NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using acalabrutinib with bendamustine and rituximab 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?

Issue date: February 2026

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using acalabrutinib with bendamustine and rituximab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 18 March 2026
- Second evaluation committee meeting: 08 April 2026
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Acalabrutinib plus bendamustine and rituximab should not be used for untreated mantle cell lymphoma in adults who are not eligible for an autologous stem cell transplant.

1.2 This recommendation is not intended to affect treatment with acalabrutinib plus bendamustine and rituximab 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

Acalabrutinib plus bendamustine and rituximab is not 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 there is not enough evidence to determine if acalabrutinib plus bendamustine and rituximab is value for money in this population.

Why the committee made these recommendations

Usual treatment for untreated mantle cell lymphoma in adults who cannot have an autologous stem cell transplant is bendamustine plus rituximab.

Clinical trial evidence shows that acalabrutinib plus bendamustine and rituximab increases how long people have before their condition gets worse compared with usual treatment.

There are uncertainties in the economic model. This is because of its structure and the assumptions used.

Because of the uncertainties in the economic model it is not possible to determine the most likely cost-effectiveness estimates for acalabrutinib plus bendamustine and rituximab.

So, acalabrutinib plus bendamustine and rituximab should not be used.

2 Information about acalabrutinib with bendamustine and rituximab

Marketing authorisation indication

2.1 Acalabrutinib (Calquence, AstraZeneca) plus bendamustine and rituximab is indicated for 'the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT)'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of acalabrutinib is £5,059.00 per 60-pack of 100-mg tablets (excluding VAT, BNF online, accessed February 2026).

2.4 The company has a commercial arrangement. This makes acalabrutinib**Error! Reference source not found.** available to the NHS with a discount and it would have also applied to this indication if acalabrutinib plus bendamustine and rituximab had been recommended. The size of the discount is commercial in confidence.

Sustainability

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

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, 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 condition and unmet need

3.1 Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma. It occurs more frequently in men than women and is more likely to occur at older ages. 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. Management of MCL can include offering an autologous stem cell transplant (ASCT), but this is only suitable for people who are fitter and healthier. Many people with MCL are not eligible to have an ASCT. The patient expert described the shock and distress of being diagnosed with an incurable condition, noting that people have anxiety, insomnia and a constant fear of dying. They explained that treatment approach is very individualised and focuses on achieving remission for as long as possible, allowing people to enjoy life. The patient expert also stated that many people have limited options for second-line treatments, so having the best first-line treatment is essential. They noted that the availability of more first-line treatment options would have a positive psychological impact on quality of life. The committee concluded that there is an unmet need in this treatment area.

Clinical management

Treatment pathway

3.2 First-line treatment for MCL for people who are ineligible for an ASCT include bendamustine plus rituximab (BR) or rituximab,

cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), followed by rituximab maintenance treatment. Rituximab, bendamustine and cytarabine (R-BAC) and bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisolone (VR-CAP) are also first-line treatment options, but are used for less than 3% of people with MCL.

Second-line treatment is zanubrutinib or ibrutinib. The NHS Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund lead) noted that since zanubrutinib was recommended in NICE's technology appraisal guidance on zanubrutinib for treating relapsed or refractory mantle cell lymphoma (TA1081), 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 acalabrutinib plus BR as a first-line treatment for MCL, followed by acalabrutinib plus rituximab maintenance. Having acalabrutinib plus BR at first line would change second-line treatment to R-CHOP because acalabrutinib, zanubrutinib and ibrutinib are all Bruton tyrosine kinase (BTK) inhibitors that work in a similar way; the clinical expert confirmed that re-treatment with another BTK inhibitor at second line after disease progression often led to poor clinical outcomes. Third-line treatment options would remain unchanged.

The clinical expert explained that results from the ENRICH study (Lewis et al., [2025]), which was published after the company submission, showed clear benefits of BR over R-CHOP. So R-CHOP is now rarely used as a first-line treatment for MCL. The committee concluded that BR followed by rituximab maintenance was the most appropriate comparator. This would be followed by second-line zanubrutinib.

