NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using obinutuzumab in combination with bendamustine in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

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

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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 appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using obinutuzumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 5 October 2016

Second appraisal committee meeting: 18 October 2016

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is not recommended within its marketing authorisation for treating follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

1.2 This guidance is not intended to affect the position of patients whose treatment with obinutuzumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Obinutuzumab (Gazyvaro, Roche Products) is a type 2 glyco-engineered antibody that binds to the CD20 protein present on B cells, except stem or plasma cells, and causes cell death.
Marketing authorisation	Obinutuzumab has a marketing authorisation in the UK in combination with bendamustine, followed by obinutuzumab maintenance, for the treatment of patients with follicular lymphoma 'who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen'.
Adverse reactions	Common adverse reactions are upper respiratory tract infection, sinusitis, urinary tract infection, nasopharyngitis, oral herpes, rhinitis, pharyngitis, lung infection and influenza. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Obinutuzumab is given by intravenous infusion. Induction: • Cycle 1: 1,000 mg on Day 1, Day 8 and Day 15 of the first 28-day treatment cycle • Cycles 2–6: 1,000 mg on Day 1 of each 28-day treatment cycle. Maintenance: • 1,000 mg every 2 months for 2 years or until disease progression (whichever occurs first).
Price	£3,312 per 1,000-mg vial (excluding VAT; British national formulary [BNF] edition 71). The company has agreed a patient access scheme with the Department of Health. If obinutuzumab had been recommended, this scheme would provide a simple discount to the list price of obinutuzumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Roche Products and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of obinutuzumab in combination with bendamustine, having considered evidence on the nature of rituximab-refractory follicular lymphoma and the value placed on the benefits of obinutuzumab plus bendamustine by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The committee discussed the clinical-effectiveness evidence presented by the company, its critique by the evidence review group (ERG) and evidence submitted by patient and professional groups. The clinical-effectiveness evidence for obinutuzumab in combination with bendamustine is in the company's submission (pages 52 to 108) and in the ERG report (pages 37 to 41).

Clinical management of follicular lymphoma

4.2 The committee discussed the current management of rituximab-refractory follicular lymphoma in the NHS and considered the potential place in the clinical-care pathway for induction with obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone (O-Benda+O).

4.3 The committee heard that the aim of treatment in follicular lymphoma is to induce response and control disease progression for as long as possible.

The clinical experts advised that many patients initially have asymptomatic slowly-progressing disease and will be on a 'watch and wait' policy until treatment becomes necessary. Once the condition has progressed to the extent that patients are symptomatic and treatment is required, most receive first-line induction with rituximab in combination with chemotherapy (R-chemotherapy) which induces a response in the majority of people, followed by rituximab maintenance therapy. Patients who are fit enough, may undergo stem cell transplant at this stage. Rituximab monotherapy is not often used as a standard first-line treatment in clinical practice in the NHS although committee heard that this may change in the future following the recent publication of NICE's guidance on non-Hodgkin's lymphoma, which recommends rituximab monotherapy as an option for stage III or IV disease which is still asymptomatic.

4.4 Second-line treatment for follicular lymphoma depends on the timing of relapse following first-line treatment, and the chemotherapy agents used first-line. People with follicular lymphoma that fails to respond to induction treatment with R-chemotherapy are considered to have uncontrolled disease, and the worst prognosis. These people are considered to be truly refractory to rituximab and in clinical practice may be offered bendamustine monotherapy. The clinical experts stated that patients whose disease initially responds to R-chemotherapy, but relapses during or within 6 months after maintenance treatment are a diverse group of patients, ranging from those whose disease relapses shortly after the initiation of maintenance treatment to those who relapse following the end of 2 years of maintenance. There is variation in clinical practice but, in general, people whose disease relapses early-on in the 2-year rituximab maintenance period are not considered suitable for further R-chemotherapy and may be considered for bendamustine monotherapy. However those whose disease remained under control for some time on rituximab maintenance, or after it had stopped, are not considered to have rituximab-refractory disease and are likely to be treated with further R-

chemotherapy (in combination with another chemotherapy agent) in preference to bendamustine monotherapy. The committee concluded that there is an unmet clinical need in patients whose disease does not respond to standard induction treatment with R-chemotherapy, and also for patients who relapse early-on in the rituximab maintenance phase.

