

# Obinutuzumab for untreated advanced follicular lymphoma

Technology appraisal guidance

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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Obinutuzumab is recommended as an option for untreated advanced follicular lymphoma in adults (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), only if:
- the person has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more
  - the company provides obinutuzumab according to the [commercial arrangement](#).
- 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 to induction therapy.

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 with certainty whether obinutuzumab increases life expectancy.

The company's revised economic analyses focuses on higher-risk subgroups. Obinutuzumab costs more than branded rituximab and even more than the biosimilar versions of rituximab. However, using the preferred assumptions and the discounted prices for obinutuzumab and rituximab, the cost-effectiveness estimate for obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment, compared with

rituximab plus chemotherapy followed by rituximab maintenance treatment, is lower than £30,000 per quality-adjusted life year gained. Therefore, obinutuzumab is recommended as an option for untreated advanced follicular lymphoma in patients at higher risk.

## 2 Information about obinutuzumab

### Marketing authorisation indication

- 2.1 Obinutuzumab (Gazyvaro, Roche) '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'.

### Dosage in the marketing authorisation

- 2.2 Obinutuzumab is given by intravenous infusion. Induction consists of obinutuzumab plus chemotherapy dosage:
- with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine and prednisolone (CVP):
    - cycle 1: 1,000 mg on days 1, 8 and 15 of the first 21-day treatment cycle
    - cycles 2 to 8: 1,000 mg on day 1 of each 21-day treatment cycle (with the CHOP regimen, obinutuzumab is given alone for the last 2 cycles), or
  - with bendamustine:
    - cycle 1: 1,000 mg on days 1, 8 and 15 of the first 28-day treatment cycle
    - cycles 2 to 6: 1,000 mg on day 1 of each 28-day treatment cycle and
  - maintenance dosage of 1,000 mg every 2 months for 2 years or until disease progression (whichever occurs first).

### Price

- 2.3 £3,312 per 1,000-mg vial (excluding VAT; BNF online, August 2017). The company has a [commercial arrangement](#). This makes obinutuzumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let

relevant NHS organisations know details of the discount.

## 3 Committee discussion

The [appraisal committee](#) 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 over many years, often without symptoms. The patient experts noted that, despite this, knowing that 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

- 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](#) also recommends rituximab induction therapy for people with advanced-stage (stages 3 and 4) 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 Drugs 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 treatment.

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 3 to 4 follicular lymphoma recommends rituximab plus 1 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 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 its [technology appraisal guidance on rituximab](#), 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 of the PRIMA study 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% to 90%) whose disease responds to induction therapy have rituximab maintenance therapy. The NHS England's Cancer Drugs Fund clinical lead 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:

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

Referring to its discussion on the treatment pathway (see [sections 3.2 to 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 3 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 through a radiological and oncological review of patient responses by an independent review committee was a secondary outcome. Patients were treated 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). Two of the prespecified subgroups in GALLIUM were patients at intermediate or high risk of mortality, categorised by Follicular Lymphoma International Prognostic Index (FLIPI) scores (n=474). In response to consultation, the company suggested that patients in these subgroups were the most relevant population (see [section 3.9](#)). The company based its analysis on these higher-risk subgroups.

### The whole population in GALLIUM 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 59.0 years. The committee heard from the clinical experts and the ERG that this reflected a younger population than would be seen in clinical practice. In response to consultation, the company changed the median age used in its economic model to 62.2 years.
- 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.

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

## **Patients who are at intermediate or high risk from GALLIUM are a clinically relevant population**

- 3.9 The summary of product characteristics states that obinutuzumab's efficacy in patients at low risk of premature mortality (that is, people with FLIPI score of 0 to 1) is 'inconclusive'. Because of this, and in response to consultation, the company changed the population in its analysis from all people with advanced follicular lymphoma to people with an intermediate or high FLIPI score (collectively called patients at higher risk because they are at higher risk of dying than patients with lower scores). The committee questioned whether clinicians use FLIPI scores to categorise severity of disease. The Cancer Drugs Fund clinical lead explained that FLIPI scores are not routinely used to inform treatment, but they are used to assess prognosis. This was confirmed by comments submitted by the clinical experts who attended the first meeting. The committee

understood that the factors used to determine FLIPI scores (such as stage of Ann Arbor classification system, haemoglobin, serum lactate dehydrogenase and number of nodal sites affected) are already routinely measured, and that using FLIPI scores to inform treatment would not be a large extra burden for the NHS. Overall, the committee was satisfied that the higher-risk subgroup (based on FLIPI scores) was the clinically relevant population to consider in this appraisal.

