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Abstract

Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation

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Background: Follicular lymphoma (FL) is a non-Hodgkin's lymphoma which typically presents when the disease is at an advanced stage. The majority of patients receive first-line therapy of rituximab in combination with chemotherapy, with two-thirds receiving cyclophosphamide, vincristine and prednisolone. The clinical and cost-effectiveness of other chemotherapies in combination with rituximab in first-line therapy is not known.
Objective: To systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of rituximab (MabThera®, Roche Products) in combination with chemotherapy, compared with chemotherapy alone, for the first-line treatment of symptomatic stage III–IV FL.
Data sources: A systematic review of literature and an economic evaluation were carried out. Key databases [including MEDLINE In-Process & Other Non-Indexed Citations; Cumulative Index to Nursing and Allied Health Literature (CINAHL); EMBASE; The Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; Science Citation Index (SCI); and BIOSIS], plus research registers and conference proceedings, were searched for relevant studies from inception up to October 2010.
Review methods: One reviewer assessed titles and abstracts of studies identified by the search strategy, obtained the full text of relevant papers and screened them against inclusion criteria. Data from included studies were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. The quality of included studies was assessed by one reviewer and checked by a second. A patient-level simulation model was developed to estimate the costs and quality-adjusted life-year (QALY) gains from the perspective of the UK NHS and Personal Social Services, with costs and benefits discounted at 3.5% annually.
Results: Four randomised controlled trials comparing rituximab plus chemotherapy (R-chemotherapy) with chemotherapy alone in untreated, symptomatic patients with stage III–IV FL were identified. R-chemotherapy compared with chemotherapy alone increased the likelihood of a response to treatment in all four trials, with no additional toxicity of clinical relevance. Overall response rates were significantly improved in all four trials, with a difference between the R-chemotherapy and chemotherapy arms of between 5% and 24%, respectively. Complete response rates were also improved, with a difference between the R-chemotherapy and chemotherapy arms of between 2% and 25%, respectively.

Exploratory meta-analyses were conducted; the level of statistical heterogeneity was very high and thus we believe the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens. Over a follow-up period of 4–5 years, R-chemotherapy significantly increased the overall survival rate compared with chemotherapy alone in three trials, although data for two trials were compromised owing to the use of additional treatments. The incremental cost-effectiveness ratio (ICER) for the addition of rituximab to CVP (cyclophosphamide, vincristine and prednisolone), CHOP (cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone) and MCP [mitoxantrone, chlorambucil (Leukeran®, Aspen) and prednisolone] was £7720, £10,834 and £9316 per QALY gained, respectively, when it was assumed that first-line rituximab maintenance was not used. A scenario analysis is also presented, assuming that responders to R-chemotherapy in first-line induction receive maintenance with rituximab, increasing the ICER to £14,959, £21,687 and £20,493 per QALY gained, respectively.

Limitations: These relate to the sources of data used for the effectiveness in first and second line and the assumed utility values; there is uncertainty about the effect of salvage treatment on patients who had been previously treated with an anthracycline regimen. There is uncertainty whether or not rituximab is as effective in second-line treatment when patients have been previously treated with rituximab.

Conclusions: The results from four randomised trials comparing R-chemotherapy with chemotherapy alone showed an improvement in clinical effectiveness outcomes, with minimal clinically relevant additional adverse events or toxicity. The cost per QALY gained is estimated to be < £25,000 for all three comparisons under our base-case assumption and is considerably lower if first-line rituximab maintenance is not assumed. More data on patients pre-treated with rituximab and on the effect of first-line maintenance with rituximab is required for future work.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Antibody An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells) or with an antigen closely related to it. Antibodies are classified, according to their mode of action, as agglutinins, bacteriolysins, haemolysins, opsonins, precipitins, etc.

Antigen A substance that is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, i.e. with specific antibodies or specifically sensitised T lymphocytes, or both. Antigens may be soluble substances (such as toxins and foreign proteins) or particulates (such as bacteria and tissue cells); however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (epitopes) combines with antibody or a specific receptor on a lymphocyte.

B cell A type of lymphocyte normally involved in the production of antibodies to combat infection. It is a precursor to a plasma cell. During infections, individual B-cell clones multiply and are transformed into plasma cells, which produce large amounts of antibodies against a particular antigen on a foreign microbe. This transformation occurs through interaction with the appropriate CD4 T-helper cells.

CD20 Unglycosylated phosphoproteins expressed only on B cells. They are regulators of transmembrane calcium conductance and are thought to play a role in B-cell activation and proliferation.

Disease-free survival* The time from complete response to relapse or death (not specified) [as defined in the R-CVP vs CVP (M39021) trial].

Event-free survival* The time period from randomisation to disease progression/relapse, death by any cause or new antilymphoma treatment (FL2000 trial). The time period from randomisation to disease progression after two cycles or partial response at six cycles or disease progression/relapse (OSHO-39 trial).

FL2000 trial (follicular lymphoma-2000 trial) An open-label randomised controlled trial (RCT) comparing R-CHVPi (rituximab, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha) with CHVPi for the first-line treatment of stage III–IV follicular lymphoma (FL).

Follicular lymphoma A type of non-Hodgkin's lymphoma (NHL), named as such because of the location (lymphoid follicles) and behaviour (growth in a follicular fashion) of the cancerous cells.

GLSG-2000 trial (German Low Grade Lymphoma Study-2000 trial) An open-label RCT comparing R-CHOP (rituximab, cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone) with CHOP for the first-line treatment of stage III–IV FL.

Granulocytopenia A decrease in the numbers of granulocytes, which are a type of white blood cell that helps to fight infection.

Indolent disease Disease that develops slowly.

Leucocytopenia A marked decrease in the numbers of white blood cells, which can increase the risk of infection.

Lymph The almost colourless fluid that bathes body tissues and is found in the lymphatic vessels that drain the tissues of the fluid that filters across the blood vessel walls from blood. Lymph carries lymphocytes that have entered the lymph nodes from the blood.

Lymphocyte White cells of the blood that are derived from stem cells of the lymphoid series. Two main classes are recognised, T and B lymphocytes, the latter responsible (when activated) for production of antibody, the former subdivided into subsets (helper, suppressor, cytotoxic T cells) and responsible both for cell-mediated immunity and for stimulating B cells.

Lymphoma Malignant tumour of lymphoid cells. Lymphomas are of either Hodgkin's or non-Hodgkin's type.

M39021 trial An open-label RCT comparing R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone) with CVP for the first-line treatment of stage III–IV FL.

Monoclonal antibodies An antibody made by a single clone of cells.

Neutropenia A marked decrease in the numbers of neutrophils (a type of granulocyte), which can increase the risk of infection.

Non-Hodgkin's lymphoma A group of lymphomas that differ in important ways from Hodgkin's disease and are classified according to the microscopic appearance of the cancer cells. There are many different subtypes of NHL; some of these are fast growing and life-threatening, whereas others are slow growing and may not require immediate treatment.

OSHO-39 trial An open-label RCT comparing R-MCP (rituximab, mitoxantrone, chlorambucil and prednisolone) with MCP for the first-line treatment of stage III–IV FL.

Overall survival The time from randomisation to the date of death by any cause.

Progression-free survival The time from randomisation to disease progression or death.

Response duration* The time from response achieved (complete or partial) to disease progression/relapse or death.

T cell A class of lymphocytes, so called because they are derived from the thymus and have been through thymic processing. Involved primarily in controlling cell-mediated immune reactions and in the control of B-cell development. The T cells co-ordinate the immune system by secreting lymphokine hormones.

Time to next antilymphoma treatment* The time from randomisation to date of next/new treatment (OSHO-39 and M39021 trials) or death (M39021 trial).

Time to progression* The time from randomisation to disease progression, relapse after response, death by any cause (M39021 trial).

Time to treatment failure* The time period from randomisation to death, relapse after response, new antilymphoma treatment or stable disease after cycle 4 (M39021 trial). The time period from start of treatment to resistance to initial therapy, disease progression or death (GLSG-2000 trial).

**No standard definitions exist. Definitions taken from four trials are included in this appraisal.*

List of abbreviations

AE	adverse event
AG	Assessment Group
AIC	Akaike information criterion
ASCT	autologous stem cell transplant
BCSH	British Committee for Standards in Haematology
BEAM	BCNU®/carmustine, cytarabine, etoposide and melphalan
BIC	Bayesian information criterion
BNF	*British National Formulary*
BSA	body surface area
CEAC	cost-effectiveness acceptability curve
CHOP	cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone
CHVP	cyclophosphamide, doxorubicin, etoposide and prednisolone
CHVPi	cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CNOP	cyclophosphamide, mitoxantrone, vincristine and prednisolone
CR	complete response/responder
CRD	Centre for Reviews and Dissemination
CRu	unconfirmed complete response/responder
CT	computerised tomography
CVP	cyclophosphamide, vincristine and prednisolone
DFS	disease-free survival
DHAP	dexamethasone, cytarabine and cisplatin
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EFSR	event-free survival after first relapse
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESHAP	etoposide, methylprednisolone, cytarabine and cisplatin
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FACT-LYM	Functional Assessment of Cancer Therapy (lymphoma)
FC	fludarabine and cyclophosphamide
FCM	fludarabine, cyclophosphamide and mitoxantrone
FL	follicular lymphoma
FL2000	follicular lymphoma-2000 trial (R-CHVPi vs CHVPi)
FLIPI	Follicular Lymphoma International Prognostic Index
FM	fludarabine and mitoxantrone
GLSG-2000	German Low Grade Lymphoma Study-2000 (R-CHOP vs CHOP)
HDT	high-dose chemotherapy
HR	hazard ratio
HRQoL	health-related quality of life
HS	health state
ICER	incremental cost-effectiveness ratio
IPI	International Prognostic Index

ITT	intention to treat
i.v.	intravenously
IWF	International Working Formulation
LDH	lactate dehydrogenase
LFT	liver function test
LY	life-year
M39021	R-CVP vs CVP trial
MCL	mantle cell lymphoma
MCP	mitoxantrone, chlorambucil and prednisolone
MIU	million international units
MS	manufacturer's submission
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NE	not estimable
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Clinical Excellence
NR	not reported
ORR	overall response rate
OS	overall survival
OSHO	East German Society of Haematology and Oncology
OSHO-39	East German Society of Haematology and Oncology R-MCP vs MCP trial
PET	positron emission tomography
PFS	progression-free survival
PFS1	progression-free survival after first line
PFS2	progression-free survival after second line
PML	progressive multifocal leucoencephalopathy
PPS	post-progression survival
PR	partial response/responder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
R	rituximab
R-C	rituximab and chlorambucil
R-chemotherapy	rituximab and chemotherapy
R-CHOP	rituximab, cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone
R-CHVP	rituximab, cyclophosphamide, doxorubicin, etoposide and prednisolone
R-CHVPi	rituximab, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha
R-CVP	rituximab, cyclophosphamide, vincristine and prednisolone
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
R-ESHAP	rituximab, etoposide, methylprednisolone, cytarabine, cisplatin
R-F	rituximab and fludarabine
R-FC	rituximab, fludarabine and cyclophosphamide
R-FCM	rituximab, fludarabine, cyclophosphamide and mitoxantrone
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
R-MCP	rituximab, mitoxantrone, chlorambucil and prednisolone
RCT	randomised controlled trial
REAL	Revised European–American Lymphoma
RMSE	root-mean-square error
RR	relative risk
Rx	maintenance rituximab

SA	sensitivity analysis
SAR	survival after first relapse
ScHARR	School of Health and Related Research
SCT	stem cell transplant
SD	standard deviation
SE	standard error
SNLG	Scotland and Newcastle Lymphoma Group
SPD	sum of the products of the greatest diameters
STiL	Study Group Indolent Lymphomas
TTF	time to treatment failure
TTNT	time to next antilymphoma treatment
TTP	time to progression
U&E	urea and electrolytes
VAS	visual analogue scale
WHO	World Health Organization
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic tissue, causing enlargement of lymph nodes and generalised symptoms. Follicular lymphoma (FL), a clinical subtype of NHL, develops slowly and often without symptoms for many years. FL takes a relapsing and remitting course, and median survival is 8–10 years, although more recent evidence suggest it could be as high as 15–20 years. In 2008, the incidence of FL in England and Wales was 3.4 per 100,000 persons. Over 70% of FLs are diagnosed in persons aged > 60 years, and 85–90% present with advanced disease, which is defined as lymph nodes on both sides of the diaphragm being involved (stage III) or disease is disseminated with one or more extralymphatic organ involved (stage IV).

Advanced FL is not curable, thus the aim of disease management is to both increase patient life expectancy and to increase patient health-related quality of life. For the majority of patients (90%), first-line therapy in stage III–IV FL is rituximab (R) (MabThera®, Roche Products) plus chemotherapy (R-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 is cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), which accounts for 16% of other chemotherapy regimens. Patients who are less fit and/or elderly may receive chlorambucil (Leukeran®, Aspen) as single-agent chemotherapy. The National Institute for Health and Clinical Excellence reviewed the use of rituximab in Technology Appraisal (TA) no. 110 in 2006, subsequently recommending the use of R-CVP as first-line treatment for symptomatic stage III–IV FL. Since TA110, the licence for rituximab has been extended so that rituximab can be administered in combination with any chemotherapy for first-line treatment of symptomatic stage III–IV FL. Rituximab monotherapy as a maintenance treatment may follow for patients who have responded to first-line treatment with R-chemotherapy, which aims to delay relapse by stabilising response to initial therapy, eradicating any residual disease and maintaining remission after successful remission induction therapy.

Objectives

The aim of this assessment is to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of rituximab (in its licensed indication) in combination with chemotherapy compared with non-rituximab-containing chemotherapy, for the first-line treatment of symptomatic stage III–IV FL.

Methods

Eleven electronic databases were searched from inception to September/October 2010: MEDLINE, including MEDLINE In-Process & Other Non-Indexed Citations; Cumulative Index to Nursing and Allied Health Literature (CINAHL); EMBASE; The Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; Science Citation Index (SCI); and BIOSIS. Ongoing research was searched using clinical trials databases and

registers. Relevant conference proceedings were searched and the reference lists of relevant articles and sponsor submissions were handsearched.

Comparative studies were selected for review if they addressed the clinical effectiveness or cost-effectiveness of adding rituximab to chemotherapy. In addition, comparative studies that involved either an intervention or comparator defined in the decision problem (i.e. R-chemotherapy or chemotherapy alone) were selected for potential use in a network meta-analysis. The studies had to include patients with symptomatic III–IV FL and to be of randomised controlled trial (RCT) design. Outcomes had to include one or more of the following: response rates, response duration, overall survival (OS), progression-free survival (PFS) or duration of disease remission. The quality of the studies was assessed using criteria based on those proposed by the NHS Centre for Reviews and Dissemination. Data were abstracted into standardised data extraction forms. Findings were tabulated and discussed in a narrative synthesis.

A systematic review of economic evaluations addressing the cost-effectiveness of the addition of rituximab to chemotherapy compared with chemotherapy alone was conducted. There was also one manufacturer submission (Roche) for this assessment, which included an economic model. In addition, a systematic review of the quality of life in FL was performed.

A probabilistic model was developed by the Assessment Group (AG) to assess the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP (mitoxantrone, chlorambucil and prednisolone) from a NHS perspective. The model has four health states: PFS after first line (PFS1), PFS after second line (PFS2), progressive disease and death. Patients start in PFS1 and receive first-line induction with chemotherapy with or without rituximab. Patients who relapse move on to 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. The model uses a 25 years time horizon and costs and benefits are discounted at 3.5%. A scenario analysis is presented incorporating first-line maintenance in responder to first-line induction with R-chemotherapy.

Results

Summary of benefits and risks

Four RCTs comparing R-chemotherapy with chemotherapy alone in untreated, symptomatic patients with stage III–IV FL were identified.

R-chemotherapy compared with chemotherapy alone increased the likelihood of a response to treatment in all four trials, with no additional toxicity of clinical relevance. Overall response rates (ORRs) were significantly improved in all four trials, with a difference between the R-chemotherapy and chemotherapy arms of between 5% and 24%, respectively. Complete response (CR) rates were also improved, with a difference between the R-chemotherapy and chemotherapy arms of between 2% and 25%. Exploratory meta-analyses were conducted to explore the results of synthesising the ORR, CR and partial response from the four trials. The level of statistical heterogeneity was very high and the AG therefore believes the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens. These are subsequently used in the decision model.

Over a follow-up period of 4–5 years, R-chemotherapy significantly increased the OS rate compared with chemotherapy alone in three trials. The trials presented evidence that

R-chemotherapy prolonged other clinical outcomes, such as response duration, time to treatment failure, time to progression, time to next antilymphoma treatment, event-free survival and disease-free survival, compared with chemotherapy alone.

Summary of cost-effectiveness

The incremental cost-effectiveness ratio (ICER) for the addition of rituximab to CVP, CHOP and MCP was £7720, £10,834 and £9316 per quality-adjusted life-year (QALY) gained, respectively, when it was assumed that first-line rituximab maintenance was not used.

When it was assumed that patients responding to first-line induction with R-chemotherapy receive first-line maintenance rituximab for up to 2 years, the ICERs increased to £14,959, £21,687 and £20,493 per QALY gained, respectively. Sensitivity analyses (SAs) indicated that the ICER was mostly sensitive to the assumptions 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, assumptions regarding resistance to rituximab and the modelled treatment pathway. Results are not directly comparable across chemotherapies, as they are selected in clinical practice with regard to factors including age, performance status and disease aggressiveness.

Discussion

The results from four randomised trials (of good quality) comparing R-chemotherapy with chemotherapy alone showed an improvement in a number of clinical effectiveness outcomes. These benefits are achieved with minimal clinically relevant additional adverse events or toxicity. It is noted that data for outcomes such as OS are compromised in three of the studies owing to the use of additional treatments. Longer OS data follow-up would strengthen the findings, as the median OS has not yet been reached in any of the trials.

This assessment provides an indication of the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP in a UK setting. The model developed by the AG extends the analysis undertaken in previous economic models in terms of a greater level of detail in the modelled treatment pathway. A wide range of assumptions have also been examined in SAs. However, there are some limitations relating to the sources of data used in the AG model for the effectiveness in first and second line and the assumed utility values. There is little evidence available regarding the effectiveness of R-CHOP and R-MCP in first-line induction. There is also uncertainty about the effect of salvage treatment in patients previously treated with an anthracycline regimen. Finally, there is uncertainty whether or not rituximab is as effective in second line when patients have been previously treated with rituximab. The context for care and the mode of delivery is identical with the comparator therapies; thus, there are no implications that do not also apply to chemotherapies alone.

Generalisability

It is noted that patients included in the trials were generally younger than those seen in clinical practice in the UK. This assessment is based on data involving the following chemotherapeutic agents: CVP, CHOP, MCP and CHVPi (cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha). It is not certain that the results can be generalised to other R-chemotherapy regimens.

Conclusions

The addition of rituximab to CVP, CHOP and MCP is likely to be clinically effective in the first-line treatment of stage III–IV FL. The cost per QALY gained is estimated to be < £25,000 for all three comparisons under our base-case assumption and is considerably lower if first-line rituximab maintenance is not assumed. The main uncertainties in terms of influencing the ICER relate to the effectiveness of rituximab retreatment (i.e. resistance) and the effect of salvage treatment in patients previously treated with anthracycline regimens. Assumptions were made and the best evidence identified was used when appropriate and available. Therefore, results have to be interpreted in line with the assumptions made and the quality of the evidence available.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Description of health problem

Epidemiology

Non-Hodgkin's lymphomas (NHLs) account for approximately 4% of all cancers diagnosed in the UK,[1] and are also the fifth most common cancer in the UK for both sexes combined (fifth in males and seventh in females).[2] In 2008, there were 10,319 new cases of NHL registered in England and Wales,[3] and 3978 registered deaths in 2008.[4]

Follicular lymphoma (FL) is a type of low-grade or indolent NHL, in which the cancer develops slowly, often without symptoms, for many years. FL is the second most common type of NHL within Western Europe and the USA,[5] and is reported to account for between 20% and 30% of all NHLs.[6–9] The UK incidence of FL is approximately 3.4 per 100,000 persons (see *Table 1*), and around 70% of all cases are diagnosed in people aged > 60 years.[10] FL occurs equally in males and females. Most patients with FL present with advanced disease; approximately 50% of patients will present with bone marrow involvement (i.e. stage IV disease; see *Staging*, later in this chapter).

Over 70% of people with FL are still alive 5 years after the diagnosis,[11] with the 10-year predicted survival rate for patients in England and Wales in 2007 reported as 50.8%.[2] In the last decade, longer median survival has been reported, with one centre reporting median overall survival (OS) of up to 18 years,[12] and the percentage of survival at 20 years as high as 44%.[13] Some have attributed this to novel therapeutic strategies,[14,15] including chemoimmunotherapy [i.e. chemotherapy and rituximab (MabThera®, Roche Products)] and radioimmunotherapy. Relevant data on incidence and prevalence are provided in *Tables 1* and *2*, respectively.

The incidence of NHL has been increasing in the UK; rates have increased by more than one-third since the late 1980s, resulting in the incidence in people aged > 75 years being three times higher in 2007 than in 1975.[18] Other countries (Western Europe, USA, Japan, Brazil, India and Singapore) have also noted increasing incidences of NHL. In westernised countries, the annual incidence of FL has increased from 2–3/100,000 during the 1950s to 5–7/100,000 recently (date not specified).[19]

It is unclear why the incidences of lymphomas are increasing, although better diagnosis, improved cancer reporting, changes in classification, unknown environmental factors, an increasing elderly population and increases in acquired immunodeficiency syndrome (AIDS)-related lymphomas will contribute to the increase in incidence. However, these factors are estimated to account for about half of the increase in observed incidence.[20]

Aetiology

The causes of NHL in general, including FL, are unclear. There are a number of well-established risk factors, such as infectious agents [e.g. human immunodeficiency virus (HIV)],[21] immunosuppression (e.g. post organ transplantation),[22] genetic susceptibility (e.g. ataxia–telangiectasia)[23] and environmental factors (e.g. exposure to agrochemicals).[24] Rare immunodeficiency conditions such as hypogammaglobulinaemia, Wiskott–Aldrich syndrome and ataxia–telangiectasia have been associated with as much as a 25% increased risk of developing lymphoma;[25] however, the primary causes of NHLs remain elusive.

TABLE 1 Incidence of FL in England and Wales[a]

NHL/FL incidence	England	Wales	England and Wales
All NHLs: no. of cases (2008)	9676	643	10,319
All NHLs: crude rate per 100,000 (2008)	18.8	21.5	18.9
FL: no. of cases (2008)	1757	112	1869
FL: crude incidence per 100,000 (2008)	3.4	3.7	3.4

a All figures calculated using data from 2008 from the Office for National Statistics[3] and the Welsh Cancer Intelligence & Surveillance Unit.[16] See *Appendix 1* for details of calculations.

TABLE 2 Non-Hodgkin's lymphoma prevalence[17] in England and Wales at 31 December 2006[a]

	1-year prevalence			5-year prevalence			10-year prevalence		
NHL/FL prevalence	England	Wales	England and Wales	England	Wales	England and Wales	England	Wales	England and Wales
NHL prevalence (2006)	6330	498[b]	6761	24,207	1516	25,723	38,227	2224	40,451
Estimated FL prevalence (based on FLs as 20–30% of NHLs)[6–9]	1266–1899	105[b]	1371[c]–2028	4841–7262	303–455	5145–7717	7645–11,468	445–667	8090–12,135

a Prevalence data relates to the proportion of the UK population alive on 31 December 2006, having previously been diagnosed with cancer.
b Data provided by the Welsh Cancer Intelligence & Surveillance Unit 2008.[16]
c Calculated using 1-year prevalence figure for Wales provided by the Welsh Cancer Intelligence & Surveillance Unit 2008.[16]

Pathology

Background

Non-Hodgkin's lymphomas are a diverse group of cancers characterised by abnormal growth of tissue in the lymphatic system. The lymphatic system comprises the tissues, organs and vessels that produce, store and deliver cells that fight infection – 'lymphocytes'. There are two main classes of lymphocytes – T lymphocytes and B lymphocytes – with each having a key role in protecting the body from pathogenic microorganisms. 'T cells' are responsible both for cell-mediated immunity and for stimulating 'B cells', which, when activated, produce antibody that kills or neutralises antigens. NHL may be classified as a B- 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 and the remaining 15% of T-cell origin.[26]

Follicular lymphoma is classified as a B-cell NHL. It is an indolent (slow-growing) cancer that affects B-cell lymphocytes (centrocytes and centroblasts). Patients with FL typically present with painless, swollen lymph nodes in the neck, armpit or groin. Systemic or 'B' symptoms are rare: these include fever, fatigue, night sweats and unexplained weight loss.[5,27] Less frequently, there may be no peripheral lymphadenopathy, or patients develop abdominal or back pain owing to intra-abdominal (often paraortic) lymph node enlargement.[5] Usually disease is disseminated and involves lymph node regions on both sides of the diaphragm (stage III) or possibly extralymphatic organs or tissues (stage IV).[6,28]

Despite being treatable, FL is characterised by a relapsing–remitting clinical course over several years, with each successive response becoming more difficult to achieve and of shorter duration.[27] The course and prognosis of FL improved only marginally from 1960 to the early 1990s, with a reported median survival of 8–10 years.[29] However, in the last decade, longer median

survival has been reported and has been attributed to novel therapeutic strategies, including chemoimmunotherapy (i.e. chemotherapy and rituximab) and radioimmunotherapy.[14,15]

Patients with 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 (DLBCL).[29,30] Resistant disease or transformation into DLBCL is the usual cause of death for patients with FL.[27] The risk of transformation to aggressive lymphoma is thought to be constant over time;[29] the annual risk of transformation has been estimated as 3% per year and the median survival after transformation has been reported as 1.7 years, although this figure comes from the pre-rituximab era.[31] It is not clear whether specific therapies can increase or decrease this risk.[32]

Diagnosis and grading

The diagnosis of FL is confirmed by lymph node biopsy, which optimally requires review by an pathologist or haematopathologist (in the UK).[32]

Staging

Once FL is identified, it is staged to find out how far the disease has spread. Staging tests determine which areas of the body are affected by FL, the number of lymph nodes affected, and whether or not other organs are affected such as the bone marrow or liver. The Ann Arbor system (see *Appendix 2*) is a clinical tool that was originally developed for Hodgkin's disease, but is also used for FL to determine the stage of the lymphoma. It classifies four stages of disease that reflect both the number of sites of involvement and the presence of disease above or below the diaphragm.[34] Each stage of disease is divided into two subsets of patients according to the absence (A) or presence (B) of systemic symptoms. Fever without other cause, night sweats and weight loss of > 10% of body weight are considered to be systemic symptoms. The tests carried out for staging include blood tests, computerised tomography (CT) scan, bone marrow biopsy. Positron emission tomography (PET) scan may also be used, although is not routine in the UK. At most, 10–15% of FLs are detected at the early stage;[35] thus the majority present with advanced-stage disease (Ann Arbor stage III–IV).

Grade

Follicular lymphoma is a low-grade or indolent B-cell disease and is diagnosed according to the World Health Organization (WHO) classification. Grade is determined by histology (i.e. by inspecting cells under the microscope), which looks at the number and size of abnormal cells taken from lymph node biopsies. The disease maybe subdivided into grades 1/2 (combined in the latest version of the WHO classification), grade 3a or 3b. These subdivisions of grade 3 are based on the presence of increasing numbers of more aggressive cells termed *centroblasts*. Grade 3b is treated in the same manner as the common high-grade NHL, DLBCL. Grades 1/2 and 3a are managed as indolent forms. Each disease stage (Ann Arbor stages I–IV) can be assigned a grade (1–3a/b).

Systems of classification

Follicular lymphoma is classified according to its morphology, immune phenotype, genetics, and clinical features of neoplasms. Since the 1970s, various classification systems have been used to differentiate NHLs, which have developed alongside an increasing understanding of the different cellular components of the lymphatic system that the cancer process affects.[36] It is useful to be familiar with previous classification systems in order to interpret the older literature for lymphomas with now outdated names. The third edition of the *International Classification of Diseases for Oncology* (ICD-O) provides a guide for translation of previous classification systems into the present.[37]

The earliest classification systems were based on the cellular morphology of neoplastic cells and their relationship to the lymphoid tissue architecture. The Rappaport Classification, which was used until the 70s, was devised before lymphoid cells were split into T and B cells.[38] In the early 1970s, the Kiel Classification system was proposed, which classified lymphomas according to their cellular morphology and their relationship to cells of the normal peripheral lymphoid system.[39] The Working Formulation devised by the National Cancer Institute in 1982 attempted to translate the recognised classification systems for NHL (it did not include Hodgkin's lymphomas). The Working Formulation was a purely histological classification and divided lymphomas into four grades (low, intermediate, high and miscellaneous), related to prognosis, and included subdivisions based on the size and shape of affected cells. However, this classification system did not differentiate between T and B cells and is now obsolete.

With the development and application of immunophenotyping and cytogenetic and molecular genetic testing, the Revised European–American Lymphoma Classification (REAL) classification system was devised in the mid-1990s and incorporated immunophenotype and genetic criteria. The WHO classification system, based on the REAL classification, is the latest classification system and the most widely used and accepted. The WHO classification was updated in 2008 and groups lymphomas by cell type and defines phenotypic, molecular and cytogenetic characteristics. There are three large groups of neoplasms: (1) B cell, (2) T cell and (3) natural killer cell neoplasms. FLs are grouped under the B-cell type (ICD-O-3 codes: 9690/3, 9691/3, 9695/3 and 9698/3).

Prognosis

Follicular lymphoma is curable for only a few patients, mainly those with localised or early-stage disease (Ann Arbor stages I and II).[40] Most advanced-stage patients respond to initial drug therapy and their symptoms go into remission. However, despite novel therapies and recent improvements in therapy, advanced FL is not considered curable. Patients with advanced FL undergo multiple relapses with the duration of remissions shortening at each subsequent treatment at recurrence.[30,41]

Prognostic factors

Prognostic factors in FL can be categorised as patient-related factors and disease-related factors. By analysing prognostic factors, indices have been developed to predict clinical outcomes such as progression-free survival (PFS) and OS. Two such indices are the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI).

Patient-related variables

The most important patient-related prognostic factors are performance status and age.[42] Performance status, is defined by the Eastern Cooperative Oncology Group (ECOG)[43] and ranges from 0 (fully active) to 4 (completely disabled); thus poorer performance status is associated with a poorer FL prognosis (see *Appendix 3* for ECOG performance status in detail). However, only 10–15% of patients with FL present with a poor performance status at the time of diagnosis.[42]

Age of > 60 years is a significant factor for prognosis.[44,45] The existence of comorbidities and alterations in immunity with age might limit the drugs that can be used.[46] In addition, alterations in pharmacokinetics and reduction in hepatic and renal function occurs with increasing age. This affects the absorption, distribution, activation, metabolism and clearance of drugs.[46] This impacts on the clinician's ability to treat elderly patients effectively. Gender has also been shown to be an important prognostic factor; the male sex is associated with a poorer clinical outcome.[28]

Disease-related factors

Histological features such as lower degree of follicularity (i.e. greater diffuse areas),[47–50] absence of interfollicular fibrosis[47] and high content of macrophages in biopsy samples[51] are associated with poor prognosis; helper T-cell infiltrates have been associated with a survival benefit.[52,53] Genetic features such as oncogenes or tumour-suppressor genes, chromosomal gains or losses and gene expression profiles have been found to affect prognosis.[42]

Factors relating to disease extent are important in predicting prognosis. Patients with limited stage disease (i.e. Ann Arbor stage I or II) are likely to have prolonged survival.[42] However, the majority of patients present with advanced disease (stage III or IV), thus the effect of other clinical parameters has been investigated. A larger number of extranodal sites involved,[44,45,54,55] presence of B symptoms,[44,54] the presence and greater extent of bone marrow involvement[56] and the presence of hepatosplenomgaly[30] have all been found to affect adversely prognosis. In addition, tumour burden has been identified as an important prognostic factor; however, it is inconsistently defined according to size of lymph node masses, number of extranodal sites involved, degree of splenomegaly or hepatomegaly and the presence of circulating lymphoma cells.[42]

Biological markers such as elevated lactate dehydrogenase (LDH) have been found to predict lower response rates and survival.[28,44,54] A normal haemoglobin level has been found to be a favourable factor for prognosis, whereas a haemoglobin level of < 12 mg/dl is a poor prognostic factor.[30]

International Prognostic Index

The IPI was originally designed as a prognostic tool for aggressive NHL (DLBCL), and is based on the presenting features and the extent of disease. The IPI has been reported to discriminate between patients with FL with significantly different survival periods,[57] and is now used as a predictive tool for survival in FL (*Table 3*).

Follicular Lymphoma International Prognostic Index (FLIPI and FLIPI2)

In 2004, the FLIPI was developed specifically for patients with FL. Evaluations of demographic, clinical and biological characteristics from > 4000 patients with FL were used in univariate and multivariate analyses to develop the FLIPI. It provides clinicians and patients with a prognostic index based on five criteria (age > 60 years, Ann Arbor stage III or IV, number of nodal sites of involvement greater than four, elevated serum LDH, and haemoglobin level of < 12 g/dl). The FLIPI assesses OS, i.e. carrying a low (zero to one risk factors), intermediate (two risk factors) or high risk (three to five risk factors).[58] The FLIPI has been further refined to accommodate more recent developments in the collection of biological data and newer treatment modalities such as immunotherapy, resulting in FLIPI2.[59] For example, β_2-microglobulin is an independent prognostic marker included in later versions of the FLIPI.

TABLE 3 International Prognostic Index

One point is assigned for each of the following risk factors	The sum of the points allotted correlates with the following risk groups
Age > 60 years	Low risk (zero to one point): 5-year survival of 73%
Ann Arbor stage III or IV disease	Low-intermediate risk (two points): 5-year survival of 51%
Elevated serum LDH	High-intermediate risk (three points): 5-year survival of 43%
ECOG/Zubrod performance status of 2, 3 or 4	High risk (four to five points): 5-year survival of 26%
More than one extranodal site	

Significance in terms of ill-health (burden of disease)

The nature of NHL in general, and the relapsing–remitting course of FL in particular, suggests that both individually and at a population level it is responsible for a considerable amount of morbidity and mortality (see *Epidemiology*). In 2009, NHL accounted for 0.8% of all deaths and 2.9% of all cancer deaths in England and Wales (see *Appendix 4* for data sources and numbers used), and is the ninth most common cause of cancer mortality in the UK.[2]

Current service provision

Objectives of treatment and important health outcomes

Advanced FL is not curable. However, because of the age distribution and presence of comorbidities, patients may remain uncured from FL but may die from other causes unrelated to the disease. The aim of disease management is both to increase patient life expectancy and to increase patient health-related quality of life (HRQoL). First-line treatment aims to produce a maximum initial response by reducing tumour burden,[60] to prolong the periods of PFS and OS, to increase the duration between episodes of disease recurrence and to minimise the symptoms associated with relapse and treatment side effects.[61]

Therefore, the following outcomes are likely to be of potential importance:

- absence of disease at given points in time following diagnosis
- absence of symptoms
- absence of side effects
- duration of survival
  - OS
  - PFS
- HRQoL
- patient and carer satisfaction.

Management of disease

Grading, staging and symptoms determine treatment pathways. *Figure 1* gives an overview of the treatment pathway for stage III/IV FL [adapted from the manufacturer's submission (MS) for this appraisal].[62] This pathway has been simplified and does not take into account the risk of transformation to DLBCL or the differences in treatment of disease that relapses early compared with later relapse. These are discussed later in this section.

Asymptomatic patients

Most patients are asymptomatic on presentation (painless swelling of one or more lymph nodes) and a 'watch and wait' approach is usually adopted. Observational studies[63,64] and three randomised controlled trials (RCTs)[65–67] have shown that prognosis is not affected by immediate treatment compared with observation until symptomatic disease progression (bulky lymphadenopathy, bone marrow compromise, splenomegaly, etc.). Thus, treatment commences only when the disease becomes symptomatic.

First-line therapy: limited disease (Ann Arbor stages I–II)

Patients diagnosed in the early stages of the disease (stages I–II) usually respond well to radiotherapy and this is the treatment of choice, usually taking the form of extended or involved field form irradiation. This can result in long-term disease-free survival (DFS) and possible cure for between 45% and 80% of patients.[35]

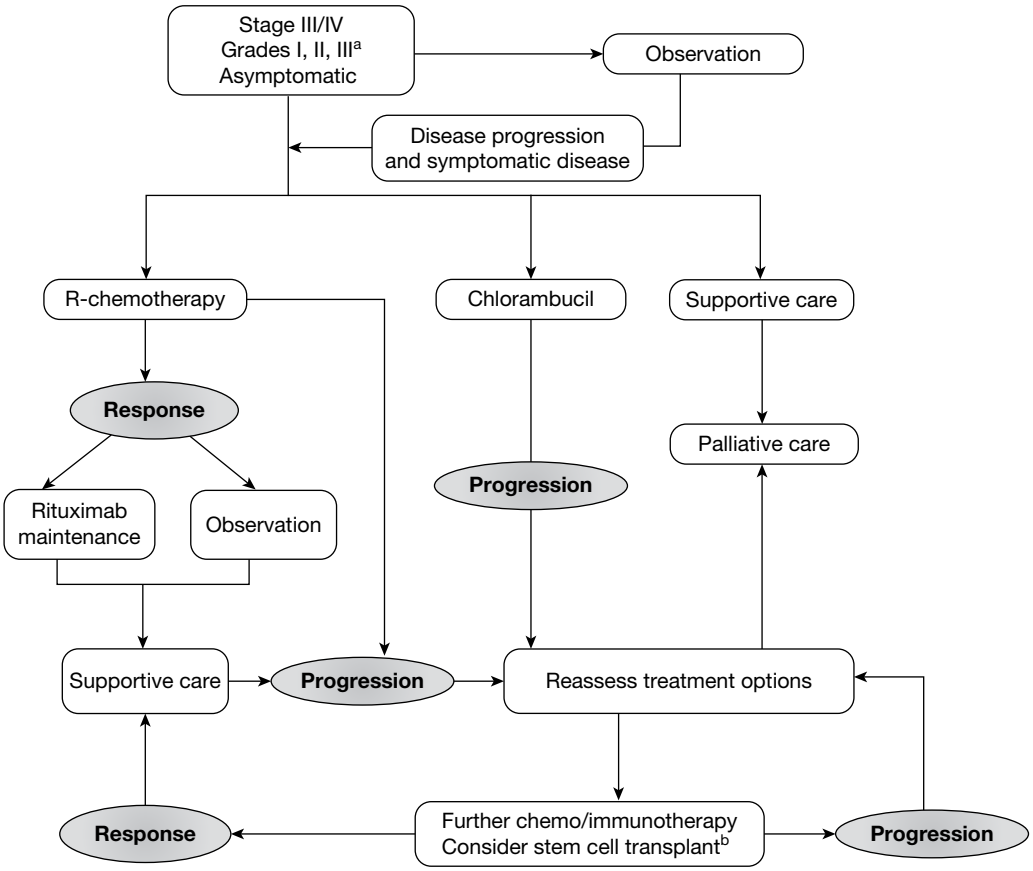


FIGURE 1 Treatment pathway for stage III/IV FL (adapted from MS).[62] a, Response can be complete or partial response. b, Note that patients who received chlorambucil in first-line treatment would not be eligible to receive stem cell transplant.

First-line therapy: advanced disease (Ann Arbor stages III–IV)

Chemoimmunotherapy [i.e. rituximab and chemotherapy (R-chemotherapy)] is the preferred treatment for first-line therapy in symptomatic advanced FL. The European Society for Medical Oncology (ESMO) clinical practice guidelines recommend that when complete remission and long PFS are the aims of treatment, rituximab in combination with chemotherapy [such as cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone (CHOP); cyclophosphamide, vincristine and prednisolone (CVP), fludarabine, cyclophosphamide (FC); fludarabine and mitoxantrone (FM) or bendamustine] should be used.[19] In 2006, National Institute for Health and Clinical Excellence (NICE) guidance stated that rituximab in combination with CVP is indicated for the first-line treatment of symptomatic FL, in line with the licensed indication at the time the guidance was issued.[68] However, in 2008 the licence for rituximab was broadened so that it can be administered with other chemotherapies; there is no consensus, however, on the preferred chemotherapy option.[69] Antibody monotherapy or single-agent alkylating agents [e.g. chlorambucil (Leukeran®, Aspen)] can be considered an alternative in previously untreated patients with FL with particularly low-risk disease or those who are unsuitable for more intensive treatments.[19]

Maintenance therapy (first line)

As disease recurrence is inevitable, ways of maintaining or improving the quality of the initial response to treatment are used, such as maintenance therapy. Maintenance treatment is a long-term approach that aims to delay relapse by stabilising the best response to initial therapy, eradicating any residual disease and maintaining remission after successful remission induction therapy.[70]

The ESMO clinical practice guidelines acknowledge recent evidence that rituximab maintenance for 2 years can prolong PFS.[71] Guidance issued in June 2011 by NICE recommended rituximab maintenance therapy as an option for the treatment of people with follicular NHL lymphoma who have responded to first-line induction therapy with rituximab in combination with chemotherapy. Prior to this, the UK standard practice has been to closely observe patients during their first remission and retreat only when there is evidence of disease progression.

Aside from rituximab, other agents have been proposed for use as maintenance therapy, such as interferon-alpha (a biological therapy). However, a meta-analysis suggests a limited benefit of interferon-alpha maintenance therapy that has to be balanced against toxicity.[72] Clinical advice is not to use interferon-alpha as patients cannot tolerate the side effects.

Consolidation therapy is another type of treatment that has been proposed following successful induction of first-line remission. Consolidation therapy is delivered immediately after a response to induction therapy; however, it differs from maintenance therapy as it is a short course of treatment that aims to rapidly improve the response to induction therapy.[60] Radioimmunotherapy agents such as ibritumomab tiuxetan (Zevalin®, Spectrum Pharmaceuticals) have been used in consolidation therapy; however, their benefit following a R-chemotherapy combination has not been established.[19]

Treatment of relapsed disease

After every relapse, a biopsy should be undertaken to determine if transformation has occurred.[5,19] When transformation does occur, there is usually rapidly increasing lymph node enlargement, elevated LDH levels and development of systemic symptoms. Histological transformation can occur in 20–70% of patients, with the variability in reported incidence reflecting, to a large extent, local practice in terms of whether or not biopsies are performed at each recurrence.[5] Treatments for FL are not effective once transformation has occurred and patients are treated as for high-grade FL or DLBCL. Median survival following transformation has been reported as 18 months, although this figure comes from the pre-rituximab era.[5]

When the disease has relapsed, treatment options are reassessed, with the selection of salvage treatment depending on the efficacy of prior regimens.[19] However, there may be some variations between clinical practice in the UK and the ESMO guidelines.

When there is early relapse following first-line R-chemotherapy treatment (< 6 months), the disease is considered as rituximab refractory in the ESMO guidelines, which state that rituximab is not indicated. However, clinical advice to the Assessment Group (AG) indicated that some clinicians may also consider which chemotherapeutic regimen was given in first-line treatment when choosing the second-line treatment. For example, if rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) had been used in first-line induction therapy and early relapse occurred, rituximab, cyclophosphamide doxorubicin/adriamycin, vincristine and prednisolone (R-CHOP) may be selected for the second-line treatment, with the rationale being that it was the CVP-component rather than the rituximab that was responsible for the early relapse. If, however, R-CHOP had been used in first-line induction therapy, and relapse is early, this is indicative of a poor prognosis (based on clinical advice sought by the AG), making high-dose chemotherapy (with or without rituximab) and stem cell transplant (SCT) an appropriate second-line treatment.

The ESMO guidelines also state that in relapses of < 12 months, a non-cross-resistant scheme should be preferred with regard to the chemotherapy selected (i.e. two differing chemotherapeutic regimens such as fludarabine after CHOP for example). Rituximab monotherapy is also recommended as a treatment option by NICE for people with relapsed or refractory disease when all alternative treatment options have been exhausted.[73]

The use of rituximab in retreatment of patients who have received rituximab at first-line treatment has been discussed previously in NICE technology appraisal (TA137), where evidence for clinical effectiveness of rituximab in second-line treatment of FL was from the EORTC 20981 trial,[74,75] the population of which were rituximab-naive patients. However, although the Committee considered that 'it was necessary to be cautious about the assumption that rituximab is as efficacious in patients who had already received it as in patients who are rituximab-naive'; clinical specialists present at the Committee stated that 'the evidence indicated that follicular NHL could be retreated with rituximab with little or no loss of efficacy'. It was noted by the Committee that although this is as an area of uncertainty, this was biologically plausible given rituximab's mechanism of action.[73] This is discussed in more detail, see *Resistance to rituximab in patients previously exposed to rituximab treatment*.

