NICE National Institute for Health and Care Excellence

NICE guidance

# Zanubrutinib for treating chronic lymphocytic leukaemia

Technology appraisal guidance
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# Your responsibility

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

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

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

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

# Contents

# 1 Recommendations

1.1 Zanubrutinib is recommended as an option for treating chronic lymphocytic leukaemia (CLL) in adults. It is only recommended if the CLL is:

- untreated and
  - there is a 17p deletion or tumour protein 53 (TP53) mutation or
  - there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR) is unsuitable, or
- relapsed or refractory.

Zanubrutinib is recommended only if the company provides it according to the commercial arrangement.

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**

Usual treatments are different for untreated CLL and for relapsed or refractory CLL. For untreated CLL with a 17p deletion or TP53 mutation (high-risk CLL) treatments include acalabrutinib, ibrutinib and venetoclax-based treatments. For untreated CLL without a 17p deletion or TP53 mutation (non-high-risk CLL) when FCR or BR is unsuitable treatments include acalabrutinib and venetoclax-based treatments. For relapsed or refractory CLL usual treatments include acalabrutinib, ibrutinib and venetoclax plus rituximab.

Clinical trial evidence suggests that zanubrutinib extends the length of time people have before their condition gets worse compared with BR and ibrutinib in untreated CLL and relapsed or refractory CLL respectively. But there are no clinical trials comparing it with other CLL treatments and the results of indirect comparisons are uncertain.

For untreated CLL, despite the uncertainty, zanubrutinib is only cost effective or cost saving compared with usual treatments in high-risk CLL, or for non-high-risk CLL when FCR or BR is unsuitable. So, it is only recommended in these populations.

For people with relapsed or refractory CLL, despite the uncertainty, zanubrutinib is cost effective or cost saving compared with the usual treatments. So, it is recommended in this population.

# 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 September 2023). The company has a commercial arrangement. 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 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) 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 can 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 aged 18 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 1 a (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 aged 18 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 (May 2021 data cut). 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, because the 95% confidence intervals crossed the line of no effect (March 2022 data cut). In ALPINE, the median follow-up in the zanubrutinib arm was 24.34 months and in the ibrutinib arm it was 23.82 months (December 2021 data cut). 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 overall survival, because 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). The committee considered that the results of both SEQUOIA and ALPINE are immature. In response to consultation, the company submitted an updated data cut from SEQUOIA (October 2022). The results confirmed that zanubrutinib remained superior to BR for progression-free survival. But there was no significant difference in overall survival. The company also submitted updated data from ALPINE (May 2023 data cut) to confirm the survival extrapolations from ALPINE data (December 2021) previously included in the economic models. The committee concluded that although the results for key clinical outcomes from both SEQUOIA and ALPINE are still immature, the results from the recent data cuts are more appropriate to inform the long term effectiveness of zanubrutinib in 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. But it recognised there were equality issues associated with excluding the group for whom FCR or BR is suitable. This is because younger people in better general health 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 considered 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. In response to consultation, the company reiterated that zanubrutinib would be used as an alternative to currently approved Bruton tyrosine kinase inhibitors (BTKis) in clinical practice, and that fixed-duration therapies are not relevant comparators. But the company provided exploratory analysis comparing zanubrutinib with ibrutinib plus venetoclax for untreated CLL in younger people who have better general health without comorbidities. The committee agreed that this analysis may provide some evidence for zanubrutinib in people with untreated CLL for whom FCR and BR is suitable. It noted that it had been incorporated into the economic model (see section 3.12).

## 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. But the company did not initially 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 people with better general health 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 venetoclax plus obinutuzumab use 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 considered that venetoclax plus obinutuzumab and ibrutinib plus venetoclax are relevant comparators to zanubrutinib for untreated CLL, regardless of TP53 mutation status and FCR and BR suitability. It requested additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus obinutuzumab and ibrutinib plus venetoclax for the untreated CLL population. In response to consultation, the company reiterated that it did not consider fixed-duration therapies, including venetoclax plus obinutuzumab and ibrutinib plus venetoclax, to be relevant comparators. But it provided exploratory cost-effectiveness analyses versus venetoclax plus obinutuzumab and ibrutinib plus venetoclax in people with untreated CLL. The committee heard from the NHS England representative that approximately 50% people with untreated CLL have venetoclax-based

treatments. It also heard from clinical experts that usually people and physicians must make a choice between fixed-duration and continuous treatments. The committee concluded that fixed-duration venetoclax-based treatments are appropriate comparators to zanubrutinib in the untreated CLL population.

