

# Zanubrutinib for treating marginal zone lymphoma after anti-CD20-based treatment

Technology appraisal guidance  
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[www.nice.org.uk/guidance/ta1001](https://www.nice.org.uk/guidance/ta1001)

## Your responsibility

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

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

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

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

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# 1 Recommendations

- 1.1 Zanubrutinib is recommended, within its marketing authorisation, as an option for treating marginal zone lymphoma in adults who have had at least 1 anti-CD20-based treatment. It is only recommended if the company provides it according to the [commercial arrangement](#).

## Why the committee made this recommendation

Standard care for marginal zone lymphoma in adults who have had at least 1 anti-CD20-based treatment is rituximab with or without chemotherapy, or chemotherapy alone.

Zanubrutinib has not been directly compared in a clinical trial with standard care. An indirect comparison of zanubrutinib with standard care suggests that zanubrutinib increases how long people have before their lymphoma gets worse and how long they live.

The cost-effectiveness estimates for zanubrutinib compared with standard care are within the range NICE normally considers an acceptable use of NHS resources. So, zanubrutinib is recommended.

## 2 Information about zanubrutinib

### Marketing authorisation indication

- 2.1 Zanubrutinib (Brukinsa, BeiGene) is indicated for the treatment of 'adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy'.

### 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 for zanubrutinib is £4,928.65 per 120-pack of 80-mg capsules (excluding VAT; BNF online accessed May 2024).
- 2.4 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.

## 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.

### Impact of the condition

3.1 Marginal zone lymphoma (MZL) is a group of rare, slow-growing non-Hodgkin lymphomas. It develops from B lymphocytes, a type of white blood cell normally found at the edges of lymph node tissue. The patient expert explained that diagnosis is often delayed and can have a significant impact on people with MZL and their families, affecting all aspects of their lives. The clinical experts explained that people are commonly diagnosed at about 75 years and that relapse typically occurs within 5 years. The patient submissions highlighted the negative psychological impact of active monitoring, when people wait until symptoms warrant treatment. They emphasised that quality of life is as important as living longer. The committee acknowledged that MZL is an incurable, rare condition that can have a negative impact on quality of life for people with MZL, and their families and carers.

### Treatment pathway

3.2 For relapsed or refractory MZL, the clinical experts explained that there are limited treatment options. They explained that choice of treatments depends on disease stage, MZL subtype, previous therapies, age, fitness, tolerance of previous treatment, availability of trials and clinician experience. They explained that people would usually be offered rituximab with or without chemotherapy, rather than chemotherapy alone. But, because of limited options, people may be offered a range of chemotherapy regimens, except fludarabine-based ones which are seldom used in practice. The clinical experts explained that people are usually offered a fixed 6 months of chemotherapy. They highlighted that with each additional line of chemotherapy, relapses often occur faster. They explained that for some older people, chemotherapy may increase the risk of frailty. The patient

submissions highlighted that having treatment in hospital can be stressful, time consuming and a financial burden. The clinical experts emphasised that there is a significant unmet need for treatments for MZL, especially after relapse on first-line treatment for people who cannot have chemotherapy. The committee acknowledged the limited treatment options for relapsed or refractory MZL and the high unmet need for effective and safe treatments that are convenient to administer.

## Positioning of zanubrutinib

- 3.3 For this evaluation, the company positioned zanubrutinib in line with its marketing authorisation, as a second-line and beyond treatment for people with relapsed or refractory MZL who have had at least 1 anti-CD20-based treatment. It suggested that relevant comparators were rituximab with or without chemotherapy, and chemotherapy alone. The committee agreed with the company's positioning of zanubrutinib, and concluded that the choice of comparators was appropriate.

## Clinical evidence

### Key clinical trials for zanubrutinib

- 3.4 The clinical-effectiveness evidence for zanubrutinib came from 2 international, multi-centre, single-arm, open-label trials: MAGNOLIA (phase 2; n=68) and AU-003 (phase 2 part of a phase 1 and 2 study; n=20). The trials included people aged at least 18 years with relapsed or refractory MZL, who had had at least 1 previous line of treatment. Only MAGNOLIA included some people based in the UK. The primary outcome was best overall response assessed by an independent review committee. The company used the secondary outcomes of progression-free and overall survival in its economic model. The committee noted that the average age of people in the trials was less than 70 years. This was younger than people likely to be seen in the NHS, where people are usually diagnosed aged around 75 years (see [section 3.1](#)). The committee also noted that the median progression-free and overall survival had not been reached in either trial. It considered that the people in the trial may not be fully representative of people

likely to have zanubrutinib in the NHS. It acknowledged that with no direct comparative clinical evidence, it was hard to interpret the trial results, and the immature survival trial data increased the uncertainty. The committee concluded that these areas of uncertainty would be considered in its decision making.