## Efficacy results

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

3.10 The company had done several analyses in the higher-risk subgroup, including the prespecified '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, 81.7% of patients at higher risk randomised to obinutuzumab compared with 72.5% 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 83.2% and 76.0%. Obinutuzumab reduced the risk of disease progression in patients at higher risk by 38% (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.47 to 0.80) according to investigator assessment, and by 33% (HR 0.67, 95% CI 0.51 to 0.88) according to the independent review committee. Because there were few events, median progression-free survival could not be estimated in either assessment. The committee recognised that there was no trial evidence on the effect of obinutuzumab on progression-free survival after 5 years. Therefore, the committee concluded that obinutuzumab delays disease progression in the short term, but that there is uncertainty about its long-term effect on progression-free survival.

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

3.11 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 committee recalled that it usually prefers 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 considered 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 it had chosen investigator-assessed progression-free survival as the primary outcome to produce 'quicker results' and to avoid inconsistent assessments in people followed up for long periods. The committee noted that, in its response to consultation, the company based its new analyses on outcomes assessed by an independent review committee; the committee agreed that this was appropriate.

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

- 3.12 GALLIUM was not designed to estimate the difference in overall survival between the 2 treatments. At the time of the analysis, 7.8% of patients at higher risk had died, at which point there was no statistically significant difference between obinutuzumab and rituximab (HR 0.76; 95% CI 0.49 to 1.16). The clinical experts stated that the lack of an overall survival benefit with obinutuzumab despite a progression-free survival benefit was possible, and that 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 also recognised that it had not been presented with evidence supporting the association between progression-free and overall survival in follicular lymphoma. The committee could not conclude that obinutuzumab prolongs overall survival compared with rituximab based on the evidence from GALLIUM.



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

- 3.13 The committee heard from clinical experts and the NHS England Cancer Drugs Fund clinical lead, who 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. However, in response to consultation, the company noted that independently assessed progression-free survival is a more conservative measure than time to next treatment. The committee acknowledged this and used the company's modelled progression-free survival to make its decision, but considered that time to next treatment was a more meaningful outcome for patients.

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

- 3.14 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. The committee noted that the differences in the EQ-5D scores between arms were not statistically significant.

## **Safety results**

## **Obinutuzumab-based therapy is associated with a higher rate of**



## **adverse events than rituximab-based therapy**

- 3.15 In the overall follicular lymphoma population of 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**

- 3.16 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 people whose disease progresses early have a worse prognosis than people whose disease progresses late. The committee accepted the separate modelling of early- and late-progressing disease and the 2-year cut-off to differentiate them.

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

- 3.17 When the company first modelled progression-free survival, it assumed proportional hazards during the first 9 years (that is, the effect of obinutuzumab relative to rituximab remains the same over time). The company based this assumption on log-cumulative hazard plots for progression-free survival from GALLIUM, which it interpreted to be parallel. However, the committee considered that the plots converged, suggesting that the proportional hazards assumption did not hold. Responding to this, the company revised its model to assume non-proportional hazards, and modelled treatment effects independently.

## **The revised extrapolation of progression-free survival is appropriate**

- 3.18 The company initially used an exponential function (assuming proportional hazards) to extrapolate and explore the likely progression-free survival benefit of obinutuzumab beyond the follow-up period of GALLIUM. At the first committee meeting, the ERG suggested that a Weibull extrapolation model assuming non-proportional hazards was more appropriate, which the committee accepted. The company argued that the Weibull function was inappropriate because it implied that the risk of progression increased with time spent in the progression-free state. After consultation, it submitted a revised model using a log-logistic extrapolation and assuming non-proportional hazards. The committee accepted that, in the full population, risk of progression may not increase with time spent in the progression-free state. It recognised that the patients who are progression free for a long time could plausibly be the patients who started with a lower baseline risk, and that their risk of progression may remain low over time. However, the committee decided that this assumption would not hold for the higher-risk subgroup because it would not include patients whose risk starts and remains low. Because of this, the committee concluded that the Weibull distribution remained a potential extrapolation option. The committee compared various functions to see whether the modelled extrapolated outcomes were clinically plausible. The company's clinical experts had originally estimated that 30% to 40% of patients in the overall population having rituximab would remain progression free at 10 years. The committee

understood that fewer patients at higher risk may remain progression free at 10 years compared with the overall follicular lymphoma population, but decided that the experts' estimates of progression-free survival for patients using rituximab were appropriate for estimating progression-free survival for patients using obinutuzumab. The log-logistic model predicted that 41.3% of patients at higher risk having rituximab would remain progression free for 10 years. Because this prediction fell outside the clinically plausible range estimated by experts, the committee considered that the log-logistic model overestimated progression-free survival. The Gompertz, Weibull and exponential distributions provided estimates within the experts' range for 10-year progression-free survival using rituximab (36.7%, 34.3% and 36.7% respectively). The committee decided that the Gompertz distribution was too pessimistic because the number of people remaining progression free declined at a much higher rate after 10 years in the obinutuzumab arm than the rituximab arm. The committee concluded that estimates based on the Weibull or exponential functions estimated progression-free survival more realistically. After the second committee meeting, the company submitted a revised model and provided incremental cost-effectiveness ratios (ICERs) based only on Weibull and exponential extrapolations, in line with the committee's preference.

