

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Obinutuzumab for untreated advanced follicular lymphoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using obinutuzumab for untreated advanced follicular lymphoma 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](https://www.nice.org.uk/guidance/indevelopment/gid-ta10137/documents)). <https://www.nice.org.uk/guidance/indevelopment/gid-ta10137/documents>

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.
- Subject to any appeal by consultees, the final appraisal determination 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: 05 October 2017

Second appraisal committee meeting: 18 October 2017

Details of membership of the appraisal committee are given in section 5.

## 1 Recommendations

- 1.1 Obinutuzumab is not recommended, within its anticipated marketing authorisation (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), for untreated advanced follicular lymphoma in adults.
- 1.2 This recommendation is not intended to affect treatment with obinutuzumab 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 clinician consider it appropriate to stop.

### Why the committee made these recommendations

Current first-line treatment for symptomatic advanced follicular lymphoma is induction therapy with rituximab plus chemotherapy followed by maintenance treatment with rituximab when there has been a response.

The main evidence on the effectiveness and safety of obinutuzumab is from an ongoing clinical trial. It shows that obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment delays disease progression more than current treatment. However, it also shows that undesirable side effects are more common with obinutuzumab than with rituximab. There are not enough data to know whether obinutuzumab increases life expectancy.

Obinutuzumab costs more than branded rituximab and even more than the biosimilar versions of rituximab. There is concern about the assumptions used in the company's cost-effectiveness modelling, for example that the treatment effect lasts 9 years when there is no evidence for this, the utility value for progressed disease and how the model predicts that obinutuzumab extends life. Using the preferred assumptions and the discounted prices, the cost-effectiveness estimate for

obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment, compared with rituximab plus chemotherapy followed by rituximab maintenance treatment, is much higher than £30,000 per quality-adjusted life year gained. Therefore obinutuzumab cannot be recommended for untreated advanced follicular lymphoma.

## 2 The technology

<b>Obinutuzumab (Gazyvaro, Roche Products)</b>	
<b>Anticipated marketing authorisation</b>	On 20 July 2017, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the marketing authorisation of obinutuzumab: 'obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma'.
<b>Recommended dose and schedule</b>	<p>Obinutuzumab is given by intravenous infusion.</p> <p>Induction with chemotherapy dosage:</p> <ul style="list-style-type: none"> <li>• With cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine and prednisolone (CVP): <ul style="list-style-type: none"> <li>• cycle 1: 1,000 mg on days 1, 8 and 15 of the first 21-day treatment cycle</li> <li>• cycles 2–8: 1,000 mg on day 1 of each 21-day treatment cycle.</li> </ul> </li> <li>• With bendamustine: <ul style="list-style-type: none"> <li>• cycle 1: 1,000 mg on days 1, 8 and 15 of the first 28-day treatment cycle</li> <li>• cycles 2–6: 1,000 mg on day 1 of each 28-day treatment cycle.)</li> </ul> </li> </ul> <p>Maintenance dosage:</p> <ul style="list-style-type: none"> <li>• 1,000 mg every 2 months for 2 years or until disease progression (whichever occurs first).</li> </ul>
<b>Price</b>	<p>£3,312 per 1,000-mg vial (excluding VAT; British national formulary [BNF] online, August 2017).</p> <p>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.</p>

### 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

#### ***Clinical need in advanced follicular lymphoma***

##### **People with follicular lymphoma want further options for treatment**

- 3.1 Follicular lymphoma progresses slowly, often without symptoms. The patient experts noted that, despite this, knowing the disease will eventually progress can cause considerable distress. People also realise that they will need further treatment when the disease progresses, which adds to the physical and psychological burden, and increases their wish to have more treatment options. The committee agreed that delaying disease progression and having treatment options would benefit people with untreated follicular lymphoma.