## UK HMRN registry comparator data

3.5 The company used data from a UK-based registry, the Haematological Malignancy Research Network (HMRN), to estimate outcomes for the comparator arm. People from the HMRN registry were chosen to align with the eligibility criteria of the zanubrutinib trials. Aggregate patient characteristics and anonymised time-to-event (progression-free and overall survival) individual patient-level data were obtained. The clinical experts considered that the data from the HMRN registry was representative of NHS clinical practice, except for the very small proportion of people who had fludarabine-based chemotherapy, which is not commonly used (see [section 3.2](#)). The committee concluded that the data collected from the HMRN registry was likely representative of standard care in the NHS.

## Clinical effectiveness

3.6 To assess the comparative effectiveness of zanubrutinib, the company used data from the HMRN registry and pooled data from MAGNOLIA and AU-003 (from here, MAGNOLIA-003) to conduct an unanchored matching-adjusted indirect comparison (MAIC). People were matched on 5 covariates: age, median time since diagnosis, number of previous lines of therapy, refractoriness to last therapy, and disease progression in the last 2 years. The company noted that fewer patient characteristics were collected in the HMRN registry at the start of treatment compared with in MAGNOLIA-003, limiting the covariates that could be included in the MAIC. The EAG had concerns about the limited number of covariates that were used in the matching and the lack of epidemiological data to better quantify the impact of confounders and potential effect modifiers. The committee noted that results from the MAIC suggested that zanubrutinib improved progression-free and overall survival compared with the HMRN treatments. The exact figures cannot be reported here because the company



considers them to be commercial in confidence. The committee acknowledged the uncertainty of the trial survival data (see [section 3.4](#)) and the limitations of the unanchored MAIC; that is, this method is particularly susceptible to large amounts of systematic error unless all prognostic variables and effect modifiers are accounted for (as described in [NICE Decision Support Unit technical support document 18](#)). It concluded that these areas of uncertainty would be considered in its decision making.

## Economic model

### Company's modelling approach

3.7 The company presented a partitioned survival model with 3 health states: progression free, progressed disease and death. The probability of being in each health state was calculated using extrapolated progression-free and overall survival. People started the model in the progression-free health state. The model included a cycle length of 4 weeks with a half-cycle correction and a 27-year time horizon. The EAG had concerns with using a partitioned survival model for relapsed or refractory MZL because of the independent modelling of progression-free and overall survival, and the relatively long time that people are in these health states. They noted that a state transition model may allow the condition to be modelled more accurately, but that data availability may limit the extent to which the model could be populated. The company confirmed that the data to populate a state transition model was not available. The committee concluded that the company's model structure was acceptable for decision making.

### Long-term extrapolations of progression-free and overall survival

3.8 The company used patient-level data from MAGNOLIA-003 to extrapolate progression-free and overall survival for zanubrutinib in the long term. The MAGNOLIA-003 data was compared with the HMRN data via a MAIC (see [section 3.6](#)). For the comparator, progression-free and overall survival were extrapolated using the HMRN treatment data. The company used independently

fitted survival models and selected the best-fitting distributions based on statistical fit, visual inspection and clinical plausibility. Because there was no evidence of a violation in the proportional hazards assumption between zanubrutinib and the HMRN treatments in progression-free and overall survival, the company considered it statistically appropriate to use the same distributions for both treatment arms. In the model, the company restricted overall survival by age- and gender-matched all-cause mortality for both treatment arms, such that the risk of death was never lower than in the general population. It also restricted progression-free survival by overall survival, such that people could not be progression free for longer than they were alive. The company's base case used the log-logistic distribution for progression-free and overall survival extrapolations for zanubrutinib and the HMRN treatments. The EAG had concerns about the immature survival data for zanubrutinib and the significant heterogeneity in extrapolations from different distributions for both treatment arms. The clinical experts considered that at 5 years, it was clinically plausible for 40% of people on the HMRN treatments to be alive. They considered that the log-logistic distributions provided the most plausible extrapolations. The committee noted that the latest data cut was in May 2022, and queried whether further data cuts were expected. The company reported that further data collection will only focus on safety and not efficacy outcomes. The committee agreed that the log-logistic distribution provided clinically plausible extrapolations and concluded that the company's base case was acceptable for decision making.

## Background mortality risk

- 3.9 In the company's base case, it used the background mortality risk of the general population. It also provided a scenario analysis using an increased background mortality risk to reflect that people with relapsed or refractory MZL are likely to have an increased risk of death compared with the general population. The company used a standardised mortality ratio (SMR) of 1.41, previously applied in [NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma](#), to the background mortality in the model. The committee noted that the overall survival curves were restricted relatively early, with the risk of death replaced with the background mortality of the general population (see [section 3.8](#)). It considered that people who had relapsed or refractory MZL would likely have a

greater risk of death than the general population. It concluded that the mortality risk of people with relapsed or refractory MZL would be higher than the age-matched general population and that an SMR of up to 1.41 should be used in the model.

