National Institute for Health and Care Excellence

Health Technology Evaluation

Zanubrutinib for treating relapsed or refractory mantle cell lymphoma after 1 or more treatments [ID6392]

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 a single technology appraisal. For the comparison with ibrutinib the NICE cost-comparison methodology may be appropriate (please refer to the 'Additional comments of the draft scope' section below for further details)	Thank you for your comment. Even if a topic is scoped as an STA, it will still possible for a company to make the case for cost comparison analysis within its submission, for consideration by committee.
	Royal College of Pathologists	Appropriate	Thank you for your comment.
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	Thank you for your comment. The scope

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		anticipated marketing authorisation and expected use of zanubrutinib within clinical practice in England and Wales. A small typographical error is noted within the draft remit (page 1 of draft scope): '*tresting*' should be replaced with '*the treatment of*'.	has been updated to include the wording 'the treatment of' in the remit/evaluation objective.
	Royal College of Pathologists	Reflective	Thank you for your comment.
Timing issues	BeiGene	This appraisal should be initiated as soon as possible. As reported in 'Appendix B – Draft scope ID6392', there were around 12,000 new non-Hodgkin's lymphoma (NHL) cases in the United Kingdom (UK) in 2017, with mantle cell lymphoma (MCL) representing less than 1% of these cases.[1,2] The prognosis is poor with a five-year survival rate of less than 50%.[2] Limited treatment options are available for patients with relapsed/refractory (R/R) MCL in England and Wales, with ibrutinib (first-generation Bruton tyrosine kinase [BTK] inhibitor) representing the only targeted treatment option available through routine commissioning. Ibrutinib use is restricted to patients at first relapsed only.[3] Therefore, there are no targeted treatment options available through routine commissioning, for patients who are R/R after more than one previous line of therapy. Zanubrutinib is a second-generation BTK inhibitor with improved specificity and selectivity over first-generation BTK inhibitors. The clinical and safety outcomes of zanubrutinib in R/R MCL have been demonstrated in two single-arm phase 2 clinical trials, in which zanubrutinib induced durable responses and demonstrated long-term progression-free survival and overall survival.[4,5] As a second-generation BTK inhibitor, zanubrutinib has also demonstrated a more tolerable safety profile over existing BTK inhibitors in other relevant blood cancers.[6,7]	Thank you for your comments. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see: https://www.nice.org.uk/guidance/indevelopment/gid-ta11485

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		A timely appraisal is therefore essential to provide patients and clinicians with an additional treatment option for R/R MCL in this patient group with a significant unmet.	
	Royal College of Pathologists	Modest. Ibrutinib is routinely available but Zanubrutinib appraisal welcomed	Thank you for your comment. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see: https://www.nice.org.uk/guidance/indevelopment/gid-ta11485

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 MCL.	Thank you for your comment.
	Royal College of Pathologists	Accurate	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	BeiGene	The wording of the population aligns with both the anticipated marketing authorisation and expected use of zanubrutinib within clinical practice in England and Wales.	Thank you for your comment.
	Royal College of Pathologists	Appropriate although because ibrutinib is used routinely and specificially 2L in the UK, 3L+ therapies are 'post BTKi' and as such would not specificially apply to ibrutinib.	Thank you for your comment. No action required.
Subgroups	BeiGene	The Company believes that it is preferable to conduct a comprehensive assessment of R/R MCL as a whole, rather than focusing on subgroups, given the relatively small patient population (<1% of NHL cases (<120 cases) are MCL).[2] This aligns with the final scope of NICE TA502 (ibrutinib for R/R MCL), in which no specific subgroups were included.[8] Zanubrutinib is expected to be effective across MCL subgroups as demonstrated through subgroup analyses in the BGB-3111-206 trial, which reported consistent clinical outcomes across subgroups, considering both disease characteristics and treatment history.[9]	Thank you for your comments. No action required.
	Royal College of Pathologists	See above comment. The most appropriate comparator for this appraisal is ibrutinib in second line.	Thank you for your comment. No action required.
Comparators	BeiGene	**<u>After 1 prior therapy</u>** **Ibrutinib** Ibrutinib currently represents the only targeted treatment option available through routine commissioning for the treatment of R/R MCL in England and Wales.[3] Following approval by NICE in 2018, real-world evidence from the Haematology Malignancy Research Network (HMRN) demonstrated that ibrutinib has become standard of care (SoC) for R/R MCL, with the majority of patients in 2015-16 receiving ibrutinib treatment.[10] The British Society of	Thank you for your comments. The list of comparators in the scope has been kept broad. Stakeholders can provide justification around the most appropriate