#### ***Treatment pathway***

##### **People with symptomatic disease are the relevant population in this appraisal**

- 3.2 The clinical experts advised that they do not routinely offer active treatment to people with asymptomatic disease, and instead use 'watchful waiting'. Although the NICE guideline on [non-Hodgkin's lymphoma](#) recommends rituximab induction therapy also for people with advanced-stage (stages III and IV) asymptomatic follicular lymphoma, the clinical experts stated that this does not reflect clinical practice. They explained that active treatment is normally reserved for people with symptomatic disease who have bulky disease at multiple sites, especially if lymph nodes cause problems because of their location, or if people have fever, night sweats or unintentional weight loss. The committee concluded that people with symptomatic disease reflect the relevant population to consider in this appraisal.

## **Rituximab plus chemotherapy is the main treatment for untreated follicular lymphoma**

3.3 The clinical experts explained that rituximab plus chemotherapy is the main ‘induction treatment’ for untreated advanced follicular lymphoma. Other potential options for induction therapy include:

- Rituximab alone: the clinical experts advised that this is rarely used to treat symptomatic disease; they may use it when chemotherapy is not indicated, or if the person would prefer starting treatment rather than ‘watchful waiting’.
- Bendamustine alone: this does not have a marketing authorisation for the first-line treatment of follicular lymphoma, but is funded for this indication through the Cancer Drug Fund. The clinical experts expressed that, in NHS clinical practice, bendamustine alone (rather than with an immunotherapy such as rituximab or obinutuzumab) is hardly ever used as first line.

The committee concluded that rituximab plus chemotherapy is the most commonly used first-line induction treatment for symptomatic advanced follicular lymphoma.

## **The chemotherapies most commonly used with rituximab are CVP, bendamustine and CHOP**

3.4 NICE technology appraisal guidance on [rituximab for the first-line treatment of stage III-IV follicular lymphoma](#) (TA243) recommended rituximab plus one of the following chemotherapy regimens:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide (VP-16), prednisolone and interferon alfa (CHVPi) and

- chlorambucil.

Rituximab plus bendamustine is also available through the Cancer Drugs Fund. The clinical experts stated that most people in the NHS have either rituximab plus CVP or rituximab plus bendamustine, or to a lesser extent, rituximab plus CHOP as induction treatment. CHOP is associated with more adverse effects than the other 2 regimens. Therefore, bendamustine and CVP are more commonly used. CHOP is more likely to be reserved for high-grade follicular lymphoma at risk of transformation to a more aggressive form (large diffuse B-cell lymphoma) and also for younger, fitter people who can better tolerate the potential cardiotoxicity of doxorubicin. The clinical experts noted that bendamustine use has declined since the Medicines and Healthcare products Regulatory Agency issued a safety alert about off-label use of bendamustine as a first-line treatment for follicular lymphoma plus an immunotherapy (such as rituximab or obinutuzumab). The committee concluded that, in clinical practice, CVP, CHOP and bendamustine are the main background chemotherapies used with induction therapy, and that the adverse effects of each chemotherapy largely drive treatment choice.

### **Rituximab maintenance therapy is recommended when there has been a response to induction therapy**

- 3.5 If the disease goes into complete or partial remission with induction therapy, rituximab monotherapy is generally given as 'maintenance treatment' for up to 2 years. The scope for this appraisal included rituximab-based chemotherapy without rituximab maintenance treatment as a comparator. The committee noted that in [NICE technology appraisal 226](#), NICE recommended rituximab maintenance treatment for follicular lymphoma that has responded to first-line induction therapy with rituximab plus chemotherapy. The clinical experts explained that using rituximab maintenance therapy is increasingly controversial, citing the PRIMA study. In this, patients were randomised to rituximab maintenance treatment or



observation only. The results showed no survival benefit, a modest benefit with respect to progression-free survival and time to next treatment, an increased risk of infections including reactivation of hepatitis B, and long-term safety concerns. Nevertheless, the clinical experts stated that, in clinical practice, most people (around 80–90%) whose disease responds to induction therapy have rituximab maintenance therapy. The NHS England representative explained that maintenance treatment is available in routine commissioning, and should be considered for all people whose disease has responded to induction treatment. The committee concluded that rituximab maintenance therapy, following response to induction therapy, reflects routine clinical practice in the NHS, and that induction not followed by rituximab monotherapy was not a relevant comparator for this appraisal.

