NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic tissue, causing enlargement of the lymph nodes and generalised symptoms. The lymphatic system produces, stores and delivers lymphocytes, which are cells that fight infection. There are two main classes of lymphocytes: T lymphocytes and B lymphocytes. NHL may be classified as B-cell or T-cell NHL, depending on whether it is B or T lymphocytes that are proliferating at an abnormal rate. Approximately 85% of all NHLs are of B-cell origin.

Follicular lymphoma is a type of low grade or indolent NHL that develops slowly, and often without symptoms, for many years. It is a slow-growing cancer that affects B-cell lymphocytes, so is classified as a B-cell NHL. 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.

The diagnosis of follicular lymphoma is confirmed by lymph node biopsy. Once follicular lymphoma has been identified, investigations are undertaken to find out which areas of the body are affected, the number of lymph nodes affected, and whether other organs are affected, such as the bone marrow or

liver. It can be classified into four stages of disease that reflect both the number of sites of involvement and the presence of disease above or below the diaphragm. At most, 10–15% of follicular lymphomas are detected at an early stage; thus the majority of people present with advanced stage disease (stage III−IV).

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 percentage survival at 20 years has been reported to be as high as 40%). This has been attributed to novel therapeutic strategies including chemoimmunotherapy and radioimmunotherapy. Advanced stage III−IV lymphomas will eventually become resistant to chemotherapy and transform to high-grade or aggressive lymphomas, such as diffuse large B-cell lymphoma.

In 2008, the incidence of follicular lymphoma in England and Wales was 3.4 per 100,000 persons equating to 1869 people. Over 70% of follicular lymphomas are diagnosed in people aged over 60 years, and 85−90% present with advanced disease, which is defined as stage III or stage IV.

1.2 Current management

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 will not present with symptoms of disease and will receive ‘watchful waiting’ until symptoms occur. Of the people who require systemic therapy, for the majority (90%) first-line therapy is rituximab and chemotherapy, with around two-thirds receiving the cyclophosphamide, vincristine and prednisolone (CVP) regimen as the chemotherapy component of treatment. The next most frequent chemotherapy regimen used with rituximab is cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), which accounts for 16% of chemotherapy regimens. People who have a lower performance status may

receive chlorambucil as single agent chemotherapy. ‘Rituximab for the treatment of follicular lymphoma’ (NICE technology appraisal guidance 110) recommends the use of rituximab plus CVP as an option for first-line induction therapy for symptomatic stage III−IV follicular lymphoma. After response to first-line induction therapy, ‘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 to prolong treatment response, where maintenance treatment is given for a maximum of 2 years or until disease progression.

After first-line induction therapy (with or without subsequent maintenance therapy), a person’s disease will relapse, 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 transformation to aggressive lymphoma has occurred, but often includes rituximab combined with a different chemotherapy regimen to that used first line (for example, rituximab-CHOP may be used second-line after rituximab-CVP first line). Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma’ (NICE technology appraisal guidance 137) recommends rituximab in combination with chemotherapy as an option for the induction of remission in people with relapsed stage III−IV follicular lymphoma. In this appraisal, the Committee accepted the manufacturer’s interpretation of the marketing authorisation, and subsequent clarification from the European Medicines Agency which allowed for the use of rituximab in combination with chemotherapy as induction therapy for people with relapsed follicular non-Hodgkin's lymphoma. This appraisal also recommends as an option rituximab monotherapy as a maintenance treatment for people with relapsed stage III or IV follicular lymphoma in remission induced with rituximab plus chemotherapy.

Eventually treatment with chemotherapy or chemoimmunotherapy is not able to induce a further stable period of remission. When this happens, high dose chemotherapy with stem cell transplantation is a treatment option. NICE

technology appraisal guidance 137 also recommends rituximab monotherapy as an option for the treatment of relapsed or refractory stage III−IV follicular lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

2 The technology

Table 1 Summary description of technology

Non-proprietary name	Rituximab
Proprietary name	Mabthera
Manufacturer	Roche Products
Dose	When used in combination with chemotherapy for induction treatment 375 mg/m^2 body surface area per cycle for up to 8 cycles, administered on day 1 of the chemotherapy cycle Initial infusion: 50 mg/hour for first 30 minutes; can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour Subsequent infusions: 100 mg/hour for first 30 minutes; can be escalated in 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour
Acquisition cost (BNF edition 61)	10 mg/ml, net price for a 10-ml vial = £174.63, 50-ml vial = £873.15

Rituximab is a genetically engineered chimeric monoclonal antibody that depletes the B-cells by targeting cells bearing the CD20 surface marker. Rituximab has been associated with infusion reactions and infections, sometimes severe, including tuberculosis and hepatitis B reactivation. It is contraindicated in people with active severe infections, and severe heart failure or severe uncontrolled cardiac disease.

Rituximab as a first-line treatment for follicular lymphoma was originally licensed in combination with CVP. This combination was the subject of 'Rituximab for the treatment of follicular lymphoma' (NICE technology appraisal guidance 110). 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 technology appraisal guidance 110 is

the wider indication; rituximab for the treatment of previously untreated stage III−IV follicular lymphoma in combination with chemotherapy.

Rituximab has other marketing authorisations for follicular lymphoma that are covered in separate NICE guidance. Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma responding to induction therapy. 'Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 226) covers first-line maintenance; 'Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma' (NICE technology appraisal guidance 137) covers subsequent line maintenance. In addition, rituximab monotherapy is indicated for the treatment of stage III−IV follicular lymphoma that is chemoresistant, or for people in their second or subsequent relapse after chemotherapy (covered in NICE technology appraisal guidance 137).

3 The evidence

3.1 Clinical effectiveness

Four randomised controlled studies were identified by the Assessment Group as meeting the criteria for inclusion in the systematic review; these also formed the basis of the manufacturer's submission. The four studies were the M39021 trial, GLSG-2000 trial, OSHO-39 trial and the FL2000 trial. The Assessment Group considered all four studies to be of good quality (see pages 52−53 of the assessment report). The trials compared:

- rituximab plus CVP with CVP (M39021)
- rituximab plus CHOP with CHOP (GLSG-2000)
- rituximab plus mitoxantrone, chlorambucil and prednisolone (MCP) with MCP (OSHO-39)
- rituximab plus cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) with CHVPi (FL2000).