Second-line rituximab maintenance

Following response to second-line induction therapy (with or without rituximab), rituximab monotherapy may also given as second-line maintenance, as recommended by NICE.[73]

Stem cell transplant

During the course of treatment, relapses become more frequent with shorter disease-free periods,[69] and chemotherapy or chemoimmunotherapy are not able to induce a further stable remission period. SCT is a treatment option for patients with relapsed FL. However, the use of and position of SCT in the treatment pathway of FL has altered since the introduction of rituximab, and the ESMO guidelines state that its use needs to be re-evaluated in the rituximab era.[19] Clinical advice provided to the AG suggests its use has declined in the treatment of FL since the introduction of rituximab in first-line induction and maintenance, and second-line induction and maintenance. In second-line treatment, SCT appears to be reserved for patients with very aggressive disease and short remission periods following first-line induction therapy or patients who have undergone transformation to DLCBL. For patients who do not have aggressive disease and for whom a reasonable remission period has been achieved following first-line treatment, SCT is considered more frequently at the third-line treatment stage. At whichever point SCT is offered in the treatment pathway, it is usually only offered to younger patients (aged < 65 years), although clinical advice suggests that it may be offered to some fit patients up to the age of 70 years.

Relevant national guidelines

A summary of the relevant European Medicines Agency (EMA) licensing and NICE guidelines relating to the use of rituximab in the treatment of FL is presented in *Table 4*.

The ESMO has produced guidelines for the diagnosis, treatment and follow-up of newly diagnosed and relapsed FL[19] as discussed above (see *Management of disease*). The British Committee for Standards in Haematology (BCSH) has produced guidelines on the diagnosis and reporting of NHLs[76,77] from the BCSH website). A guideline on the investigation and management of follicular lymphoma is also available from the BCSH website. Archived guidance from the BCSH exists on the diagnosis and therapy for nodal NHL.[27]

Variation in services and/or uncertainty about best practice

Although R-chemotherapy is the preferred treatment for first-line therapy in symptomatic advanced FL, there is no consensus on the preferred chemotherapy.[69] No direct trials have been undertaken that compare one R-chemotherapy regimen with another R-chemotherapy regimen; although there are four ongoing Phase III RCTs comparing one or more R-chemotherapy regimens against another R-chemotherapy[78–81] (see *Chapter 3*, *Results*, for further details of ongoing trials). Siddhartha and Vijay[82] conducted a meta-analysis to compare R-CHOP and R-CVP with respect to response rates (two separate analyses were provided for first-line

TABLE 4 Relevant NICE guidance for the treatment of advanced FL

Stage of disease	Treatment	Licensed by EMA	Recommendation by NICE	Conditions of NICE recommendation
First-line induction	R-CVP	✓	✓	Previously untreated patients Symptomatic patients
First-line induction	R-chemotherapy[a]	✓	✗ **Considered in this assessment report**	Not applicable
First-line maintenance	R-monotherapy	✓	✗ **Ongoing technology appraisal**	Being appraised: Only for responders to first-line induction therapy with rituximab in combination with chemotherapy
Second-line induction	R-chemotherapy[a] R-monotherapy	✓	✓	R-monotherapy only when all alternative treatment options have been exhausted (i.e. if there is resistance to or intolerance of chemotherapy)
Second-line maintenance	R-monotherapy	✓	✓	Only for responders to second-line induction therapy of rituximab or R-chemotherapy

a Chemotherapy can be any regimen.

treatment only and first-line plus relapsed treatment) and differences were noted in the quality of the responses achieved. A greater proportion of complete responses (CRs) were observed following R-CVP than R-CHOP. However, overall response rate (ORR) was better following the R-CHOP regimen [owing to more partial responses (PRs)]. It is difficult to know if there is a different effect in quality of response to R-CVP or R-CHOP; however, clinical advice to the AG noted that R-CHOP is more likely given to patients with bulky or more aggressive disease, who are more likely to achieve a PR than a CR.

However, treatment/efficacy outcomes are not the only factors to consider when choosing chemotherapy. Clinical advice suggests that elderly patients or patients with comorbidities, particularly cardiac problems, are less likely to receive CHOP, as it is an anthracycline-based chemotherapy. In addition, where SCT is a potential future treatment, the chemotherapeutic agent selected must not interfere with the potential to harvest stem cells. Thus, in SCT candidates, fludarabine, a purine analogue therapy, is to be avoided as these can compromise the quality of the stem cell harvests.

The manufacturer sought clinical guidance from two clinicians whose responses also reflected the need for an individualised choice of chemotherapeutic agent in patients.[62] The clinicians also highlighted other important factors in treatment selection, including patient choice (e.g. acceptability of alopecia, which is higher after CHOP, and side effects tolerance) and the need to achieve a rapid response if a compression syndrome is present (e.g. deep-vein thrombosis, leg oedema).

Current usage in the NHS

Figures reported in the MS[62] from an unpublished survey of UK haemato-oncologists ($n = 50$) suggest that approximately 92% of all eligible previously untreated stage III–IV patients with FL in the UK currently receive rituximab in combination with chemotherapy as standard treatment (these data were made available by the manufacturer to the AG).[62] The remaining 8% receive single-agent chlorambucil, FM, Bexxar (a radiolabelled monoclonal antibody) or alternative chemotherapy. Of the patients receiving a rituximab-containing regimen, approximately 67% are treated with R-CVP and a further 16% are treated with R-CHOP. The remainder receive

rituximab combined with other chemotherapies, which includes R-chlorambucil (R-C), rituximab, fludarabine and cyclophosphamide (R-FC), rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) and R-fludarabine (R-F).[62] The AG requested access to the survey data from Roche and the results are presented in *Table 5*.

Clinical advice sought by the AG suggests that this seems a reasonable estimate, indicating that the great majority of patients receive R-chemotherapy. Chlorambucil as a single-agent chemotherapy regimen is reserved only for patients deemed too unfit or unwell for a R-chemotherapy regimen. The proportions of R-CHOP and R-CVP administered are difficult to quantify according to clinical advice; historically R-CVP has been the first choice chemotherapy arm; however, R-CHOP is the international standard. However, at present R-CHOP is not currently recommended by NICE, which is likely to affect its current uptake within the UK. Clinical advice suggests that the use of other chemotherapy regimens in combination with rituximab such as R-MCP (rituximab, mitoxantrone, chlorambucil and prednisolone), R-CNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine and prednisolone), R-CHVP (rituximab, cyclophosphamide, doxorubicin, etoposide and prednisolone), R-FCM, R-FM, R-F and R-C is very infrequent within the NHS.

Current service cost

Because treatment of FL is part of general haematological or oncology services, the cost of caring for this group of patients is very difficult to derive from the routine financial information available for the NHS. However, consideration of the variety of treatments to which an individual might be exposed during the course of their illness suggests that the costs of caring for FL are likely to be considerable. In this, the support required from both primary and palliative care services in the terminal stages of the disease should not be underestimated.

Significance for the NHS

Rituximab with CVP is currently recommended by NICE for the first-line treatment of FL.[83] Thus, given the number of patients with FL, the introduction of rituximab with other chemotherapies would incur costs. However, neither new equipment nor intensive training would be required.

TABLE 5 Survey results (patients $n = 120$) for the first-line treatment of untreated stage III–IV FL in the UK[62]

Treatment	No.	%
R-CVP	80	67
CVP	1	1
R-CHOP	19	16
Chlorambucil	6	5
R-C	4	3
R-FC	5	4
FM	1	1
R-FM	1	1
R-F	1	1
Bexxar	1	1
Alternative chemotherapy	1	1

Description of technology under assessment

Identification of patients and important subgroups

Rituximab in combination with chemotherapy is considered as a possible option for the treatment of symptomatic stage III–IV FL.

Place in treatment pathway

This assessment report is concerned with the use of R-chemotherapy as first-line induction treatment. However, rituximab with or without chemotherapy is recommended by NICE at other points within the treatment pathway, and these impact on the cost-effectiveness of R-chemotherapy in first-line induction therapy (see *Table 4* for NICE recommendations of rituximab).

Therapeutic classification

Rituximab is a genetically engineered 'monoclonal antibody' that has been designed to recognise an antigen/surface marker on B lymphocytes called CD20. Monoclonal antibodies are produced by fusing single antibody-forming cells (generated in laboratory mice) to tumour cells (grown in culture), producing large quantities of identical antibody molecules from a single, cloned antibody-producing cell, hence the name 'monoclonal antibodies'.[36]

The CD20 antigen/surface marker is present on the surface of B lymphocytes in > 90% of NHLs.[84] When rituximab attaches to the antigen, this causes cell death[85] so that cancerous and normal B lymphocytes are destroyed. Although fully developed B lymphoma cells have CD20 on their surface, early B cells do not have the CD20 protein and are not killed.

Brand and generic name

Rituximab is the generic name; Roche's brand name is MabThera (Genentech Inc.). Rituximab is also known as IDEC-C2B8 and Rituxan®.[86]

Dosage form and route

Rituximab is sold as a concentrate for solution for intravenous infusion. A 10-ml single-use vial is available and contains 100 mg of rituximab (sold in packs × two vials).[85] A 50-ml single-use vial is also available (500 mg/50 ml).

Method of administration

Premedication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy. Premedication consisting of an antipyretic and an antihistaminic, for example paracetamol and diphenhydramine, should always be administered before each infusion of rituximab.[85]

First infusion

The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.[85]

Subsequent infusions

Subsequent doses of rituximab can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.[84] The prepared rituximab solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.[85]

Licensed indications

Rituximab is licensed for the treatment of previously untreated patients with stage III–IV FL in combination with chemotherapy. This current licence was issued in January 2008 and does not restrict the type of chemotherapy. The original licence agreement restricted use of rituximab in combination with CVP only and this is reflected in the existing NICE guidance.[83]

Rituximab is also licensed for treatment of FL at other stages within the treatment pathway, other types of NHL, and has indications for treatment of chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis. The indications for use in FL and NHL are included below for completeness:

- Rituximab maintenance therapy is indicated for patients with FL who are responding to induction therapy with chemotherapy with or without rituximab.
- Rituximab monotherapy is indicated for treatment of patients with stage III–IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- Rituximab is indicated for the treatment of patients with CD20-positive DLBCL in combination with CHOP.

Contraindications

Rituximab is contraindicated for use in NHL in patients who have known hypersensitivity to the active substance or to any of the excipients or to murine proteins, in active severe infections or inpatients in a severely immunocompromised state.[85]

Warnings

Infusion reactions

Infusion-related side effects (including cytokine release syndrome) are reported commonly with rituximab and predominantly occur during the first infusion and include symptoms such as fever and chills, nausea and vomiting, allergic reactions (such as rash, pruritus, angioedema, bronchospasm and dyspnoea), flushing and tumour pain.[86] Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion, which can be increased on improvement of symptoms. Patients who develop severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately.[85]

Before each dose of rituximab, patients should be given an analgesic and an antihistamine to reduce these effects and consideration should be given to premedication with a corticosteroid. In all patients, the infusion should not be restarted until symptoms have resolved and laboratory values and chest radiographs appear normal. Patients who have experienced severe cytokine release syndrome should be closely monitored, as although they may show an improvement in symptoms, this may be followed by deterioration. Thus, such patients must be evaluated for evidence of tumour lysis syndrome and pulmonary infiltrations with chest radiography.

Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab. Patients with a high tumour burden and those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely.[86]

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. However, in contrast to cytokine release syndrome, true hypersensitivity reactions typically occurs within minutes after starting infusion.[85]

Pregnancy and lactation

Rituximab should be avoided during pregnancy unless the potential benefit to the mother outweighs risk of B-lymphocyte depletion in the fetus. It is also contraindicated in women who are breastfeeding. Effective contraception is required during treatment and for 12 months after treatment.[86]

Cardiovascular disease

Rituximab should be used with caution in patients who are receiving cardiotoxic chemotherapy or who have a history of cardiovascular disease because exacerbation of angina, arrhythmia and heart failure have been reported. Transient hypotension occurs frequently during infusion and antihypertensive drugs may need to be withheld for 12 hours before infusion.[86]

Infections

Serious infections, including fatalities, can occur during therapy with rituximab. Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infection.[86]

Personnel involved

Treatment should be undertaken under close supervision of a specialist.[86] The delivery of rituximab requires no additional personnel to the administration of chemotherapy, namely a senior clinician (specialist registrar or above), a specialist nurse and a specialist pharmacist.

Setting

Outpatients would receive intravenous transfusion in the same chemotherapy suite as would be used for the administration of chemotherapy.

Equipment required

Full resuscitation equipment should be at hand.[86] The intervention would require no equipment outside of that normally associated with a chemotherapy suite. Some clinics advise that rituximab is infused while the patient is on a bed, rather than in a chair.

Length of treatment

Each service user would expect to receive one treatment on day one of each cycle, every 3 weeks, for up to eight cycles; in other words, eight intravenous days (4–6 hours each) at the chemotherapy suite, over the course of 24 weeks.

Follow-up required

The ESMO guidelines suggest follow-up treatment both during and after treatment. However, clinical advice to the AG suggests that follow-up differs in UK clinical practice, particularly with regard to the frequency of cross-sectional imaging, which is not undertaken routinely in the absence of clinical suspicion of progression.The BCSH guidelines[87] on the investigation and management of follicular lymphoma specifically states that routine scans are not recommended.

During treatment, the ESMO guidelines state that 'adequate radiological tests should be performed mid-term and after completion of chemotherapy'. Where an insufficient or no response is found, patients should be evaluated for early salvage regimens. The ESMO guidelines[19] suggest the following as follow-up after treatment; however, it is noted that clinical advice does not agree with the frequency of imaging:

- History and physical examination every 3 months for 2 years, every 4–6 months for a further 3 years, and subsequently twice a year with special attention to transformation and secondary malignancies including secondary leukaemia.
- Blood count and routine chemistry every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.
- Minimal adequate radiological or ultrasound examinations every 6 months for 2 years and annually thereafter. (Note that this is not recommended by the clinical advice sought by the AG.)

Anticipated costs associated with intervention

The recommended dose of rituximab is 375 mg/m^2; the net price for a 10-ml vial is £174.63 and for a 50-ml vial £873.15.[86]

Chapter 2

Definition of the decision problem

Decision problem

Intervention

Rituximab is indicated for the treatment of previously untreated patients with stage III–IV FL in combination with chemotherapy at a recommended dose of 375 mg/m^2 of body surface area (BSA) per cycle, for up to eight cycles. This assessment includes interventions where rituximab is given in combination with the following chemotherapy regimens:

- CVP
- CHOP
- CNOP
- CHVP
- MCP
- FCM (fludarabine, cyclophosphamide and mitoxantrone)
- FM
- bendamustine
- fludarabine
- chlorambucil.

When this appraisal started, bendamustine was not currently licensed as a first-line treatment with rituximab for first-line treatment of FL. However, as the anticipated date of licensing was not known and could occur within the time scales of the appraisal, bendamustine was included as a combination chemotherapy agent (with rituximab). At the time of writing, bendamustine remains unlicensed for use in this population for the first-line treatment indication.

Population including subgroups

The population comprised adults with symptomatic stage III–IV FL (a NHL) who have not received any previous treatment. Indolent FL is considered within this appraisal. Where data are presented for elderly patients with FL (aged ≥ 65 years), these will be examined as a subgroup.

Relevant comparators

Non-rituximab-containing chemotherapies are the relevant comparators, and for this assessment the following comparators are considered:

- CVP
- CHOP
- CNOP
- CHVP
- MCP
- FCM
- FM
- bendamustine
- fludarabine
- chlorambucil.

Outcomes

The outcomes considered in this appraisal mostly relate to clinical effectiveness and cost-effectiveness and include:

- OS
- PFS
- response rates
- duration of disease remission/response duration
- adverse effects of treatment
- HRQoL.

Overall aims and objectives of assessment

This assessment will address the question 'What is the clinical effectiveness and cost-effectiveness of rituximab (in its licensed indication) with chemotherapy for the first-line treatment of symptomatic stage III–IV FL?'

The aim of this review is to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of rituximab (in its licensed indication) in combination with chemotherapy compared with non-rituximab-containing chemotherapy, for the first-line treatment of symptomatic stage III–IV FL. Note that owing to the scope specifying the intervention as *rituximab given in combination with chemotherapy*, interventions including rituximab in combination with other treatments, such as radioimmunotherapy or bone marrow/SCT, are not considered as an intervention for this appraisal.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

This systematic review was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[88]

Identification of studies

The PRISMA flow diagram shown in *Figure 2* provides a summary of the study identification process.

Search strategy

The search aimed to systematically identify all literature relating to the clinical effectiveness of (1) the intervention: rituximab in combination with chemotherapy or (2) the comparators, i.e. chemotherapy alone for the treatment of FL. The searches were conducted in September and October 2010.

Sources searched

Eleven electronic databases were searched from inception: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); CINAHL; EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; Science Citation Index (SCI); and BIOSIS.

Ongoing research was searched using clinical trials databases and registers including NIHR Clinical Research Network Portfolio; National Research Register (NRR) archive 2000–7; Current Controlled Trials (CCT) and ClinicalTrials.gov.

Relevant conference proceedings were searched, including the American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESCO), American Society of Hematology (ASH), the British Society for Haematology (BSH) and the European Hematology Association (EHA).

In addition, the reference list of relevant articles and the MS[62] was handsearched. The review team also contacted experts in the field and scrutinised the bibliographies of retrieved papers to identify relevant evidence.

Search terms

A combination of free text and thesaurus terms were used. 'Intervention' terms (e.g. rituximab, MabThera, Rituxan) or chemotherapy terms (CHOP, CVP, etc.) were combined with 'population' search terms (e.g. lymphoma, non-Hodgkin's). Copies of the search strategies used in MEDLINE are included in *Appendix 5* (these were adapted for use in other databases).

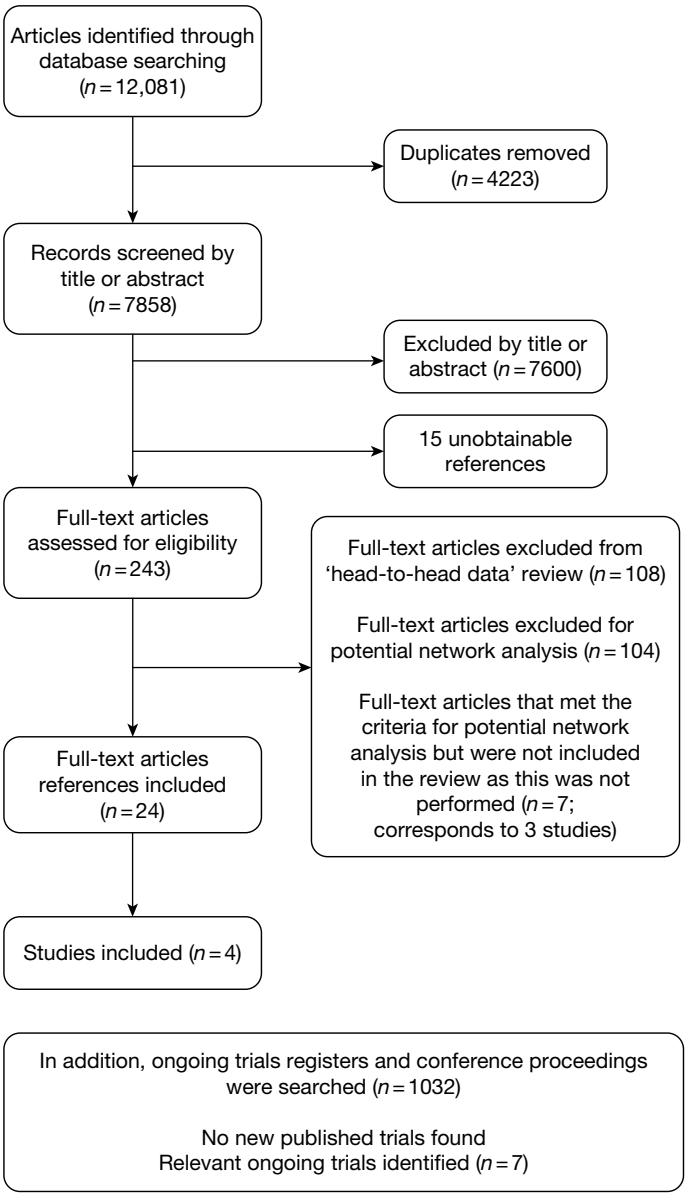


FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses-adapted flow diagram.

Search restrictions

Searches were not restricted by language or publication date. Where possible, a filter was applied in order to limit search results to systematic reviews/meta-analyses, economic/cost evaluations, quality-of-life studies or RCTs. Examples of the RCT filter, cost-effectiveness filter and quality-of-life filter are provided in *Appendix 5*.

Inclusion and exclusion criteria

Study design

According to the accepted hierarchy of evidence, RCTs were included for the clinical effectiveness review, as they provide the most authoritative form of evidence. In the event of insufficient data being available from RCTs, it was planned that observational studies or clinical trials would be considered; however, this was not required in this review.

Intervention(s)

Rituximab in combination with any of the following chemotherapy regimens: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM, bendamustine, fludarabine or chlorambucil.

Comparator(s)

The comparator was chemotherapy without rituximab, which for this review was considered to be one of the following: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM, bendamustine, fludarabine or chlorambucil.

Potential for a network meta-analysis

The literature search was undertaken to allow identification of trials involving either an intervention or comparator defined in the decision problem, as it was anticipated that the work may require a network meta-analysis to be undertaken to determine efficacy. It was planned to populate such an analysis with all identified trials involving either an intervention or a comparator. Although it is noted that the network meta-analysis could potentially be strengthened by the inclusion of RCTs involving two pharmaceuticals that were neither interventions nor comparators (provided there were RCTs comparing these pharmaceuticals with an intervention or a comparator), literature searches for all RCTs from these pharmaceuticals were not conducted, as they are likely to have little impact on the results of interest and would have significant resource implications. In addition, where the evidence allowed, interventions were planned to be compared with each other.

Population

The population comprised adults with symptomatic stage III–IV FL who had not received any previous treatment.

Outcomes

The primary outcome of interest for this appraisal in relation to clinical effectiveness was OS. Secondary outcomes were PFS, response rates (CR, PR and ORR), duration of disease remission/response duration, and adverse/toxic effects of treatment.

Overall survival was defined and calculated as the time from randomisation to the date of death by any cause. PFS was defined and calculated as the time from randomisation to disease progression or death. Response rate was defined in the terms laid down by Cheson *et al.*[87] (see *Appendix 6*). ORR combined CRs and PRs. Unconfirmed complete responses (CRus) were considered as PRs so that the CR and PR rates were comparable between studies. However, it is noted this may result in an underestimation of CR, as clinical advice suggests that CRus are more likely to follow a similar clinical course to CRs. Duration of disease remission/response duration was taken as the time from response achieved (CR or PR) to disease progression or death. Adverse events (AEs) were defined as any adverse change from the patient's baseline condition, including intercurrent illness that occurred during the course of the clinical trial after the start of treatment, whether or not considered related to trial treatment. HRQoL was also considered as a secondary outcome.

Exclusion criteria

Reviews of primary studies were not included in the analysis, but were retained for discussion and identification of additional trials. Studies that were considered methodologically unsound were excluded from the review as well as the following publication types: non-randomised studies; animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English-language papers and reports in which insufficient methodological details are reported to allow critical appraisal of study quality. In addition, although not stated in the protocol, studies that included populations other than those described above or studies that

included NHL populations but did not provide outcome data separately for patients with FL who were excluded.

Study selection

Studies were selected for inclusion through a two-stage process according to the above inclusion/exclusion criteria. Titles and abstracts were examined for inclusion by one reviewer. Screening was checked by a second reviewer on 10% of citations. The kappa coefficient (range 0–1) calculated to measure inter-rater reliability was good, approaching 'very good' at 0.79. Discrepancies were resolved by discussion between the two reviewers when necessary, and did not require involvement of a third reviewer. Full manuscripts of selected citations were retrieved and assessed by one reviewer against the inclusion/exclusion criteria.

Data extraction strategy

Data were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies were resolved by discussion and did not require input from a third reviewer. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy

The methodological quality of each included study was assessed by one reviewer and checked by a second reviewer, according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (CRD) for RCTs.[90]

The following factors were considered: method of randomisation, allocation concealment, blinding of patients, outcome assessors and data analysts, numbers of participants randomised, baseline comparability between groups, specification of eligibility criteria, whether or not intention-to-treat (ITT) analysis was performed, completeness of follow-up and whether or not study power calculations were performed and reported.

Methods of data synthesis

Data were tabulated and discussed in a narrative review. Exploratory meta-analyses were performed to estimate a summary measure of the effect of response rates (ORR, CR and PR) based on ITT analyses. CRus were considered as PRs in the meta-analyses so that the CR and PR rates were comparable between studies. However, it is noted this may result in an underestimation of CR, as clinical advice suggests that CRus are more likely to follow a similar clinical course to CRs. Heterogeneity in these analyses was explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the chi-squared test for homogeneity and the I^2-statistic. Meta-analysis was carried out using random-effects models, using the Cochrane Collaboration Review Manager© (RevMan) software, version 5.0 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Meta-analysis was not performed for the outcome of PFS as only one study was identified measuring this outcome. Meta-analysis was not performed for the outcome of OS because of problems with the data in three of the trials. The population in two studies were given subsequent treatment as part of the study intervention. The German Low Grade Lymphoma Study-2000 (GLSG-2000) trial[91,92] randomised responders who were aged < 60 years old to receive either interferon maintenance or dose-escalation chemotherapy and SCT; responders aged > 60 years old were given interferon maintenance therapy. Responders in the trial[93] East German Society of Haematology and Oncology (OSHO-39; R-MCP vs MCP) were all given interferon maintenance therapy. Thus, the subsequent maintenance therapy confounds the OS data. The population in the (follicular lymphoma-2000 FL2000) trial[94] included 10% patients with stage II FL and included the biological therapy interferon as part of the 6-month induction treatment phase and as a consolidation treatment for a further 12 months.

Other time-to-event data were presented in the included studies such as event-free survival (EFS), DFS, time to progression (TTP). No meta-analyses were performed on these additional time-to-event outcomes owing to inconsistencies in the way the outcomes were defined. These issues are discussed in more detail below (see *Results*, below). A network meta-analysis was not carried out. The reasons for this are discussed below (see *Quantity and quality of research available*).

Results

Quantity and quality of research available

Number of studies identified

The search retrieved 7858 unique citations relating to clinical effectiveness (4223 duplicates were removed). Of these, 7600 articles were excluded at title/abstract stage, 243 articles were examined at full-text level, and 15 articles were unobtainable from the interlibrary loans service (see *Appendix 7*). In addition, 1032 articles were examined from ongoing trials registers and conference proceedings.

Number and type of studies included

Four RCTs were included: M39021 trial by Marcus *et al.*,[95,96] GLSG-2000 by Hiddemann *et al.*,[91,92] OSHO-39 trial by Herold *et al.*[93] and the FL2000 trial by Salles *et al.*[94] Overall, 24 published reports were identified which related to the four included studies, and these are listed in *Appendix 8*. The principal source/sources for each study are listed in *Table 6*.

Number and type of studies excluded

In total, 212 citations were excluded from the full text selection (see *Appendix 9*). Studies that could potentially have provided head-to-head data for the interventions and comparators accounted for 108 excluded articles; 44 were excluded because they were not RCTs, i.e. case reports, literature reviews, commentaries and single-arm interventions; 29 studies were excluded because the interventions used were not relevant; 13 studies were excluded because the patient group was clinically heterogeneous and data for patients with FL were not reported separately; nine studies were excluded because patients did not have FL (e.g. Hodgkin's disease or NHL unspecified) or had aggressive disease; six studies did not provide first-line treatment; five non-English-language studies were excluded; two were study protocols; and one did not provide relevant outcome data.

One hundred and four citations that were potential candidates to inform a network meta-analysis were excluded. Fifty-four were excluded because the participants did not have FL (e.g. NHL not specified) or the disease was not indolent; 21 were excluded because the population was heterogeneous and data relating to FL were not reported separately; 15 were excluded because the interventions were not relevant; eight were excluded because they were not RCTs; four were excluded because they were non-English-language reports; one was excluded as outcome data were not relevant; and one study was not included as it did not report on first-line treatment.

TABLE 6 Primary reports for each trial

Trial	Primary report(s)
M39021	Marcus *et al.* 2008,[95] 2005[96]
GLSG-2000	Hiddemann *et al.* 2005,[92] Buske *et al.* 2008[91]
OSHO-39	Herold *et al.* 2007[93]
FL2000	Salles *et al.* 2008[94]

Studies identified for a potential network meta-analysis

Three additional studies (corresponding to seven references – see *Appendix 10* for list) met the criteria for providing evidence within a network meta-analysis, i.e. the population included FL (with analysis for FL presented separately), the therapy being investigated was either a relevant intervention or comparator (as stated in the decision problem – see *Chapter 2*) and appropriate outcomes were reported (as stated in the decision problem – see *Chapter 2*) (*Figure 3*).

Incorporating these three studies into a network of evidence would facilitate the comparison of interventions when a direct head-to-head trial was not available (as depicted in *Figure 3*). However, the network meta-analysis was not undertaken, as it was not deemed appropriate given that treatment efficacy is not the only factor in terms of choice of chemotherapy selection (see *Chapter 1* for discussion of other factors). Additionally, head-to-head data were available to inform a comparison between a chemotherapy regimen and that regimen with the addition of rituximab. It is noted that NICE has a strong preference for evidence from head-to-head RCTs that directly compare the technology with the appropriate comparator in the relevant patient groups as stated in the NICE methods guide (p. 15).[97]

Ongoing trials

Seven ongoing studies were identified (*Table 7*).[70,77–80,98,99] Four studies are investigating one R-chemotherapy against another R-chemotherapy; one study is closed [a randomised phase III study of the STiL (Study Group Indolent Lymphomas)] with study follow-up complete and initial results reported as a conference abstract;[78] one study is ongoing but not recruiting (ML17638)[98] and two studies are ongoing and still recruiting [Purine-Alkylator Combination In Follicular lymphoma Immuno-Chemotherapy for Older patients (PACIFICO[80]) and Polish Lymphoma Research Group 4[79] (PLRG4)]. The study population in the PACIFICO trial[81] is patients with FL aged >60 years or aged <60 years but with an anthracycline-based therapy contraindicated. Two ongoing studies are investigating the use of rituximab in maintenance following first-line induction therapy; one study is closed with follow-up completed [Primary Rituximab and Maintenance (PRIMA) study[71]], whereas the other study (ML17638)[98] is ongoing but not recruiting. One study[99] is investigating one chemotherapy compared with another chemotherapy regimen [British Lymphoma Investigation Group (BNLI) MCD vs FMD].

Summary of trials

Four multicentre, open-label trials were included, which randomised between 322 and 630 participants. The GLSG-2000[91,92] and OSHO-39 trials[93] were undertaken in Germany; the M39021 trial[95,96] was undertaken in centres across 11 countries including the UK, and FL2000 trial[94] was undertaken in centres within France and Belgium. Three trials compared a R-chemotherapy regimen with a chemotherapy-alone regimen; the FL2000 trial compared a

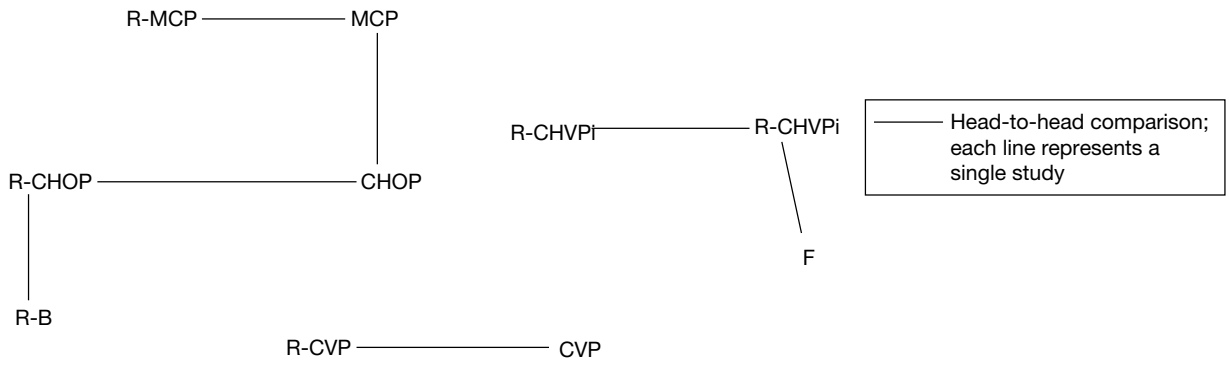


FIGURE 3 Network of evidence. F, fludarabine; R-B, rituximab and bendamustine; R-CHVP, rituximab, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha.

TABLE 7 Ongoing trials in FL that meet the inclusion/exclusion criteria

	Study						
Study characteristics	**PRIMA study[71]**	**STiL trial (Rummel *et al.*[78])**	**BNLI MCD vs FMD[99]**	**R-CVP vs R-CHOP vs R-FM[79]**	**ML17638[99]**	**PACIFICO[81]**	**PLRG4[80]**
Study identifier	UKCRN ID 2249	ClinicalTrials.gov ID NCT00991211	UKCRN ID 908	ClinicalTrials.gov ID NCT00774826	ClinicalTrials.gov ID NCT01144364	UKCRN ID 6898	ClinicalTrials.gov ID NCT00801281
Participants	FL	FL and MCL	FL	FL (including stage II)	FL	FL	FL
	$n=1200$	$n=549$	$n=400$	$n=431$	Target sample size 100–500	$n=680$	$n=250$
	Age: >18 years	Age: ≥18 years	Age: 18–70 years	Age: 18–75 years	Age: 60–75 years	Age: ≥60 years, or <60 years but anthracycline-based therapy contraindicated	Age: ≥18 years
Treatment	After induction of response with rituximab and chemotherapy: 1. Maintenance therapy with rituximab 2. No maintenance therapy	1. Rituximab + bendamustine 2. R-CHOP	1. MCD 2. FMD	1. R-CVP 2. R-CHOP 3. R-FM	After brief induction with chemotherapy (FMD) plus rituximab: 1. Rituximab maintenance 2. No further therapy	1. R-CVP 2. R-FC	1. R-CVP 2. R-CHOP
Status	Closed: follow-up complete	Closed: follow-up complete	Closed: follow-up complete	Ongoing treatment phase: not recruiting	Ongoing treatment phase: not recruiting	Ongoing treatment phase: recruiting	Ongoing treatment phase: recruiting

FMD, fludarabine, mitoxantrone, dexamethasone; MCD, mitoxantrone, chlorambucil and dexamethasone; MCL, mantle cell lymphoma; UKCRN, UK Clinical Research Network.

R-chemotherapy biological regimen with a chemotherapy biological regimen alone. The median follow-up ranged from 47 to 60 months (*Table 8*).

Population

Baseline demographic data are provided in *Table 9*. The target population were advanced-stage patients with FL who were symptomatic and requiring treatment (detailed eligibility criteria for each study are presented in the data extraction tables in *Appendix 11*). The M39021[95,96] and GLSG-2000 trials[91,92] recruited patients with stage III–IV FL, whereas the FL2000 trial[94] recruited patients with stage II-IV FL. The OSHO-39 trial[93] included CD20-positive patients with indolent NHL, which included lymphoplasmacytic lymphoma or mantle cell lymphoma (MCL); however, the primary analysis population was defined as the population of patients with FL. The OSHO-39[93] and GLSG-2000[92] trials limited to grade 1 or 2 FL (WHO classification); the M39021 trial[95,96] included grade 1–3 FL; and the FL2000 trial[94] included grades 1, 2 and 3a FL.

The median age of patients randomised across the trials ranged from 52 to 61 years. Two trials presented the percentage of participants aged over 60 years: 26% in the M39021 trial[95,96] and 52% in FL2000 trial.[94] The majority of patients had stage IV FL (69–77% in the three studies that reported these data). Most participants had an ECOG performance status of 0–1, ranging

TABLE 8 Summary of included studies

Trial	Study type, country	Numbers randomised	Intervention	Comparator	Follow-up
M39021[95,96]	Multicentre, open-label RCT 47 centres in Australia, Belgium, Brazil, Canada, France, Israel, Poland, Portugal, Spain, Switzerland and the UK	*n* = 322[a] Stage III–IV FL	R-CVP (*n* = 162)	CVP (*n* = 159)	Median 53 months (no range reported)
GLSG-2000[91,92]	Multicentre, open-label RCT 200 institutions in Germany	*n* = 630[b] Stage III–IV FL	R-CHOP (*n* = 279)	CHOP (*n* = 278)	Median 56 months (no range reported)
OSHO-39[93]	Multicentre, open-label RCT 34 centres in Germany	*n* = 376 (including MCL) *n* = 201/376 were FL Stage III–IV FL	R-MCP (*n* = 105)	MCP (*n* = 96)	Median 47 months (49 months for R-MCP and 42 months for MCP) (no range reported)
FL2000[94]	Multicentre, open-label RCT 54 centres in France and Belgium	*n* = 360[c] Stage II–IV	R-CHVPi (*n* = 175)	CHVPi (*n* = 183)	Median 60 months (range 0.2–6.4 years)

CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha; MCL, mantle cell lymphoma.
a One CVP enrolled patient withdrew consent.
b *n* = 630 enrolled. In June 2003, applied one-sided sequential test showed a significantly longer time to treatment failure for the R-CHOP arm ($p = 0.001$) and randomisation was stopped. Buske *et al.*[91] report on 557/630 evaluable patients at a median follow-up of 56 months.
c One patient withdrew consent after registration and one patient had a major inclusion violation (which was registered at relapse).

from 91% to 97%. Bone marrow involvement was present in 62–74% of patients, and 22–44% presented with one or more B symptoms (defined as fever, weight loss or night sweating). Elevated LDH levels (a marker of aggressive disease) were recorded in 26–37% of patients.

Within the individual studies, the treatment groups were well balanced with respect to demographic and disease characteristics, with the exception of gender in OSHO-39 trial[92] (more males in the R-MCP group; no *p*-value reported) and the GLSG-2000 trial (higher proportion of males in the CHOP arm; $p = 0.027$). The populations were reasonably similar when compared across the four studies, although there were some differences, including younger median age (52–53 years) in the M39021 trial,[95,96] and larger proportion of patients aged > 60 years and inclusion of stage II participants in the FL2000 trial.[93] The study populations included were generally reflective of the general FL population, with the exception of age – the median age of participants in the trials being younger than seen in clinical practice (70% are aged > 60 years when diagnosed).[10] The younger median age of trial participants meant that ECOG performance status was better than that seen in clinical practice. In addition, the M39021[95,96] and OSHO-39[93] trials excluded patients with an ECOG performance status of > 2.

Interventions and comparators

The interventions in each of the four studies were a R-chemotherapy combination; each trial used a different chemotherapy agent. The comparator within each trial was the chemotherapy regimen minus rituximab. These are described in *Table 10*. Two studies provided subsequent treatment following response to first-line treatment. The OSHO-39 trial[93] planned to provide all responders with interferon-alpha maintenance [3 × million international units (MIU)/week] until disease progression. The GLSG-2000 trial[92,93] randomised responding patients who were aged < 60 years to a high-dose chemotherapy regimen followed by autologous stem cell transplant (ASCT) or interferon-alpha maintenance treatment (3 × 5 MIU/week until disease progression of intolerable AEs). Patients aged ≥ 60 years received interferon-alpha maintenance.

TABLE 9 Baseline demographic data for the four included studies[a]

	M39021[95,96]		GLSG-2000[91,92]		OSHO-39[93]		FL2000[94]	
Demographics	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)
Age and gender								
Median age in years (range)	52	53	57 (27–90)	57 (21–81)	60 (33–78)	57 (31–75)	61 (25–75)	
Aged > 60 years: no. (%)	41 (25)	44 (28)	NR	NR	NR	NR	89 (51)	96 (52)
Male: no. (%)	88 (54)	85 (53)	120 (43)	146 (53)	53 (50)	36 (37)	96 (55)	82 (45)
Female: no. (%)	74 (46)	74 (47)	159 (57)	132 (47)	52 (50)	60 (63)	79 (45)	101 (55)
Ann Arbor stage, no. (%)								
II	2 (1)	2 (1)	0	0	0	0	23 (13)	18 (10)
III	45 (28)	45 (28)	NR	NR	30 (29)	22 (23)	152 (87)	165 (90)
IV	114 (70)	112 (70)	194 (70)	191 (69)	75 (71)	74 (77)		
Not evaluable/missing	1 (1)	0 (0)	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)
Performance status (ECOG), no. (%)								
0	93 (57)	90 (57)	97 (35)	88 (32)	68 (65)	54 (56)	164 (94)	167 (91)
1	65 (40)	60 (38)	155 (56)	167 (60)	29 (28)	36 (38)		
> 1	4 (2)	8 (5)	18 (6)	19 (7)	7 (7)	6 (6)	11 (6)	16 (9)
Not evaluable/missing	0 (0)	1 (0.6)	9 (3)	4 (1)	1 (1)	0 (0)	0 (0)	0 (0)
IPI, no. (%)								
0	1 (1)	1 (1)	NR		NR		NR	NR
1	72 (44)	69 (43)	NR		NR		NR	NR
2	57 (35)	57 (36)	NR		NR		NR	NR
3	19 (12)	21 (13)	NR		NR		60 (34)	71 (39)
4	2 (1)	3 (2)	NR		NR			
Not evaluable/missing	11 (7)	8 (5)	NR		NR		NR	NR
FLIPI, no. (%)								
Low (0–1)	80 (49)	75 (47)	39 (14)	31 (11)	8 (8)	6 (6)	28 (16)	37 (20)
Intermediate (2)			114 (41)	119 (43)	38 (36)	37 (39)	63 (36)	59 (32)
High (3–5)	71 (44)	75 (47)	123 (44)	123 (44)	59 (56)	53 (55)	79 (45)	83 (45)
Not evaluable/missing	11 (7)	9 (6)	3 (1)	5 (2)	0 (0)	0 (0)	5 (3)	4 (2)
Other factors, no. (%)								
B symptoms presence	65 (40)	51 (32)	108 (39)	113 (41)	≥ 46 (44)	≥ 34 (35)	38 (22)	52 (28)
Bone marrow involvement	103 (64)	102 (64)	180 (65)	179 (64)	73 (70)	71 (74)	108 (62)	121 (66)
More than extranodal site	28 (17)	27 (17)	NR	NR	NR	NR	60 (34)	73 (40)
Elevated LDH[b]	39 (26)	39 (26)	73 (26)	66 (24)	31 (30)	30 (31)	64 (37)	66 (36)
β_2-Microglobulin > 3 mg/l[c]	146 (99)	141 (100)	NR	NR	NR	NR	62 (35)	56 (31)
Haemoglobin < 12 g/dl	NR	NR	54 (19)	56 (20)	NR	NR	37 (21)	30 (16)

CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha; NR, not reported.

a Percentages may not add up to 100% owing to rounding.

b Percentages not based on the 162 and 159 patients, R-CVP and CVP groups, respectively, owing to missing patient values (seven patients in the CVP group and 10 patients in the R-CVP group).

c Percentages not based on the 162 and 159 patients, R-CVP and CVP groups, respectively, owing to missing patient values (18 patients in the CVP group and 15 patients in the R-CVP group).