4.5 The patient expert stated that follicular lymphoma is a devastating disease, which is incurable. Patients are aware that they will develop rituximab-refractory disease at some stage, after which the treatment options are limited. The patient expert stressed the importance of effective and well tolerated alternative treatments, such as bendamustine, which can also be used as an interim treatment in patients eligible for stem cell transplant. It is important for the mental wellbeing of patients to know that new treatment options are available should their disease relapse. The committee recognised that the management of follicular lymphoma is changing with the emergence of new therapeutic options. The committee concluded that new treatments for follicular lymphoma that is refractory to induction treatment with R-chemotherapy, or relapses soon after, would be welcomed by clinicians and patients.

4.6 The committee noted that the evidence base for the marketing authorisation of obinutuzumab was a subgroup from the GADOLIN trial of people with follicular lymphoma (see section 4.5). This subgroup was about 81% of the total trial population. The committee was aware that patients were included in the trial if their disease was refractory to induction treatment with rituximab monotherapy, refractory to induction treatment with R-chemotherapy, or relapsed during or within 6 months of completing 2-year maintenance treatment with rituximab monotherapy. It noted that GADOLIN compared induction using obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone (O-Benda+O), against induction with bendamustine alone with no maintenance therapy. The clinical experts stated that results from people

in the trial who had rituximab monotherapy as induction treatment are not relevant to clinical practice in England, because this is not standard of care. They considered that the most likely use of O-Benda+O in England would be for people with disease that is refractory to induction with R-chemotherapy, or who relapse early-on during rituximab maintenance treatment. The committee discussed the relevant comparators for O-Benda+O in clinical practice. It heard from the clinical experts that bendamustine is becoming a popular choice of first-line treatment with clinicians and patients because of its good rate of response and good tolerability. The committee also heard that if patients have bendamustine first line they would not be offered it as a second-line treatment because of cumulative toxicity. The committee concluded that people with disease that is refractory to induction with R-chemotherapy, or who relapse early-on during rituximab maintenance, are the most relevant patient group in clinical practice in the UK, and that the comparator in this group would be bendamustine. However, it is possible that patients whose disease responds to induction with obinutuzumab plus bendamustine might be considered for stem cell transplant rather than maintenance obinutuzumab.

Results of GADOLIN

4.7 The primary outcome measure in GADOLIN was progression-free survival. The committee noted that in the intention-to-treat population there was a statistically significant improvement in median progression-free survival of 15.4 months for O-Benda+O (hazard ratio 0.47, $p<0.0001$). The clinical experts considered that the median progression-free survival of 29.2 months seen in the O-Benda+O arm is considerably better than generally observed in clinical practice for patients with rituximab-refractory follicular lymphoma. The committee noted that the Kaplan–Meier curves for progression-free survival begin to diverge after 6 months, which corresponds with the end of induction treatment. The committee was uncertain whether the observed improvement in progression-free survival

was due to induction treatment with obinutuzumab plus bendamustine, or to the additional obinutuzumab maintenance therapy (noting that there was no maintenance therapy in the bendamustine arm). The committee also noted that there was no difference in response rates at the end of the induction period in the two arms, which could indicate that all the benefit came from the subsequent obinutuzumab maintenance treatment. The committee heard that although there was an equivalent rate of response in the two arms there was some evidence of a better response in the combination arm, as shown by the data on minimum residual disease, although this is not a prognostic indicator used in routine clinical practice. The committee concluded that O-Benda+O results in longer progression-free survival than bendamustine induction treatment alone, but the mechanism and reason for this improvement is uncertain.

