

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final appraisal determination

### Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of NICE technology appraisal guidance 110)

#### 1 Guidance

1.1 Rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- $\alpha$  (CHVPi) **or**
- chlorambucil

is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.

#### 2 Clinical need and practice

2.1 Non-Hodgkin's lymphoma is a cancer of the lymphatic tissue, which causes enlargement of the lymph nodes and generalised symptoms. The lymphatic system produces, stores and delivers lymphocytes, which are cells that fight infection. Follicular lymphoma is a type of low-grade or indolent non-Hodgkin's lymphoma that develops slowly, and often without symptoms, for many years. It affects B-cell lymphocytes and is therefore classified as a B-cell non-Hodgkin's lymphoma. Patients with follicular lymphoma typically present with painless, swollen lymph nodes in

the neck, armpit or groin. Systemic or 'B' symptoms are rare and include fever, fatigue, night sweats, and unexplained weight loss.

2.2 When a diagnosis of follicular lymphoma is confirmed, investigations are undertaken to find out which areas of the body are affected, the number of lymph nodes involved, and whether other organs are affected, such as the bone marrow or liver. It can be classified into four stages of disease (I–IV) that reflect both the number of sites involved and the presence of disease above or below the diaphragm. At most, 10–15% of follicular lymphomas are detected at an early stage; the majority of people present with advanced disease (stage III–IV). In 2008, the incidence of follicular lymphoma in England and Wales was 3.4 per 100,000 persons, equating to 1900 people. More than 70% of follicular lymphomas are diagnosed in people aged over 60 years.

2.3 Follicular lymphoma is characterised by a relapsing and remitting clinical course over several years, with each successive response to treatment becoming more difficult to achieve and of shorter duration. In the early 1990s, median survival was expected to be 8–10 years. However, in the past decade, longer median survival has been reported (for example, survival at 20 years has been reported to be as high as 44%). Advanced stage III–IV lymphomas eventually become resistant to chemotherapy and transform to high-grade or aggressive lymphomas, such as diffuse large B-cell lymphoma.

2.4 Advanced follicular lymphoma is not curable and so the aim of disease management is to both increase life expectancy and to increase health-related quality of life. A proportion of people with stage III–IV follicular lymphoma do not present with symptoms of disease and receive 'watchful waiting' until symptoms occur. Of the people who need systemic therapy, for the majority (90%) first-line therapy is rituximab and chemotherapy, with around two-thirds

receiving the CVP regimen as the chemotherapy component of treatment. The next most frequent chemotherapy regimen used with rituximab is CHOP, which accounts for approximately 16% of chemotherapy regimens. People who have a lower performance status may receive chlorambucil as single-agent chemotherapy.

- 2.5 Maintenance treatment is given after response to first-line induction treatment. 'Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma' (NICE technology appraisal guidance 226) recommends rituximab monotherapy as an option for maintenance treatment after first-line induction therapy with rituximab plus chemotherapy. After first-line induction therapy (with or without subsequent maintenance therapy), a person's disease eventually relapses, requiring further treatment. The treatment chosen for relapsed disease will depend on the first-line treatment regimen used, the duration of response to treatment and whether the disease has transformed to aggressive lymphoma.

### **3 The technology**

- 3.1 Rituximab (MabThera, Roche Products) is a genetically engineered chimeric (mouse/human) monoclonal antibody that depletes B cells by targeting cells bearing the CD20 surface marker. Rituximab as a first-line treatment for follicular lymphoma was originally licensed in combination with CVP. The marketing authorisation was subsequently revised (January 2008) to allow the use of a wider range of chemotherapy regimens. The subject of this review of 'Rituximab for the treatment of follicular lymphoma (NICE technology appraisal guidance 110) is the wider indication: rituximab for the treatment of previously untreated stage III–IV follicular lymphoma in combination with chemotherapy (not just CVP).

- 3.2 Rituximab has been associated with infusion-related reactions and infections, sometimes severe or life-threatening. Severe reactions are more common in people with high tumour burden, and the incidence and severity of infusion reactions decreases with successive infusions. It is contraindicated in people with active severe infections, and in people with severe heart failure or severe uncontrolled cardiac disease. For full details of side effects and contraindications, see the summary of product characteristics.
- 3.3 The recommended dose of rituximab in combination with chemotherapy for induction treatment of previously untreated patients with follicular lymphoma is 375 mg/m<sup>2</sup> body surface area, per cycle, for up to eight cycles, administered on day 1 of the chemotherapy cycle. The cost of one 10-ml (100-mg) vial is £174.63 and one 50-ml (500-mg) vial is £873.15 (excluding VAT; 'British national formulary' [BNF] edition 61). For a person with a body surface area of 1.85 m<sup>2</sup> and assuming vial wastage, the cost per infusion of rituximab induction treatment is £1222.41 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

## **4 Evidence and interpretation**

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

### **4.1 *Clinical effectiveness***

- 4.1.1 The Assessment Group identified four randomised controlled trials that met the criteria for inclusion in the systematic review. The trials compared:

- rituximab plus CVP with CVP alone (M39021)
- rituximab plus CHOP with CHOP alone (GLSG-2000)
- rituximab plus MCP with MCP alone (OSHO-39)

- rituximab plus CHVPi with CHVPi alone (FL2000).

4.1.2 The M39021, GLSG-2000 and OSHO-39 trials used the licensed administration schedule for rituximab (375 mg/m<sup>2</sup> per cycle for up to eight cycles), whereas the FL2000 trial used a different administration schedule that did not include rituximab in the first two cycles of CHVPi. The Assessment Group considered all four trials to be of good quality.