**Rituximab plus chemotherapy followed by rituximab maintenance is the appropriate comparator**

3.6 Based on information from the clinical experts and NHS England, the committee did not consider the following 3 comparators specified in the final scope to be relevant (see sections 3.2–3.5):

- rituximab monotherapy
- rituximab-based chemotherapy without rituximab maintenance treatment
- bendamustine monotherapy.

Referring to its discussion on the treatment pathway (see sections 3.2–3.5), the committee concluded that the appropriate comparison should be between obinutuzumab plus either CHOP, CVP or bendamustine followed by obinutuzumab maintenance treatment, and rituximab plus either CHOP, CVP or bendamustine followed by rituximab maintenance treatment, in line with the company's decision problem.

## ***Clinical evidence***

### **The main evidence is from GALLIUM, an open-label randomised controlled trial**

3.7 The main clinical evidence for this appraisal came from an ongoing, open-label phase III randomised controlled trial (GALLIUM). GALLIUM compared the efficacy and safety of induction therapy with obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment (n=601) with rituximab plus chemotherapy induction therapy followed by rituximab maintenance treatment (n=601) in adults with advanced follicular lymphoma (grades 1 to 3a). The primary outcome was progression-free survival assessed by the investigator, defined as the time from day of randomisation until first symptomatic deterioration, disease transformation or death from any cause, whichever occurred first. Progression-free survival assessed by an independent review committee was a secondary outcome. Patients had treatment across 177 trial sites in 18 countries, including the UK (n=293 patients). Each site chose 1 of the 3 chemotherapeutic regimens (CHOP, CVP or bendamustine) to accompany obinutuzumab or rituximab (that is, all patients at a given site had the same concomitant chemotherapy, whether with obinutuzumab or rituximab).

### **The trial population reasonably reflects the NHS population**

3.8 The committee discussed whether the population in GALLIUM reflected people who would be offered treatment in the NHS with respect to:

- Age: the median age of patients in GALLIUM was 59 years. The committee heard from the clinical experts and the ERG that this reflected a younger population than would be seen in clinical practice.
- Ethnicity: the committee heard that some ethnic groups were under-represented in GALLIUM (for example, black people of African or Caribbean family origin).
- Chemotherapeutic regimen used with obinutuzumab or rituximab: the committee noted the discrepancy between the distribution of

concomitant chemotherapies used in GALLIUM and clinical practice. In particular, patients in GALLIUM were more likely to have bendamustine than in the NHS. The committee was not presented with evidence on the differential effectiveness of the chemotherapies given with obinutuzumab or rituximab. However, it took the view that any differences in the proportions of treatments used between the trial and NHS practice would be unlikely to affect the generalisability of the trial's results.

Overall, the committee was satisfied that the trial population reasonably reflected people with advanced follicular lymphoma having treatment in the NHS.

## ***Efficacy results***

### **Obinutuzumab delays disease progression in the short term, but its long-term effect on progression-free survival is unknown**

3.9 The company had done several analyses including the pre-specified 'primary analysis' for progression-free survival on 31 January 2016 and the post-hoc 'updated analysis' on 10 September 2016. The committee noted that, as of September 2016, 80.0% of patients randomised to obinutuzumab compared with 73.3% of those randomised to rituximab were alive and free of disease progression (as assessed by investigators). For progression-free survival assessed by the independent review committee, the respective proportions were 82.0% and 76.5%. Obinutuzumab reduced the risk of disease progression by 32% (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.54 to 0.87) according to investigator assessment, and by 28% (HR 0.72, 95% CI 0.56 to 0.93) according to the independent review committee. Because there were few events, median progression-free survival could not be estimated in either assessment. The committee agreed that the results reflected a statistically significant, but clinically modest, improvement with obinutuzumab in terms of delaying disease progression in the short term. It noted that the

Kaplan–Meier curves for obinutuzumab-based and rituximab-based therapy started to converge at the later follow-up time points. This suggested a diminishing effect of obinutuzumab over time in the 23% of patients whose disease progressed during the trial. The committee recognised that there was no evidence on the long-term effect of obinutuzumab on progression-free survival. Therefore, the committee concluded that obinutuzumab delays disease progression in the short term, but its long-term effect on progression-free survival is unknown.