The M39021 trial provided the main clinical evidence in NICE technology appraisal guidance TA110, which appraised rituximab in combination with CVP as a first-line treatment for stage III and IV follicular lymphoma.

The M39021, GLSG-2000 and OSHO-39 trials used the licensed administration schedule for rituximab (375 mg/m^2 per cycle for up to 8 cycles) whereas the FL2000 trial used a difference administration schedule which did not include rituximab in the first two cycles of CHVP (Table 1). In the FL2000 trial, there were differences between the number of courses of CHVP administered in the active treatment group and the comparator group (see page 112 of the assessment report).

Table 2 Summary of the RCTs in the systematic review (pages 44 and 49 of the assessment report)

Trial and principal citation	Study type Country	Numbers randomised	Interventions, dose and duration	Follow-up	Primary outcome
M39021 (Marcus et al. 2008; Marcus et al. 2005)	Multicentre, open label randomised controlled trial 47 centres in Australia, Belgium, Brazil, Canada, France, Israel, Poland, Portugal, Spain, Switzerland, and the UK	n = 322[a] Stage III−IV follicular lymphoma	R-CVP (n = 162) CVP (n = 159) Rituximab: 375 mg/m^2 infusion on day 1 CVP: 750 mg/m^2 cyclophosphamide intravenously on day 1; 1.4 mg/m^2 of vincristine, up to a maximal dose of 2 mg intravenously on day 1; and 40 mg/m^2 of prednisone per day orally on days 1 to 5 Every 21 days for a maximum of 8 cycles	Median 53 months	Time to treatment failure
GLSG-2000 (Hiddemann et al. 2005; Buske et al. 2008)	Multicentre, open label randomised controlled trial 200 institutions in Germany	n = 630[b] Stage III−IV follicular lymphoma	R-CHOP (n = 279) CHOP (n = 278) Rituximab: 375 mg/m^2 infusion on the day before the respective CHOP course CHOP: 750 mg/m^2 cyclophosphamide; 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine: all given intravenously on day 1. Prednisolone given 100 mg/m^2 orally daily on days 1 to 5 Every 21 days for a total of 6 to 8 cycles	Median 56 months	Time to treatment failure
OSHO-39 (Herold et al. 2007)	Multicentre, open label randomised controlled trial 34 centres in Germany	n = 376 [including mantle cell lymphoma] n = 201/376 were follicular	R-MCP (n = 105) MCP (n = 96) Rituximab: 375 mg/m^2 intravenous infusion on day 1 (8mg/m^2 mitoxantrone	Median 47 months (49 months for R-MCP and 42	Overall response rate

		lymphoma Stage III−IV follicular lymphoma	intravenously on days 3 and 4; 3 x 3 mg/m^2 chlorambucil and 25 mg/m^2 prednisolone, orally on days 3 to 7) MCP: 8 mg/m^2 mitoxantrone intravenously on days 1 and 2; 3 x 3 mg/m^2 chlorambucil and 25 mg/m^2 prednisolone orally on days 1 to 5 Every 28 days for a maximum of 8 cycles	months for MCP)	
FL2000 (Salles et al. 2008)	Multi-centre, open label randomised controlled trial 54 centres in France and Belgium	n = 360[c] Stage II−IV	R-CHVPi (n = 175) CHVPi (n = 183) Rituximab: 375 mg/m^2 infusion on days 1 and 8 of cycle 3 and 4, and day 1 of cycles 5 and 6. (Thus, CHVP only in cycles 1 and 2) CHVPi: 600 mg/m^2 cyclophosphamide on day 1 and 25 mg/m^2 doxorubicin on day 1 and 100 mg/m^2 etoposide, all administered intravenously on day 1; 40 mg/m^2 prednisolone orally from day 1 to day 5 Interferon-α subcutaneously 3 x 4.5* MIU/week *3 MIU for patients older than 70 years CHVPi: 6 monthly cycles followed by 6 bi-monthly cycles) and 18 months Ifn-α R-CHVPi: 6 monthly cycles CHVP or R-CHVP (see column to left) and 18 months concurrent Ifn-α	Median 60 months	Event-free survival

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi , cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; MCP, mitoxantrone, chlorambucil and prednisolone; MIU, million international units; R, rituximab; TTF, time to treatment failure.

[a] One CVP enrolled patient withdrew consent

[b] n = 630 enrolled. In June 2003, applied one-sided sequential test showed a significantly longer TTF for the R-CHOP arm (p = 0.001) and randomisation was stopped. Buske et al. report on 557/630 evaluable patients at a median follow-up of 56 months

[c] 1 patient withdrew consent after registration, 1 patient had a major inclusion violation (which was registered at relapse)

Population

The M39021 and GLSG-2000 trials recruited patients with stage III−IV follicular lymphoma. The FL2000 trial recruited patients with stage II–IV follicular lymphoma, and OSHO-39 trial included patients with CD-20 positive indolent NHL (201 of the 376 patients enrolled had follicular lymphoma). However, the primary analysis population was defined in the OSHO-39 trial as that with follicular lymphoma. The median age of patients randomised across the trials ranged from 52 to 61 years. The majority of patients had stage IV follicular lymphoma.

Response to treatment

In three studies, rituximab with chemotherapy was associated with a statistically significantly improved overall response to treatment compared with chemotherapy alone, the FL2000 did not report a p-value (see table 3). The overall response rate in the four studies ranged from 81–96% for the rituximab-chemotherapy arm and 57− 91% for the chemotherapy alone arm.