## Relapsed or refractory CLL population

3.7 The company did not initially 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 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 considered that venetoclax plus rituximab is a relevant comparator for people with previously treated relapsed or refractory CLL. It requested additional clinical and cost-effectiveness evidence of zanubrutinib compared with venetoclax plus rituximab in the relapsed or refractory CLL population. In response to consultation, the company reiterated that it did not consider fixed-duration venetoclax plus rituximab a relevant comparator. But the company provided exploratory cost-effectiveness analyses versus venetoclax plus rituximab in people with relapsed or refractory CLL. The committee recalled that people with untreated CLL who had venetoclax-based treatments can have venetoclax plus rituximab for relapsed CLL, if their disease is not refractory to venetoclax. It concluded that venetoclax plus rituximab is a relevant comparator for people with previously treated relapsed or refractory CLL.

## 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 SEQUOIA (May 2021) and ELEVATE-TN, an open-label, phase 3, randomised controlled trial.

- 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 done using evidence from ALPINE and ASCEND, an open-label, phase 3, randomised controlled trial.

  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, and in the relapsed or refractory CLL population. The company considered the MAIC results to be 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. But 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 overall survival is 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. But 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.

3.9 In response to consultation, the company updated the MAIC for zanubrutinib compared with acalabrutinib in the untreated CLL population for whom FCR or BR is unsuitable using the most recent SEQUOIA data from October 2022. The

company considered the results to be consistent with the results from the original MAIC based on the data from May 2021 In response to consultation, the company also provided additional indirect treatment comparison results as follows:

- Zanubrutinib compared with venetoclax plus obinutuzumab in untreated CLL population for whom FCR or BR is unsuitable: An unanchored MAIC was done using evidence from SEQUOIA (October 2022) and CLL14, an open-label, phase 3, randomised controlled trial comparing the efficacy and safety of combined treatments of venetoclax plus obinutuzumab versus obinutuzumab plus chlorambucil in people with untreated CLL who have comorbidities.
- Zanubrutinib compared with ibrutinib plus venetoclax in untreated CLL population who were older and in poorer general health with comorbidities: An unanchored MAIC was done using evidence from SEQUOIA (October 2022) and GLOW, an open-label, phase 3, randomised controlled trial assessing the progression-free survival of ibrutinib plus venetoclax compared with obinutuzumab plus chlorambucil in people with untreated CLL.
- Zanubrutinib compared with ibrutinib plus venetoclax in untreated CLL population who were younger and in better general health without comorbidities: An unanchored MAIC was done using evidence from SEQUOIA (October 2022) and CAPTIVATE, a phase 2, single arm trial of ibrutinib plus venetoclax in people with untreated CLL.

- Zanubrutinib compared with venetoclax plus rituximab in relapsed or refractory CLL population: Results of Chanan-Khan et al. (2022), a published network meta-analysis (NMA), aligned to October 2022 SEQUOIA data.

  The company concluded that the MAIC results demonstrated there was no statistically significant difference in survival between zanubrutinib and venetoclax plus obinutuzumab or ibrutinib plus venetoclax in untreated CLL. The company considered the MAIC results to be confidential and cannot be reported here. The company also considered that the NMA results favoured zanubrutinib for progression-free survival (hazard ratio: 0.69 [95% confidence interval: 0.32 to 1.46]) and favoured venetoclax plus rituximab for overall survival (hazard ratio: 1.27 [95% confidence interval: 0.47 to 3.33]). The EAG considered that, because of the wide confidence intervals, there is substantial uncertainty in the MAIC and NMA results. The EAG noted that for the MAICs versus venetoclax plus obinutuzumab using CLL14 data and ibrutinib plus venetoclax using GLOW data, the exclusion of cumulative illness rating scale (CIRS) score greater than 6 as a covariate is likely to overestimate the effectiveness of zanubrutinib. The company explained that inclusion of CIRS score reduced the effective sample size considerably with little impact on the hazard ratios. For the MAIC versus ibrutinib plus venetoclax in older people with or without comorbidities, the EAG considered that using the SEQUOIA arm A only, instead of pooled arm A and arm C, favours zanubrutinib. This is because of the fewer events reported in arm A. The company explained that GLOW did not include people with high-risk CLL, and arm C of SEQUOIA trial only included people with high-risk CLL. The committee noted that all the indirect treatment comparison results are uncertain, but acknowledged the missing direct trial evidence and immaturity of trial data. It considered these were the best available estimates of comparative effectiveness of zanubrutinib versus relevant comparators for its decision making. The committee concluded that despite the uncertainties, the results of the indirect treatment comparisons are acceptable for decision making.