**There is merit in determining progression by both investigator and independent committee**

3.10 The committee discussed whether the investigator or the independent review committee assessment of progression-free survival was more appropriate for inferring the effectiveness of obinutuzumab. The benefits of investigator assessment included that:

- it reflected the primary end point in GALLIUM
- it took into account symptomatic deterioration, which could be better assessed by investigators rather than by independent review
- it included progression in clinically assessable lymph nodes that may not appear on routine radiographic scans (for example, those in the neck)
- it determined length of treatment in GALLIUM.

However, the committee recalled that it usually preferred outcomes assessed by an independent review committee from trials in which both investigators and patients knew the treatment allocation. This is because the risk of bias introduced by an open-label design is minimised when subjective outcomes are assessed independently. The clinical experts stated that in clinical practice, disease progression is usually determined by radiographic evidence and usually occurs before symptomatic deterioration. They thought that the discrepancy in the results was because of strict adherence to the protocol-defined progression criteria by

the independent committee. The company explained that investigator-assessed progression-free survival was chosen as the primary outcome to produce 'quicker results' and to avoid inconsistent assessments in people followed up for long periods. The committee agreed that there was merit in considering both measures of disease progression.

**GALLIUM does not provide robust information on whether obinutuzumab-based treatments prolong survival compared with rituximab-based treatments**

3.11 GALLIUM was not designed to estimate the difference in overall survival between the 2 treatments. At the time of the analysis, 7.9% of patients had died, at which point there was no statistically significant difference between obinutuzumab and rituximab (HR 0.82; 95% CI 0.54 to 1.22). The clinical experts stated that the lack of an overall survival benefit with obinutuzumab despite a progression-free survival benefit was possible. However, there is often a discrepancy between the 2 outcomes in slowly growing lymphomas such as follicular lymphoma. The committee recognised that in addition to the trial being underpowered to show a difference in overall survival, the data were highly immature. The committee could not conclude that obinutuzumab has an effect on overall survival.

**Time to next treatment may be more meaningful to patients than progression-free survival**

3.12 In the updated analysis (September 2016), 14.3% of patients in the obinutuzumab arm and 20.0% of those in the rituximab arm had second-line treatment (HR 0.68, 95% CI 0.52 to 0.90). The clinical experts and the representative from NHS England explained that time to next treatment is more relevant to patients than progression-free survival. The disease may progress slightly on radiographic scans, but with little or no impact on the patient's wellbeing and symptoms. As a result, people with follicular lymphoma may have a gap between disease progression and time to next treatment. So, ultimately what matters to patients is when they need a subsequent treatment. The committee noted the clinical experts' comment

that time to next treatment would be longer in clinical practice than in clinical trials because clinicians assess patients less frequently in practice. The committee concluded that time to next treatment may be more meaningful to patients than progression-free survival.

## ***Safety results***

### **Obinutuzumab-based therapy is associated with a higher rate of adverse events than rituximab-based therapy**

3.13 In GALLIUM, more patients in the obinutuzumab arm than in the rituximab arm had adverse events of grade 3 or more (76.6% compared with 70.0%), serious adverse events (46.6% compared with 40.0%), adverse events leading to stopping any treatment (16.0% compared with 14.4%) and fatal adverse events (4.0% compared with 3.4%). The committee concluded that obinutuzumab is associated with a higher burden of adverse events than rituximab, and that it was important to adequately capture this in the economic model.

## ***Cost effectiveness***

### **Different modelled states for early- and late-progressing disease are acceptable**

3.14 To estimate cost effectiveness, the company used a state-transition Markov model with 4 states:

- progression-free state (which the company further divided into 2 sub-states: on and off treatment)
- early progressed-disease state (progression within 2 years after starting treatment)
- late progressed-disease state (progression 2 or more years after starting treatment)
- death.