Table 3 Key results for response data (from page 56 of the Assessment Report)

	M39021		GLSG-2000		OSHO-39		FL2000			
							6 month follow-up data		18 month follow-up data	
	R-CVP N=162	CVP N=159	R-CHOP N= 279	CHOP N= 278	R-MCP N=105	MCP N=96	R-CHVPi N= 175	CHVPi N=183	R-CHVPi N= 175	CHVPi N=183
OR: n (%)	131 (81)	90 (57)	268 (96)	253 (91)	97 (92)	72 (75)	164 (94)	156 (85)	142 (81)	131 (72)
p value reported in study	< 0.0001		0.0046		0.0009		Not reported		Not reported	
CR: n (%)	49 (30)	12 (8)	53 (19)	47 (17)	52 (50)	24 (25)	63 (36)	29 (16)	90 (51)	71 (39)
p value reported in study	< 0.001		No p value reported		0.0004		Not reported[d]		Not reported[e]	
PR: n (%)	82 (51)	78 (49)	215 (77)	206 (74)	45 (43)	48 (50)	101 (58)	127 (69)	52 (30)	60 (33)
	No p value reported		No p value reported		No p value reported		Not reported[d]		Not reported[e]	
Stable disease: n (%)	12 (7)	33 (21)	6 (2)[b]	17 (6)[b]	Not reported[c]	Not reported[c]	2 (1)	9 (5)	1 (1)	3 (2)
p value reported in study	No p value reported		No p value reported		No p value reported		Not reported[d]		Not reported[e]	

[a] Percentages may not add up due to rounding

[b] Includes 'minor response' as well as stable disease

[c] Stable disease not reported but "< partial response" reported at cycle 6: R-MCP = 7 and MCP = 22 and at cycle 8: R-MCP = 8 and MCP = 24

[d] Authors report $p < 0.001$ obtained using a global $\chi 2$ test for all response strata [does not include ORR;

[e] Authors report $p = 0.035$ obtained using a global $\chi 2$ test for all response strata [does not include ORR]

CR, complete response; NR not reported, OR, overall response; PR, partial response.

Overall survival

The overall survival rate in the four studies ranged from 83−90% in the rituximab plus chemotherapy groups and 77−84% in the chemotherapy alone groups (table 4). For the M39021, GLSG-2000 and OSHO-39 trials, there was an increased likelihood of survival for patients receiving rituximab plus

chemotherapy compared with chemotherapy alone. However, it was noted that the treatment effect on overall survival was confounded in the latter two trials owing to additional trial treatments administered after response to first-line treatment. The FL2000 trial provided contradictory evidence with an increased likelihood of survival in the CHVPi alone arm compared with the rituximab plus CHVPi arm.

Table 4 Key overall survival results from the four studies (page 58 of the assessment report)

	M39021		GLSG-2000		OSHO-39		FL2000	
	R-CVP n = 162	CVP n =159	R-CHOP n =279	CHOP n = 278	R-MCP n = 105	MCP n = 96	R-CHVPi n = 175	CHVPi n =183
Median Follow-up	53 months		56 months		47 months		60 months	
OS rate %	83[a]	77[a]	90[c]	84[c]	87[e]	74[e]	84[g]	79[g]
p value reported in trial		< 0.0290		0.0493		0.0096		0.1552
Median OS	Not reached	Not reached	Not reached	Not reached	Not reached	Not reached	Not reported	Not reported
Number of deaths	23[b]	35[b]	6[d]	17[d]	15[f]	25[f]	Not reported	Not reported
p value reported in trial	No p value reported			0.016	No p value reported		No p value reported	
Hazard ratios[h]		0.64		0.58		0.40		1.46

CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclop hosphamide, vincristine and prednisolone; MCP, mitoxantrone, chlorambucil and prednisolone; OS, overall survival; R, rituximab.

[a] KM estimate at 4 years

[b] Deaths may include patients who have received second-line treatment: median 42 month follow-up; number deaths at 4-year follow-up not reported

[c] 5-year rate

[d] Deaths after 3 years reported (not reported for 5 years)

[e] 4-year OS rates

[f] Deaths at 4 years; cause-specific deaths in follicular lymphoma were n = 7 R-MCP and n = 17 in MCP

[g] 5-year rate

[h] Calculated by the Assessment Group

Other time-to-event data

Other time-to-event data were reported in the four studies (see table 5 below and table 14 on pages 61−62 of the assessment report) but they were inconsistently defined between the four studies and therefore not directly comparable.

Table 5 Key overall results for other time-to-event data (from pages 61−62 of the assessment report)

	M39021		GLSG-200		OSHO-39		FL2000	
	R-CVP	CVP	R-CHOP	CHOP	R-MCP	MCP	R-CHVPi	CHVPi
Median PFS					NR	28.8		
Months					p < 0.0001			
Median TTF	27	7	NR	35				
Months	p < 0.0001		p < 0.0001					
Median EFS					NR	26	NR	35
Months					p < 0.0001		p = 0.0004	
Median response duration	38	14			NR	35		
Months	p < 0.0001				p < 0.0001			

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; EFS, event free survival, MCP, mitoxantrone, chlorambucil and prednisolone; NR – not reached; PFS, progression free survival, R- rituximab, TTF, time to treatment failure

[a] Adverse events recorded from first 6 months of treatment

[b] Data for the M39201 trial taken from the manufacturer's submission

Subgroup analysis

The Assessment Group presented analyses of a number of subgroups in its report: FLIPI (Follicular Lymphoma International Prognostic Index) score, IPI (International Prognostic Index) score, age, quality of response to induction therapy and other prognostic factors. Rituximab plus chemotherapy compared with chemotherapy alone improved treatment outcomes for all subgroups (see pages 63−67 of the Assessment Report for details).

Adverse events

Key safety data for grade 3 and 4 adverse events from the four clinical trials are summarised in Table 6. Although an increased statistically significant 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 in the rituximab plus chemotherapy arms (infection is associated with leukocyto-, neutro- and granulocyto-penia). However, considerable numbers of patients experienced grade 3 or 4 alopecia in both the rituximab plus CHOP and CHOP arms of the GSLG-2000 trial. This side effect is associated with the CHOP component of the treatment.