4.1.3 The four trials reported different efficacy outcomes but they all reported overall survival, which was defined as time from randomisation to the date of death by any cause. The OSHO-39 trial was the only trial to report progression-free survival defined as randomisation to disease progression or death from non-Hodgkin's lymphoma.

#### **Rituximab plus CVP versus CVP alone**

4.1.4 The M39021 trial was an open-label multicentre trial that compared rituximab plus CVP with CVP alone. The trial recruited patients with stage III or IV follicular lymphoma (162 patients to rituximab plus CVP and 159 patients to CVP alone). The median age of patients was 52 years in the rituximab plus CVP group and 53 years in the CVP alone group. Most patients had an ECOG performance status of 0 to 1 and patients with an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2 were excluded from the trial. The median follow-up was 53 months.

4.1.5 The primary outcome measure of the M39021 trial was time to treatment failure and secondary outcomes included overall survival, response rates (overall, complete and partial), response duration, time to next antilymphoma treatment and disease-free survival. The median time to treatment failure in the rituximab plus CVP group was 27 months compared with 7 months in the

CVP alone group ( $p < 0.0001$ ). Overall survival rate at 4 years was 83% in the rituximab plus CVP group and 77% in the CVP alone group ( $p < 0.0290$ ). The median overall survival was not reached. The overall response rate was 81% in the rituximab plus CVP group and 57% in the CVP alone group ( $p < 0.0001$ ). Complete response in the rituximab plus CVP group was 30% and in the CVP alone group was 8% ( $p < 0.001$ ) and partial response was 51% in the rituximab plus CVP group compared with 49% in the CVP alone group ( $p$  value not reported).

### **Rituximab plus CHOP versus CHOP alone**

- 4.1.6 The GLSG-2000 trial was an open-label multicentre trial that compared rituximab plus CHOP with CHOP alone. The trial recruited patients with stage III and IV follicular lymphoma (279 patients to rituximab plus CHOP and 278 to CHOP alone). The median age of patients was 57 years for both treatment groups and most patients had an ECOG performance status of 0 to 1. The median follow-up was 56 months.
- 4.1.7 The primary outcome measure was time to treatment failure and secondary outcomes included overall survival, response rates (overall, complete and partial), response duration and time to next antilymphoma treatment. The median time to treatment failure was not reached in the rituximab plus CHOP group and was 35 months in the CHOP alone group ( $p < 0.0001$ ). The overall survival rate at 5 years was 90% in the rituximab plus CHOP group and 84% in the CHOP alone group ( $p = 0.0493$ ). The median overall survival was not reached. The overall response rate was 96% in the rituximab plus CHOP group and 91% in the CHOP alone group ( $p = 0.0046$ ). Complete response in the rituximab plus CHOP group was 19% and 17% in the CHOP alone group ( $p$  value not reported). Partial response was

77% in the rituximab plus CHOP group compared with 74% in the CHOP alone group (p value not reported).

#### **Rituximab plus MCP versus MCP alone**

- 4.1.8 The OSHO-39 trial was an open-label multicentre trial that compared rituximab plus MCP with MCP alone. The trial recruited patients with CD20-positive indolent non-Hodgkin's lymphoma, which included lymphoplasmacytic lymphoma and mantle cell lymphoma. The primary analysis population was defined as the population of patients with follicular lymphoma (105 patients to rituximab plus MCP and 96 patients to MCP alone). The median age of patients was 60 years in the rituximab plus MCP group and 57 years in the MCP alone group. Most patients had an ECOG performance status of 0 to 1, and patients with an ECOG performance status of more than 2 were excluded from the trial. The median follow-up was 49 months for the rituximab plus MCP group and 42 months for the MCP alone group.
- 4.1.9 The primary outcome measure of the OSHO-39 trial was overall response rate and secondary outcomes included progression-free survival, overall survival, response rates (overall, complete and partial), response duration, event-free survival and time to next antilymphoma treatment. The overall response rate was 92% in the rituximab plus MCP group and 75% in the MCP alone group ( $p < 0.0009$ ). The overall survival rate at 4 years was 87% for the rituximab plus MCP group and 74% for the MCP alone group ( $p = 0.0096$ ). The median overall survival was not reached. Complete response in the rituximab plus MCP group was 50% compared with 25% in the MCP alone group ( $p = 0.0004$ ). Partial response in the rituximab plus MCP group was 43% and 50% in the MCP alone group (p value not reported). Median progression-free survival was not reached in

the rituximab plus MCP group and was 28.8 months in the MCP alone group ( $p < 0.0001$ ).

### **Rituximab plus CHVPi versus CHVPi alone**

- 4.1.10 The FL2000 trial was an open-label multicentre trial that compared rituximab plus CHVPi with CHVPi alone. The trial recruited patients with stage II–IV follicular lymphoma (175 patients to rituximab plus CHVPi and 183 patients to CHVPi alone). The median age of patients was 61 years. Most patients had an ECOG performance status of 0 to 1. The median follow-up was 60 months.
- 4.1.11 The primary outcome measure of the trial was event-free survival and secondary outcomes included overall survival, response rates (overall, complete and partial) and response duration. The outcomes were evaluated at 6 and 18 months; 18-month results are reported here. Event-free survival was not reached in the rituximab plus CHVPi group compared with 35 months in the CHVPi alone group ( $p = 0.0004$ ). The overall survival rate at 5 years was 84% in the rituximab plus CHVPi group and 79% in the CHVPi alone group (not significant). The median overall survival was not reached. The overall response rate was 81% in the rituximab plus CHVPi group and 72% in the CHVPi alone group ( $p$  value not reported). Excluding unconfirmed complete responses, the complete response rate was 51% in the rituximab plus CHVPi group and 39% in the CHVPi alone group ( $p$  value not reported). Partial response was 30% in the rituximab plus CHVPi group and 33% in the CHVPi alone group ( $p$  value not reported).