## Uncertainty in the untreated high-risk CLL population

3.10 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 using 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

3.11 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 arm 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. In response to consultation, the company provided updated data from SEQUOIA (October 2022) and ALPINE (May 2023), which confirmed that the safety profile of zanubrutinib is consistent with the earlier data cuts. The committee concluded that zanubrutinib is a tolerable and safe treatment for previously untreated CLL and relapsed or refractory CLL.

# Economic model

## Modelling approach

3.12 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. ALPINE results were used directly 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. The committee considered that the 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. In response to consultation, the company provided updated economic models for untreated CLL and relapsed or refractory CLL using a cost-utility approach comparing zanubrutinib with acalabrutinib and ibrutinib in both populations. The company also adapted the respective economic models providing exploratory analysis comparing zanubrutinib with venetoclax plus obinutuzumab and ibrutinib plus venetoclax in people with untreated CLL and with venetoclax plus rituximab in people with relapsed or refractory CLL. The committee noted areas of uncertainty, particularly around the assumption of constant relative hazards, long term survival extrapolations, utility values and incorporation of adverse events for most of the comparisons. It acknowledged that the trial data for zanubrutinib is still immature. The committee concluded that the updated economic models, for both untreated CLL and relapsed or refractory CLL, are acceptable for decision-making.

## Survival extrapolations

3.13 To model the long term survival in the untreated CLL model, the company used time to progression and preprogression survival data from SEQUOIA extrapolated over 30 years by fitting 6 parametric distributions. Progression-free survival curves were derived using time to progression and preprogression survival data. The generalised gamma distribution was chosen as the company's base-case distribution for both time to progression and preprogression survival. Postprogression survivalwas 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 BR 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 overall survival 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 overall survival 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. 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 noted that data immaturity is not exclusive to this CLL appraisal alone. In response to consultation, the company used the later data cut from SEQUOIA (October 2022) to update the survival extrapolations for zanubrutinib, acalabrutinib and ibrutinib in the untreated CLL model. Also, the company used updated data from SEQUOIA and data from ASCEND to predict postprogression survival for venetoclax plus obinutuzumab and ibrutinib plus venetoclax in the untreated CLL model. The company also provided survival extrapolations for venetoclax plus rituximab in relapsed or refractory CLL using hazard ratios from a published NMA applied to an extrapolated zanubrutinib curve. The company also used a later data cut from ALPINE (May 2023) to justify the choice of survival extrapolations from ALPINE in the relapsed or refractory CLL model. The committee acknowledged the company's use of the latest data cut from SEQUOIA to inform the long-term survival extrapolations. But it recalled that the latest ALPINE data (May 2023) was only used to validate the survival extrapolations from an earlier data cut (December 2021). It considered that, despite the evidence from SEQUOIA and ALPINE being immature, it is the best evidence available to inform the long-term survival extrapolations. The committee concluded that the long-term survival extrapolations are uncertain, but appropriate for decision making.

## Source of utility values

3.14 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 the relapsed or refractory CLL model, 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 considered 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. In response to consultation, the company explored alternative utility values in cost–utility scenario analysis. But the EAG still considered that there is considerable uncertainty in the utility estimates in both the untreated CLL and relapsed or refractory CLL economic models, particularly with the inclusion of venetoclax-based treatments in the cost–utility analysis. The committee considered that the utility values used in the economic models are still uncertain. It acknowledged that the company had explored alternative utility values in its scenario analyses. The committee concluded that the utility values used in the economic analysis are acceptable for decision making.