Table 6 Adverse events for all four trials (grades 3 and 4 combined)

	M39021		GLSG-2000		OSHO-39		FL2000	
Adverse events: n (%)	R-CVP n=162	CVP n=159	R-CHOP n=223	CHOP n=205	R-MCP n=105	MCP n=96	R-CHVPi n=175	CHVPi n=183
Low haemoglobin level	-	-	20 (9)	21 (10)	3 (3)	4 (4)	6 (3)	9 (5)
Leucocytopenia	19 (12)	14 (9)	154 (69)	125 (61)	75 (72)	56 (58)	-	-
Neutropenia	39 (24)	22 (14)	-	-	-	-	103 (59)	114 (62)
Granulocytopenia	-	-	140 (63)	109 (53)	-	-	-	-
Reduced platelet count	-	-	13 (6)	16 (8)	4 (4)	7 (7)	5 (3)	6 (3)
Alopecia	-	-	149 (67)	125 (61)	-	-	-	-
Infection	-	-	11 (5)	14 (7)	7 (7)	8 (8)	4 (2)	0 (0)
Cardiac dysfunction	-	-	7 (3)	2 (1)	-	-	2 (1)	3 (2)
Cardiac arrhythmia	-	-	4 (2)	0 (0)	-	-	-	-
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; MCP - mitoxantrone, chlorambucil and prednisolone; R- rituximab								

Meta-analysis

Three exploratory meta-analyses were conducted by the Assessment Group to explore the overall response rate, complete response and partial response rates 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. These were subsequently used in the economic model (see page 67 of the Assessment Report for details).

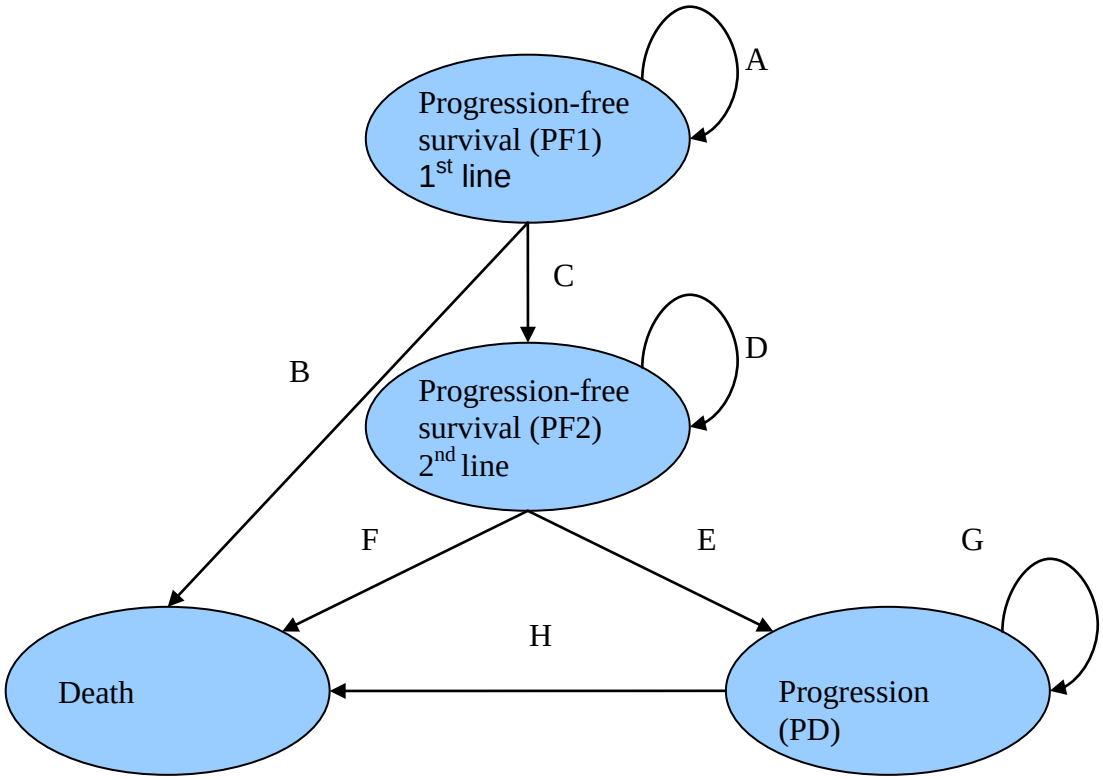
3.2 Cost effectiveness

Manufacturer's submission

The manufacturer of rituximab provided an economic model that was an update of the original analysis submitted for NICE technology appraisal guidance 110, which evaluated rituximab plus CVP versus CVP alone.

The manufacturer submitted a Markov economic model that estimated the costs and benefits resulting from the first-line treatment of follicular lymphoma over the patient's life time. The population included in the economic analysis was patients with previously untreated follicular lymphoma who were suitable for rituximab in combination with chemotherapy. The model had four distinct health states: progression-free survival–first-line (PF1), progression free survival–second-line (PF2), progressive disease (PD), and death, as shown in figure 1. All people enter the model in the PF1 health state ('A' in the figure below) and start first-line treatment. At the end of each cycle, patients either remain in the PF1 state or move to PF2 ('C') or die ('B'). Once a patient is in the PF2 health state, they can remain in that state ('D') and continue to receive either rituximab chemotherapy or chemotherapy, or they can die at the end of each cycle ('F') or they can transition to the PD state ('E'). Patients in the progressive disease state either remain in that state ('G') or die at the end of each cycle ('H'). The model compared the cost effectiveness of the addition of rituximab to CVP, CHOP, MCP and CHVPi for patients with advanced follicular lymphoma in the UK. The model had a starting age of 60 years and a follow-up period of 25 years. A half-cycle correction was applied to the model.

Figure 1 Schematic representation of the manufacturer's model structure



Efficacy data for first-line induction therapy was based on the individual clinical trials. After first-line therapy it was assumed that patients would receive either CHOP or R-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 rituximab-naive patients.

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 0−2. Utilities were elicited using the EQ-5D questionnaire. The following utility values were used in the model: PF1 = 0.88 (disease-free); PF2 = 0.79 (remission/full response); progressive disease = 0.62. Adverse events were not included in the model.

Drug costs used the planned dose from the trials assuming a body surface area of 1.85m^2. In the CVP, CHOP, MCP and CHVP groups the monthly drug

costs of chemotherapy alone were £72, £360, £182 and £413 respectively and with the addition of rituximab £1830, £2119, £1501, £1626. Administration costs were taken from NHS reference costs and estimated to be £268 for rituximab-chemotherapy and £186 for chemotherapy alone, based on an assumption that rituximab treatment was administered as a hospital day case. The cost associated with monitoring/surveillance after induction treatment was derived from a study commissioned by the manufacturer. Supportive care costs for patients in the progressive health state were derived from the post-protocol treatment from the EORTC 20891 trial and the average cost of palliative care in the UK taken from the literature.