### **Adverse events**

- 4.1.12 All four trials reported grade 3 and 4 adverse events. Although an increased incidence of leukocytopenia, neutropenia and granulocytopenia was observed in the trials in the rituximab plus



chemotherapy arms, this was not associated with an increase in the rate of infection (infection is associated with leukocytopenia, neutropenia and granulocytopenia). However, considerable numbers of patients experienced grade 3 or 4 alopecia in both the rituximab plus CHOP and CHOP alone arms of the GLSG-2000 trial. This side effect is associated with the CHOP component of the treatment.

### **Subgroup analyses**

- 4.1.13 Rituximab plus chemotherapy compared with chemotherapy alone improved treatment outcomes for all subgroups analysed (Follicular Lymphoma International Prognostic Index [FLIPI] score, International Prognostic Index score, age, quality of response to induction therapy and other prognostic factors). The four trials presented analyses of treatment outcomes according to FLIPI score and they showed that treatment outcomes were improved for most FLIPI groups. The GLSG-2000 trial found that time to treatment failure was prolonged in the rituximab plus CHOP group regardless of whether patients were younger or older than 60 years of age.

### **Meta-analysis**

- 4.1.14 Three exploratory meta-analyses were conducted by the Assessment Group to explore the overall response rate, complete response rate and partial response rate from the four trials. There were several problems with the validity of these analyses and specifically there were high levels of statistical heterogeneity. Therefore the Assessment Group decided that the response rates from the individual trials were a more robust estimate of the efficacy of the specific rituximab plus chemotherapy regimens.

## 4.2 **Cost effectiveness**

- 4.2.1 The manufacturer submitted an economic model and the Assessment Group developed its own economic model and critiqued the economic model submitted by the manufacturer.
- 4.2.2 The Assessment Group identified three economic models from four published trials (Dundar et al. 2006, 2009; Hornberger et al. 2008; Ray et al. 2010) that met the criteria for inclusion in the systematic review of economic evaluations. One of these (Dundar et al. 2006) was the Evidence Review Group report prepared for NICE technology appraisal guidance 110 in which the addition of rituximab to CVP in first-line induction treatment was evaluated. The three identified economic models were similar and used a Markov approach. Three of the economic evaluations (Dundar et al. 2006, 2009 and Hornberger et al. 2008) only considered rituximab plus CVP, whereas the other study (Ray et al. 2010) evaluated the cost effectiveness of rituximab plus CVP, CHOP, MCP or CHVPi. The two UK economic evaluations (Dundar et al. 2006, 2009; Ray et al. 2010) produced broadly similar estimates of the incremental cost-effectiveness ratio (ICER) for rituximab plus CVP versus CVP alone (£8290 per quality-adjusted life year [QALY] gained and £8613 per QALY gained respectively). The ICERs for the addition of rituximab to CHOP, MCP and CHVPi were £10,676, £7455 and £8498 per QALY gained respectively.

### **Manufacturer's submission**

- 4.2.3 The manufacturer of rituximab provided an economic model that evaluated the cost effectiveness of the addition of rituximab to CVP, CHOP, MCP and CHVPi for patients with advanced follicular lymphoma. The model was a Markov model that estimated the costs and benefits resulting from the first-line treatment of follicular lymphoma over the patient's lifetime. The

population included in the economic analysis was patients with previously untreated follicular lymphoma for whom rituximab plus chemotherapy was suitable.

4.2.4 The model has four distinct health states: progression-free survival first-line, progression-free survival second-line, progressive disease, and death. The model has a starting age of 60 years and a follow-up period of 25 years. A half-cycle correction was applied to the model.

4.2.5 Efficacy data for first-line induction therapy was based on the individual clinical trials. For the comparison of rituximab plus CVP versus CVP alone, individual patient-level data were available. Therefore two analyses were presented for rituximab plus CVP versus CVP alone. The first analysis fitted separate curves to each arm using individual patient-level data, whereas the second analysis used the same method used in the other comparisons which was based on an extrapolation technique (exponential distribution estimated using ordinary least squares regression). After first-line therapy it was assumed that patients would receive either CHOP or rituximab plus CHOP as second-line treatment, which could be followed by rituximab maintenance for those responding to second-line treatment. Efficacy data for second-line treatment was taken from the EORTC 20981 trial that reported the effectiveness of rituximab in second-line treatment of follicular lymphoma in patients not previously treated with rituximab.

4.2.6 The utility values used in the model were derived from a study commissioned by the manufacturer. This study included 222 patients with follicular lymphoma and ECOG performance status 0 to 2. Utilities were elicited using the EQ-5D questionnaire. The following utility values were used in the model: PF1 = 0.88; PF2 = 0.79 and progressive disease = 0.62.