## Treatment effect waning

3.10 In the company's model structure, the efficacy of zanubrutinib naturally waned over the time horizon with the hazard ratios of both progression-free and overall survival tending to 1. In its base case, the company assumed no additional treatment effect waning. At the request of the EAG at clarification, the company provided scenario analyses on additional treatment effect waning over varying periods. One of these was based on the median time to stopping zanubrutinib calculated in the model. The company considered it clinically inappropriate to assume that 50% of people would continue to have treatment without gaining any benefit from zanubrutinib. The clinical experts explained that relapses often occur continually in MZL and so there would be some treatment effect waning for both the zanubrutinib and HMRN treatment arms. They considered that zanubrutinib would likely have a longer time to relapse than the HMRN treatments, but agreed that there is limited evidence on the length of time it takes for a relapse to occur because of the immaturity of the zanubrutinib data. The committee considered that it was uncertain whether additional treatment effect waning should be modelled. It noted that there may be differential waning depending on whether people have zanubrutinib or the HMRN treatments. It concluded that the company's base case, which already accounted for some treatment effect waning, was appropriate for decision making.

## Cost-effectiveness estimates

### Company and EAG base cases

3.11 In the EAG's base case, it accepted the company's comparator that included the HMRN treatments, the log-logistic distributions for long-term extrapolations of progression-free and overall survival (see [section 3.8](#)) and no additional

treatment effect waning (see [section 3.10](#)). It used different utility values for the progressed disease health state based on [NICE's technology appraisal guidance on lenalidomide with rituximab for previously treated follicular lymphoma](#), applied different disutility values and durations specific to each adverse event, and used eMIT prices. At the factual accuracy check, the company accepted the EAG's base case such that all assumptions were aligned in the company's revised base case.

## Committee's preferred assumptions

- 3.12 The committee's preferred assumptions were largely in line with the company's revised model and the EAG's base case (see [section 3.11](#)). Except the committee considered that an increased background mortality risk should be applied to reflect that people with relapsed or refractory MZL are likely to have an increased risk of death compared with the general population (see [section 3.9](#)).

## Acceptable ICER

- 3.13 [NICE's health technology evaluations manual](#) notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The manual also states that decisions about the acceptability of the technology will consider aspects that relate to uncaptured benefits and non-health factors. The committee recalled the statements from the clinical and patient experts about the significant unmet need for effective and safe treatments in this rare condition. It also noted that zanubrutinib has a novel mechanism of action and, as an oral treatment, would be easily administered and fit into the existing care pathway. The committee acknowledged the high unmet need for novel treatments, but it also noted the high levels of uncertainty, including:
- the representativeness of the populations from MAGNOLIA and AU-003, the immature progression-free and overall survival data and the lack of direct comparative trial evidence (see [section 3.4](#))

- the limitations of the unanchored MAIC and lack of adjustment for all potential confounders and effect modifiers (see [section 3.6](#))
- the uncertainty in the long-term extrapolations of progression-free and overall survival (see [section 3.8](#)).

Balancing the unmet need and the uncertainties, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per quality-adjusted life year [QALY] gained).

## Company and EAG cost-effectiveness estimates

3.14 The committee considered the cost effectiveness of zanubrutinib compared with the HMRN treatments. In both the company's revised and the EAG's base case, and the scenario that included an increased background mortality risk (SMR of 1.41; see [section 3.9](#)), the deterministic and probabilistic ICERs were below the range the committee considered to be acceptable for this evaluation (see [section 3.13](#)). The exact ICERs cannot be reported here because some prices are commercial in confidence.

## Other factors

### Equality

3.15 The committee did not identify any equality issues.

### Uncaptured benefits

3.16 The committee considered if zanubrutinib was innovative. It did not identify additional benefits of zanubrutinib not captured in the economic modelling. So, the committee concluded that all additional benefits of zanubrutinib had already been taken into account.

## Severity

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

## Conclusion

### Recommendation

3.18 The ICERs using the committee's preferred assumptions were below the range the committee considered to be acceptable for this evaluation (see [sections 3.13 and 3.14](#)). So, zanubrutinib is recommended, within its marketing authorisation, for treating MZL in adults who have had at least 1 anti-CD20-based treatment.

## 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 marginal zone lymphoma and the healthcare professional 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](#).

### Chair

**Stephen O'Brien**

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.

**Sharlene Ting**

Technical lead

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