For the comparison of rituximab plus CVP versus CVP individual patient level data were available. Therefore two analyses were presented for rituximab plus CVP versus CVP. The first analysis fitted separate curves to each arm using individual patient-level data, whereas the second analysis used the same method as used in the other comparisons based on an extrapolation technique (exponential distribution estimated using ordinary least squares regression for rituximab plus CVP). The addition of rituximab to CVP, CHOP, MCP and CHVPi compared with chemotherapy alone resulted in an incremental cost-effectiveness ratio (ICER) of £1529 (using patient level data)/£5611 (using ordinary least squares regression), £5758, £4861 and £9251 per quality adjusted life year (QALY) gained respectively (see table 7).

Table 7 Manufacturer's base-case analysis for each pair-wise comparison

	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (£ per QALY)
CVP Rituximab-CVP	£43,061 £44,386	£1,325	5.828 6.695	0.867	£1,529
CVP OLS Rituximab-CVP OLS	£44,570 £47,056	£2,486	5.544 5.987	0.443	£5,611
CHOP Rituximab-CHOP	£42,717 £49,029	£6,312	6.479 7.575	1.096	£5,758
MCP Rituximab-MCP	£42,072 £48,340	£6,268	6.532 7.821	1.289	£4,861
CHVPi Rituximab-CHVPi	£47,885 £54,132	£6,247	6.487 7.162	0.675	£9,251

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; ICER, incremental cost-effectiveness ratio; MCP, mitoxantrone, chlorambucil and prednisolone; OLS, ordinary least squares; QALY, quality-adjusted life year.

Published literature

The Assessment Group identified three published studies that met the criteria for inclusion in the systematic review of economic evaluations. One of these was the Evidence Review Group report submitted 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 (see page 86 of the assessment report). Two of the studies only considered rituximab plus CVP, whereas the other study evaluated the cost effectiveness of rituximab plus CVP, CHOP, MCP or CHVPi. The two UK economic evaluations produced broadly similar estimates of the ICER for R-CVP versus CVP (£8,290 per QALY gained and £8,613 per QALY gained). The ICERs for the addition of rituximab to CHOP, MCP and CHVPi were £10,676, £7,455 and £8,498 per QALY gained respectively. A review of these studies identified some limitations in the description of the treatment pathway, sources of effectiveness and the assumptions that were made.

Economic model

The Assessment Group developed an individual patient model that simulated 100,000 patients each with individual baseline characteristics. The key objective was to assess 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 there were issues in the design of the FL2000 trial (see page 6 of the overview) and the combination of CHVPi is not used frequently in UK clinical practice.

The Assessment Group gained advice from their clinical advisers regarding the treatment pathway following first-line induction therapy with CVP or CHOP with or without rituximab (table 8). The pathways for MCP and rituximab-MCP were assumed to be identical to CHOP and rituximab-CHOP based on the rationale that both are anthracycline regimens.

Table 8 Summary of treatment pathway in patients in first-line induction with CVP or CHOP with or without rituximab (from page 114 of the assessment report)

Response status and time of relapse	First-line therapy				
		CVP	**Rituximab plus CVP**	**CHOP**	**Rituximab plus CHOP**
	Age				
Relapse within 6 months after start of therapy (non-responders)	< 65 years	rituximab-CHOP	rituximab-CHOP	rituximab-HDT (+/- ASCT)	HDT (+/- ASCT)
	≥ 65 years	rituximab-FC	rituximab-FC	rituximab-FC	FC
Responders at 6 months, but relapse within 6 months after end of therapy	< 65 years	rituximab-CHOP	rituximab-CHOP	rituximab-HDT (+/- ASCT)	HDT (+/- ASCT)
	≥ 65 years	rituximab-FC	rituximab-FC	rituximab-FC	FC
Responders at 6 months, but relapse more than 6 months after end of therapy	< 65 years	rituximab-CHOP	rituximab-CHOP	rituximab-HDT (+/- ASCT)	rituximab-HDT (+/- ASCT)
	≥ 65 years	rituximab-FC	rituximab-FC	rituximab-FC	rituximab-FC
ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; FC, fludarabine, cyclosphosphomide; HDT, high dose therapy.					

The treatment pathways used in the economic model are presented in the assessment report (figures 10−13, pages 116−119).

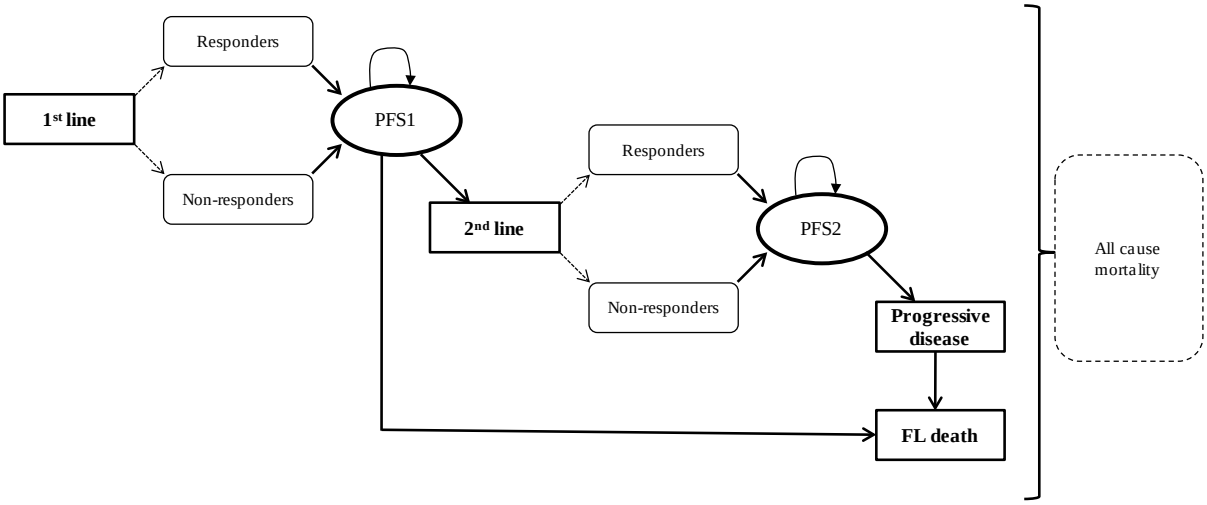
An alternative treatment pathway after first-line rituximab maintenance treatment in patients treated with first-line induction with rituximab was developed to reflect NICE technology appraisal 226, which recommended rituximab monotherapy as an option for the maintenance treatment of follicular lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

