered that the results from the 2 single-arm trials were generally supportive of the results from RAY, although it noted that the overall-response rates and progression-free survival were slightly lower in the single-arm trials than in the ibrutinib arm of RAY. It concluded that it was appropriate to pool the results from the 3 studies to give a larger patient population, given the general lack of evidence for treating relapsed or refractory mantle cell lymphoma with ibrutinib.

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Indirect comparison

3.6 The committee noted that in the absence of any direct trial evidence for ibrutinib against a comparator reflective of current UK clinical practice, the company did an indirect treatment comparison using results from RAY and from the OPTIMAL study (Hess, 2009) that compared temsirolimus with clinician's choice of single-agent chemotherapy. The indirect treatment comparison compared ibrutinib against clinician's choice of single-agent chemotherapy in OPTIMAL, using temsirolimus as the common comparator. The committee noted that the company adjusted the treatment effect of chemotherapy, as estimated from the indirect comparison, to take into account the additional effect of adding rituximab (R-chemo). This adjustment used data on the benefit of R-chemo compared with single-agent chemotherapy from the Haematological Malignancy Research Network (HMRN) audit of 118 patients with mantle cell lymphoma that had been treated with first-line therapy. The committee understood that this resulted in a progression-free survival hazard ratio for ibrutinib compared with R-chemo of 0.28 (representing a 72% reduction in the risk of disease progression with ibrutinib compared with R-chemo).

3.7 The committee acknowledged the limitations of the indirect comparison that were highlighted by both the company and the evidence review group (ERG), such as differences in the patient populations in OPTIMAL and RAY. It also noted that the HMRN audit did not specifically relate to patients with relapsed or refractory mantle cell lymphoma. It also understood that the ERG did not agree with the company's 2-stage approach to estimating treatment effects for ibrutinib compared with R-chemo, and that the ERG had done a separate analysis based on a single-stage approach using a random effects network meta-analysis instead of fixed effects. This resulted in a hazard ratio for progression-free survival of 0.27 (HR 0.27; 95% credible interval 0.06 to 1.26), similar to the company's estimate of 0.28. However, the committee noted that because of concerns about the evidence used to inform the indirect comparisons, the ERG considered that the results of both analyses should be interpreted with caution. The committee also noted that the company's alternative approach to estimating the effectiveness of ibrutinib compared with R-chemo (that is, assuming that temsirolimus has equal efficacy to R-chemo based on the results from RAY) produced a less-favourable hazard ratio of 0.43. The committee concluded that there is considerable uncertainty associated with the indirect comparisons and

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that the benefit of ibrutinib compared with R-chemo is unclear, although it accepted that the available evidence and experience from clinical practice strongly suggest that ibrutinib is more effective.

Subgroups

3.8 The committee discussed the efficacy results for subgroups of patients, based on the number of previous lines of therapy. It noted that the results suggest greater efficacy in patients who had ibrutinib after only 1 previous line of therapy, compared with 2 or more therapies. The clinical expert also stated that ibrutinib is particularly beneficial after the first relapse. The committee considered the updated RAY data, which have a median follow-up of 39 months. These provide further evidence of a greater benefit of ibrutinib when taken after only 1 previous line of therapy. Updated median overall survival was 42.1 months for ibrutinib and 27.0 months for temsirolimus in the 1 previous therapy subgroup, compared with 22.1 months and 17.0 months respectively after 2 or more therapies. The committee understood that the data were potentially confounded by crossover of patients in the temsirolimus arm to the ibrutinib arm (39% in the 1 previous therapy subgroup). It was also concerned that the subgroups were defined post hoc. However, the committee noted responses to the appraisal consultation document from professional groups. These state that evidence from clinical practice supports the RAY results, and that earlier use of ibrutinib in relapsed or refractory disease is the most beneficial. The committee concluded that the evidence from RAY and clinical experience suggest that ibrutinib is most effective in people who have had only 1 previous line of therapy.

Cost effectiveness

The company's model and the ERG's exploratory analyses

3.9 The committee noted that the company had developed a Markov model comparing ibrutinib with R-chemo, comprising 3 states (pre-progression, post-progression and death), and that this approach had been used in previous NICE appraisals. The committee was aware that overall-survival data from the ibrutinib

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studies were not directly extrapolated but were modelled using progression-free-survival data from the pooled ibrutinib dataset. The committee considered that the company's approach is appropriate given the immaturity of the overall-survival data at the time of the modelling.

3.10 The committee considered the ERG's critique of the company's model. It noted the ERG's comments that the company's Markov approach imposed structural constraints, which did not make the best use of the trial data on survival, and that the overall survival predicted by the model did not provide a good visual fit to the observed Kaplan–Meier survival curve from the trials. The committee understood that the ERG favoured a partitioned survival model using overall-survival data for ibrutinib directly from the trials rather than using progression-free survival, and had explored the effect of using this approach in an exploratory analysis (set B). The committee examined the ERG's set B exploratory analysis but was concerned that the partitioned survival approach resulted in efficacy estimates for R-chemo that were higher than those for ibrutinib, giving higher quality-adjusted life year (QALY) gains for R-chemo than ibrutinib. By contrast, it heard from the clinical expert that experience has shown that ibrutinib is more effective than R-chemo for treating relapsed or refractory mantle cell lymphoma. This is partly because relapsed or refractory disease will already have been treated with R-chemo and rituximab maintenance therapy, which will become progressively less effective with further relapse. The committee concluded that the results of the partitioned survival analysis are not clinically plausible, acknowledging the ERG's comments that they are associated with major uncertainty because they used the outputs of a highly uncertain meta-analysis.