Outcomes

The clinical efficacy outcomes reported in the four studies[91–96] are shown in *Table 11*; primary outcomes are highlighted in grey. All four studies[91–96] included the appropriate outcome measure of OS; defined as the time from randomisation to the date of death by any cause. The OSHO-39 trial[93] was the only trial to report PFS, defined as randomisation to disease progression or

TABLE 10 Treatment regimens

Author/ study	Treatment regimens	Cycles	Response assessment	Amendment to dose or cycles
M39021[95,96]	**CVP:** 750 mg/m^2 cyclophosphamide i.v. on day 1; 1.4 mg/m^2 of vincristine, up to a maximal dose of 2 mg i.v. on day 1; and 40 mg/m^2 of prednisone per day p.o. on days 1–5 **Rituximab:** 375 mg/m^2 infusion on day 1	Every 21 days for a maximum of eight cycles	Assessed after cycle 4 and at the end of treatment	Insufficient therapeutic response, i.e. disease progression or stable disease after cycle 4 were withdrawn from study treatment. Those achieving at least a PR continued to eight cycles
GLSG-2000[91,92]	**CHOP:** 750 mg/m^2 cyclophosphamide; 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine: all given i.v. on day 1. Prednisolone given 100 mg/m^2 daily on days 1–5 p.o. **Rituximab:** 375 mg/m^2 infusion on the day before the respective CHOP course	Every 21 days for a total of six to eight cycles	Assessed every two cycles and 4 weeks after completion of last course	Patients, in either study arm, with disease progression at any time during the study were taken off the study Patients achieving CR after four cycles were treated with a total of six cycles; all other patients received eight cycles
OSHO-39[93]	**MCP:** 8 mg/m^2 mitoxantrone i.v. on days 1 and 2; 3 × 3 mg/m^2 chlorambucil and 25 mg/m^2 prednisolone p.o. on days 1–5 **Rituximab:** 375 mg/m^2 i.v. infusion on day 1 (8 mg/m^2 mitoxantrone i.v. on days 3 and 4; 3 × 3 mg/m^2 chlorambucil and 25mg/m^2 prednisolone p.o. on days 3–7)	Every 28 days for a maximum of eight cycles	After completion of induction treatment, patients were observed every 8 weeks during the first year, at 3-month intervals during the second year, and then every 6 months from the third year onwards	Patients with disease progression after two cycles of therapy or who had not reached a PR or CR after six cycles of therapy were prematurely withdrawn from study CR or a PR after six cycles of treatment received a further two cycles of treatment
FL2000[94]	**CHVPi:** 600 mg/m^2 cyclophosphamide i.v. on day 1 and 25 mg/m^2 i.v. doxorubicin on day 1 and 100 mg/m^2 etoposide, all administered i.v. on day 1; 40 mg/m^2 prednisolone p.o. from days 1–5 Interferon-alpha s.c. 3 × 4.5* MIU/week (*3 MIU for patients > 70 years) **Rituximab:** 375 mg/m^2 infusion on days 1 and 8 of cycles 3 and 4, and day 1 of cycles 5 and 6 (thus, CHVP only in cycles 1 and 2)	**CHVPi:** Six monthly cycles followed by six bimonthly cycles) and 18 months of interferon-alpha **R-CHVPi:** Six monthly cycles CHVP or R-CHVP (see column to left) and 18 months concurrent interferon-alpha	Evaluation of response performed after six chemotherapy courses (6 months) and at the end of the whole treatment (18 months)	No dose reduction of chemotherapy was planned or allowed (but could be delayed for 7 days if the absolute neutrophil count was < 1.5 g/l or the platelet count was < 100 g/l)

CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha; i.v., intravenously; p.o., orally; s.c., subcutaneously.

TABLE 11 Clinical efficacy outcomes reported in four studies[90–95]

Study	PFS	OS	ORR	CR	PR	RD	EFS	TTF	TTNT	DFS	TTP
M39021[95,96]		✓	✓	✓	✓	✓		✓	✓	✓	✓
GLSG-2000[91,92]		✓	✓	✓	✓	✓		✓	✓		
OSHO-39[93]	✓	✓	✓	✓	✓	✓	✓		✓		
FL2000[94]		✓	✓	✓	✓	✓	✓				

RD, response duration; TTF, time to treatment failure;TTNT, time to next antilymphoma treatment.
Cells in grey represent the primary outcome of the trial.

death from NHL. All four studies[91–96] appropriately reported response rates (according to the International Workshop criteria described by Cheson *et al.*[89]). Two studies[91–93] did not use the category of 'unconfirmed complete responder' (CRu), instead counting such patients within the PR category. The FL2000 trial[94] and M39021 trial[95,96] used the category of CRus and presented the numbers separately from CRs and PRs. No studies reported the duration of disease remission, although the studies did report a number of time-to-event outcomes which approximated disease remission, for example all four studies reported response duration as an outcome.

Other time-to-event outcomes reported by one or more of the studies were EFS, time to treatment failure (TTF), time to next antilymphoma treatment (TTNT), DFS and TTP. However, these outcomes were inconsistently defined by the four studies[91–96] and thus not directly comparable across the four studies. For example, the M39021[95,96] and GLSG-2000 trials[91,92] measured TTF and both studies considered a treatment failure as disease progression. However, the M39021 trial[95,96] additionally considered death by any cause, relapse after response, new antilymphoma treatment or stable disease after cycle 4 as treatment failures, whereas the GLSG-2000 trial[91,92] also considered resistance to initial therapy and death not specified as treatment failures. In addition, when the definitions for each time-to-event outcome were cross-referenced against each other, no outcomes were directly comparable (e.g. we examined whether or not PFS as measured in the OSHO-39 trial[93] may have matched the definition used for EFS as measured by FL2000 trial;[94] however, this was not the case). *Appendix 12* provides the definitions for each outcome described in the four studies.[91–96]

All four studies reported data on AEs. The M39021, OSHO-39 and FL2000 trials[93–96] graded AEs in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system,[100] and the GLSG-2000 trial[91,92] used the WHO toxicity criteria[101] to record AEs. The GLSG-2000 and OSHO-39 trials[93] reported data for grade 1, 2, 3 and 4 AEs separately,[92,93] and the M39021 and FL2000 trials[94–96] reported AEs for grades 3 and 4 combined. None of the studies reported HRQoL as an outcome.

Quality assessment

All four included studies[91–96] were randomised and allocation was concealed using centralised allocation to treatment. Numbers randomised were stated in all four studies. None of the studies were blinded; all were open label and none of the studies reported attempting to conceal treatment allocation from the outcome assessors. Power calculations were undertaken by all four included studies.[91–96] At least 80% of patients were followed up in all four studies. All four studies reported baseline characteristics and were mostly balanced between treatment groups; with the exception of gender in OSHO-39 trial[93] (greater number of males in the R-MCP group; no p-value reported) and the GLSG-2000 trial (higher proportion of males in the CHOP arm; $p = 0.027$). The M39021[95,96] and FL-2000 trials[94] reported no significant differences in baseline data. All studies specified eligibility criteria.

Co-interventions were used in three studies.[91–94] Interferon maintenance therapy was given to patients in the OSHO-39 trial[93] achieving a partial or complete remission; this was initiated within 4–8 weeks after treatment completion. In the GLSG-2000 trial,[91,92] patients < 60 years who had achieved either CR or PR were offered a second randomisation of Dexa-BEAM regime (salvage chemotherapy) followed by stem cell harvest and radiochemotherapy, or long-term interferon maintenance, whereas patients aged > 60 years were given interferon maintenance. Patients in both arms in the FL2000 trial[94] were given interferon-alpha as part of initial treatment (6 months) and then as a consolidation treatment for a further 12 months. In addition, 11% of patients in the FL2000 trial[94] had stage II FL. Reasons for withdrawals were unclear in the four studies.[91–96] Most withdrawals were stated as being a result of disease progression; however,

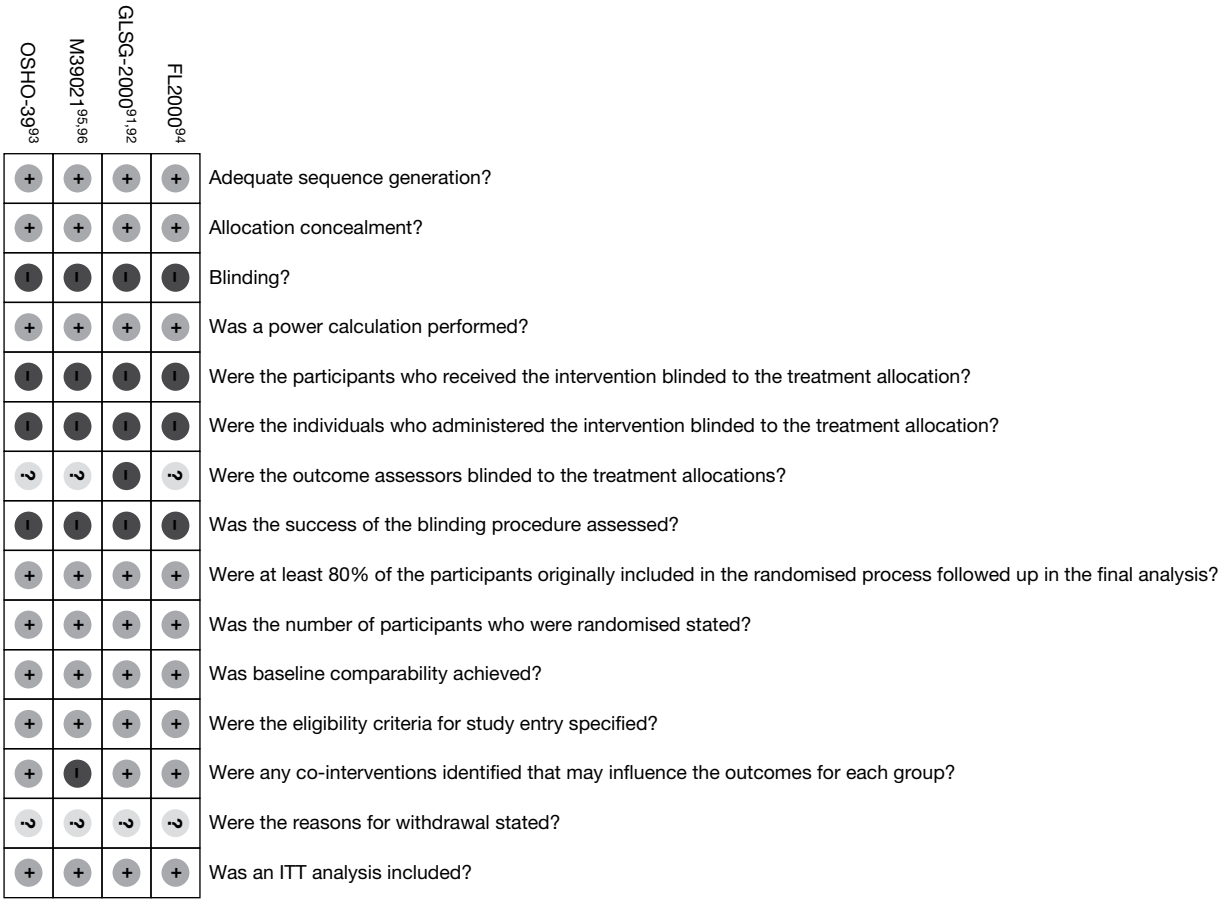


FIGURE 4 Quality assessment of the included trials (+, yes; – , no; ?, unclear).

withdrawals relating to AEs were not explicitly stated. All four studies[91–96] reported using ITT analyses. See *Figure 4* for overview of the quality assessment.

Assessment of effectiveness

Response to treatment

Response to treatment is reported in *Table 12*. ORR was significantly improved for patients receiving R-chemotherapy than those who received chemotherapy alone in three studies[91–93,95,96] (the FL2000 trial[94] did not report a *p*-value). The ORR in the four studies ranged from 81% to 97% for the R-chemotherapy arm and from 57% to 91% for the chemotherapy-only arm. The difference in ORR between the treatment and comparator arms in each of the four studies ranged between 5% and 24%; the greatest difference was between the R-CVP and CVP arm. R-CHOP, R-CHVPi and R-MCP were the regimens that provided the highest ORR of 96%, 94% and 92%, respectively. CHOP alone provided a high ORR of 91%.

Difference in the CR rates between treatment and comparator arms in the four studies[91–96] ranged from 2% to 25%, and was reported as significant in two studies.[93,95,96] The regimens providing the highest CR rates were R-CHVPi and R-MCP (51% and 50%, respectively). The number of CRs in the GLSG-2000 trial[91,92] for both R-CHOP and CHOP (19% and 17%, respectively) were notably lower than those reported in the other studies. The greatest difference in CR between treatment and comparator arms was reported in the OSHO-39 trial[93] between R-MCP and MCP (25%).

The difference in PR rate ranged from 2% to 11%. None of the four studies reported a *p*-value for the difference between treatment and comparator arms.

The GLSG-2000[91,92] and FL2000 trials[94] reported low numbers of patients within the stable disease category. However, the M39021 trial[95,96] reported greater numbers of patients with stable disease (7% in R-CVP and 21% in CVP). Meta-analysis of response rates in the four trials has been explored (see *Meta-analysis*, for further discussion).

Chi-squared test for response rates

The AG performed a chi-squared test on the response rate data to compare the numbers within each category of response between the two trial arms for each of the four trials. The results showed that there was a statistically significant difference in the numbers in the response categories for the R-chemotherapy arm compared with the chemotherapy-alone arm for R-CVP compared with CVP, R-MCP compared with MCP and R-CHVPi compared with CHVPi 6-month response rate ($p < 0.001$ for all comparisons). The difference between the categories of response was not statistically significant for R-CHOP compared with CHOP ($p = 0.15$) and for the R-CHVPi compared with CHVPi 18-month response rate ($p = 0.12$).

A second analysis was performed for each trial, which combined relevant categories of response (e.g. progressive disease or death) where necessary so that the number of observations within each category was greater than five per cell. Where grouping was performed, death was categorised with progressive disease. In one analysis, stable disease was categorised with disease progression and death, as clinical advice to the AG indicates that patients with stable disease are treated as patients with disease progression and not responders. In terms of statistical significance at the 5% level, the effects of grouping altered only on comparison of R-CHVPi and CHVPi at 18 months, which became statistically significant. Analyses are presented in full in *Appendix 13*.

Overall survival

The OS rate in the four studies[91–96] ranged from 83% to 90% in the R-chemotherapy arms and from 77% to 84% in the chemotherapy-alone arms (*Table 13*). The difference in OS rate was significantly improved in three trials when R-chemotherapy was compared with chemotherapy alone; the exception being the FL2000 trial[94] ($p = 0.1552$). The median OS was reported as not reached in three studies and was not reported in the FL2000 trial.[94] The OS data from the GLSG-2000[91,92] and OSHO-39[93] trials were confounded owing to the effects of subsequent therapy provided to all responders to first-line treatment. The FL2000 trial[94] also provided additional treatment (interferon-alpha) to both treatment arms during the 6-month remission induction phase. In addition, the FL2000 trial[94] provided a further 12-month treatment phase in which the chemotherapy-alone arm received bimonthly CHVP and both treatment arms received interferon-alpha.

Overall survival: hazard ratios

The hazard ratios (HRs) for OS were not available in the manuscripts for each of the individual trials. The AG used Kaplan–Meier plot data provided in the health economic model in the MS,[61] which provided a series of survival probability estimates at monthly time points for two of the four trials: M39021 and OSHO-39.[93,95,96] Visual inspection of these probability estimates alongside the Kaplan–Meier data provided in the publications for each trial indicated that these data were reasonable. Kaplan–Meier data for OS for the FL2000 trial[94] and the most-up-to-date data for the GLSG-2000 trial[91] were digitised by the AG using TechDig© software to estimate survival probability estimates at time points along the Kaplan–Meier curve.

The corresponding HRs were calculated by taking the ratio of the cumulative hazard from the R-chemotherapy and chemotherapy arms from the OS Kaplan–Meier curves. The cumulative hazard was calculated by summing the negative log of the survival probabilities $\{H(t) = -S\log[S(t)]\}$ for each treatment arm, restricted to the clinical follow-up reported in the publications.[102] There are limitations with this method of calculating HRs, namely that it relies

TABLE 12 Response to treatment[a] in the four included studies[91–96]

	M39021[95,96]		GLSG-2000[91,92]		OSHO-39[93]		FL2000[94] 6-month follow-up data		FL2000[94] 18-month follow-up data	
	53 months		56 months		47 months		60 months		60 months	
Median follow-up	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) (95% CI 74% to 87%)	90 (57) (95% CI 49% to 64%)	268 (96) (no CI reported)	253 (91) (no CI reported)	97 (92) (no CI reported)	72 (75) (no CI reported)	164 (94) (no CI reported)	156 (85) (no CI reported)	142 (81) (no CI reported)	131 (72) (no CI reported)
p-value reported in study	<0.0001		0.0046		0.0009		NR		NR	
RR[b] (95% CI)	1.43 (1.22 to 1.67)		1.06 (1.01 to 1.10)		1.23 (1.08 to 1.40)		1.10 (1.02 to 1.18)		1.13 (1.01 to 1.27)	
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		NR[c]		NR[d]	
RR[b] (95% CI)	4.01 (2.22 to 7.25)		1.12 (0.79 to 1.60)		1.98 (1.33 to 2.95)		2.27 (1.54 to 3.35)		1.33 (1.05 to 1.67)	
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		NR[c]		NR[d]	
RR[b] (95% CI)	1.03 (0.83 to1.29)		1.04 (0.95 to 1.14)		0.86 (0.64 to 1.15)		0.83 (0.71 to 0.98)		0.91 (0.67 to 1.23)	
Stable disease: *n* (%)	12 (7)	33 (21)	6 (2)[e]	17 (6)[e]	NR[f]	NR[f]	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		NR[c]		NR[d]	
Progressive disease: *n* (%)	17 (10)	31 (19)	3 (1)	6 (2)	3 (3) (After two cycles)	10 (10) (After two cycles)	8 (5)	18 (10)	31 (18)	47 (26)
p-value reported in study	No *p*-value reported		No *p*-value reported		No *p*-value reported		NR[c]		NR[d]	

CI, confidence interval; NR, not reported; OR, overall response; RR, relative risk.

a Percentages may not add up owing to rounding.

b Relative risk of being a responder to R-chemotherapy compared with chemotherapy alone calculated in Review Manager.

c Authors report $p<0.001$ obtained using a global chi-squared test for all response strata (does not include ORR).

d Authors report $p=0.035$ obtained using a global chi-squared test for all response strata (does not include ORR).

e Includes 'minor response' as well as stable disease.

f Stable disease not reported but '< PR' reported at cycle 6: R-MCP = 7 and MCP = 22, and at cycle 8: R-MCP = 8 and MCP = 24.

TABLE 13 Overall survival in the four included studies[91–96]

	M39021[95]		GLSG-2000[91,92]		OSHO-39[93]		FL2000[94]	
	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 (95% CI 77 to 89[a])	7 (95% CI 70 to 83[a])	90 (CI NR[b])	84 (CI NR[b])	87 (CI NR[c])	74 (CI NR[c])	84 (95% CI 78 to 84[d])	79 (95% CI 72 to 84[d])
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	NR	NR
No. of deaths	23[e]	35[e]	6[f]	17[f]	15[g]	25[g]	NR	NR
p-value reported in trial	No *p*-value reported		0.016		No *p*-value reported		No *p*-value reported	
HRs[h]	0.64		0.58		0.40		0.69	

CI, confidence interval; HR, hazard ratio.
a Kaplan–Meier estimate at 4 years.
b Five-year rate.
c Four-year OS rates.
d Five-year rate.
e Deaths reported from Solal-Celigny *et al.*[102] may include patients who have received second-line treatment: median 42-month follow-up; number of deaths at 4-year follow-up[95] not reported.
f Deaths after 3 years reported[91] (not reported for 5 years).[91]
g Deaths at 4 years; cause-specific deaths in FL were *n* = 7 in R-MCP and *n* = 17 in MCP.[93]
h Calculated by the AG using the method described in *OS: hazard ratios*.

on the data from the trial publications rather than patient-level data and that estimating survival probabilities from digitised curves are subject to inaccuracies. As such, these estimates provide an indication of the HR for OS rather than definitive values. Given resource constraints and data limitations, it was not possible to calculate the standard errors (SEs) and confidence intervals (CIs) to give an indication of the uncertainty in the data.

For all four trials,[91–96] there was an increased likelihood of survival if receiving R-chemotherapy. For R-CVP compared with CVP, there was 36% increased survival benefit, for R-CHOP compared with CHOP there was a 42% increased survival benefit, for R-MCP compared with MCP a 60% increased survival benefit and for RCHVPi compared with CHVPi there was a 31% survival benefit. However, it is noted that the treatment effect on OS is confounded in the latter three trials owing to additional trial treatments administered after response to first-line treatment.

Progression-free survival

The median PFS was significantly prolonged in OSHO-39 trial[93] for the R-chemotherapy arm (R-MCP) (28.8 months MCP vs median not reached R-MCP; $p < 0.0001$). PFS was not reported in the other three trials.

Other time-to-event data

Several other efficacy outcomes, namely time-to-event data, were reported in the four studies.[91–96] As stated above (see *Summary of trials*), these outcomes were inconsistently defined between the four studies and thus not directly comparable (see *Appendix 12*). In addition, the time-to-event data were confounded in GLSG-2000[91,92] and OSHO-39[93] trials owing to the effects of subsequent treatment provided to responders to first-line treatment in these trials. However, we present a summary of the findings in *Table 14*.

TABLE 14 Summary of other time-to-event data (includes PFS)

	M39021[95,96]		GLSG-2000[91,92]		OSHO-39[93]		FL2000[94]	
	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, months	53		56		47		60	
Median PFS, months	–	–	–	–	Not reached	28.8	–	–
p-value	–		–		< 0.0001		–	
No. of events (%)	–		–		30 (29)	50 (52)	–	
% PFS at 4 years	–		–		71	40	–	
Median TTF, months	27 (95% CI 25 to 37)	7 (95% CI 6 to 9)	Not reached	35	–	–	–	–
p-value	< 0.0001		< 0.0001		–		–	
Median EFS, months	–	–	–	–	Not reached	26	Not reached	35
p-value					< 0.0001		0.0004	
Five-year EFS	–	–	–	–	–	–	53% (95% CI 45% to 60%)	37% (95% CI 29% to 44%)
p-value							0.001	
Median response duration, months	38, (95% CI 28 to NE)	14, (95% CI 9 to 18)	–	–	Not reached	35	–	–
p-value	< 0.0001		–		< 0.0001		–	
Duration of response at *x* years	–		66%[a]	35%[a]	–		64%[b] (95% CI 55% to 72%)	44%[b] (95% CI 32% to 54%)
p-value			< 0.0001[a]				0.012[b]	
Median TTNT, months	49 (95% CI 32 to NE)	12 (95% CI 10 to 18)		–	Not reached	29.4	–	–
p-value	< 0.0001		0.001[c]		0.0002		–	
Median DFS, months	Not reached (95% CI 35 to NE)	21 (95% CI 14 to 38)	–	–	–	–	–	–
p-value	0.0001		–		–		–	
Median TTP, months	34 (95% CI 27 to 48)	15 (95% CI 12 to 18)	–	–	–	–	–	–
p-value	< 0.0001		–		–		–	

NE, not estimable; NR, not reported.
a Duration of response at 5 years.
b Duration of response estimated at 4 years.
c Time to next antilymphoma treatment reported from median 18-month follow-up in Hiddemann *et al.*[92]

The median response duration was significantly prolonged for the R-chemotherapy arm compared with the chemotherapy-alone arms ($p < 0.001$) in the M39021 and OSHO-39 trials.[93,95,96] Two studies reported the duration of response, which differed significantly between treatment and comparator arms; at 5 years in the GLSG-2000 trial[91,92] ($p < 0.0001$) and the 4-year estimates presented in the FL2000 trial[94] ($p = 0.012$). Significantly prolonged ($p < 0.0001$) median TTF was reported for the R-chemotherapy arm compared with chemotherapy-alone arm in the M39021 and GLSG-2000 trials.[91,92,95,96] Similarly, median EFS was significantly improved in the R-chemotherapy arms in two studies compared with the chemotherapy-alone arms [median EFS MCP 26 months, not reached in R-MCP ($p < 0.0001$); median EFS 35 months in CHVPi, not

reached in R-CHVPi ($p = 0.0004$)].[93,94] The M39021, GLSG-2000 and OSHO-39 trials reported a statistically significant difference in TTNT.[91–93,95,96] The M39021 trial[95,96] reported significantly improved DFS and TTP for R-CVP compared with CVP.

Clinical efficacy in subpopulations

Overall, R-chemotherapy compared with chemotherapy alone improved treatment outcomes for all subgroups (including FLIPI score, IPI score, age, quality of response to induction therapy and other prognostic factors). It is noted that the univariate analyses presented may be misleading owing to interaction between variables.

Follicular Lymphoma International Prognostic Index score

All four studies[91–96] presented analysis of treatment outcomes according to FLIPI score subgroups. The M39021 trial[95] found after undertaking univariate analyses that median TTP was significantly improved in the R-CVP group at 53-month follow-up for all FLIPI groups (low, intermediate and high risk) (*Table 15*). Similarly, the GLSG-2000 study[91] found significantly prolonged 5-year TTF associated with the addition of rituximab in all FLIPI subgroups [84% vs 46% for low risk ($p = 0.0021$); 73% vs 37% for intermediate risk ($p < 0.0001$) and 49% vs 23% for high risk ($p < 0.0001$)].

Marcus *et al.*[95] conducted a multivariate analysis (which included the FLIPI score as a composite along with other prognostic factors that are not incorporated in the FLIPI), which found that only the FLIPI low-risk and intermediate groups combined (0–2) compared with high-risk groups (3–5) was a significant prognostic parameter for TTP in addition to trial treatment.

The MS[62] presented data on the OSHO-39 trial,[93] which demonstrated that treatment with R-MCP significantly increased the 4-year PFS rate, as well as prolonging the median TTP or death in patients with intermediate ($p = 0.0016$), as well as high-risk ($p = 0.0011$) FLIPI subgroups. Among patients with high-risk disease, a significant improvement in OS was also seen among those treated with R-MCP compared with MCP ($p = 0.0096$).[104] No such significant improvement between treatment arms was noted for median OS for the FLIPI intermediate subgroup ($p = 0.8607$). These data are presented in the MS[61] and are reproduced in *Table 16*; FLIPI 0–1 data were not presented.

In the FL2000 trial,[94] when patients with either a low ($n = 65$) or an intermediate ($n = 122$) FLIPI score were grouped together, no significant difference in EFS or OS was seen between the treatment arms. However, significant improvements in 5 years' EFS ($p < 0.001$) and OS ($p = 0.025$) were seen between the treatment arms in the high-risk FLIPI subgroup. Cox regression analysis, which included the FLIPI score (low and intermediate vs high) and the treatment arm, confirmed the impact of both parameters on EFS [FLIPI, HR = 2.08 (95% CI 1.6 to 2.8); R-CHVPi treatment, HR = 0.59 (95% CI 0.44 to 0.78)] and OS [FLIPI, HR = 4.11 (95% CI 2.34 to 7.23); R-CHVPi treatment, HR = 0.67 (95% CI 0.41 to 1.11)].

TABLE 15 Results of univariate analyses on TTP in M39021 trial[95] for FLIPI subgroups

Subgroup	R-CVP	CVP	*p*-value
FLIPI 0–1 (low risk)	Not reached (95% CI 38 months to NE)	22 months (95% CI 16 to 40 months)	0.0085
FLIPI 2 (intermediate risk)	37 months (95% CI 28 months to NE)	17 months (95% CI 13 to 35 months)	0.0003
FLIPI 3–5 (high risk)	26 months (95% CI 16 to 34 months)	11 months (95% CI 10 to 15 months)	0.0004

NE, not estimable.

TABLE 16 Progression-free survival and OS by FLIPI subgroup in the OSHO-39 trial[93] (reproduced from MS)[62]

Subgroup	Parameter	MCP	R-MCP	*p*-value
FLIPI 2 (intermediate risk)	Median PFS	37 months	Not reached	0.0016
	Four-year PFS	43%	82%	–
FLIPI 3–5 (high risk)	Median PFS	26.5 months	Not reached	0.0011
	Four-year PFS	36%	61%	–
FLIPI 2 (intermediate risk)	Median OS	Not reached	Not reached	0.8607
	Four-year OS	90%	92%	–
FLIPI 3–5 (high risk)	Median OS	54 months	Not reached	0.0096
	Four-year OS	63%	81%	–

International Prognostic Index

Marcus *et al.*[95] conducted a univariate analysis of the M39021 trial data, which found significantly prolonged median TTP for all IPI risk groups (*Table 17*). Similarly analysis of the GLSG-2000 trial data[91] found significantly prolonged TTF at 18-month follow-up by IPI risk group (*Table 18*).

Age

Eighteen-month follow-up data in the GLSG-2000 trial[92] found that TTF was prolonged in the R-CHOP arm for patients of any age (*Table 19*). The relative risk (RR) of treatment failure in the R-CHOP arm compared with the CHOP arm was 0.417 (95% CI 0.233 to 0.747) for patients aged < 60 years and was 0.354 (95% CI 0.175 to 0.715) for patients aged ≥ 60 years.

Quality of response

Salles *et al.*[94] analysed the response duration for the subgroup of patients who were in CR/CRu at 18 months of treatment in the FL2000 trial. The response duration was significantly different between the two treatment arms, with 4-year estimates of 44% (95% CI 32% to 54%) compared with 64% (95% CI 55% to 72%) in the CHVPi and R-CHVPi arms, respectively ($p = 0.012$). Therefore, as well as rituximab and chemotherapy increasing the number of CR/CRus, patients are also more likely to have a longer response duration.

Other prognostic factors

Marcus *et al.*[95] conducted several univariate analyses for a number of prognostic factors (*Table 20*) in the M39021 trial. The R-CVP treatment arm was associated with a significant prolonged TTP when compared with CVP alone for all subgroups investigated including baseline histology, presence or absence of B symptoms, and presence or absence of bulky disease. A significant improvement in TTP was seen in patients with baseline-only haemoglobin of at least 12 g/dl; however, no difference in TTP was observed between the R-CVP and CVP arms in patients with baseline haemoglobin of < 12g/dl ($p = 0.3941$).

Marcus *et al.*[95] also undertook two multivariate analyses: one that included the IPI as a composite along with other prognostic factors not incorporated in the IPI and one that included the individual factors which make up the FLIPI and IPI, together with other prognostic factors. These analyses found that only haemoglobin level (< 12 g/dl) and number of nodal areas involved (> 1) were statistically significant predictors of TTP in addition to trial treatment.

Buske and Hoster[105] conducted a multivariate analysis on the GLSG-2000 trial[92] data at 20-month follow-up including the individual FLIPI risk factors. This found that a serum LDH level higher than the upper normal limit (RR 2.6, 95% CI 1.5 to 4.5) and a haemoglobin level of < 12 g/dl (RR 2.5, 95% CI 1.4 to 4.3) were independently associated with a shorter TTF in addition to trial treatment. However, age (≥ 60 years vs < 60 years; RR 0.9, 95% CI 0.5 to 1.5) and the number of nodal areas (> 4 vs ≤ 4; RR 1.5, 95% CI 0.8 to 2.6) did not significantly influence the TTF.

TABLE 17 Median TTP by IPI subgroup in the M39021 trial[95]

Subgroup	Parameter	R-CVP	CVP	*p*-value
IPI 0–1 (low risk)	Median TTP	44 months (95% CI 30 months to NE)	20 months (95% CI 13 to 26 months)	< 0.0001
IPI 2 (intermediate risk)	Median TTP	27 months (95% CI 20 to 39 months)	14 months (95% CI 10 to 17 months)	0.0003
IPI 3–4 (high risk)	Median TTP	40 months (95% CI 11 months to NE)	12 months (95% CI 8 to 25 months)	0.0333

NE, not estimable.

TABLE 18 Median TTF by IPI subgroup in the GLSG trial[92]

Subgroup	Estimated median TTF for CHOP	*p*-value for Cox regression	Estimated RR for treatment failure for R-CHOP (95% CI)
IPI 1–2	Not reached	0.001	0.412 (0.242 to 0.701)
IPI 3–5	29 months	0.009	0.331 (0.144 to 0.761)

RR, relative risk.

TABLE 19 Median TTF by age subgroup (< 60 years vs ≥ 60 years) in GLSG-2000 trial[92]

Age (years)	Estimated median TTF for CHOP[a]	*p*-value for Cox regression	Estimated RR for treatment failure for R-CHOP (95% CI)
< 60	Not reached	0.003	0.417 (0.233 to 0.747)
≥ 60	29 months	0.004	0.354 (0.175 to 0.715)

a Median not reached for R-CHOP arm for < 60 years or ≥ 60 years.

Meta-analysis

Three exploratory meta-analyses were conducted to explore the results of synthesising the ORR, CR and PR from the four trials.

There were several problems with the validity of these analyses. First, the level of statistical heterogeneity calculated in RevMan using the I^2-statistic was very high (range $I^2 = 56–88\%$). The I^2-statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance),[106] and an I^2-value > 50% is considered to be a high enough level of heterogeneity to suggest meta-analysis is not appropriate. Ideally, this high level of heterogeneity would be explored further and explained by estimating the predictive distribution of a new study. This was not undertaken owing to resource constraints.

Reasons for the high level of heterogeneity could be because of differences in treatment effects in the four trials.[91–96] Examination of the CIs for the results from the individual trials showed that there was little overlap in the meta-analyses for CR, and to a lesser extent for PR, indicating evidence for heterogeneity of intervention effects. Indeed, the GLSG-2000 trial[91,92] observed much higher ORR (a combination of CR and PR) for both the R-chemotherapy and chemotherapy-alone arms in comparison with the other studies. This was mostly accounted for by an increase in the numbers of PR (20% CR and 77% PR in the R-CHOP arm), whereas in the OSHO-39 trial[93] there was a more even split between the CR/PR categories (R-MCP CR = 50% and PR = 43%). As well as evidence for different intervention effects in the four trials, there are other possible

TABLE 20 Univariate analyses in the M39021 trial[95]

Subgroup	R-CVP	CVP	*p*-value
Histology at central review (IWF)			
Class B	34 months (95% CI 27 months to NE)	17 months (95% CI 11 to 24 months)	0.0037
Class C			
Class D			
Histology at central review (IWF)			
Class C	35 months (95% CI 26 months to NE)	15 months (95% CI 10 to 21 months)	<0.0001
Class D	Not reached (95% CI 30 months to NE)	14 months (95% CI 7 to 24 months)	0.0046
B symptoms[a] ≥1	32 months (95% CI 22 months to NE)	17 months (95% CI 12 to 23 months)	0.0014
No B symptoms[a]	37 months (95% CI 26 months to 48)	14 months (95% CI 11 to 20 months)	<0.0001
Bulky disease			
Yes	38 months (95% CI 25 months to 48)	13 months (95% CI 11 to 21 months)	<0.0001
No	32 months (95% CI 26 months to NE)	16 months (95% CI 13 to 21 months)	<0.0001
Haemoglobin			
≥12 g/dl	39 months (95% CI 31 months to NE)	17 months (95% CI 13 to 22 months)	<0.0001
<12 g/dl	11 months (95% CI 9 to 28 months)	12 months (95% CI 10 to 16 months)	0.3941

IWF, International Working Formulation; NE, not estimable.
a B symptoms defined as fever, weight loss and night sweats.

explanations for the high level of heterogeneity. First, each study administered a different therapeutic intervention with respect to the chemotherapy regimen used; this included different chemotherapeutic agents (CVP, CHOP, MCP and CHVPi) and different regimens of treatment (treatment every 3 weeks vs every 4 weeks; six cycles of treatment vs eight cycles of treatment). Second, there was a difference in the sample sizes of the studies; for example, the GLSG-2000 trial[91,92] was the largest trial with an ITT population of $n = 557$ patients, whereas the OSHO-39 trial[93] was substantially smaller ($n = 201$).

The AG also notes that the choice of chemotherapeutic regimen is not solely determined by clinical efficacy. For example, R-CHOP is less likely to be given to patients who are elderly or unfit, but more likely to be given to treat aggressive or bulky disease, which may impact on the perceived efficacy. Additionally, the analyses assume that rituximab has no synergistic interaction with the chemotherapeutic component of a regimen for the treatment effect. The AG also comment that the analyses of ORR, CR and PR are not independent analyses given that the same patients are counted in more than one analysis.

The AG therefore believes the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens. These are subsequently used in the decision model (see *Chapter 4*) rather than meta-analysed response rates. The results from the meta-analyses are presented in *Appendix 14* for completeness, but the use of these are strongly cautioned against.

Safety data

The evaluation of the safety of R-chemotherapy is mainly derived from data reported from the four included trials,[91–96] which are described above (see *Summary of trials*). AE data were extracted from the four trials (see *Appendix 11* for completed data extraction forms). In addition, postmarketing surveillance data from the MS are presented.[62]

The M39021, OSHO-39 and FL2000 trials[93–96] graded AEs in accordance with the NCI-CTC grading system,[100] but the GLSG-2000 trial[91,92] used the WHO toxicity criteria[101] to record AEs. However, there are no substantial differences between these two scales.[107]

Treatment completion and withdrawals

The M39021, OSHO-39 and FL2000 trials[93–96] reported data on the number of treatment cycles that were completed. No data were presented on the planned cycle completion, doses of study drugs administered and withdrawal numbers or reasons in the GLSG-2000 trial.[91,92]

Overall, a greater proportion of patients in the R-chemotherapy arms received the planned number of cycles when compared with the chemotherapy-alone arm (*Table 21*). No differences in dose of chemotherapy received were noted between the R-chemotherapy and chemotherapy-alone arms, with the exception of cyclophosphamide in the M39021 trial.[95,96] Reasons for withdrawal from treatment appeared to be mostly owing to disease progression or treatment failure (e.g. failing to achieve a response to treatment after a defined number of cycles). However, there was a lack of transparency in the studies regarding withdrawals for other reasons such as AEs/reactions. This is considered in more detail by trial.

M39021 trial

A Consolidated Standards of Reporting Trials diagram[108] was reported for the M39021 trial,[95,96] which showed the flow of patients through the trial. This showed that 137/162 (85%) of patients in the R-CVP arm and 108/159 (68%) patients in the CVP arm completed eight cycles.[95,96] The MS[62] provided further details on cycle completion, with 6/162 (4%) of patients in the R-CVP arm withdrawn before cycle 4 compared with 13/159 (8%) in the CVP arm. Thus, 19/162 (12%) patients in the R-CVP arm were withdrawn after cycle 4 compared with 38/159 (24%) in the CVP arm. The majority of patients appear to have been withdrawn owing to an insufficient treatment response (defined as disease progression or stable disease after cycle 4). However, a number of patients were withdrawn before cycle 4 for which the reasons are not made explicit. The authors note that two patients were withdrawn as a result of grade 3 or 4 rituximab infusion-related reactions and one patient withdrew consent and thus withdrew from the trial; however, this does not account for all patients.

Marcus *et al.*[96] report the proportion of patients in the M39031 trial who received the planned doses of chemotherapy. The proportion of patients that received > 90% of the planned dose of prednisolone and vincristine at each administered cycle was comparable between the R-CVP and CVP arms. However, the proportion of patients who received > 90% of cyclophosphamide was higher in the CVP group (> 94%) than the R-CVP group (> 85%). The authors state that this was 'mainly due to dose modifications in the R-CVP group for NCI–CTC grades 3 and 4 neutropenia'. Clinical advice suggests this is now less of a problem as granulocyte-stimulating factor is routinely used to treat neutropenia. Ninety-six per cent of patients received > 90% of the planned dose of rituximab at each administered cycle.[96]

TABLE 21 Number of treatment cycles administered

	M39021[95,96]		GLSG-2000[92]		OSHO-39[93]		FL2000[94]	
	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)
Patients who received planned no. of cycles, *n* (%)	137 (85)	108 (68)	NR	NR	92 (88)	64 (67)	166 (95)	172 (94)

NR, not reported.

OSHO-39 trial

In the OSHO-39 trial,[93] 88% of patients in the R-MCP arm and 67% in the MCP arm completed all eight cycles of treatment. Treatment failure owing to disease progression after two cycles occurred in three patients in the R-MCP arm and in 10 patients in the MCP arm. Failure to achieve at least a PR after six cycles occurred in seven patients in the R-MCP arm and 22 patients in the MCP arm. Numbers of patient withdrawals ($n = 16$) prior to the study drug administration and the associated reasons were reported; however, this includes patients with MCL as well as FL. The authors state that all other withdrawals were because of non-response/treatment failure during therapy (which was defined as disease progression after two cycles of therapy or failure to reach a PR or CR after six cycles of therapy). The authors do not state if there were any withdrawals because of AEs or reactions.

The mean dose of study drugs administered in the OHSO-39 trial[92] were rituximab, 660–680 mg/cycle; mitoxantrone, 24–28 mg/cycle; chlorambucil, 68–81 mg/cycle and prednisolone, 226–231 mg/cycle. The authors stated that the dose intensity of the chemotherapy did not differ between treatment arms.[93] Interferon-alpha maintenance treatment (3×4.5 MIU/week until disease progression) was initiated in 97% and 92% of responding patients in the R-MCP and MCP arms, respectively.

FL2000 trial

In the FL2000 study,[94] the MS[62] noted that 95% of patients in the R-CHVPi arm and 94% of patients in the CHVPi arm received the initial six cycles of treatment. Among patients who did not progress during therapy, 161 (98%) and 153 (98%) of the patients received the planned chemotherapy courses during the first 6 months in the R-CHVPi and CHVPi arms, respectively. In the CHVPi arm, 116 (87%) of 134 patients without death or progression received the six planned cycles of chemotherapy consolidation; the R-CHVPi arm did not receive this chemotherapy consolidation. Two hundred and thirty-seven (66%) patients followed the interferon treatment according to the protocol, with dose adaptation (45 patients) or short (< 4 weeks) interruptions (55 patients), without significant differences in adaptation between the two study arms. In addition, interferon treatment was stopped in 50 patients resulting from disease progression (R-CHVPi arm, 19 cases, and CHVPi arm, 31 cases, respectively) and was interrupted either for > 1 month (16 cases) or definitively (72 cases) resulting from toxicity. These major interruptions were observed in 41 patients in the RCHVPi arm and 47 patients in the CHVPi arm. One patient withdrew consent after registration, and one patient had a major inclusion violation (registered at relapse) and thus were withdrawn from the treatment in the FL2000 trial.[94] No further details are provided on withdrawals in the FL2000 trial[94] during treatment; although not all patients received the planned six cycles of initial treatment.

Adverse events of any grade

Adverse events of any grade were reported as more frequent in the R-MCP arm than in the MCP arm in the OSHO-39 trial[93] (99% vs 86% of patients, respectively). However, the M39021 trial[95,96] reported that the proportion of patients that reported at least one AE was comparable between the CVP (95%) and R-CVP (97%) groups. Marcus *et al.*[96] report that AEs associated with the gastrointestinal and nervous systems as well as general disorders and administration site reactions were the most commonly occurring types of events in both treatment groups in the M39021 trial.[95,96] Fatigue, neutropenia and back pain were the most common severe AEs and occurred at a slightly higher frequency in patients receiving R-CVP. These data were not available within the manuscripts[95,96] reporting on the M39201 trial but appear to be confirmed by data presented in the MS,[62] which reports on all grades of AEs in the M39201 trial.

Grade 1 and 2

The OSHO-39[93] and GLSG-2000[92] trials reported grade 1 and 2 AEs. The authors in each trial reported that there were no significant differences between the treatment arms. The most common grade 1/2 AE in the OSHO-39 trial[92] study was infection, which affected 42% of patients receiving R-MCP, and 35% receiving MCP. In the GLSG-2000 trial,[92] the most commonly reported grade 1/2 AE was low haemoglobin level, with 50% of R-CHOP and 49% of CHOP patients affected. Neurotoxicity was another frequent grade 1 or 2 AE reported in the GLSG-2000 trial[92] (R-CHOP 34%, CHOP 42%). Reduced platelet count was also a common AE, especially in the OSHO-39 trial[93] (R-MCP 30%, MCP 33%), whereas the GLSG-2000 trial[92] reported lower incidences for patients receiving the CHOP-based treatments (R-CHOP 17%, CHOP 16%). Nausea and vomiting was another frequent grade 1 or 2 AE in both trials (R-CHOP 45%, CHOP 44% in the GLSG-2000 trial and R-MCP 24%, MCP 15).[93] For a detailed list of grade 1 and 2 AEs see *Table 22*.