Clinical effectiveness

ECHO

3.3 Evidence for acalabrutinib plus BR came from ECHO. This is an ongoing global, randomised, double-blind, placebo-controlled, phase 3 trial enrolling people 65 years and over with previously untreated MCL. A total of 598 people were randomised to have acalabrutinib 100 mg twice daily plus BR (n=299) or placebo with BR (n=299). People randomised to the placebo plus BR arm who had disease progression can cross over to have acalabrutinib monotherapy until disease progression or unacceptable toxicity. The primary outcome measure is progression-free survival (PFS). The results were from a data cut off (DCO) of February 2025. The company reported results from 2 separate analysis datasets: an intention-to-treat (ITT) analysis set and an analysis set in which COVID-19 deaths were censored. Results from the ITT analysis set showed that median PFS was statistically significantly longer in the acalabrutinib arm than in the placebo arm (72.5 months compared with 47.8 months; hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53 to 0.87). Results from the analysis set in which COVID-19 deaths were censored also showed that median PFS was statistically significantly longer in the acalabrutinib arm than in the placebo arm. The company considered the exact results to be confidential so they cannot be reported here. A key secondary outcome measure is overall survival (OS). The median OS was not estimable for either of the trial arms because of the immaturity of the OS data. Results from the ITT analysis set suggested a potential OS benefit with acalabrutinib plus BR compared with placebo plus BR, but the results were not statistically significant (HR 0.87, 95% CI 0.67 to 1.13). The committee concluded that acalabrutinib plus BR provided a significant clinical benefit in terms of PFS compared with placebo plus BR. But the benefit of in terms of OS was uncertain.

SACT data and generalisability of ECHO

3.4 OS data from the Systemic Anti-Cancer Therapy (SACT) dataset was available for people who had first-line BR for MCL and were diagnosed from 2017 to 2022 (n=389). SACT data showed a median OS of 40.51 months with a median follow up of 25.1 months. In the ECHO ITT analysis set, over 50% of people who had placebo plus BR were still alive at the latest available DCO, so median OS was not estimable (median follow up 51.9 months). The EAG noted substantial differences between the ECHO and SACT datasets for people having first-line BR. It stated that this raised uncertainty about the generalisability of ECHO to UK clinical practice. The company highlighted limitations of comparing data from SACT and ECHO. This included differences in population ages and being unable to determine whether people had rituximab maintenance treatment in the SACT dataset.

The clinical expert noted that the stricter inclusion criteria of clinical trials can often lead to higher OS being observed compared with real-world data. The committee highlighted that in ECHO, people in the placebo plus BR arm were allowed to cross over to acalabrutinib monotherapy upon disease progression. It noted that this may partly explain why a higher median OS was observed for people who had first-line BR in ECHO compared with the SACT data, although people in the SACT data set would likely have had ibrutinib, another BTK inhibitor, at second line. The committee acknowledged that median OS in ECHO for people who had first-line BR was likely higher what would be expected in UK clinical practice. But the relative treatment effect between acalabrutinib plus BR and placebo plus BR (see section 3.3) was robust and appropriate for decision making. The committee noted that ideally PFS and OS data from the SACT dataset would be used in the economic model for BR because it is most representative of clinical practice and more closely aligns with the benefits and costs for the relevant population. But the Cancer Drugs Fund

lead confirmed that PFS data was not collected in the SACT dataset. The committee concluded that ECHO provides a robust estimate of relative treatment effect, and in the absence of more generalisable data, PFS and OS data from ECHO should be used for BR in the economic model. It also concluded that further validation of ECHO with other sources of real-world evidence or the recently published ENRICH study may help reduce uncertainty around the higher OS for BR in ECHO.