Table 9 Treatment pathway incorporating rituximab maintenance (from page 115 of the assessment report)

Response status and time of relapse	Age	Rituximab-CVP	Rituximab-CHOP /Rituximab-MCP
		Second-line treatment	
Relapse within 12 months after start of induction therapy (that is, relapse after about less than 6 months after start of maintenance)	< 65 years	CHOP	HDT (+/- ASCT)
	≥ 65 years	FC	FC
Relapse after 12 months after start of induction therapy (that is, relapse after more than 6 months after start of maintenance)	< 65 years	Rituximab-CHOP	Rituximab-HDT (+/- ASCT)
	≥ 65 years	Rituximab-FC	Rituximab-HDT (+/- ASCT)
ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; FC, fludarabine, cyclosphosphomide; HDT, high dose therapy.			

The Assessment Group's model has four health states: progression-free survival after first-line treatment (PFS1), progression-free survival after second-line treatment (PFS2), progressive disease and death. Patients start in PFS1 and receive first-line induction with chemotherapy with or without rituximab. Patients who relapse move onto PFS2 and are assumed to receive second-line treatment with or without maintenance rituximab. After progression, patients enter a progressive state and remain in that state until 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 receiving rituximab in the PFS1 state also receive rituximab as first-line maintenance treatment. The model uses a 25-year time horizon and costs and benefits are discounted at 3.5%.

Figure 2 Schematic of the Assessment Group's model structure (from page 122 of the assessment report)



In PFS1, patients received CVP, CHOP or MCP with or without rituximab. In the base case, patients remaining in PFS1 at the end of the induction treatment were assumed to be monitored but to not receive any further treatments. For each of the therapies examined, the response rates from the applicable trials were used to classify patients into responders and non-responders. . Time to progression individual patient data from the M39021 trial were used in the model to develop progression-free survival curves for responders and non-responders, as appropriate. For the comparisons of CHOP and rituximab-CHOP and MCP and rituximab-MCP individual patient data were not available from the first-line induction trials. Further 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.

Patients entering second-line treatment were treated with either CHOP, rituximab-CHOP, fludarabine and cyclosphosphomide (FC) or rituximab-FC or with high dose therapy and autologous stem cell transplantation. As for first-line, patients treated in second-line were classified as either responders or non-responders. Responders to CHOP, rituximab-CHOP, FC or rituximab-FC

then received maintenance rituximab for up to 2 years at the end of the induction phase as per NICE technology appraisal guidance 137. Data for CHOP and rituximab-CHOP were taken from the EORTC 20981 trial. As evidence was unavailable for the effectiveness of FC regimens, it was assumed the FC regimens were 20% less effective than CHOP based regimens. Data for high dose therapy and autologous stem cell transplantation were taken from a study by Sebban et al. (see page 144 of the assessment report). Patients remaining in PFS2 at the end of treatment induction, maintenance or autologous stem cell transplantation were assumed not to receive further treatment, but were monitored.

Patients relapsing from PFS2 moved to progressive disease. Those patients were assumed to incur additional costs associated with palliative and terminal care as appropriate.

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. Only grade 3 and 4 adverse events were included and it was assumed that they would both incur the same costs. The grade 3 and 4 events included were leukopenia, granulocytopenia, neutropenia, anaemia, alopecia, infection, cardiac arrhythmia and cardiac dysfunction. The Assessment Group also assumed that each adverse event led to a reduction in health-related quality of life by 15% for 45 days. Grade 3 and 4 neutropenia and leukopenia were also included in the first-line maintenance setting (see table 41, page 149 of the Assessment Report).

Costs

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. Patients treated with CHOP or rituximab-CHOP were assumed to receive a maximum of 8 cycles in first-line induction and 6 cycles in second-line induction. Patients treated with FC or rituximab-FC were assumed to receive a maximum of 4 cycles in second-line induction.

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.

The costs associated with the administration of each cycle of treatment were derived from NHS reference costs 2009/2010. 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.

The drug acquisition and administration costs by chemotherapy cycle per patient in first-line induction are shown in table 10.

Table 10 Drug acquisition and administration costs by chemotherapy cycle per patient in first-line induction (from page 153 of the assessment report)

	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
Drug acquisition cost/cycle	£60.48	£1,282.89	£233.08	£1,455.49	£218.78	£1,441.19
Administration cost/cycle	£297.93	£336.49	£297.93	£336.49	£568.55	£607.10
Total treatment cost/cycle	£358.41	£1,619.38	£531.01	£1,791.98	£787.33	£2,048.29
Total treatment cost/patient according to the protocol defined dose	£2,867	£12,955	£4,248	£14,336	£6,299	£16,386

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; cyclophosphamide, vincristine and prednisolone; MCP - mitoxantrone, chlorambucil and prednisolone; R- rituximab

Cost associated with end of treatment induction/maintenance

After first- and second-line induction treatment the monitoring was separated into two phases: first 6 months after the end of treatment induction, and remaining months. The monitoring after maintenance treatment with rituximab was also separated into two phases: first 24 months after end of maintenance treatment, and remaining months.

Unit costs were extracted from the NHS reference costs 2009/2010 and costs used in the Sheffield Teaching Hospital Trust.

Costs associated with management in third/subsequent lines

Patients that progressed after second-line treatment with CHOP, rituximab-CHOP, FC or rituximab-FC (induction or maintenance) and who were still alive were assumed to undergo third or subsequent line of therapy. The management costs were estimated from the post-protocol treatments observed in the EORTC 20981 trial. The frequency of resources used was multiplied by the unit costs used by the manufacturer in NICE technology appraisal guidance 137.

Patients treated with high-dose therapy with or without rituximab were assumed to go directly on to palliative care and no costs were applied for the further lines of treatment.

Costs associated with palliative and/or terminal care

The costs associated with palliative care were estimated from the cost of palliative care for different types of advanced cancers from the start of strong opioid treatment until death (estimated to be £180.68 per month). In addition, the cost associated with terminal care was included. This cost was only applied to patients for whom the cause of death was attributable to follicular lymphoma. This cost was estimated to be £4077 per death.

