National Institute for Health and Care Excellence

Health Technology Evaluation

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]
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	Royal College of Pathologists	Yes a STA seems a reasonable approach to evaluating this.	Thank you for your comment.
	AstraZeneca	AstraZeneca agrees with the evaluation route proposed (single technology appraisal) for acalabrutinib in combination with bendamustine and rituximab (ABR).	Thank you for your comment.
Wording	Royal College of Pathologists	High dose cytarabine containing regimens will generally be offered to younger patients, this technology (ABR) will be offered to older, non transplant eligible patients.	Thank you for your comment. No change to scope required.
	AstraZeneca	AstraZeneca agrees with the wording of the draft remit proposed.	Thank you for your comment.
Timing issues	Royal College of Pathologists	This represents a potential new standard of care for MCL, an incurable lymphoma and should be considered in a timely manner.	Thank you for your comment.

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	AstraZeneca	There remains an urgent need for a more targeted therapy with improved outcomes for patients with previously untreated mantle cell lymphoma (MCL), a rare type of B cell non-Hodgkin lymphoma (NHL). MCL has long proven a challenging entity to treat, and disproportionally impacts the elderly with a median age of diagnosis at 74 in the UK (1, 2). Despite many advances in the field of lymphoma, MCL remains largely incurable and associated with poor outcomes. There are around 590 new cases of MCL diagnosed in the UK each year (3). Currently, there are limited targeted therapies available in the UK for patients with untreated MCL, and the 5-year survival rate is estimated at 47% (4). The standard of care therapy for previously untreated patients with MCL is rituximab-based chemoimmunotherapy (CIT) followed by rituximab maintenance (5-7), providing a median profession-free survival (PFS) of 3 to 5 years. Targeted agents such as Bruton tyrosine kinase inhibitors (BTKi), which are mainstays of treatment in relapsed and refractory MCL (8-10), are establishing new, paradigm-changing roles in first-line treatment of MCL, and several studies have now incorporated BTKi into the first line (11-14). Improving the efficacy of first-line treatment, and specifically maximising the duration of first remission, remains of critical importance to obtain favourable long-term outcomes. The Phase 3 study for ABR, ECHO, was designed to explore the use of acalabrutinib (a BTKi) in patients with previously untreated MCL in combination with the standard of care (BR + rituximab maintenance, hereon referred to as BR for simplicity), with the aim of achieving significant long-term benefit while limiting toxicity, which is also an important goal in the elderly population. In the trial, ABR demonstrated a statistically significant and clinically meaningful improvement in PFS versus standard of care in previously untreated patients with MCL. The safety and tolerability of acalabrutinib was consistent with its known safety profile, and no new safety signals were identified (12). Acalabrutinib is the first BTKi to show a	Thank you for your comments. No change to scope required.

Section	Stakeholder	Comments [sic]	Action
		favourable trend in overall survival vs. standard-of-care CIT in this setting (12). The data from the ECHO trial demonstrates that ABR provides substantial benefits as frontline therapy in MCL. Given that acalabrutinib's oral administration offers patient convenience and aligns with the need for effective, less toxic treatments for patients with MCL, it is crucial to prioritise the evaluation of ABR to optimise long-term outcomes and prevent delays in access.	
Additional comments on the draft remit	Royal College of Pathologists	[None]	N/A
	AstraZeneca	[None]	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Royal College of Pathologists	The background information is accurate.	Thank you for your comment.
	AstraZeneca	The Background is accurate, however AstraZeneca proposes one minor amendment. At the beginning of page 2 and in the Comparators section, TA370 is listed as an option for first-line treatment of MCL, and it is stated that “bortezomib” is recommended as an option for previously untreated MCL in adults for whom haematopoietic stem cell transplantation is unsuitable. To avoid confusion, this should be corrected to reflect the accurate treatment regimen which includes “bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP)”. Bortezomib	Thank you for your comments. The wording has been updated to be clear that bortezomib is used in combination with rituximab, cyclophosphamide,

