National Institute for Health and Care Excellence

Health Technology Evaluation

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable ID6596

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	Johnson & Johnson Innovative Medicine	The proposed evaluation route (i.e., STA) is appropriate.	No action required
Wording	Johnson & Johnson Innovative Medicine	The wording is appropriate	No action required
Additional comments on the draft remit	Johnson & Johnson Innovative Medicine	We do consider the appraisal as urgent given the following: • MCL is a rare, incurable, high-grade and aggressive subtype of non-Hodkin's lymphoma (NHL) with a complex aetiology that presents with an extensive range of symptoms • MCL is associated with a significant clinical, psychological and economic burden	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisals work programme.

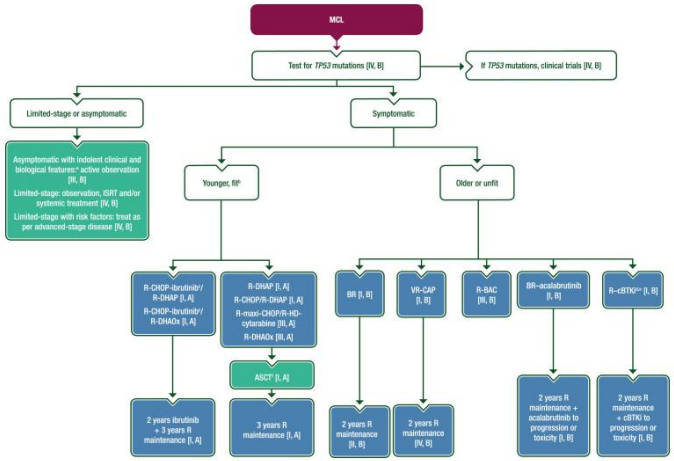
Section	Stakeholder	Comments [sic]	Action
		• MCL is an incurable disease with rapid progression and the poorest prognosis of all types of NHL, highlighting the need for efficacious first-line treatments • The standard of care (SoC) for patients with previously untreated MCL who are fit enough to receive it is ASCT. ASCT is associated with substantial toxicity which exacerbates the existing disease burden to MCL patients. Furthermore, ASCT is associated with a substantial costs to the NHS • Ibrutinib with immunochemotherapy is a fixed-duration oral treatment regimen that offers efficacious outcomes and a tolerable safety profile for adult patients with previously untreated MCL • If recommended, ibrutinib will address the significant unmet need in untreated MCL patients by providing patients and their clinicians with an effective treatment option which can delay or prevent disease progression, and offer an improved safety profile compared to the highly toxic current SoC with the ASCT regimen. Furthermore, with a daily oral dosage, patients would be able to take their treatment at home, without the burden of frequent and lengthy hospital stays, allowing them to work, spend time with friends and maintain their way of life for longer, whilst also helping to free up valuable NHS resources.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Johnson & Johnson	No comments to add	No action required

Section	Consultee/ Commentator	Comments [sic]	Action
	Innovative Medicine		
Population	Johnson & Johnson Innovative Medicine	The license does, and HTA submission will, focus on a patient population who are transplant eligible. Transplant-eligible patients tend to be younger and fitter than their ineligible counterparts and as such are associated with better outcomes. Despite this, the majority of patients still experience disease relapse. After relapse, patients experience significantly worse outcomes with each subsequent line of therapy, with the greatest decline in prognosis occurring after the failure of 1L therapy. Therefore, the availability of effective first line treatment options that delay, and ultimately prevent progression of disease for patients with MCL are crucial. Choice of first-line treatment for patients with MCL in the UK is dependent on eligibility for ASCT, which is based on patient fitness. Assessment of a patients fitness is carried out by the medical team responsible for the patients treatment and is based on factors including age, weight, mobility, comorbidities, and cognitive health. In clinical practice, patients with MCL who are eligible for ASCT are generally <65 years old. There are no MCL-specific assessments to determine patient fitness, and therefore eligibility for treatment with ASCT. The BSH guidelines recommends options such as The Geriatric 8 screening tool, The Cumulative Illness Rating Scale for Geriatrics and the Geriatric Assessment in Haematology to assess patient frailty. However, there is no consensus on the best approach to determine ASCT-	Thank you for your comment. ‘when a stem cell transplant is suitable’ has been added to the description of the population in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		eligibility. Due to the lack of prospective data, formal consensus or guidelines for eligibility criteria for ASCT, this process varies across NHS trusts. This submission will focus on patients who are eligible for ASCT and as such the relevant treatment pathway is that for ASCT-eligible patients only. Current SoC for patients eligible for ASCT is rituximab-based immunochemotherapy induction treatment followed by HDT conditioning and ASCT consolidation, followed by rituximab maintenance therapy, hereafter referred to as the ASCT regimen.	
Subgroups	Johnson & Johnson Innovative Medicine	Subgroup analyses were performed on the primary endpoint (FFS), including clinically relevant subgroups based on baseline clinical disease characteristics, cytology of MCL, p53 expression and receipt of rituximab maintenance.	Thank you for your comment. These subgroups have been added to the scope.
Comparators	Johnson & Johnson Innovative Medicine	*Which induction regimens are used most commonly for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable?* • Notably, acalabrutinib containing regimens would not be appropriate comparators. ASCT is the only comparator of relevance to this appraisal. Please see information listed under 'population' above for the justification. If recommended by NICE it is anticipated that Acalabrutinib with bendamustine and rituximab (subject to NICE evaluation) will only be used for patients who are ineligible to receive ASCT, consistent with the most recent ESMO and BSH guidelines (Figure 1). The distinction is consistent with comments made by the manufacturer during the scoping exercise for ID6155 clarifying that acalabrutinib with bendamustine and rituximab is intended for patients who are ineligible for ASCT.	Thank you for your comment. Acalabrutinib with bendamustine and rituximab has been left in the scope in line with the population included in the scope for the evaluation ID6155.