The committee questioned the rationale for separating early and late disease progression. The clinical experts explained that the natural history of disease that progresses early differs from that of disease that progresses late. For example, people whose disease progresses early are more likely to have subsequent treatment, which may affect their quality of life. However, the clinical experts stated that in clinical practice, the definition of early disease progression is somewhat vague, although progression within 2–3 years after starting treatment is generally considered to be early. The company stated that it chose 2 years based on published studies. The committee accepted the separate modelling of early- and late-progressing disease and the 2-year cut-off to differentiate them.

**The economic model structure does not accurately reflect the natural history of the disease**

3.15 The committee reflected on whether the model should use time to next treatment instead of progression-free survival. It recalled that disease progression is assessed more frequently in clinical trials than in practice. Moreover, the model did not account for the time between disease progression and subsequent treatment (see section 3.12), nor did it explicitly model response to determine whether people were offered maintenance therapy. The committee agreed that the model structure may not accurately reflect patients' experience during disease progression. This is because patients stay in this disease state (the early or late progressed-disease state) for many years, have many subsequent lines of treatment and their health-related quality of life does not remain the same during that time. The committee concluded that the structure of the model did not accurately reflect the natural history or patient experience of treated follicular lymphoma.

## ***Modelling of treatment effect***

### **The progression-free survival curve for obinutuzumab is generated from the rituximab curve**

3.16 To capture the effect of obinutuzumab-based therapy compared with rituximab-based therapy on progression-free survival, the company first extrapolated the curve reflecting progression-free survival, as assessed by the investigators, in the rituximab arm to the time when disease would have progressed in all patients. It then applied to that curve the hazard ratio reflecting the effect of obinutuzumab in GALLIUM to generate the curve reflecting the effect of obinutuzumab on progression-free survival.

### **A constant treatment effect of 9 years is too optimistic**

3.17 In extrapolating progression-free survival, the company assumed that the benefit of obinutuzumab over rituximab would last for 9 years after starting treatment (6.5 years after the 2.5 years of maximum treatment duration with obinutuzumab) and then stop. This was based on the company having interpreted the results of PRIMA to show that the effect of rituximab maintenance treatment compared with 'observation only' did not decrease during the 9-year follow-up. However, the committee did not consider that generalising evidence from 1 population who had rituximab (PRIMA) to a different population who had obinutuzumab (GALLIUM) necessarily reflected the course of patients having obinutuzumab-based therapy. In GALLIUM, the effect was seen in around 20% of patients who had disease progression (as assessed by investigators), during a maximum of 5 years' follow-up, with a median follow-up of 41.1 months. Because of this, the committee considered that assuming that this effect persists over 9 years was speculative, and arguably at odds with the Kaplan–Meier curves showing convergence at later follow-up time points (see section 3.9). In one of its exploratory analyses, the ERG limited the benefit to 5 years to reflect the longest follow-up in GALLIUM. The committee considered this duration of effect to be more appropriate than the company's because it does not assume a treatment effect beyond the



trial follow-up. Given the evidence, to account for the uncertainty resulting from immature data and characterise the impact on cost effectiveness, the committee preferred the analyses assuming no effect beyond the trial follow-up as per the ERG's exploratory analysis.

**It is preferable to model treatment effects independently**

3.18 In modelling progression-free survival, the company assumed proportional hazards during the first 9 years (that is, the effect of obinutuzumab relative to rituximab is the same over time). This was because the log-cumulative hazard plots for progression-free survival from GALLIUM appeared to be parallel. However, the committee found that the plots converged to a degree. It also recalled that the shape of the Kaplan–Meier curve for progression-free survival suggested that the effect of obinutuzumab diminished over time (see section 3.9), suggesting that the proportional hazards assumption did not hold. The committee agreed that, over the course of follicular lymphoma, treatments change from induction with chemotherapy to maintenance without chemotherapy, to retreatment over a relatively long time. So, applying the same effect in all of these phases may not reflect true effectiveness. The committee did not agree with the company's assumption of proportional hazards, preferring to model treatment effects independently.