- 4.2.7 Drug costs used the planned dose from the trials assuming a body surface area of 1.85 m<sup>2</sup>. In the CVP, CHOP, MCP and CHVPi groups the monthly drug costs of chemotherapy alone were £72, £360, £182 and £413 respectively; when rituximab was added these costs increased to £1830, £2119, £1501 and £1626 respectively. Administration costs were taken from NHS reference costs and estimated to be £268 for rituximab plus chemotherapy and £186 for chemotherapy alone, based on an assumption that rituximab treatment was administered as a hospital day case. The economic model also includes costs associated with monitoring/surveillance and supportive care.
- 4.2.8 The base-case analysis showed that addition of rituximab to CVP compared with CVP alone resulted in an ICER of £1529 per QALY gained (incremental cost £1325 and incremental QALY 0.867) using patient-level data, and £5611 per QALY gained (incremental cost £2486 and incremental QALY 0.443) using ordinary least squares regression. The addition of rituximab to CHOP, MCP and CHVPi compared with CHOP, MCP and CHVPi alone resulted in ICERs of £5758 (incremental cost £6312 and incremental QALY 1.096), £4861 (incremental cost £6268 and incremental QALY 1.289), and £9251 (incremental cost £6247 and incremental QALY 0.675) per QALY gained respectively.
- 4.2.9 The Assessment Group reviewed the manufacturer's economic model and highlighted some inconsistencies, such as the derivation of the transition probability, calculation of post-progression survival and estimation of costs. It noted that the manufacturer used time-to-event data from clinical trials in which responders to first-line induction treatment received subsequent treatments, which may have over-estimated the effect of rituximab. The Assessment Group noted that the manufacturer

had assumed that patients receive either CHOP or rituximab plus CHOP as second-line treatment, which it did not consider reflected the range of treatments used in clinical practice. The Assessment Group did not think that it was appropriate that the manufacturer used different utility values for patients in progression-free survival first-line and progression-free survival second-line.

### **The Assessment Group's model**

- 4.2.10 The Assessment Group developed an individual patient model that simulated 100,000 patients. The model assessed the cost effectiveness of the addition of rituximab to three chemotherapy regimens: CVP, CHOP and MCP in patients with previously untreated stage III–IV follicular lymphoma. The addition of rituximab to CHVPi was not assessed because the Assessment Group thought that there were limitations in the design of the FL2000 trial such as the administration schedule, which did not include rituximab in the first two cycles of CHVPi. Also, their clinical advisers suggested that the combination of CHVPi was not used frequently in UK clinical practice.
- 4.2.11 The Assessment Group's model has four health states: first-line treatment and progression-free survival, second-line treatment and progression-free survival, progressive disease and death. In the model, patients are separated into responders and non-responders according to the response rates after first- or second-line treatments. In a separate scenario analysis, patients responding to first-line induction treatment with rituximab receive rituximab as first-line maintenance treatment. The model uses a 25-year time horizon and costs and benefits are discounted at 3.5%.
- 4.2.12 For each of the therapies examined, the response rates from the applicable trials were used to classify patients into responders

and non-responders. Individual patient data for time to progression from the M39021 trial were used in the model to develop progression-free survival curves for responders and non-responders. For the comparisons of CHOP alone with rituximab plus CHOP, and MCP alone with rituximab plus MCP, individual patient data were not available from the first-line induction trials. Furthermore, the Assessment Group considered that these trial data could be subject to confounding by the use of stem-cell transplantation or interferon as maintenance therapy in responders to treatment. The Assessment Group chose instead to use the data from the M39021 trial as a proxy to develop the progression-free survival curves.

4.2.13 The planned doses from the three main trials were used to calculate the drug acquisition costs. The planned number of cycles was also used in the economic model. The number of cycles a patient received was calculated from the progression-free survival curve to account for patients that withdrew as a result of disease progression before the end of planned treatment. Chemotherapies were assumed to be administered on a day-case basis. In addition to the administration costs, patients who received rituximab were assumed to incur additional pharmacy costs. The costs associated with transport were also included, assuming that 30% of patients required NHS transportation. In the CVP, CHOP and MCP groups the drug acquisition costs per cycle of chemotherapy alone were £60.48, £233.08 and £218.78 respectively, and with the addition of rituximab were £1282.89, £1455.49 and £1441.19 respectively.

4.2.14 The Assessment Group used the same report for the utility values in the economic model as the manufacturer (Pettengell et al. 2006). However, the Assessment Group used aggregated health states from an additional analysis, which were considered

more appropriate than the disaggregated values in the main analysis (as used by the manufacturer) because the health-state utilities in the main analysis were calculated from the degree of response to therapy and not the number of lines of treatment. The utility values in first-line treatment and progression-free survival and second-line treatment and progression-free survival were assumed to be 0.805, and 0.7363 for patients in the progressive health state.

- 4.2.15 The economic model includes the impact of adverse events that occurred in the first-line induction setting in terms of management costs and impairment of quality of life.
- 4.2.16 The deterministic base-case cost-effectiveness analysis showed that the addition of rituximab to CVP, CHOP and MCP resulted in ICERs of £7720 (incremental cost £7389 and incremental QALY 0.96), £10,834 (incremental cost £5725 and incremental QALY 0.53) and £9316 (incremental cost £5267 and incremental QALY 0.57) per QALY gained respectively.
- 4.2.17 The Assessment Group carried out a probabilistic sensitivity analysis that showed that the ICERs for the addition of rituximab to CVP, CHOP and MCP were estimated to be £7735, £10,855 and £9313 per QALY gained respectively.
- 4.2.18 The Assessment Group explored a scenario in which first-line maintenance treatment was incorporated into the treatment pathway to reflect the recommendations made in the guidance on rituximab for maintenance treatment of follicular lymphoma (NICE technology appraisal guidance 226). Assuming that responders to rituximab plus chemotherapy receive first-line maintenance rituximab, the ICERs estimated by the Assessment Group for the addition of rituximab to CVP, CHOP and MCP were £14,959 (incremental cost £18,727 and incremental QALY

1.25), £21,687 (incremental cost £19,150 and incremental QALY 0.88) and £20,493 (incremental cost £17,976 and incremental QALY 0.88) per QALY gained respectively.