## **The treatment effect duration is more than 5 years but much less than 20 years**

- 3.19 When extrapolating progression-free survival, the company initially 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 because the company had interpreted the results from 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. The committee preferred to see analyses assuming no effect beyond the GALLIUM trial follow up of 5 years. In response to consultation, the company provided evidence

of a treatment effect for obinutuzumab in a different setting (obinutuzumab compared with rituximab in chronic lymphocytic leukaemia; median progression-free survival of 2.4 years compared with 1.3 years). The company also provided additional evidence for the duration of rituximab's treatment effect, and argued that obinutuzumab would have a similar effect because it has a similar mechanism of action to rituximab (2 studies of rituximab plus chemotherapy compared with chemotherapy alone reported treatment effects of 8.4 years and 8.7 years). The company revised its economic model to assume non-proportional hazards between obinutuzumab and rituximab (see [section 3.17](#)), which lowered the treatment effect of obinutuzumab compared with rituximab. The company argued that this removed the need to limit the duration of the treatment effect. The committee noted that the company's model (which used a log-logistic progression-free survival extrapolation) implied a treatment effect of obinutuzumab compared with rituximab of approximately 20 years. The committee was also aware that using a Weibull extrapolation without limiting the treatment effect duration implied a treatment effect of approximately 33 years, and using an exponential extrapolation without limiting the treatment effect duration implied an indefinite treatment effect. The committee acknowledged that treatment effect duration was uncertain, but recalled that it had not seen any clinical evidence of a 20-year treatment effect. Based on the clinical evidence presented by the company, the committee concluded that the treatment effect duration was longer than 5 years but much less than 20 years. After the second committee meeting, the company provided ICER estimates based on treatment effect durations of 5 years and 9 years, which the committee used to make its decision.

## **There is uncertainty about the size of the overall survival benefit of obinutuzumab**

- 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 overall survival data from GALLIUM were highly immature, and that the relationship between

progression-free and overall survival was not well established in follicular lymphoma (see [section 3.12](#)). Because of this, the committee considered the company's approach to modelling overall survival represented an optimistic scenario and concluded that the evidence did not support the company's original modelling of overall survival. In response to consultation, the company argued that the overall survival benefit modelled was similar to the benefit of obinutuzumab in the rituximab-refractory follicular lymphoma setting and the benefit of rituximab in the first-line induction setting. The Cancer Drugs Fund clinical lead suggested that a progression-free survival benefit was likely to translate to overall survival benefit, but that this would be hard to quantify given the different lines of treatment patients had. The Cancer Drugs Fund clinical lead advised that there was evidence of a benefit in prognosis from rituximab, and that it would be reasonable to assume a similar benefit in obinutuzumab. The committee agreed that there was a likely overall survival benefit, but that there was uncertainty about the size of this benefit because of the lack of evidence from the GALLIUM trial.

## Health-related quality of life

### The utility value for the progressed-disease state is acceptable

- 3.21 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 values from the literature for the progressed-disease state (Wild et al. 2006; Wild et al. 2005). The company used utility values of 0.62 (Wild et al. 2006) and 0.77 (Wild et al. 2005) to reflect the early and late-progressing disease states (because people whose disease progresses early have a worse prognosis than people whose disease progresses late). 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. The company chose not to use values derived from GALLIUM to populate the progressed-disease states because, in its opinion, data from GALLIUM were collected only once after progression and so did not capture advanced stages of progression. The committee was concerned that these values lacked face validity because they were lower than expected for a patient

population with the prospect of a long life expectancy after disease progression. However, it acknowledged that the quality of life of patients with progressed disease was uncertain and concluded that the company's approach was acceptable.

## Resource use

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

3.22 In the company's analysis, the acquisition costs of obinutuzumab and rituximab were confidential because of nationally available confidential discounts. In its base case, the company initially 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 NHS England representative that the NHS uses a Commissioning for Quality and Innovation (CQUIN) for 'hospital medicines optimisation' to promote fully optimising 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. After the second committee meeting, the company updated its model to reflect this.

### **Subcutaneous rituximab would incur a lower administration cost than intravenous administration**

3.23 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 representative from NHS England that the proportion used by the company was reasonable.