**There is no evidence that delaying disease progression will also prolong life**

3.19 The company did not model overall survival based only on evidence from the main trial, GALLIUM. Instead, it applied a monthly death rate derived from patients in GALLIUM whose disease had progressed within 2 years to reflect death in the early progressed-disease state, and applied a death rate from patients in PRIMA whose disease progressed late (after 2 years) to reflect death in the late disease state. The company's reason for this was because no patients whose disease had progressed late in GALLIUM died. The company applied the trial-derived death rates only if they were higher than those of the age-equivalent general UK population.

3.20 The company estimated overall survival as the estimated time spent in the progression-free state plus the estimated time spent in the post-progression state. This meant that the increase in progression-free survival with obinutuzumab-based therapy translated into an overall survival gain. The committee recalled that the estimated time spent progression free was based on the company having assumed that the effect of obinutuzumab seen during the trial continued for up to 9 years after starting treatment. It also recalled that overall survival data from GALLIUM were highly immature (see section 3.11), and that the relationship between progression-free and overall survival was not well established in follicular lymphoma (see section 3.9). Because of this, the committee considered the company's approach to modelling overall survival to represent an optimistic scenario, particularly given the evidence from PRIMA. PRIMA showed no survival benefit of 2-year rituximab maintenance treatment compared with observation only, in patients with follicular lymphoma whose disease had responded to first-line induction treatment with rituximab plus chemotherapy. The committee concluded that the company's modelling of overall survival was not supported by evidence. Given the lack of evidence from GALLIUM, and in the absence of analyses more recent than September 2016 or observational data on obinutuzumab from disease or treatment registries, the committee agreed that it should see an analysis in which none of the progression-free survival benefit translates to overall survival. It considered that there might be other benefits of progression-free survival not explicitly modelled or captured in the calculation of the quality-adjusted life year measure, for example, the delay in the time to next treatment, the psychological benefit of delaying treatment, and an improved health-related quality of life from avoiding adverse events associated with successive lines of treatment; these benefits could be reflected in this scenario.

## ***Health-related quality of life***

### **There is no meaningful difference in health-related quality of life for people having obinutuzumab or rituximab**

3.21 In GALLIUM, data were collected on health-related quality of life using 2 tools: a lymphoma specific tool, the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) questionnaire, and a generic tool, EQ-5D-3L. Patients were asked to fill in FACT-Lym at baseline, on completing induction, on completing maintenance and at 36-month follow-up. There were no statistically significant differences in average scores between the treatment arms at any time points. GALLIUM collected EQ-5D summary scores at baseline, during treatment (induction and maintenance), after treatment, at the last assessment before progression and at the first assessment after progression. The company analysed and presented EQ-5D scores according to the economic model health states. The committee noted that the differences in the EQ-5D scores between arms were not statistically significant.

### **The utility value for the progressed-disease state is too low**

3.22 The company used utility values derived from EQ-5D measures from GALLIUM for the progression-free state (for both on- and off-treatment states) but used a value from the literature for the progressed-disease state (Wild et al., 2006). According to the company's submission, Wild et al. collected data from 222 patients with follicular lymphoma in 8 UK centres using the EQ-5D questionnaire. Depending on the clinical information, Wild et al. analysed the EQ-5D data to derive utility for the progression-free state (0.81) and the progressed-disease states (0.62). The company chose not to use values derived from GALLIUM to populate the progressed-disease states because, in its opinion, data from GALLIUM did not capture advanced stages of progression. The company used the same value (0.62, Wild et al.) to reflect both early and late progressed-disease states. The committee considered this value to lack face validity because it was lower than expected for a patient population

with the prospect of a long life expectancy after disease progression. The utility values from GALLIUM after progression (0.78 for early and 0.81 for late progressed-disease states) were higher than the utility value used in the model (0.62). The committee noted that the ERG was unable to retrieve the full publication by Wild et al. and so did not critically appraise it. The committee could not address whether the population in Wild et al. reflected the populations with early and late progressed disease in the NHS. The committee recalled its earlier discussion concerning the gap between disease progression and worsening of symptoms needing treatment (see section 3.12), during which time quality of life would likely remain stable. It thought that a utility value of 0.62 for the entire duration of the progressed-disease state was low. The committee also noted its preference (based on the NICE [guide to the methods of technology appraisal](#)) for utilities derived from the same source as the clinical evidence. It agreed to consider scenario analyses from the company and the ERG using values from GALLIUM for the post-progression state.

