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:

- bendamustine plus rituximab is also suitable and
- 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 plus rituximab, or dexamethasone plus 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.

For people who have had previous treatment, the cost-effectiveness estimates for zanubrutinib are only within what NICE usually considers an acceptable use of NHS resources when bendamustine plus rituximab is also suitable. Zanubrutinib is recommended for this group. For people who have not had previous treatment and if chemoimmunotherapy is unsuitable, the cost-effective estimates for zanubrutinib are above what NICE usually considers an acceptable use of NHS resources. Zanubrutinib is not recommended 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 plus rituximab, dexamethasone plus rituximab and cyclophosphamide, and rituximab or chlorambucil alone

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 bendamustine plus rituximab (BR) and dexamethasone plus rituximab and cyclophosphamide (DRC) if chemoimmunotherapy is suitable. The clinical experts further explained that patient- and disease-related factors can influence the choice of first-line treatment. They stated that BR tends to produce a more rapid and deeper response, so may be preferred if disease burden needs to be quickly reduced. But BR has a less favourable toxicity profile than DRC, so DRC may be preferred in people who are frail or have comorbidities. 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. But, 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 the time course of this appraisal, a separate NICE appraisal of ibrutinib for treating Waldenström’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). After these treatments, practice varies, but repeated rounds of chemotherapy are often used. When chemoimmunotherapy is unsuitable, treatment options include rituximab or chlorambucil monotherapy, or best supportive care. The company noted that rituximab and chlorambucil are not widely used, particularly chlorambucil because it may be more toxic than rituximab. But the committee noted both were used in clinical practice. The clinical experts explained that, if zanubrutinib were recommended, it would be used as early as possible in the treatment pathway. But the committee noted that, when chemoimmunotherapy is suitable, zanubrutinib’s licence limited it to use after at least 1 treatment. The committee was aware 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. It also concluded that rituximab or chlorambucil alone were relevant comparators when chemoimmunotherapy is unsuitable. This is when the marketing authorisation allows zanubrutinib as a first-line treatment 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 Waldenström’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 Waldenström’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 of this. 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, it 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 multiple previous treatments. One clinical expert stated 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. But 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. But 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 immature. This is to be 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 was 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) in people who had had previous treatment 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 DRC data came from a population having this type of chemoimmunotherapy as a first-line treatment, which does not correspond with the marketing authorisation for zanubrutinib (see section 2.1). Also, it is different from the population 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 company attempted to match the populations used in the indirect treatment comparisons and make 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. Both the STC or MAIC approach for the indirect comparison, suggested that there was improved overall and progression-free survival with zanubrutinib compared with both BR and DRC. 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 with both the MAIC and the STC. But it noted that MAIC methods are more transparent and that there was insufficient justification given by the company to switch from its original MAIC to the STC. So, the committee concluded that its preferred
approach was the original MAIC analysis. But it acknowledged that this was an area of uncertainty. The committee noted that, for the BR and DRC comparisons, the hazard ratios in the company’s indirect comparisons for progression-free survival were low compared with those typically seen with other cancer treatments. But it concluded that there was a high degree of uncertainty in the size of the treatment effect of zanubrutinib compared with both comparators. This was because of the limitations of the indirect comparisons.

It is unclear whether overall survival is better with DRC than with BR but the committee accepted the company’s estimates as the best available

3.6 The overall-survival hazard ratios for BR compared with zanubrutinib were lower than the hazard ratios for DRC compared with zanubrutinib. This was regardless of whether the STC or MAIC approach was used. The committee noted that these hazard ratios suggested DRC may be more effective 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 clinical experts explained that real-world data comparisons have consistently shown a favourable progression-free survival outcome for BR compared with DRC. But they added that the data for overall survival is less conclusive. This is because people with Waldenstrom’s macroglobulinaemia often do not die because of the condition itself. Also, DRC tends to be used in people who are frail or have comorbidities, which may affect their life expectancy. The committee was not aware of any direct comparative evidence to determine whether BR and DRC would be equally effective had they been studied at the same stage in the treatment pathway. So, the committee accepted the company’s estimates for its decision making.
Zanubrutinib is clinically effective compared with rituximab when chemoimmunotherapy is unsuitable

