NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when a stem cell transplant is suitable [ID6596]

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ibrutinib with R-CHOP in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ibrutinib with R-CHOP in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 21 July 2026
- Second evaluation committee meeting: 4 August 2026
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), alternating with rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) or rituximab, dexamethasone, cytarabine and oxaliplatin (R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy, should not be used for untreated mantle cell lymphoma in adults when an autologous stem cell transplant (ASCT) is suitable.

1.2 This recommendation is not intended to affect treatment with ibrutinib with R-CHOP that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, ibrutinib with R-CHOP would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because more evidence is needed to understand whether ibrutinib with R-CHOP is value for money in this population.

Why the committee made these recommendations

Usual treatment for untreated mantle cell lymphoma depends on whether an autologous (using the person's own cells) stem cell transplant is suitable. If it is, people usually have chemotherapy, followed by an ASCT, and then maintenance treatment. Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, then ibrutinib only, would be an alternative to an ASCT in this population.

Evidence from a clinical trial suggests that ibrutinib with R-CHOP increases how long people have before their condition gets worse and how long people live compared with usual treatment. But by how long is uncertain because the trial is still ongoing.

There are uncertainties in the economic model. This is because of how it modelled:

- the short-term risks and long-term benefits of usual treatment,
- the benefits of ibrutinib with R-CHOP, and
- the cost of usual treatment.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for ibrutinib with R-CHOP. So, ibrutinib with R-CHOP should not be used.

2 Information about ibrutinib

Marketing authorisation indication

2.1 Ibrutinib (IMBRUVICA, Johnson & Johnson Innovative Medicine) in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) alternating with rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP; or rituximab, dexamethasone, cytarabine and oxaliplatin [R-DHAOx]) without ibrutinib, followed by ibrutinib monotherapy, is indicated 'for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ibrutinib.

Price

2.3 The list price of ibrutinib is £5,723.20 per 28-pack of 560-mg tablets (excluding VAT, BNF online, accessed June 2026).

2.4 The company has a commercial arrangement, which would have applied if ibrutinib with R-CHOP had been recommended.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Johnson & Johnson Innovative Medicine will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson Innovative Medicine, 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.

The condition

Details of the condition and unmet need

3.1 Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma characterised by malignant B-cell growth in the mantle zone of lymph nodes. MCL is considered incurable with current treatment options and is typically a relapsing–remitting condition. Most people are diagnosed with MCL at advanced stages and survival outcomes are poor. The patient expert described the shock and distress of being diagnosed with an incurable condition. They noted that people diagnosed with MCL have anxiety, insomnia and a constant fear of dying. They explained that the treatment approach is individualised and focuses on achieving remission for as long as possible. The patient expert described the importance of the first period of remission for long-term survival and quality of life, so having the best first-line treatment is essential. They highlighted that usual first-line treatment, which is intensive chemotherapy and autologous stem cell transplant (ASCT), can be difficult to tolerate. It also comes with many short- and long-term risks. They explained that concern about tolerability and side effects means that not everyone who is eligible for ASCT will

choose to have it. The committee concluded that there is an unmet need for better-tolerated effective treatments for this condition.

Clinical management

3.2 The clinical experts explained that the aim of treatment for MCL is to induce remission for as long as possible, prolong survival, and minimise treatment-related toxicity. The treatment pathway depends on whether a person is eligible for ASCT. In the NHS, ASCT eligibility usually includes people who are 65 years old or younger who do not have comorbidities that would prevent intensive treatment. The experts explained that eligibility is based on clinical assessments and clinician judgement around fitness. The clinical experts noted that the treatment pathway for people with MCL who are eligible for ASCT is well-defined and follows guidelines from the British Society for Haematology. First-line treatment is split into 3 distinct phases. In the induction phase, treatment usually includes rituximab-based immunochemotherapy containing high-dose cytarabine. The clinical experts noted that the most common is the 'NORDIC' regimen (also known as R-Maxi-CHOP), or a variation of it, which is used in around 80% of NHS trusts. This includes a high-dose regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone alternating with rituximab plus high-dose cytarabine. Some people instead have rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). This is followed by rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin (R-DHAOx). The clinical experts noted that there was no clear evidence showing which of the NORDIC regimen or R-CHOP alternating with R-DHAP or R-DHAOx regimen was better. The aim of the induction phase is to reduce the number of cancerous cells and improve the likelihood of successful transplant. Then, in the consolidation phase, stem cells are mobilised and collected from the blood. High-dose therapy is used to kill any remaining cancer cells. In the NHS, this is usually done with a regimen of carmustine, etoposide, cytarabine, and melphalan (BEAM), administered