4.8 The committee noted that the overall survival data presented by the company were immature. It noted that at the most recent data cut, 28.1% and 18.3% of patents had died in the bendamustine-alone arm and the O-Benda+O arm respectively. The committee considered whether the statistically significant progression-free survival benefit of O-Benda+O is likely to translate into improved overall survival in the longer term.. The committee discussed the potential relationship between progression free and overall survival, but given the immaturity of the survival data concluded that the relationship was unclear. The committee heard from a clinical expert that updated overall survival data would soon be available from GADOLIN. The committee agreed that this data would be helpful to address the uncertainty about the reliability of the limited data on overall survival for O-Benda+O compared with bendamustine. The committee concluded that although O-Benda+O is clinically effective compared to bendamustine alone for progression-free survival in follicular lymphoma, it is uncertain whether this translates into corresponding improvements in overall survival and the potential magnitude of any overall survival gain is uncertain.

4.9 The committee considered the adverse events associated with O-Benda+O. It noted that the company reported adverse-event data for all patients who had any component of obinutuzumab or bendamustine treatment in the GADOLIN trial, and 98.8% of patients in both trial arms had at least 1 adverse event. In the O-Benda+O arm 39.0% of patients had a serious adverse event compared with 34.5% in the bendamustine monotherapy arm. The committee concluded that the safety profile of O-Benda+O is similar to bendamustine .

Cost effectiveness

4.10 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. The cost-effectiveness evidence is in the company's submission (pages 109 to 176), in the company's response to clarification and in the ERG report (pages 78 to 140).

4.11 The company submitted a de novo model (health state transition Markov model) comparing O-Benda+O with bendamustine alone in patients with rituximab-refractory follicular lymphoma. The committee noted that similar models had been used in other follicular lymphoma appraisals. The committee noted that the model population was based on the GADOLIN trial and combined patients with follicular lymphoma who were refractory to induction treatment with rituximab monotherapy or R-chemotherapy, or were refractory during, or within 6 months of completing maintenance treatment with rituximab monotherapy. It discussed whether it was more appropriate to consider the model population as whole or particular subgroups of patients in the model. It acknowledged that it had previously heard that clinicians would consider O-benda–O to be potentially most useful in patients whose disease was refractory to R-chemotherapy induction (see section 4.4) and it also noted that the ERG had undertaken an exploratory analysis in this patient population. However it agreed that the population who might be offered this combination in clinical practice was potentially broader than just people with R-chemotherapy refractory

disease. The committee therefore concluded that the structure of the company model was acceptable and that it would not limit its consideration to a subgroup with R-chemotherapy refractory disease.

4.12 The committee considered the way that overall survival had been estimated by the company. It noted the semi-Markov approach using time pre-progression and time post-progression to calculate overall survival. The company considered this approach to be the most appropriate because of the indolent nature of follicular lymphoma and the immaturity of the overall survival data from GADOLIN. The company used a Weibull distribution in the model base case, fitted independently to the two trial arms pre-progression, and a common Weibull distribution for both arms post progression. It justified the choice of Weibull on the basis that it was a satisfactory (although not the best) fit to the trial data, and gave the most plausible prediction of overall survival at 20 years. The committee heard from the ERG that the company's modelling of overall survival seemed to fit with the observed Kaplan–Meier overall survival data for O-Benda+O. However for bendamustine the modelled overall survival did not fit particularly well with the trial data, and potentially underestimated the overall survival in the bendamustine arm. The committee accepted that the company had presented its rationale for the choice of extrapolation method, but concluded that the extrapolated survival for bendamustine did not appear to be a particularly good fit for the trial data, albeit that the trial data are immature.