Grade 3 and 4 adverse events

All fours studies reported grade 3 and 4 AEs; the GSLG-2000[92] and OSHO-39[93] trials reported grade 3 and 4 AEs separately, whereas the M39021[95,96] and FL2000[94] trials combined the numbers

TABLE 22 Adverse events (grades 1 and 2) reported in the GLSG-2000[92] and OSHO-39[93] trials[a] (grade 1/2 AEs not reported in M39021 trial[95,96] and FL2000 trial[94])

	[b]GLSG-2000[92]		[c]OSHO-3[93]	
AEs: *n* (%)	**R-CHOP (*n*=223)**	**CHOP (*n*=205)**	**R-MCP (*n*=105)**	**MCP (*n*=96)**
Low haemoglobin level	112 (50)	100 (49)	18 (17)	18 (19)
Leucocytopenia	54 (24)	57 (28)	3 (3)	8 (8)
Granulocytopenia	42 (19)	41 (20)	–	–
Reduced platelet count	38 (17)	33 (16)	31 (30)	32 (33)
Infection	74 (33)	59 (29)	44 (42)	34 (35)
Bleeding	9 (4)	6 (3)	–	–
Nausea/vomiting	100 (45)	90 (44)	25 (24)	14 (14)
Stomatitis	58 (26)	59 (29)	11 (10)	7 (7)
Obstipation (severe constipation)	33 (15)	27 (13)	–	–
Diarrhoea	25(11)	23 (11)	11 (10)	4 (4)
Fever	65 (29)	45 (22)	NR	NR
Cardiac dysfunction	7 (3)	8 (4)	NR	NR
Alopecia	42 (19)	51 (25)	NR	NR
Cardiac arrhythmia	13 (6)	8 (4)	NR	NR
Neurotoxicity	76 (34)	86 (42)	NR	NR
CNS toxicity	4 (2)	4 (2)	NR	NR
Allergy	13 (6)	0 (0)	NR	NR
Rash	NR	NR	16 (15)	1 (1)
Heartburn	NR	NR	15 (14)	3 (3)
Insomnia	NR	NR	15 (14)	7 (7)
Bone pain	NR	NR	10 (10)	10 (10)
Gastrointestinal	NR	NR	9 (9)	5 (5)
Other (not specified)	NR	NR	11 (10)	8 (8)

CNS, central nervous system; NR, not reported.

a Numbers and percentage may not add up owing to rounding.

b Not stated if number of patients reporting each event or overall number of events.

c Authors state that data are the number of patients reporting each event (not stated if a patient could be counted more than once).

of grade 3 or 4 AEs. The most common AEs observed in the four trials were related to the blood and bone marrow, including leucocytopenia, neutropenia and granulocytopenia. For two trials, the most common grade 3 and 4 AEs were reduced leucocyte (white blood cell) levels; this was observed in 69% of R-CHOP and 61% CHOP patients in the GLSG-2000 trial[92] and 72% R-MCP and 58% MCP patients in the OSHO-39 trial.[93] The statistical significance of the difference in grade 3/4 leucopenia between the treatment arms in the OSHO-39 trial[93] was not reported by the authors, whereas the difference between the R-CHOP and CHOP treatment arms in the GLSG-2000 trial[92] was reported as not significant.

The most common AE in the M39021 trial[95,96] was neutropenia (24% in R-CVP and 14% in CVP arms); however, the authors do not state if this was a statistically significant difference between treatment arms. In the FL2000 trial,[94] the most common grade 3/4 AE was neutrophil toxicity (59% R-CHVPi and 62% in CHVP arms). However, the FL2000 trial[94] only noted a significant difference in grade 3 or 4 AEs for neutrophil toxicity during the 12-month consolidation period, which was more frequent in the chemotherapy-alone arm than the rituximab-containing arm ($p < 0.001$) (results presented in the data extraction form for the FL2000 trial[94] in *Appendix 11*).

There were a number of patients who had a low granulocyte count of grade 3 or 4 severity in the GSLG-2000 trial[92] and the difference between the treatment arms was statistically significant (R-CHOP 63%, CHOP 53%; $p = < 0.01$). In addition, grade 3 or 4 alopecia was a frequently observed AE in both arms of the GLSG-2000 trial[92] (R-CHOP 67%, CHOP 61%).

Blood or bone marrow AEs may be associated with infection. However, the difference in frequency of blood or bone marrow AEs between treatment arms is of minor clinical significance as they did not translate into a difference in infection rates between the treatment arms for all three studies. Infections of grade 3 or 4 were observed in 8% of the MCP group and 7% of the R-MCP group; 5% R-CHOP arm and 7% CHOP arm and 2% of the R-CHVPi arm and 0% CHVPI arm.[92–94] The MS[61] reports all grades of infections for three trials, and follows a similar pattern (33% R-CVP and 32% CVP, 38% R-CHOP and 36% CHOP, 49% R-MCP and 43% MCP).

More detail on grade 3/4 AEs combined for the four trials and grade 3 or 4 AEs reported separately (only for the GSLG-2000[92] and OSHO-39[93] trials) are reported in *Tables 23* and *24*, respectively.

Infusion-related reactions

Infusion-related reactions were observed in 7% of courses during the first infusion in the GSLG-2000 trial[92] and early cessation of rituximab therapy was required in two patients. Fourteen (9%) patients in the M39201 trial[95,96] had a grade 3 or 4 rituximab infusion-related reaction, and two of these patients were withdrawn from study treatment. More patients in the R-CVP group than in the CVP group experienced an AE within 24 hours of an infusion (71% vs 51%, respectively). One grade 3 infusion-related reaction was reported in the OSHO-39 trial[93] in the MS[62] and related to the full study population of FL and MCL.

Death and life-threatening adverse events

Overall, there were very few AEs reported as life-threatening or leading to death within the trials. The M39201 trial[95,96] reported that five patients experienced a total of six life-threatening events following R-CVP; however, no treatment-related deaths occurred. The remaining three studies did not report whether or not AEs were either life-threatening or led to death.

The number of deaths reported for the chemotherapy-alone arms were consistently higher compared with the R-chemotherapy arms in all four trials. A total of 49 deaths were reported in the M39201 trial[96] from 30-month follow-up[96] (21 in the R-CVP arm and 28 in the CVP arm;

TABLE 23 Adverse events (grade 3 and 4 combined) for all four trials[a]

	M39021[95,96]		GLSG-2000[92]		OSHO-39[93]		[b]FL2000[94]	
AEs: *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[c]	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)
Bleeding	–	–	0 (0)	0 (0)	–	–	–	–
Nausea/vomiting	–	–	9 (4)	12 (6)	1 (1)	6 (6)	–	–
Stomatitis	–	–	2 (1)	4 (2)	1 (1)	1 (1)	–	–
Obstipation (severe constipation)	–	–	4 (2)	2 (1)	–	–	–	–
Diarrhoea	–	–	4 (2)	6 (3)	2 (2)	2 (2)	–	–
Fever	–	–	0 (0)	2 (1)	–	–	2 (1)	2 (1)
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)	–	–	–	–
Neurotoxicity	–	–	2 (1)	4 (2)	–	–	–	–
CNS toxicity	–	–	2 (1)	0 (0)	–	–	–	–
Allergy	–	–	2 (1)	0 (0)	–	–	–	–
Rash	–	–	–	–	0	2 (2)	–	–
Heartburn	–	–	–	–	1 (1)	0 (0)	–	–
Insomnia	–	–	–	–	0 (0)	0 (0)	–	–
Bone pain	–	–	–	–	2 (2)	0 (0)	–	–
Gastrointestinal	–	–	–	–	2 (2)	2 (2)	–	–
Other	–	–	–	–	0 (0)	2 (2)	–	–

CNS, central nervous system.

a Numbers and percentage may not add up owing to rounding.

b Adverse events recorded from first 6 months of treatment. AEs from consolidation treatment phase (additional 12 months) available in the data extraction form in *Appendix 11*.

c Data for the M39201 trial[95,96] taken from the MS[62] and could not be confirmed in the manuscripts.

patients may have received second-line therapy at this stage). Twenty-three deaths (17 CHOP and six R-CHOP) and 40 deaths (25 MCP and 15 R-MCP) occurred in study GLSG-2000[91] and study OSHO-39,[93] respectively. In the FL2000 trial,[94] a total of 45 patients had died at the time of the analysis at 42 months (16 R-CHVPi and 29 CHVPi). The majority of deaths were attributed to lymphoma progression. The GLSG-2000 study[92] reported the additional reasons for death in detail (*Table 25*); however, the other three trials did not report this information.

Subgroup analyses

The MS[61] reported data on the safety from the GLSG-2000 trial[92] for the elderly population (≥ 60 years of age, $n = 221$). As for the whole trial population, the most common AEs were blood and bone marrow disorders, gastrointestinal disorders, skin toxicities, neurological disorders, cardiac disorders, infections and fever. Most of the AEs were mild to moderate in intensity, except for alopecia, leucopenia and neutropenia, which were mainly of grade 3/4 in intensity. The most common grade 3/4 AEs in the elderly population were blood and bone marrow disorders and alopecia. The remaining three trials did not provide AE data for subgroup populations.

TABLE 24 Adverse events (grade 3 and 4 separately) reported in the GLSG-2000[92] and OSHO-39[93] trials (grade 3/4 AEs not reported separately in the M39021 trial[95,96] and FL2000 trial[94])

	GLSG-2000[92]				OSHO-39[93]			
	Grade 3		Grade 4		Grade 3		Grade 4	
AEs: *n* (%)	R-CHOP (*n* = 223)	CHOP (*n* = 205)	R-CHOP (*n* = 223)	CHOP (*n* = 205)	R-MCP (*n* = 105)	MCP (*n* = 96)	R-MCP (*n* = 105)	MCP (*n* = 96)
Haemoglobin level	18 (8)	18 (9)	2 (1)	2 (1)	2 (2)	3 (3)	1 (1)	1 (1)
Leucocyte/white blood cells	96 (43)	78 (38)	58 (26)	47 (23)	25 (24)	21 (22)	50 (48)	35 (36)
Granulocyte count	49 (22)	47 (23)	91 (41)	62 (30)	–	–	–	–
Platelet count	9(4)	10 (5)	4 (2)	6 (3)	4 (4)	6 (6)	0 (0)	1 (1)
Bleeding	0 (0)	0 (0)	0 (0)	0 (0)	–	–	–	–
Nausea/vomiting	9 (4)	12(6)	0 (0)	0(0)	1 (1)	6 (6)	0 (0)	0 (0)
Stomatitis	2 (1)	4 (2)	0 (0)	0(0)	1 (1)	1 (1)	0 (0)	0 (0)
Obstipation (severe constipation)	4(2)	2 (1)	0 (0)	0(0)	–	–	0 (0)	0 (0)
Diarrhoea	4 (2)	6 (3)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (2)
Fever	0 (0)	2 (1)	0 (0)	0 (0)	–	–	–	–
Alopecia	140 (63)	115 (56)	9 (4)	10 (5)	–	–	–	–
Infection	11 (5)	12 (6)	0 (0)	2 (1)	6 (6)	7 (7)	1 (1)	1 (1)
Cardiac dysfunction	4 (2)	2(1)	2 (1)	0 (0)	–	–	–	–
Cardiac arrhythmia	2 (1)	0 (0)	2 (1)	0 (0)	–	–	–	–
Neurotoxicity	2 (1)	4 (2)	0 (0)	0 (0)	–	–	–	–
CNS toxicity	2 (1)	0 (0)	0 (0)	0 (0)	–	–	–	–
Allergy	2 (1)	0 (0)	0 (0)	0 (0)	–	–	–	–
Rash	–	–	–	–	0 (0)	2 (2)	0 (0)	0 (0)
Heartburn	–	–	–	–	1 (1)	0 (0)	0 (0)	0 (0)
Insomnia	–	–	–	–	0 (0)	0 (0)	0 (0)	0 (0)
Bone pain	–	–	–	–	2 (2)	0 (0)	0 (0)	0 (0)
Gastrointestinal	–	–	–	–	2 (2)	1 (1)	0 (0)	1 (1)
Other	–	–	–	–	0 (0)	1 (1)	0 (0)	1 (1)

CNS, central nervous system.

Postmarketing data (taken from the manufacturer's submission)

Over 1 million patients (length of exposure not known), predominantly NHL patients, have received rituximab since its first marketing authorisation. Worldwide safety data submitted to the Periodic Safety Update Reports (PSURs) (with a cut-off date of April 2007) have recorded 13,008 AEs. Of these reported AEs, 10,184 were classified as serious. For 7174 events, the report came from spontaneous sources (postmarketing experience). Other sources include clinical trials in oncology and rheumatoid arthritis (company- and investigator-sponsored trials). The MS[62] presents a summary of AEs in the global safety database for rituximab (as of 30 April 2007) and this is presented in *Table 26*. The most frequently reported events were infection and infestation (15%), blood and lymphatic system disorders (14%), general disorders and administration site conditions (11%) and respiratory, thoracic and mediastinal disorders (10%).

The updated summary of product characteristics from the EMA[84] also discusses cases of progressive multifocal leucoencephalopathy (PML) being associated with the use of rituximab. All patients treated with MabThera for rheumatoid arthritis must be given a patient alert card with each infusion, which contains important safety information for patients including signs and symptoms to watch out for. However, cases of PML reported during postmarketing use of rituximab in NHL are very rare (numbers/percentages are not reported).

TABLE 25 Number of deaths and reasons for death in the four trials

	[a]M39021[96]		[b]GLSG-2000[92]		OSHO-39[93]		[c]FL2000[94]	
Death and reasons for death	**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)**
Total nos. (%) of deaths	21 (13)	28(18)	6	17	15 (14)	25 (26)	16	29
Reasons for death								
Lymphoma/progressive disease	13 (8)	22 (14)	1 (0)	9 (4)	7	17	–	–
Infection	–	–	4 (2)	4 (2)	–	–	–	–
Cardiac failure	–	–	0	1 (0)	–	–	–	–
Apoplectic insult	–	–	0	1 (0)	–	–	–	–
GVHD after ASCT	–	–	0	1 (0)	–	–	–	–
Unknown	–	–	1 (0)	1 (0)	–	–	–	–

GVHD, graft-versus-host disease.
a Data from 30-month follow-up.
b Data from 18-month follow-up.
c Data from MS.[62]

TABLE 26 Adverse events in the global rituximab safety database as of 30 April 2007 (all sources and indications): reproduced from the MS[62]

System organ class	SAEs	% SAEs	Total AEs	% Total AEs
Blood and lymphatic system disorders	1586	16	1775	14
Cardiac disorders	566	6	604	5
Congenital, familial and genetic disorders	9	0	10	0
Ear and labyrinth disorders	31	0	44	0
Endocrine disorders	13	0	15	0
Eye disorders	61	1	106	1
Gastrointestinal disorders	601	6	767	6
General disorders and administration site conditions	770	8	1400	11
Hepatobiliary disorders	163	2	165	1
Immune system disorders	399	4	480	4
Infections and infestations	1852	18	1986	15
Injury, poisoning and procedural complications	177	2	281	2
Investigations	433	4	603	5
Metabolism and nutrition disorders	118	1	137	1
Musculoskeletal and connective tissue disorders	331	3	523	4
Neoplasms benign, malignant and unspecified (including cysts and polyps)	495	5	513	4
Nervous system disorders	454	4	611	5
Pregnancy, puerperium and perinatal conditions	15	0	30	0
Psychiatric disorders	58	1	78	1
Renal and urinary disorders	174	2	188	1
Reproductive system and breast disorders	26	0	44	0
Respiratory, thoracic and mediastinal disorders	1136	11	1348	10
Skin and subcutaneous tissue disorders	271	3	711	5
Social circumstances	6	0	8	0
Surgical and medical procedures	47	0	51	0
Vascular disorders	392	4	530	4
Total	**10,184**	**100**	**13,008**	**100**

SAE, serious adverse event.

Discussion

The results from four randomised trials[91–96] (of good quality) comparing the combination of R-chemotherapy with chemotherapy alone showed an improvement in a number of clinical effectiveness outcomes. This included trials evaluating R-CVP,[95,96] R-CHOP,[91,92] R-MCP[93] and R-CHVPi[94] in each case against their respective chemotherapy regimen.

Evidence from the four trials[91–96] on the primary outcome of interest in this appraisal, OS, showed a benefit for rituximab and chemotherapy compared with chemotherapy alone, for all chemotherapy regimens. The difference in OS rates ranged from 6% to 14% when the R-chemotherapy arms were compared with the chemotherapy-alone arms. The difference in OS rates was statistically significant in three trials, the exception being the FL2000 trial[94] ($p = 0.1552$). However, the follow-up period for the four trials is approximately 4–5 years and the median OS has yet to be reached for each arm (intervention and comparator) within each trial. The median survival of FL is reported as 8–10 years,[29] although some have commented that this figure has increased in the last decade,[14,15] and thus the evidence for the effect of R-chemotherapy on OS might be strengthened by a longer follow-up period. It is also noted that data in three trials are confounded by additional trial treatments (interferon-alpha maintenance/consolidation and SCT – for further details see *Summary of trials*), which needs to be considered when interpreting the OS and other time-to-event data. However, given the relapsing and remitting nature of FL, it is unlikely that a trial could be ethically undertaken to remove the effect of subsequent therapies, i.e. when a patient relapses they will receive subsequent treatment to induce remission.

Progression-free survival was measured only in the OSHO-39 trial[93] and was significantly prolonged for the R-chemotherapy arm compared with the chemotherapy-alone arms (R-MCP) (median 28.8 months for MCP and not reached for R-MCP, $p < 0.0001$). Other time-to-event data such as EFS, TTP and TTNT showed similar benefits in effect, although these were inconsistently defined and not directly comparable between trials.

Overall response rates were significantly improved in all four trials,[91–96] with a difference in 5–24% between the R-chemotherapy and chemotherapy arms. CR rates were also improved, with a difference between the R-chemotherapy and chemotherapy arms of 2–25%, which was reported as significant in three studies[93–96] (the GLSG-2000 trial[92] of R-CHOP vs CHOP did not report a *p*-value). Differences in PR rates were generally smaller (level of significance not reported); however, this might be explained by a potential way R-chemotherapy shifts patients from non-responders to PRs and PRs to CRs. There was some evidence that the response quality differed among the four R-chemotherapy combinations. For example, greater ORR was observed in the GSLG-2000 trial[91,92] (R-CHOP vs CHOP) compared with the M39021 trial[95,96] (R-CVP vs CVP), whereas CR rates were greater in the M39021 trial[95,96] than the GLSG-2000 trial.[91,92] Others have noted these differences between R-chemotherapy regimens.[81] Clinical advice to the AG noted that R-CHOP/CHOP is reserved for more aggressive disease, and this would have implications on the quality of response. However, the baseline characteristics of the patients were generally similar in each of the four trials.[91–96]

Considerable statistical heterogeneity was observed in exploratory meta-analyses undertaken to provide a summary of effect of response rates. Differences in treatment effects, study sample sizes, and chemotherapeutic agents and regimens are plausible reasons for this heterogeneity. Owing to the high level of heterogeneity, meta-analysis of response rates is not considered appropriate. Thus, response rate results from individual studies are considered more robust.

The safety data show that the addition of rituximab to chemotherapy does not result in clinically relevant adverse outcomes. Although an increased statistically significant incidence of leucocytopenia, neutropenia and granulocytopenia was observed in the trials in the

R-chemotherapy arms, this was of limited clinical significance as the rate of infection did not increase in the R-chemotherapy arms (infection is associated with leucocytopenia, neutropenia and granulocytopenia). However, considerable numbers of patients were affected by grade 3 or 4 alopecia in both the R-CHOP and CHOP arms of the GSLG-2000 trial.[91,92] This side effect is as a result of the CHOP component of the treatment and is an important side effect to consider particularly in terms of patient acceptance, tolerance and choice.

It is noted that the median age of patients within the trials (52–61 years) is considerably younger than that seen in clinical practice, where over 70% are aged > 60 years at diagnosis and clinical advice suggests that the ECOG performance status is better than that seen in UK clinical practice.[10] This affects the generalisability of the findings to the clinical FL population; however, limited analyses undertaken within the trials did not show a differential affect for different clinical and demographic subgroups. Specifically, the GSLG-2000 trial[91,92] showed that adding rituximab to chemotherapy was beneficial for both patients aged > 60 years and aged < 60 years.

Our own searches of the randomised evidence were exhaustive and we are confident that we have not missed any published reports of RCTs or other systematic reviews of R-chemotherapy in the treatment of FL.

In conclusion, the addition of rituximab to chemotherapy results in better clinical outcomes for patients when compared with chemotherapy alone, for all chemotherapeutic backbones examined in this review, i.e. CVP, CHOP, MCP and CHVPi. This is achieved with minimal additional AEs or toxicity, which are deemed to be clinically relevant.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

This chapter describes a review of the existing evidence on the cost-effectiveness of the addition of rituximab to chemotherapy in patients with untreated, symptomatic stage III/IV FL. This includes a systematic review of published evidence and evidence included in the MS.[62]

Methods

A systematic search was performed to identify studies addressing the cost-effectiveness of the addition of rituximab to chemotherapy for the first-line treatment of FL. Only full economic evaluations published in English addressing the cost-effectiveness of the addition of rituximab to chemotherapy compared with chemotherapy alone in patients with FL were included in the review.

Eight databases were searched for relevant published literature including MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations (Ovid); CINAHL; EMBASE; NHS EED and HTA databases; SCI; and BIOSIS. In addition, literature searches were undertaken for the clinical effectiveness review and quality-of-life review (see *Identification of studies*) and relevant cost papers were identified from these searches. In addition, the reference lists of relevant articles and the MS[62] were handsearched. Full details of the search strategies used in MEDLINE are presented in *Appendix 5* (these have been adapted for use in other databases). Searches were not restricted by language or publication date.

Studies were selected for inclusion through a two-stage process. Titles and abstracts were examined for inclusion by one reviewer. Full manuscripts of selected citations were retrieved and assessed by one reviewer. The quality of the cost-effectiveness studies were assessed using a critical appraisal checklist adapted from the Drummond and Jefferson[109] and Eddy[110] checklists.

Results

Identified studies

The search retrieved 280 citations relating to cost-effectiveness (*Figure 5*). Two hundred and fifty-four articles were excluded at title stage, and 21 articles were excluded at abstract level. Four studies (corresponding to five references) were examined at full-text level[111–115] and three studies (corresponding to four references) were identified as meeting the inclusion criteria of the systematic review of economic evaluations.[111–113,115] This included the Evidence Review Group (ERG) report submitted to NICE for TA110[112] in which the addition of rituximab to CVP in first-line induction treatment was evaluated. Gomez *et al.*[114] was excluded from the review as this reference was unobtainable.

An economic model was described in two studies: an HTA monograph[113] and an ERG report.[112] Both studies are based on a critique undertaken by the ERG of the model submitted by the manufacturer (Roche) for TA110,[83] a single technology appraisal (STA).

Overall, three different economic models were identified.

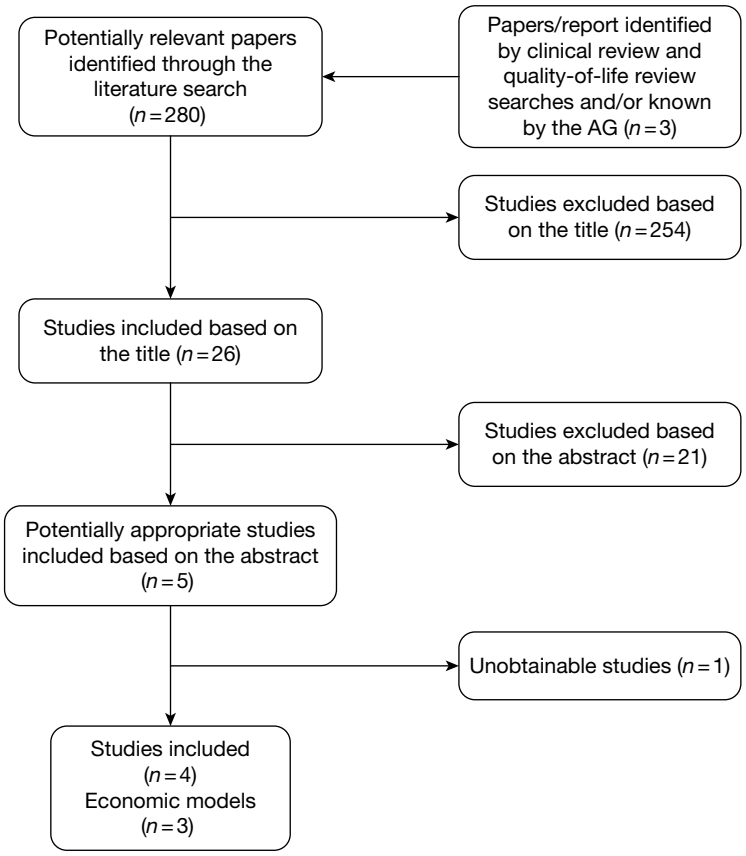


FIGURE 5 Flow diagram of economic evaluation selection/exclusion.

Summary of published cost-effectiveness studies

The three identified economic models[111–113,115] were similar and used a Markov approach. There were differences in the comparators used between the studies. Dundar *et al.*[112,113] and Hornberger *et al.*[115] evaluated the cost-effectiveness of the addition of rituximab to CVP only. Ray *et al.*[111] reported the cost-effectiveness of the addition of rituximab to a CVP, CHOP, MCP and CHVPi regimen.

Ray *et al.*[111] and Dundar *et al.*[112,113] adopted the perspective of the UK NHS and Personal Social Services (PSS) with costs and benefits discounted at an annual rate of 3.5%. Hornberger *et al.*[115] conducted an economic evaluation in the USA, with costs and benefits discounted at 3.0%.

The impact of main model parameters was examined in univariate sensitivity analyses (SAs)in all economic evaluations identified by the AG.[111–113,115] Probabilistic sensitivity analyses (PSAs) were performed in the two UK models only.[111–113]

The two UK economic evaluations produced broadly similar incremental cost-effectiveness ratios (ICERs) for the comparison of R-CVP with CVP. Dundar *et al.*[112,113] reported a cost per quality-adjusted life-year (QALY) gained of £8290 for the addition of rituximab to a CVP regimen in the MS[62] model. Ray *et al.*[111] reported an ICER of £8613 per QALY gained for the same comparison and reported an ICER of £10,676, £7455 and £8498 per QALY gained for the addition of rituximab to a CHOP, MCP and CHVPi regimen, respectively. The two UK economic evaluations[111–113] showed that the addition of rituximab to chemotherapy compared with chemotherapy alone has a cost per QALY gained under £20,000. In the US, Hornberger *et al.*[115] reported a cost per QALY gained of US$28,565 for the comparison between R-CVP and CVP.

A tabulated summary of key features and data sources for studies included in the review is presented in *Table 27*.

A full description of each of the three cost-effectiveness studies along with a quality assessment checklist is presented below.

Critical appraisal of economic evaluation

The included cost-effectiveness studies;[111–113,115] were assessed against a critical appraisal checklist adapted from the Drummond and Jefferson[109] and Eddy[110] checklists (*Table 28*).

Description and results of the published economic evaluations

Review of Ray et al. *An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of FL in the UK*

Overview The aim of the study was to estimate the cost-effectiveness of the addition of rituximab to four chemotherapy regimens (CVP, CHOP, MCP, CHVPi) for patients with advanced FL in the UK. The model used a Markov approach and followed patients over a lifetime in three possible health states (HSs): PFS; progressive disease and death. The study adopted the perspective of the UK NHS and costs and QALYs were discounted at 3.5%. The mean age of patients entering the model was 53 years old. This study was commissioned by Roche and was available as a full paper.

TABLE 27 Tabulated summary of UK cost-effectiveness studies

Parameters	Ray *et al.*[111]	Dundar *et al.*[112,113] (including ERG report)	Hornberger *et al.*[115]
Comparators	R-CVP vs CVP R-CHOP vs CHOP R-MCP vs MCP R-CHVPi vs CHVPi	R-CVP vs CVP	R-CVP vs CVP
Model structure	Markov model with three HSs: PFS; progressive disease; death	Markov model with three HSs: PFS; progressive disease; death	Markov model with three HSs: PFS; progressive disease; death
Age (years)	53	53	50
BSA at baseline	NR: M39021 trial[95,96]	NR	1.72
Time horizon	Lifetime (not specified)	10 years and 25 years	30 years
Sources of effectiveness evidence (first-line induction)	R-CVP vs CVP[95,96] R-CHOP vs CHOP[69,91] R-MCP vs MCP[93] R-CHVPi vs CHVPi[94]	R-CVP vs CVP[95,96]	R-CVP vs CVP[95,96] (only 40 months) Extrapolation based on observational studies
Sources of effectiveness evidence (second-line/progression)	Scotland and Newcastle Lymphoma Group[116]	Scotland and Newcastle Lymphoma Group[116]	Observational studies[5,27,28,117]
Utilities	PFS: 0.805 Disease progression: 0.618 Source: Oxford Outcome Study[118,119]	NR Source: Oxford Outcome Study[118,119]	PFS: 0.805 Disease progression: 0.618 Source: Oxford Outcome Study[118,119]
Base-case results (£/QALY gained)	R-CVP vs CVP: £8613 R-CHOP vs CHOP: £10,676 R-MCP vs MCP: £7455 CHVPi vs CHVPi: £8498	R-CVP vs CVP: £8290 (MS: 25 years) ERG estimate: £9015	R-CVP vs CVP: US$28,565

NR, not reported.

TABLE 28 Critical appraisal checklist of the included economic evaluations

Critical appraisal items		Ray *et al.*[111]	Dundar *et al.*[112,113] (including ERG report)	Hornberger *et al.*[115]
Modelling assessments should include				
1	A statement of the problem	Yes	Yes	Yes
2	A discussion of the need for modelling vs alternative methodologies	Yes	Yes	Yes
3	A description of the relevant factors and outcomes	Yes	Yes	Yes
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. (Note: *n* = no. of HSs within submodel)	Yes	Yes	Yes
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Yes No reference to a hierarchy of evidence	Yes No reference to a hierarchy of evidence	Yes
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data	Yes	Yes	Yes
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a SA	Yes	Yes	Yes
8	The results derived from applying the model for the base case	Yes	Yes	Yes
9	The results of the SAs; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold	Yes	Yes	Yes
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Yes	Yes	Yes
11	A description of the validation undertaken including: ■ concurrence of experts ■ internal consistency ■ external consistency ■ predictive validity	Unclear	Yes Model checked by the ERG	Unclear
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Unclear	Yes	Yes
13	A description of research in progress that could yield new data that could alter the results of the analysis	Unclear	Unclear	Unclear

Summary of effectiveness data The effectiveness in first-line induction was derived from four randomised Phase III clinical trials in patients with FL assessing the addition of rituximab to CVP,[95,96] CHOP,[91,92] MCP[93] and CHVPi.[94] Publicly available data were used, i.e. from journal manuscripts, as the authors did not have access to individual patient-level data for those trials. Ray *et al.*[111] estimated the risk of progression by fitting a Weibull and exponential distributions to the data for the 'chemotherapy' arm only. The exponential distribution was selected for CVP, CHOP and MCP, whereas CHVPi was modelled using a Weibull distribution. The best fit was selected after analyses of the R^2-value. Ray *et al.*[111] also calculated a HR for the addition of rituximab compared with chemotherapy alone derived from the PFS curves from the paper (through a calculation of the cumulative hazard by summing the negative log of the survival probabilities). These HRs were then applied to the estimated baseline curves to represent the risk of progression for patients receiving rituximab in addition to chemotherapy. The authors assumed that at the end of the PFS period, all patients progressed rather than dying. The rate of mortality while in PFS was assumed to be that reported in UK life tables. After relapse following first-line induction treatment, patients entered a 'progressive' HS (including subsequent relapses and lines of treatment) with patients remaining in this HS until death. The rate of progression

from the 'progressive' HS to death was calculated using registry data from the Scotland and Newcastle Lymphoma Group (SNLG) assuming an exponential distribution. Deaths from other causes were included using the rates reported in UK life tables. Utility values were estimated using the European Quality of Life-5 Dimensions (EQ–5D) and were extracted from the Oxford Outcome Study,[118,119] which was conducted in a cohort of 222 patients with FL in the UK. Patients in PFS were assumed to have a utility value of 0.805, whereas patients in the progressive HS had a utility value of 0.618. AEs were not included in the base-case analysis. However, a scenario analysis was conducted to estimate the impact of including additional costs associated with treating AEs and infusion site reactions on the cost-effectiveness of rituximab added to chemotherapy.

Summary of resource utilisation and cost data Drug costs were taken from the *Monthly Index of Medical Specialities* using the mean doses administered in the trials[91–93,95,96] (except for CHVPi). Administration costs were taken from the NHS reference costs and transformed into a monthly cost (£309 per month for chemotherapy alone and £430 per month for R-chemotherapy). Drug costs for patients in the 'progressive' HS were derived from the published literature and assumptions (£195 per month).[83,120] The model also incorporated the cost of routine management for patients in PFS (one outpatient visit every 3 months) and in the progressive HS (one outpatient visit every month: £103). The cost of AEs was not included in the base case.

Summary of cost-effectiveness In the base-case analysis (*Table 29*), the addition of rituximab to CVP, CHOP, MCP and CHVPi led to a gain of 0.914, 0.831, 1.184 and 0.458 discounted QALYs, respectively, compared with chemotherapy alone.[111] The incremental discounted cost of the addition of rituximab to chemotherapy was estimated to be £7878, £8872, £8826 and £3892, respectively. The ICER associated with the addition of rituximab to CVP, CHOP, MCP and CHVPi compared with chemotherapy alone was estimated to be £8613, £10,676, £7455 and £8498 per QALY gained, respectively.

One-way SAs showed that the results were most sensitive to the time horizon and whether or not the treatment effect extended beyond the trial period. PSAs were also conducted. The uncertainty regarding the estimates of costs and QALYs were expressed using cost-effectiveness acceptability

TABLE 29 Summary of the cost-effectiveness of the addition of rituximab to chemotherapy compared with chemotherapy alone (adapted from table 4 in Ray *et al.*[111])

Regimen	LY	QALY	Cost (£)	£/QALY gained
CVP vs R-CVP				
CVP	6.710	4.748	20,708	
R-CVP	7.764	5.392	28,582	**8613**
CHOP vs R-CHOP				
CHOP	7.887	5.504	20,922	
R-CHOP	8.842	6.335	29,794	**10,676**
MCP vs R-MCP				
MCP	7.954	5.563	20,900	
R-MCP	9.312	6.747	29,725	**7455**
CHVPi vs R-CHVPi				
CHVPi	7.900	5.508	29,621	
R-CHVPi	8.428	5.966	33,513	**8498**

curves (CEACs) and cost-effectiveness frontiers. There was a high probability that the addition of rituximab to chemotherapy has a cost per QALY gained of < £20,000.

Ray *et al.*[111] also conducted incremental analysis comparing across chemotherapy regimens. The authors reported that MCP was cost-effective compared with CVP alone (£235 per QALY gained). CHOP, CHVPi and R-CVP were dominated by MCP, as those regimens provided lower QALYs at a higher cost. Similarly, R-CHOP and R-CHVPi were dominated by R-MCP. This analysis assumed that the treatment effect extended over a lifetime. Ray *et al.*[111] also presented an additional scenario by restricting the treatment effect of the addition of rituximab to 53 months. Overall, the authors found that MCP dominated R-CVP and CHOP. R-MCP dominated R-CHVPi and CHVPi. R-CHOP was extendedly dominated by R-MCP.

Comments It was not possible for the AG to check the economic model as only the publication was available in the public domain. Based on the description of the model, this appears to be a reasonably well-conducted cost-effectiveness analysis. The generalisability of results from this study are, however, limited. The baseline age of the modelled cohort is not representative of patients with FL who are in first-line treatment in the UK (younger). Furthermore, the authors only explored the use of exponential or Weibull distributions to represent the rate of progression in patients treated in first-line induction. Alternative distributions might provide a better fit to the data. Similarly, the rate of progression in second line was modelled using an exponential distribution and no goodness-of-fit statistics were provided.

An important limitation is the source of effectiveness used for patients treated in first-line induction with CHOP, MCP and CHVPi, with or without rituximab. Responders to first-line induction with CHOP with or without rituximab were randomised to maintenance with interferon or SCT.[91,92] Responders to MCP with or without rituximab received maintenance interferon.[93] Similarly, the effectiveness for patients treated with CHVPi in first line with or without rituximab is confounded by the introduction of interferon during induction and the differences in treatment received post induction.[94] This is likely to overestimate the absolute gain in life-years (LYs)/QALYs associated with the addition of rituximab to chemotherapy. The model also did not consider that at the end of the PFS period, the outcome could be death rather than progression.

Some assumptions were also made by the authors and were not discussed. Patients were assumed to receive the same treatment post progression, irrespective of the choice of first-line treatment. Similarly, the source of effectiveness used to represent the rate of progression after relapse did not incorporate changes in the treatment pathways in the UK for relapsed patients (use of R-chemotherapy in combination with maintenance rituximab). It was also unclear from the study if patients were previously treated with rituximab or the type of chemotherapy received in first-line induction.

Finally, Ray *et al.*[111] conducted incremental analyses comparing across chemotherapy regimens. After discussion with clinical experts, the AG disagrees with this approach as the choice of chemotherapy is also based on patients' characteristics and not solely the effectiveness of the chemotherapy (see *Methods*, for further discussion).

Review of Dundar et al. *Rituximab for the first-line treatment of stage III–IV FL*

Two studies were available: an HTA monograph[113] and the ERG report.[112] Both studies are based on a critique undertaken by the ERG of the model submitted by the manufacturer (Roche) in TA110,[83] a STA.

There is no published work with a first-hand description of the model. Our review is based on the ERG report[112] for TA110,[83] as this provided more detailed description on the economic evaluation submitted by the manufacturer. The submission made by the manufacturer was not publicly available.

Overview The aim of the study was to evaluate the MS[62] that estimated the cost-effectiveness of the addition of rituximab to CVP for first-line treatment of patients with advanced FL in the UK. The economic evaluation submitted by the manufacturer shared several features with the model published by Ray *et al.*[111] The model used a Markov approach and followed patients over 25 years in three possible HSs: PFS, progressive disease and death. The study also adopted the perspective of the UK NHS, with costs and QALYs discounted at 3.5%. The mean age of patients entering the model was 53 years.

Summary of effectiveness data The effectiveness in first-line induction was derived from a randomised Phase III clinical trial in patients with FL assessing the addition of rituximab to CVP.[95,96] Log-logistic distributions were fitted to individual patient-level data from the trial to represent the risk of progression after first-line induction treatment. AEs were omitted. After relapse following first-line induction, patients entered a 'progressive' HS (which included subsequent relapses and lines of treatment), with patients remaining in this HS until death. The rate of progression from the 'progressive' HS to death was calculated using registry data from the SNLG assuming an exponential distribution. Deaths from other causes were included using UK life tables. Utility values were estimated using the EQ-5D and were extracted from the Oxford Outcome Study.[117,118] The utility values used for the PFS and 'progressive' HS were marked as commercial in confidence.

Summary of resource utilisation and cost data Patients were assumed to receive eight cycles of treatments (assigned to the first cycle in the model). The surveillance costs in PFS were calculated to be £32.33 per month assuming four annual oncology visits.[112] Drug costs for patients in the progressive HS were derived from the published literature and assumptions and were assumed to be £193.33 per month.[120]

Summary of cost-effectiveness In the base-case analysis, the addition of rituximab to CVP led to a gain of 1.251 discounted QALYs compared with chemotherapy alone. The incremental discounted cost of the addition of rituximab to chemotherapy alone was estimated to be £10,370. The ICER associated with the addition of rituximab to CVP compared with chemotherapy alone was estimated to be £8290 per QALY gained. One-way SAs showed that the results were most sensitive to the time horizon and treatment length and whether or not the treatment effect extended beyond the trial. PSAs were conducted and indicated that at a threshold of £30,000 per QALY gained, there was 100% probability that R-CVP was cost-effective compared with CVP. The ERG corrected errors identified in the MS[62] and made some modifications to the economic model (translation of gain in PFS into OS and use of a Weibull distribution to represent the risk of progression in the 'progressive' HS. The ICER estimated by the ERG was £9015 per QALY gained (with 64% of PFS translating into OS). If no OS gain was assumed, the ICER increased to £20,593 per QALY gained.

Comments made by the Evidence Review Group As the report[112] is based on a previous review of the economic model submitted by the manufacturer, the AG did not perform an independent assessment of this economic evaluation owing to resource constraints and the availability of a previous critic of the model (i.e. the ERG assessment). The ERG identified mistakes/inconsistencies after reviewing the economic model. More details are available in the ERG report.[111] In addition to the errors, the ERG highlighted some limitations in the manufacturer's model:

- The manufacturer assumed that most of the gain in PFS translated into a gain in OS (79% according to the ERG).
- The baseline age was not representative of the patients in the UK receiving first-line therapy.
- Utility values used – the manufacturer did not age adjust utility values, and utilities were calculated from a small sample size (especially for the 'progressive' HS).
- The progression rate for patients in the 'progressive' HS. The ERG indicated that the exponential distribution selected by the manufacturer did not provide a good fit to the data and that a Weibull distribution would provide a more reasonable fit. Furthermore, the ERG questioned data from the SNLG in the absence of details about the characteristics of included patients.
- The cost in the 'progressive' HS included the cost of first-line therapy, and therefore inflated the cost for patients remaining longer in the 'progressive' HS.

Review of Hornberger et al. *Economic evaluation of rituximab and CVP for advanced FL*

Overview The aim of the study was to assess the cost-effectiveness of R-CVP compared with CVP in the USA. The economic evaluation shared several features with the model assessed by the ERG in TA110[83,112,113] and Ray *et al.*[111] The model used a Markov approach and followed patients over 30 years in three possible HSs: PFS, progressive disease and death. The study adopted a societal perspective with costs and QALYs discounted at 3.0%. The mean age of patients entering the model was 50 years.

Summary of effectiveness data The effectiveness in first-line induction was derived from a randomised Phase III clinical trial in patients with FL assessing the addition of rituximab to CVP.[95,96] The PFS and OS Kaplan–Meier from the M39021 trial[95,96] was used for the first 4 years and extrapolated beyond the trial based on published findings of a long-term observational study.[5,28,29,117] An annual mortality rate of 6.9% was applied.

The utility values for the time spent in each HS was extracted from the Oxford Outcome Study.[118,119] The utility values for patients in progression-free and progression HS were 0.805 and 0.618, respectively. The economic model also incorporated the disutility associated with chemotherapy (–0.15), SCT (–0.20) and end of life (–0.30).[121] There is no indication on how long the disutility was assumed to be.

Summary of resource utilisation and cost data Unit drug costs were derived from Medicare J-codes using the Mosby 2006 drug costs. The model assumed a BSA of 1.72 m^2 and drug wastage was considered. Administration costs were derived from the number of hours of infusions and the cost per hour of administration from the current procedural terminology.[122] The models incorporated grade 3 and 4 AEs that had at least a 2% rate difference between the two arms. The cost of subsequent treatment regimens was derived from the cost of most common regimens recommended by the National Comprehensive Cancer Network. Maintenance after second-line induction for responders to chemotherapy was considered in the analysis.

Subsequent treatments had no impact on OS and were included only for costing purpose. Subsequent treatments were applied at the median TTP and 1 year thereafter. Salvage therapy was also included and it was assumed that 10% of patients undergo SCT as part of subsequent therapy. Finally, the economic evaluation included the cost of end of life.[123]

Summary of cost-effectiveness In the base-case analysis, the addition of rituximab to CVP led to a gain of 0.93 discounted QALYs compared with chemotherapy alone. The incremental discounted cost of the addition of rituximab to chemotherapy alone was estimated to be

US$26,439. The ICER associated with the addition of rituximab to CVP compared with chemotherapy alone was estimated to be US$28,565 per QALY gained.

One-way SAs showed that the results were most sensitive to utility values and the cost for a course of rituximab. Hornberger *et al.*[115] reported that none of the SAs generated a cost per QALY gained of > US$50,000 per QALY gained.

Comments It was not possible for the AG to check the economic model as only the publication was available in the public domain. Based on the description of the model, this appears to be a reasonably well-conducted cost-effectiveness analysis.[115] The generalisability of results from this study, however, may be limited as the study was conducted in the USA. Furthermore, the baseline age of the modelled cohort (50 years) was not representative of patients with FL in who were in first-line treatment in the UK. Hornberger *et al.*[115] provided a very detailed description of the derivation of costs. However, the description of clinical effectiveness was poor. It is unclear how the PFS and OS Kaplan–Meier were extrapolated after 4 years.

Assessment of the manufacturer's submission

There was one industry submission to NICE from Roche.[62] The MS[62] included a full report and an electronic model submitted in Microsoft Excel© version 12 (Microsoft Corporation, Redmond, WA, USA). The economic model submitted by the manufacturer was reviewed to check that the parameters presented in the report corresponded to those used in the economic model. The economic model included in the MS[62] was assessed using a critical appraisal checklist adapted from the Drummond and Jefferson[109] and Eddy[110] checklists (*Table 30*).

