NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Zanubrutinib for treating chronic lymphocytic leukaemia

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 evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all relevant evidence been considered?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2023

Note that this document is not NICE's final guidance on zanubrutinib. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using zanubrutinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 August 2023
- Second evaluation committee meeting: 12 September 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Zanubrutinib is not recommended, within its marketing authorisation, for treating chronic lymphocytic leukaemia (CLL) in adults.

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

The treatment options are different for untreated CLL (with or without a 17p deletion or tumour protein 53 [TP53] mutation), and for relapsed or refractory CLL. There are no clinical trials comparing zanubrutinib with several relevant comparator treatments. Also, the results of trials that are available with some of the currently used treatments are uncertain.

The main conclusions are that:

- The company's submission did not include evidence for people with untreated CLL for whom fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR) is suitable. Because FCR or BR suitability criteria are not used in clinical practice, this could potentially create an equality issue by denying younger and fitter people access to a new treatment option.

- The SEQUOIA trial is applicable to people regardless of suitability for FCR or BR, so providing analysis for everyone with untreated CLL would address the equality issue.

- In untreated CLL, venetoclax-based regimens are used so should be included.

- In relapsed or refractory CLL, venetoclax plus rituximab is used so should be included.

Because of the uncertainty in the clinical- and cost-effectiveness evidence for zanubrutinib in all CLL populations, the cost-effectiveness estimates for zanubrutinib are highly uncertain. So, it is not recommended.

2 Information about zanubrutinib

Marketing authorisation indication

2.1 Zanubrutinib (Brukinsa, BeiGene) is indicated for 'the treatment of adult patients with chronic lymphocytic leukaemia'.

Dosage in the marketing authorisation

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

Price

2.3 A 120-pack of 80-mg zanubrutinib capsules costs £4,928.65 (excluding VAT; BNF online accessed July 2023). The company has a commercial arrangement (simple discount patient access scheme). This makes zanubrutinib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 evaluation committee considered evidence submitted by BeiGene, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells and is the most common type of leukaemia in England. The patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The committee noted the increased prevalence of CLL with age and the additional effect of the condition on family and carers. It concluded that CLL substantially affects quality of life both physically and psychologically.

Clinical management

3.2 The treatment options are different for untreated CLL and relapsed or refractory CLL. The clinical and patient experts said that the population of people with untreated CLL is heterogeneous. They have different mutation statuses and comorbidities, and this affects their treatment options. People with untreated CLL with a 17p deletion or tumour protein 53 (TP53) mutation (high-risk) usually have acalabrutinib, ibrutinib, venetoclax, idelalisib plus rituximab or venetoclax plus obinutuzumab. People with untreated CLL without a 17p deletion or TP53 mutation (non-high-risk) usually have fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR), bendamustine plus rituximab or venetoclax plus obinutuzumab. For people for whom FCR or BR is unsuitable, acalabrutinib, obinutuzumab plus chlorambucil or venetoclax plus obinutuzumab are offered instead. Since April 2023, NICE's technology appraisal guidance on ibrutinib with venetoclax also recommends it for use in all untreated CLL populations. People with relapsed or refractory CLL usually have acalabrutinib, ibrutinib, venetoclax, idelalisib plus rituximab or venetoclax plus rituximab. The clinical experts explained that idelalisib plus rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with an increased infection risk. They also highlighted that current treatments for CLL, such as intensive chemotherapies including FCR and BR, have short and long term side effects. The patient expert highlighted that there are limited options for people with relapsed or

refractory CLL. They explained that the uncertainty of whether another treatment will be available if the current treatment is not well tolerated because of side effects, can cause a lot of anxiety. Patient and clinical experts agreed that there is an unmet need for effective targeted treatment options for people with CLL that are well tolerated and with fewer side effects. The committee concluded that zanubrutinib would be welcomed as a new treatment option.