Section	Consultee/ Commentator	Comments [sic]	Action
		 Figure 1. First-line management of MCL, ESMO guidelines	
Outcomes	Johnson & Johnson Innovative Medicine	The outcomes are appropriate	No action required
Equality	Johnson & Johnson Innovative Medicine	We do not have equality issues to highlight at this stage.	No action required

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Johnson & Johnson Innovative Medicine	*Please select from the following, will ibrutinib with R-CHOP 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.* Option C *Would ibrutinib with R-CHOP be a candidate for managed access?* No *Do you consider that the use of ibrutinib with R-CHOP 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.* It is anticipated that the Economic model may not capture disutility associated with the ASCT procedure, as appropriate utility values for the time horizon of impact are not available.	Thank you for your comment. The committee will consider the health-related quality of life relating to the intervention and comparator(s) throughout the course of the evaluation. See figure 4.1 in NICE health technology evaluations: the manual for a hierarchy of preferred health-related quality-of-life methods.

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		ASCT imparts a substantial clinical burden and negatively affects patient QoL. This toxic and complex treatment involves conditioning with high-dose therapy (HDT), which causes side effects such as sore mouth, nausea, vomiting, diarrhoea, constipation, anaemia and thrombocytopenia. Another significant concern is the risk of severe infection due to immunosuppression, which can result in serious complications or death. Nearly half (46%) of patients will experience at least one side effect following ASCT, including infections, GI, neuropsychiatric, pulmonary and hepatic complications. These AEs significantly impact patients' QoL causing considerable physical, emotional and psychological burden with the risk of serious infections that may result in death further exacerbating patient anxiety surrounding treatment. Beyond the high rates of severe side effects, patients undergoing ASCT must also endure the complex treatment procedure. ASCT can involve hospitalisation for up to a month, followed by intensive post-treatment monitoring, including weekly follow-ups and blood tranfusions. During this period, it is common for patients to see an increase in symptoms, such as fatigue and nearly half of patients (47%) experience treatment-related pain. It can take patients up to six months to recover and return to normal day to day life (such as work). This lengthy recovery results in a significant and long-lasting HRQoL impairment, as patients must physically and psychologically recover from the treatment. A 2024 long-term QoL study in the US on patients with MCL following treatment with ASCT sought to understand the patient experience following treatment, specifically with regards to functional and work status. The study	

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		looked at annual survey data from 106 patients with MCL who received treatment with ASCT between 2000 and 2023. The median age of patients at ASCT was 59 and the median age at survey response was 68 years (median follow-up from treatment with ASCT regimen was 9.3 years). Amongst 106 patients who completed at least one survey, 18% and 16% patients reported poorer physical and cognitive function, respectively, compared with the general population. These patients were also significantly less likely to be in work. Furthermore, 5–12% had more symptoms of anxiety, depression, fatigue, sleep disturbance, and pain. These long-term QoL study results demonstrate that the detriment to QoL following treatment with ASCT is persistent and long lasting. Finally, lymphoma patients treated with ASCT describe the experience as being “in and out of hospital constantly” and that this “added so much disruption to [their] family’s lives”. Another patient described the experience as the “lowest point of [their] life”, noting that it took them “two to five months to feel [they] were recovering”. These individual statements clearly demonstrate the significant additional burden existing first-line treatment has on patients’ lives, over and above the clinical burden of the disease. As we develop the submission we will continue to search for information on disutility over the full time-horizon of its impact, however, we anticipate that this may be unavailable.	

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

Lymphoma Action