Economic model

Company's modelling approach

3.5 The company used a partitioned survival model (PSM) with 3 mutually exclusive health states: progression free, progressed disease and death. Everyone entered the model in the progression-free state, where they had first-line treatment. The proportions of the cohort in the progression-free and death states in each model cycle were derived from parametric survival curves fitted independently to each arm of the ECHO study for acalabrutinib plus BR and BR alone. The proportion of people with progressed disease was calculated as the difference between the cumulative survival probabilities of OS and PFS. Costs of subsequent second and third treatment lines were included in the progressed-disease state, with proportions of people needing treatment after progression derived from the ECHO study. The distribution of treatments was based on clinical expert opinion. The company stated that there was no clear consensus on the preferred modelling approach for MCL. It explained that PSMs are widely accepted and commonly used in oncology. Also, NICE's Decision Support Unit technical support document 19 (DSU TSD 19) states that partitioned survival modelling is well understood, intuitive, and easy to communicate. The company highlighted that a PSM allowed PFS and OS data from the ECHO trial to be directly incorporated into the model.

The EAG was concerned that the PSM structure substantially underestimated the quality-adjusted life year (QALY) benefits of subsequent treatments. It explained that the model ignored PFS benefits and underestimated OS benefits of subsequent treatments but included their costs. This created a bias in favour of acalabrutinib plus BR. The EAG was especially concerned about the bias created from including third-line treatments including a CAR-T (brexucabtagene autoleucel) in this way in the model. The EAG would have preferred a Markov state transition model structure that explicitly captured the PFS benefits of subsequent treatments. The committee noted that it would be difficult to build and populate an appropriate Markov model with the data available. But it acknowledged that the limitations of the PSM highlighted by the EAG created uncertainty about the model structure. Markov models with explicit modelling of second-line treatments have been used in previous appraisals on MCL, such as NICE's technology appraisal guidance on bortezomib for previously untreated mantle cell lymphoma (from here TA370). It also noted that DSU TSD 19 recommends that state transition modelling should be used alongside the PSM approach to help verify the plausibility of the PSM's extrapolations and to address uncertainties. The committee also considered the relevance of third-line treatments in the model (see section 3.11) and noted that the more subsequent lines of treatment available, the greater the need for these to be modelled explicitly. It acknowledged the lack of routinely commissioned third-line treatment options for MCL. And it noted that uncertainties around both the PSM and Markov model approaches were compounded by the immaturity of the OS data in ECHO. The committee concluded that the company's PSM was acceptable for decision making, but that best practice would be to create a Markov model to validate the PSM and reduce structural uncertainty. The committee considered the uncertainty of the model in its decision making.

Censoring COVID-19 deaths

3.6 In ECHO, confirmed or suspected COVID-19 deaths were included as PFS events in independent review committee-assessed and investigator-assessed analyses. This included the COVID-19 deaths of people whose disease did not progress before death. Censoring COVID-19 deaths improved median PFS in both the acalabrutinib plus BR and placebo plus BR arms. The OS relative treatment effect of acalabrutinib plus BR also became more pronounced. The exact results are considered confidential and cannot be reported here. The company noted that the COVID-19 pandemic had a relevant impact on the efficacy outcomes of ECHO. It explained that because the pandemic has now ended, it was more appropriate to use data censored for COVID-19 related deaths in the economic model. So the company censored COVID-19 related deaths in its base-case analysis.

The EAG acknowledged that the COVID-19 pandemic would have affected OS, but thought that it was not appropriate to censor COVID-19-related deaths in the model population. The EAG's clinical expert noted that BTK inhibitors could affect other respiratory infections. COVID-19 and other respiratory illnesses remain in widespread circulation and are relevant considerations for treatment selection for people with MCL. The EAG preferred to use data from the ITT population for its base-case analysis. The committee noted that the company's method of censoring events assumed they happened at random. But this was not the case for COVID-19-related deaths, because people who are older or have certain comorbidities are more likely to die of COVID-19. This would result in a healthier cohort remaining under follow up, which is potentially biased. The committee acknowledged that other methods to adjust for events may have been more appropriate. The company and clinical expert stated that there was no biological reason why the impact of the COVID-19 pandemic would be different across trial arms. So it was unlikely to affect the relative

effectiveness acalabrutinib plus BR. It also highlighted that using data from the ITT population maintained randomisation from ECHO and reduced bias. The committee concluded that analysis using the ITT population should be used.