4.13 The committee noted that the ERG had done an exploratory analysis using a partitioned-survival modelling approach which fitted parametric functions to the bendamustine overall survival data from GADOLIN. The ERG used the Kaplan–Meier overall survival estimates from GADOLIN for the O-Benda+O arm (until the last event at approximately 31 months) and assumed the same hazard of death as predicted by the parametric overall survival curve for bendamustine beyond this point. The committee noted

that the ERG's analysis using the Weibull distribution predicted that 2.93% of people treated with bendamustine monotherapy would be alive at 20 years whereas the company's estimate was 1.2%. The committee noted that the ERG's overall survival curves appeared to be a better fit to the trial data than the company's estimates. The clinical expert and the company acknowledged that the overall survival data are immature, and indicated that there is a more recent interim report from the trial with updated overall survival results that might help to address some of the uncertainty.The committee heard a verbal report of the updated results and expressed an interest in any further analyses using the data. The committee concluded that there is considerable uncertainty about the long-term overall survival estimates from the company's economic model.

4.14 The committee considered the results of the ERG's exploratory analysis for the cost effectiveness of O-Benda+O compared with bendamustine alone in the whole population of the GADOLIN trial. It noted that the ERG had made the following amendments to the company model:

- Using a partitioned survival approach to estimate overall survival.
- Adjusting utility estimates for the effects of aging.
- Assuming lower disease progression costs for subsequent treatments.
- Using the generic acquisition cost for bendamustine.
- Correcting minor programming errors in the model.
- Using alternative drug administration costing assumptions.
- Using utility estimates from GADOLIN.

The committee noted that the key driver of the differences in the cost-effectiveness estimates between the ERG and the company was related to the overall survival benefit used in the model. The quality-adjusted life year (QALY) gain was1.31 in the company model and 0.63 in the ERG model (based on a much less favourable life year gain of 0.44 years estimated by the ERG, compared with 1.53 years estimated by the

company). This essentially doubled the company's ICER. The committee concluded that uncertainty in the incremental overall survival benefit of O-Benda+O compared with bendamustine made it difficult to determine a precise ICER.

4.15 The committee considered the likely cost effectiveness of O-Benda+O compared with bendamustine alone based on the analyses presented by the company and the ERG. It noted that the company's base-case ICER was above that which is normally considered a cost-effective use of NHS resources. The ICER calculated by the ERG was approximately double the company's estimate. The committee noted that updated overall survival data from GADOLIN would soon be available, which could potentially result in changes to the ICER. The committee concluded that on the basis of current evidence, the true cost effectiveness of O-Benda+O compared with bendamustine alone probably lies somewhere between the company and the ERG's estimates, and therefore it could not recommend O-Benda+O for treating rituximab-refractory follicular lymphoma as a cost-effective use of NHS resources.

4.16 The committee considered whether obinutuzumab in combination with bendamustine was an innovative medicine for the treatment of follicular lymphoma. The committee concluded that it could not identify any specific health related benefit that had not already been captured in the QALY calculation.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.17 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to

suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab**	**Section**
Key conclusion		
Obinutuzumab, in combination with bendamustine followed by obinutuzumab maintenance is not recommended within its marketing authorisation for treating follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.		1.1
The committee concluded that although O-Benda+O is clinically effective compared to bendamustine alone for progression-free survival in follicular lymphoma, it is uncertain whether this translates into corresponding improvements in overall survival and the potential magnitude of any overall survival gain is uncertain.		4.8
The committee noted that the company's base-case ICER was above that which is normally considered a cost-effective use of NHS resources. The ICER calculated by the ERG was approximately double the company's estimate. The committee concluded that on the basis of current evidence, the true cost effectiveness of O-Benda+O compared with bendamustine alone probably lies somewhere between the company and the ERG's estimates, and therefore it could not recommend O-Benda+O for treating rituximab-refractory		4.15