3.7 The clinical evidence for the chemoimmunotherapy unsuitable comparators (rituximab monotherapy and chlorambucil monotherapy) came from 2 main studies:

- The clinical evidence for rituximab came from a single-arm study of 69 people, including 34 people with Waldenstrom’s macroglobulinaemia who had not had previous treatment (unknown whether chemoimmunotherapy was considered suitable) and 35 people with relapsed or refractory Waldenstrom’s macroglobulinaemia (Gertz et al., 2004; Gertz et al., 2009).
- The clinical evidence for chlorambucil came from a randomised controlled trial of 46 people with Waldenstrom’s macroglobulinaemia who had not had previous treatment (unknown whether chemoimmunotherapy was considered suitable). The trial compared continuous chlorambucil therapy with intermittent chlorambucil therapy (Kyle et al., 2000).

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 subgroup, 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 is unsuitable would be similar to its effectiveness in people whose condition is relapsed or refractory. The company based its cost-effectiveness estimates for this population on an indirect comparison of zanubrutinib compared with rituximab, which it considered to be a more relevant comparator that chlorambucil. This was based on data from the Rory Morrison Registry showing that rituximab is more widely used than chlorambucil as a first-line treatment for Waldenstrom's
macroglobulinaemia. The company also stated that rituximab is better tolerated and more clinically effective than chlorambucil. The committee noted that trial evidence used by the company for the effectiveness of rituximab (Gertz et al., 2004; Gertz et al., 2009) comprised about 50% of people with relapsed or refractory Waldenstrom’s macroglobulinaemia and about 50% of people who had not had treatment. It also noted that it was unknown whether chemoimmunotherapy was considered suitable or not for people having rituximab as a first-line treatment. The company agreed that suitability for chemoimmunotherapy was not stated. But it added that the baseline characteristics of people in the rituximab trial were similar to the definition for people who had not had treatment in the ASPEN trial. The committee still considered that there was uncertainty about the comparability of these groups. This was because the inclusion criteria for the rituximab trial did not specify the suitability of chemoimmunotherapy, which could imply that there were different baseline characteristics. The company attempted to match the populations used in the indirect treatment comparison and make adjustments to minimise bias in the results by using a MAIC. The specific results of the analysis are confidential and cannot be shared here. But the comparison of zanubrutinib with rituximab suggested that zanubrutinib improved progression-free survival and overall survival. Also, the hazard ratios were lower than those for the comparisons of zanubrutinib with BR or DRC. This suggested more benefit with zanubrutinib compared with rituximab than in the comparisons of zanubrutinib with BR or DRC. 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 it may depend 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 the MAIC results when chemoimmunotherapy was unsuitable. But it agreed that zanubrutinib was
clinically effective compared with the company’s preferred comparator rituximab.

The company’s economic model

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

3.8 The company developed a cohort partitioned survival model to project the long-term clinical and economic consequences. This 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. But, overall, the committee concluded that it was acceptable for decision making.

The extrapolations of overall survival for zanubrutinib in the relapsed or refractory population are plausible but uncertain

3.9 The company used parametric models to extrapolate the data over a 30-year time horizon to estimate overall survival beyond the data collection periods for zanubrutinib and its comparators in the relapsed or refractory population. This population comprises people who had had at least 1 treatment. 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 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

3.10 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 it had removed these costs in its updated base case after consultation. The company stated that the populations in the BR and DRC trials did not have follow-on ibrutinib. But it added that the extrapolated modelled overall survival beyond the end of the study period may have included some benefit from follow-on ibrutinib. The company explained 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 that 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 or 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 curves for overall survival in the BR and DRC arms should be adjusted downwards, while keeping the zanubrutinib curves the same. This was so that the probability of survival was 50% lower than the survival in the zanubrutinib arm at 6 years. The company also included this adjustment in its base case for the population for whom chemoimmunotherapy is unsuitable. This used the BR or DRC curves for overall survival as surrogate estimates for rituximab monotherapy. The clinical experts considered that some
adjustment may be warranted. They noted that zanubrutinib delivers benefit both 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 added that any adjustment would mean, in effect, that the overall-survival hazard ratio from the company’s MAIC was not directly used in the analysis. 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 might have been justified to account for the potential effect of follow-on treatments not available in the NHS. But it concluded that the ERG’s base case was more reflective of the relative difference in overall survival of zanubrutinib compared with BR and DRC. This was because it was based on estimates from the MAIC, while the company’s downward adjustment of the effectiveness of BR and DRC was based on clinical opinion. The committee concluded that this meant the company’s approach was highly uncertain.
Using the DRC data to estimate long-term survival with rituximab when chemoimmunotherapy is unsuitable is highly uncertain but appropriate