Extrapolation of PFS and OS data

3.7 The company assessed the proportional hazards assumption between the treatment arms in ECHO using the Schoenfeld residual test and visual inspection of Schoenfeld residual and log-cumulative hazards plots. The Schoenfeld residual tests suggested there was no statistically significant evidence to reject the null hypothesis of proportional hazards. But the company noted deviations at the tails of the Schoenfeld residual plots, and a non-zero gradient for residuals was observed over the follow-up period. The company explained that this indicated that it may not be reasonable to assume proportionality. The company also noted that visual inspection of the log-cumulative hazards plot curves did not appear to be parallel over time, with crossing of hazards observed. So it preferred to fit independent parametric models to COVID-censored PFS and OS data from ECHO and chose the gamma distribution for extrapolation. The company confirmed that both extrapolations were capped at age-matched general population mortality.

The EAG argued that in all cases the proportional hazards assumption test was non-significant, and the log-cumulative hazard functions were mostly parallel. It noted applying independently fitted curves in the economic model was inconsistent with the company's decision to use Cox proportional hazards modelling for the clinical-effectiveness analyses to show the benefit of acalabrutinib plus BR. The EAG preferred to assume the proportional hazards assumption held and that a hazard ratio from joint models should be applied to a proportional hazards compliant parametric survival curve for BR. The EAG preferred to use the ITT data and the Gompertz distribution to extrapolate the PFS and OS curves.

The committee noted that it did not have enough information to determine the most plausible extrapolation approach. It requested additional analyses to test the approaches used, including presenting the shape of the empirical hazards, the estimated hazards and the shape of the estimated hazard ratios over time based on the chosen model using the ITT data. It requested scenarios using alternative extrapolations, including both independent and joint models as appropriate. The committee was also concerned that the PFS and OS curves were capped by age-matched general population mortality but it had not seen at what point this cap was applied. Treatment for MCL is not intended to be curative so people would live with the condition until death. The committee noted that capping at age-matched general population mortality would not account for the disease burden experienced by this population. So, it suggested that a standardised mortality ratio should also be applied to the background mortality. The committee concluded that the PFS and OS extrapolations were highly uncertain and that further analysis was needed from the company.

Progressed-disease utility value

3.8 The company stated that the progressed-disease health-state utility value (HSUV) obtained from ECHO lacked face validity. The exact HSUV is confidential and cannot be reported here. The company noted that the ratio of progression-free HSUV to progressed-disease HSUV was much lower in previous NICE technology appraisals in MCL than in ECHO. So, the company calculated progressed-disease utility by multiplying the age- and sex-matched general population HSUV with a progressed-disease HSUV multiplier. The age- and sex-matched HSUV decreased over time throughout the model so the progressed-disease HSUV also decreased over time. The multiplier was informed by HSUVs from NICE's technology appraisal guidance on ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502). The company explained that at the time of

submission, this was the most recent technology appraisal in MCL, so it best reflected the current treatment landscape. The company's multiplier was calculated by removing the absolute decrement of HSUVs in TA502 (0.10) from the ECHO-derived estimate for the progression-free state, divided by the ECHO-derived estimate. The exact value of the company's progressed-disease HSUV multiplier is considered confidential and cannot be reported here.

The EAG agreed that the ECHO-derived progressed-disease HSUV lacked face validity. It noted that the clinical trial populations that informed TA502 had more advanced MCL than those in ECHO, as the appraisal was for a second-line treatment. The EAG preferred to use HSUVs from TA370 to inform the progressed-disease HSUV. The EAG was concerned that using the company's HSUV multiplier overestimated progressed disease HSUV and may not sufficiently capture the decrement associated with different lines of treatment. The EAG noted that the absolute difference between progression-free and progressed-disease HSUVs decreased over time. The EAG preferred to calculate a time-dependent progressed-disease HSUV. It used the progression-free HSUV at the start of the model (0.787), and over 2.06 years reduced this to the HSUV for people whose disease progressed from the second-line treatment state in TA370 (0.45). This was done in the model using an exponential function, and 2.06 years was based on the estimated mean PFS for BTK inhibitors at first line of 24.7 months.