in hospital over several days. The stem cells are then reinfused and return to the bone marrow where they begin producing healthy blood cells. Finally, in the maintenance phase, people have 2 to 3 years of treatment with rituximab with the aim of prolonging remission.

Second-line treatment in the NHS is usually zanubrutinib or ibrutinib. The NHS England Cancer Drugs Fund clinical lead noted that since zanubrutinib was recommended in NICE's technology appraisal guidance on zanubrutinib for treating relapsed or refractory mantle cell lymphoma, there has been a considerable increase in second-line zanubrutinib use and a decrease in ibrutinib use. Third-line options may include alternative chemotherapy regimens. Brexucabtagene autoleucel is currently available through the Cancer Drugs Fund as a third-line option for people who are eligible for chimeric antigen receptor T-cell (CAR-T) therapies.

The company positioned ibrutinib as an alternative to ASCT in the first-line treatment setting. With ibrutinib, people have induction treatment with ibrutinib and rituximab-based immunochemotherapy, followed by ibrutinib maintenance, with or without rituximab, for 2 years. The clinical experts thought that ibrutinib would allow people to avoid the toxicity associated with ASCT without a loss of efficacy, and so could represent a step-change in treatment. The committee noted that the indication wording for ibrutinib specified that people would otherwise be eligible for ASCT. The committee noted that, if ibrutinib were to become available, ASCT would be largely displaced from the treatment pathway. So, it questioned whether the NHS would continue to routinely assess eligibility for ASCT. The clinical experts explained that there is no universal definition used in the NHS for ASCT eligibility. But they added that people who have ASCT are usually 65 or younger and have multiple investigations to determine their eligibility before starting treatment. They also noted the availability of ibrutinib, and the perception that it is a lower-toxicity treatment. They agreed that this could lead to a widening of the patient population to include people who previously could have had ASCT but might have

chosen not to because of toxicities. But, the clinical experts thought that the NHS patient population would be constrained by the toxicity of the chemotherapy given with ibrutinib, and so said that they would be unlikely to consider a substantially broader population. The committee noted that it can only appraise ibrutinib within its marketing authorisation, so only those who would be considered eligible for ASCT would be able to have treatment if it were recommended in the NHS. The clinical experts did not believe that the relative efficacy or safety of ibrutinib would be significantly different in people who may be eligible for ASCT, but who choose not to have it. The committee thought that how the eligible population in the NHS is defined might change because of the change to the treatment pathway. So it wanted to consider how this would be reflected in any recommendation. It thought that the impact of this was unknown but that it would increase the decision risk associated with this evaluation. The committee asked for more information from stakeholders on how its guidance for ibrutinib could be worded to account for future changes to the treatment pathway. In particular, the committee would be interested to understand how eligibility for ibrutinib would be determined if healthcare professionals no longer routinely assessed people for ASCT eligibility.

Clinical effectiveness

TRIANGLE study

3.3 The main clinical evidence came from TRIANGLE, an open-label, phase 3, randomised controlled trial in people with previously untreated stage 2 to 4 MCL who were eligible for ASCT. It was an investigator-initiated trial done across 165 sites in 13 European countries, but none were in the UK. The trial compared the following:

- ibrutinib plus R-CHOP alternating with R-DHAP or R-DHAOx without ibrutinib, followed by ibrutinib maintenance with optional rituximab, and
- standard care, which was rituximab-based induction followed by high-dose therapy and ASCT consolidation, with optional rituximab

maintenance.