Clinical effectiveness

Data sources

3.3 The company presented clinical effectiveness evidence for zanubrutinib in people with untreated CLL from SEQUOIA, an open-label, phase 3, randomised controlled trial, which included people 18 years and over with untreated CLL for whom FCR is unsuitable. Cohort 1 of SEQUOIA compared zanubrutinib monotherapy (n=241) with BR (n=238) in people without a 17p deletion. Cohort 2 of SEQUOIA is a single arm efficacy and safety assessment of zanubrutinib (n=111) in people with a 17p deletion. Cohort 1a (China only) and cohort 3 (single arm venetoclax plus zanubrutinib) were not considered appropriate for this appraisal. For the population with previously treated relapsed or refractory CLL, the company presented clinical effectiveness evidence from ALPINE. This was an open-label, phase 3, randomised controlled trial comparing zanubrutinib (n=327) with ibrutinib (n=325). ALPINE included people 18 years and over with CLL that had relapsed or was refractory to at least 1 prior systemic therapy.

Clinical study results

3.4 In SEQUOIA cohort 1, the median follow-up in the zanubrutinib arm was 26.35 months and in the BR arm it was 25.92 months. The median follow-up in cohort 2 was 30.52 months. For cohort 1, zanubrutinib was superior to BR for progression-free survival and response rate. But there was no significant difference in overall survival (OS), as the 95% confidence intervals crossed the line of no effect. In ALPINE, the median follow-up in

the zanubrutinib arm was 24.34 months and in the ibrutinib arm it was 23.82 months. There was statistically significant improvement in overall response for zanubrutinib compared with ibrutinib. Zanubrutinib also demonstrated a statistically significant difference in progression-free survival and time to treatment failure. But there was no significant difference in OS, as the 95% confidence interval crossed the line of no effect. The company submission highlighted the lower hazard ratio with narrower confidence intervals from a later data cut (8 August 2022). This highlighted that the difference in the number of deaths between zanubrutinib and ibrutinib further increased, suggesting that a statistically significantly improvement in OS may be demonstrated with more mature data. The company also highlighted that a data cut from 2023 was available for SEQUOIA. The committee noted that the results of both SEQUOIA and ALPINE are immature. It concluded that results for key clinical outcomes from the latest data cut for both SEQUOIA and ALPINE may better inform the long-term effectiveness of zanubrutinib for all CLL populations.

Untreated CLL population for whom FCR or BR is suitable

3.5 The company's submission did not present cost-effectiveness analysis for people with untreated CLL for whom FCR or BR is suitable. This population was in the NICE scope and is included in the marketing authorisation for zanubrutinib. The company highlighted that there was a lack of clinical trial evidence available for zanubrutinib in this population. Instead, it used evidence from SEQUOIA cohort 1 to inform the clinical efficacy of zanubrutinib in people with untreated CLL for whom FCR or BR is unsuitable. In SEQUOIA, the company categorised cohort 1 as people for whom FCR or BR were unsuitable. The EAG questioned the company’s categorisation because people could have been randomised to BR in the trial so people had to be able to have it. It considered the participants to be suitable, in line with the British Society for Haematology guidelines. The EAG had concerns about the data from SEQUOIA cohort 1 being used as proxy for the group for whom FCR or BR is unsuitable but

not for the group for whom FCR or BR is suitable. The clinical experts suggested that cost-effectiveness evidence comparing zanubrutinib with treatments for the group for whom FCR or BR is suitable should have been presented in the company's submission. They explained that the distinction of suitability for FCR or BR is no longer used in clinical practice and only applies in clinical trials. The experts agreed that evidence from SEQUOIA would extend to all people with untreated CLL regardless of FCR or BR suitability. Because SEQUOIA included people with untreated CLL for whom BR is suitable, the committee noted that it likely provides evidence for the group for whom FCR or BR is suitable. The committee acknowledged that the company was not seeking a recommendation for zanubrutinib in this group, and that no comparative evidence was presented for this group. However, it recognised there were equality issues associated with excluding the group for whom FCR or BR is suitable. This is because younger and fitter people with untreated CLL for whom FCR or BR is suitable, will not be able to access treatment with zanubrutinib if it is recommended only for people for whom these treatments are unsuitable. The committee concluded that people with untreated CLL for whom FCR and BR is suitable, is an important subgroup and evidence from SEQUOIA could be used for this population.