The committee preferred the EAG's method to calculating progressed-disease HSUV and acknowledged that it was a pragmatic approach within the constraints of a PSM. But it thought that the HSUV should be applied when people enter the progressed-disease health state, not at the start of the model. This was because the way it was modelled meant that anyone moving to the progressed-disease health state after 2.06 years in the model would immediately get a HSUV value of 0.45. So, many people

with progressed disease would have a HSUV of 0.45 for the whole time that they were in the progressed disease health state. The committee noted that a progressed-disease HSUV of 0.45 from 2.06 years onwards may be too low and may not reflect current clinical practice. It noted that there were more treatment options since TA370 was published, so the progressed-disease HSUV may remain higher for longer. The clinical expert confirmed that people with progressed disease have heterogeneous symptoms and their quality of life varies. The committee concluded that the model should be updated so that the time-dependent progressed-disease HSUV is applied from the time of health-state entry, rather than model entry. It also requested further analysis to determine the external validity of 0.45 as a progressed-disease HSUV, with alternative sources explored. Finally, the committee requested additional scenarios to explore decreasing the progressed-disease HSUV over different lengths of time from health state entry, such as 5 years.

Subsequent treatment durations

3.9 The company applied subsequent treatment costs as a one-off cost to people whose disease progressed in each cycle. The cost was calculated from number of PFS events in each cycle, multiplied by the proportion of PFS events that were non-fatal, and the proportion of people with progressed disease who had subsequent treatment. One-off costs were applied based on the distribution of subsequent treatment options and time on treatment. The duration of subsequent treatments was modelled based on the time on treatment from a variety of sources. The EAG noted that the company used a variety of approaches for calculating subsequent treatment durations, including using median PFS data from relevant studies for R-BAC and VR-CAP. The EAG was concerned that using PFS data may overestimate subsequent treatment duration, because some people in the progression-free state would stop treatment before progression. The EAG preferred to calculate subsequent treatment durations by using mean estimates of treatment durations where possible.

The EAG assumed chemotherapy treatments would be given for a maximum 6 cycles, which is consistent with R-CHOP treatment when it is used at first line. The committee concluded that the EAG's approach for calculating subsequent treatment durations after acalabrutinib plus BR or BR was more appropriate for decision making.

Second-line subsequent treatment distributions

3.10 The company determined second-line subsequent treatment distributions based on clinical expert opinion. It explained that distributions from ECHO did not represent UK clinical practice. The EAG agreed that the company's approach to determining second-line subsequent treatment distributions was appropriate. The committee noted that based on the company's clinical expert opinion, 100% of people who had BR at first line would have ibrutinib if they had a second-line treatment. The Cancer Drugs Fund lead confirmed that people would likely have zanubrutinib rather than ibrutinib since TA1081 was published (see section 3.2). The committee concluded that it was appropriate to use the company's clinical expert opinion to determine second-line subsequent treatment distributions after acalabrutinib plus BR or BR. But it requested that the company update its model using second-line zanubrutinib instead of ibrutinib. It noted that this analysis should also include the relevant relative dose intensity, treatment duration and adverse events for zanubrutinib.

Including third-line subsequent treatments

3.11 The company included third-line subsequent treatments, including CAR-T therapies, in its base-case analysis. It did a post-hoc analysis of time to next treatment 2 (TTNT2) to help understand the impact of treatment sequencing. TTNT2 was defined as the time from randomisation to third-line treatment after randomised treatment was stopped, or death. The results showed that there was a was a 24% reduction in risk (HR 0.76, 95% CI 0.59 to 0.98) of needing third-line treatment with acalabrutinib plus BR compared with placebo plus BR for the ECHO ITT analysis set. The

company argued that these results showed that subsequent treatment was needed less often and later with acalabrutinib plus BR, reflecting better disease control. It stated that the TTNT2 analysis reduced the uncertainty of model inputs associated with subsequent treatments and supported including third-line treatments in the base-case results.