Description of the manufacturer's submission

Overview

The MS[62] used a state-transition model with individuals moving between four possible HSs: PFS/first-line induction treatment (PFS1); PFS/second-line treatment (PFS2); progressive disease; and death (*Figure 6*). The model compared the cost-effectiveness of the addition of rituximab to CVP, CHOP, MCP and CHVPi for patients with advanced FL in the UK. The starting age in the model was 60 years and patients were followed up for 25 years. The study adopted the perspective of the UK NHS, with costs and QALYs discounted at 3.5%. A tabulated summary of key features and data sources of the economic model included in the MS[62] is presented in *Table 31*.

Summary of effectiveness data

The effectiveness in first-line induction treatment was derived from four randomised Phase III clinical trials in patients with FL comparing the addition of rituximab to CVP,[95,96] CHOP,[91,92] MCP[93] and CHVPi.[94] Individual patient-level data from the M39021 trial from journal manuscripts[95,96] and the MS[62] were used to estimate the rate of progression among patients treated with CVP or R-CVP in first-line induction assuming a log-logistic distribution. Individual patient-level data for the trials that compared CHOP with R-CHOP, MCP with R-MCP and CHVPi with R-CHVPi[91–94] were not available to the manufacturer and therefore only publicly available data were used. A similar methodology to Ray *et al.*[111] was used by fitting a Weibull or exponential distribution (to the digitised data from the papers) to patients treated in first line with chemotherapy alone. The exponential distribution was selected for CHOP and MCP, whereas the Weibull distribution was chosen for CHVPi based on the R^2-value. A HR was then applied to the estimated curves for the first 53 months to estimate the reduction in the risk of progression for patients receiving rituximab in addition to chemotherapy. Deaths in PFS1 were derived from the number of deaths and follow-up duration from the M39021 trial.[95,96]

TABLE 30 Critical appraisal checklist of the economic model included in the MS[62]

Checklist		MS[61]
Modelling assessments should include		
1	A statement of the problem	Yes
2	A discussion of the need for modelling vs alternative methodologies	Yes
3	A description of the relevant factors and outcomes	Yes
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. Note: *n*= no. of HSs within submodel	Yes
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Yes
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	Yes
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Yes
8	The results derived from applying the model for the base case	Yes
9	The results of the SAs; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold	Yes
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Yes
11	A description of the validation undertaken including: concurrence of experts internal consistency external consistency predictive validity	Unclear
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Unclear
13	A description of research in progress that could yield new data that could alter the results of the analysis	Unclear

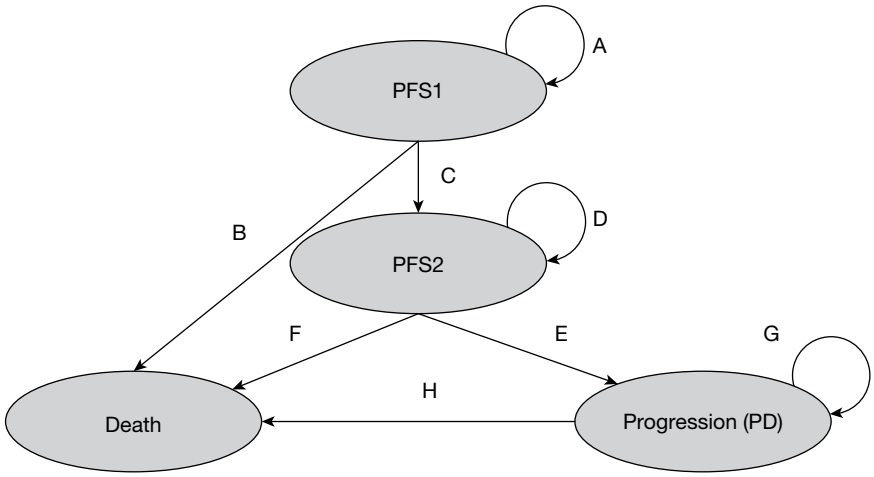


FIGURE 6 Model structure included in the MS[62] (reproduction of figure 3 from pp. 104 of the MS[62]).

TABLE 31 Tabulated summary of the economic model included in the MS[62]

Parameters	MS[61]
Comparators	R-CVP vs CVP
	R-CHOP vs CHOP
	R-MCP vs MCP
	R-CHVPi vs CHVPi
Model structure	State transition approach with four HSs: PFS1, PFS2, progressive disease, death
Age, BSA at baseline	Age 60 years; BSA 1.8528 m^2
Time horizon	25 years
Sources of effectiveness evidence (first-line induction)	R-CVP vs CVP[95,96]
	R-CHOP vs CHOP[91,92]
	R-MCP vs MCP[93]
	R-CHVPi vs CHVPi[94]
	Parametric extrapolation (log-logistic, Weibull, exponential)
Sources of effectiveness evidence (second line/progression)	EORTC 20981 trial;[74,75] inclusion of second-line maintenance
	Parametric extrapolation (exponential)
Utilities	PFS1: 0.88
	PFS2: 0.79
	Progressive disease: 0.62
	Source: Oxford Outcome Study[118,119]
Base-case results (£/QALY gained)	R-CVP vs CVP: £1529–5611
	R-CHOP vs CHOP: £5758
	R-MCP vs MCP: £4861
	R-CHVPi vs CHVPi: £9251

The effectiveness in PFS2/second-line treatment was based on data from the EORTC 20981 trial[74,75] conducted among patients treated with CHOP or R-CHOP with or without maintenance rituximab in second line. Digitised data from the paper[74,75] were used in the absence of individual patient-level data. The manufacturer used exponential distributions to estimate the risk of progression. The manufacturer stated that:

> In order to avoid overcomplicating the model, the transition probabilities of progressing from PFS2 were not varied over time. Varying the probabilities over time would require tracking patients' progression within the model and would result in an exponential increase of the size and complexity of the model with limited impact to the cost effectiveness of rituximab in first-line.

The most up-to-date data from the EORTC 20981 trial[74] were used to estimate the progression rate from PFS2 to the progressive HS, and from the progressive HS to death [post-progression survival (PPS)]. The PPS have been calculated as a function of PFS and OS, assuming that the rate of progression in PPS equalled the sum of the rate of progression in OS and PFS. The manufacturer also attempted to apply a rule so that patients treated with rituximab in first-line induction and who relapse within 6–12 months would not receive rituximab in second-line induction.

Utilities were extracted from a study commissioned by the manufacturer (Oxford Outcomes Study).[118,119] The following utility values were used in the economic model; PFS1 = 0.88 (disease free); PFS2 = 0.79 (remission/full response); progressive disease = 0.62. AEs were not included in the MS.[62]

Summary of resource utilisation and cost data

Drug costs were taken from the *British National Formulary* (BNF),[86] using the planned dose from the trials. Administration costs were taken from NHS reference costs. The manufacturer also assumed 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 HS (£500.53 per month) were derived from the cost used in the MS[62] for an ongoing NICE appraisal[124] from the post-protocol treatment from the EORTC 20891 trial[74,75] and the cost of palliative care in the UK.[125]

Summary of cost-effectiveness

Two analyses were presented for R-CVP compared with CVP. The first analysis fitted separate curves to each arm using individual patient-level data, whereas the second analysis assumed a HR (for R-CVP) for the first 53 months and fitted a parametric curve to CVP using the same approach as for CHOP, MCP and CHVPi.

In the base-case analysis, the addition of rituximab to CVP, CHOP, MCP and CHVPi led to a gain of 0.867/0.443, 1.096, 1.289 and 0.675 discounted QALYs compared with chemotherapy alone, respectively. The incremental discounted cost of the addition of rituximab to chemotherapy was estimated to be £1325/£2486, £6312, £6268 and £6247, respectively. Thus, the addition of rituximab to CVP, CHOP, MCP and CHVPi compared with chemotherapy alone resulted in an ICER of £1529/£5611, £5758, £4861 and £9251 per QALY gained, respectively (*Table 32*).

One-way SAs showed that the results were robust to parameter changes with none of the SAs increasing the ICER above £20,000 per QALY gained. PSAs were conducted. The PSA results indicated that the addition of rituximab to chemotherapy compared with chemotherapy alone was highly cost-effective assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY gained. No incremental analysis was presented to compare across chemotherapy regimens.

Critique of the manufacturer's submission

The AG reviewed the economic model and report included in the MS.[62] A detailed critique is presented below. In summary, there are concerns with the MS[62] analyses.[62] Errors and inconsistencies were identified in the economic model. The model had also limitations relating to the source of effectiveness for patients treated in first or second line. For readability, we critique each section in turn.

Review of previous analyses and quality-of-life data

No economic review or quality-of-life reviews were included in the MS.[62]

Sources of effectiveness for CHOP, MCP and CHVPi with or without rituximab

The trials used[91–94] were likely to overestimate the effect of rituximab given that responders to first-line induction treatment received subsequent treatments with interferon maintenance or SCT (see *Chapter 3*, *Summary of trials*). This issue was not discussed in the MS.[62]

Method used to estimate the rate of progression in the absence of patient-level data

Owing to the lack of individual patient-level data, the manufacturer assumed that the TTP was represented by either a Weibull or an exponential distribution, with these distributions estimated using ordinary least squares regression method. This approach is commonly used in

TABLE 32 Summary of the cost-effectiveness of the addition of rituximab to chemotherapy compared with chemotherapy alone included in the MS[62]

Regimen	LYs	QALY	Cost (£)	£/QALY gained
CVP vs R-CVP				
CVP	7.618	5.828	43,061	
R-CVP	8.386	6.695	44,386	**1529**[a]
CVP	7.342	5.544	44,570	
R-CVP	7.668	5.987	47,056	**5611**[b]
CHOP vs R-CHOP				
CHOP	8.279	6.479	42,717	
R-CHOP	9.407	7.575	49,029	**5758**
MCP vs R-MCP				
MCP	8.332	6.532	42,072	
R-MCP	9.671	7.821	48,340	**4861**
CHVPi vs R-CHVPi				
CHVPi	8.297	6.487	47,885	
R-CHVPi	9.039	7.162	54,132	**9251**

a Using individual patient-level data.
b Same approach as for CHOP, MCP and CHVPi.

health economic models when only data from manuscripts are available. However, it appears that there a number of errors and inconsistencies in the process used by the manufacturer to estimate the exponential distribution. By definition, the exponential distribution is composed of only one parameter (λ), as the rate is constant and does not vary with time. However, the manufacturer fitted a linear regression model ($y = \alpha \times t + \lambda$) to the transformed data (log scale) that contained two parameters: λ (constant) and α (variable time dependent). In some parts of the economic model, the rate of progression was calculated using λ only or the sum of λ and α. The inconsistency in the approach used limits the interpretation of the estimated coefficients used throughout the economic model. Furthermore, this approach is not correct, as this sometimes includes or excludes a time-dependent variable. The linear model has to be of the following form in order to estimate the parameter of the exponential distribution: $y = \alpha \times t$.

Inconsistencies and errors were identified between the risk of progression presented in the report and the risk of progression used in the economic model, notably in second line. In most cases, the fitted exponential distribution (using an ordinary least squares methodology) was not found to provide a reasonable fit to the data. Therefore, it appears that the manufacturer adjusted the parameters of the exponential distribution 'manually' by adding extra parameters in order to provide a reasonable visual fit to the data. This was not discussed by the manufacturer in the report and was identified by the AG only after review of the economic model. In some instances, the unadjusted coefficients were used (instead of the coefficient artificially adjusted to fit the data) in the economic model. For example, considering the PFS for patients treated with R-CHOP as induction in second line and maintenance with rituximab (*Figure 7*). The curve presented by the manufacturer in the report (grey line) was estimated after the addition of extra parameters (manual adjustment). However, in the economic model the dashed grey curve (before adjustment) was used (estimated by the AG), which provided a poorer fit.

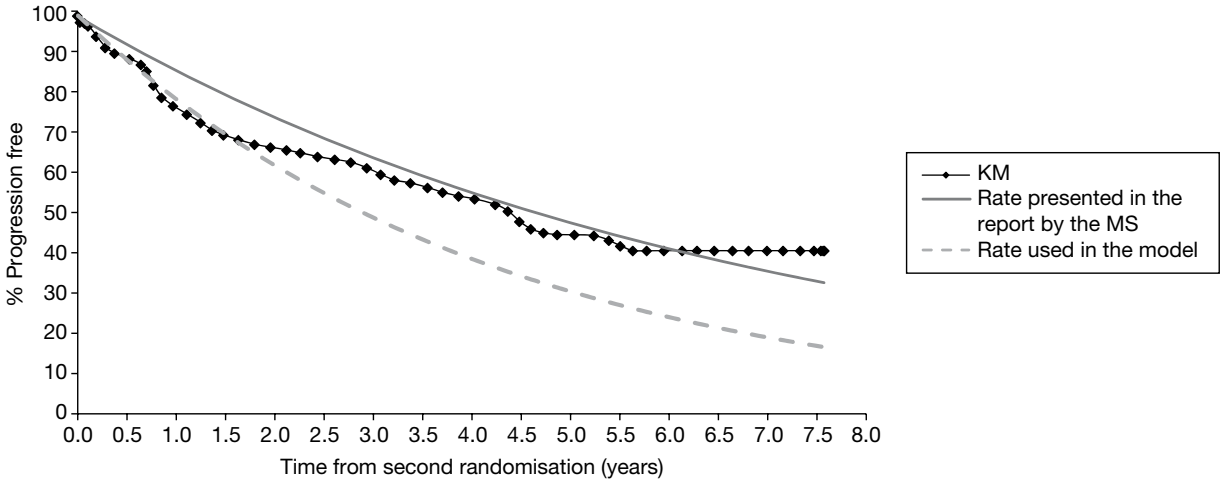


FIGURE 7 Kaplan–Meier plot and exponential distributions presented in the MS[62] and used in the economic model for patients that respond to R-CHOP second-line induction treatment and receive maintenance rituximab. KM, Kaplan–Meier.

Approach used to estimate the hazard ratio

The HRs were calculated by taking the cumulative hazard (estimated by the sum of the negative log of the survival) from the PFS Kaplan–Meier curve estimated from the appropriate trials. The AG acknowledges that the approach was necessary in the absence of individual patient-level data. However, the AG note that such an approach might introduce bias, as the calculated cumulative hazard is dependent on the number of point estimates considered. A better approach would be to estimate the HR from the baseline parametric survival curve.

Duration of benefits

The manufacturer assumed that the treatment effect (HR) lasts 53 months based on the median follow-up duration in the M39021 trial.[95,96] However, the follow-up was different in other trials used.[91–94]

Rule for patients previously treated with rituximab

The manufacturer wished to apply a rule whereby patients that relapsed within 6–12 months after first-line induction treatment with rituximab would not be eligible for rituximab in second-line treatment if previously exposed to rituximab. However, the decision of the manufacturer to simplify the economic model structure meant that several assumptions had to be made as the model was not able to track patients over time.

Treatment pathway

The manufacturer assumed that patients can receive only CHOP or R-CHOP in second-line treatment (followed, or not, by maintenance rituximab). Discussion with clinical experts indicated that CHOP-containing regimens are aggressive and therefore mainly used in younger patients. Older patients are likely to receive less aggressive chemotherapy regimens, such as FC with or without rituximab. Furthermore, clinical experts indicated that anthracycline-containing regimens (CHOP, MCP, CHVP) should only be used once in a lifetime and therefore patients previously treated with anthracycline regimens are likely to receive SCT in second line if they are fit enough or less aggressive chemotherapies (FC) if they are not considered to be sufficiently fit.

Source of effectiveness for patients treated in second line

The manufacturer used data from the EORTC 20981 trial[74,75] to estimate the risk of progression for patients treated with CHOP or R-CHOP in second line with or without maintenance.

However, patients in this study were rituximab naive, i.e. not previously treated with rituximab. The applicability of outcomes from this study to patients previously treated with rituximab is unclear. Furthermore, because data from second randomisation (i.e. after response induction) were used, the time spent in second-line induction (where the risk is zero for responders) was missing from calculations of PFS and OS. Furthermore, outcomes for non-responders were missed.

Estimation of post-progression survival

The manufacturer estimated PPS as a function of PFS and OS from the EORTC 20981 trial.[74,75] The AG, however, has some concerns about the approach used by the manufacturer. The manufacturer calculated PPS as the additive risk of OS and PFS (using the coefficients of the exponential distribution) so that PPS = OS + PFS. It is unclear why the addition of the coefficient of PFS and OS would be equal to the coefficient of PPS. Furthermore, the manufacturer used direct coefficients of the exponential distribution to estimate PPS before their 'manual adjustment' (curves are artificially modified to fit the data). This means that the curves for OS and PFS used to calculate PPS no longer fitted the data (*Figures 8* and *9*). Finally, the manufacturer used the combined data for patients randomised to observation or maintenance, therefore implying that the PPS would be the same following CHOP or R-CHOP induction.

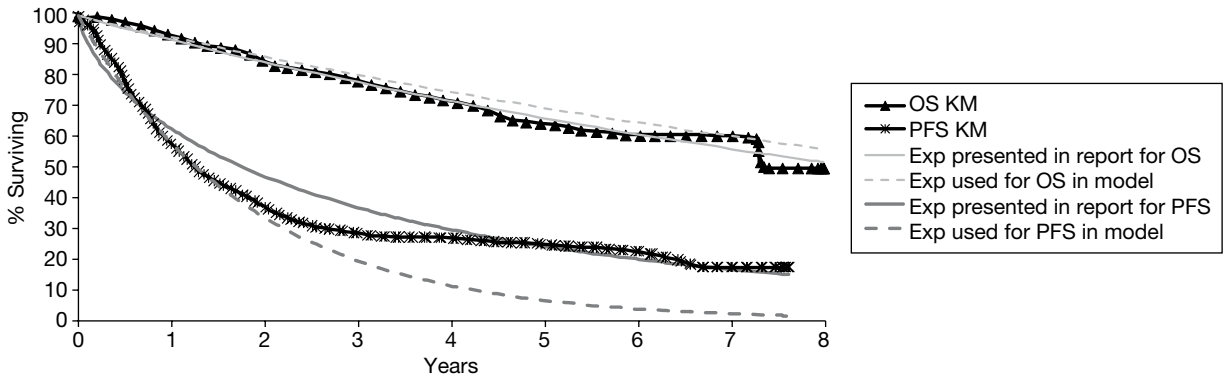


FIGURE 8 Kaplan–Meier plot and exponential distribution used to calculate PPS reported in the MS[62] and actually used in the economic model for patients receiving observation after response to second-line induction treatment. Exp, exponential distribution; KM, Kaplan–Meier.

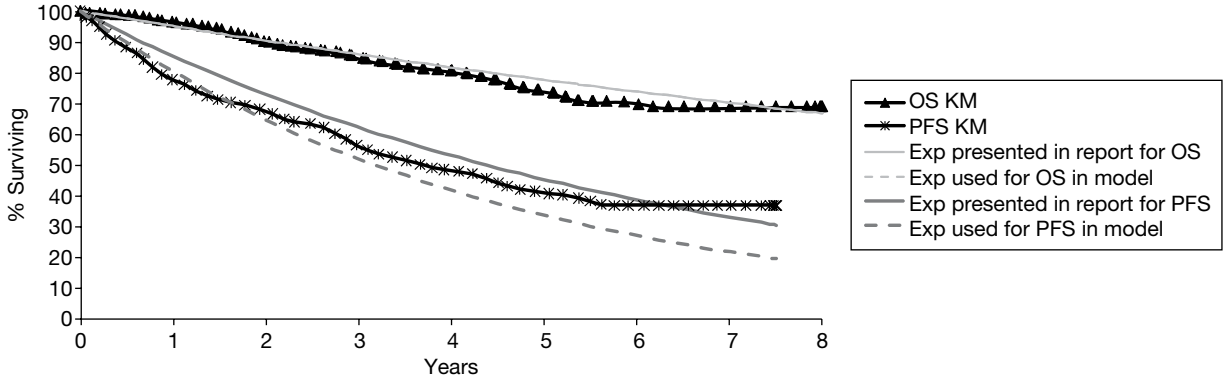


FIGURE 9 Kaplan–Meier plot and exponential distribution used to calculate PPS reported in the MS[62] and actually used in the economic model for patients receiving maintenance rituximab after response to second-line induction treatment. Exp, exponential distribution; KM, Kaplan–Meier. Note: The curve for OS used in the model is superimposed on the curve for OS presented in the report as this was derived correctly by the MS.[62]

Model structure

Although Markov models are commonly used for oncology treatments, the Markov approach requires assumptions and can be inflexible. The manufacturer used exponential distributions to 'avoid over-complicating' the model. However, in most cases, the exponential distribution did not fit the data well.

Adverse events

The MS[62] did not include the impact of AEs either in terms of costs or impact on quality of life, stating that there is no clinically significant difference between the rates and/or severity of AEs observed in the rituximab arms of each of the four first-line clinical trials[91–96] when compared with the respective comparator arms. However, the clinical effectiveness review indicated that a greater number of blood and bone marrow AEs occurred in the R-chemotherapy arm than in the chemotherapy-alone arm, for example neutropenia, leucocytopenia. Despite these AEs not resulting in a difference in infection rates and thus being clinically significant, they would still incur costs to treat and their exclusion might bias the cost-effectiveness in favour of rituximab.

Treatment/management costs

Several errors/inconsistencies were identified by the AG after review of the economic model. First, the planned number of cycles in the EORTC 20981 trial[74,75] (used to represent second-line treatment) is six cycles of CHOP or R-CHOP. Assuming a cost per cycle of £1462 for R-CHOP (estimated by the manufacturer), the maximum cost that a patient can incur is £8772 (£1462 × 6). In the economic model, the cost for patients treated with R-CHOP (accounting for the fact that some patients receive less than the planned dose owing to progression) was estimated to be £11,305 by the MS.[62] This is because of an error in the translation between month and cycle. The same error was found for the calculation of the cost of administration in second line.

The MS[62] also used a complicated formula to estimate the cost associated with maintenance based on the area under the curve from the most up-to-date EORTC 20981 trial data.[74] The cost was then applied to the first cycle in the economic model. The AG had some difficulty in following the logic; however, we believe that costs were discounted twice.

Inconsistencies were also identified in the approach used to estimate the management costs in the 'progressive' HS. The manufacturer calculated a cost per month including the cost associated with the post-protocol treatment from the EORTC 20981 trial[74,75] and the cost of palliative care.[125] This had the effect of inflating the cost for patients who spend a longer time in the 'progressive' HS and bias the cost-effectiveness in favour of rituximab.

The manufacturer also assumed no drug wastage. This might not be true if chemotherapies are not given in a large centre and vial sharing is not possible.

Utilities

The economic model included in the MS[62] used utility values from the Oxford Outcomes Study.[118,119] The manufacturer assumed that the utility in PFS1 was similar to the utility of patients considered to be disease free (0.88, 95% CI 0.81 to 0.95). The utility for patients in remission/full response to therapy (0.79, 95% CI 0.72 to 0.86) was used to represent the utility for patients in PFS2. Finally, the utility for progressive disease was assumed to be 0.62 (95% CI 0.48 to 0.76). As suggested by the ERG in the ongoing appraisal for first-line maintenance,[126,127] it seems inappropriate to assume that patients in PFS1 and PFS2 have different utility values given that these patients are in remission. This choice by the manufacturer to use the utility for patients considered to be 'disease free' to represent the utility in patients in PFS1 also appears to be inappropriate as these patients are in a 'remission' state and not 'disease free'.

Other assumptions

The MS[62] assumed that there were no resistance effects among patients previously treated with rituximab implying that the efficacy would be equal regardless of previous treatment. The MS[62] referred to two studies to support the assumption of the absence of a resistance effect to rituximab.[128,129] However, the AG does not believe that the data from these two studies provide conclusive evidence that the resistance of rituximab is not a consideration. Further studies identified by the AG in other types of lymphoma[130–132] suggest that there might be a resistance effect to rituximab.

Relevance of cost-effectiveness evidence for NICE decision-making

Three modelling studies (corresponding to four references)[62,111–113] are potentially relevant for UK decision making. However, there are number of issues in the economic models identified that require further considerations (see *Systematic review of existing cost-effectiveness evidence* and *Assessment of the manufacturer's submission*). These include:

- The baseline age of the modelled cohort. The baseline age was not representative of the age of patients receiving first-line treatment in the UK.
- The sources of effectiveness for patients treated with CHOP, MCP and CHVPi in first-line induction treatment with or without rituximab. The effectiveness values were derived from trials where patients have received subsequent treatment, such as interferon maintenance or SCT. Further details are available in *Chapter 3* (see *Summary of trials*).
- The source of effectiveness in patients receiving second-line treatment induction with or without maintenance rituximab. The effectiveness values were derived from patients not previously treated with rituximab. Additionally, in the MS,[62] the time period when patients receive second-line induction treatment and outcomes for non-responders were not captured.
- The choice of utility values. There was a mismatch between the utility values used and the HSs.
- Costs for patients treated in second-line or in progressive disease; errors/inconsistencies were identified in the model in the MS.[62]
- Constraints imposed by the chosen model structure. The identified models used a Markov approach that required strong assumptions about timing and progression rate. For example, the manufacturer fitted exponential distributions in patients treated in second line and these did not fit the data.
- Incorporation of death from non-FL causes.

Independent economic assessment

Methods

Introduction

The review of published economic evaluations[111–113,115] were used. The main limitations identified were the description of the treatment pathway, the sources of effectiveness and assumptions that were made.

Previous guidance by NICE (TA110) was issued for the use of rituximab in combination with CVP for the first-line induction treatment of FL.[83] Since this guidance was produced, the licence of rituximab was extended for use in combination with any chemotherapy-containing regimen.[85] In 2008, NICE issued guidance recommending the use of rituximab in combination with chemotherapy in second-line induction treatment and for rituximab monotherapy as

maintenance treatment in patients responding to second-line induction chemotherapy with or without rituximab.[72] At the time of writing, NICE is currently considering the use of rituximab monotherapy for first-line maintenance treatment of patients responding to first-line induction treatment with rituximab in addition to chemotherapy.[127] The final guidance is expected to be issued after delivery of this assessment report. A summary of previous guidance issued by NICE is presented in *Chapter 1* (see *Current service provision* and *Table 4*).

This section describes the development of a de novo economic model addressing the main limitations identified in existing economic evaluations.[62,111–113,115] The key objective of the economic assessment is to address the cost-effectiveness of the addition of rituximab to chemotherapy in previously untreated, stage III/IV, patients with FL in England and Wales in line with changes in the licensing of rituximab[85] and previous guidance issued by NICE.[73,82]

Population appraised

The population under assessment is previously untreated, symptomatic, stage III–IV patients with FL in England and Wales.

Interventions/comparators

A probabilistic decision analytic model was developed to estimate the costs and QALYs of the addition of rituximab to three chemotherapy regimens: CVP, CHOP and MCP. The choice of chemotherapies was primarily based on available data[91–96] and the robustness of the evidence in order to address the NICE scope defined for this appraisal.[133]

No comparison was provided for the addition of rituximab to a CHVP regimen with interferon. This was because of issues in the design of the FL2000 trial,[94] which compares the addition of rituximab with a CHVP regimen with interferon. There were differences in the interventions in the FL2000 trial.[94] The control/comparator group received 12 courses of a CHVP regimen administered every 28 days for six courses and then every 56 days for an additional six courses combined with 18 months of interferon, whereas the active treatment group received only six courses of a CHVP regimen administered every 28 days in addition to rituximab, with interferon delivered for 18 months. Clinical opinion suggests that CHVP regimens are very rarely used in the UK, and that interferon might not be used because of toxicity.

Description of the de novo economic model

The main source of effectiveness data were obtained from the three main trials conducted in first-line induction treatment which compared CVP against R-CVP,[95,96] CHOP against R-CHOP[91,92] and MCP against R-MCP.[93]

The economic model was programmed using R software® (The R Foundation for Statistical Computing, Vienna, Austria), version 2.11.1, and uses a 25-year time horizon in the base case to capture costs and benefits as in the MS.[62] Shorter horizons (5 years, 10 years) and a lifetime horizon are presented in SAs. In accordance with the NICE guide for the methods of technology appraisal,[97] the economic model adopts the perspective of the UK NHS and PSS with costs and benefits discounted at an annual rate of 3.5%.

Treatment pathway and clinical practice in the UK

The modelled treatment pathway incorporates guidance issued by NICE[73,83] for the treatment of patients with FL in England and Wales and tries to replicate the treatment pathway observed in clinical practice. Owing to the possibility that first-line maintenance rituximab could be recommended by NICE, an alternative scenario including this option has been included.

Clinical opinion was sought and two clinicians completed a short questionnaire via a telephone interview. A summary of the answers is presented in *Table 33*. Overall, clinical opinion suggested that:

- In clinical practice, patients relapsing within 6–12 months after rituximab in combination with chemotherapy are not likely to be retreated with rituximab as recommended by the ESMO guideline.[19] An exception was for patients previously treated with R-CVP.
- Anthracycline-containing regimens (CHOP, MCP) can be given only once in a lifetime. Thus, in second-line treatment, patients previously treated with an anthracycline-containing regimen will be considered for alternative treatments with salvage therapy [high-dose chemotherapy (HDT)] with or without rituximab in addition to ASCT, if aged < 65 years and are fit enough. Older or unfit patients are likely to receive less aggressive chemotherapies with or without rituximab, such as FC (note: this reflects the view of the clinical experts consulted by the AG). Rituximab may not to be given in second line as part of the salvage treatment for those patients previously treated with rituximab that relapse within 6–12 months after first-line induction treatment.
- Patients who are not in complete or partial remission at the end of first-line induction treatment (i.e. stable disease) with chemotherapy with or without rituximab are likely to be offered second-line treatment despite the absence of progression.

Clinicians were only asked to define the treatment pathway in patients treated with CVP- or CHOP-containing regimens with or without rituximab. The pathway for MCP and R-MCP were assumed to be identical to CHOP and R-CHOP on the rationale that both were anthracycline regimens. The AG stresses that the treatment pathway defined in *Table 33* is a simplification of treatment options given in second line and acknowledges that the treatment decisions taken includes other parameters, such as the presence of comorbidities and patient's preferences.

The treatment pathways used in the economic model are presented in *Figures 10–13*, based on our discussions with clinical experts (see *Table 33*) and previous guidance issued by NICE.[72,82] Within the model, an age cut-off of 65 years was selected to classify eligibility for treatment in second line; however, the AG acknowledges that in clinical practice, patient age would not be the sole criteria as older patients who were fit enough may be eligible for SCT. Non-responders that did not progress at the end of treatment induction, were assumed to receive second-line treatment at the end of first-line induction treatment. Furthermore, we considered early relapse as relapse within 12 months after the start of treatment.

For the scenario analysis, clinical opinion was sought to determine the treatment pathway after first-line maintenance treatment in patients treated in first-line induction with rituximab.

TABLE 33 Summary of the 'most likely' treatment options in patients treated in first-line induction with CVP or CHOP, with or without rituximab, as indicated by clinical experts

Response status and time of relapse	Age (years)	First-line therapy			
		CVP	R-CVP	CHOP	R-CHOP
Relapse within 6 months **after start** of therapy (non-responders)	< 65	R-CHOP	R-CHOP	R-HDT (± ASCT)	HDT (± ASCT)
	≥ 65	R-FC	R-FC	R-FC	FC
Responders at 6 months, but relapse **within 6 months after end** of therapy	< 65	R-CHOP	R-CHOP	R-HDT (± ASCT)	HDT (± ASCT)
	≥ 65	R-FC	R-FC	R-FC	FC
Responders at 6 months, but relapse **> 6 months after end** of therapy	< 65	R-CHOP	R-CHOP	R-HDT (± ASCT)	R-HDT (± ASCT)
	≥ 65	R-FC	R-FC	R-FC	R-FC

This is largely unknown, as first-line maintenance is not currently part of clinical practice. After discussion with clinical experts, the treatment pathway presented in *Table 34* was used in the economic model for responders to first-line induction with rituximab in addition to chemotherapy.

Note that the choice of second-line treatment for patients treated with chemotherapies only (i.e. without rituximab) in first-line induction was not amended (see *Figures 10–13*), as first-line maintenance is only considered an option by NICE in the ongoing appraisal for patients treated with rituximab in addition to chemotherapy in first-line induction therapy.

In addition to the base case, a range of SAs were conducted exploring the impact of the treatment pathway. As described later (see *Effectiveness in patients treated with CHOP with or without rituximab in second line*), there is a gap between evidence available and the treatment in clinical practice. No robust evidence were available for the effectiveness of FC-containing regimens with or without rituximab in patients aged ≥ 65 years at the time of relapse after first-line induction treatment. There were also no trials identified providing a direct comparison of ASCT in addition to salvage therapy with HDT with or without rituximab in patients with relapsed FL. Finally, the identified studies in patients with relapsed FL[74,75,134] were conducted in cohorts of patients with FL that were not previously treated with rituximab (see *Resistance to rituximab in patients previously exposed to rituximab treatment*).

The following assumptions were explored in SAs:

- Patients previously treated with R-CVP not being retreated with rituximab if relapsing < 12 months after the start of treatment (in the base case, those patients receive rituximab despite early relapse).
- Patients previously treated with an anthracycline-containing regimen and aged < 65 years old receiving CHOP or R-CHOP in second line (in the base case, those patients receive salvage therapy with or without rituximab ± ASCT).
- Patients aged > 65 years old receiving a CHOP-containing regimen (CHOP or R-CHOP) (in the base case, those patients receiving FC or R-FC).
- Patients receiving second-line treatment after progression only (in the base case, patients with stable disease at the end of treatment induction are considered to be non-responders and undergo further line of treatment).

An additional scenario is also presented assuming that patients responding to first-line induction treatment with rituximab in combination with chemotherapy receive first-line maintenance rituximab for up to 2 years. This scenario is presented to explore the potential impact of the addition of first-line maintenance into the treatment pathway if NICE issue positive guidance. No final guidance was issued by NICE at the time of writing of this report.[127]

TABLE 34 Treatment pathway incorporating maintenance

		Second-line treatment	
Response status and time of relapse	**Age (years)**	**R-CVP**	**R-CHOP/R-MCP**
Relapse within 12 months **after start** of induction therapy (i.e. relapse after about < 6 months after start of maintenance)	< 65	CHOP	R-HDT (± ASCT)
	≥ 65	FC	FC
Relapse after 12 months **after start** of induction therapy (i.e. relapse after > 6 months after start of maintenance)	< 65	R-CHOP	R-HDT (± ASCT)
	≥ 65	R-FC	R-HDT (± ASCT)

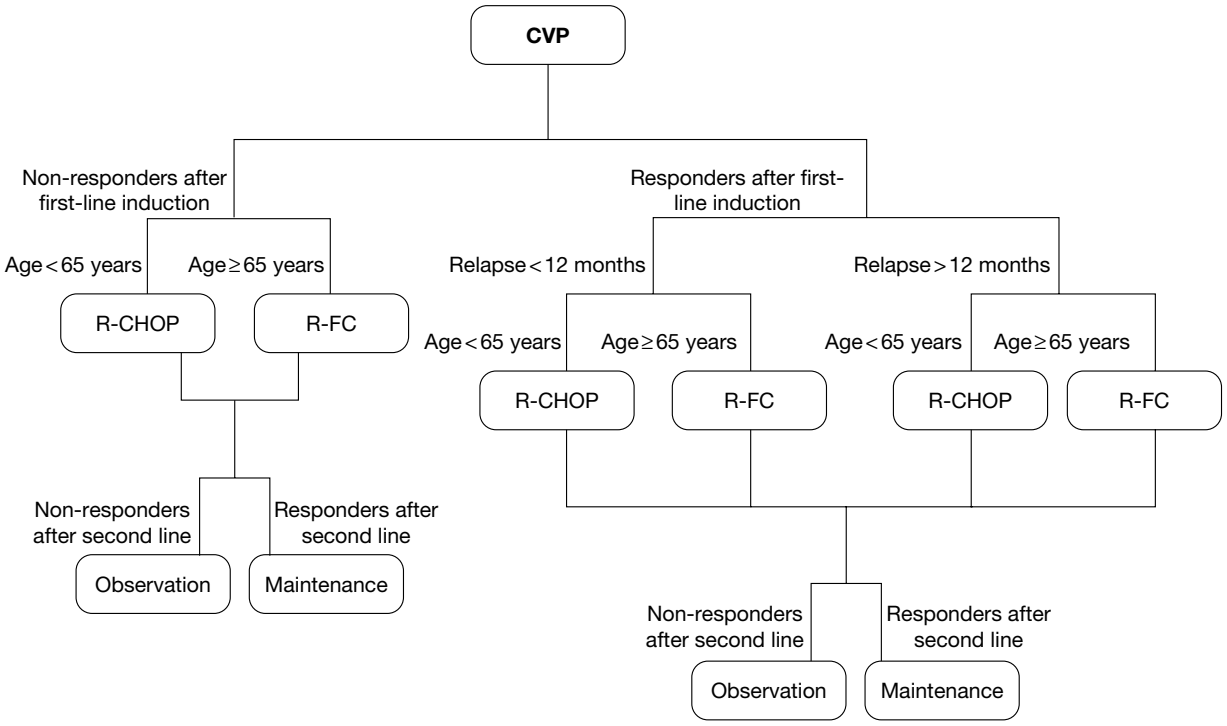


FIGURE 10 Treatment pathways modelled in the economic model for CVP.

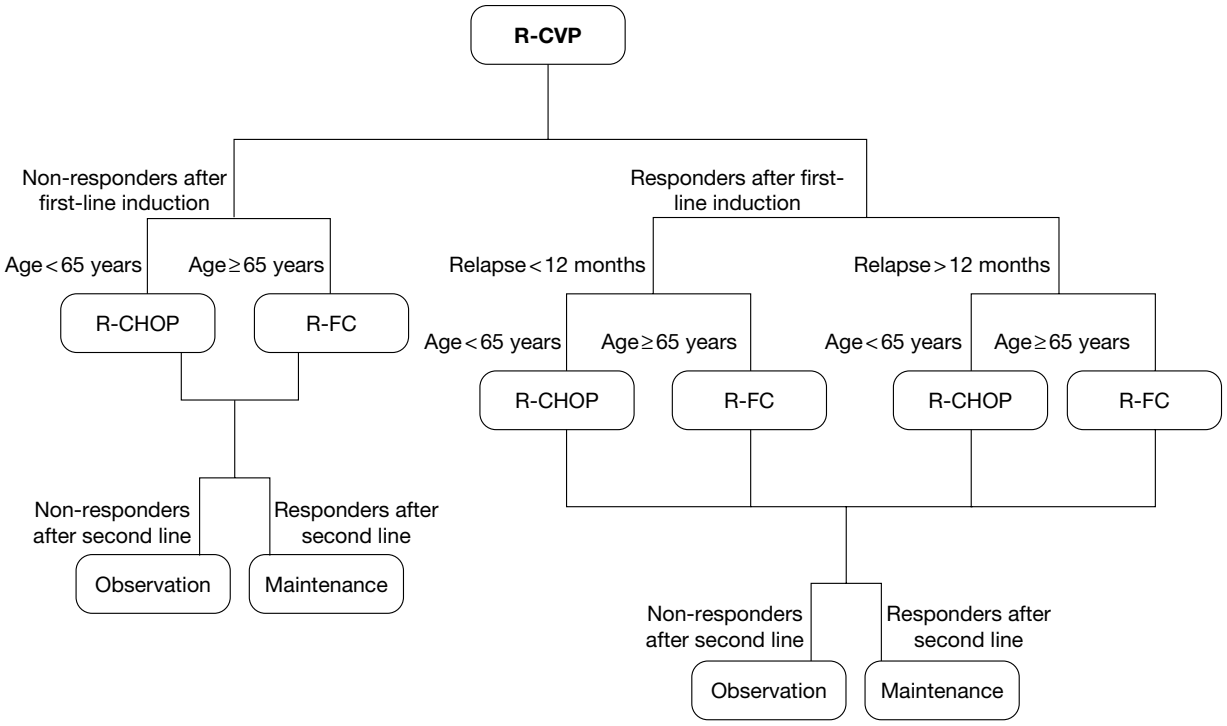


FIGURE 11 Treatment pathways modelled in the economic model for R-CVP.

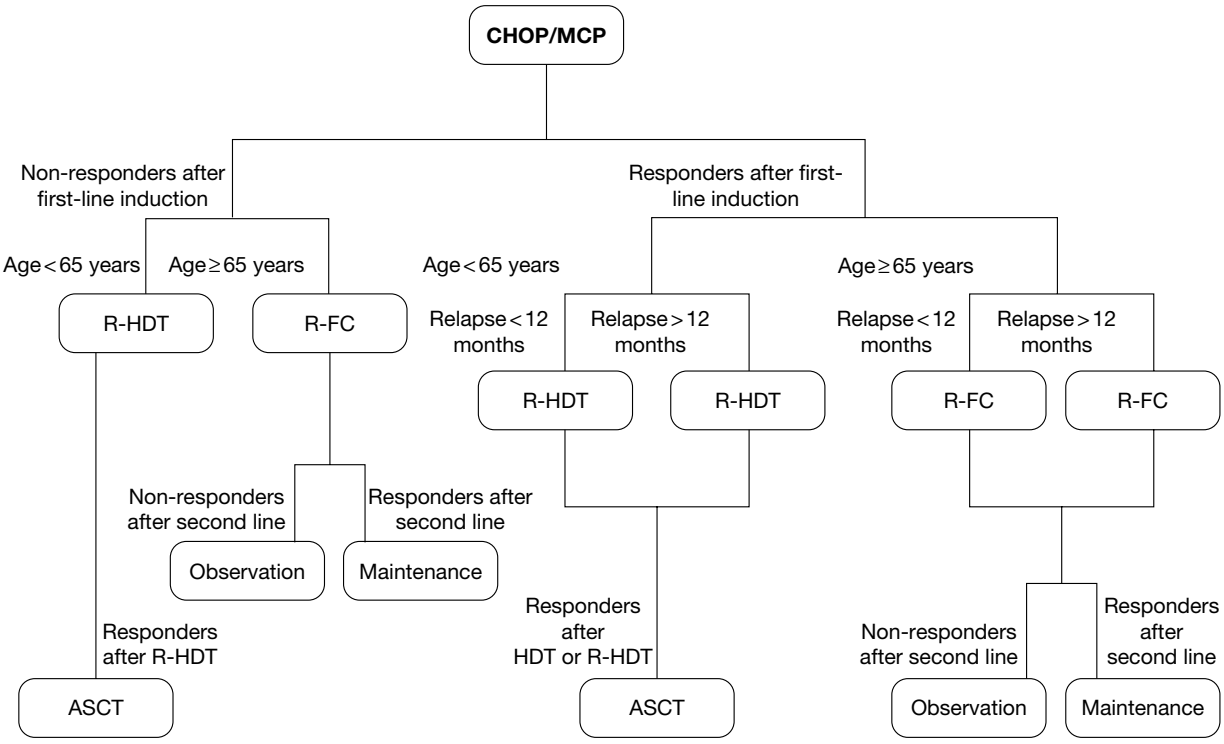


FIGURE 12 Treatment pathways modelled in the economic model for CHOP/MCP.