3.11 The committee re-examined the company's Markov approach, which it considered led to more plausible results (incremental QALYs for ibrutinib compared with R-chemo ranging from 0.82 to 1.87 depending on the scenario), although it acknowledged the considerable uncertainty associated with these estimates. The committee noted that in the company's base-case analysis, incorporating the updated patient access scheme, the incremental cost-effectiveness ratio (ICER) for ibrutinib compared with R-chemo was £62,650 per QALY gained. It also noted that the company carried out a range of scenario analyses to test the assumptions in the model. These included estimating the effectiveness of ibrutinib compared with R-chemo using temsirolimus as a proxy for R-chemo. The committee noted that this scenario used the efficacy data from

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RAY and resulted in an estimated ICER for ibrutinib compared with R-chemo of £69,142 per QALY gained. The committee also noted that the ICER was above £59,000 per QALY gained in all but 1 of the scenarios presented by the company. In that 1 scenario, the company applied a hazard ratio to post-progression survival for R-chemo. This was adjusted to be as close as possible to the anticipated survival based on the results of the HMRN audit (that is, 8.4 months for patients on second-line treatment). This resulted in an ICER of £49,849 per QALY gained. However, the committee understood that time-to-event estimates for progression-free survival and post-progression survival for ibrutinib were taken from the 1 previous therapy subgroup, and therefore that the analysis reflects this subgroup.

3.12 The ERG did a set of exploratory analyses (set A) that made adjustments to some of the parameter values in the company's model. These mostly resulted in a lower ICER for ibrutinib compared with R-chemo than that estimated by the company. However, the committee was minded not to accept the results of the ERG's amendments because these represented the extreme (lowest) end of the ERG's wide estimate of possible ICERs, depending on the model and parameters used. The committee concluded that the ICERs presented by the company for the whole population of people with relapsed or refractory mantle cell lymphoma, incorporating the confidential patient access scheme for ibrutinib, are above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

3.13 The committee recognised the high clinical need of people with mantle cell lymphoma and that ibrutinib has several benefits including oral administration, manageable adverse reactions and low toxicity. It therefore considered that ibrutinib is a step change in managing relapsed or refractory mantle cell lymphoma. However, it did not consider that any additional health-related benefits, that had not been captured fully in the QALY calculation, would be enough to lower the ICER for the whole population to within the range normally considered cost effective.

3.14 The committee recalled its earlier conclusion that trial evidence and clinical experience suggest that ibrutinib is most effective in people who have had only 1 previous line of therapy (see section 3.8). It therefore considered whether ibrutinib could be considered cost effective in this group of patients. It noted that

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the company's ICER of £49,849 per QALY gained may be a conservative estimate because updated trial data from RAY suggest that the model underestimates survival for this subgroup. The committee also noted that overall survival in RAY may have been confounded by the crossover of 39% of people from the temsirolimus arm to the ibrutinib arm. The committee concluded that the most plausible ICER in this group of patients is likely to be lower than the company's estimate of £49,848 per QALY gained.

End-of-life considerations

3.15 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. It accepted that ibrutinib is indicated for people with a short life expectancy, noting that the estimates presented for people with relapsed or refractory mantle cell lymphoma ranged from 5.2 months to 9.7 months. It also accepted that there is enough evidence to indicate that ibrutinib offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The committee concluded that ibrutinib met all the criteria to be considered a life-extending end-of-life treatment.

3.16 Taking all the evidence and uncertainties together, and given the extra weight applied to QALYs at the end of life, the committee concluded that the company's ICERs for the whole population of people with relapsed or refractory mantle cell lymphoma are above the range normally considered to be a cost-effective use of NHS resources. However, the committee concluded that ibrutinib is a cost-effective use of NHS resources for people who have had only 1 previous line of therapy, and that ibrutinib can be recommended for use in this group of people.

Potential equality issues

3.17 The committee noted the potential equality issue raised by the company and patient groups that ibrutinib would offer an alternative to less effective but better tolerated chemotherapy agents for older or frailer people. It also noted the issue raised that oral administration allows an effective treatment option for people

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without access or transport to an infusion unit and significantly reduces multiple hospital visits. The committee acknowledged that access to ibrutinib may enhance treatment in these groups of people.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

3.18 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.

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4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 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 relapsed or refractory mantle cell lymphoma and they have had only 1 previous line of therapy and the healthcare professional responsible for their care thinks that ibrutinib is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 NHS England and Janssen have agreed a commercial access agreement that makes ibrutinib available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to Janssen Customer Services on 01494 567 400 or janssenukcustomerservices@its.jnj.com.

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5 Appraisal committee members and NICE project team

Appraisal committee members

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

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.

Aimely Lee
Technical Lead

Zoe Charles
Technical Adviser

Thomas Feist, Marcia Miller and Liv Gualda
Project Managers

ISBN: 978-1-4731-2808-8

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