TRIANGLE also contained a third treatment arm that combined ibrutinib with ASCT. This third arm showed no extra benefit of adding ibrutinib to ASCT and was not considered further. The primary outcome was failure-free survival. This was defined as time from randomisation to stable disease at the end of induction treatment, progressive disease or death from any cause. Failure-free survival is an extension of progression-free survival because it adds a response element – cancer that did not have a complete or partial response at the end of induction treatment was counted as a treatment failure, even if it was stable. Health-related quality of life was not collected in TRIANGLE. Median failure-free survival, progression-free survival and overall survival were not reached in either arm. Ibrutinib statistically significantly improved failure-free survival compared with ASCT (hazard ratio 0.64, 95% confidence interval [CI] 0.43 to 0.95, p=0.0068) and statistically significantly improved progression-free survival (hazard ratio 0.63, 95% CI 0.42 to 0.95, p=0.0060) and overall survival (hazard ratio 0.52, 95% CI 0.34 to 0.80, p=0.0023). The company noted that absolute number of adverse events was similar between treatment arms, but that the duration of treatment exposure was significantly longer in the ibrutinib arm. The committee concluded that TRIANGLE provided evidence that ibrutinib extended failure-free, progression-free, and overall survival compared to ASCT, but that the survival data remained immature.

Rituximab maintenance

3.4 The company highlighted that, when TRIANGLE was designed, rituximab maintenance was not part of routine clinical practice and so was not mandated in the trial protocol. So, around 60% of people in each arm of TRIANGLE had rituximab maintenance. The company noted that current treatment guidelines now recommend rituximab maintenance. Based on clinical advice, it estimated that around 85% of people in the NHS would have it. Some people would be unable to have maintenance treatment

because of infections or difficulties travelling for treatment. The clinical experts at the meeting agreed that the vast majority would have rituximab maintenance in NHS practice. The company used an inverse probability of censoring weights analysis to adjust the TRIANGLE results to reflect 85% rituximab maintenance use. It noted that the adjusted hazard ratios were similar to the unadjusted results. The EAG thought that there was uncertainty about the proportion of people who would have rituximab maintenance in NHS practice. So, it requested a scenario in which 100% of people had rituximab maintenance. It also questioned whether the inverse probability of censoring weights analysis was the most appropriate adjustment method and requested a scenario using 2-stage estimation. The EAG agreed with the company that the hazard ratios were similar across the unadjusted and adjusted analyses. This was irrespective of the proportion having rituximab maintenance or which analysis method was used. The committee considered that, in current NHS practice, nearly everyone who completes consolidation treatment would be offered rituximab maintenance. The committee noted that similar proportions of people in each arm of TRIANGLE had rituximab maintenance. It concluded that the similarity of the adjusted and unadjusted analyses suggested that increased rituximab maintenance use would not be expected to materially alter the relative treatment effect of ibrutinib compared with ASCT. So, the unadjusted values from TRIANGLE could be used in the economic model.

Other clinical evidence

3.5 The company used 4 additional sources of clinical evidence to inform the economic model (see section 3.6), which attempted to model each line of treatment separately. They were:

- RAY-3001, which was an open-label, phase 3 randomised controlled trial for people with relapsed or refractory MCL. It compared ibrutinib with temsirolimus, but the company only used data from the ibrutinib arm. Because the company had access to the trial individual-patient

data, it was able to use data from the subgroup of people who had had exactly 1 prior line of treatment (referred to as subgroup 1 from here). The company used RAY-3001 to inform transition probabilities for second- and third-line treatment, including progression and mortality, and utility values for the second-line and progressed-disease health states.

- MANTLE-FIRST, which was a retrospective cohort study in relapsed or refractory MCL that included people having ibrutinib, bendamustine plus rituximab, bendamustine plus rituximab plus cytarabine, or other regimens. MANTLE-FIRST was used to account for the relative effectiveness of subsequent treatments in the model.
- SHINE, which was a double-blind, phase 3 randomised controlled trial in people with untreated MCL that was not eligible for ASCT. It compared ibrutinib plus bendamustine and rituximab with placebo plus bendamustine and rituximab. The company used SHINE to inform utility values for the first-line failure-free health state. This was because health-related quality-of-life data was not collected in TRIANGLE and data from an ASCT-eligible population could not be identified.
- SPARK, which was a single-arm, phase 2 trial of ibrutinib in relapsed or refractory MCL. It was pooled with RAY-3001 to inform utility values for the second-line and progressed-disease health states.

