NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Zanubrutinib for treating Waldenstrom's macroglobulinaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using zanubrutinib 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, 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see 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 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, sex, 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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using zanubrutinib in the NHS in England.

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

The key dates for this appraisal are:

Closing date for comments: 20 July 2022

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Zanubrutinib is recommended as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 treatment, only if:

- they would otherwise have treatment with bendamustine and rituximab
- the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with zanubrutinib 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.

Why the committee made these recommendations

Standard care for Waldenstrom's macroglobulinaemia varies but typically includes chemoimmunotherapy combinations such as bendamustine and rituximab, or dexamethasone, rituximab and cyclophosphamide. When chemoimmunotherapy is unsuitable, rituximab or chlorambucil alone are typically offered.

Clinical evidence from an indirect comparison suggests that people with Waldenstrom's macroglobulinaemia may live longer and have a better quality of life with zanubrutinib than with standard care. Long-term evidence on the effectiveness of zanubrutinib is not yet available. So, it is unclear how much longer people having zanubrutinib live.

The cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources in people who have had at least 1 treatment, but only if they would otherwise have bendamustine and rituximab. So, zanubrutinib is recommended for this group. The company did not submit any evidence for the initial treatment of Waldenstrom's macroglobulinemia with zanubrutinib compared with alternative therapies in people for who chemoimmunotherapy is unsuitable. So, no recommendation could be made for this group.

2 Information about zanubrutinib

Marketing authorisation indication

2.1 Zanubrutinib (Brukinsa, BeiGene) has a marketing authorisation in the UK for 'the treatment of adult patients with Waldenström's macroglobulinaemia (WM) in adults who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for zanubrutinib.

Price

2.3 The list price of zanubrutinib 120x80 mg capsules is £4,928.65 (excluding VAT; company submission). The company has a commercial arrangement (simple discount patient access scheme). This makes zanubrutinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

Current management

Comparators are bendamustine and rituximab (BR), dexamethasone, rituximab and cyclophosphamide (DRC), and rituximab or chlorambucil

3.1 Waldenstrom's macroglobulinaemia is an incurable form of non-Hodgkin's lymphoma. It typically affects older people and has a long trajectory, with a median overall survival of 16 years in people with symptoms. Because

the condition progresses slowly, many people die from causes other than Waldenstrom's macroglobulinaemia. The clinical experts explained that, although there is variation in the clinical pathway, the first-line treatment options are commonly BR and DRC if chemoimmunotherapy is suitable. Although purine analogues such as fludarabine were included in the NICE scope, their use is no longer recommended because of toxicity concerns and the risk of secondary malignancies. This is reflected in the latest clinical guidelines on managing Waldenstrom's macroglobulinaemia from the British Society of Haematology. An autologous stem cell transplant is also an option for people who are fit enough. However, because Waldenstrom's macroglobulinaemia mainly affects older people, this is not suitable for most. Until recently, when the condition relapsed or became refractory to first-line treatment most people were offered ibrutinib (a Bruton's tyrosine kinase inhibitor), which was available via the Cancer Drugs Fund. But, during this appraisal, a separate NICE appraisal of ibrutinib for treating Waldenstrom's macroglobulinemia was done. This found that ibrutinib could not be recommended for routine use in the NHS for this indication. Other second-line treatment options include rituximab-containing regimens (such as BR or DRC, if not used as a first-line treatment). When chemoimmunotherapy is unsuitable, treatment options include rituximab or chlorambucil monotherapy, or best supportive care. The committee noted that there is variation in the treatment pathway for people with Waldenstrom's macroglobulinaemia, particularly when it is relapsed or refractory. It concluded that BR and DRC were the 2 most relevant comparators when chemoimmunotherapy is suitable and zanubrutinib would be used after at least 1 treatment. It also concluded that rituximab or chlorambucil were relevant comparators when chemoimmunotherapy is unsuitable and zanubrutinib is a first-line option.