The EAG acknowledged the observed reduction of people needing third-line treatments after acalabrutinib plus BR. But it was uncertain whether this represented a delay in treatment need driven by longer PFS, or absolute effect that would continue indefinitely over the modelled time horizon. The EAG thought the difference in proportions of people having third-line treatments between the 2 ECHO trial arms was highly uncertain. It was also uncertain about whether the difference represented UK clinical practice. So the EAG removed third-line subsequent treatments from its base-case analysis. It noted that this approach would avoid capturing the costs of third-line subsequent treatments without capturing OS benefits. The clinical expert confirmed that there are no routine third-line treatment options for MCL, other than CAR-T therapy (brexucabtagene autoleucel) for those who are eligible. The committee was aware that brexucabtagene autoleucel is currently only available through the Cancer Drugs Fund; see NICE's technology appraisal guidance on brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma (from here TA677). Section 2.2.15 of NICE's manual on technology appraisal and highly specialised technologies guidance says that technologies recommended with managed access are not considered established practice in the NHS. The committee acknowledged the relevance of TA677 to this appraisal, and noted that it is currently being reviewed. It noted that there are no well-established third-line treatment options for MCL other than brexucabtagene autoleucel, which is not routinely commissioned. The committee noted that removing third-line treatments from the economic model would reduce uncertainty caused by the limitations of the PSM (see

section 3.5). So it concluded that third-line subsequent treatments should not be included in the economic model.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.12 The cost-effectiveness results cannot be reported here because they incorporate confidential discounts for drugs included in the model. Both the company's and the EAG's base-case estimates were above £30,000 per QALY gained. The committee concluded that it was unable to determine its preferred base-case incremental cost-effectiveness ratio (ICER), or determine an acceptable ICER (see section 3.13). This was because it would like to see additional information from the company to address uncertainties in the clinical and economic evidence (see section 3.14).

Acceptable ICER

3.13 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible ICER of £20,000 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 the high level of uncertainty, specifically that:

- the ECHO trail was not fully generalisable to NHS clinical practice and may overestimate absolute survival (see section 3.4)
- the economic model structure was uncertain (see section 3.5)
- determining the most accurate extrapolation of PFS and OS curves cannot be done without further analysis (see section 3.7)

- progressed-disease HSUV was not adequately captured (see section 3.8).

The committee noted the level of uncertainty could change once the additional information requested is shared. It concluded that it could not determine an acceptable ICER, but because of the uncertainty it would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee noted it would reconsider this once further analyses have been provided.

Committee's preferred assumptions

3.14 To address the uncertainties (see section 3.13), the committee requested additional analyses using the following assumptions:

- BR as the only relevant comparator for people with untreated MCL who are not eligible for an ASCT (see section 3.2)
- using the ITT population in model (see section 3.6)
- subsequent treatment durations calculated using mean estimates of treatment durations where possible and limiting chemotherapies to 6 cycles (see section 3.9)
- second-line treatment distributions based on clinical expert opinion, with zanubrutinib modelled rather than ibrutinib (see section 3.10)
- third-line treatments not included in the model (see section 3.11).

Equality

3.15 The committee did not identify any equality issues, and none were raised by the company or other stakeholders.

Uncaptured benefits

3.16 The committee considered whether there were any uncaptured benefits of acalabrutinib plus BR. It did not identify additional benefits of acalabrutinib

plus BR not captured in the economic modelling. So the committee concluded that all additional benefits of acalabrutinib plus BR had already been taken into account.

Conclusion

Recommendation

3.17 The committee recalled the uncertainties with the clinical and economic evidence and the additional information it had requested from the company. It noted that this meant it could not determine the most plausible ICER. So acalabrutinib plus BR should not be used.

4 Evaluation committee members and NICE project team

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.

Evaluation committee members

Chair

James Fotheringham

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.

Giacomo De Guisa
Technical lead

Michelle Green
Technical adviser

Leena Issa
Project manager

Lorna Dunning
Associate director

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