Untreated CLL population for whom FCR or BR is unsuitable

3.6 The company compared zanubrutinib with acalabrutinib and ibrutinib in the untreated CLL population that are ‘high-risk’ and for whom FCR or BR is unsuitable. It also compared zanubrutinib with acalabrutinib in the untreated CLL population that are non ‘high-risk’ and for whom FCR or BR is unsuitable. However, the company did not present evidence comparing zanubrutinib with ibrutinib plus venetoclax or venetoclax plus obinutuzumab for people with untreated CLL for whom FCR or BR is unsuitable and may be ‘high-risk’. It considered that ibrutinib plus venetoclax was not routinely commissioned by NHS England and did not reflect established NHS clinical practice. The company also considered that venetoclax plus obinutuzumab is not commonly used, typically only

being used for fitter people for whom FCR or BR is suitable and where it is only commissioned for use in the Cancer Drugs Fund. The EAG disagreed with the exclusion of venetoclax plus obinutuzumab as a relevant comparator because it was recommended in NICE's technology appraisal guidance on venetoclax with obinutuzumab. This was supported by clinical advice to the EAG that venetoclax plus obinutuzumab is an option for people with untreated CLL and disagreed that the use of venetoclax plus obinutuzumab was low in the UK. The clinical experts highlighted that the untreated CLL treatment pathway has become more complex with the introduction of venetoclax-based combination treatments. They explained that ibrutinib plus venetoclax, although recently recommended, is an effective treatment across all untreated CLL populations. Venetoclax plus obinutuzumab is also recommended as an initial therapy for the untreated CLL population for whom FCR or BR is unsuitable, irrespective of TP53 mutation status. The NHS England representative said that venetoclax plus obinutuzumab is a first line treatment option used for the untreated CLL population. They also noted that even though ibrutinib plus venetoclax was only recently recommended in NICE's technology appraisal guidance on ibrutinib with venetoclax, it is fast becoming a standard care option for people with untreated CLL. The committee acknowledged that venetoclax plus obinutuzumab and ibrutinib plus venetoclax are important treatment options for untreated CLL, regardless of TP53 mutation status and FCR and BR suitability. The committee concluded that venetoclax plus obinutuzumab and ibrutinib plus venetoclax are relevant comparators to zanubrutinib for untreated CLL. So, they requested additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus obinutuzumab and ibrutinib plus venetoclax for the untreated CLL population.

Relapsed or refractory CLL population

3.7 The company did not present evidence comparing zanubrutinib with venetoclax plus rituximab for the previously treated relapsed or refractory

CLL population. It considered that venetoclax plus rituximab is primarily used for CLL previously treated with a bruton tyronsine kinase inhibitor (BTKi) such as ibrutinib and acalabrutinib. It also considered that people can only have zanubrutinib if they have not previously had a BTKi. So, zanubrutinib provides a treatment alternative to ibrutinib and acalabrutinib, which were the only comparators included in its cost minimisation analysis for this population. The NHS England representative stated that since the end of 2021, people who had fixed duration venetoclax-based regimens, including venetoclax plus obinutuzumab and ibrutinib plus venetoclax, are able to have venetoclax plus rituximab for relapsed CLL, if their disease is not refractory to venetoclax. The committee concluded that venetoclax plus rituximab is a relevant comparator for people with previously treated relapsed or refractory CLL. So, they requested additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus rituximab in the relapsed or refractory CLL population.

Indirect treatment comparisons

3.8 In the absence of direct trial evidence, the company did matching adjusted indirect comparisons (MAICs) for zanubrutinib compared with acalabrutinib.

- Untreated CLL population for whom FCR or BR is unsuitable: An unanchored MAIC was done using evidence from the SEQUOIA and ELEVATE-TN, an open-label, phase 3, randomised controlled trial. Two matching models were considered, and analyses were conducted for progression-free survival and OS. Weighted Cox proportional hazard regression models were fitted to derive estimates of comparative effectiveness. The company concluded that the MAIC results demonstrate that zanubrutinib is at least non-inferior to acalabrutinib in the untreated CLL population for whom FCR or BR is unsuitable, including ‘high-risk’ disease. The company considered the MAIC results are confidential and cannot be reported here.