follicular lymphoma as a cost-effective use of NHS resources.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee understood that follicular lymphoma is a devastating disease, which is incurable. Patients are aware that they will develop rituximab-refractory disease at some stage, after which the treatment options are limited. The committee heard about the importance of effective and well tolerated alternative treatments, such as bendamustine, which can also be used as an interim treatment in patients eligible for stem cell transplant. It is important for the mental wellbeing of patients to know that new treatment options are available should their disease relapse. The committee recognised that the management of follicular lymphoma is changing with the emergence of new therapeutic options. The committee concluded that new treatments for follicular lymphoma that is refractory to induction treatment with R-chemotherapy would be welcomed by clinicians and patients.	4.5
The technology		
Proposed benefits of the technology How innovative is the technology in its	The committee concluded that it could not identify any specific health related benefit that had not already been captured in the QALY calculation.	4.16

potential to make a significant and substantial impact on health-related benefits?		
What is the position of the treatment in the pathway of care for the condition?	The committee heard that in clinical practice, people with disease that is refractory to induction with R-chemotherapy, or who relapse early-on during rituximab maintenance treatment, are considered for treatment with bendamustine. The committee also considered patients whose disease initially responds to R-chemotherapy, but relapses during or within 6 months after maintenance treatment. The clinical experts said that there is variation in clinical practice but, in general, people whose disease relapses early-on in the 2-year rituximab maintenance period are not considered suitable for further R-chemotherapy and may be considered for bendamustine monotherapy. The committee concluded that O-Benda+O is most likely to be used in patients whose disease does not respond to standard induction treatment with R-chemotherapy, and also for patients who become refractory early-on in the rituximab maintenance phase.	4.4
Adverse reactions	The committee considered the adverse events associated with O-Benda+O. It noted that the	4.9

	company reported adverse-event data for all patients who had any component of obinutuzumab or bendamustine treatment in the GADOLIN trial. The committee concluded that the safety profile of O-Benda+O is similar to bendamustine.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that the evidence base for the marketing authorisation of obinutuzumab was a subgroup from the GADOLIN trial of people with follicular lymphoma .This subgroup was about 81% of the total trial population. The committee was aware that patients were included in the trial if their disease was refractory to induction treatment with rituximab monotherapy, refractory to induction treatment with R-chemotherapy, or relapsed during or within 6 months of completing 2-year maintenance treatment with rituximab monotherapy. It noted that GADOLIN compared induction using obinutuzumab plus bendamustine followed by maintenance treatment with obinutuzumab alone (O-Benda+O), against induction with bendamustine alone with no maintenance therapy.	4.6
Relevance to general clinical practice in the NHS	The committee concluded that people with disease that is refractory to induction with R-chemotherapy, or who relapse early-on during	4.6

	rituximab maintenance, are the most relevant patient group in clinical practice in the UK, and that the comparator in this group would be bendamustine. However, it is possible that patients whose disease responds to induction with obinutuzumab plus bendamustine might be considered for stem cell transplant rather than maintenance obinutuzumab.	
Uncertainties generated by the evidence	The committee noted that the Kaplan–Meier curves for progression-free survival begin to diverge after 6 months, which corresponds with the end of induction treatment. The committee was uncertain whether the observed improvement in progression-free survival was due to induction treatment with obinutuzumab plus bendamustine, or to the additional obinutuzumab maintenance therapy. The committee also noted that there was no difference in response rates at the end of the induction period in the two arms, which could indicate that all the benefit came from the subsequent obinutuzumab maintenance treatment. The committee noted that the overall survival data presented by the company was immature. It noted that at the most recent data cut, 28.1% and 18.3% of patents had died in the bendamustine-alone arm and the O-Benda+O arm respectively. The committee discussed the potential relationship between	4.7 4.8