The committee concluded that because most people in TRIANGLE remained alive and failure free, and because TRIANGLE did not collect health-related quality-of-life data, the company needed to use other sources of evidence in the model, but that this introduced additional uncertainty.

Economic model

Company's modelling approach

3.6 The company used a semi-Markov model with 4 health states: failure-free first-line treatment, progression-free second-line treatment, progressed

disease and death. The model used a lifetime 43-year time horizon. People entered the model in the failure-free first-line health state, where they could be on or off treatment, and remained there until treatment failure or death. Treatment failure was defined as stable disease at the end of induction, or disease progression. Those whose treatment failed moved to the progression-free second-line state, where they started active second-line treatment and remained until disease progression or death. People whose disease progressed after second-line treatment moved to the progressed-disease state, where some were assumed to have third-line treatment and all remained until death. The committee concluded that the company's approach was appropriate for this evaluation, particularly with the explicit modelling of second- and third-line treatments.

First-line transitions

Pre-failure mortality

3.7 The company modelled the transition from the failure-free first-line state to the death state using pre-failure mortality data from TRIANGLE. It applied a constant per-cycle probability of death, with a higher probability of death for people in the ASCT arm than the ibrutinib arm. The company explained that it preferred this constant per-cycle approach because there were few pre-failure mortality events in TRIANGLE (11 in the ibrutinib arm and 22 in the ASCT arm), so usual parametric extrapolation was not suitable. It considered that applying a higher mortality risk with ASCT was clinically plausible because of the toxicity and risk associated with intensive treatment and transplant. The EAG thought that the TRIANGLE data provided inadequate evidence to support different pre-failure mortality rates between the arms, because the number of events was small. It also thought that applying a higher ASCT mortality risk constantly over the full model time horizon lacked face validity. This was because any excess mortality associated with ASCT would be expected to be greatest in the short term and then reduce over time. The EAG also noted that much of this excess mortality occurred in the model after the

TRIANGLE follow-up period. The EAG would have preferred the company to use parametric modelling or separate tunnel states to capture a short-term ASCT-related mortality risk, but the company did not provide these. So, in its base case the EAG assumed equal pre-failure mortality for both arms, using the per-cycle probability from the ibrutinib arm. The clinical experts explained that the main mortality risk of ASCT is in the immediate 6-to-12-month period after transplant. But, they also noted that there are more subtle long-term mortality risks, including those from depleted immunity or appearance of secondary cancers. These are difficult to separate from mortality risks in the general population and would likely not be captured in a clinical trial. The committee discussed the company's approach of using a constant higher risk of pre-failure mortality for ASCT, based on short-term data, over the entire time horizon of the model. It thought that this approach would likely overestimate the expected risk of excess mortality compared with ibrutinib. In contrast, the committee thought that the EAG's approach would likely underestimate the excess mortality of ASCT, particularly considering the increased risk in the early period after transplant. So, acknowledging the limited data, the committee asked the company to provide full parametric extrapolation of the pre-failure mortality data for both arms of TRIANGLE. In addition to fitting standard parametric curves, the company should consider flexible modelling for ASCT that would allow different hazard rates for the early and late periods after transplant. The committee asked for the company to provide evidence on the appropriate length of time after transplant that any excess mortality should apply.