- Relapsed or refractory CLL: An anchored MAIC was done using evidence from ALPINE and ELEVATE-RR, an open-label, phase 3, randomised controlled trial, which had ibrutinib as a common comparator. Additionally, an unanchored MAIC was conducted using evidence from ALPINE and ASCEND, an open-label, phase 3, randomised controlled trial. The company concluded that, for both the anchored and unanchored MAICs, the results demonstrate that zanubrutinib is at least non-inferior to acalabrutinib in relapsed or refractory CLL. The company considered the MAIC results are confidential and cannot be reported here.

The EAG considered the methodological conduct and outcomes reported in all the MAICs to be appropriate and acknowledged that uncertainty with unanchored analyses is unavoidable. However, the EAG noted that the company's interpretation of the MAIC results confuses a lack of statistically significant difference with non-inferiority. This is because the 95% confidence interval for both progression-free survival and OS are wide, and include clinically meaningful differences in survival. The EAG considered that the results of the MAIC are insufficient to conclude non-inferiority of zanubrutinib compared with acalabrutinib. The committee questioned the results of the MAIC analyses, including whether the confidence intervals from the MAIC results were adequately modelled. The company highlighted that the confidence intervals for these results had been incorporated in the probabilistic sensitivity analysis which did not alter the cost-effectiveness conclusion. However, in the presence of the wide confidence intervals, the committee was uncertain that the MAIC results were adequately captured in the economic analysis. It considered that because a cost minimisation analysis approach in the economic models is adopted by assuming equal efficacy based on the MAIC results, such analysis cannot fully capture the uncertainty associated with the wide 95% confidence intervals. The committee concluded that the results from the MAIC analysis used to inform the clinical effectiveness of

zanubrutinib compared with acalabrutinib in both the untreated CLL and relapsed or refractory CLL populations are uncertain.

Uncertainty in the untreated 'high-risk' CLL population

3.9 For the comparison of zanubrutinib with acalabrutinib in the untreated 'high-risk' CLL population, data for zanubrutinib cohort 1 and cohort 2 of SEQUOIA were pooled. This created a cohort that included people with and without a 17p deletion to match the eligibility criteria for ELEVATE-TN. ELEVATE-TN also provided data for acalabrutinib for a population combining both 'high-risk' and non 'high-risk' groups. Data for people with untreated 'high-risk' CLL, comparing zanubrutinib with ibrutinib were based on ALPINE. The EAG highlighted that ALPINE enrolled a relapsed or refractory CLL population with only 23% of participants considered 'high-risk'. At technical engagement, the company highlighted that in several previous technology appraisals there was a lack of data for people with 'high-risk' CLL. It said that in NICE's technology appraisal guidance on acalabrutinib and NICE's technology appraisal guidance on ibrutinib, data from relapsed or refractory CLL was accepted as proxy for the untreated 'high-risk' CLL population. Clinical expert and professional organisation comments at technical engagement explained that people with TP53 disruption in the relapsed or refractory setting do not have the same genetic profile as people with TP53 disruption in the untreated setting. But they considered that it will take a long time for real world data and long term follow up data to be available to inform relevant comparisons. The committee concluded that the use of ALPINE data in relapsed or refractory CLL as a proxy for the 'high-risk' untreated CLL population is not optimal, but the lack of data is inherent to this population so it is acceptable to use.