The availability of an effective and well-tolerated oral treatment is highly valued and addresses a significant unmet need

3.2 The patient expert explained that Waldenstrom's macroglobulinaemia and its treatment can have a profound effect on quality of life. The condition

itself can cause severe pain, fatigue, reduced mobility and increased susceptibility to infections. Current chemoimmunotherapy treatments can cause severe adverse reactions and the need for frequent hospital visits. Even though Waldenstrom's macroglobulinaemia may respond well to first-line treatment, the constant threat of relapse can be a huge burden on people with the condition and their families. For people who cannot have chemoimmunotherapy, treatment options are very limited. The patient expert said that people with the condition are acutely aware that there are a limited number of treatment options. Also, there is a desire among the patient community to have additional options as their condition progresses. The committee noted that zanubrutinib is a Bruton's tyrosine kinase inhibitor and has a different mechanism of action to existing chemoimmunotherapy treatments. Both the patient and clinical experts emphasised that zanubrutinib is highly effective and better tolerated than existing chemoimmunotherapy options. It is also an oral treatment, which is greatly valued by people with the condition because it avoids the need for hospital visits and infusions. The patient expert said that zanubrutinib had rapidly and dramatically made him "feel better" and improved his quality of life. He explained that it had allowed him to participate in general day-to-day activities and return to the normal life he had enjoyed before diagnosis. He explained that this was in stark contrast to his experience with chemoimmunotherapy treatments, with which he had had significant intolerance issues and side effects, some of which were persistent. The committee concluded that the availability of an effective and well-tolerated oral treatment would be highly valued by people with Waldenstrom's macroglobulinaemia and would address a significant unmet need.

Clinical effectiveness

The ASPEN study provides generalisable evidence for zanubrutinib but its comparator, ibrutinib, is not relevant for this appraisal

3.3 The clinical evidence for zanubrutinib came from the ASPEN study, a randomised clinical trial that compared zanubrutinib with ibrutinib. The

committee noted that ibrutinib was not a comparator in this appraisal (see section 3.1). The people in the trial were divided into 2 cohorts:

- Cohort 1 included 201 people with Waldenstrom's macroglobulinaemia who had a mutation in the myeloid differentiation primary response gene (mutated MYD88 type). The people in this cohort were randomised to either zanubrutinib or ibrutinib.
- Cohort 2 included 28 people with Waldenstrom's macroglobulinaemia (wild type MYD88 type) and they were all assigned to zanubrutinib.

One clinical expert explained that the trial was designed this way because earlier studies had suggested that ibrutinib may work less well in people without the MYD88 mutation. The committee understood that about 90% of people with Waldenstrom's macroglobulinaemia have the MYD88 mutation. But, overall, they expected that zanubrutinib would work equally well in people who did and did not have the MYD88 mutation. The company stated that comparing the data for zanubrutinib from the 2 cohorts supported the assumption that there was no difference in outcomes. The committee considered that the trial data from cohort 1 (which the company used in its model) was generalisable to both people with and without the MYD88 gene mutation. Cohort 1 included:

- 164 people (83 in the zanubrutinib arm) with relapsed or refractory Waldenstrom's macroglobulinaemia who had had at least 1 treatment
- 37 people (19 in the zanubrutinib arm) who had not had any treatment and for whom chemoimmunotherapy was unsuitable.

The median age of people in the trial was 70. Also, almost everyone had an Eastern Cooperative Oncology Group performance status of 0 or 1, and many had had a lot of previous treatments. One clinical expert noted that the trial population reflected the patient population in the NHS. The committee concluded that ASPEN provided clinical evidence for zanubrutinib that is generalisable to UK clinical practice. However, it

concluded that it had not compared zanubrutinib with the relevant comparators for this appraisal.