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		Haematology (BSH) guidelines also recommend ibrutinib for use in R/R MCL patients following one prior line of therapy.[11] The licensed indication for ibrutinib ("*as a single agent is indicated for the treatment of adult patients with R/R MCL*") aligns with the anticipated licensed indication for zanubrutinib. The Company therefore anticipate that zanubrutinib will provide an alternative treatment option to ibrutinib at first relapse, and hence ibrutinib is the relevant comparator for zanubrutinib in R/R MCL in this appraisal. **After 2 or more prior therapies** **Brexucabtagene autoleucel** Brexucabtagene autoleucel (Brexu-cel) is not considered a relevant comparator to zanubrutinib, and hence should **be removed from the final scope**, for the following reasons: • The licensed indication for brexucabtagene autoleucel is restricted to patients who have received at least two lines of systemic therapy including a BTK inhibitor.[12] Conversely, the trial eligibility criteria for zanubrutinib (BGB-3111-206 and AU-003)[13,14] excluded patients who had received treatment with a BTK inhibitor prior to enrolment. Hence there is no overlap in the eligible populations of the two treatments. This positions brexucabtagene autoleucel beyond zanubrutinib in the treatment pathway, as a subsequent treatment option rather than a relevant comparator. This is reflected in the BSH guidelines which recommend that *"MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel*".[11] • Brexucabtagene autoleucel is not available via routine commissioning, and hence as per NICE's position statement cannot be considered as a relevant treatment (comparator or subsequent therapy) within this appraisal.[15]	comparators and the committee will consider this during the appraisal. The rituximab-based chemotherapy agents have been updated to 'Rituximab with or without chemotherapy' in the comparators section of the scope.

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		Chemotherapy with or without rituximab 'Chemotherapy with or without rituximab' is not the key comparator for zanubrutinib in this appraisal for the following reasons: • As documented above, ibrutinib is current SoC in UK clinical practice in R/R MCL, having displaced 'chemotherapy with or without rituximab' following its approval by NICE in 2018. Real-world evidence from the HMRN shows that ibrutinib use has increased from 0% to the majority treatment between 2011 and 2015-2016 in patients with R/R MCL.[10] • Zanubrutinib is anticipated to displace ibrutinib as a second-generation BTK inhibitor therapy, which positions 'chemotherapy with or without rituximab' as subsequent treatment rather than a comparator treatment. The Company would also like to highlight the paucity of evidence available to inform the clinical effectiveness of 'chemotherapy with or without rituximab'. A recent systematic literature review (SLR), conducted in May 2024, has identified no suitable clinical trial or observational study datasets to facilitate an indirect treatment comparison (ITC) versus zanubrutinib. This challenge is consistent with the appraisal of zanubrutinib in R/R marginal zone lymphoma (MZL), which relied on real-world evidence from the HMRN to form an external control arm for the comparison with 'chemotherapy with or without rituximab'.[16] A similar approach would be required for this appraisal, if 'chemotherapy with or without rituximab'' is considered a relevant comparator in this appraisal. If the Committee does consider this comparator to be relevant for zanubrutinib in this appraisal, the Company requests that the following language "Chemotherapy with or without rituximab" is rephrased to "Rituximab with or without chemotherapy" to reflect the wording of the background information section within 'Appendix B – Draft scope ID6392'	