Adverse events

3.10 For the untreated CLL population, across cohorts 1 and 2 of SEQUOIA, the incidence of adverse events was generally comparable between the zanubrutinib and BR arms. But fewer people in the zanubrutinib arms

experienced grade 3 or higher treatment emergent adverse events or serious adverse events. Low atrial fibrillation rates were reported for zanubrutinib, occurring in 8 (3.3%) people in cohort 1 and 5 (4.5%) people in cohort 2, similar to those reported in the BR arm (2.6%). No sudden deaths were reported in either study arm. For the relapsed or refractory CLL population, evidence from ALPINE showed that the incidence of adverse events was generally comparable between the zanubrutinib and ibrutinib arms, though fewer people in the zanubrutinib arms experienced serious adverse events. The rate of atrial fibrillation was significantly lower in the zanubrutinib arm compared with ibrutinib. There were no deaths because of cardiac disorders with zanubrutinib whereas ibrutinib was associated with deaths related to adverse cardiovascular events. The clinical experts agreed that the available evidence for zanubrutinib suggests a toxicity profile better than ibrutinib, and similar or better than acalabrutinib. The committee concluded that zanubrutinib is a tolerable and safe treatment for previously untreated CLL and relapsed or refractory CLL.

Economic model

Modelling approach

3.11 For the untreated CLL population, the company presented a semi-Markov model with a lifetime horizon of 30 years. The company used a cost minimisation analysis, justified by the unanchored MAIC analysis. This compared data from SEQUOIA and ELEVATE-TN for the comparison with acalabrutinib and ALPINE results as a proxy for untreated 'high-risk' CLL for comparison with ibrutinib. For the relapsed or refractory CLL population, the company presented a partitioned survival model with a lifetime horizon of 30 years. A cost minimisation analysis was also used, justified by MAIC analyses. This compared data from ALPINE with either ELEVATE-RR or ASCEND for the comparisons with acalabrutinib and ALPINE results for comparison with ibrutinib. In both models, people received venetoclax plus rituximab in the progressed disease health state, which was associated with a one-time monitoring cost of laboratory

tumour lysis syndrome prophylaxis. Both models accounted for the cost of grade 3 or higher adverse events. Quality-adjusted life years (QALYs) were affected by assuming equivalent effectiveness across all treatment arms in both models. The EAG considered that the cost minimisation analysis was not the most appropriate method to represent the decision problem because the MAICs did not provide sufficient evidence of non-inferiority. It acknowledged that the company provided several scenario analyses using a cost-utility approach, but highlighted that the company's models were built for cost minimisation analysis. So, strong assumptions were made by the company in its cost-utility analysis scenarios. Instead, the EAG modified the company's model for cost-utility analysis, acknowledging the need for strong assumptions and introduced uncertainty, to present an alternative application of the cost-utility analysis and improve the accuracy of the results. The committee considered that the company's use of a cost minimisation analysis to be flawed. It further considered the cost-utility approach to be more appropriate, particularly when incorporating the uncertainty in the hazard ratios from MAIC analyses. However, the committee was aware that both the company's models for the cost-utility scenario analysis and the EAGs modified cost-utility models had serious weaknesses. The committee considered that company's models, as set up for cost minimisation analysis, were not appropriate for decision making, but uncertainties remain in the cost utility analyses presented by the company and the EAG. The committee concluded that economic models, for both untreated CLL and relapsed or refractory CLL, built for a cost-utility analysis are more appropriate for decision making.

Survival extrapolations

3.12 To model the long term survival in the untreated CLL model, the company used time to progression and pre-progression survival data from SEQUOIA extrapolated over 30 years by fitting 6 parametric distributions. Progression-free survival curves were derived using time to progression and pre-progression survival data. The generalised gamma distribution

was chosen as the company's base-case distribution for both time to progression and pre-progression survival. OS was modelled from the overall survival curves of MURANO, an open-label, phase 3, randomised controlled trial comparing the efficacy and safety of venetoclax plus rituximab compared with bendamustine plus rituximab in people with relapsed or refractory CLL. The exponential distribution was selected in the company's base case model. To model the long term survival in the relapsed or refractory CLL model, progression-free survival and OS for zanubrutinib was extrapolated by applying parametric models to ALPINE data. The Weibull distribution was selected by the company to extrapolate both progression-free survival and OS for zanubrutinib in the base case model. The EAG highlighted that follow up data from SEQUOIA and ALPINE used in the economic models are of relatively short duration, with immature data with low event numbers for key survival outcomes. It considered that in the absence of real world evidence, the selection of survival models is heavily reliant on clinical expert opinion. The company acknowledged the immature trial data but suggested that the economic models made the best use of the data available. It highlighted that the level of data immaturity reported in the zanubrutinib clinical trials is aligned with that in previous appraisals. The clinical experts agreed that SEQUOIA and ALPINE data are immature, but acknowledged that this is inherent to trials for CLL. They highlighted that substantial real world evidence would take a long time to become available and that, at the time of the appraisal, this is the best evidence available. The committee acknowledged that data immaturity is not exclusive to this CLL appraisal alone. However, it was aware that a more recent data cut from the SEQUOIA trial is available. The committee concluded that long term survival extrapolations using the most recent data is more appropriate.