Zanubrutinib is clinically effective, but the data is immature for progression-free and overall survival

3.4 The committee noted that, at a median follow up of 19.5 months in ASPEN, the very good partial response rate was 28.4% in the zanubrutinib arm and 19.2% in the ibrutinib arm. This response occurred at a median time of 4.8 months in the zanubrutinib arm. It also noted that there was not a complete response in anyone. However, 1 clinical expert said that this was not unexpected because it is acknowledged that this class of drugs is not curative. The clinical expert also noted that it was important to consider the durability of that response, and not just its depth. Median progression-free and overall survival had not been reached at the point of data cut-off, so the survival data for zanubrutinib was currently immature. This was expected because Waldenstrom's macroglobulinaemia is a slowly progressing condition. At 12 months, 97.0% (95% confidence interval 90.9 to 99.0) of people in the zanubrutinib arm were alive, and the condition had not yet progressed in 89.7% (95% confidence interval 81.7 to 94.3). Although ibrutinib was not a comparator in this appraisal, the committee noted that overall (93.9%) and progression-free survival (87.2%) was similar to that with zanubrutinib at 12 months. The clinical experts explained that zanubrutinib would be expected to have similar clinical efficacy to ibrutinib in clinical practice because they are in the same drug class. The committee concluded that zanubrutinib is clinically effective, but that data on progression-free and overall survival was immature.

Zanubrutinib is more clinically effective than chemoimmunotherapy, but the size of the benefit compared with BR and DRC is uncertain

3.5 Clinical evidence for the chemoimmunotherapy comparators (BR and DRC) came from 2 main studies:

- The clinical evidence for BR came from a single-arm study of 71 people with relapsed or refractory Waldenstrom's macroglobulinaemia (Tedeschi et al., 2015).
- The clinical evidence for DRC came from a single-arm trial of 72 people with Waldenstrom's macroglobulinaemia who had not had previous treatment but for whom chemoimmunotherapy was considered suitable (Dimopoulos et al., 2007; Kastritis et al., 2015).

The committee noted that the populations in these studies differed from that in ASPEN. About 81% of people in ASPEN had zanubrutinib after previous treatment. The remainder, for whom chemoimmunotherapy was unsuitable, had zanubrutinib as a first-line treatment (see section 3.3). The committee noted that the DRC data came from people for whom chemoimmunotherapy was suitable but who had not had previous treatment. This population does not correspond with the marketing authorisation for zanubrutinib (see section 2.1). Also, it is different from the population in ASPEN. The company attempted to match the populations used in the indirect treatment comparisons and make to adjustments to minimise bias in the results. It presented results for zanubrutinib compared with BR in a population whose condition was relapsed or refractory and compared it with DRC in a population who had not had previous treatment. The company's original submission used a matching-adjusted indirect comparison (MAIC). The ERG noted the limited patient data available for the comparator studies. It thought that this may have led to differences in clinically relevant risk factors between the comparator groups that could not be adjusted for. In response to technical engagement, the company used another method for indirect comparison, a simulated treatment comparison (STC). The company explained that the STC was its preferred approach because it meant that a larger sample size could be maintained, more data used and covariates adjusted for more effectively. Using either the STC or MAIC approach for the indirect comparison, there was improved overall and progression-free survival with zanubrutinib compared with both BR and DRC. The overall