Time-to-failure extrapolation

3.8 The company modelled the transition between the failure-free first-line health state and the progression-free second-line health state using time-to-failure data from TRIANGLE. In the time-to-failure data, people who died before treatment failure were censored to avoid double counting with the pre-failure mortality risk described in section 3.7. The company then reconstructed failure-free survival by combining the time-to-failure

extrapolation with the pre-failure mortality risk. It then used the clinical plausibility of these reconstructed failure-free survival landmark values to select the most appropriate extrapolation curves. In its base case, the company used an exponential curve for the ibrutinib arm and a gamma curve for the ASCT arm. The EAG thought that reconstructed failure-free survival was not suitable for validating the time-to-failure extrapolations because it incorporated the company's assumptions about differential pre-failure mortality. The EAG did not think this was adequately supported by the TRIANGLE data. It also noted that the clinical opinion used to validate the extrapolations was not obtained through structured expert elicitation. It presented a scenario using a log-normal curve for the ASCT arm. This scenario had the best statistical fit to the time-to-failure data and produced more optimistic long-term outcomes for ASCT, meaning ibrutinib was less cost-effective. But when combined with the EAG's base-case assumptions, this scenario led to long-term failure-free and overall-survival estimates that exceeded the clinical experts' upper plausible limits. So the committee considered the scenario to be implausible when applied to the EAG base case. The committee concluded that the company should provide an updated approach, with more information on time-to-failure extrapolation after implementation of the pre-failure-mortality scenarios requested in section 3.7. Specifically, the committee would like to see an assessment of:

- the implied failure-free- and overall-survival hazard ratios between the arms
- how the implied failure-free- and overall-survival hazard ratios vary over time
- how the survival landmarks differ under different assumptions, and
- whether the survival landmarks reflect clinical expectation.

It also requested that the time-to-failure extrapolations themselves should be validated by clinical experts.

Second-line transitions

Evidence used for second-line transitions

3.9 The company explained that most people in TRIANGLE remained alive and failure free, so TRIANGLE could not robustly inform later-line outcomes. Instead, the company used RAY-3001 to inform transitions from the progression-free second-line and progressed-disease health states. The company considered RAY-3001 to be the most suitable source because most people in the NHS have zanubrutinib or ibrutinib as second-line treatment. The company assumed equal efficacy between zanubrutinib and ibrutinib, so that the ibrutinib arm of RAY-3001 could be generalised to the NHS. The company also had access to the individual-patient data of RAY-3001 and were able to use subgroup 1 (see section 3.5), who more closely reflect the NHS population for this point in the pathway. The EAG noted that there was uncertainty about using RAY-3001 for both treatment arms. It noted that RAY-3001 did not include people who had received ibrutinib at first line. Clinical advice to the EAG suggested that efficacy of Bruton's tyrosine kinase (BTK) inhibitors (such as ibrutinib and zanubrutinib) would be lower in people with previous exposure. So, the EAG reasoned that use of the RAY-3001 data for the ibrutinib arm of the model may overestimate the effectiveness of zanubrutinib for people who had had ibrutinib. The clinical experts explained that the efficacy of second-line zanubrutinib after first-line ibrutinib would likely depend on when the relapse happened. The clinical experts said that they would be far less likely to give zanubrutinib to someone whose cancer had relapsed while on ibrutinib. This is because this may indicate that the cancer is resistant to BTK inhibition. Conversely, the clinical experts explained that they probably would try zanubrutinib for people whose cancer relapsed after the end of treatment with ibrutinib. They noted the relatively low relapse rates with ibrutinib in the first few years of treatment. They explained that this meant that most people who would have second-line treatment would be considered for zanubrutinib. But, the clinical experts also explained that it was difficult to know exactly

how BTK inhibitor re-exposure would alter efficacy given that these treatments have only recently become available. The EAG also noted that only a minority of people in RAY-3001 had ASCT as first-line treatment. So, by using RAY-3001 for the ASCT arm, the model would largely not capture any long-term benefits of ASCT. The committee considered that this issue was likely unresolvable with current evidence and clinical experience. So, it concluded that RAY-3001 could be used to model second- and third-line transitions but that it would account for the resulting uncertainty in its decision making.