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		monotherapy is not recommended for untreated MCL (15). Although VR-CAP is recommended by NICE, UK clinical experts experienced in managing patients with first-line MCL highlighted that VR-CAP is not considered a treatment option for first-line MCL in the UK due to increased toxicity and need for frequent monitoring. Relevant comparators for ECHO are explained further in the Comparators response below.	doxorubicin and, prednisone (VR-CAP).
Population	Royal College of Pathologists	Yes. I would expect this to be offered largely to the >65 non-transplant eligible population.	Thank you for your comment. No change to scope required.
	AstraZeneca	AstraZeneca agrees that the population is defined appropriately, but for clarity would like to highlight that until now, first-line MCL treatment has required dichotomising patients based on ASCT eligibility, which is based on a range of factors including patient choice, the timing of relapse, age, previous treatment and general health and fitness (16). Patients deemed transplant-eligible typically receive CIT, consolidative ASCT in first remission, and rituximab maintenance. For the older, less fit population who are not fit for dose-intensified regimens, patients receive either BR or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line standard of care in MCL (17-19). The most used CIT, BR, is the standard of care in the UK. The population is currently defined as adults with previously untreated MCL. However, the evidence base for the Phase 3 ECHO trial focuses on patients with untreated MCL who are likely considered unsuitable candidates for ASCT.	Thank you for your comment. No change to scope required.
Subgroups	Royal College of Pathologists	At the current time, no. Subgroup analysis of this study is likely to be presented at scientific meetings in the future (Like Dec 2024).	Thank you for your comment.

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	AstraZeneca	No subgroups are expected to be relevant for separate consideration in this submission.	Thank you for your comment.
Comparators	Royal College of Pathologists	Yes. This will largely be offered to patients who are non transplant eligible so it is debatable whether high dose cytarabine regimens +- autoSCT are valid comparators, but there will be some overlap between what is considered transplant eligible vs non-eligible.	Thank you for your comment. The list of potential comparators is inclusive of all that may be considered. No change to scope required.
	AstraZeneca	The comparators currently listed in the draft scope (i.e., chemotherapy in combination with rituximab, including BR; cytarabine-based immunochemotherapy (R-BAC); radiotherapy; and bortezomib (VR-CAP)) encompass treatments available for adults with previously untreated MCL irrespective of eligibility for ASCT. As stated above in response to the Population section, the population eligible for ABR are unsuitable for ASCT, therefore, the comparators should focus on this specific patient population. To understand the standard treatments currently used in the NHS for this population and to identify appropriate comparators for ABR, AstraZeneca conducted one-on-one interviews with several haematology-oncology consultants in the UK who treat MCL. All clinicians independently agreed that the treatments used in the UK for patients with untreated MCL who are considered unsuitable candidates for ASCT are BR and R-CHOP, with BR considered as the standard of care. Although VR-CAP is recommended in the guidelines for patients with first-line MCL who are unsuitable for ASCT, all clinicians stated that this therapy is no longer used in the UK due to increased toxicity and need for frequent monitoring. Similarly with R-BAC, this regimen is associated with significant infective and haematological toxicity and is	Thank you for your comments. The list of potential comparators is inclusive of all that may be considered. No change to scope required.

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		therefore not frequently used. Finally, radiotherapy is reserved for patients with early-stage MCL and therefore falls outside the remit of the ECHO population which includes patients with advanced disease who are unsuitable for ASCT. The insights gathered from the UK clinicians on the appropriate comparators align with the British Society for Haematology (BSH) guidelines for treating first-line MCL patients unsuitable for transplant, which describe the increased toxicity of both R-BAC and VR-CAP and the use of radiotherapy in patients with early-stage MCL (19-21).	
Outcomes	Royal College of Pathologists	Yes	Thank you for your comment.
	AstraZeneca	AstraZeneca confirms that all the outcomes listed are appropriate and will capture the most important health-related benefits (and harms) of the technology.	Thank you for your comment.
Equality	Royal College of Pathologists	No equality issues relating to this technology	Thank you for your comment.
	AstraZeneca	No equality issues were identified.	Thank you for your comment.
Other considerations	Royal College of Pathologists	[None]	N/A
	AstraZeneca	[None]	N/A

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Questions for consultation	Royal College of Pathologists	[None]	N/A
	AstraZeneca	*Where do you consider acalabrutinib with bendamustine and rituximab will fit into the existing care pathway for untreated mantle cell lymphoma?* As stated in the Comparators section above, ABR is anticipated to displace treatments currently used in first-line MCL for patients unsuitable for ASCT. *Would people treated with acalabrutinib with bendamustine and rituximab potentially be suitable for stem cell transplantation?* As stated in the Population section above, the population eligible for ABR with untreated MCL is more closely aligned with the group of patients who are considered unsuitable candidates for ASCT. *Please select from the following, will acalabrutinib with bendamustine and rituximab 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):* ABR will be prescribed in secondary care with routine follow-up in secondary care (C).	Thank you for your comments. No change to scope required. Thank you for your comments. No change to scope required. Thank you for your comments. No change to scope required.

