National Institute for Health and Care Excellence

Health Technology Evaluation

Zanubrutinib for treating relapsed or refractory marginal zone lymphoma [ID5085]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BeiGene	It is appropriate to refer zanubrutinib to NICE for single technology appraisal.	Thank you for your comment. No further action needed.
Wording	BeiGene	The wording of the draft remit which references appraising the clinical and cost-effectiveness of zanubrutinib is appropriate and aligned with both the marketing authorisation and anticipated use of zanubrutinib within clinical practice in England and Wales.	Thank you for your comment. No further action needed.
Timing issues	BeiGene	This appraisal should be initiated as soon as possible. As reported in 'Appendix B – Draft scope ID5085', there were around 14,200 new non-Hodgkin lymphoma cases in the UK each year between 2016 and 2018 with marginal zone lymphoma (MZL) representing approximately 5 to 15% of cases.[1,2] The natural history of MZL is characterised by a continuing	Thank you for your comment. The unmet need in this area will be explored during the appraisal process. No further action needed.

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		pattern of relapse and remission.[3] However, patients with relapsed/refractory (R/R) MZL have limited treatment options. The European Society for Medical Oncology (ESMO) guidelines recommend repeating rituximab-based chemoimmunotherapy (CIT) or rituximab monotherapy if prior therapy has achieved a long-term remission.[4] However, rituximab-based CIT can become less effective with each line of therapy and the tumour can become refractory to treatment.[5–7] Furthermore, heavily treated patients with multiple relapses can become chronically immunosuppressed and are no longer suitable for further CIT. Off-label treatments and enrolment into clinical trials are therefore considered on a patient-individual basis.[4] There is therefore a high unmet need for a new targeted, chemotherapy-free, and well-tolerated treatment with proven efficacy in this patient population. Zanubrutinib is the only licensed therapy for patients with R/R MZL in the UK. The clinical efficacy of zanubrutinib in R/R MZL was demonstrated in two single-arm phase 2 clinical trials, in which zanubrutinib induced durable tumour responses and demonstrated long-term progression-free survival. Zanubrutinib showed consistent clinical efficacy in all MZL subtypes, independent of disease characteristics and treatment history, including patients that were refractory to previous therapies.[8,9] A timely appraisal is therefore essential as zanubrutinib is a new efficacious, safe, and well-tolerated treatment option and will address an urgent unmet need for patients with R/R MZL. **References** 1. Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆. Annals of Oncology. 2021 Mar 1;32(3):298–308.	

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		2. Cancer Research UK. Non-Hodgkin lymphoma statistics [Internet]. 2015 [cited 2023 Jul 27]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma 3. Zinzani PL. The many faces of marginal zone lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:426–32. 4. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2020 Jan;31(1):17–29. 5. Conconi A, Martinelli G, Thiéblemont C, Ferreri AJM, Devizzi L, Peccatori F, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. Blood. 2003 Oct 15;102(8):2741–5. 6. Becnel MR, Nastoupil LJ, Samaniego F, Davis RE, You MJ, Green M, et al. Lenalidomide plus rituximab (R2) in previously untreated marginal zone lymphoma: subgroup analysis and long-term follow-up of an open-label phase 2 trial. Br J Haematol. 2019 Jun;185(5):874–82. 7. Coleman M, Andorsky DJ, Yacoub A, Melear JM, Fanning SR, Kolibaba KS, et al. Patients with Relapsed/Refractory Marginal Zone Lymphoma in the MAGNIFY Phase IIIb Interim Analysis of Induction R2 Followed By Maintenance. Blood. 2020 Nov 5;136(Supplement 1):24–5. 8. MAGNOLIA CSR, A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma. 9. BeiGene. Clinical study report, A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma (Data on file). 2021.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BeiGene	The Company agrees that the background information gives a reasonable summary of clinical practice for MZL.	Thank you for your comment. No further action needed.
Population	BeiGene	The wording of the population is aligned with both the UK marketing authorisation and anticipated use of zanubrutinib within clinical practice in England and Wales: adults with MZL who have had at least one anti-CD20-based therapy.[1] **References** 1. BRUKINSA 80 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2022 Oct 31]. Available from: https://www.medicines.org.uk/emc/product/14001/smpc#gref	Thank you for your comment. No further action needed.
Subgroups	BeiGene	The Company believe it is preferable to conduct a comprehensive assessment of R/R MZL as a whole, rather than focusing on subgroups based on disease subtype or number of prior lines of therapy. Once patients with MZL relapse, there is no differentiation based on specific disease subtype or number of lines received, as supported by the ESMO guidelines and clinical expert opinion sought by the Company through 1:1 interviews with four UK KOLs.[1] While first-line treatments are stratified according to disease subtype, the ESMO guidelines consolidate patients with R/R MZL under one singular classification of “patients with recurrent disease”. This is also supported by clinical experts who agree that at relapse, the	Thank you for your comment. The subgroups have been removed from the scope as suggested.