survival hazard ratios for BR compared with zanubrutinib were lower than the hazard ratios for DRC compared with zanubrutinib, regardless of the approach used. The committee noted that these hazard ratios suggested DRC may be less effective when used first line than BR used second line. But it could not determine whether this reflected a real difference in the benefits of these comparators, or resulted from a difference in the populations being compared in each indirect comparison. The specific results of the analysis are confidential and cannot be shared here. The committee was not aware of any direct comparative evidence to determine whether DRC would be as effective as BR had they been studied at the same stage in the patient pathway. The committee noted that the hazard ratios for progression-free and overall survival were low compared with those typically seen in cancer treatments, suggesting that zanubrutinib is a highly effective treatment. While the hazard ratio point-estimates generated by the MAIC and the STC were different, the confidence intervals had substantial overlap. The committee agreed that this showed some consistency in the results generated by the 2 methods. The clinical experts confirmed that the hazard ratios generated in the analyses to compare zanubrutinib with BR and DRC seemed plausible. The committee considered that there were uncertainties and limitations for both the MAIC and the STC. However, it noted that MAIC methods are more transparent and that there was insufficient justification given by the company to switch from the original MAIC to the STC. The committee concluded that its preferred approach was therefore the original MAIC approach but acknowledged that this was an area of uncertainty. The committee agreed that zanubrutinib is more clinically effective than chemoimmunotherapy treatments. However, it concluded that there was a high degree of uncertainty in the size of the treatment effect in the NHS patient population because of the limitations of the indirect comparisons.

It is uncertain how effective zanubrutinib is compared with rituximab or chlorambucil when chemoimmunotherapy is unsuitable

3.6 The committee noted that, in ASPEN, there were 19 people (about 19%) in the zanubrutinib arm who had not had previous treatment and for whom chemoimmunotherapy was not considered suitable. There was a very good partial response in 26% of this population, compared with 29% in the relapsed or refractory population. The company considered that it was reasonable to consider that the clinical effectiveness of zanubrutinib taken as a first-line treatment by people for whom chemoimmunotherapy was unsuitable and zanubrutinib taken after chemoimmunotherapy by people whose condition was relapsed or refractory would be similar. The clinical experts stated that, when chemoimmunotherapy is considered unsuitable, it is typically because someone is too frail or has other comorbidities, and that these factors may affect outcome. The clinical experts expected people having zanubrutinib as their first treatment would do at least as well as people whose condition was relapsed or refractory. The committee noted that no comparison with chlorambucil or rituximab was presented in the company's submission. But people would typically have them as their first treatment option when chemoimmunotherapy is not suitable. The clinical experts said that rituximab or chlorambucil monotherapy would not work as quickly or have the same durability as standard combined chemoimmunotherapy regimens. The committee noted that the proportion of people in ASPEN for whom chemoimmunotherapy was not suitable was small, and considered whether this would be the same in clinical practice. The clinical experts advised that the proportion of people for whom chemoimmunotherapy is considered unsuitable may depend, to some degree, on the alternative treatment options that are available. They estimated that the figure could be up to 15% if effective options were available that better suited that group (for example, oral treatment that avoided the need for hospital visits). The committee concluded that there was uncertainty about whether Waldenstrom's macroglobulinaemia responds to zanubrutinib in the same way in people unable to tolerate chemoimmunotherapy who have not had previous treatment as in people

whose condition is relapsed or refractory after chemoimmunotherapy. However, it noted the view of the clinical experts that people having zanubrutinib as their first treatment would do at least as well as those whose condition was relapsed or refractory. So, the assumption of equivalent efficacy between first- and second-line treatment by the company may have been reasonable. Also, the comparators (monotherapy when chemoimmunotherapy is unsuitable) may be less effective than chemoimmunotherapy. This would increase the potential benefit of zanubrutinib compared with the comparators for this group. The committee concluded that the exact size of the benefit in this population was uncertain because of the lack of any direct or indirect evidence comparing zanubrutinib with the relevant comparators. So, there was a lack of evidence to incorporate into an economic model.

The company's economic model

The structure of the company's model is appropriate for decision making

3.7 The company developed a cohort partitioned survival model (PSM) to project the long-term clinical and economic consequences. The PSM consisted of 3 mutually exclusive health states: preprogression, postprogression and death. The committee noted the ERG's concerns that this type of model relies on estimating progression-free and overall survival over a long period. This can be uncertain if the trial data for these outcomes is immature, as was the case in ASPEN. However, overall, the committee concluded that it was acceptable for decision making.