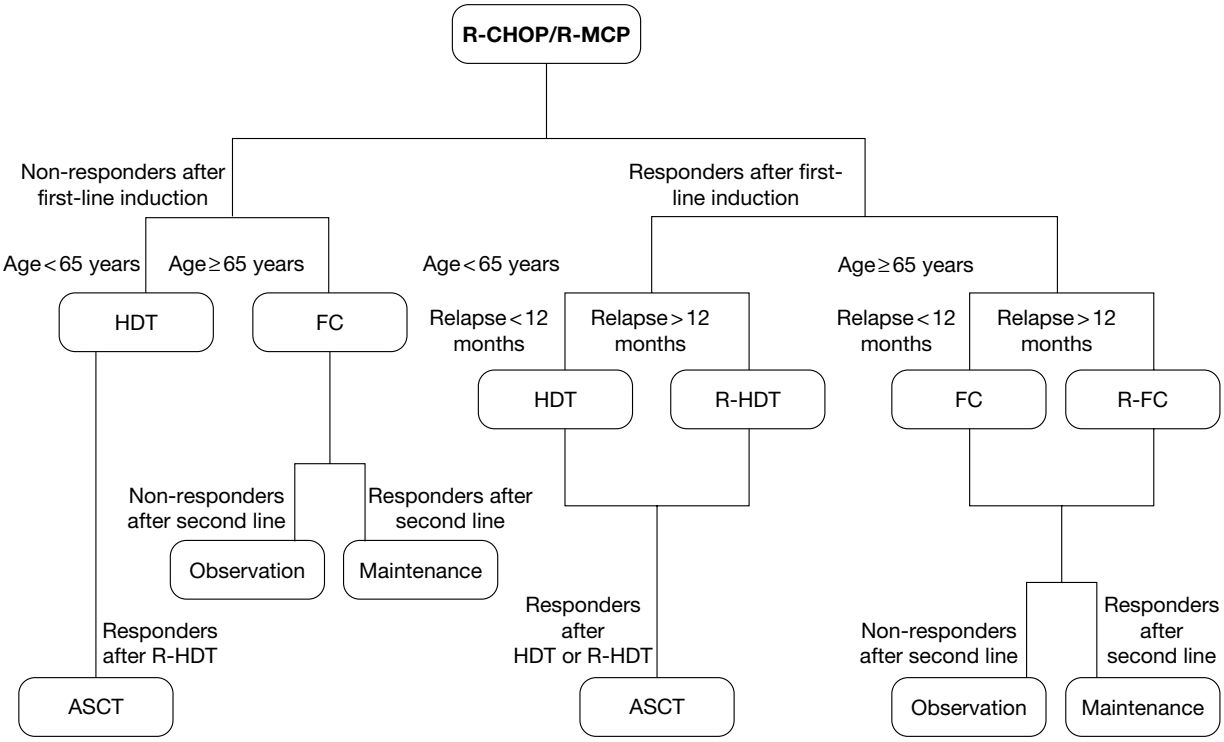


FIGURE 13 Treatment pathways modelled in the economic model for R-CHOP/R-MCP.

Definition of progression

In the economic model, the need for further treatments is driven by the presence of progression, i.e. that patient receive second-line treatment only after relapse/progression. However, trials use different definitions for the TTP (see *Chapter 3*, *Summary of trials* and *Appendix 12*). A comparison of TTF (that includes next antilymphoma treatment and stable disease at cycle 4 as event), TTP and TTNT curves from the M39021 trial[95,96] suggests that some patients might have received further/second-line treatments before progression.

In the economic model, we used TTP from the M39021 trial,[95,96] as patient-level data were available (data provided by Roche, 15 February 2011, personal communication) for this outcome. PFS or EFS have been used in second line according to the data available. The AG acknowledges the potential differences between the outcomes, and refers to progression outcomes as PFS for simplicity and consistency.

Structure of the economic model

The structure of the economic model developed by the AG is similar to the model included in the MS[62] in terms of HSs, with patients moving between four possible HSs: PFS1 (first-line induction treatment/progression-free), PFS2 (second line/progression free), progressive disease (including subsequent lines of chemotherapy), and death.

Health states were selected to represent the natural history in patients with patients with FL to incorporate previous NICE guidance.[72] The AG acknowledges that patients are likely to receive more than two lines of therapy in clinical practice; however, there is no robust evidence available that would allow the effectiveness after second-line treatment to be modelled with accuracy.

The economic model developed by the AG for this appraisal differs from the economic model included in the MS[62] in the following manner:

- use of a continuous time method over a traditional Markov process
- treatment pathways reflecting more accurately clinical practice in England and Wales (see *Figures 10–13*)
- responders and non-responders are modelled as two separate subgroups
- use of a different source of evidence to model the effectiveness in patients treated with CHOP or MCP with or without rituximab (see *Progression-free survival in patients treated with CHOP in first-line induction with or without rituximab*).

The economic model treats responders and non-responders as two separate subgroups and therefore does not use the PFS curve calculated for the whole trial population. This choice has been made after reviewing the evidence available in first-line induction for patients treated with CHOP or MCP with or without rituximab (see *Effectiveness in patients treated with MCP with or without rituximab in first line*). This choice of model structure allows the implementation of maintenance after first- or second-line induction treatment.[73,127]

A simplified schematic of the model structure is provided in *Figure 14*. A cohort of 100,000 individual patients were simulated, each with individual demographic characteristics (age, gender and BSA). The age at death owing to non-FL causes was sampled from a Gompertz distribution estimated from life tables in the UK,[135] conditional on the patient being alive at the start of the simulation. In PFS1, patients received CVP, CHOP or MCP with or without rituximab. 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[91–93,95,96] were used to classify patients into responders and non-responders.

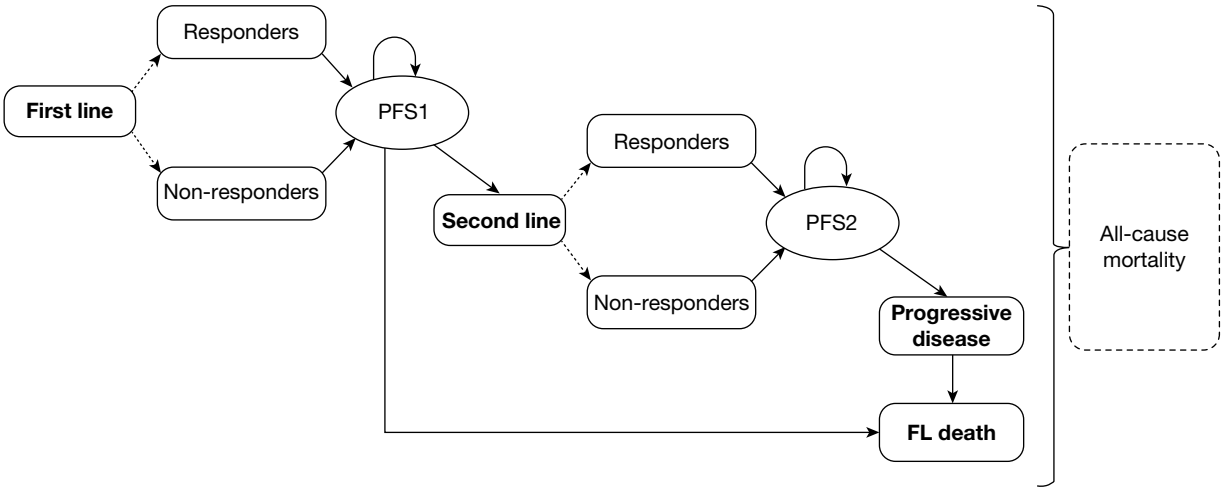


FIGURE 14 Economic model structure.

The TTP is then sampled according to the PFS curves for responders and non-responders as appropriate, with non-responders having a faster disease progression (see *Figure 27*). If the estimated time of progression is later than the estimated time to non-FL death, patients are assumed to die before progression. For patients progressing before the age at death from all causes, the event (relapse or death) is determined based on the proportion of progression attributable to death (see *Death in progression-free survival after first line*). Patients do not continue in the simulation if progression is attributable to death. Patients dying incur no further costs and accrue no further QALYs. Patients relapsing move to second-line treatment.

Patients treated in second line are classified as either responders or non-responders. Responders to CHOP, R-CHOP, FC or R-FC receive maintenance rituximab for up to 2 years at the end of the induction phase as per NICE guidance.[73] Patients responding to HDT or R-HDT receive ASCT. Patients remaining in PFS2 at the end of treatment induction, maintenance or ASCT are assumed not to receive further treatment but would be monitored. The TTP is sampled and patients who progress before the age at death from all causes receive further lines of therapies (third/subsequent line). The time to death from the receipt of second-line treatment is also calculated to identify the cause of death (FL or all causes). Patients dying incur no further costs and accrue no further QALYs. Patients relapsing move to progressive disease. Those patients are assumed to incur additional costs associated with palliative and terminal care as appropriate.

Patient characteristics

A patient's baseline characteristics were derived from registry data in England[3,135] and Wales (data provided by the Welsh Cancer Intelligence & Surveillance Unit, 2008[16]) and the demographics from the trials conducted in patients with FL.

Gender

The proportion of male patients (47%) is estimated from registry data in England[3] and Wales (data provided by the Welsh Cancer Intelligence & Surveillance Unit, 2008[16]).

Baseline age

The baseline age is derived from registry data in England[3] and Wales (data provided by the Welsh Cancer Intelligence & Surveillance Unit, 2008[16]) using a two-stage process. For consistency, a 5-year age band was assumed for patients aged ≥ 85 years (*Figure 15*). We then estimated the age

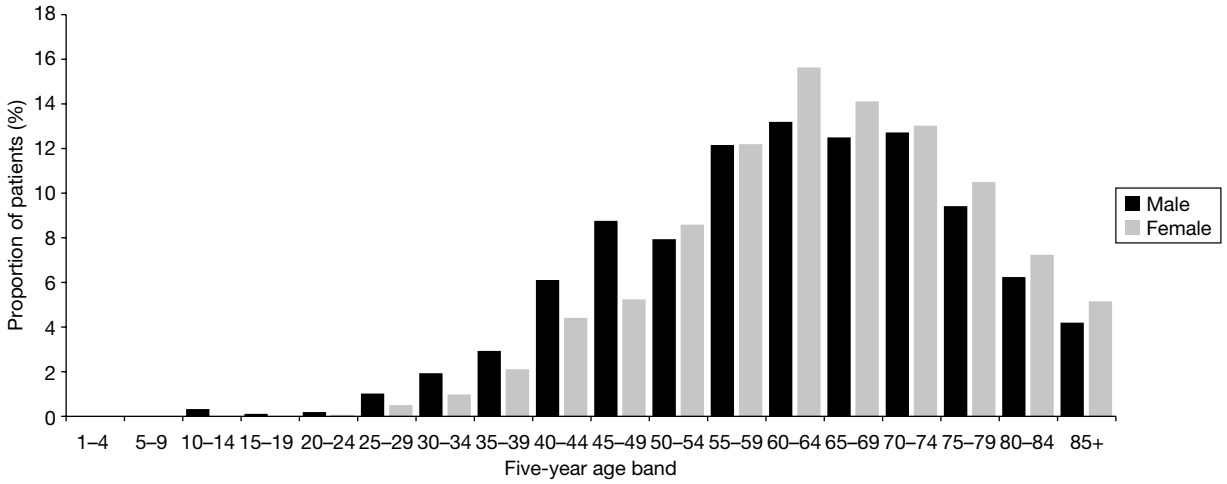


FIGURE 15 Age distribution of patients diagnosed with FL in England[3] and Wales. (Data provided by the Welsh Cancer Intelligence & Surveillance Unit, 2008.[16])

within each age band, assuming a uniform distribution (i.e. equal probability). First, the age band of the patients was sampled. Then the precise age was estimated assuming a uniform distribution within the age band.

Body surface area

The BSA is estimated from the height (cm) and weight (kg) of patients from patient-level data from the PRIMA study,[71,124] by gender, using the Mosteller formula: $\sqrt{[(\text{cm} \times \text{kg})/3600]}$ (*Table 35*). Age-specific BSA values were considered but were not used as the use of an average greatly reduced the uncertainty associated with the BSA.

In the PSA, height and weight were sampled independently assuming no correlation. Although this is a limitation, we did not have access to patient-level data from the trial.[71]

Age at death from all causes

The age at death from all causes is derived from UK life table data[135] by fitting a Gompertz distribution to the data for males and for females.

The coefficients of the Gompertz distribution are presented below (see *Analytic methods* and *Table 54*). The AG acknowledges a limitation in the approach used, namely that deaths from FL were not excluded from the survival curve and therefore, double counting may occur. However, as it is possible that some of the deaths observed in the trials may be owing to non-FL causes this may be partly offset. The AG believes that the exclusion/inclusion of FL-related deaths from life tables data is likely to have a very minimal impact on the ICER.

Response rate after first-line induction treatment

In the economic model, patients are separated into responders and non-responders according to the response rates after first- or second-line induction treatment. The response rates in first-line induction treatment were extracted from the proportion of responders observed in the three main first-line remission induction trials (*Table 36*).[91–93,95,96]

Owing to absence of relevant data for PFS by response category, no distinction was made between partial and CRs.

TABLE 35 Height, weight and estimated BSA in patients with FL from the PRIMA study[71,124] by gender

Gender	Height (cm ± SD)	Weight (kg ± SD)	Estimated BSA (Mosteller formula)
Male	175.01 ± 7.3	79.68 ± 13.34	1.97
Female	161.44 ± 6.75	67.83 ± 14.39	1.74

SD, standard deviation.

TABLE 36 Response rate in first-line induction

First-line induction	CVP[95,96]	R-CVP[95,96]	CHOP[91,92]	R-CHOP[91,92]	MCP[93]	R-MCP[93]
Total no. of patients	159	162	278	279	96	105
No. of responders	90	131	253	268	72	97
Response rate (%)	56.60	80.86	90.01	96.06	75.00	92.38

Progression-free survival in patients treated with CVP in first-line induction with or without rituximab

Progression-free survival in responders to CVP and R-CVP

Individual patient-level data from the M39021 trial[95,96] have been provided by the manufacturer after a request from the AG (Roche, personal communication). The manufacturer provided the Kaplan–Meier plots from first randomisation (i.e. from start of treatment) and consequently, the Kaplan–Meier curve is flat for responders for the first 6 months corresponding to the initial period of induction treatment. Because of this, it was not appropriate to fit a distribution the entire Kaplan–Meier curve. Consequently, in the economic model, we assumed no progression for responders during treatment induction (196 days for eight cycles of 21 days + 28 days), with a distribution fitted from the end of this period.

To preserve the correlation between treatments in the PSA, the AG fitted a parametric distribution to all responders using treatment as a covariate. This was shown to provide an adequate fit to the data (*Figures 16–18*). The parametric distribution was selected through an iterative process after evaluating goodness-of-fit criteria, the visual plot of the curve to the observed data, the plausibility of the extrapolation at the end of clinical evidence and the plot of the hazard.

Different parametric models incorporate different hazard functions. Exponential models are only suitable if the observed hazard is approximately constant and positive. Weibull and Gompertz models incorporate monotonic hazards, whereas the logged models (log-logistic, log-normal) can incorporate non-monotonic hazards, but typically have long tails owing to a reducing hazard as time increases beyond a certain point.[136]

The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated, and suggest that the log-normal model provides the best fit to the data (*Table 37*). Broadly similar AIC and BIC values were observed for the log-logistic and Gompertz distribution. However, goodness-of-fit criteria provide an indication of the goodness of fit to only the observed period and do not categorically indicate that one distribution should be preferred to the remaining distributions. The observed Kaplan–Meier data were plotted against the five fitted parametric distributions (exponential, Weibull, Gompertz, log-logistic and log-normal). The Gompertz, log-logistic and log-normal distributions provided a plausible fit to the observed

TABLE 37 Goodness-of-fit criteria for the risk of progression among responders to CVP first-line induction with or without distribution[95,96]

Model	Observed	ll(null)	ll(model)	df	AIC	BIC
Exponential	221	–333.225	–316.846	2	637.692	644.488
Weibull	221	–330.528	–315.636	3	637.271	647.466
Gompertz	221	–322.177	–309.133	3	624.266	634.460
Log-logistic	221	–323.495	–307.567	3	621.134	631.328
Log-normal	221	–320.175	–304.582	3	615.165	625.359

df, degrees of freedom.
Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

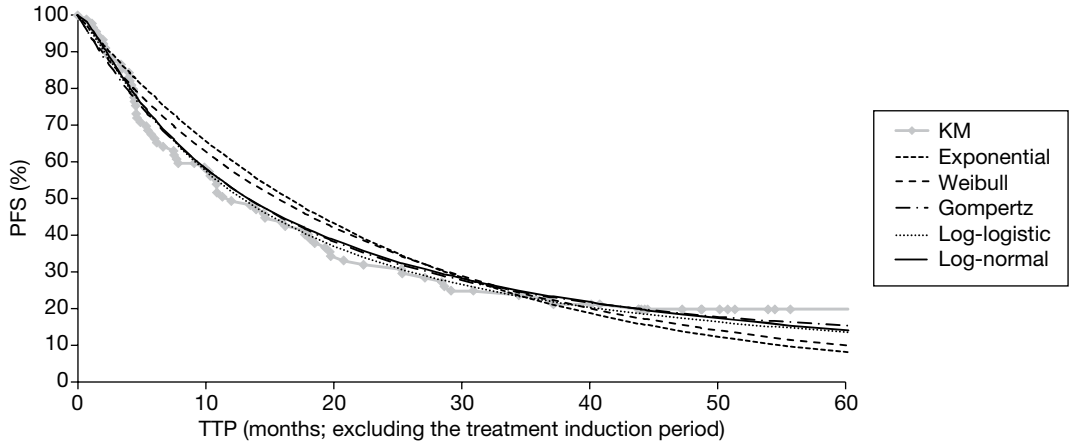


FIGURE 16 Plot of the observed Kaplan–Meier data and predicted distributions for patients treated with CVP.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication). KM, Kaplan–Meier.

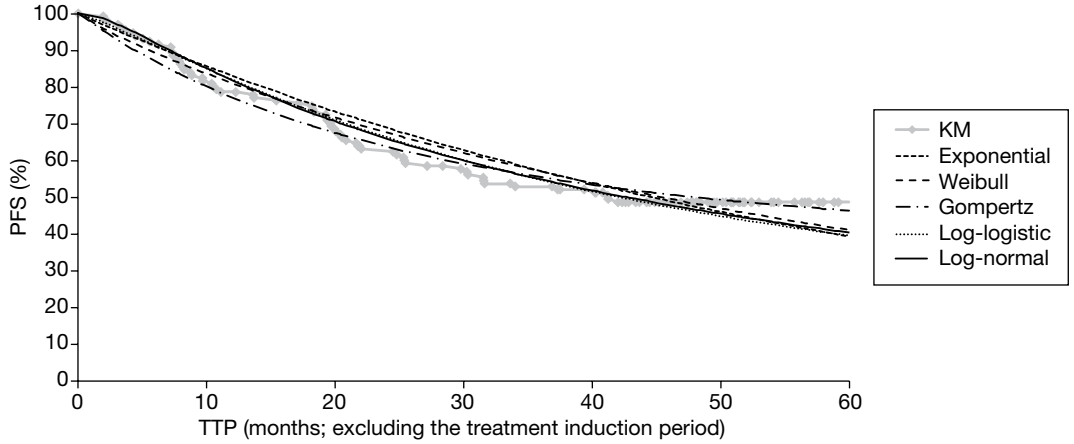


FIGURE 17 Plot of the observed Kaplan–Meier data and predicted distributions for patients treated with rituximab in addition to CVP.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication). KM, Kaplan–Meier.

data (see *Figures 16* and *17*). Similarly, visual inspection of the plot of the hazard (see *Figure 18*) suggests that the log-normal, log-logistic and Gompertz distributions were suitable, as the plot was broadly linear.

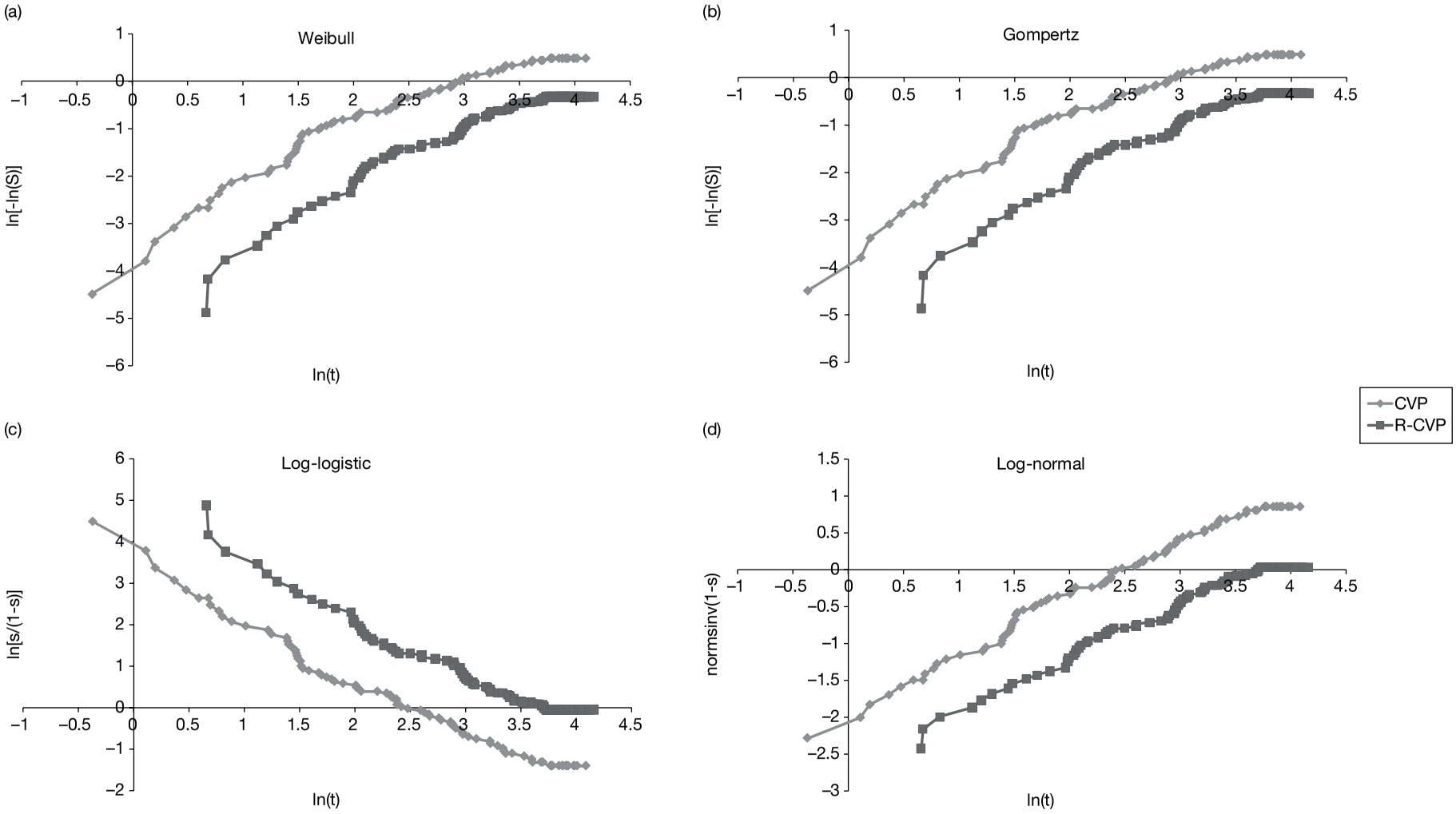


FIGURE 18 Plot of hazard for responders treated with CVP with or without rituximab.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

As single parametric distributions provided reasonable and plausible fit to the data, the AG did not considered other methodologies, such as the use of piecewise exponentials.

From the values of the AIC/BIC, the visual inspections of the fit to the observed period and hazards, the AG believes that the Gompertz, log-logistic and log-normal distributions provided a reasonable and plausible fit to the data. However, the AG believed that the log-normal distribution provided a more plausible long-term extrapolation compared with the Gompertz distribution (see *Figure 44*). The risk of progression using the Gompertz distribution flatten out after about 60 months, implying that about 40% of responders would never progress. FL is considered as an incurable disease and therefore the use of the Gompertz distribution may be implausible. In the base case, the log-normal distribution was selected by the AG as this was believed to be the most plausible parametric extrapolation. The Weibull and Gompertz distributions have been used in SA as these provided a different extrapolation. The AG did not test the log-logistic as the curve was very similar to the log-normal distribution. The log-normal regression model and variance–covariance matrix are presented in *Table 38*.

Progression-free survival in non-responders to CVP and R-CVP

A similar process to that detailed for responders to CVP and R-CVP has been used to estimate the risk of progression among non-responders to CVP and R-CVP; however, Kaplan–Meier data from the start of treatment induction was used[95,96] (data provided by Roche, personal communication). The goodness-of-fit criteria (*Table 39*), visual plot of the Kaplan–Meier to the observed period (*Figures 19* and *20*) and the plot of the hazard (*Figure 21*) indicate that the Gompertz, log-logistic and log-normal distributions again provide a plausible fit to the data. In the base-case analysis, the log-normal distribution was selected (*Table 40*), with other distributions tested in SA.

TABLE 38 Log-normal regression model for responders to CVP-containing regimen with or without rituximab[95,96]

No. of subjects = 221			No. of observations = 221		
No. of failures = 136					
Time at risk = 5913.331					
			LR $\chi^2(1) = 31.18$		
Log-likelihood = –304.582			Prob > $\chi^2 = 0$		
_t	**Coef.**	**SE**	***z***	***p>z***	**95% CI**
trt	1.16341	0.204687	5.68	0	0.76223 to 1.56459
_cons	2.591318	0.152575	16.98	0	2.292276 to 2.89036
/ln_sig	0.335348	0.065793	5.1	0	0.206395 to 0.464301
sigma	1.398427	0.092007			1.229239 to 1.590901
Variance–covariance matrix					
	_t: trt	**_t: _cons**	**ln_sig: _cons**		
_t:trt	0.041897				
_t:_cons	–0.02258	0.023279			
ln_sig:_cons	0.001846	0.001042	0.004329		

Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

TABLE 39 Goodness-of-fit criteria for the risk of progression among non-responders to CVP first-line induction with or without distribution[95,96]

Model	Observations	ll(null)	ll(model)	df	AIC	BIC
Exponential	93	–158.965	–158.490	2	320.979	326.044
Weibull	93	–156.174	–155.819	3	317.637	325.235
Gompertz	93	–149.751	–149.509	3	305.019	312.616
Log-logistic	93	–147.759	–147.431	3	300.863	308.461
Log-normal	93	–147.316	–147.070	3	300.139	307.737

df, degrees of freedom.
Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

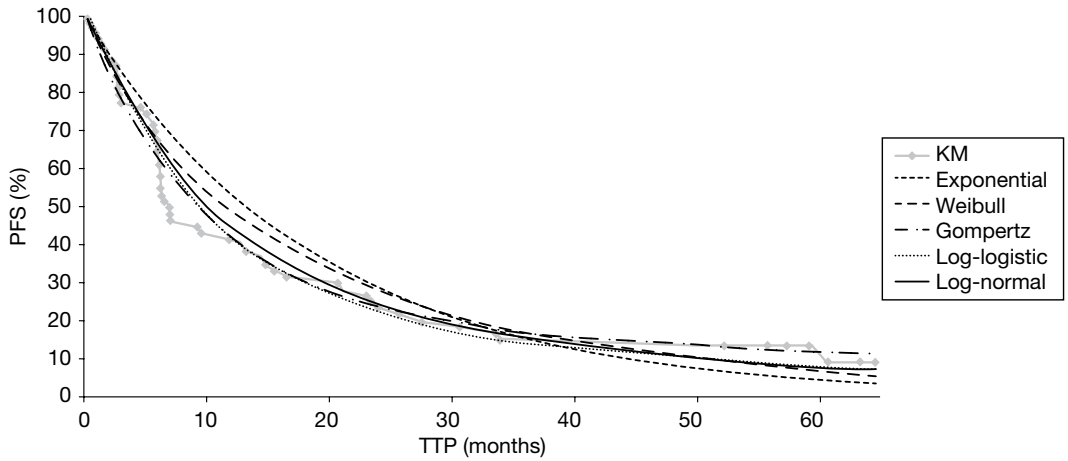


FIGURE 19 Plot of the observed Kaplan–Meier data and predicted distributions for non-responders treated with CVP.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication). KM, Kaplan–Meier.

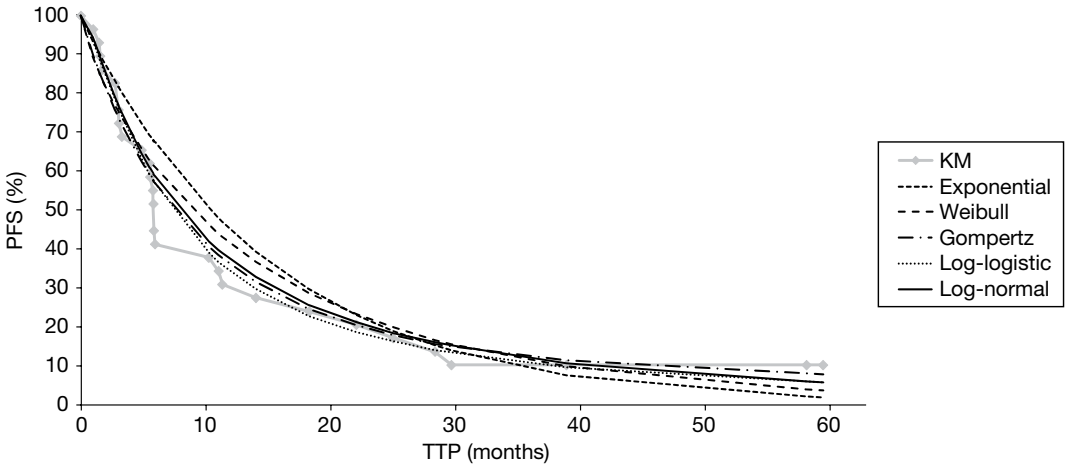


FIGURE 20 Plot of the observed Kaplan–Meier data and predicted distributions for non-responders treated with rituximab in addition to CVP.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication). KM, Kaplan–Meier.

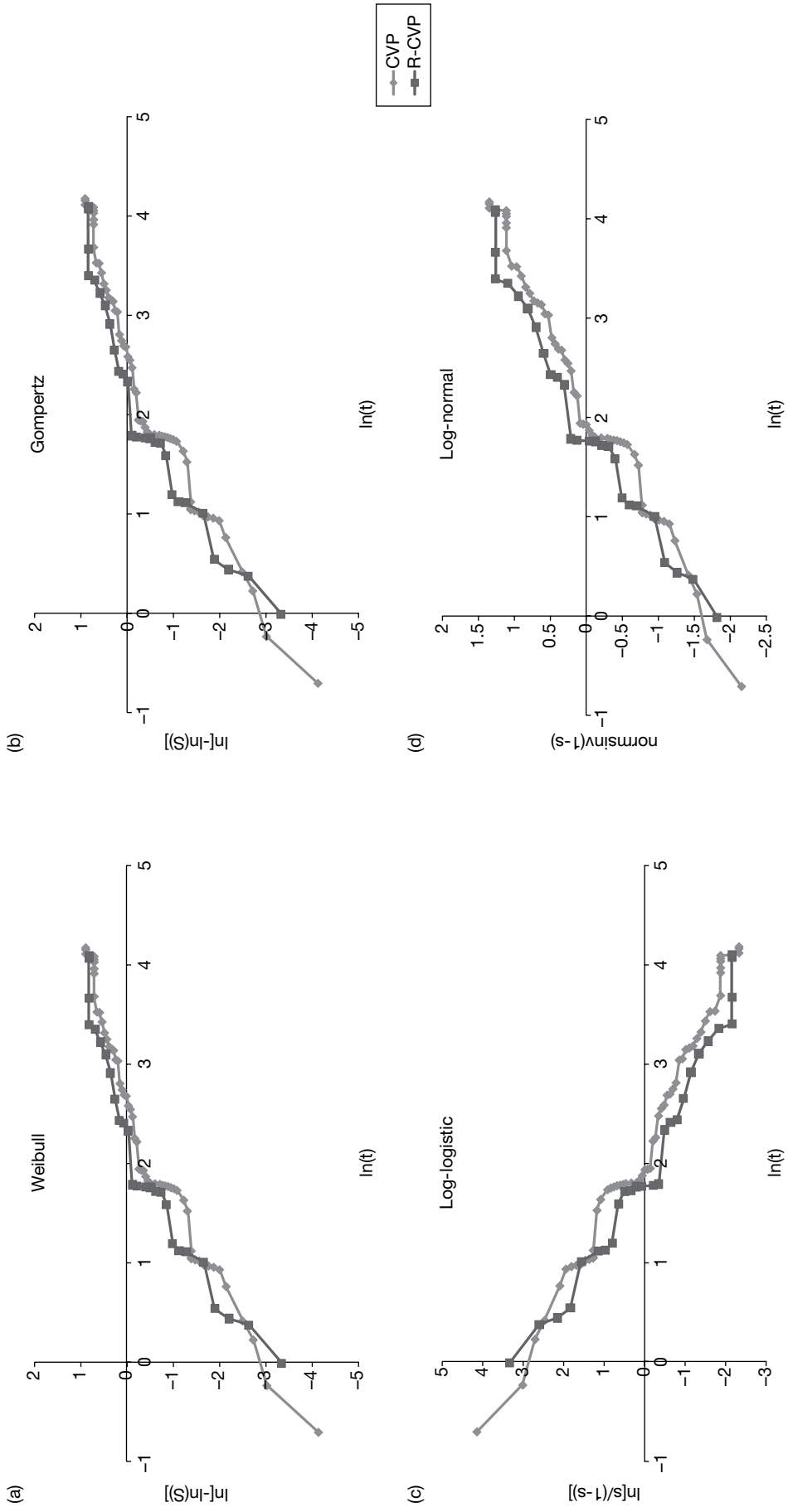


FIGURE 21 Plot of hazard for non-responders treated with CVP with or without rituximab.[95,96] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

Progression-free survival in patients treated with CHOP in first-line induction with or without rituximab

Progression-free survival in responders to CHOP and R-CHOP

In the GLSG 2000 trial,[91,92] patients of < 60 years of age achieving CR or PR following first-line induction treatment were randomised to either SCT or maintenance with interferon. Patients aged ≥ 60 years received maintenance with interferon. Consequently, the reported effectiveness in responders is confounded by the effect of maintenance interferon or SCT.

The AG believes that data from the GLSG 2000 trial[91,92] would lead to an overestimate of the absolute gain of the addition of rituximab to CHOP because of the additional treatments provided to responders. Alternative sources of effectiveness have therefore been considered to model the risk of progression among responders to CHOP first-line induction with or without rituximab.

The PRIMA study[71] provides data on the progression rate of patients responding to first-line induction with chemotherapy in combination with rituximab only (R-CVP, R-CHOP, R-FCM). Patients were randomised to maintenance rituximab or observation up to 2 years from the end of first-line treatment induction (R-CHOP, R-CVP or R-FCM). The majority of patients (90%) had stage IV FL and most of patients received R-CHOP as first-line induction treatment (74%).

Individual patient-level data from the PRIMA study[71] were made available to the AG by the manufacturer (Roche, personal communication). The Kaplan–Meier curves for the responders randomised to observation for R-CHOP and R-CVP from the end of treatment induction have been compared (*Figure 22*). Although apparently visually different, the difference between the two curves was not statistically significant ($p = 0.0970$). However, the AG acknowledges that the absence of statistical differences might be attributable to small sample sizes (R-CVP, $n = 113$; R-CHOP, $n = 386$) and that this does not necessarily means that the two curves are similar.[71]

No robust sources of effectiveness were identified for the risk of progression for patients treated with CHOP first-line induction without rituximab. Most of the studies identified have been

TABLE 40 Log-normal regression model for non-responders to CVP-containing regimen with or without rituximab[95,96]

No. of subjects = 93			No. of observations = 93		
No. of failures = 80					
Time at risk = 1425.807					
			LR $\chi^2(1) = 0.49$		
Log-likelihood = –147.07			Prob > $\chi^2 = 0.4823$		
_t	**Coef.**	**SE**	***z***	***p>z***	**95% CI**
trt	–0.20573	0.292553	–0.7	0.482	–0.77912 to 0.367666
_cons	2.273996	0.16551	13.74	0	1.949602 to 2.59839
/ln_sig	0.254605	0.081224	3.13	0.002	0.095409 to 0.413802
sigma	1.289952	0.104776			1.100108 to 1.512558
Variance–covariance matrix					
	_t: trt	**_t: _cons**	**ln_sig: _cons**		
_t:trt	0.085587				
_t:_cons	–0.02731	0.027394			
ln_sig:_cons	–0.00035	0.000945	0.006597		

Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

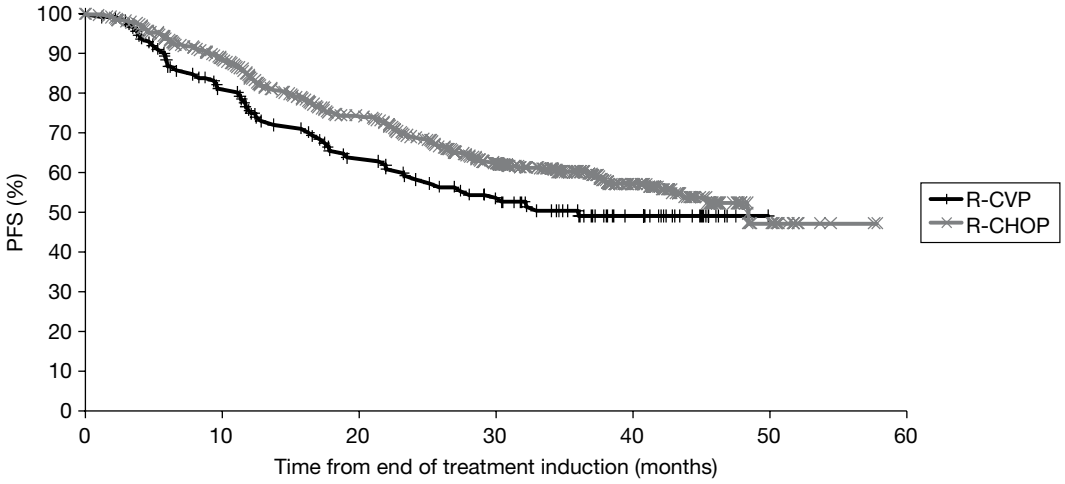


FIGURE 22 Comparison of the Kaplan–Meier data for responders to R-CHOP and R-CVP in the PRIMA study.[71] Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

conducted in populations with other lymphomas, used a different study designs (retrospective) or were confounded by subsequent therapies for patients in remission.[137,138] Clinical opinion was sought about the mechanism of action of rituximab. This suggested that the addition of rituximab might provide the same relative benefit compared with chemotherapy alone, irrespective of the choice of chemotherapy.

Although patient-level data from the PRIMA study[71] (data provided by Roche, personal communication) could have been used, the AG was not comfortable to use direct data from the trial owing to the high degree of censoring, which was noted by the ERG in the ongoing appraisal on rituximab for first-line maintenance treatment.[126] Furthermore, if a parametric function is fitted to patient-level data from the PRIMA study,[71] the curve between R-CHOP and R-CVP curves would cross, as the curve for R-CVP becomes relatively flat after about 50 months. It is unclear if this is only an artefact of the limitation in the data used.[71,95,96]

Given the limited evidence available on the progression for patients treated with CHOP and R-CHOP in first-line induction, the absence of a statistically significant difference for the risk of progression among responders to first-line induction with R-CVP and R-CHOP ($p = 0.0970$) and the suggestion by clinicians of a similar mechanism of action of rituximab for the different type of chemotherapies assessed, the AG used patient-level PFS data from the M39021 trial[95,96] (data provided by Roche, personal communication) as a proxy of the PFS for patients responding to CHOP and R-CHOP, respectively.

The assumptions made were supported by additional analyses comparing the risk of progression among responders to R-CVP from the PRIMA study[71] (data provided by Roche, personal communication) and responders to R-CVP from the M39021 trial[95,96] (data provided by Roche, personal communication). Overall, the PFS from end of treatment induction was found to be broadly similar between the two trials (*Figure 23*).

Progression-free survival in non-responders to CHOP and R-CHOP

In the absence of evidence, the progression rates in patients that do not respond to first-line induction treatment with CHOP with or without rituximab were assumed to be equal to the rates of progression observed with CVP in combination with or without rituximab (see *Progression-free survival in patients treated with CVP in first-line induction with or without rituximab*).

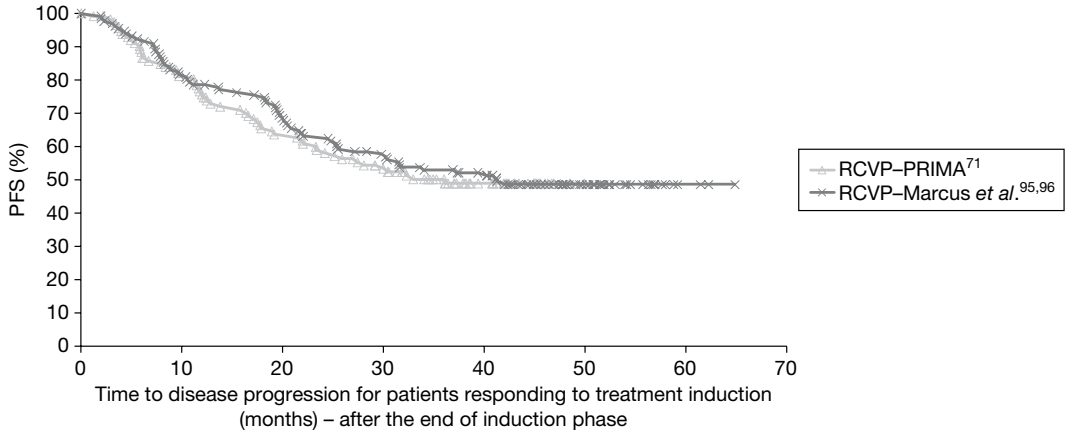


FIGURE 23 Plot of the risk of progression among patients responding to first-line induction treatment with R-CVP from the PRIMA[71] study and M39021[95,96] trial. Analysis of individual patient-level data provided by the manufacturer (Roche, personal communication).

Although this is a limitation, it is consistent with the assumption that the rates of progression for responders to CHOP and R-CHOP equalled that of CVP and R-CVP.

Additionally, it is believed that this assumption would have little impact on the ICER, as only a small proportion of patients do not respond to first-line induction treatment with R-CHOP or CHOP (3.94% and 8.99%, respectively).[91,92] Clinical opinion was sought and suggested that this is a reasonable assumption.

Comparison of the modelled R-CHOP by the Assessment Group against data from an alternative randomised controlled trial[77]

Rummel *et al.*[78] report data from a Phase III trial comparing R-CHOP with R-bendamustine in patients treated for FL, Waldenström's, marginal zone lymphoma, small lymphocytic lymphoma and MCL. Fifty-four per cent of patients had FL and patients treated with R-CHOP received a maximum of six cycles. The median age was 63 years and 77% of patients had stage IV disease. Thirty-three per cent and 48% of patients randomised had a FLIPI score of 2 or 3/>3, respectively. The median observation time was 36 months. The response rate for all patients randomised to R-CHOP was 91.3% (all lymphoma types) and the median overall PFS (from randomisation) was 46.7 months in patients with FL who are treated with R-CHOP in first-line induction (which included all patients with FL). Although patients' characteristics for patients with FL are not presented separately, patients' characteristics for the whole trial population randomised to R-CHOP[78] are broadly similar to the characteristics of the population included in other first-line induction trials for FL.[91–93,95,96]

The PFS for patients with FL from Rummel *et al.*[78] was compared with our estimated combined PFS (responders and non-responders) for patients treated with R-CHOP assuming a response rate of 91.3% and that patients receive up to six cycles of treatment in the induction phase. Overall, the PFS predicted by the AG for R-CHOP is broadly similar to the PFS reported in Rummel *et al.*[78] (*Figure 24*).

Effectiveness in patients treated with MCP with or without rituximab in first line

As with CHOP-containing regimens, data from the first-line trial for R-MCP and MCP[93] are confounded by responders receiving subsequent maintenance therapy with interferon-alpha. No robust alternative sources were identified by the AG.

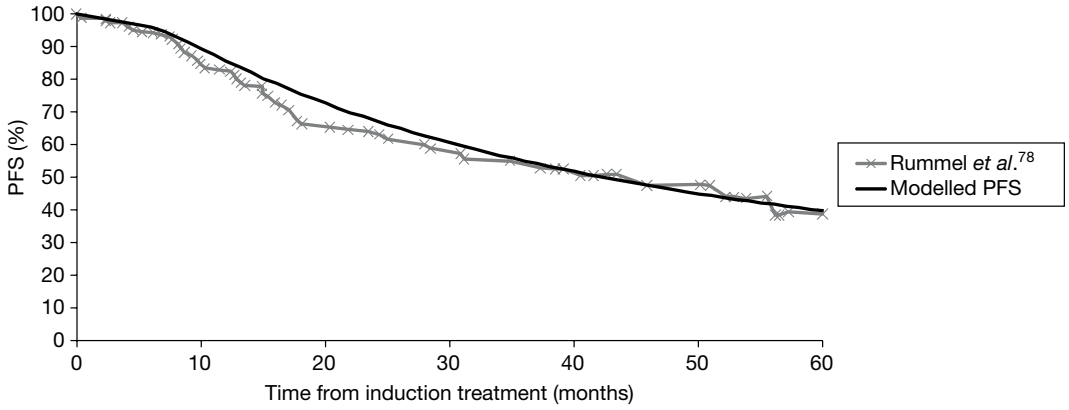


FIGURE 24 Comparison of the PFS from Rummel *et al.*[78] and predicted using the AG method.