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		treatment approach becomes uniform regardless of the subtype at diagnosis. Zanubrutinib is expected to be effective across the MZL subgroups as demonstrated in two single-arm phase 2 clinical trials in which zanubrutinib showed consistent clinical efficacy in all MZL subtypes, independent of disease characteristics and treatment history.[2,3] Due to the limited number of patients enrolled in the clinical trials and the limited amount of evidence available in the literature, stratifying by disease subtype and line of treatment will introduce uncertainty into the analyses presented in the submission and make it difficult to draw statistically significant conclusions. As such, it is not clinically appropriate to stratify patients with R/R MZL by disease subtype and line of treatment and such analyses would introduce uncertainty into any analyses conducted due to the limited sample sizes of patients. **References** 1. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2020 Jan;31(1):17–29. 2. MAGNOLIA CSR, A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma. 3. BeiGene. Clinical study report, A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma (Data on file). 2021.	

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Comparators	BeiGene	The Company requests that the following comparator "Chemotherapy with or without rituximab" is rephrased to "**Rituximab with or without chemotherapy**" to highlight the role of rituximab monotherapy in the context of R/R MZL. This adjustment also reflects the wording of the background information section within 'Appendix B – Draft scope ID5085' which states that "symptomatic treatment for MZL typically involves rituximab (an anti-CD20 antibody) alone or in combination with chemotherapy". Rituximab monotherapy is often the preferred treatment option in patients with R/R MZL, who have previously received CIT combination therapy during earlier phases of treatment. As patients relapse, they are less able to tolerate intense CIT regimens in further lines of therapy as supported by disease management data provided by the Haematological Malignancy Research Network (HMRN). The HMRN is a UK registry which gathers information on lymphomas and other blood disorders from a population-based patient cohort. HMRN data collected from a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020 confirmed that [redacted]. Similarly, [redacted].[1] As such, rituximab monotherapy should be considered a key comparator within the appraisal and the wording of the scope should be updated to include rituximab monotherapy. The following treatments listed as comparators within 'Appendix B – Draft scope ID5085' are not considered appropriate for adults with MZL who have had at least one anti-CD20-based therapy, as confirmed following four 1:1 interviews with clinical experts:	Thank you for your comment. **Rituximab with or without chemotherapy** The scope has been updated to include "Rituximab with or without chemotherapy" as a potential comparator. The option of chemotherapy (without rituximab) has been retained. **Splenectomy** The ESMO guidelines state that "For the patients who do not respond to rituximab, splenectomy [IV, B] or the addition of ChT may be considered." The scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive. So, splenectomy has been left in the scope.