## Incorporating adverse events in the economic analysis

3.15 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 in the 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. For the untreated CLL population, the adverse event profiles of zanubrutinib, ibrutinib and acalabrutinib were taken from SEQUOIA, ELEVANTE-TN and RESONATE-2. For the relapsed or refractory population, the adverse event profiles 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. But 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. In response to consultation, the company highlighted that accounting for adverse events in the first model cycle only is common in economic modelling. The same method has been used in other recent and relevant NICE appraisals for CLL treatments , including NICE's technology appraisal guidance on ibrutinib with venetoclax and NICE's technology appraisal guidance on acalabrutinib. The committee considered that, while the impact of adverse events for the full model time horizon is uncertain, modelling this is difficult. It also acknowledged that the approach used by the company to model the impact of adverse events in this appraisal is consistent with previous appraisals for CLL. The committee concluded that the company's approach to model the impact of adverse events in the economic analysis is acceptable for decision making.

# Cost-effectiveness estimates

## Untreated CLL population

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. Because of these confidential discounts, the exact results cannot be reported here. For the untreated CLL population that is high-risk or for whom FCR or BR is unsuitable, the company's probabilistic base-case cost–utility analysis results for zanubrutinib compared with ibrutinib and acalabrutinib demonstrated that zanubrutinib was dominant (had lower incremental costs and more incremental QALYs) compared with ibrutinib and acalabrutinib. These were consistent with the company and EAG's results at the first committee meeting. For zanubrutinib compared with venetoclax plus obinutuzumab and ibrutinib plus venetoclax the company's base case ICERs were above the range normally considered cost effective. The committee recalled that it had heard from the clinical experts that zanubrutinib was most likely to be used in place of either ibrutinib or acalabrutinib. It therefore concluded that zanubrutinib was cost-effective for these populations. The company also presented ICERs for zanubrutinib compared with ibrutinib plus venetoclax for the population for whom FCR or BR is suitable. This was substantially above the range normally considered cost effective. The company did not compare zanubrutinib with acalabrutinib and ibrutinib in this population, because they are not recommended by NICE and therefore not used in the NHS in these people. The committee therefore considered that zanubrutinib is not a cost-effective use of NHS resources compared with ibrutinib plus venetoclax for the untreated CLL population for whom FCR or BR is suitable.

## Relapsed or refractory CLL

3.17 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. Because of these confidential discounts, the exact results cannot be reported here. The company's probabilistic base-case cost–utility analysis results for zanubrutinib compared with ibrutinib and

acalabrutinib for the relapsed or refractory CLL population demonstrated that zanubrutinib was dominant (had lower incremental costs and more incremental QALYs) compared with ibrutinib and acalabrutinib. The company's probabilistic base-case ICERs for zanubrutinib compared with venetoclax plus rituximab for the relapsed or refractory CLL population was within the range normally considered cost effective (significantly above £30,000 savings per QALY lost). The committee considered that zanubrutinib is a cost-effective use of NHS resources for the relapsed or refractory CLL population.

# Other factors

## Equality issues

3.18 The company's submission did not initially 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 people who have better general health 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. In response to consultation, the company provided an analysis for zanubrutinib versus ibrutinib plus venetoclax in younger people who have good general health without comorbidities, which it considered relevant to represent people with untreated CLL for whom FCR or BR is suitable (see section 3.5). The committee noted that the cost-effectiveness estimates were considerably higher than those that represent an effective use of NHS resources when compared with ibrutinib plus venetoclax in this population. The committee noted the equalities issue and considered flexibility as part of the principles that guide the development of NICE guidance and standards. But even considering greater flexibility, the ICERs for the population for whom FCR and BR are suitable were substantially higher than what is considered a cost-effective use of resources.

## Severity

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

## Innovation

3.20 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. But, the committee considered that these additional benefits are likely captured in the cost– utility analysis. The committee concluded that all additional benefits of zanubrutinib have been considered.

# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

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 chronic lymphocytic leukaemia 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 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 the technology 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

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# Accreditation