Subsequent treatment distribution

3.10 The company modelled a second-line treatment distribution based on clinical advice. It assumed that after first-line ibrutinib, 58% would have zanubrutinib, 31% rituximab, bendamustine and cytarabine (R-BAC), 10% bendamustine and rituximab (BR), and 1% best supportive care. After first-line ASCT, the company assumed that most people would have a BTK inhibitor, with 85% having zanubrutinib and 10% having ibrutinib, and only small proportions would have chemotherapy or best supportive care. The EAG largely agreed with the company's assumptions for people who had ASCT first line. It also presented a scenario analysis with an alternative distribution for the ibrutinib group, based on advice from its clinical expert. In this scenario, people had chemotherapy second-line rather than a second BTK inhibitor. The committee recalled that people who had late relapse after the end of treatment with ibrutinib would likely have zanubrutinib (see section 3.9). It also recalled that the TRIANGLE evidence suggested that most people who have ibrutinib have late relapse. So, the committee requested a scenario in which everyone in the ibrutinib arm whose cancer relapses before the end of treatment has second-line treatment in line with the EAG's scenario distribution for ibrutinib (that is, mostly chemotherapy). Whereas, everyone whose cancer relapses after the end of treatment with ibrutinib has second-line treatment in line with the company's base-case distribution for ibrutinib (that is, mostly zanubrutinib). The committee requested a further scenario

where everyone whose cancer relapses after the end of treatment with ibrutinib has subsequent treatment in line with the company's base-case distribution for ASCT (that is, almost all zanubrutinib).

Subsequent treatments: relative efficacy adjustment

3.11 The company reasoned that the types of second-line treatment received would affect the risk of progression. So, in the model, the company used time-to-progression data for ibrutinib from RAY-3001 as the baseline risk. It then applied weighted hazard ratios to this to account for the differences in second-line treatment. These hazard ratios were derived from the assumed second-line treatment distribution (see section 3.10), and a relative efficacy estimate from MANTLE-FIRST (see section 3.5). The company assumed that zanubrutinib had equal efficacy to ibrutinib, and that BR, R-BAC and best supportive care all had the same progression hazard ratio compared with ibrutinib or zanubrutinib. Under the company's base-case assumptions, this resulted in a weighted second-line progression hazard ratio of 1.103 for people who had first-line ibrutinib and 1.012 for people who had first-line ASCT. So, people in the first-line ibrutinib arm were modelled to progress faster on second-line treatment because a higher proportion were assumed to have chemotherapy. The EAG considered that applying a single hazard ratio to BR, R-BAC and best supportive care was unlikely to be valid. The EAG explored scenarios using the hazard ratios as reported by the MANTLE-FIRST publication. This included assuming no difference between ibrutinib and R-BAC and a larger benefit for ibrutinib compared with BR or best supportive care. The committee noted that the time of relapse was a key factor in determining second-line treatment selection (see section 3.10). So, the committee asked the company to provide a scenario in which the second-line progression hazard ratios applied in the model reflected the updated second-line treatment distributions as requested in section 3.10. These hazard ratios should reflect the differences in treatment received depending on whether relapse occurs before or after the end of treatment with ibrutinib. The committee also noted that MANTLE-FIRST reported an

overall-survival benefit for ibrutinib compared with R-BAC. So, the committee also asked the company to provide a scenario in which the second-line treatment to death transition probability was also adjusted to account for the types of second-line treatment used.

ASCT costs

3.12 The company included costs for ASCT as 3 separate components: stem cell apheresis, high-dose therapy and the transplant procedure itself. For the apheresis cost, the company used an NHS reference cost that was based on inpatient admissions only. The clinical experts explained how most apheresis can be done as a day-case. So, the committee asked the company to update the model by using the NHS reference cost for day-case apheresis.

For the transplant procedure, the company used the cost estimate from NICE's non-Hodgkin lymphoma guideline, inflated to current prices (£42,041). It noted that the original source of this figure was a tariff cost. It also noted that NICE's guideline committee thought that an alternative NHS reference cost was a considerable underestimate. The company highlighted that a similar approach had been accepted in previous NICE appraisals. The EAG noted that there was limited information on which cost components were included in the guideline estimate. It thought this created a risk of double counting when separate apheresis and high-dose therapy costs were also applied. It also noted that the guideline estimate was around 10 years old. The EAG instead preferred to use the 2024/25 NHS reference cost for peripheral blood ASCT (£21,247), while accepting the need for separate costs for apheresis and high-dose therapy. NICE highlighted NHS England's 2026/27 payment scheme tariff (£35,274), which is an update of the tariff used in the guideline, as a further source for transplant cost. The clinical experts cautioned that the use of tariff costs or reference costs, which are averages of all types of ASCT done in the NHS, may underestimate the cost of ASCT for MCL. This is because BEAM ASCTs are most common for this condition. They are typically