Source of utility values

3.13 In both the untreated CLL and relapsed or refractory CLL economic models, the company considered that utility values collected from SEQUOIA and ALPINE, respectively, lacked face validity. This is because

they were too high when compared with utility values from the age-sex matched general population. Instead, it used UK general population age-sex matched utility values for the progression-free health state and utility values from Holzner et al. (2004) for the progressed disease health state. The EAG highlighted that the cost-effectiveness results from both the untreated CLL and relapsed or refractory CLL models were sensitive to changes in utility values when a cost utility analysis approach was chosen in the company's scenario analysis. It considered that the utility values used in the company's economic models were uncertain. The EAG explored this uncertainty by using trial-based utility values and alternative disutility values for progressed disease. The committee noted that, in both the untreated CLL and relapsed or refractory CLL models, the use of zanubrutinib resulted in fewer QALYs compared with acalabrutinib. But because of the cost-savings associated with zanubrutinib, changes to utility values had a small impact on overall cost-effectiveness conclusions. The committee concluded that the utility values used in the company's economic models are uncertain and alternative utility values should be explored using a cost utility analysis approach.

Incorporating adverse events in the economic analysis

3.14 For both the untreated CLL and relapsed or refractory CLL base case models, the company included the impact of adverse events on costs only, applied to the proportion experiencing the event. The impact of adverse events on health related quality of life was considered in a scenario cost utility analysis, with utility decrements applied to the proportion experiencing the event. It was assumed that all adverse events occur and are resolved in the first 4 weeks of treatment and their impact was only applied in the first cycle of the model. Adverse events associated with primary treatment were considered and not adverse events for subsequent lines of treatment. The adverse event profile of zanubrutinib and ibrutinib were taken from ALPINE and the adverse event profiles of acalabrutinib was taken from ASCEND. The EAG considered the assumption that all adverse events occur and are resolved in the first 4

weeks of treatment to be unrealistic. It highlighted that some of the adverse events, such as cataracts or hypertension, would take longer than 4 weeks to resolve. It also considered a cost-utility analysis captures the impact of adverse events on both the costs and health related quality of life. The clinical experts considered that the modelling of long term impact of adverse events is difficult. However, the committee was uncertain of the impact of adverse events on the costs and health benefits for the duration of 30 years' time horizon of the model. The committee concluded that cost utility analysis including the impact of adverse events on both costs and health related quality of life for the full 30 years duration of the model time horizon would be more appropriate for decision making.

Cost-effectiveness estimates

Untreated CLL population that is 'high-risk' or for whom FCR or BR is unsuitable

3.15 The cost-effectiveness estimates used by the committee for decision-making took into account all of the available confidential discounts, including those for comparators and follow up treatments. The company's probabilistic base-case cost minimisation analysis results for zanubrutinib compared with ibrutinib and acalabrutinib for the untreated CLL population that is 'high-risk' or for whom FCR or BR is unsuitable, demonstrated that zanubrutinib was less expensive than the comparators when assuming equal health benefits for all treatments. Incorporating the EAG's preferred assumptions for a cost utility analysis demonstrated that zanubrutinib was dominant (had lower incremental costs and more incremental QALYs) compared with ibrutinib and acalabrutinib. However, the committee recalled its conclusions:

- Venetoclax plus obinutuzumab and ibrutinib plus venetoclax are relevant comparators for the untreated CLL population (section 3.7).
- Economic model built for a cost utility analysis is more appropriate for decision making (section 3.12).