## ***Resource use***

### **Vial sharing is a realistic assumption for intravenous rituximab**

3.23 In the company's analysis the acquisition costs of obinutuzumab and rituximab were confidential because of nationally available confidential discounts. The company, in its base case, assumed vial sharing for both obinutuzumab and rituximab. The committee heard from the NHS England representative that obinutuzumab is given as a fixed dose, so there would be no vial sharing. For rituximab, however, it heard from the representative that the NHS, through a Commissioning for Quality and Innovation (CQUIN) for 'hospital medicines optimisation', actively promotes 'fully' optimising use of medicines commissioned by specialised services. This includes vial sharing for rituximab because of its many indications across oncology, dermatology, rheumatology and nephrology. The committee concluded that the model should allow for some vial sharing for intravenous rituximab but not for obinutuzumab.

**Subcutaneous rituximab would incur a lower administration cost than that modelled**

3.24 The committee was aware that rituximab can be given intravenously or subcutaneously, and that subcutaneous rituximab is cheaper to administer. In the model, the company assumed that rituximab would only be given intravenously during induction but that, based on its market research, a proportion of patients would have rituximab subcutaneously during the maintenance phase, which would incur a lower administration cost. The committee heard from the NHS England representative that the proportion used by the company was reasonable.

**The cost of rituximab intravenous infusion is less than the cost in the model**

3.25 The company assumed the same administration costs for intravenous rituximab and obinutuzumab during induction (£407 for the first infusion, which takes longer, and £361 for subsequent infusions) and during maintenance (£337). However, the committee understood that an obinutuzumab infusion takes much longer than a rituximab infusion, and so would have a higher administration cost. Also, after the first 2 treatment cycles, according to the marketing authorisation, rituximab can be given safely at a faster rate than in the first 2 cycles, so should incur a lower administration cost than modelled. The committee concluded that the costs applied by the company did not reflect reality.

**The availability of cheaper rituximab biosimilars reduces the cost effectiveness of obinutuzumab**

3.26 The committee was aware that 2 biosimilar versions of rituximab have a marketing authorisation, both of which are intravenous formulations. NHS England encourages use of biosimilars because they are similarly effective and less expensive. The rituximab biosimilars have discounted price agreements with NHS England by tender, which the manufacturers shared with NICE in confidence. The committee agreed that most commissioners in England would prefer biosimilar to branded rituximab.

The ERG used the price for biosimilar rituximab in the company's base-

case and scenario analyses, and in its own exploratory analyses. The committee agreed that analyses using the acquisition costs of biosimilar rituximab would be the basis of its recommendation.

### **Subsequent treatment costs are not incorporated properly in the model**

3.27 The company included the cost of treatments taken after obinutuzumab or rituximab by applying a single cost at progression. It assumed that next-line treatment would be the same between both treatment arms and for early or late disease progression, and that costs and outcomes would be similar. The clinical experts explained that people with early-progressing disease would have more aggressive treatment than people with later-progressing disease. The committee heard from the company that it did not model the effectiveness and costs of subsequent treatment explicitly. Instead, the company considered that GALLIUM (early progression) or PRIMA (late progression), which both allowed subsequent treatment, captured any resulting survival benefit. The committee questioned the company's approach of applying a single overall cost for subsequent treatments, noting that delaying progression with obinutuzumab as seen in GALLIUM, should result in lower subsequent treatment costs.