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		For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. As acalabrutinib is an oral therapy in combination with the existing treatment option, BR, the setting for prescribing and routine follow-up is unlikely to significantly differ for ABR in comparison to the comparators and subsequent treatments. *Would acalabrutinib with bendamustine and rituximab be a candidate for managed access?* AstraZeneca anticipates that routine commissioning is appropriate for ABR based on the strength of the available evidence from the pivotal Phase 3 ECHO study. *Do you consider that the use of acalabrutinib with bendamustine and rituximab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* Being able to delay or prevent the progression of disease allows patients to continue with their normal daily activities for longer, and therefore this may have a wider benefit to patients' productivity and the quality of life of informal caregivers that is not captured in the QALY calculation. Additionally, acalabrutinib's oral administration offers patient convenience compared to other treatment options, which may result in benefits that are not captured.	Thank you for your comments. No change to scope required. Thank you for your comments. No change to scope required. Thank you for your comments. No change to scope required.

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Additional comments on the draft scope	Royal College of Pathologists	[None]	N/A
	AstraZeneca	[None] **References:** 1. Patmore RS, Alexandra Gwen ; Appleton, Simon et al. Mantle Cell Lymphoma Management and Outcome in the U.K's Population-Based Haematological Malignancy Research Network. Blood. 2016;128(22). 2. Jain P WM. Mantle cell lymphoma in 2022-A comprehensive update on molecular pathogenesis, risk stratification, clinical approach, and current and novel treatments. American Journal of Hematology. 2022;97(5):638-56. 3. Haematological Malignancy Research Network (HMRN). Statistics: UK incidence. [Available from: https://hmrn.org/statistics/incidence/uk. 4. Haematological Malignancy Research Network (HMRN). Statistics: Survival. [Available from: https://hmrn.org/statistics/survival. 5. Flinn IW vdJR, Kahl B, Wood P, Hawkins T, MacDonald D, et al. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-	N/A

		CVP: results of the BRIGHT 5--year follow-up study. J Clin Oncol. 2019;37(12):984-91. 6. Kluin-Nelemans HC HE, Hermine O, Walewski J, Trnery M, Geisler S, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520-31. 7. Visco C CA, Nassi L, Patti C, Ferrero S, Barbero D, et al. Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: A multicentre, phase 2 trial from Fondazione Italiana Linfomi. Lancet Haematol. 2017;4:e15-e23. 8. Wang M, Jurczak, W., Trněný, M., Belada, D., Wrobel, T., et al. . Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2024;142. 9. Wang M RS, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-67. 10. Song Y ZK, Zou D, Zhou J, Hu J, Yang H, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine KinaseZanubrutinib for relapsed/refractory MCL. Clin Cancer Res. 2020;26(16):4216-24. 11. Wang ML. Jurczak W JM, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med. 2022;386:2482-94. 12. AstraZeneca. Calquence combination regimen demonstrated statistically significant and clinically meaningful improvement in progression-free survival in 1st-line mantle cell lymphoma in ECHO Phase	

		III trial 2024 [Available from: https://www.astrazeneca.com/media-centre/press-releases/2024/calquence-combination-improved-pfs-in-1l-mcl.html. 13. Dreyling M, Tam, C. S., Wang, M., Smith, S. D., Ladetto, M., Huang, H., … Gouill, S. L. . A Phase III Study of Zanubrutinib Plus Rituximab Versus Bendamustine Plus Rituximab in Transplant-Ineligible, Untreated Mantle Cell Lymphoma. Future Oncology. 2020;17(3):255-62. 14. A Randomized, Open-label, Multi-center, Phase III Study of Orelabrutinib in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) vs. R-CHOP Alone in Patients With Treatment-naïve Mantle Cell Lymphoma: ClinicalTrials.Gov; [Available from: https://clinicaltrials.gov/study/NCT05051891. 15. NICE. Bortezomib for previously untreated mantle cell lymphoma 2015 [Available from: https://www.nice.org.uk/guidance/ta370/resources/bortezomib-for-previously-untreated-mantle-cell-lymphoma-pdf-82602782522053. 16. UK M. High-dose therapy and autologous stem cell transplantation. 2007. 17. Flinn IW vdJR, Kahl BS, Wood P, Hawkins TE, Macdonald D, et al Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944-52. 18. Rummel MJ NN, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell	

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		lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-10. 19. Eyre TA BM, McCulloch R, O'Reilly M, Sanderson R, Menon G, et al. Diagnosis and management of mantle cell lymphoma: A BritishSociety for Haematology Guideline. British Journal of Haematology. 2024;204(1):108-26. 20. Robak T HH, Jin J, Zhu J, Liu T, Samoilova O, et al. . Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015;372(10):944–53. 21. Tisi MC NL, Patti C, Spina M, Ferrero S, Tani M, et al. Rituximab plus bendamustine and cytarabine (R-BAC) in elderlypatients with newly diagnosed mantle cell lymphoma: long termfollow-up and Mrd results of a phase 2 study from the FondazioneItaliana Linfomi. Blood. 2021;138(Supp 1):384.	

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

Lymphoma Action