3.11 For the population for whom chemoimmunotherapy is unsuitable, the company modelled the cost effectiveness of zanubrutinib compared with rituximab. To represent progression-free survival and overall survival in the rituximab population, it used the modelled progression-free survival and overall survival for BR or DRC from its model for the relapsed or refractory population. The hazard ratios derived from the company’s MAIC analysis comparing zanubrutinib with rituximab were then applied to the BR and DRC curves to generate curves for progression-free and overall survival for zanubrutinib. To reflect the cost of rituximab monotherapy, the company removed the treatment acquisition and administration costs of bendamustine from the BR-modelled costs, and of dexamethasone and cyclophosphamide from the DRC-modelled costs. This left only the costs of rituximab monotherapy in the analysis. The company explained that it used BR- and DRC-modelled estimates as a surrogate for rituximab. This was because of a lack of data for rituximab monotherapy to include in its economic model. The clinical experts stated that rituximab is less clinically effective than BR or DRC. The company agreed, stating that it considered its modelling approach to be conservative. The committee recalled that the data for BR had been from people whose condition was relapsed or refractory and for DRC had been from people who had not had previous chemoimmunotherapy (see section 3.7). This meant that the analysis in which DRC data was used as a baseline control arm was potentially more applicable to how rituximab monotherapy would be used in clinical practice (that is in people who had not had previous chemoimmunotherapy). The committee concluded that it preferred using DRC rather than BR as a surrogate for rituximab. It also noted that the company had already reduced the estimated survival for DRC in its model (on the basis of no follow-on ibrutinib being available, see section 3.10). It did not consider any further reduction was justified on the basis that the modelling approach was considered conservative. The committee also concluded that, although highly uncertain, the company’s approach was
broadly appropriate for decision making for the population for whom chemoimmunotherapy is unsuitable.

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

3.12 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. But 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 postprogression 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

3.13 The company’s base case assumed life-long treatment effectiveness. But 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 NHS England’s Cancer Drugs Fund clinical lead 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 blended comparator are more uncertain than for the separate comparisons**

3.14 The company provided cost-effectiveness results for the comparison of zanubrutinib with BR and with DRC separately, and for the blended comparator. The blended comparator was produced using a weighted average of the results of the BR and DRC comparisons. The weighted average was calculated 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). It also meant that it 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 the more uncertain. The committee concluded that it would take into account the cost-effectiveness results for both the blended and the pairwise comparisons. But it also took into account the greater uncertainty around the estimates compared with DRC, and from the blended comparator.

Cost-effectiveness results

The ICER is under £30,000 per QALY gained only if zanubrutinib is used after at least 1 treatment and when compared with BR

3.15 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 3.10)
- not to apply any treatment effect cut-off (see section 3.13).

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 that it may
have been reasonable to apply some adjustment to overall survival in the comparator arm, but not the full adjustment proposed by the company. For the population for whom chemoimmunotherapy is unsuitable, the committee considered that the comparison in which DRC data was used as a baseline control arm was the most appropriate (see section 3.11). Again, it thought that some adjustment of overall survival may have been reasonable. The only ICER that was under £30,000 per quality-adjusted life year (QALY) gained was from the comparison of zanubrutinib with BR in people for whom chemoimmunotherapy was suitable after 1 or more treatments.

**Because of the uncertainty an acceptable ICER is comfortably within the acceptable range of £20,000 to £30,000 per QALY gained**

NICE’s guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered that an acceptable ICER for zanubrutinib would need to be comfortably below £30,000 per 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 it was an effective treatment
- the uncertainty around the indirect comparisons and long-term survival.