The extrapolations of overall survival for zanubrutinib are plausible but uncertain

3.8 To estimate overall survival beyond the data collection periods for zanubrutinib and its comparators, the company used parametric models to extrapolate the data over a 30-year time horizon. The models generated 5- and 10-year survival estimates, which are confidential and cannot be shared here. The clinical experts explained that long-term overall survival

on zanubrutinib and ibrutinib was likely to be similar (see section 3.4). So, the committee compared the modelled 5-year overall survival estimates in the zanubrutinib arm with long-term trial data from study 118E for ibrutinib. The 5-year overall survival data for ibrutinib was broadly consistent with the 5-year overall survival data estimated for zanubrutinib. The committee noted that, in the comparison with BR, the modelled estimates based on the STC indirect comparison were slightly higher, and those based on the MAIC approach slightly lower, than the 5-year estimates for ibrutinib. The committee accepted that the extrapolated survival estimates for zanubrutinib were appropriate for decision making, noting that there were uncertainties in the data that underpinned them.

Some adjustment of overall survival for comparators may be reasonable but is very uncertain and has a large effect on cost effectiveness

3.9 In the first committee meeting, the committee concluded that ibrutinib should not be included as a subsequent treatment option because it is not available via routine commissioning. The committee noted that, in its original submission, the company had included the costs of follow-on treatment with ibrutinib but removed these costs in its updated base case after consultation. The company stated that the patient populations in the BR and DRC trials did not have follow-on ibrutinib. But the extrapolated modelled overall survival beyond the end of the study period may have included some benefit from follow-on ibrutinib. The company explained that this was because it had sought clinical opinion on the expected long-term survival outcomes for BR and DRC. This was to select a modelled distribution that gave clinically plausible extrapolated long-term survival outcomes. The company further stated this opinion was based on current practice at that time, when 72% of people had ibrutinib after BR or DRC via the Cancer Drugs Fund. The company suggested that its modelled estimates of overall survival on BR and DRC may have been overestimated. This was because ibrutinib is no longer available in the NHS, and people on BR or DRC are expected to have poorer outcomes without this effective follow-on treatment. The company stated that its

original modelled estimate of the difference in survival at 6 years between zanubrutinib and BR and DRC was smaller than that presented by an ERG during the NICE technology appraisal of ibrutinib for treating Waldenstrom's macroglobulinaemia. This difference was based on clinical expert opinion. The company suggested that the overall survival curves in the BR and DRC arms should have been adjusted so that the probability of survival was 50% lower than the survival in the zanubrutinib arm at 6 years. The clinical experts considered that that adjustment may be warranted. They noted that zanubrutinib delivers benefit as an improvement on chemoimmunotherapy and as an additional treatment line for people with relapsed or refractory disease. They also noted that people in the BR and DRC trials may have had other effective treatments that are not available in the NHS, such as bortezomib. The clinical experts stated that it was challenging to confirm the level of adjustment needed. This was because of the difficulty in considering hypothetical situations that do not reflect current or previous clinical practice in the NHS. The ERG noted that the company had already used the parametric distribution giving the second most pessimistic modelled overall survival in the BR arm. So, even if the most pessimistic modelled distribution had been selected to reflect the absence of ibrutinib as a subsequent treatment, the effect on the cost-effectiveness results was minor. The ERG further considered that the extent of adjustment was based on a clinical opinion rather than data. It preferred not to include adjustment of overall survival in the comparator overall survival arms. The committee noted that the level of adjustment had a large effect on the incremental cost-effectiveness ratios (ICERs). It concluded that the modelled overall survival of BR and DRC was highly uncertain. It agreed that some adjustment to postprogression survival in the BR or DRC modelled arms may have been needed to account for the potential effect of follow-on treatments not available in the NHS. However, it concluded that the level of this adjustment was highly uncertain.