Utility data

The Assessment Group used the same data for the utility values in the economic model (that is, the Oxford Outcomes Study). However, the

Assessment Group noted that the report, in addition to the main analysis, provided additional analyses aggregating health states into 'disease progression' and 'progression free'. This was considered more appropriate than the disaggregated values in the main analysis (as used by the manufacturer) as 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 PFS1 and PFS2 were assumed to be 0.805, and 0.7363 for patients in the progressive health state (see pages 162-166 of the Assessment Report.

Results of the cost-effectiveness analysis

The results of the model are presented as incremental cost per QALY gained. Both deterministic and probabilistic sensitivity analyses were conducted, as described below.

Base case

The results of the deterministic base-case cost-effectiveness analysis are presented in table 11. The ICERs for the addition of rituximab to CVP, CHOP and MCP are £7720, £10,834 and £9316 per QALY gained respectively.

Table 11 Assessment Group's base-case cost-effectiveness analysis

	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (£ per QALY)
CVP	£30,793		5.99		
Rituximab-CVP	£38,183	£7,389	6.95	0.96	£7,720
CHOP	£34,983		6.84		
Rituximab-CHOP	£40,708	£5,725	7.37	0.53	£10,834
MCP	£36,103		6.79		
Rituximab-MCP	£41,370	£5,267	7.36	0.57	£9,316

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; ICER, incremental cost-effectiveness ratio; MCP, mitoxantrone, chlorambucil and prednisolone; QALY, quality-adjusted life year.

The ICER in the probabilistic sensitivity analysis for the addition of rituximab to CVP, CHOP and MCP is estimated to be £7735, £10,855 and £9313 per QALY gained respectively.

Sensitivity analyses

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. Changes to management costs and health state utilities had only a small impact in the estimates of incremental cost effectiveness (see pages 177 to186 in the assessment report).

Scenario analysis including first-line maintenance with rituximab in responders to rituximab-chemotherapy

The Assessment Group explored a scenario in which first-line maintenance treatment was incorporated into the treatment pathway to reflect the recommendations made in technology appraisal number 226. The ICERs estimated by the Assessment Group for the addition of rituximab to CVP, CHOP and MCP were £14,959, £21,687 and £20,493 per QALY gained respectively, assuming that responders to rituximab-chemotherapy receive first-line maintenance rituximab (see table 12).

Table 12 Scenario analysis incorporating first-line maintenance in the treatment pathway

	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (£ per QALY)
CVP	£30,793		5.99		
R-CVP	£49,520	£18,727	7.25	1.25	£14,959
CHOP	£34,983		6.84		
R-CHOP	£54,134	£19,150	7.67	0.88	£21,687
MCP	£36,103		6.79		
R-MCP	£54,079	£17,976	7.36	0.57	£20,493

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; ICER, incremental cost-effectiveness ratio; MCP, mitoxantrone, chlorambucil and prednisolone; QALY, quality-adjusted life year; R, rituximab.

The ICER in the probabilistic sensitivity analysis for the addition of rituximab to CVP, CHOP and MCP is estimated to be £15,017, £21,625 and £20,418 per

QALY gained respectively, assuming that responders to rituximab-chemotherapy receive first-line maintenance rituximab.

Sensitivity analysis incorporating first-line maintenance in responders to rituximab-chemotherapy

The Assessment Group undertook some sensitivity analyses to assess the impact of parameters and assumptions on the cost per QALY. Changes to the modelled treatment pathway, effectiveness of first-line maintenance therapy led to small changes in the estimates of incremental cost effectiveness. These are reported on pages 191−197 of the assessment report.

Varying the time horizon

The ICER was sensitive to the assumption about the time horizon with an improvement in the ICER for all comparisons as the time horizon increases. Assuming a life time horizon reduced the ICERs by approximately £1000. Assuming a five year time horizon increased the ICERs to £54,094, £91,356 and £80,497 per QALY gained for the addition of rituximab to CVP, CHOP and MCP respectively (see page 191 of the assessment report).

Use of alternative distributions to model the effectiveness in first-line treatment

The ICER was sensitive when a Gompertz distribution was used instead of a log-normal distribution. The effect of using a Gompertz distribution reduced the ICERs in each of the comparisons to under £15,000 per QALY gained (see page 191 of the assessment report).

Resistance to rituximab

The ICER was sensitive when a lower effectiveness of second-line rituximab treatments was assumed in patients treated with rituximab first-line. Assuming a 25% reduction in efficacy of rituximab when used as second-line treatment in patients previously treated with rituximab increased the ICERs to £21,624, £31,646 and £29,731 per QALY gained, for the addition of rituximab to CVP, CHOP and MCP respectively (see page 193 of the assessment report).

Maximum time a patient can stay in PFS1

In the base case, a proportion of patients might not progress, and therefore remain in PFS1 during the entire simulation. The Assessment Group examined a scenario in which the survival curves were truncated, assuming that patient could remain in PFS1 only for a maximum duration (between 5−19 years). The ICER was sensitive to this assumption. If it was assumed that the maximum amount of time a patient stayed in PFS1 was 10 years, the ICERs increased to £19,516, £31,050 and £29,618 per QALY gained respectively (see page 194 of the assessment report).

Differences between the manufacturer's model and the Assessment Group's model

The Assessment Group listed the following differences in the modelling approach and assumptions used by the manufacturer and the Assessment Group (see pages 198−199 in the assessment report):

- The manufacturer and Assessment Group used different time-to-event data. The Assessment Group used time-to-event data from the M39021 trial as a proxy for each of the regimens modelled, rather than trial data specific to each of the chemotherapy combinations.
- There were differences in the modelled treatment pathway, including the use of high dose therapy and FC as second-line therapy.
- There were some errors in the approach used by the manufacturer to model second-line treatment. These included:
  - the derivation of the transition probability
  - the calculation of post-progression survival

  - errors in the estimation of costs in second-line treatment.
- The manufacturer fitted exponential distributions to data in second-line treatment from the EORTC 20981 trial, whereas the Assessment Group used log-normal distribution.
- The economic model submitted by the manufacturer did not include the time spent in second-line induction treatment. Progression-free survival and overall survival are calculated after second-line induction treatment. The Assessment Group model included the time spent in induction treatment.
- The Assessment Group used a different approach to model the overall survival in second-line treatment using direct Kaplan Meier curves for overall survival. The manufacturer estimated overall survival derived from progression-free survival and an estimated post-progression survival.
- The Assessment Group used different utility values (PFS1: 0.805; PFS2: 0.805; PD: 0.7363) compared with the utility values included in the manufacturer's submission (PFS1: 0.88; PFS2: 0.79; PD: 0.62).
- The model developed by the Assessment Group was more flexible, allowing tracking of the patients over time, requiring fewer assumptions and therefore providing a more accurate description of outcomes over time.