- The use of long term survival extrapolations based on the most recent data is more appropriate (section 3.13).
- Alternative utility values should be explored (section 3.14).
- The impact of adverse events on costs and QALYs for the full model time horizon is more appropriate (section 3.15).

The committee considered that, in the presence of uncertainty because of missing relevant comparators and existing economic models, any cost-effectiveness estimates for zanubrutinib are highly uncertain. So, the committee concluded that zanubrutinib is not recommended for untreated CLL.

Relapsed or refractory CLL

3.16 The cost-effectiveness estimates used by the committee for decision-making took into account all of the available confidential discounts, including those for comparators and follow up treatments. The company's probabilistic base-case cost minimisation analysis results for zanubrutinib compared with ibrutinib and acalabrutinib for relapsed or refractory CLL demonstrate that zanubrutinib was less expensive than the comparators when assuming equal health benefits for all treatments. Incorporating the EAG's preferred assumptions for a cost utility analysis demonstrated that zanubrutinib was dominant (had lower incremental costs and more incremental QALYs) compared with ibrutinib. For the comparison with acalabrutinib, the exact incremental cost-effectiveness ratios (ICERs) for zanubrutinib are confidential and cannot be reported here. The committee recalled its conclusions:

- Venetoclax plus rituximab is a relevant comparator in the relapsed or refractory CLL population (section 3.8).
- Economic model built for a cost utility analysis is more appropriate for decision making (section 3.12).

- The use of long term survival extrapolations based on the most recent data is more appropriate (section 3.13).
- Alternative utility values should be explored (section 3.14).
- The impact of adverse events on costs and QALYs for the full model time horizon is more appropriate (section 3.15).

The committee considered that, in the presence of uncertainty because of missing relevant comparisons and existing economic models, any cost-effectiveness estimates for zanubrutinib are highly uncertain. So, the committee concluded that zanubrutinib is not recommended for relapsed or refractory CLL.

Other factors

Equality issues

3.17 The company's submission did not include evidence for people with untreated CLL for whom FCR or BR is suitable. Patient and clinical experts highlighted that this would potentially deny younger and fitter people access to a new, well tolerated treatment option. The committee considered that people with untreated CLL for whom FCR or BR is suitable to be an important subgroup. However, the committee could not make a recommendation about the clinical and cost-effectiveness of zanubrutinib for this population because the company did not present any evidence. It considered this to be an equality issue that could not be resolved in the absence of evidence for this population.

Severity

3.18 NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.19 The committee considered whether zanubrutinib was innovative. The company submission highlighted that zanubrutinib is likely to reduce the

risk of adverse events compared with ibrutinib and acalabrutinib, particularly for cardiac events and tolerability issues. However, as the company's base-case analysis was a cost minimisation analysis, these potential benefits were not captured. The committee considered that these additional benefits are likely to be captured using a cost utility analysis, which is considered a more appropriate model. The committee concluded that all additional benefits of zanubrutinib would be considered if the company presents a cost-utility analysis.

Conclusion

Recommendation

3.20 The committee's main conclusions were that:

- the company's positioning of zanubrutinib only in the population for whom FCR or BR is unsuitable creates an important equality issue for younger, fitter patients for whom FCR or BR is suitable, especially since the FCR or BR suitability criteria is not used in clinical practice,
- the SEQUOIA trial is applicable to people regardless of suitability for FCR or BR, so providing analysis for everyone with untreated CLL would address the equality issue,
- venetoclax-based regimens are used for untreated CLL, so should be included in this analysis, and
- venetoclax plus rituximab is also used in relapsed or refractory CLL, so should be included in this analysis.

The current cost-effectiveness estimates compared with ibrutinib and acalabrutinib in both untreated CLL and relapsed or refractory CLL populations were also highly uncertain because of uncertainties in the current economic models. So, zanubrutinib is not recommended for treating CLL in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in zanubrutinib being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Zain Hussain
Technical lead

Sally Doss
Technical adviser

Louise Jafferally
Project manager

ISBN: [to be added at publication]