more intensive, toxic, require longer inpatient stay, and have longer recovery times than other types of ASCT. The committee noted that there was uncertainty in the types of procedures and treatments included in the reference cost and the tariff cost. So, the committee asked stakeholders to provide additional information on this. The committee requested that the company add the costs of any investigations, procedures, or additional length of stay that are not included in the tariff or reference costs to the model. The committee also asked the company to consider a micro-costing approach to the ASCT cost, if a transparent breakdown of the procedures included in the tariff or reference cost could not be found.

Other cost issues: relative dose intensity and wastage

3.13 The company applied the relative dose intensity (RDI) from TRIANGLE for first-line ibrutinib (95.2%). But, because RDI was not collected for other treatments in TRIANGLE, it assumed 100% RDI for the drug components of ASCT and subsequent treatments. The company also included vial wastage for intravenous treatments, and after clarification provided a scenario that included pack wastage for ibrutinib. The EAG preferred to apply 100% RDI to all drug treatments, including ibrutinib, and to include both vial wastage and ibrutinib pack wastage in its base case. The committee lead team agreed that, in the absence of RDI for other treatments in the model, RDI should be applied consistently. The company suggested applying the RDI for ibrutinib to all treatments in the model. The committee concluded that this approach to RDI was appropriate if specific RDI values for all treatments in the model could not be identified. It also concluded that the pack wastage for ibrutinib should be included.

Utility values

3.14 TRIANGLE did not collect health-related quality-of-life data. So, the company had to use utility values from alternative sources. For the failure-free first-line health state, a utility value was estimated using Euroqol 5-dimensions (EQ-5D) data from the SHINE trial. The data was adjusted to

better reflect the TRIANGLE population, and the same value was applied to both treatment arms (the company considered the exact value to be confidential and so it cannot be reported here). Utility values for the progression-free second-line (0.78) and progressed-disease (0.68) health states were derived from pooled EQ-5D data from the ibrutinib arms of the RAY-3001 and SPARK studies. The company noted that these values had previously been accepted in other NICE appraisals. The model also applied a one-off disutility to account for adverse events, with a slightly larger quality-adjusted life year (QALY) decrement for ASCT (-0.0181) than for ibrutinib (-0.0138). The EAG generally considered the company's approach to be reasonable given the data limitations. The committee recalled comments from the patient and clinical experts about the intensity and toxicity of ASCT. The committee agreed that there would likely be a short-term utility benefit for ibrutinib that the model was not capturing. So, the committee asked the company to provide a scenario in which treatment-dependent utility values are applied in the failure-free first-line treatment health state. These utilities should apply for the early period during and after transplant (the company should provide evidence as to the appropriate length of time for this), then equalise with ibrutinib for the rest of the model time horizon for the failure-free first-line health state.

Severity

3.15 NICE's methods on conditions with a high degree of severity did not apply.

Other factors

Equality and health inequalities

3.16 The committee noted that although ASCT eligibility typically includes people aged 65 or younger, this is not an absolute limit in the NHS. Healthcare professionals also consider eligibility based on fitness and clinical assessment. The committee reflected on how changes to the treatment pathway would impact on the eligible population and requested

further information on this in response to consultation. No further equality or health inequality issues were raised by the company or other stakeholders.

Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of ibrutinib with R-CHOP. It noted comments from the clinical experts and the NHS England Cancer Drugs Fund clinical lead that ASCT is a high resource treatment that requires inpatient stay and long-term recovery. Given that ibrutinib would be expected to be significantly less resource intensive, the clinical experts thought that it could allow substantial system benefits by freeing-up hospital capacity. The committee agreed that this was plausible, but noted that it had asked for additional analyses on the costing of ASCT, including costs for additional investigations, procedures, and length of stay. So, the committee concluded that it would prefer to see the results of those analyses before stating whether there are any uncaptured benefits of ibrutinib.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.18 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that there were several uncertainties, including that:

- the NHS population for ibrutinib may potentially be broader than the population included in the clinical trial (see section 3.2)

- several model inputs were obtained from external sources with different patient populations due to limitations of the data from TRIANGLE (see section 3.4)
- second-line and progressed-disease transitions for both arms were modelled using RAY-3001, in which most people did not have ASCT (or ibrutinib) as a first-line treatment (see section 3.9).

The committee identified several other uncertainties in the modelling and requested more information and analyses from stakeholders to address these (see section 3.19).

But, the committee did recognise that the clinical evidence for ibrutinib was based on a large randomised controlled trial that included the most clinically relevant comparator. The committee also noted that the company had explicitly modelled second- and third-line treatments. Also, it thought that there may be uncaptured benefits associated with ibrutinib (see section 3.17). So, the committee concluded that an acceptable ICER would be around the middle of the range that that NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained). But, the committee noted it would reconsider this once further analyses have been provided.

Committee's requested information and analyses

3.19 To address the uncertainties, the committee requested additional information and analyses. From all stakeholders, it requested:

- Information on how the population in its recommendations for ibrutinib could be worded to account for future changes to the treatment pathway. In particular, how eligibility for ibrutinib would be determined if healthcare professionals no longer routinely assess people for ASCT eligibility (see section 3.2).
- Information on the types of investigations, procedures, and treatments included in the NHS tariff cost or reference cost for ASCT (see section 3.12).

From the company, it requested:

- Full parametric extrapolation of the pre-failure mortality data for both arms of TRIANGLE. In addition to standard curves, the company should also consider flexible modelling for the ASCT arm that would allow different hazard rates for the early and late periods after transplant. The company should provide evidence on the appropriate length of time after transplant that any excess mortality should apply (see section 3.7).
- An assessment of the implied failure-free and overall-survival hazard ratios between the arms and:
  - how these vary over time and under different assumptions,
  - how the survival landmark values differ under different assumptions, and
  - whether those landmark values reflect clinical expectation.

  It also asked that the time-to-failure extrapolations, as well as the failure-free survival extrapolations, should be validated by clinical experts (see section 3.8).
- A scenario in which:
  - everyone in the ibrutinib arm who relapses before the end of treatment (approximately 2.5 years) has second-line treatment in line with the EAG's subsequent treatment distribution scenario for ibrutinib (that is, mostly chemotherapy), and
  - everyone who relapses after the end of treatment with ibrutinib has subsequent treatment in line with the company's base-case distribution for ibrutinib (that is, mostly zanubrutinib).

  The company should provide another scenario in which everyone who relapse after the end of treatment with ibrutinib has subsequent treatment in line with the company's base-case distribution for ASCT (that is, almost all zanubrutinib; see section 3.10).

- Scenarios in which:
  - the second-line progression hazard ratios applied in the model reflect the updated treatment distributions
  - the progression-free second-line to death transition is adjusted by the types of treatment received (see section 3.11).
- Separate costs for any investigations or procedures that are not thought to be included in the NHS reference or tariff costs for ASCT. The company should consider a micro-costing approach to ASCT if information is limited on the types of investigations and procedures included in the reference and tariff costs. It should also update the apheresis cost to day-case (see section 3.12).
- A treatment specific RDI is applied for all treatments, where available, and in the absence of data it should use the ibrutinib RDI from TRIANGLE for all remaining treatments in the model (see section 3.13).
- That treatment-dependent utility values are provided for ASCT that apply in the early period during and after transplant, which capture the expected utility decrement associated with ASCT (see section 3.14).

Conclusion

3.20 The committee recalled the uncertainties with the clinical and economic evidence and the additional information it had requested from the company and other stakeholders. It noted that this meant it could not determine the most plausible ICER and therefore could not recommend ibrutinib with R-CHOP.

4 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. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a

conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas

Vice 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, a project manager, and an associate director or principal technical adviser.

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Technical lead

Michelle Green

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

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