4.2.19 The Assessment Group performed a probabilistic sensitivity analysis for the addition of rituximab to CVP, CHOP and MCP, which assumed that responders to rituximab plus chemotherapy receive first-line maintenance rituximab and which resulted in ICERs of £15,017, £21,625 and £20,418 per QALY gained respectively.

4.2.20 The Assessment Group performed a range of univariate sensitivity analyses to assess the impact of main parameters and assumptions. The ICER was sensitive to the assumption about the time horizon, the choice of parametric distribution to model the effectiveness in first-line induction, the maximum time a patient can remain progression-free, and resistance to rituximab. For the base-case analysis, assuming a 25% reduction in efficacy of rituximab when used as second-line treatment in patients previously treated with rituximab increased the ICERs to £14,870, £26,939 and £21,253 per QALY gained, for the addition of rituximab to CVP, CHOP and MCP respectively.

### **4.3 Consideration of the evidence**

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rituximab in combination with chemotherapy, having considered evidence on the nature of advanced follicular lymphoma and the value placed on the benefits of rituximab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.



4.3.2 The Committee considered current practice in the UK for the treatment of advanced follicular lymphoma. The clinical specialist explained that the goal of treatment is to maintain quality of life and to ensure that people are able to maintain employment and live independently for as long as possible. The availability of rituximab treatment was considered to have transformed clinical practice. The Committee heard from the clinical specialist that rituximab plus CVP (as recommended the original NICE technology appraisal guidance 110, now replaced by this guidance) is the most commonly used first-line treatment option. However, some patients, for example those with bulky disease, may be more appropriately treated with more aggressive regimens such as rituximab plus CHOP. The Committee understood that for first-line induction treatment rituximab plus CVP or rituximab plus CHOP are used to treat the majority of patients with advanced follicular lymphoma.

4.3.3 The Committee explored the use in clinical practice of first-line chemotherapy treatments other than CVP and CHOP. The clinical specialist explained that patients need different treatments depending on their overall health status with increasing age and therefore a range of treatment options is needed. Some people are not fit enough to receive rituximab plus CVP and clinicians might wish to offer other treatment options such as rituximab plus chlorambucil. The Committee heard that currently a patient can receive rituximab or chlorambucil but not a combination of rituximab plus chlorambucil, which might be considered inconsistent by some clinicians, although evidence of effectiveness for the combination is very limited. The Committee understood that being able to provide a range of treatments was valued by clinicians. It recognised that treatment with CVP or CHOP may

not be suitable for all patients and that for these patients chlorambucil may have a role in treatment.

4.3.4 The Committee discussed patient experiences of rituximab treatment. The Committee heard from patient experts that they considered they had benefited from treatment with rituximab and that it had improved their quality of life, enabling them to look to the future. The patient experts also explained that the choice of treatment and availability of an effective treatment has a positive effect on patients' families in terms of the families' quality of life. The Committee recognised the importance of rituximab as an option for the treatment of follicular lymphoma.

4.3.5 The Committee discussed consultation comments that suggested that rituximab plus bendamustine should be considered as an option for the first-line treatment of follicular lymphoma. It heard from the manufacturer that at the time of rituximab's marketing authorisation no data were submitted for the combination of rituximab plus bendamustine, and that the manufacturer of bendamustine was submitting a separate marketing authorisation for bendamustine plus rituximab for the first-line treatment of indolent non-Hodgkin's lymphoma. A NICE technology appraisal of bendamustine plus rituximab as first-line treatment of indolent non-Hodgkin's lymphoma is planned in 2012. The Committee understood that the use of rituximab plus bendamustine for the first-line treatment of follicular lymphoma would be considered in this planned appraisal. Consequently, the consideration of rituximab plus bendamustine is not included in this current appraisal.

### ***Clinical effectiveness***

4.3.6 The Committee considered the clinical effectiveness of rituximab plus CVP, CHOP, MCP and CHVPi for the treatment of

advanced follicular lymphoma. The Committee noted that the evidence came from four good-quality randomised controlled trials. The Committee accepted that the results of the individual trials indicated that the addition of rituximab to CVP, CHOP, MCP and CHVPi improved clinical outcomes including overall survival and overall response compared with chemotherapy alone. The Committee noted the length of follow-up in the four trials was short compared with the natural course of follicular lymphoma but it agreed that this was common in trials involving follicular lymphoma. The Committee then discussed the adverse events reported in the trials and noted that the addition of rituximab to CVP, CHOP, MCP and CHVPi did not significantly increase adverse-event rates. The Committee concluded that in the clinical trials rituximab plus CVP, CHOP, MCP and CHVPi had been demonstrated to be more effective than CVP, CHOP, MCP and CHVPi alone for the treatment of advanced follicular lymphoma.