The Assessment Group considered that the above differences in the two models resulted in the differences in the ICERs (see table 13).

Table 13 Comparison of the ICER produced by the manufacturer and the Assessment Group's model

	Assessment Group's model	Manufacturer's model
Rituximab-CVP versus CVP	£7,720	£1,529
Rituximab-CHOP versus CHOP	£10,834	£5,758
Rituximab-MCP versus MCP	£9,316	£4,861
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; MCP, mitoxantrone, chlorambucil and prednisolone.		

4 Issues for consideration

4.1 Clinical effectiveness

UK clinical practice for the treatment of follicular lymphoma

For the first-line treatment of follicular lymphoma, NICE originally appraised rituximab in combination with CVP. Rituximab now has a marketing authorisation for this indication for use in combination with any chemotherapy. Rituximab is also recommended as an option by NICE for maintenance therapy and for the treatment of relapsed disease.

- Which chemotherapy regimens with or without rituximab are used in UK clinical practice for first-line treatment of follicular lymphoma?
- At which points in the treatment pathway is rituximab used and with which patient populations?
- Is the efficacy of rituximab affected by its prior use and duration of response to treatment with prior rituximab?

Clinical-effectiveness data

Four trials were identified, each comparing the addition of rituximab to a different chemotherapy regimen. In each trial, the length of follow-up is short when compared with the natural history of follicular lymphoma. Further, overall survival data may be confounded by the provision of subsequent treatments.

- Are there sufficient clinical data of rituximab plus chemotherapy to inform conclusions on the effectiveness of rituximab when added to any chemotherapy regimen?

- How do the treatment regimens used in the clinical trials relate to those used in UK clinical practice?
- Has the addition of rituximab to any chemotherapy regimen been shown to be clinically effective?

Generalisability of populations in trials

The median age of patients in the four trials is considerably younger (52 to 61 years) than that seen in clinical practice, where more than 70% of patients are aged over 60 years. In addition, the ECOG performance status is better in the trials than that seen in UK clinical practice.

- Does the Committee consider that the population is generalisible to the population in England and Wales?

4.2 Cost effectiveness

Treatment pathway

The manufacturer's model included a number of simplifying assumptions about the treatment pathway only allowing for R-CHOP or CHOP second-line therapy.

- Does the Committee consider that this is a valid approach?

Estimate of progression-free survival

The Assessment Group used patient-level time to event data from the M39021 trial (comparing rituximab-CVP with CVP as a proxy for progression-free survival in responders and non-responders to CHOP and rituximab-CHOP, or MCP and rituximab-MCP.

- Does the Committee consider that this is a valid approach?

Utility values

Although using the same source as the manufacturer, the Assessment Group used aggregated data obtaining a smaller difference in utility for the progression-free and progressed health states.

- Which utility values does the Committee consider are the most appropriate for inclusion in the economic modelling?

Estimates of cost effectiveness

In the base-case analysis, the Assessment Group exclude the use of maintenance therapy after first-line induction therapy. The use of maintenance therapy after first-line induction therapy is explored in a scenario analysis.

- Is it more appropriate to consider the estimates of cost effectiveness with or without the use of first-line maintenance treatment?

Sensitivity of the ICERs to assumptions about rituximab efficacy

The ICERs are sensitive to assumptions made about the efficacy of rituximab used later on in the treatment pathway.

- Is it appropriate to assume that the efficacy of rituximab is not reduced when used later on in the treatment pathway after previous rituximab therapy?

5 Equalities issues

No equality and diversity issues were identified in the scoping of this appraisal.

6 Ongoing research

There are several studies ongoing in follicular lymphoma comparing different rituximab regimens.

Study	Patients	Treatment
STiL trial (Rummel 2009)	Follicular lymphoma and mantle cell lymphoma n = 549 Age: 18 and over	Rituximab + bendamustine Rituximab-CHOP
Rituximab−CVP versus Rituximab−CHOP versus Rituximab−FM	Follicular lymphoma (including stage II) n = 431 Age: 18−75	Rituximab-CVP Rituximab-CHOP Rituximab-FM
PACIFICO	Follicular lymphoma n = 680 Age: ≥ 60 years, or < 60 years but anthracycline-based therapy contra-indicated.	Rituximab-CVP Rituximab-FC
PLRG4 (Polish Lymphoma Research Group)	Follicular lymphoma n = 250 Age: ≥ 18 years	Rituximab-CVP Rituximab-CHOP
CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisone ; CVP, cyclophosphamide, vincristine and prednisone; FC, fludarabine and cyclophosphamide; FL, follicular lymphoma.		

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by ScHARR, University of Sheffield:

- Papaioannou D, Rafia R, Rathbone J, Stevenson M and Buckley Woods H (2011) Rituximab for the first-line treatment of stage III−IV follicular lymphoma (review of NICE technology appraisal guidance 110). Health Technology Assessment

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Roche Products

II Professional/specialist, patient/carer and other groups:

- The Lymphoma Association
- Royal College of Pathologists and the BSH
- NHS North of Tyne

Appendix B: Related NICE recommendations

‘Rituximab for the treatment of follicular lymphoma’ (NICE technology appraisal guidance 110):

> ‘Rituximab within its licensed indication (that is, in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.’

‘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):

> ‘Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin’s lymphoma.
>
> Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.
>
> Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).’

‘Rituximab for the treatment of follicular non-Hodgkins lymphoma (maintenance treatment following response to first-line chemotherapy)’ (NICE technology appraisal guidance 226):

> ‘Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin’s lymphoma that has

responded to first-line induction therapy with rituximab in combination with chemotherapy.'