The committee noted the uncertainty about the level of adjustment to the overall-survival estimates for BR and DRC. It also noted that the company’s probabilistic ICER from the comparison of zanubrutinib with DRC in people for whom chemoimmunotherapy was suitable after 1 or more treatments was not under £30,000 per QALY gained. This was even when the company’s full suggested reduction in DRC efficacy was included, which the committee considered to lack evidence. Similarly, it
was over £30,000 per QALY gained in comparison with rituximab in people for whom chemoimmunotherapy is unsuitable. This was using the DRC curve as a baseline control arm, also with the full downward adjustment of that curve proposed by the company. The estimates from the ERG without any curve adjustment were substantially higher. The committee concluded that an acceptable ICER would need to be comfortably within the range of £20,000 to £30,000 per QALY gained. It concluded that the ICER for zanubrutinib was only likely to be comfortably within the £20,000 to £30,000 range compared with BR when chemoimmunotherapy was suitable after 1 or more treatments. But this was only if at least some downward adjustment was assumed to be reasonable.

Innovation

**Zanubrutinib is a step-change in managing Waldenstrom’s macroglobulinaemia**

3.17 The committee accepted that zanubrutinib has several benefits over chemoimmunotherapy 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 treatment options available in UK clinical practice.

Conclusions

**Zanubrutinib is recommended after at least 1 treatment when BR is also suitable**

3.18 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 below £30,000 per QALY gained. Also, the pairwise ICERs of zanubrutinib compared with DRC were consistently above £30,000 per QALY gained. The committee also concluded that it was only
possible to recommend zanubrutinib in people who had had previous treatment and when BR is also suitable. 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 also concluded that it was not possible to recommend zanubrutinib for the population for whom chemoimmunotherapy is unsuitable. This was because the ICER for zanubrutinib compared with rituximab was not below £30,000 per QALY gained.

The recommendations may affect the treatment pathway for Waldenstrom’s macroglobulinaemia

3.19 The committee recognised that its recommendation could affect the treatment pathway for Waldenstrom’s macroglobulinaemia. This was because whether BR would be considered a second-line or later treatment would be related to the treatments people had already had. The committee considered opinion from the clinical and patient experts that:

- although DRC is generally better tolerated, there are certain clinical indications for choosing BR first
- only some people who have BR first line would be able to have retreatment with BR
- people for whom chemoimmunotherapy is not suitable have a particular unmet need for more treatment options.

The committee was aware that the recommendation would exclude some people for whom the whole marketing authorisation for zanubrutinib applied. It recognised that they would be disappointed by the recommendation. But, based on the evidence available, zanubrutinib is not cost effective as a first-line treatment when chemotherapy is unsuitable, or for people who would have DRC after at least 1 treatment. For second-line use when chemoimmunotherapy is unsuitable, the company did not provide any information on the relevant comparators, or clinical or cost effectiveness. So, the committee was unable to make any recommendation for that population. The committee concluded that the
treatment pathway may change for the treatment of Waldenstrom’s macroglobulinaemia for people who are able to tolerate chemoimmunotherapy. It may mean that people would be more likely to have the generally better-tolerated DRC as their first-line treatment to preserve the option of zanubrutinib second line. But for some people, the benefits of first-line BR would outweigh the risk of being ineligible for zanubrutinib later. Unfortunately, the pathway when chemoimmunotherapy is unsuitable would be unchanged. Despite these disadvantages, the committee considered that it was not possible to make a different recommendation. It concluded that zanubrutinib could only be recommended for treating Waldenstrom’s macroglobulinaemia in adults who have had at least 1 treatment, but only when BR is also suitable.

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 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.

4.2 **Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry** states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since
2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have 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 2 months of the first publication of the final appraisal document.

4.4 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 Waldenstrom’s macroglobulinaemia and the doctor responsible for their care thinks that zanubrutinib is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Appraisal committee members and NICE project team

Chair
Dr Jane Adam
Chair, appraisal committee
August 2022

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 and Dilan Savani**
Technical leads

**Mary Hughes**
Technical adviser

**Thomas Feist**
Project manager

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