- 4.3.7 The Committee discussed whether the results of the clinical trials could be considered representative of the population in UK clinical practice. The Committee noted that the population in the four trials was younger than the median age of people with advanced follicular lymphoma in the UK. It discussed whether this would have had a favourable impact on the efficacy of rituximab in the trials. The Committee heard from the clinical specialist that even though the trials did enrol younger people, some rituximab plus chemotherapy combinations, such as rituximab plus CHOP, tended to be given to younger people because of the aggressive nature of the chemotherapy regimen. The Committee was aware of the subgroup analysis by age from one of the four trials that showed that time to treatment failure was prolonged in the rituximab plus CHOP group regardless of the age of the patient. The Committee was persuaded that the

results reported in the trials could be considered as broadly representative of the outcomes of rituximab treatment in UK clinical practice.

- 4.3.8 The Committee considered the evidence of effectiveness for the combination of rituximab with chemotherapy regimens not included in the clinical trials. The Committee heard from the clinical specialist that the clinical trial data suggest that rituximab improves clinical outcomes when added to a range of chemotherapy regimens and that this would also be observed for the combination of rituximab with chemotherapy regimens not reflected in the clinical trial data. However, it was recognised that the data to support this were limited. The Committee noted comments from consultation that there are randomised studies comparing different rituximab chemotherapy regimens that have been published as abstracts. However, the Committee considered that these data include rituximab in all treatment groups and therefore do not provide direct evidence of the benefit of adding rituximab to chemotherapy. The Committee also understood that there is one uncontrolled study that investigated the efficacy of rituximab plus chlorambucil in 27 patients. The Committee heard from the manufacturer that the conclusions of the study suggested that a randomised controlled trial would be useful. However, the Committee recognised that it was unlikely that a randomised controlled trial would be conducted. The Committee considered that there was uncertainty as to the relative effect and absolute response rates of the addition of rituximab to chemotherapy regimens other than those studied in the clinical trials. However, on balance, the Committee was persuaded that on the basis of the evidence submitted and comments provided rituximab would provide an additional clinical benefit when added to chemotherapy.

### **Cost effectiveness**

4.3.9 The Committee considered the evidence of the cost effectiveness of rituximab plus CVP, CHOP, MCP and CHVPi compared with chemotherapy alone for the treatment of advanced follicular lymphoma. The Committee discussed the deterministic ICERs from the Assessment Group's model and noted that the Assessment Group had not included the combination of rituximab plus CHVPi in its economic model because there were issues with the design of the trial and the combination was not frequently used in UK clinical practice. It also noted that rituximab plus chemotherapy was compared with chemotherapy alone and not with other rituximab plus chemotherapy regimens and so comparisons could not be made between chemotherapy regimens. The Assessment Group calculated an ICER of £7720 per QALY gained for rituximab plus CVP, £10,800 per QALY gained for rituximab plus CHOP and £9320 per QALY gained for rituximab plus MCP (see section 4.2.16). The Committee also noted the ICERs presented by the manufacturer for rituximab plus CVP, CHOP, MCP and CHVPi, which ranged between £1530 and £9250 per QALY gained (see section 4.2.8). The Committee noted the Assessment Group's concerns about the manufacturer's model (see section 4.2.9) and considered the Assessment Group's calculations for rituximab plus CVP, CHOP and MCP. It agreed that the manufacturer's comparison of rituximab plus CHVPi versus CHVPi alone would need to inform the decision-making for the addition of rituximab to CHVPi. The Committee noted that the base-case ICERs were within an acceptable range of what would be considered cost effective. However, neither analysis included the use of rituximab first-line maintenance treatment, and both assumed that the efficacy of rituximab was maintained when used again as a second-line induction treatment after first-

line rituximab. The Committee concluded that on the basis of current clinical practice these two factors needed to be considered when making the decision on the cost effectiveness of rituximab plus CVP, CHOP, MCP and CHVPi.

4.3.10 The Committee considered whether it was appropriate to assume that the effect of rituximab is maintained in patients whose follicular lymphoma has relapsed and whose disease is re-treated with rituximab. The Committee noted that the Assessment Group's and manufacturer's models assumed that there was no loss of efficacy of rituximab in patients who are re-treated with rituximab. The Committee also noted that the Assessment Group had performed a sensitivity analysis that explored the impact of reduced effectiveness of rituximab among previously treated patients and which showed that the ICER was sensitive to this assumption. The analyses by the Assessment Group suggested that if there was a 25% reduction in efficacy with re-treatment with rituximab then the ICERs increased from £7720–£10,800 to £14,900–£26,900 per QALY gained. The Committee heard from the clinical specialist that there was limited evidence to suggest whether or not there might be a loss of efficacy after re-treatment with rituximab. The Committee concluded that the efficacy of rituximab after re-treatment was a key uncertainty in the economic modelling.

4.3.11 The Committee discussed the role of rituximab maintenance treatment in clinical practice. It recognised that rituximab maintenance treatment after first-line induction therapy was recommended as a treatment option in the guidance on rituximab for maintenance treatment of follicular lymphoma (NICE technology appraisal guidance 226). The Committee therefore considered the Assessment Group's scenario analysis in which first-line maintenance treatment with rituximab was

incorporated into the treatment pathway. The Committee was aware that the inclusion of rituximab first-line maintenance treatment increased the ICERs to £15,000–£21,600 per QALY gained and that in the Assessment Group's model it was suggested that rituximab first-line maintenance treatment is not cost effective. The Committee concluded that in view of the recommendations in NICE technology appraisal guidance 226 it was appropriate to consider the ICERs from the Assessment Group's scenario analysis and that in light of the differences between the estimates of cost effectiveness, NICE technology appraisal guidance 226 and this current appraisal should be considered for review together.