To provide an estimation of the cost-effectiveness of rituximab in addition to MCP, a scenario analysis is presented, assuming that the PFS for responders and non-responders treated with MCP with or without rituximab are identical to the PFS in patients treated with CVP/CHOP with or without rituximab.

It is commented that although the PFS for responders and non-responders are assumed equal for R-CVP, R-CHOP and R-MCP, and are assumed equal for CVP, CHOP and MCP, the differences in response rates (see *Table 36*), number of cycles and time between cycles (see *Table 44*) result in different prognoses between interventions (see *Figure 25*).

Summary of modelled progression-free survival in first-line induction

The modelled combined PFS (including both responders and non-responders) for patients treated with CVP, CHOP and MCP with or without rituximab is presented in *Figure 25*.

Effectiveness of rituximab first-line maintenance for patients that respond to first-line induction with chemotherapy in combination with rituximab (scenario analysis)

First-line maintenance was incorporated into the economic model by altering the risk of progression for patients responding to first-line induction with R-chemotherapy. The HR from the PRIMA study[71] was used to alter the risk of progression (observation vs maintenance). Although there were differences in the HR for patients treated with R-CHOP (HR 0.51, 95% CI 0.39 to 0.65) and R-CVP (HR 0.68, 95% CI 0.45 to 1.02), we used data for the whole randomised population as differences might have been attributable to small sample sizes. Consequently, a HR of 0.55 (95% CI 0.44 to 0.68) was applied to the rate of progression for responders to R-chemotherapy for the first 42 months as clinical opinion suggests that the lasting effect ranges between 36 and 48 months.[127] SAs were conducted varying the lasting effect of first-line maintenance rituximab between 36 and 72 months.

Response rates in patients receiving second-line chemotherapy

The response rates for patients treated with CHOP and R-CHOP second-line induction treatment were extracted from the EORTC 20981 trial (*Table 41*).[74,75] The response rates were not available for FC-containing regimens used in older patients. As FC-containing regimens are less aggressive therapies, a lower effectiveness is expected. In the absence of evidence, we arbitrarily assumed that FC is 20% less effective than CHOP. SAs were conducted varying the response rates for patients treated with FC with or without rituximab.

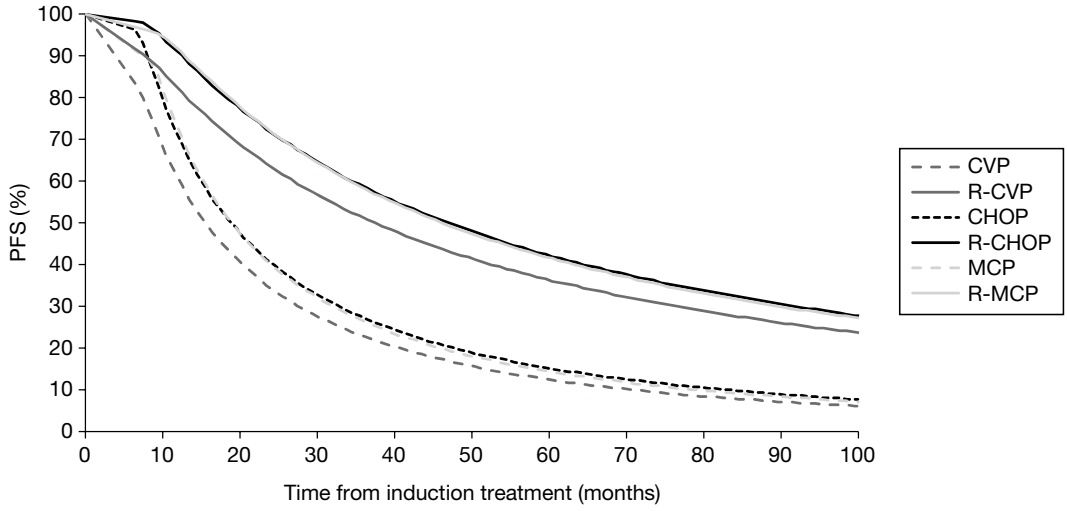


FIGURE 25 Progression-free survival for all patients treated with CVP, CHOP and MCP with or without rituximab.

Effectiveness in patients treated with CHOP with or without rituximab in second-line

Data from the EORTC 20981 trial[74,75] were used to model the PFS in patients with FL who were treated with CHOP and R-CHOP in second-line induction, with or without rituximab maintenance. Patients were included in the EORTC 20981 trial[74,75] if they had relapsed but had no more than two previous non-anthracycline-containing chemotherapy regimens. The study was conducted before the introduction of rituximab and therefore patients are rituximab naive, i.e. not previously exposed to rituximab. The initial results of the EORTC 20981trial[75] were updated in a second publication[74] that included 6 years of follow-up data. Patients were randomised to second-line induction treatment with either CHOP or R-CHOP; those patients who achieved a CR or PR had a second randomisation to either maintenance treatment with rituximab (once every 3 months) or observation for 2 years or until relapse.

Where possible, data from the latest follow-up duration[74] were used in the economic model. The PFS and OS curves for responders to CHOP and R-CHOP second-line induction treatment were extracted from the latest follow-up of the EORTC 20981 trial.[74] However, the PFS and OS curves for non-responders to treatment induction were extracted from data presented by the manufacturer in a previous submission to NICE.[73]

van Oers *et al.*[74] reported only OS data for all responders regardless of whether treatment induction was CHOP or R-CHOP randomised to either maintenance treatment with rituximab or observation. Data by treatment induction have been presented by the manufacturer in a previous NICE appraisal;[73] however, this used a shorter follow-up duration (median = 39.4 months from first randomisation). These data indicated that the OS curves for patients randomised to observation or maintenance rituximab were broadly similar whether patients received CHOP or R-CHOP in second-line treatment induction (see figure 10 in MS[62] for TA137). In the economic model, it was assumed that the OS for patients treated with CHOP or R-CHOP was the same, although patients receiving observation did less well than those who had maintenance with rituximab.

The PFS and OS for responders using the latest follow-up data from the EORTC 20981[74] are presented from second randomisation, i.e. from the end of treatment induction. Consequently, the risk of PFS and OS are assumed to be zero during treatment induction in the economic model. A summary of data used in the economic model is presented in *Table 42*.

TABLE 41 Response rates among patients receiving second-line induction treatment[91,92]

Second line	CHOP[91,92]	R-CHOP[91,92]	FC	R-FC
Total no. of patients	231	234	No data	No data
No. of responders	145	189	No data	No data
Response rate (%)	62.77	80.77	50.22[a]	64.62[a]

a Assumed to be 20% lower than CHOP, R-CHOP.

It was not possible to have access to individual patient-level data from the EORTC 20981 trial,[74,75] and therefore only data available in the public domain were used.

The digitised Kaplan–Meier curves included in the MS[62] were used to fit several parametric distributions to represent the risk of progression or the risk to death. In the absence of individual patient-level data, the distributions have been fitted using the Solver function within Microsoft Excel in order to find the parameter values that minimise the root-mean-square error (RMSE) between the observed and predicted Kaplan–Meier. The best distribution was selected using an iterative approach after analysing the visual plot of the curve, the hazard plot and the RMSE. Overall, the Weibull and exponential distributions provided the poorest fit to the data. The Gompertz and log-logistic distribution provided a reasonable fit to only part of the data. The log-normal distribution fitted all the data reasonably well.

The plot of the PFS Kaplan–Meier and predicted log-normal distribution for patients responding to second-line treatment induction with CHOP and R-CHOP are presented in *Figures 26* and *27*.

The plot of the OS Kaplan–Meier and log-normal distribution for patients responding to second-line treatment induction is presented in *Figure 28*.

Finally, the plot of the OS and PFS Kaplan–Meier for non-responders to CHOP and R-CHOP in second-line treatment is presented in *Figure 29*.

However, the distribution that provided the best fit to the data (the log-normal) hampered uncertainty analysis. In the PSA, we varied the mean PFS and OS by ± 5% by changing the mean parameter of the log-normal distribution but assuming the same standard deviation (SD). PFS and OS curves were sampled independently; however, the same random number was used to preserve the correlation between OS and PFS.

Effectiveness in patients treated with FC in combination or not with rituximab in second-line treatment

Clinical opinion sought by the AG suggested that FC or R-FC would be used for patients that cannot tolerate aggressive therapy (such as CHOP or HDT with or without ASCT), in particular older patients.

The published literature was searched for potential sources to estimate the effectiveness of FC-containing regimens with or without rituximab in patients with relapsed FL aged > 65 years; however, no data were identified. The AG was aware of a trial conducted in second-line treatment that compared fludarabine, cyclophosphamide, mitoxantrone (FCM) with R-FCM,[139] with or without maintenance rituximab. The median age of patients randomised to FCM or R-FCM was approximately 60 years. This trial also had a different maintenance schedule compared with that of van Oers *et al.*,[74,75] which compared CHOP with R-CHOP in second-line induction. A previous NICE technology appraisal[73] reported that the data were not mature in the R-FCM

TABLE 42 Summary of data from the EORTC 20981 trial[74,75]

	PFS		OS	
Treatment	**First randomisation**	**Second randomisation**	**First randomisation**	**Second randomisation**
Non-responders				
CHOP	✓ TA137[73]		✓ TA137[73]	
R-CHOP	✓ TA137[73]		✓ TA137[73]	
Responders				
CHOP: observation		✓ van Oers *et al.*[74]		✓ Combined observation arm van Oers *et al.*[74]
R-CHOP: observation		✓ van Oers *et al.*[74]		
CHOP: maintenance		✓ van Oers *et al.*[74]		✓ Combined maintenance arm van Oers *et al.*[74]
R-CHOP: maintenance		✓ van Oers *et al.*[74]		

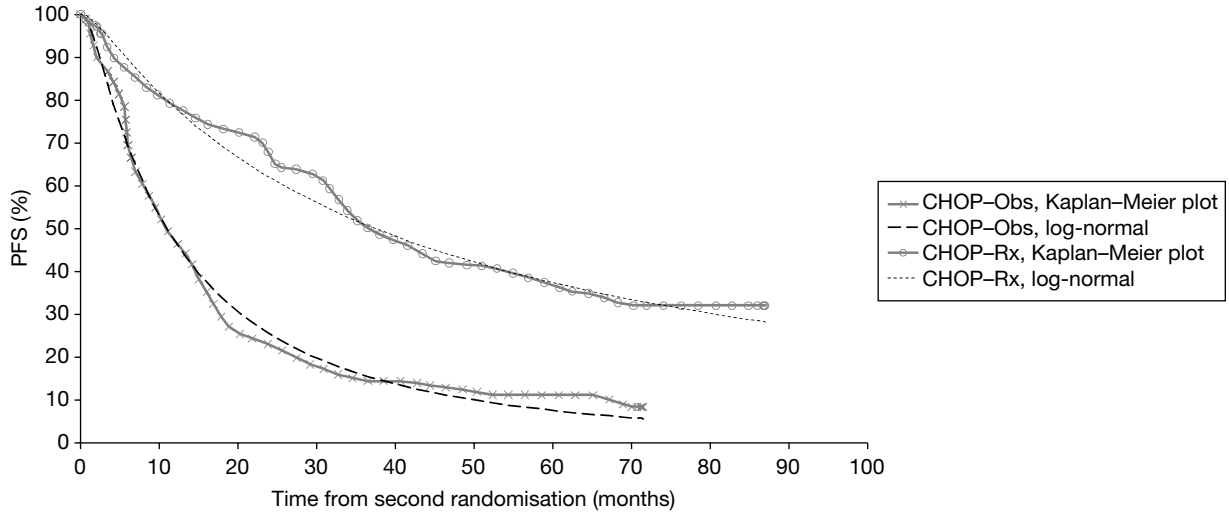


FIGURE 26 Plot of the Kaplan–Meier data and log-normal distribution for patients responding to CHOP second-line induction (from the end of treatment induction) with or without maintenance rituximab.[63,74] Obs, observation; Rx, maintenance rituximab.

compared with FCM trial but, despite this limitation, the outcomes for R-FCM and R-CHOP are broadly similar.

The PFS and OS curves for responders and non-responders to CHOP and R-CHOP[73–75] in second line (see *Effectiveness in patients treated with CHOP with or without rituximab in second line*) have been used a proxy for the risk of progression for patients treated with FC and R-FC. However, because we assumed a lower response rate for FC-containing regimen (20% lower) and the shorter induction period for FC/R-FC (four cycles instead of six), the overall modelled effectiveness for FC-containing regimens will be reduced compared with CHOP-containing regimens. SAs were conducted varying both the response rate and PFS curves (see *Appendix 15*).

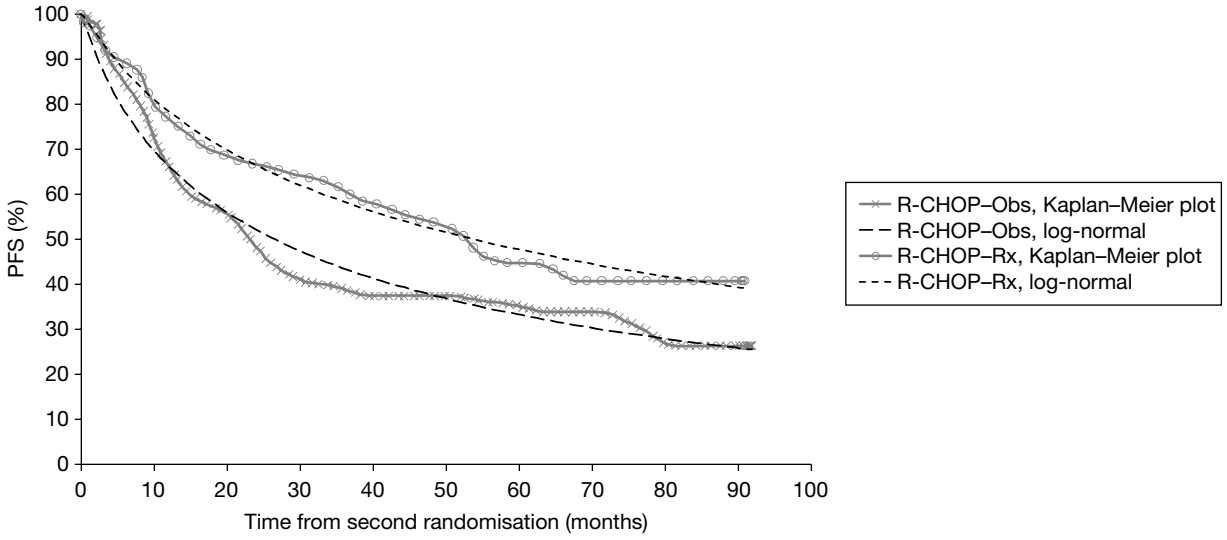


FIGURE 27 Plot of the Kaplan–Meier data and log-normal distribution for patients responding to R-CHOP second-line induction (from the end of treatment induction) with or without maintenance rituximab.[63,74] Obs, observation; Rx, maintenance rituximab.

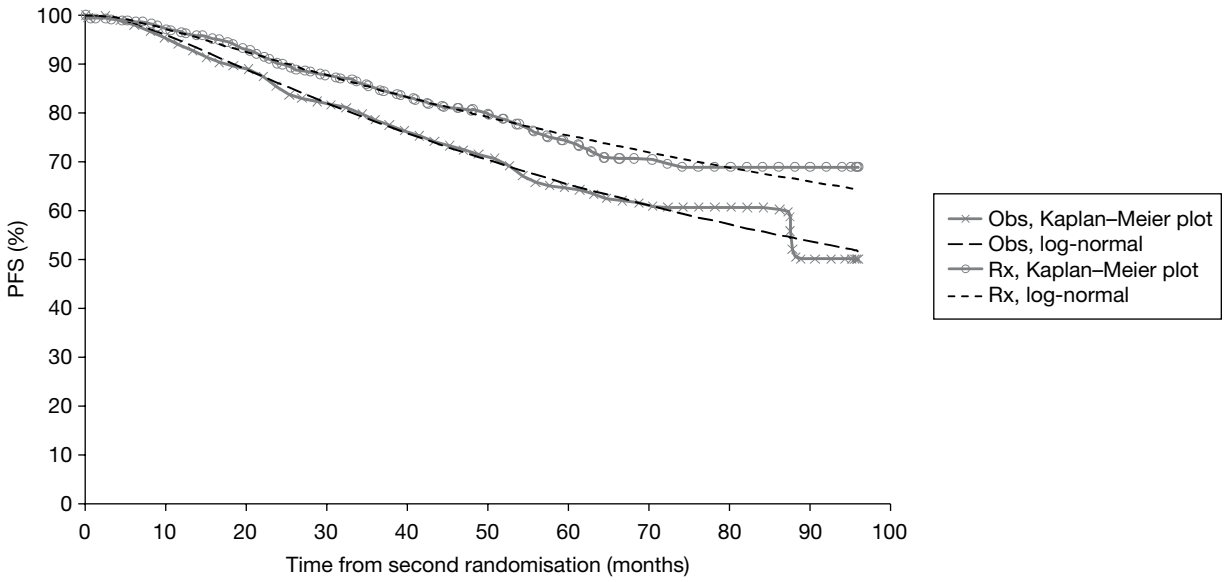


FIGURE 28 Plot of the OS Kaplan–Meier data and log-normal distribution for responders to second-line induction (from end of treatment induction) with or without maintenance rituximab.[63,74] Obs, observation; Rx, maintenance rituximab.

Effectiveness in patients receiving salvage therapy with high-dose therapy with or without rituximab and autologous stem cell transplantation in relapsed patients with follicular lymphoma

Clinical advice sought by the AG indicated that patients previously treated with an anthracycline-containing regimen (CHOP, MCP) would not be retreated with an anthracycline regimen and would probably receive salvage therapy with HDT with or without rituximab before ASCT in cases for those that respond to chemotherapy.

Discussion with clinical experts suggested that the most commonly used HDT are up to four cycles of ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) or DHAP (dexamethasone, cytarabine and cisplatin) chemotherapy with or without rituximab. Stem cell

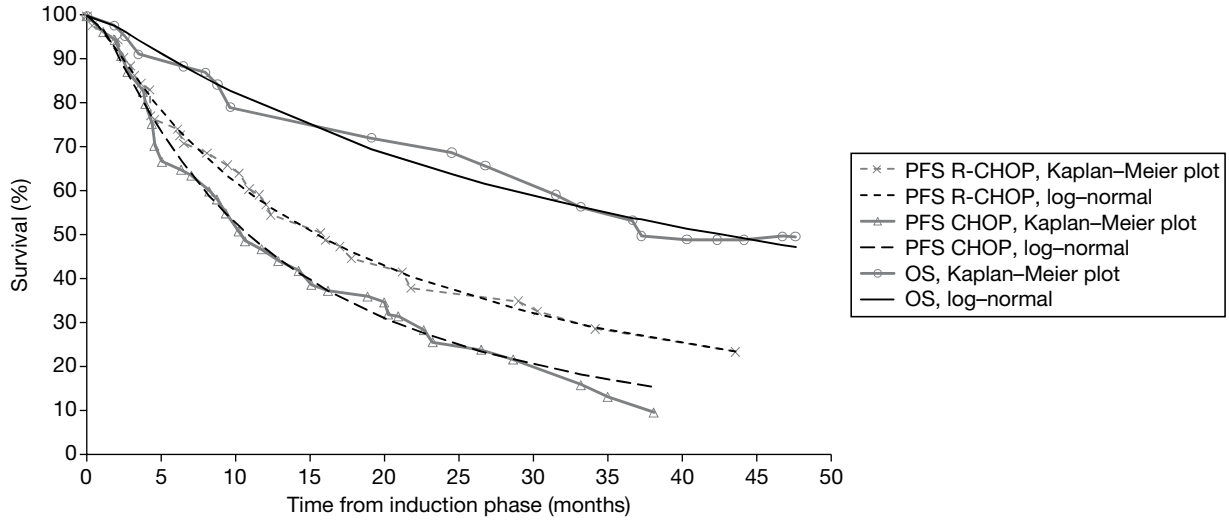


FIGURE 29 Plot of the OS and PFS Kaplan–Meier data and log-normal distribution for non-responders to second-line induction treatment (from start of induction treatment).[73]

harvest is then obtained for responders only, with patients for whom the harvest was successful eligible for BEAM (BCNU®/carmustine, cytarabine, etoposide and melphalan) conditioning plus ASCT (*Figure 30*).

The literature was searched to identify studies that reported the impact of the addition of rituximab to salvage therapy before ASCT in patients with relapsed FL, although given the resource constraints it was not possible to perform a systematic search of the literature.

Sebban *et al.*[134] reported the impact of rituximab with or without HDT with transplant at the time of relapse in patients with FL. This retrospective study included patients that received CHVP alone or in addition to interferon in first-line induction. Relapsed patients receive salvage therapies, with the most used regimens being dexamethasone, high-dose cytarabine and cisplastin, ifosfamide, carboplatin and etoposide, mesna, mitoxantrone and etoposide, and fludarabine-based regimens. Rituximab was also offered to a proportion of patients with or without chemotherapy as part of the salvage treatment. Sebban *et al.*[134] reported that the 5-year EFS after first relapse (EFSR) was 52% in patients receiving rituximab as part of the salvage therapy (with or without chemotherapy) and 29% in patient receiving salvage therapy without rituximab. The 5-year survival after first relapse (SAR) rate was 81% and 44%, respectively.

Clinical opinion was sought regarding the validity of using evidence from this study[134] to model the effectiveness of salvage therapy in addition to ASCT with or without rituximab. Overall, the clinical experts found the study appropriate, but cautioned that there were potential limitations in the study design. The addition of rituximab to salvage therapy is associated with considerable benefit, although it is unclear if the magnitude of the observed improvement is because of the retrospective nature of the study.[134] The study was also conducted in a pre-rituximab era, and therefore patients were not previously exposed to rituximab. Also, the proportion of patients that responded to HDT (for whom the harvest was successful) is unclear from the study, as well as the proportion of patients that received ASCT in both arms.

Despite these potential limitations, data from Sebban *et al.*[134] were used in the economic model to represent the effectiveness of salvage therapy with or without rituximab. Data for EFSR and SAR after salvage therapy with or without rituximab were taken from figure 3 in Sebban *et al.*[134] TechDig© software was used to estimate the data points and allow parametric distributions to be

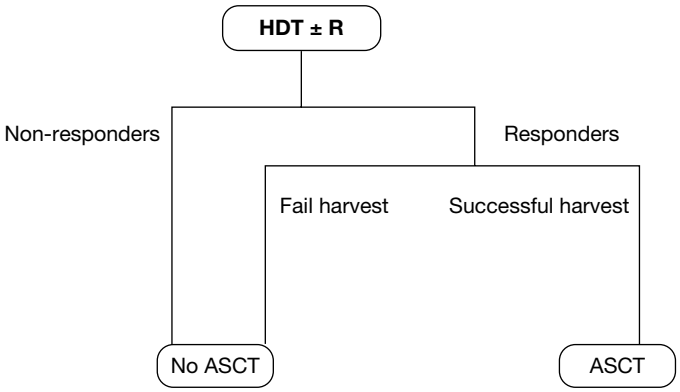


FIGURE 30 Treatment pathway for patients treated with HDT with or without rituximab.

fitted. We examined different distributions using the Solver function within Microsoft Excel and overall, the log-normal was found to provide the best fit to the data. The plot of the Kaplan–Meier and estimated log-normal data is presented in *Figure 31* for EFS and *Figure 32* for OS.

The mean effectiveness was varied by ± 5% in the PSA, with the SD of the log-normal distribution assumed constant.

Resistance to rituximab in patients previously exposed to rituximab treatment

A key assumption of the economic model submitted by the manufacturer is the absence of resistance in patients previously treated with rituximab.

Evidence of resistance in patients with relapsed FL have been estimated in cohorts of patients that have not been previously exposed to rituximab, although clinical opinion expressed in a previous NICE appraisal of rituximab[73] suggested that there might be little or no loss of efficacy for retreatment with rituximab, given its mechanism of action. In the MS,[62] two studies are referenced to support the assumption of the absence of a resistance effect to rituximab.[128,129] However, the AG does not believe that the data from these two studies[128,129] provide conclusive evidence that resistance to rituximab can be discounted.

Johnston *et al.*[128] report that second-line response rates were only marginally reduced in patients with FL when compared with first-line response rates (ORR 88% to 76%, CR 52% to 44% and PR 36% to 32% in first line and second line, respectively). However, a comparison between patients who had received chemotherapy alone in first and second line and patients who had received R-chemotherapy in first and second line demonstrated that PFS following the second-line treatment was no different between the two patients groups, indicating that the second rituximab treatment had little benefit. There were several problems, however, with the study undertaken by Johnston *et al.*[128] in terms of its ability to prove or disprove resistance to rituximab. First, the number of patients with FL ($n = 50$) was small and the patients were not representative of UK patients with FL (median age at start of second treatment was young: 59 years). In addition, the comparisons being made were not ideal in determining the existence of rituximab resistance: R-chemotherapy (first line) and R-chemotherapy (second line) were compared with chemotherapy alone (first line) and chemotherapy alone (second line). The correct comparison would be R-chemotherapy (first line) + R-chemotherapy (second line) compared with chemotherapy alone (first line) and R-chemotherapy (second line). A substantial number of patients were also receiving R-monotherapy, which is not recommended in the UK unless all other options have been exhausted.

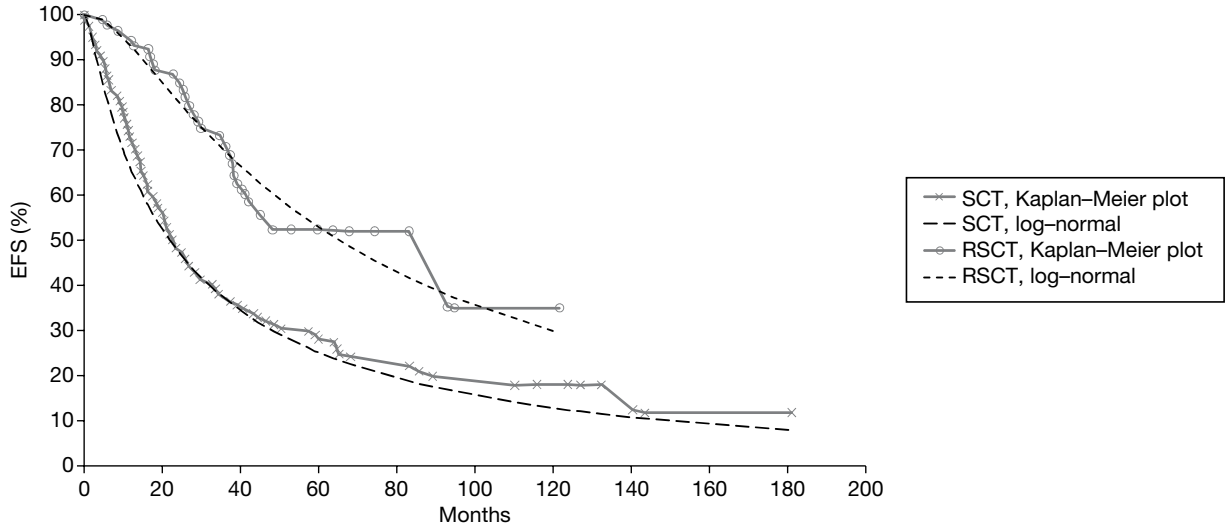


FIGURE 31 Event-free survival for patients treated with ASCT and salvage chemotherapy with or without rituximab.[134]

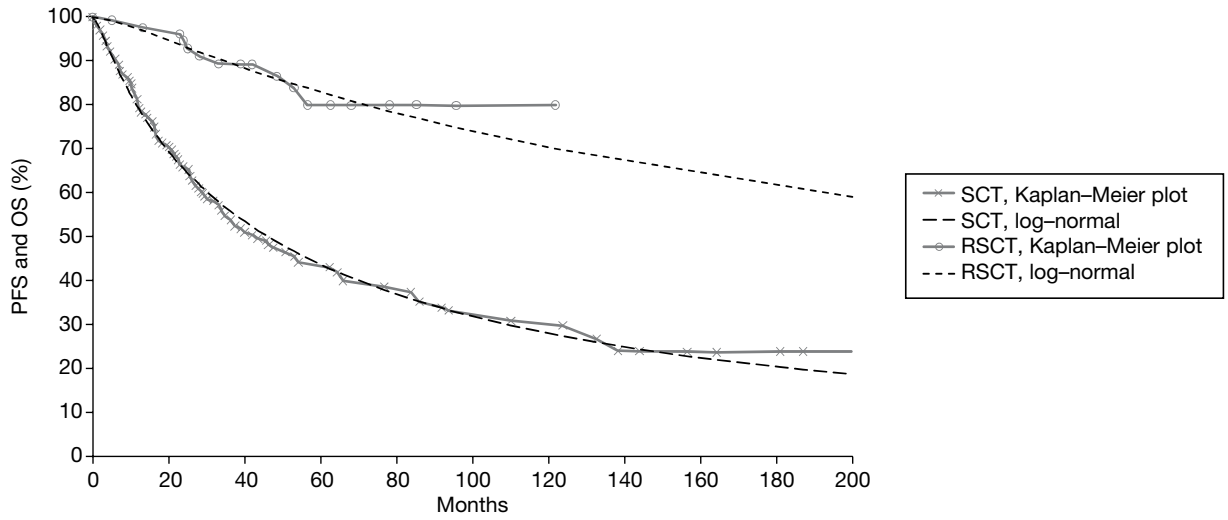


FIGURE 32 Overall survival for patients treated with ASCT and salvage chemotherapy with or without rituximab.[134]

Coiffier *et al.*[129] presented results from a small sample of patients ($n = 59$) who received one of the following combinations: R-monotherapy/R-monotherapy; R-chemotherapy/R-chemotherapy, R-monotherapy/R-chemotherapy; and R-chemotherapy/R-monotherapy. The findings showed that the second-line response rate and TTP did not appear to be affected by rituximab in patients who had received rituximab in first line. However, the number of patients who received R-monotherapy is unknown and the participants in the study were patients diagnosed with a B-cell lymphoma, thus the numbers of patients with FL within the study is unknown.

From a non-systematic review of the literature via web searching, the AG identified further studies conducted in other types of lymphoma suggesting that retreatment with rituximab might be associated with a loss of efficacy.[130–132]

Borgerding *et al.*[130] reported a very low response rate in a cohort of 28 patients with DLBCL after prior exposure to rituximab. The authors reported an ORR of 32% (9 of 28 patients). Furthermore, Weide *et al.*[132] examined the use of bendamustine in combination with

mitoxantrone and rituximab (BMR) in patients with stage III/IV relapsed or refractory indolent lymphomas and MCL with or without prior rituximab-containing chemoimmunotherapy treatment. Fifty-seven patients were recruited, 39% of whom had received prior R-chemotherapy. The median age was 66 years (range 40–83 years). Approximately 50% of patients had FL. The ORR was 89% (35% CR and 54% PR). ORR in R-chemotherapy pre-treated patients was lower at 76% (38% CR and 38% PR).

Similarly, Martin *et al.*[131] report a Phase III trial comparing the response rates to R-ICE (rituximab, ifosfamide, carboplatin and etoposide) and R-DHAP salvage therapy followed by HDT with ASCT (CORAL trial) for patients with relapsed or refractory DLBCL. Martin *et al.*[131] report that prior exposure to rituximab was associated with a significant loss of efficacy. Patients in the rituximab group had a significantly worse PFS (17% vs 57% at 3 years) and OS (38% vs 67% at 3 years) compared with patients who were not previously treated with rituximab. Prior exposure to rituximab was an independent adverse prognostic factor for both PFS (RR 2.0, 95% CI 1.2 to 3.3, $p = 0.008$) and OS (RR 2.2, 95% CI 1.3 to 3.9, $p = 0.004$). The AG acknowledges that the effectiveness between patients previously treated with rituximab and those naive to rituximab might be confounded by the level of disease aggressiveness; those relapsing early on rituximab might have a more aggressive disease.

Overall, the two studies[128,129] reported by the manufacturer do not provide conclusive evidence to prove or disprove rituximab resistance. Further studies identified by the AG[130–132] suggest that there might be a resistance effect to rituximab. The AG sought clinical advice on this issue, which indicated that resistance of rituximab is unknown; however, the clinicians believed that there is little or no loss of effectiveness considering its mechanism of action.

In the base case, no resistance is assumed. SAs are conducted, exploring the potential development of resistance after rituximab retreatment. SAs are conducted by increasing the rate of progression in patients receiving rituximab in second line when they had previously been treated with rituximab.

Incorporation of adverse events in the economic assessment

The economic model includes the impact of AEs in terms of management costs and impairment in quality of life. Only grade 3 and 4 AEs were included, as these are deemed of clinical and economic importance by the AG. Furthermore, only those that occurred in the first-line induction setting were included because of the lack of robust data in patients treated in second-line and subsequent lines of treatment.

After reviewing the relative frequency of AEs within patients treated with chemotherapy with and without rituximab and the likely management cost and impact on HRQoL, the AG included the following AEs in first-line induction: leucopenia, granulocytopenia, neutropenia, anaemia, alopecia, infection, cardiac arrhythmia and cardiac dysfunction.

Only grade 3/4 neutropenia and leucopenia have been included in first-line maintenance as these were the most commonly reported grade 3 or 4 AEs in the PRIMA study.[71]

The management costs associated with the treatment of AEs were extracted from the costs used in a submission by the manufacturer for an ongoing NICE appraisal.[124] It is also assumed that grade 3 and 4 AEs would incur the same costs. We further assumed that each AE led to a reduction in HRQol by 15% for 45 days. It was not possible to independently estimate the management costs of AEs and the effect on HRQoL owing to resource constraints. The management costs were varied by ± 20% in SAs. The disutility was also varied in SAs.

The AG acknowledges the limitations of the inclusion of AE in the economic model, in that it is very simplistic. However, SAs presented later indicated that AE had a limited impact on the ICER (see *Appendix 15*). *Table 43* provides a summary of AEs included in the economic model.

Drug acquisition and administration costs

The planned dose from the three main trials[92,93,95,96] were used to calculate the drug acquisition cost in the absence of detailed information about dose reduction/increase for each separate arms in the trials.

The planned number of cycles were also used in the economic model. Patients treated with CHOP or R-CHOP were assumed to receive a maximum of eight cycles in first-line induction and six cycles in second-line induction. A SA was conducted assuming that patients received a maximum of six cycles of CHOP and R-CHOP in first-line induction. Patients treated with FC or R-FC were assumed to receive a maximum of four cycles in second-line induction. A SA was conducted assuming that patients treated with FC-containing regimens would receive a maximum of six cycles. The planned dose and maximum number of cycles used in the economic model are summarised in *Table 44*.

In the economic model, the number of cycles a patient receives is calculated from the PFS curve to account for patients that withdraw before the end of planned treatment owing to progression. Withdrawal from toxicity was not modelled; however, this was shown to be uncommon in the first-line trials.[91–93,95,96]

The acquisition costs of the intervention are calculated from the protocol defined/planned dose, the BSA (see *Table 35*) and unit costs extracted from the BNF.[86] No vial sharing is assumed.

The costs associated with the administration of each cycle of treatment are derived from *NHS Reference Costs 2009/10*[140] and assumptions included in the MS.[62] Chemotherapies are assumed

TABLE 43 The rates of AEs and management costs used in the economic model

	Rates (%)						Cost used in the economic model (£)	
AE	CVP[95,96]	R-CVP[95,96]	CHOP[92]	R-CHOP[92]	MCP[93]	R-MCP[93]		Source for costs
Leucopenia	8.81	11.73	60.98	69.06	58.33	71.43	0	MS for ongoing NICE appraisal[124]
Granulocytopenia	–	–	53.17	63.06	–	–	1514	MS for ongoing NICE appraisal[124]
Neutropenia	13.84	24.07	–	–	–	–	3272	MS for ongoing NICE appraisal[124]
Anaemia	–	–	10.24	8.97	4.17	2.86	445	SA09F: Other red blood cell disorders without CC[140]
Alopecia	–	–	60.98	66.82	–	–	44	MS for ongoing NICE appraisal; assumed to be the same as depression[124]
Infection	–	–	6.83	4.95	8.33	6.67	1077	MS for ongoing NICE appraisal[124]
Cardiac dysfunction	–	–	0.98	3.14	–	–	606	MS for ongoing NICE appraisal; assumed to be the same as arrythmia[124]
Cardiac arrhythmia	–	–	0.00	1.79	–	–	606	MS for ongoing NICE appraisal[124]

CC, complications and comorbidities.

to be administered on a day-case basis. The unit costs and Healthcare Resource Groups used are presented in *Table 45*. In addition to the administration costs from the NHS reference costs, patients who receive rituximab are assumed to incur additional pharmacy costs based on the costs included in the MS[62] (£15.54). A SA is conducted assuming a cost of £32 as used by the manufacturer in an ongoing NICE appraisal for maintenance rituximab.[124] Pharmacy costs were included separately because the manufacturer stated that other treatment costs (i.e. chemotherapy drugs, including any pharmacy dispensing costs and associated drugs to manage the side effects of the chemotherapy) are excluded from NHS reference costs. Finally, the cost associated with transport is also included assuming that 30% of patients require NHS transportation.[62]

A summary of drug acquisition and administration costs by chemotherapy cycle in first-line induction per patient is presented in *Table 46*, assuming a BSA of 1.80.

It is not clear from Sebban *et al.*[134] which salvage therapies or which rituximab regimens was used. It is also unclear what were the proportion of patients that responded to salvage therapy, the proportion that had a successful harvest and the proportion of patients that receive ASCT.

In the economic model, we assumed that patients receive two cycles of ESHAP with or without rituximab before ASCT with BEAM. The planned dose has been extracted from the clinical policies and protocol document from Surrey, West Sussex and Hampshire Cancer Network,[141] presented in *Table 47*. We assumed that rituximab is administered at 375 mg/m^2. The cost of salvage therapy with or without rituximab in patients with relapsed FL is estimated from the BNF.[85]

In the base case, we assumed the response rates for HDT with or without rituximab to be 10% higher than the response rates for CHOP and R-CHOP in second-line treatment.[74,75] We further assumed that 80% of patients have a successful harvest after response to HDT. The AG stresses that these assumptions have been made with extremely limited supportive data. SAs were conducted varying both the response rate for HDT and proportion of patients with successful harvest.

TABLE 44 Dose and number of cycles used in the economic model

Treatment	CVP[95,96]	R-CVP[95,96]	CHOP[92]	R-CHOP[92]	MCP[93]	R-MCP[93]
Cyclophosphamide	750 mg/m^2 i.v. day 1	750 mg/m^2 i.v. day 1	750 mg/m^2 i.v. day 1	750 mg/m^2 i.v. day 1		
Vincristine	1.4 mg/m^2 i.v. day 1	1.4 mg/m^2 i.v. day 1	1.4 mg/m^2 i.v. day 1	1.4 mg/m^2 i.v. day 1		
Prednisone/ prednisolone[a]	40 mg/m^2 days 1–5	40 mg/m^2 days 1–5	100 mg/m^2 days 1–5	100 mg/m^2 days 1–5	25 mg/m^2 days 1–5	25 mg/m^2 days 1–5
Mitoxantrone					8 mg/m^2 i.v. days 1 and 2	8 mg/m^2 i.v. days 1 and 2
Chlorambucil					3 × 3 mg/m^2, orally, days 1–5	3 × 3 mg/m^2, orally, days 1–5
Doxorubicin			50 mg/m^2 i.v. day 1	50 mg/m^2 i.v. day 1		
Rituximab		375 mg/m^2 i.v. day 1		375 mg/m^2 i.v. day 1		375 mg/m^2 i.v. day 1
Maximum no. of cycles	8	8	6–8[b]	6–8[b]	8	8
Interval between cycles	21	21	21	21	28	28

i.v., intravenously.
a Prednisone is assumed to be similar to prednisolone.
b Assuming eight cycles in the economic model in first-line induction and six cycles in second-line induction.

TABLE 45 Drug administration costs

Regimen	Administration cost (£)	Source
R-chemotherapy	309.17	SB14Z: Deliver complex chemotherapy, including prolonged infusional treatment at first attendance[140]
Maintenance	284.45	SB15Z: Deliver subsequent elements of a chemotherapy cycle[140]
Chemotherapy alone	270.62	SB13Z: Deliver more complex parenteral chemotherapy at first attendance[140]
Pharmacy cost	15.54	MS[61]
Transport	39.24	PTS: Patient Transport Services[140]

TABLE 46 Drug acquisition and administration costs by chemotherapy cycle per patient in first-line induction

	Costs (£)					
	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
Drug acquisition cost/cycle	60.48	1282.89	233.08	1455.49	218.78	1441.19
Administration cost/cycle[a]	297.93	336.49	297.93	336.49	568.55[b]	607.10[b]
Total treatment cost/cycle	358.41	1619.38	531.01	1791.98	787.33	2048.29
Total treatment cost/patient according to the protocol defined dose	2867	12,955	4248	14,336	6299	16,386

a This includes the cost associated with NHS transportation. It is assumed that 30% of patients require NHS transportation.
b Assuming 2 days of administration.

For patients responding to HDT with or without rituximab and for whom the harvest was successful, the cost of ASCT + BEAM was assumed to be £30,400, based on a costing exercise commissioned by the London Specialised Commissioning Group.[142] The cost includes pre-transplant mobilisation, stem cell harvest and storage, pre-transplant assessment, patient work-up, transplant admission and cost up to 1 year after discharge.

Management at the end of treatment induction/maintenance: monitoring and surveillance cost

The management of the disease at the end of treatment induction and/or maintenance is adapted from the monitoring reported in the MS[62] after discussion with our clinical experts. Compared with the monitoring reported in the MS,[62] the monitoring defined by our clinical experts (*Table 48*) was less intensive, particularly with regard to scanning and imaging.

The AG comments that the monitoring used in the economic model is simplistic, but that SAs indicated that the results were not markedly influenced by this parameter (see *Appendix 15*).

After first- and second-line induction treatment the monitoring was separated into two phases:

- first 6 months after the end of treatment induction
- remaining months.

The monitoring after maintenance treatment with rituximab has also been separated into two phases:

- first 24 months after the end of maintenance
- remaining months.

TABLE 47 Treatment protocol for ESHAP[141]

Day	Drug	Dose
1–4 (four doses)	Cisplatin	25 mg/m^2/day
1–5 (five doses)	Methylprednisolone	500 mg/day
1 **only**	Cytarabine	2000 mg/m^2
1–4 (four doses)	Etoposide	40 mg/m^2/day
1–6 (six doses)	Corticosteroid eye drops, e.g. prednisolone 0.5%	One drop

TABLE 48 Monitoring and management at the end of treatment induction/maintenance

	Frequency	
Items	Treatment induction: first 6 months after end of treatment induction	Maintenance: first 24 months after end of maintenance
Period 1		
Haematologist led	One every month	One every 3 months
CT scans	One CT scan at end of treatment	One CT scan at end of treatment
FBC, patient history, physical examination, LFT, U&E	One every month	One every 3 months
Period 2		
	Remaining months	**Remaining months**
Haematologist led	One every 4 months	One every 4 months
CT scans	No CT scan	No CT scan
FBC, patient history, physical examination	One every 4 months	One every 4 months
Immunoglobulin tests, LFT, U&E, LDH	One every 4 months	One every 4 months

FBC, full blood count; LFT, liver function test; U&E, urea and electrolytes.

Unit costs have been extracted from the *NHS Reference Costs 2009/10* and costs used in the Sheffield Teaching Hospital Trust (2005–6, personal communication). Costs are summarised in *Table 49*.

Health service costs associated with management in third/subsequent lines

Patients that progress after second-line treatment with CHOP, R-CHOP, FC or R-FC (induction or maintenance) and who are still alive are assumed to undergo third/subsequent lines of therapy. A one-off cost was applied in the economic model according to the choice of treatment received in second-line (induction and maintenance).

The management costs were estimated from the post-protocol treatments observed in the EORTC 20981 trial.[74,75] The frequency of resources used for patients treated with CHOP only, R-CHOP only, CHOP in addition to maintenance rituximab, and R-CHOP in addition to maintenance rituximab[74] were multiplied by the unit costs used by the manufacturer in a previous NICE appraisal (*Table 50*).[73] Unit costs were not inflated as main costs were drug and procedure costs.