### ***Cost-effectiveness results***

#### **The company's base-case ICER comparing obinutuzumab with rituximab is between £20,000 and £30,000 per QALY gained**

3.28 The committee considered the incremental cost-effectiveness ratios (ICERs) from the company's base case, recalculated by the ERG to include the discounted prices for biosimilar rituximab. The ICER for obinutuzumab-based therapy compared with rituximab-based therapy was between £20,000 and £30,000 per QALY gained. However, the committee concluded that the company's base case was not appropriate for decision-making because of the concerns about the structure and assumptions of the model.

## ***ERG exploratory analyses***

### **The ERG's preferred assumptions increase the ICER**

3.29 The committee noted that using some of the ERG's preferred assumptions had a negligible effect on the ICERs (for example, adjusting the proportion of women to be the same as seen in NHS clinical practice, incorporating adverse event disutilities and using a re-estimated adverse event rate). Using some of the ERG's preferred assumptions increased the ICERs by up to 10% (for example, increasing the age at baseline to be the same as seen in NHS clinical practice, incorporating an age-related utility decrement and using different death rates for the treatment arms for the progression-free disease state and early progressed-disease state). However, using the independent review committee progression-free survival and the Weibull curve increased the ICER by 19%.

### **Most of the ERG's changes to the model are acceptable**

3.30 The ERG's preferred base case included changes described in section 3.29, which cumulatively increased the company's base case by 44%. Moreover, considering a shorter duration of treatment effect of 5 years (see section 3.17) along with the ERG's preferred assumption roughly doubled the company's base-case ICER. The committee agreed with most of the ERG's changes, except the following:

- Distribution per chemotherapy regimen: Based on the clinical experts' opinion that the use of bendamustine is declining, the committee was inclined to accept the values derived from the company's market research (29% bendamustine, 13% CHOP and 36% CVP) and noted that these would decrease the ICER slightly.
- No vial sharing: The committee expected that vial sharing would reduce costs in the rituximab arm and that this would increase the ICER.

### **The most plausible ICER is much higher than £30,000 per QALY gained**

3.31 The committee assessed the impact of some of its preferred assumptions from the ERG's exploratory analyses, including:

- a treatment effect duration that does not continue beyond the trial follow-up
- a utility value for progressed-disease states from GALLIUM
- an age-related utility decrement
- disutility for adverse events.

However, the committee did not see any analysis that explored:

- using time to next treatment instead of progression-free survival to capture treatment effect
- modelling effectiveness independently for obinutuzumab and rituximab (that is, assuming no proportional hazards)
- assuming no overall survival gain with obinutuzumab
- implementing vial sharing for rituximab (no wastage) correctly
- using lower administration costs for rituximab intravenous infusion after the first 2 doses
- including more valid reflections of subsequent treatment costs.

Overall, the committee concluded that the ICER for obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment, compared with rituximab plus chemotherapy followed by rituximab maintenance treatment is much higher than £30,000 per quality-adjusted life year (QALY) gained. It therefore did not consider obinutuzumab to be a cost-effective use of NHS resources for untreated follicular lymphoma.

### ***End of life***

#### **Obinutuzumab is not a life-extending treatment**

3.32 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund](#)



[technology appraisal process and methods](#). The committee heard from the company that life expectancy for people with treated follicular lymphoma exceeds 2 years, and that the company had not made a case for obinutuzumab as a life-extending treatment. The committee concluded that obinutuzumab for first-line treatment of advanced follicular lymphoma did not meet the end-of-life criteria.

## ***Innovation***

### **Obinutuzumab is not innovative**

3.33 The company explained that it considered obinutuzumab to be innovative. However, the committee heard from the clinical experts that obinutuzumab's mechanism was similar to that of rituximab, so it did not reflect a 'step change' in treatment. The committee did not identify health benefits excluded from the modelling. It concluded that obinutuzumab was new, but not innovative.

## **4 Proposed date for review of guidance**

4.1 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.

Dr Amanda Adler  
Chair, appraisal committee  
September 2017

## **5 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 B](#).

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.

#### **Anwar Jilani**

Technical Lead

#### **Ahmed Elsada and Jasdeep Hayre**

Technical Advisers

#### **Jeremy Powell**

Project Manager

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