- 4.3.12 The Committee discussed the treatment pathway after first-line therapy used in the economic model. The Committee noted that the manufacturer assumed that after first-line treatment, patients would receive rituximab plus CHOP or CHOP alone. The Committee heard from the Assessment Group that the treatment pathways in its model also included CHOP, but after discussions with the clinical advisers the model had also been developed to include fludarabine-cyclophosphamide and stem-cell transplant. The advisers to the Assessment Group stated that subsequent treatment after first-line treatment would depend on what first-line treatment the patient had received and how soon the patient relapsed. The Committee also heard from the clinical specialist, who confirmed that the treatment pathways used in the Assessment Group's model reflect clinical practice in the UK. The Committee concluded that the treatment pathways used in the Assessment Group's model were appropriate.
- 4.3.13 The Committee discussed the estimates of the most plausible ICER. The Committee noted that in the base-case analyses the ICERs from the Assessment Group were within acceptable

levels and suggested that rituximab plus CVP, CHOP or MCP are cost-effective options for the treatment of advanced follicular lymphoma. The Committee recognised that the Assessment Group had not included the combination of rituximab plus CHVPi in its model. The Committee accepted that using the manufacturer's estimates, and taking into account the Assessment Group's concerns, the ICER was still likely to be within acceptable levels. However, the Committee did not consider that the analyses fully reflect how rituximab is used in clinical practice and the ICERs increase when it is assumed that rituximab first-line maintenance treatment is provided. It considered that the efficacy of rituximab when used as a re-treatment is also uncertain, and if there is a loss of efficacy then this would further increase the ICER. However, the Committee was persuaded that this uncertainty was not such that it increased the ICERs to above the threshold range (£20,000–30,000) that would normally be considered cost effective. The Committee therefore concluded that rituximab plus CVP, CHOP, MCP or CHVPi is both clinically effective and cost effective for the treatment of symptomatic advanced follicular lymphoma in previously untreated people and is an appropriate use of NHS resources.

- 4.3.14 The Committee was mindful that in clinical practice chemotherapy regimens other than CVP, CHOP, MCP and CHVPi may be used. The Committee noted that the addition of rituximab to chemotherapy regimens other than CVP, CHOP, MCP and CHVPi had not been modelled by either the Assessment Group or the manufacturer. It agreed that recommending rituximab with any chemotherapy was not appropriate despite its conclusion on likely clinical effectiveness (see section 4.3.8); that would result in recommending combinations yet to be appraised (see section 4.3.5), and cost



effectiveness cannot be assumed without evidence. However the Committee specifically discussed the addition of rituximab to chlorambucil, noting the consultation comments and evidence from clinical specialists that rituximab plus chlorambucil would be a useful option in older patients or patients with a lower performance status. It noted that this group may be disadvantaged by guidance only recommending rituximab with more aggressive chemotherapy regimens, as had been studied in the clinical trials. It requested that the Assessment Group provide informal cost-effectiveness advice and heard that, based on their base-case analysis, the ICER for rituximab plus chlorambucil would still be within the cost-effective range if the QALY gain for rituximab plus chlorambucil was half that for rituximab plus CHOP. The Committee was mindful of the limited clinical data and the absence of a formal cost-effectiveness analysis, but for the group of patients likely to receive rituximab plus chlorambucil in the NHS, the Committee concluded that rituximab plus chlorambucil was an appropriate use of NHS resources.



<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The availability of rituximab treatment was considered by the clinical specialist to have transformed clinical practice. Patient experts considered that they had benefited from treatment with rituximab and that it had improved their quality of life. The choice of treatment and availability of an effective treatment had a positive effect on patients' families in terms of the families' quality of life.	4.3.2, 4.3.3, 4.3.4
What is the position of the treatment in the pathway of care for the condition?	The appraisal considers a single position in the treatment pathway: rituximab in combination with chemotherapy for the treatment of previously untreated stage III or IV follicular lymphoma.	
Adverse effects	The addition of rituximab to CVP, CHOP, MCP and CHVPi did not significantly increase adverse-event rates.	4.3.6
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The evidence came from four good-quality randomised controlled trials.	4.3.6
Relevance to general clinical practice in the NHS	The results reported in the trials could be considered as broadly representative of the outcomes of rituximab treatment in UK clinical practice.	4.3.6 and 4.3.7
Uncertainties generated by the evidence	Rituximab may be combined with a number of chemotherapy regimens not included in the clinical trials. The Committee considered that there was uncertainty as to the relative effect and absolute response rates of the addition of rituximab to chemotherapy regimens other than those studied in the clinical trials. However, on balance, the Committee was persuaded that on the basis of the evidence submitted and comments provided rituximab would provide an additional clinical benefit when added to chemotherapy.	4.3.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	There were no subgroups for which there was evidence of differential effectiveness.	