Utility values in the economic model are appropriate given the available evidence

3.10 The utility value for preprogression was obtained from EQ-5D collected during the ASPEN study. The committee noted that the value was higher than that for the general UK population, which it thought was unrealistic. However, it noted that this is commonly seen when comparing trial populations with the general population. There was not enough data in ASPEN to estimate the utility value for progressed Waldenstrom's macroglobulinaemia. So, the company and ERG agreed a reduction of 0.18 on the preprogression value. This was based on previous NICE technology appraisal guidance on ibrutinib for treating relapsed or refractory mantle cell lymphoma and on ibrutinib for treating Waldenstrom's macroglobulinaemia. The committee acknowledged that this value was uncertain but was suitable for decision making. It also noted that adjusting this value did not have a big effect on the cost-effectiveness results.

Assuming that zanubrutinib suddenly stops working at 5 years is clinically implausible

3.11 The committee heard that the company's base case assumed life-long treatment effectiveness. However, the ERG thought that this was not realistic and implemented a 5-year treatment effect cut-off. This was based on NICE's technology appraisal guidance on lenalidomide with rituximab for previously treated follicular lymphoma. Once people had been on zanubrutinib for 5 years, the hazard ratio for progression-free and overall survival was assumed to become equal to that in the comparator arms. The people in the model continued to take zanubrutinib until their condition progressed rather than a stopping rule being applied. The clinical lead for cancer drugs in the NHS stated that the risk of people's condition progressing while they were on treatment was already accounted for in the model. So, it was overly pessimistic to apply a sudden treatment effect cut-off. The clinical experts agreed with this view. They explained they have experience in other indications in which people

have been taking the same type of drug, ibrutinib, for many years and are still deriving benefit. The committee concluded that there was insufficient evidence to justify this treatment effect cut-off. It noted that 'treatment waning effects' (meaning a reduced treatment effect over time) are typically applied after treatment has stopped, not while people are still on treatment. The committee concluded that a treatment effect cut-off was implausible and should not have been applied in the absence of any evidence to support this assumption.

Cost-effectiveness results for the separate comparisons and blended comparator are taken into account but the blended is more uncertain

3.12 The company used a blended comparator in its cost-effectiveness model. That is, it compared zanubrutinib with a combination of BR and DRC. The company did separate cost-effectiveness analyses for each comparator. It then produced a weighted average of these results using the estimated proportions of who would have each treatment in clinical practice. The company used data from the Rory Morrison Registry to estimate that, in the absence of ibrutinib, 49% of people would have BR and 51% would have DRC. The clinical experts agreed that it was reasonable to estimate that about 50% of people would have each treatment. This was because typically people would initially have treatment with either BR or DRC, and their second-line treatment would be whichever they had not had first line (BR followed by DRC, or DRC followed by BR). The company also presented scenarios to account for variation in clinical practice across the UK, with use of BR and DRC varying between 40% and 60%. The committee recalled that the data for BR had been from people whose condition was relapsed or refractory and who had had previous treatment. It also recalled that the data for DRC had been in people who had not had previous chemoimmunotherapy. This meant that the comparison with BR was more applicable to how zanubrutinib would be used within its marketing authorisation (that is after 1 or more treatments), and was more robust than the comparison with DRC. The committee noted that there was methodological difficulty with the blended comparator. This was

because it relied on an assumption of the proportions of people who would have BR or DRC in clinical practice. It also included the comparison with DRC, which was particularly uncertain. The committee concluded it would take into account the cost-effectiveness results for both the blended and the pairwise comparisons. But it also took account of the greater uncertainty around the estimates compared with DRC, and from the blended comparator.