	progression free and overall survival, but given the immaturity of the survival data concluded that the relationship was unclear. The committee heard from a clinical expert that updated overall survival data would soon be available from GADOLIN. The committee concluded that it is uncertain whether progression free survival gain translates into improvements in overall survival and the potential magnitude of any overall survival gain is uncertain.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee considered people with follicular lymphoma that did not respond to induction treatment with R-chemotherapy or early on in rituximab maintenance therapy to be most relevant. The differential effectiveness in this combined subgroup was not considered.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The primary outcome measure in GADOLIN was progression-free survival. The committee noted that in the intention-to-treat population there was a statistically significant improvement in median progression-free survival of 15.4 months for O-Benda+O (hazard ratio 0.47, $p<0.0001$). The committee noted that the overall survival data presented by the company was were immature. It noted that at the most recent data cut, 28.1% and 18.3% of patents had died in	4.8

	the bendamustine-alone arm and the O Benda+O arm respectively. The committee considered whether the statistically significant progression-free survival benefit of O Benda+O is likely to translate into improved overall survival in the longer term. The committee discussed the potential relationship between progression free and overall survival, but given the immaturity of the survival data concluded that the relationship was unclear suggesting that progression-free survival may not be associated with a corresponding overall survival gain and casting doubt on whether progression-free survival can be considered a surrogate marker or predictor of overall survival benefit. The committee considered the overall survival benefit based on the extrapolation of immature data to be highly uncertain.	
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted a de novo model (health state transition Markov model) comparing O-Benda+O with bendamustine alone in patients with rituximab-refractory follicular lymphoma. The committee noted that similar models had been used in follicular lymphoma other technology appraisals. The committee was aware that the subgroup of particular interest in the trial was people with follicular melanoma refractory to R-	4.11

	chemotherapy. However it agreed that the population who might be offered this combination in clinical practice was potentially broader than just R-Chemotherapy refractory patients. The committee therefore concluded that the structure of the company model was acceptable and that it would not limit its consideration to a subgroup with R-chemotherapy refractory disease.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that there is considerable uncertainty about the long-term overall survival estimates in the company's economic model. The company's modelling of overall survival seemed to fit with the observed Kaplan–Meier overall survival data for O-Benda+O but did not fit particularly well with the trial data, and potentially underestimated the overall survival in the bendamustine arm. The ERG's analysis which used the Kaplan–Meier overall survival estimates from GADOLIN for the O-Benda+O arm (until the last event at approximately 31 months) and assumed the same hazard of death as predicted by the parametric overall survival curve for bendamustine beyond this point, predicted that 2.93% of people treated with bendamustine monotherapy would be alive at 20 years (compared with the company's estimate of 1.2%). The committee noted that the ERG's overall survival curves	4.12 4.13

	appeared to be a better fit to the trial data than the company's estimates.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee was aware of the utility values in the company's model and considered the impact on the ICER of using the ERG's alternative estimates. None identified.	4.12
Are there specific groups of people for whom the technology is particularly cost effective?	No groups were identified.	–
What are the key drivers of cost effectiveness?	The committee noted that the key driver of the differences in the cost-effectiveness estimates between the ERG and the company was related to the overall survival benefit used in the model. The quality-adjusted life year (QALY) gain was1.31 in the company model and 0.63 in the ERG model (based on a much	4.13

	less favourable life year gain of 0.44 years estimated by the ERG, compared with 1.53 years estimated by the company). This essentially doubled the company's ICER.	
Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that the company's base-case ICER (which is commercial in confidence and cannot be shown) was above that which is normally considered a cost-effective use of NHS resources. The ICER calculated by the ERG was approximately double the company's estimate. The committee concluded that on the basis of current evidence, the true cost effectiveness of O-Benda+O compared with bendamustine alone probably lies somewhere between the company and the ERG's estimates.	4.14
Additional factors taken into account		
Patient access schemes (PPRS)	The Committee was aware that the company has agreed a patient access scheme with the Department of Health.	Section 2
End-of-life considerations	Not applicable.	–
Equalities considerations and social value judgements	No equalities issues were identified.	–

5 Recommendations for research

5.1 Updated overall survival data from GADOLIN.

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
September 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker
Technical Lead

Eleanor Donegan
Technical Adviser

Liv Gualda
Project Manager

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