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that in the clinical trials rituximab plus CVP, CHOP, MCP and CHVPi had been demonstrated to be more effective than CVP, CHOP, MCP and CHVPi alone for the treatment of advanced follicular lymphoma.</p>	<p>4.3.6</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer's model evaluated the cost effectiveness of rituximab plus CVP, CHOP, MCP and CHVPi. The Assessment Group's model included rituximab plus CVP, CHOP and MCP but it did not include the combination of rituximab plus CHVPi because there were issues with the design of the trial and the combination was not frequently used in UK clinical practice.</p>	<p>4.3.9</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that neither the manufacturer nor the Assessment Group included the use of rituximab first-line maintenance treatment in their base-case analyses. They also assumed that the efficacy of rituximab was maintained when used again as second-line induction treatment after first-line rituximab. The Committee concluded that on the basis of current clinical practice these two factors needed to be considered when making the decision on the cost effectiveness of rituximab plus CVP, CHOP, MCP and CHVPi.</p>	<p>4.3.9</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>The health-related quality-of-life benefits were not a key driver of the recommendations in this appraisal.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No subgroups were identified.</p>	

<p>What are the key drivers of cost effectiveness?</p>	<p>The ICERs increased when it was assumed that rituximab was used as first-line maintenance treatment. They also increased if it was assumed that there was a reduction in efficacy when rituximab is used as a re-treatment.</p>	<p>4.3.10, 4.3.11</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Assessment Group calculated an ICER of £7720 per quality-adjusted life year (QALY) gained for rituximab plus CVP, £10,800 per QALY gained for rituximab plus CHOP and £9320 per QALY gained for rituximab plus MCP. The Committee agreed that the manufacturer's comparison of rituximab plus CHVPi versus CHVPi alone would need to inform the decision-making for the addition of rituximab to CHVPi. The Committee did not accept that the analyses fully reflected how rituximab was used in clinical practice and the ICERs increased when it was assumed that rituximab first-line maintenance treatment was provided and if there was a loss of efficacy when rituximab was used as a re-treatment. However, the Committee was persuaded that this uncertainty was not such that it increased the ICERs to above the threshold range (£20,000–30,000) that would normally be considered cost effective. The Committee was mindful of the limited clinical data and the absence of a formal cost-effectiveness analysis, but for the group of patients likely to receive rituximab plus chlorambucil in the NHS, the Committee concluded that rituximab plus chlorambucil was an appropriate use of NHS resources.</p>	<p>4.3.9, 4.3.13, 4.3.14</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The manufacturer did not submit a patient access scheme.</p>	
<p>End-of-life considerations</p>	<p>The supplementary advice was not relevant to this appraisal.</p>	
<p>Equalities considerations and social value judgements</p>	<p>No equalities issues were raised in the appraisal.</p>	

## 5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website ([www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

## 6 Related NICE guidance

### Published

- Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma. NICE technology appraisal guidance 226 (2011). Available from [www.nice.org.uk/guidance/TA226](http://www.nice.org.uk/guidance/TA226)

- Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of NICE technology appraisal guidance 37). NICE technology appraisal guidance 137 (2008). Available from [www.nice.org.uk/guidance/TA137](http://www.nice.org.uk/guidance/TA137)
- Improving outcomes in haematological cancers – the manual. NICE cancer service guidance haemato-oncology (2003). Available from [www.nice.org.uk/guidance/CSGHO](http://www.nice.org.uk/guidance/CSGHO)

## **7 Review of guidance**

- 7.1 The guidance on this technology will be considered for review with NICE technology appraisal 226 in May 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens  
Chair, Appraisal Committee  
October 2011

## Appendix A: Appraisal Committee members and NICE project team

### **A** *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

#### **Professor Kathryn Abel**

Director of Centre for Women's Mental Health, University of Manchester

#### **Dr David Black**

Director of Public Health, Derbyshire County Primary Care Trust

#### **Dr Daniele Bryden**

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

#### **Dr Andrew Burnett**

Director for Health Improvement and Medical Director, NHS Barnet, London

#### **David Chandler**

Lay member

#### **Dr Mary Cooke**

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester



**Dr Chris Cooper**

General Practitioner, St John's Way Medical Centre, London

**Professor Peter Crome**

Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

**Dr Christine Davey**

Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

**Richard Devereaux-Phillips**

Director, Public Policy and Advocacy NW Europe, BD, Oxford

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Wasim Hanif**

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

**Dr Alan Haycox**

Reader in Health Economics, University of Liverpool Management School

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Dr Janice Kohler**

Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

**Professor Eugene Milne**

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

**Dr Neil Myers**

General Practitioner, Glasgow

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Professor Katherine Payne**

Professor of Health Economics, University of Manchester

**Dr Danielle Preedy**

Lay member

**Dr Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS  
Foundation Trust

**Dr Surinder Sethi**

Consultant in Public Health Medicine, North West Specialised Services  
Commissioning Team, Warrington

**Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of  
Birmingham

**Professor Paul Trueman**

Professor of Health Economics, Brunel University, London

**Dr Judith Wardle**

Lay member

**B NICE project team**

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

**Sally Doss**

Technical Lead

**Zoe Garrett**

Technical Adviser

**Lori Farrar**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by School of Health Related Research (SchARR):

- Papaioannou D, Rafia R, Rathbone J et al. Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of TA 110). Health Technology Assessment

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Roche Pharmaceuticals

II Professional/specialist and patient/carer groups:

- Leukaemia CARE
- Lymphoma Association
- Macmillan Cancer Support
- British Society for Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- North Tyneside PCT
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Leukaemia and Lymphoma Research
- National Institute for Health Research Health Technology Assessment Programme
- School of Health & Related Research Sheffield

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on rituximab by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Anne Parker, nominated by Healthcare Improvement Scotland – clinical specialist
- Andrew Barton, nominated by Lymphoma Association – patient expert
- Karen Jolliffe, nominated by Lymphoma Association – patient expert

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Pharmaceuticals