Cost-effectiveness results

The ICER is only within what NICE usually considers cost-effective use after at least 1 treatment and when BR would otherwise be used

3.13 The committee noted that the company had agreed a patient access scheme for zanubrutinib. There are confidential prices for BR and DRC, so the exact ICERs cannot be reported here. The committee's preferred modelling assumptions after the first meeting were:

- using the MAIC rather than the STC method for indirect comparisons of the clinical data because, although both were uncertain, insufficient justification was given for using the STC and the MAIC was a more transparent approach (see section 3.5)
- excluding the costs of ibrutinib as a subsequent treatment (see section 3.9)
- not to apply any treatment effect cut-off (see section 3.11).

The committee noted that the company had updated its base case to reflect the committee's preferred modelling assumptions. It also noted the base case included an additional adjustment of overall survival in the BR and DRC modelled arms. The ERG's exploratory base case also included the committee's preferred assumptions but did not include the company's new adjustment of overall survival. The committee considered it reasonable to apply some adjustment to overall survival in the comparator arm, but not necessarily the adjustment proposed by the company. The committee recalled its conclusion from the first meeting that an acceptable

ICER would need to be comfortably below £30,000 per quality-adjusted life year (QALY) gained to be considered a cost-effective use of NHS resources. This decision took into account:

- the unmet need for a new treatment option
- the likelihood that zanubrutinib was an effective treatment
- the uncertainty around the indirect comparisons and long-term survival.

The committee first considered the ICER for zanubrutinib compared with the blended comparator, which represented an estimate for the whole population who had had previous treatment. When confidential discounts for the comparator treatments were included, the company's base-case ICER was not comfortably below £30,000 per QALY gained. This was so even with overall survival estimates adjusted as proposed by the company. The committee then considered the separate pairwise ICERs for BR and DRC. For BR, the committee was satisfied that the probabilistic ICER was comfortably below £30,000 per QALY gained, including some adjustment for comparator overall survival. But both the company's and the ERG's ICERs for zanubrutinib compared with DRC were above £30,000 per QALY gained. The committee noted that the company did not present an ICER for the population within its marketing authorisation who can have zanubrutinib first line when chemoimmunotherapy is not suitable. Also, it noted that no clinical or cost-effectiveness evidence was presented comparing zanubrutinib with the relevant comparators for this group, that is rituximab or chlorambucil monotherapy.

Innovation

Zanubrutinib is a step-change in managing Waldenstrom's macroglobulinaemia

3.14 The committee accepted that zanubrutinib has several benefits for people, including oral administration, manageable adverse reactions, low toxicity and fewer hospital visits. The committee concluded that zanubrutinib

could be considered a step-change in managing Waldenstrom's macroglobulinaemia compared with the chemoimmunotherapies BR and DRC.

Conclusions

Zanubrutinib is recommended after at least 1 treatment when BR would otherwise be used

3.15 The committee concluded that it was not possible to recommend zanubrutinib for all people who had had previous treatment. This was because the ICER for zanubrutinib compared with the blended comparator was not comfortably below £30,000 per QALY gained, even with the company's proposed adjustment. Also, the pairwise ICERs of zanubrutinib compared with DRC were consistently above £30,000 per QALY gained. The committee further concluded that it was possible to recommend zanubrutinib in people who had had previous treatment and would otherwise have BR. This was because the ICER for this group was below £30,000 per QALY gained, so was an acceptable use of NHS resources. The committee recognised that people currently taking BR as their first-line treatment option would not be in the group who would otherwise have BR as a second-line treatment. However, zanubrutinib used as an alternative to BR was the only analysis presented that provided a cost-effective ICER. The committee concluded that it was unable to recommend zanubrutinib for the population for whom chemoimmunotherapy is unsuitable. This was because it had not been provided with an estimate of clinical and cost effectiveness compared with alternative therapies for this group. So, the committee concluded that zanubrutinib could only be recommended for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 treatment, but only if they would otherwise have treatment with BR.

4 Proposed date for review of guidance

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

Dr Jane Adam
Chair, appraisal committee
June 2022

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.

Alex Sampson
Technical lead

Mary Hughes

Technical adviser

Thomas Feist

Project manager

ISBN: [to be added at publication]