## **The modelled administration costs are acceptable for decision making**

- 3.24 The company initially 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 administration costs were likely to be higher for obinutuzumab because obinutuzumab infusions take longer than rituximab infusions. In response to consultation, the company revised the administration costs to reflect this. However, the Cancer Drugs Fund clinical lead noted that the administration costs were not correct because of differences in the number of appointments needed for each accompanying chemotherapy treatment; for example, obinutuzumab with bendamustine costs more to administer than obinutuzumab with CVP or CHOP (£1,352 compared with £1,047 respectively). The company updated its model using administration costs based on national reference costs specific to each chemotherapy treatment, plus pharmacy and transport costs. The ERG agreed with the company's chosen source for administration costs. The committee acknowledged that, although the tariff costs suggested by the Cancer Drugs Fund clinical lead were more recent than the national reference costs, the effect on the ICER was likely to be modest. The committee concluded that the administration costs modelled by the company were acceptable for decision making.

## **The availability of cheaper rituximab biosimilars should be taken into account**

- 3.25 The company's model assumed that a proportion of patients have rituximab maintenance treatment subcutaneously, and that the remaining patients have rituximab intravenously. The committee was aware that 2 biosimilar versions of intravenous rituximab have a marketing authorisation. NHS England encourages use of biosimilars through a CQUIN for 'hospital medicines optimisation' because biosimilars are similarly effective to branded medications and less expensive. The manufacturers of rituximab biosimilars have discounted price agreements with NHS England, which they shared with NICE in confidence. 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 initially decided that analyses using the acquisition costs of biosimilar rituximab would be the basis of its recommendation. However, in response to consultation, the company argued that the uptake of biosimilars would not be 100%, referencing uptake of etanercept and infliximab biosimilars described in the commissioning framework for biological medicines. Following this, the committee heard from the Cancer Drugs Fund clinical lead that uptake of biosimilar rituximab was around 40% in October 2017 and 65% in November 2017, and is increasing rapidly. The company modelled 40% biosimilar uptake in its final model. The committee agreed to use the most recent biosimilar uptake estimate (65%) for decision making.

## **The company did not incorporate the subsequent treatment costs properly in the model**

- 3.26 The company modelled the costs of subsequent lines of treatment taken after obinutuzumab or rituximab by applying a single cost at disease 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 committee understood that, in clinical practice, subsequent treatment costs would be likely to increase with time spent in the progressed-disease state. It was unsure about whether obinutuzumab's effect in delaying progression would result in a decrease in time spent in the progressed-disease state because of the uncertainty about whether obinutuzumab prolonged survival (see [section 3.20](#)). The committee decided that the subsequent treatment costs could be better captured in the model, although it was uncertain about how this would affect the ICER.

## **Cost-effectiveness results**

### **The company modelled most of the committee's preferred assumptions**

- 3.27 The company's final model assumed:



- vial sharing for rituximab only
- that administration costs could be based on NHS reference costs, accounting for differences between any accompanying chemotherapy treatment.

The company presented scenario analyses that considered Weibull and exponential extrapolations for progression-free survival and varied the treatment effect duration between 5 years and 9 years. Although the committee agreed that the company's model could have better captured subsequent treatment costs, it concluded that the model captured most of its preferred assumptions and was appropriate for decision making.

## **The most plausible ICER comparing obinutuzumab with rituximab is less than £30,000 per QALY gained**

- 3.28 The company presented ICER estimates for Weibull and exponential extrapolations for progression-free survival and for treatment effect durations of 5 years and 9 years. The ERG recalculated the ICERs from these analyses to include the confidential discounted biosimilar prices and a 65% uptake of biosimilar rituximab. The recalculated ICERs were less than £30,000 per quality-adjusted life year (QALY) gained for obinutuzumab-based therapy compared with rituximab-based therapy. The committee acknowledged that there was substantial uncertainty in the evidence base and ICER in terms of the treatment effect duration and immaturity of the clinical data. However, the committee concluded that obinutuzumab, provided with the discount agreed in the patient access scheme, is a cost-effective use of NHS resources for adults with untreated follicular lymphoma with a FLIPI score of 2 or more.

## **End of life**

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

- 3.29 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 concluded that obinutuzumab for first-line treatment of advanced follicular lymphoma did not meet the end-of-life criteria.

## Innovation

### Obinutuzumab is not innovative

- 3.30 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 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated advanced follicular lymphoma and the doctor responsible for their care thinks that obinutuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

## 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 and Lucy Beggs**

Technical leads

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

Technical advisers

#### **Jeremy Powell**

Project manager

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## Accreditation