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		• As highlighted in the ESMO guidelines, **splenectomy** was traditionally considered as the recommended first-line treatment for patients with splenic MZL. However, as a major, non-curative surgical procedure that may have severe, acute, and potentially fatal downstream complications, it has largely replaced by rituximab (with or without CIT) and only considered in very select cases where rituximab is not indicated.[2] Data from the HMRN registry shows that out of [redacted] patients diagnosed with MZL between 2005 to 2020, only [redacted] patients had received a splenectomy, which was performed close to diagnosis as part of their first-line treatment. Furthermore, splenectomy is not noted as a treatment option in patients with R/R MZL in the ESMO guidelines. As such, splenectomy is therefore not considered relevant to this appraisal. • As highlighted in the ESMO guidelines, autologous **stem cell transplantation** may be considered in fit patients with clinically aggressive relapse. [2] However, as highlighted by Lymphoma Action UK, the purpose of stem cell transplantation is to enable patients to tolerate higher dose CIT regimens, rather than serving as an alternative treatment choice.[12] The low use of autologous stem cell transplantation in clinical practice is confirmed from UK HMRN registry data, which [redacted] in a cohort of [redacted] patients diagnosed with MZL between 2005 to 2020. As such, stem cell transplantation is not considered relevant to this appraisal. The approach to care for patients with R/R MZL involves observation and systemic treatment. For MZL patients with recurrent disease, ESMO guidelines recommend treatment with rituximab-based CIT or rituximab monotherapy.[2] **Best supportive**	**Autologous stem cell transplantation** Thank you for providing data from the HMRN registry. Autologous stem cell transplantation has been removed as a comparator. **Best supportive care** From BeiGene's scoping consultation response that "Clinical guidelines only recommend a repetition of rituximab monotherapy or rituximab-based CIT if prior therapy has achieved a long-term remission of symptomatic disease (24 months). For patients that relapsed quicker (<24 months) or were not responding to prior therapy, there are no therapeutic options available." NICE considers that there is potentially a population who may be eligible for zanubrutinib for whom rituximab monotherapy or rituximab-based CIT would not be suitable. In this scenario, the only suitable treatment option would be best supportive care. So, best

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		care (BSC) may only be considered once patients have exhausted all viable treatment options, including clinical trials and are too frail to tolerate any active therapy, including zanubrutinib. As such, BSC would be considered as end-of-life care and not as a comparator for zanubrutinib in patients able to receive treatment. **References** 1. HMRN Registry Report MZL. Data on file. 2023 2. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2020 Jan;31(1):17–29.	supportive care has been retained as a comparator in this scope.
Outcomes	BeiGene	All outcomes listed are appropriate	Thank you for your comment. No further action needed.
Equality	BeiGene	There are no significant equality considerations associated with this appraisal. MZL is a disease which mainly impacts the elderly and there is a need for new treatment options that are well-tolerated and suitable for heavily treated patients with R/R MZL, particularly those who are chronically immunosuppressed. Zanubrutinib is a simple oral regimen and does not require frequent hospital visits as with other MZL treatments which require intravenous administration. Zanubrutinib will therefore be a welcomed treatment option for older, frail or less fit patients.	Thank you for your comment. No further action needed.
Other considerations	BeiGene	There are no additional issues to comment on.	Thank you for your comment. No further action needed.

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Questions for consultation	BeiGene	It is anticipated that zanubrutinib will be used as a second line and subsequent therapy regimen for patients with R/R MZL after at least one prior anti-CD20 antibody-based regimen, in line with its marketing authorisation. There is no standard of care for patients with R/R MZL. Clinical guidelines only recommend a repetition of rituximab monotherapy or rituximab-based CIT if prior therapy has achieved a long-term remission of symptomatic disease (24 months).[1] For patients that relapsed quicker (<24 months) or were not responding to prior therapy, there are no therapeutic options available.[1] The Company does not consider zanubrutinib a candidate for managed access. The Company considers that zanubrutinib will result in some substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation. Zanubrutinib is considered an innovative 'step-change' in the management of R/R MZL as the first targeted therapy to be approved in the treatment landscape. Zanubrutinib would introduce a new chemotherapy-free treatment mechanism of action, expanding treatment choice for MZL patients and enabling greater patient autonomy and ability to make more tailored treatment decisions. As a simple oral regimen, zanubrutinib does not require frequent hospital visits as the case with CIT which require intravenous administration. This will lead to improvements in quality of life for patients and will also ease the burden on caregivers. These benefits related to expanded treatment choice and reduced burden of administration for patients and their caregivers might not be adequately captured by QALY calculations.	Thank you for your comment. The company has an opportunity to highlight the benefits of zanubrutinib in its submission. No further action needed.

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		References 1. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2020 Jan;31(1):17–29.	
Additional comments on the draft scope	BeiGene	The list of comparator companies should be reduced to include only companies who manufacture a non-generic therapy which is licensed for patients with R/R MZL in the UK.	NICE health technology evaluations: the manual (PMG36) notes that comparator technologies may include branded and non-proprietary (generic) medicines and biosimilars. So, it is appropriate to include companies who manufacture relevant generic therapies in the stakeholder list.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Lymphoma Action UK