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		which lists a numbers of rituximab-based chemotherapies used to treat R/R MCL. This aligns with BSH guidelines that reference rituximab-based therapies as options to treat R/R MCL,[11] reflecting that rituximab is the backbone of these treatment options, rather than chemotherapy alone. **Allogeneic haemopoietic stem cell transplant (AlloSCT)** AlloSCT is not considered a relevant comparator to zanubrutinib, and hence should **be removed from the final scope**, for the following reasons: • Real-world evidence collected from a cohort of patients in the HMRN with R/R MCL (N=140) indicated that 2% of patients (n=3; one allograft and two autologous) received treatment with a stem cell transplant between 2004 and 2017, demonstrating that such interventions are not SoC in the UK.[10] • The BSH guidelines clearly recommend alloSCT for only *"fit patients with an appropriate donor following failure with immunochemotherapy, covalent BTKi* [such as zanubrutinib] *and CAR-T failure"*.[11] Furthermore, the guidelines go on to say: *"The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT",* aligning to the observations from the HMRN cohort. [11] Based on the BSH guidelines R/R MCL patients would only be eligible for an alloSCT after relapsing following a minimum of three lines of treatment, including a BTKi therapy. Therefore, alloSCT is considered a subsequent intervention, not a comparator intervention, to zanubrutinib, and only in a very small minority of patients.	
	Royal College of Pathologists	As above. All relevant current 3L options are listed	Thank you for your comment.

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Outcomes	BeiGene	All outcomes listed are appropriate.	Thank you for your comment.
	Royal College of Pathologists	Yes	Thank you for your comment.
Equality	BeiGene	The Company does not foresee any significant equality considerations associated with this appraisal.	Thank you for your comment.
	Royal College of Pathologists	No specific comments	Thank you for your comment.
Questions for consultation	BeiGene	***Where do you consider zanubrutinib will fit into the existing care pathway for mantle cell lymphoma?*** As documented in response to the comparators included in the draft scope, zanubrutinib is anticipated to offer an additional treatment option for R/R MCL, in line with the anticipated licensed indication. ***Please select from the following, will zanubrutinib be:*** *A. Prescribed in primary care with routine follow-up in primary care* *B. Prescribed in secondary care with routine follow-up in primary care* ***C. Prescribed in secondary care with routine follow-up in secondary care*** *D. Other (please give details):* ***For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.*** It is anticipated that the setting for prescribing and routine follow-up for zanubrutinib will not differ from relevant comparator treatments.	Thank you for your comments.

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		Do you consider that the use of zanubrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The QALY calculation is expected to capture all substantial health-related benefits of zanubrutinib. However, it is important to note that as zanubrutinib is an oral medicine that can be administrated within the home setting, this may 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. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The nature of the data behind the benefits of zanubrutinib will be available from two pivotal clinical trials for zanubrutinib (206 and AU-003),[4,5] a clinical and economic SLR, an indirect treatment comparison (ITC) in the absence of head-to-head trial data versus the treatment alternatives, and cost-effectiveness and budget impact analyses developed in MS Excel. ***NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims.*** N/A ***Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*** N/A	

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Additional comments on the draft scope	BeiGene	Any additional comments on the draft scope The Company consider that NICE's cost-comparison methodology may be appropriate for the comparison with ibrutinib for the following reasons: • Zanubrutinib, a second generation BTKi, is anticipated to offer an alternative treatment option to first-generation BTKi inhibitor, ibrutinib. The anticipated licensed indication for zanubrutinib aligns closely with the licensed indication for ibrutinib. • Supported by clinical trials which have evaluated the effectiveness of zanubrutinib compared to ibrutinib in similar blood cancers, it is anticipated that zanubrutinib will be at least as effective with no additional safety concerns compared to ibrutinib in R/R MCL.[17,18] With the existing Patient Access Scheme (PAS), zanubrutinib is anticipated to be cost saving versus ibrutinib, within the cost-comparison framework. The economic benefit of zanubrutinib versus ibrutinib has been confirmed by NICE in a recent and relevant blood cancer appraisal, where NICE stated that zanubrutinib was the most cost-effective BTKi within the treatment class.[19]	Thank you for your comment. Even if a topic is scoped as an STA, it will still possible for a company to make the case for cost comparison analysis within its submission, for consideration by committee.
	Royal College of Pathologists	I am really supportive of this appraisal. Zanubrutinib is a highly active BTKi. It is know to be a safer BTKi than ibrutinib and likely to be at least as effective in MCL (where there is no direct comparative randomised data). Its use would be rapidly widespread were it approved.	Thank you for your comment. NICE has scheduled this topic into its work programme. For more information, please see: https://www.nice.org.uk/guidance/indevelopment/gid-ta11485

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

Lymphoma Action