Patients treated with HDT with or without rituximab are assumed to go directly on to palliative care and no costs were applied for the further lines of treatments. This assumption was made in the absence of data about the post-progression treatment after HDT with or without ASCT

TABLE 49 Unit costs applied to estimate monitoring cost

Resource	Unit cost (£)	Definition/source
Hospital clinic visit with haematologist	128.67	Code: 303 – Clinical haematology consultant led: follow-up attendance non-admitted face to face[140]
CT scan	146.16	Code: RA14Z – CT scan, more than three areas[140]
FBC	5.50	Sheffield hospital (Sheffield Teaching Hospital Trust, 2005–6, personal communication)
Patient history/physical examination	5.44	Code: DAP842–Other pathology service[140]
Full profile (U&E, LFT, calcium)	14.98	Sheffield hospital (Sheffield Teaching Hospital Trust, personal communication)
Serum IgG, IgA, IgM and electrophoresis	21.99	Sheffield hospital (Sheffield Teaching Hospital Trust, personal communication)
LDH test	11.12	Sheffield hospital (Sheffield Teaching Hospital Trust, personal communication)

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; U&E, urea and eclectrolytes.

TABLE 50 Post-protocol treatment and mean cost associated with third-line/subsequent line of therapy according to the choice of second-line induction treatment/maintenance

		Treatment received in second line, %[74]			
Treatment	Unit cost (£)[72]	CHOP	R-CHOP	CHOP-Rx	R-CHOP-Rx
Chemotherapy	3232	49.28	33.67	34.21	38.46
Radiotherapy	1620	23.19	18.37	17.11	17.58
ASCT	18,998	4.35	8.16	7.89	5.49
Allogeneic SCT	41,721	7.25	7.14	10.53	4.40
Rx, single	8490	37.68	13.27	10.53	5.49
Rx, combination	11,206	28.99	14.29	17.11	8.79
Other	0	11.59	12.24	7.89	18.68
Total cost (£)		**12,265**	**8644**	**10,085**	**5857**

Rx, maintenance rituximab.

and the assumption that fewer treatments are available after relapse to ASCT or HDT. A SA was conducted assuming no costs for third-line treatment for all patients.

Health service costs associated with palliative and/or terminal care

The costs associated with palliative care were estimated from the cost of palliative care for different type of advanced cancers (breast, colon, lung, uterus, ovary, prostate, stomach/oesophagus) from the start of strong opioid treatment until death.[143] The average cost per month was calculated excluding the cost of hospitalisation, as it is likely that hospitalisation costs represent terminal care. The costs per month have been inflated to 2010 prices and are estimated to be £180.68 per month.

In addition to the cost of palliative care, the cost associated with terminal care, i.e. the management before death, was included. This cost was applied only to patients whose cause of death is attributable to FL. The cost of terminal care is sourced from the NICE clinical guidance on cancer palliative/supportive care[125] and includes the cost of support provided by specialist hospital/community palliative care teams, including hospice type care, day care, hospital inpatient/outpatient support, bereavement services and continuous support for dying patients. The cost per cancer death is assumed to be £4077 (£3236 inflated to 2010 prices).[125]

The AG acknowledges that it is possible that there might be double-counting, as two separate sources have been used. SAs were conducted assuming no cost for terminal care.

Death in progression-free survival after first line

We used PFS as a proxy for progression; however, PFS includes both relapse and death as an event. The MS[62] reported that seven deaths occurred in the CVP arm and three deaths in the R-CVP arm. At the end of the trial follow-up period, it was estimated that the number of events (death and/or progression) were 136 and 98, respectively, based on the Kaplan–Meier curves and number of patients randomised. Consequently, we estimated that 5.15% (CVP) and 3.06% (R-CVP) of progression events were attributable to death. The rate of death in CVP was applied to CHOP and MCP. The rate of death in R-CVP was applied to R-CHOP and R-MCP. The rate is then varied using a beta distribution in the PSA.

Health-state utilities

This section of the report presents a systematic review of HS utilities in patients with FL and describes the assignment of utilities in the economic model.

Systematic review of health-state utilities in patients with follicular lymphoma

Methods A systematic search was performed to identify studies addressing the impairment in quality of life in patients with FL. Full papers and abstracts were included in the review. Only studies conducted in patients with FL or studies conducted in a mix of similar patients when the majority of patients had FL have been included. As the AG was aware of data using the EQ-5D in patients with FL and, given resource constraints, only studies assessing the quality of life using the EQ-5D have been considered for the review, as this is the preferred valuation method of HRQol by NICE.[97] The AG acknowledges that this may be a limitation.

The following databases were searched for relevant published literature: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); CINAHL; EMBASE; The Cochrane Library including the CDSR, CENTRAL, DARE, NHS EED and HTA databases; SCI; and BIOSIS. Ongoing research have been searched using clinical trials databases and registers, including NIHR Clinical Research Network Portfolio; National Research Register (NRR) archive 2000–7; Current Controlled Trials and ClinicalTrials.gov. Finally, relevant conference proceedings were searched, including the ASCO, ESCO, ASH, BSH and the EHA. Full details of the main search strategy for this review are presented in *Appendix 5*. In addition, the MS[62] was handsearched[62] to identify relevant references.

Studies were selected for inclusion through a two-stage process. Titles and abstracts were examined for inclusion by one reviewer. Full manuscripts of selected citations have been retrieved and assessed by one reviewer.

Results The search retrieved 712 citations relating to quality of life (*Figure 33*). Six hundred and sixty-nine articles were excluded at title stage, and 28 articles were excluded at abstract level. Fifteen studies have been examined at full-text level and two studies (corresponding to three references) were identified meeting the criteria for the systematic review of quality-of-life data. The study conducted by Wild *et al.*[118,119] is unpublished and was commissioned by the manufacturer. The full report was made available to the AG and is referred as the 'Oxford Outcome Study'. The second study, by Friedlich *et al.*[144] was available in only the abstract form and was conducted in a mix of patients with follicular and other indolent lymphomas. A summary of included studies is below. Reasons for exclusion were the absence of EQ-5D data

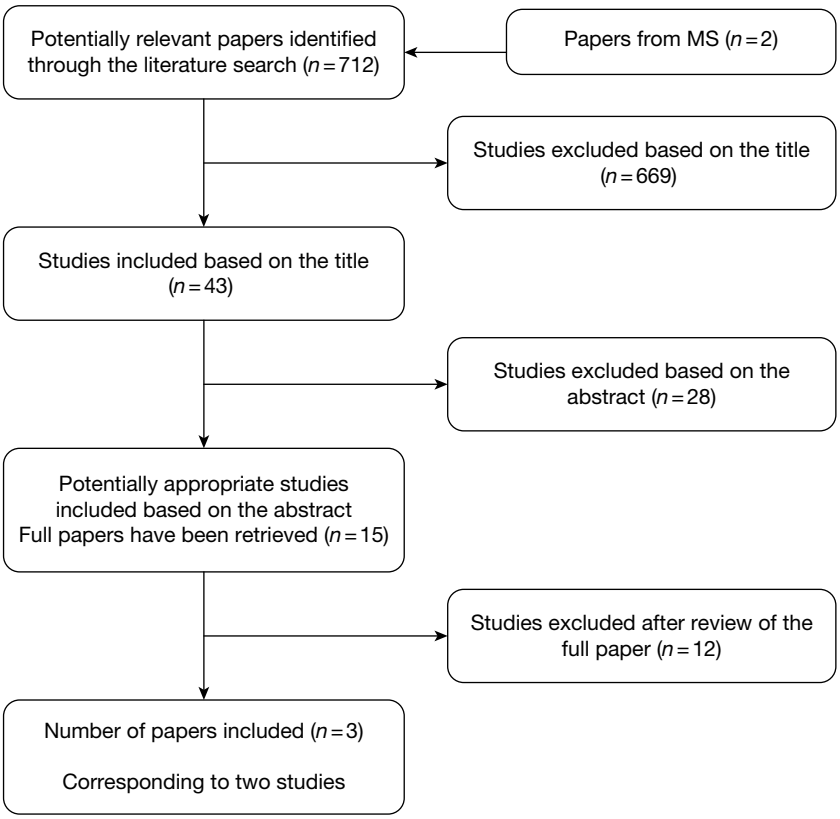


FIGURE 33 Flow diagram of quality-of-life review selection/exclusion.

(use of other instruments or EQ-5D data not presented), Q-TWiST analysis or utilities estimated in a different population.

Review of the Oxford Outcomes Study

The review is based on the unpublished report of the study[119] made available to the AG by the manufacturer. This study was commissioned by the manufacturer and was used in their economic model.

Method The study included 222 patients, aged ≥ 18 years with histologically confirmed FL and an ECOG performance status of 0–2. Patients were recruited from eight UK sites. Utilities were elicited from patients using the ED-5D questionnaire. The visual analogue scale (VAS) score is also presented. Patients also completed other outcome measures such as the Functional Assessment of Cancer Therapy-G [FACT (general)] and FACT-LYM (lymphoma).

Of the 222 returned case report forms, 215 participants returned completed EQ-5D questionnaires and 218 returned completed VAS data. The main analysis separated patients into five possible health states (HSs):

- active disease: newly diagnosed (HS1)
- active disease relapsed (HS2)
- PR to therapy (HS3)
- CR to therapy/remission (HS4)
- disease free (no detectable diseases) (HS5).

The authors state:

> Four of the five categories relate to the known stage of the disease and in particular to patients response to treatment. Patients who are disease free have essentially had the best response to treatment, those in remission the next, followed by PR and, finally, those without response (or whose response has relapsed). The newly diagnosed stage represents patients who have active disease and have started (or may be about to start) treatment, but for whom their response to treatment and therefore the relevant response categorisation is unknown.

Additional analyses are also presented aggregating the following HSs:

- 'partial response to therapy' (HS3), 'complete response to therapy/remission' (HS4), 'disease free' (no detectable diseases) (HS5)
- 'active disease: newly diagnosed' (HS1), 'active disease relapsed' (HS2).

Differences in the HSs utilities between groups have been examined using the Kruskal–Wallis *H*-test or Mann–Whitney *U*-test. Analyses are also presented estimating HS utility using ordinary-least-square regression analysis. The study also examined the impact of current and previous treatment with chemotherapy, but was not powered to examine this issue.

Results HSs utilities for the five HSs defined in the main analysis are presented in *Table 51*.

Additional analyses aggregating HSs are presented in *Table 52*.

Comments The definition of selected HSs is poorly described. Following the short description provided by the authors, it appears that the HSs relate to the degree of response to chemotherapy but not the number of previous lines of chemotherapy (*Table 53*). Forty-two per cent of patients achieving PR to therapy received two or more chemotherapies; the proportion of patients in remission/full response to therapy that received two or more previous chemotherapy is about 28%.

In the main analysis, in which patients were separated into five possible HSs, there are some concerns about the small sample size of patients included within each HSs (range 27–50). Inaccuracy could be easily introduced when working with such small sample sizes. The description of included patients is also poorly detailed within the report, but is available in a related publication.[145] Thirty-three per cent of patients had stage I/II FL. Utility values are expected to be lower when only patients with FL with stage III/IV are included. Finally, there are some inconsistencies between the subgroup analyses (see *Table 52*) when HSs were aggregated.

Review of Friedlich et al.

Only the abstract form of the study[144] was available. The study was conducted in patients with indolent lymphoma or FL attending an outpatient malignant haematology clinic in Toronto (Canada). Patients were asked to complete a questionnaire including utility measures (EQ-5D, FACT).

Eighty-four patients completed the questionnaire. The mean age was 58.7 years (SD 13.8) and 55% were male. The majority of patients had FL (55%). Similarly, the majority of patients had stage III/IV FL (65%).

TABLE 51 Health-state utilities presented in the main analysis with patients assigned to five possible health states[118,119]

			Range	
Disease state	*n*	Mean (SD) [SE]	Minimum	Maximum
Active disease: newly diagnosed (HS1)	50	0.83 (0.22) [0.03]	–0.24	1.00
Active disease: relapsed (HS2)	33	0.62 (0.32) [0.06]	–0.08	1.00
PR to therapy (HS3)	39	0.77 (0.21) [0.03]	0.02	1.00
Remission/full response to therapy (HS4)	66	0.79 (0.23) [0.03]	–0.08	1.00
Disease free (HS5)	27	0.88 (0.15) [0.03]	0.49	1.00

TABLE 52 Aggregation of health-state utilities[118,119]

Heath state	*n*	Mean	SE
Pre-progression (HS3, HS4, HS5)	132	0.805	0.018
Disease progression (HS1, HS2)	84	0.7363	NR
Progression free (HS3, HS4, HS5)[a]	134	0.7699	NR

NR, not reported.
a It is unclear how this was calculated; there appears to be an error as 134 does not equal 39 + 66 + 27 (see *Table 51*).

TABLE 53 Number of patients in each disease state that have received from zero to six previous treatments[118,119]

	Disease state (%)				
No. of previous chemotherapies	Active disease: newly diagnosed (*n* = 51)	Active disease: relapsed (*n* = 34)	PR to therapy (*n* = 40)	Remission/full response to therapy (*n* = 67)	Disease free (*n* = 26)
0	94.1	20.6	10.0	22.4	11.5
1	2.0	17.6	47.5	49.3	30.8
2	2.0	20.6	20.0	13.4	23.1
3	2.0	26.5	5.0	6.0	23.1
4	0.0	5.9	7.5	6.0	3.8
5	0.0	8.8	7.5	3.0	7.7
6	0.0	0.0	2.5	0.0	0.0

The mean utility score for the population was 0.84 ± 0.24 SD. The authors reported that utilities were higher ($p = 0.049$) in patients being observed (0.91 ± 0.16 SD) compared with those in first remission (0.84 ± 0.25 SD), subsequent remissions (0.81 ± 0.20 SD) or those who were receiving active chemotherapy (0.75 ± 0.27 SD). The authors also reported that patients who were being followed in ongoing remission also trended to higher health status values (mean 0.88 ± 0.21) compared with those who were not in remission (0.80 ± 0.22 SD, $p = 0.15$).

Health-state utilities used in the economic model

The economic model included in the MS[61] uses utility values from the Oxford Outcomes Study.[118,119] The manufacturer assumed that the utility in PFS1 was similar to the utility of patients considered to be disease free (0.88, 95% CI 0.81 to 0.95). The utility for patients in remission/full response to therapy (0.79, 95% CI 0.72 to 0.86) was used to represent the utility for patients in PFS2. Finally, the utility for progressive disease was assumed to be 0.62 (95% CI 0.48 to 0.76).

The ERG in the ongoing appraisal for first-line maintenance suggested that it is inappropriate to assume that patients in PFS1 and PFS2 have different utility values given that these patients are in remission.[126] The ERG also noted that the utility for patients in the progressive state was estimated from a small sample size ($n = 33$) and did not account for patients that would be in 'remission' in the third/subsequent lines of treatment. In addition to these limitations, the AG noted that using the utility for patients considered to be 'disease free' to represent the utility in patients in PFS1 also appears to be inappropriate as these patients are in a 'remission' state and not 'disease free'.[118,119]

The Oxford Outcomes Study[118,119] reported additional analyses aggregating health states into 'disease progression' and 'progression free' (see *Table 52*). This was considered more appropriate by the AG 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. Furthermore, aggregating utility values provided larger sample sizes and was expected to decrease the uncertainty and potential inaccuracy in the mean estimate. There also appears to be some errors in some of the subgroup analysis (see *Table 50*).

In the base case, the utility value in PFS1 and PFS2 was assumed to be 0.805, against 0.7363 for patients in the progressive health state (see *Table 52*). SAs were conducted to examine the impact of HRQoL in the ICER. HS utilities were varied by ± 20%. The values included in the MS[62] were also examined in SAs. HS utilities from a separate source[144] were also tested.

Utilities were varied in the PSA assuming a beta distribution. We assumed that the SE for the utility in progressive state was 5% around the mean in the absence of information in the study. Utility values were not age adjusted.

Analytic methods

Results are presented in terms of mean undiscounted LYs, discounted lifetime costs and discounted QALYs.

The following strategies were compared and the ICER was calculated for:

- CVP against R-CVP
- CHOP against R-CHOP
- MCP against R-MCP.

Incremental analyses to determine the most cost-effective combination of chemotherapy with or without rituximab were not conducted by the AG as this was not considered relevant. Discussions with our clinical experts suggested that the choice of chemotherapy was based on additional factors such as patient's disease characteristics and/or the presence of comorbidities as well as the efficacy of the regimen.

A range of scenarios were presented varying the main model assumptions to identify parameters that had the greatest impact on the ICER.

Probabilistic sensitivity analysis were also carried out using Monte Carlo simulation. The uncertainty in each parameter was represented using a probability distribution. The distribution with the key model parameters are presented in *Table 54*. The decision uncertainty was shown as the probability that each intervention is the most cost-effective at a given cost-effectiveness threshold. The probability of being the most cost-effective intervention was provided for WTP thresholds of £20,000 and £30,000 per QALY gained.

Results of the School of Health and Related Research economic assessment

Results are presented for two scenarios:

- base-case analysis assuming no first-line maintenance in patients responding to R-chemotherapy first-line induction
- scenario analysis incorporating first-line maintenance in patients responding to R-chemotherapy first-line induction.

Base-case analysis assuming no first-line maintenance in patients responding to R-chemotherapy first-line induction

Deterministic results

The results of the deterministic base-case cost-effectiveness analysis are presented in *Tables 55–57*. Analyses indicate that the addition of rituximab to CVP leads to a gain of 0.96 discounted QALYs for an additional cost of about £7389. The cost per QALY gained of CVP in combination with rituximab compared with CVP alone is £7720 (see *Table 55*).

TABLE 54 Summary of parameters used in the economic model

Description	Deterministic	PSA – distribution	Source
Gender distribution			
No. of males	879	✓ (Beta distribution)	Registry data in England[3] and Wales[a]
No. of females	990		
Age distribution	See *Figure 15*	✗	Registry data in England[3] and Wales[a]
All-cause mortality (Gompertz distribution)			
Scale (male)	0.0000312171	✗	Derived from UK life table[135]
Shape (male)	0.0965411930		
Scale (female)	0.0000115556		
Shape (female)	0.1042325152		
BSA	See *Table 35*	✓ (Normal distribution)	Derived from the height and weight from the PRIMA study[71,124]
Response rate	See *Tables 36* and *41*	✓ (Beta distribution)	First-line induction trials[91–93,95,96] and second-line induction trial[74,75]
PFS in responders and non-responders to first-line induction treatment	See *Tables 39* and *42*	✓ (Multivariate normal distribution)	Analysis of patient-level data from the M39021 trial,[95,96] provided by the manufacturer (Roche, personal communication)
PFS for responders in second-line treatment with CHOP or R-CHOP with or without maintenance (log-normal distribution – see* Figures 26 *and* 27*)			
Scale (CHOP)	2.394999	✓ (Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	Derived from van Oers *et al.*[74]
Shape (CHOP)	0.167823		
Scale (CHOP–R)	3.623044		
Shape (CHOP–R)	0.381342		
Scale (R-CHOP)	3.277728		
Shape (R-CHOP)	0.633029		
Scale (R-CHOP–R)	3.984251		
Shape (R-CHOP–R)	0.643069		

TABLE 54 Summary of parameters used in the economic model (*continued*)

Description	Deterministic	PSA – distribution	Source
PFS for non-responders in second-line treatment with CHOP or R-CHOP with or without maintenance (log-normal distribution – see* Figure 29*)			
Scale (CHOP)	2.389454	✓ (Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	Derived from van Oers *et al.*[74]
Shape (CHOP)	0.210479		
Scale (CHOP–R)	2.741266		
Shape (CHOP–R)	0.359914		
OS for responders in second line (log-normal distribution – see* Figure 28*)			
Scale (observation)	4.623707	✓ (Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	Derived from van Oers *et al.*[74]
Shape (observation)	0.288565		
Scale (maintenance)	5.104284		
Shape (maintenance)	0.385508		
OS for non-responders in second line (log-normal distribution – see* Figure 29*)			
Scale	3.759047	✓	Derived from Van Oers *et al.*[73]
Shape	0.453447	(Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	
PFS for patients receiving salvage treatment in second line (log-normal distribution – see* Figure 31*)			
Scale (HDT)	3.092036	✓	Derived from Sebban *et al.*[134]
Shape (HDT)	0.406642	(Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	
Scale (HDT + R)	4.179713		
Shape (HDT + R)	0.137204		
OS for patients receiving salvage treatment in second line (log-normal distribution – see* Figure 32*)			
Scale (HDT)	3.835276	✓ (Normal distribution, the scale parameter was varied assuming a SE of 5% around the scale)	Derived from Sebban *et al.*[134]
Shape (HDT)	0.498643		
Scale (HDT + R)	5.675053		
Shape (HDT + R)	0.506431		
Proportion of AE	See *Table 43*	✓ (Beta distribution)	First-line induction trials[91–93,95,96]
Cost of AE	See *Table 43*	✓ (Normal distribution, assuming a SE of 5% around the mean costs)	MS for ongoing maintenance appraisal[124]
Health-state utility			
PFS1, PFS2	0.805 (0.018 SE)	✓	Wild *et al.*[118,119]
Progressive disease	0.7633 (SE assumed to be 5% around the mean)	(Beta distribution)	Wild *et al.*[118,119]
Monitoring cost, administration cost	See *Tables 45* and *49*	✓ (Log-normal distribution or normal distribution assuming a SE of 5% around the mean costs)	See *Tables 45* and *49*
Cost: third line	See *Table 50*	✓ (Normal distribution, assuming a SE of 5% around the mean costs)	Derived from van Oers *et al.*[74] and units used in TA137 by the MS[73]
Cost: palliative care	£4077	✓ (Normal distribution, assuming a SE of 5% around the mean costs)	Guidance on Cancer Services[125]

a Welsh Cancer Intelligence & Surveillance Unit 2008.[16]

The addition of rituximab to CHOP leads to a gain of 0.53 QALYs for an additional cost of £5725. The cost per QALY gained of CHOP in combination with rituximab compared with CHOP alone is £10,834 (see *Table 56*).

Finally, the addition of rituximab to MCP leads to a gain of 0.57 QALYs for an additional cost of about £5267. The cost per QALY gained of MCP in combination with rituximab compared with MCP alone is £9316 (see *Table 57*).

Patients treated without rituximab in first-line induction spend less time in PFS1, but generally more time in PFS2 and in the progressive disease health state compared with patients receiving chemotherapies in addition to rituximab (*Figure 34*). A similar pattern is observed for the accrued QALYs (*Figure 35*). The fact that more patients in the R-chemotherapy group do not progress before death than in the chemotherapy group means that the average time in PFS1 is longer for the R-chemotherapy group, but the average duration in PFS2 and disease progression are shorter, as the patients who remain in PFS1 have zero times within these states.

The addition of rituximab is associated with an increase in treatment costs, the management of AEs and monitoring/surveillance in first-line induction treatment compared with patients treated with chemotherapy alone (*Figures 36–38*). However, patients treated with chemotherapy alone incur more costs in second line and subsequent lines of treatment.

Probabilistic results

Results from the PSA differ slightly compared with the deterministic results owing to non-linearities within the model. The ICER in the PSA for the addition of rituximab to CVP, CHOP and MCP is estimated to be £7735, £10,855 and £9313 per QALY gained, respectively (*Tables 58–60*). The probabilities of being cost-effective at different WTP thresholds are presented in *Figures 39–41* for R-CVP compared with CVP, R-CHOP compared with CHOP and R-MCP compared with MCP, respectively. The CEACs show that the addition of rituximab to

TABLE 55 Base-case deterministic cost-effectiveness of the addition of rituximab to CVP estimated by the AG

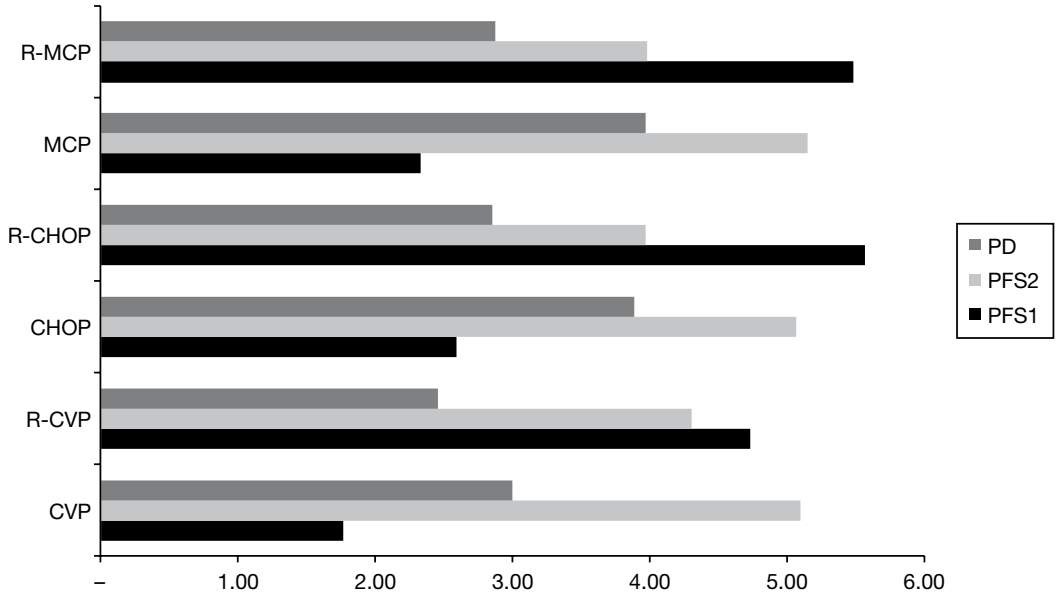
Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
CVP	9.86	30,793	5.99
R-CVP	11.50	38,183	6.95
Cost per QALY (£)			**7720**

TABLE 56 Base-case deterministic cost-effectiveness of the addition of rituximab to CHOP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
CHOP	11.55	34,983	6.84
R-CHOP	12.40	40,708	7.37
Cost per QALY (£)			**10,834**

TABLE 57 Base-case deterministic cost-effectiveness of the addition of rituximab to MCP estimated by the AG

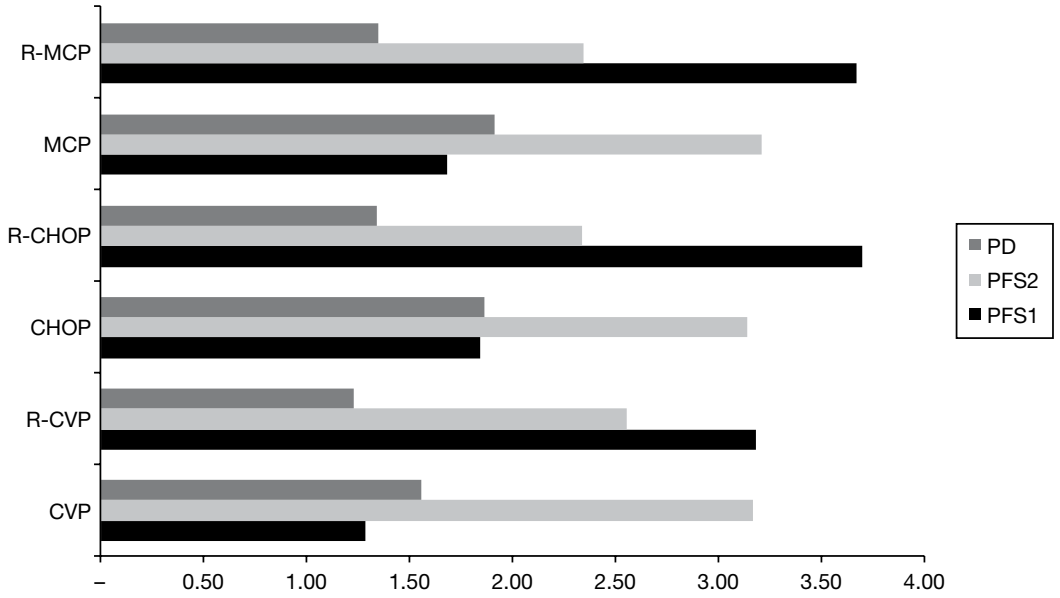
Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
MCP	11.45	36,103	6.79
R-MCP	12.35	41,370	7.36
Cost per QALY (£)			**9316**



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
PD	3.00	2.46	3.89	2.86	3.98	2.88
PFS2	5.09	4.30	5.07	3.97	5.15	3.99
PFS1	1.77	4.74	2.59	5.57	2.33	5.49

Undiscounted LYs

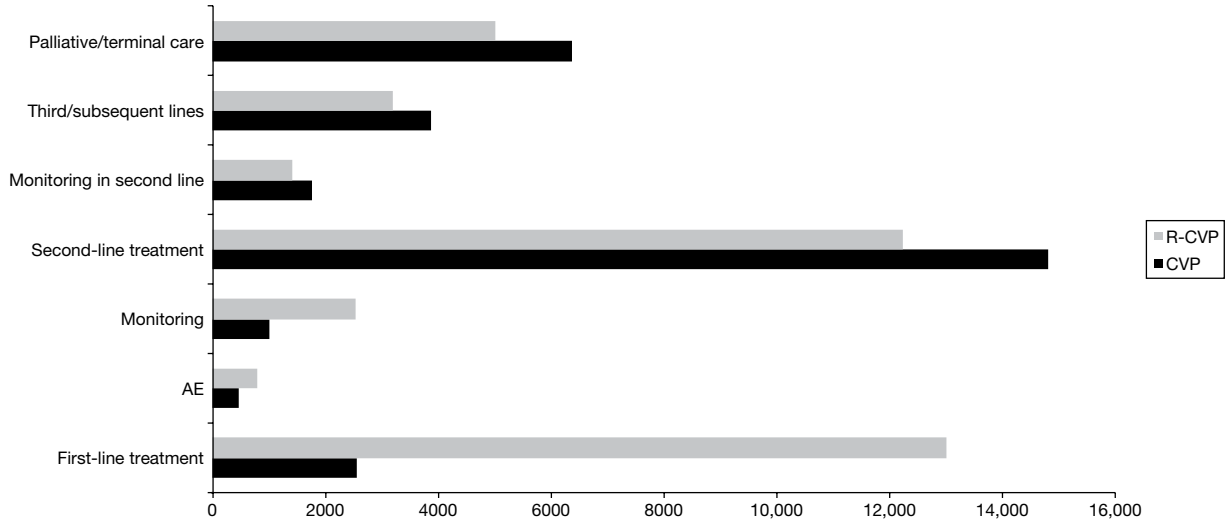
FIGURE 34 Base-case analysis: undiscounted LYs. PD, progression.



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
PD	1.55	1.23	1.86	1.34	1.91	1.35
PFS2	3.16	2.55	3.14	2.33	3.20	2.34
PFS1	1.28	3.17	1.84	3.69	1.68	3.66

Discounted QALYs

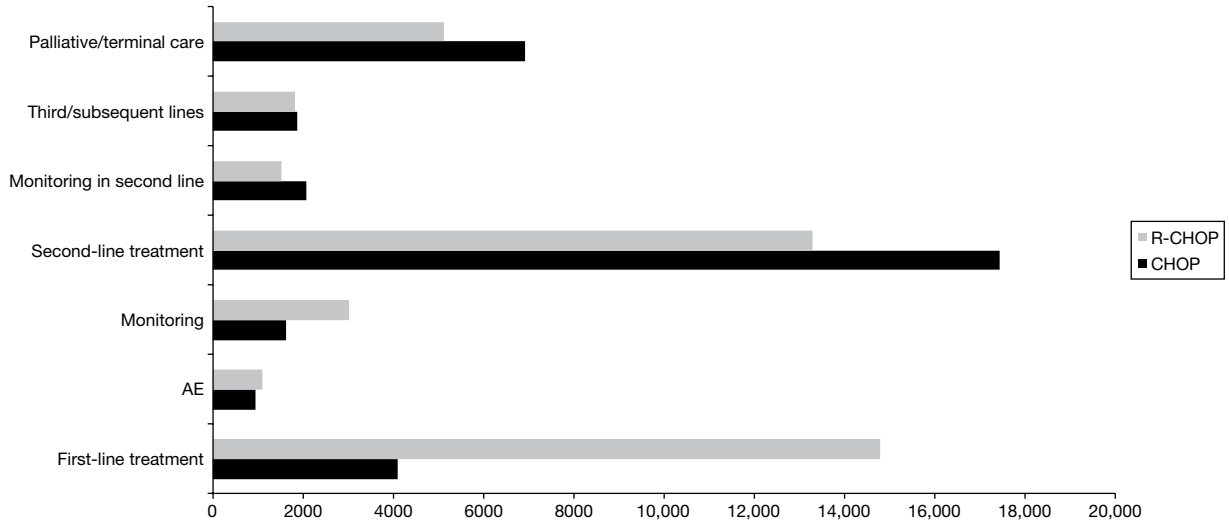
FIGURE 35 Base-case analysis: discounted QALYs. PD, progression.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-CVP	13,002	793	2536	12,243	1413	3183	5013
CVP	2544	456	997	14,812	1759	3860	6364

Discounted costs (£)

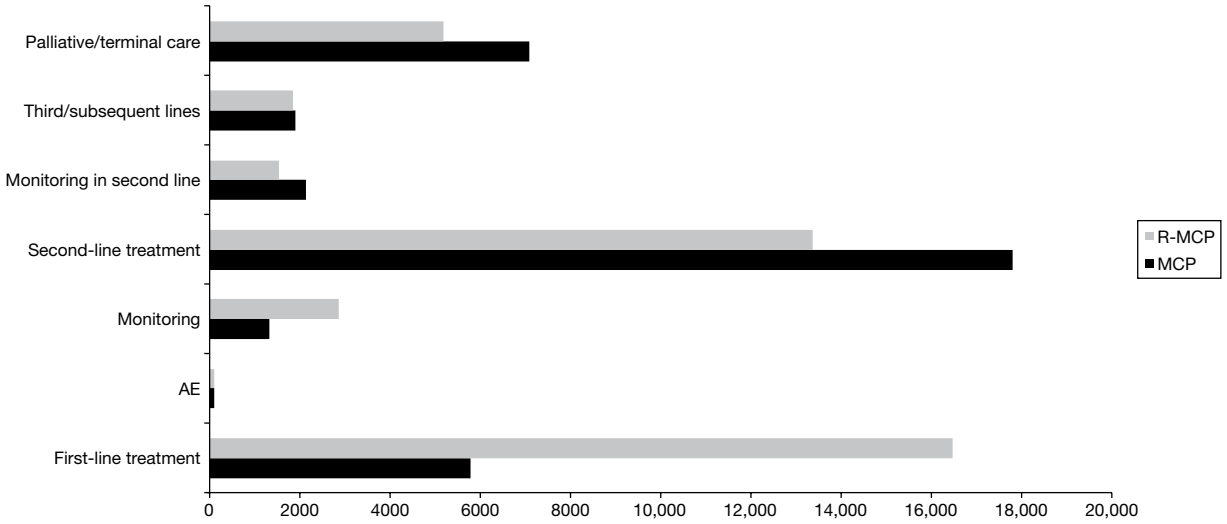
FIGURE 36 Base-case analysis: management and treatment costs for patients treated with CVP in first-line induction with or without rituximab.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-CHOP	14,792	1104	3023	13,306	1525	1827	5131
CHOP	4096	955	1610	17,452	2081	1873	6916

Discounted costs (£)

FIGURE 37 Base-case analysis: management and treatment costs for patients treated with CHOP in first-line induction with or without rituximab.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-MCP	16,488	84	2874	13,379	1533	1839	5174
MCP	5791	107	1311	17,797	2125	1894	7078

FIGURE 38 Base-case analysis: management and treatment costs for patients treated with MCP in first-line induction with or without rituximab.

chemotherapy (CVP, CHOP and MCP) in first-line induction have a high probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY gained.

The probabilities of the addition of rituximab to CVP being cost-effective compared with CVP alone are 100% when assuming a WTP of £20,000 and £30,000 per QALY gained, respectively (see *Table 58* and *Figure 39*).

The probabilities of the addition of rituximab to CHOP being cost-effective compared with CHOP alone are 88.50% and 95.70%, assuming a WTP of £20,000 and £30,000 per QALY gained, respectively (see *Table 59* and *Figure 40*).

The probabilities of the addition of rituximab to MCP being cost-effective compared with MCP alone are 92.10% and 96.70% assuming a WTP of £20,000 and £30,000 per QALY gained, respectively (*Table 60* and *Figure 41*).

Univariate sensitivity analyses: impact of main model parameters

A range of univariate SAs were undertaken to assess the impact of main model parameters and assumption on the cost per QALY gained. Full results of SAs performed are presented in *Appendix 15* for the comparison between R-CVP and CVP, R-CHOP and CHOP, and R-MCP and MCP. The main findings from the SAs are described below.

SA1: Varying the time horizon We explored different time horizon (5 years, 10 years and lifetime). The ICER was sensitive to the assumption about the time horizon and becomes more favourable to rituximab for all comparisons as the time horizon increases (*Table 61*).

SA2: Varying the discount rates We explored different assumptions about the discount rates, assuming either no discounting and either costs or benefits discounted. Results were not sensitive to the assumption about discounting (see *Appendix 15*). As an illustration, the ICER for R-CHOP

TABLE 58 Base-case analysis: probabilistic cost-effectiveness of the addition of rituximab to CVP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at £20,000	Probability CE (%) at £30,000
CVP	9.91	30,651	6.02		
R-CVP	11.56	38,050	6.97		
Cost per QALY (£)			**7735**	**100.00**	**100.00**

CE, cost-effectiveness.

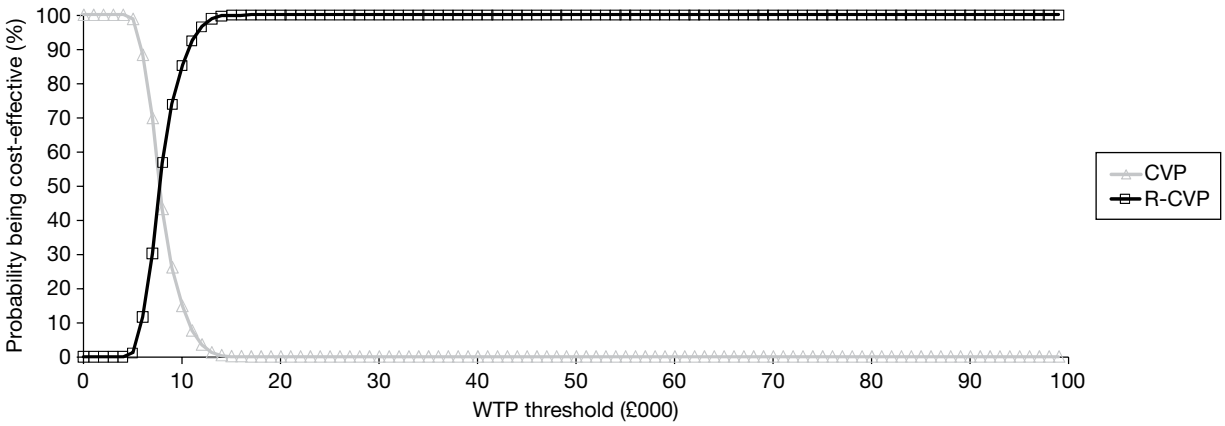


FIGURE 39 Base-case analysis: CEAC for R-CVP vs CVP alone.

TABLE 59 Base-case analysis: probabilistic cost-effectiveness of the addition of rituximab to CHOP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at 20,000	Probability CE (%) at 30,000
CHOP	11.60	34,881	6.85		
R-CHOP	12.39	40,608	7.38		
Cost per QALY (£)			**10,855**	**88.50**	**95.70**

CE, cost-effectiveness.

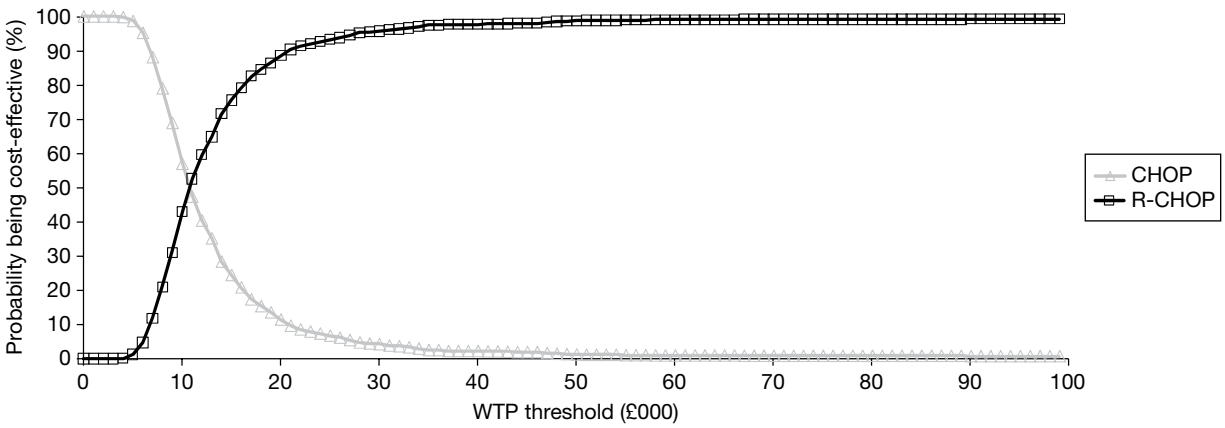


FIGURE 40 Base-case analysis: CEAC for R-CHOP vs CHOP alone.

TABLE 60 Base-case analysis: probabilistic cost-effectiveness of the addition of rituximab to MCP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at £20,000	Probability CE (%) at £30,000
MCP	11.50	35,970	6.80		
R-MCP	12.21	41,248	7.37		
Cost per QALY (£)			**9313**	**92.10**	**96.70**

CE, cost-effectiveness.

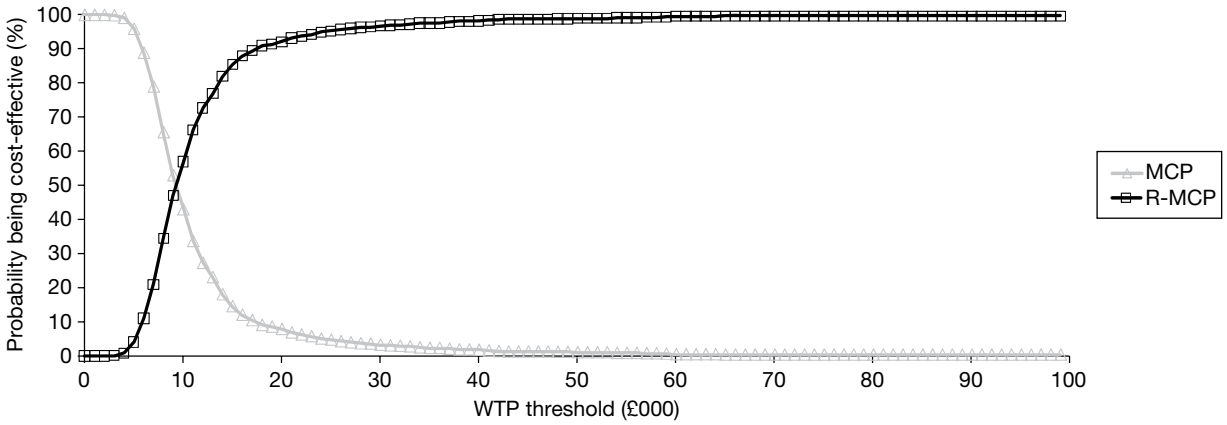


FIGURE 41 Base-case analysis: CEAC for R-MCP vs MCP alone.

compared with CHOP ranged from £11,788 (assuming no discounting for costs but QALY discounted at 3.5%) to £7634 (assuming no discounting for QALYs but costs discounted at 3.5%) per QALY gained.

SA3: Parametric distribution used to model the effectiveness in first line In the base case, the effectiveness was modelled fitting a log-normal to the Kaplan–Meier curve from the M39021 trial.[95,96] In SAs, we explored the use of two alternative distributions (Gompertz and Weibull distributions). These two distributions were selected as they provided a plausible but different extrapolation compared with the log-normal distribution. The ICER was broadly similar (*Table 62*) assuming a Weibull distribution compared with our base-case assumption (log-normal extrapolation). However, the ICER was particularly sensitive if a Gompertz distribution was selected (see *Table 60*). For example, the ICER of R-CHOP against CHOP was £3941 per QALY gained when assuming a Gompertz distribution compared with £10,834 using a log-normal distribution (base-case assumption).

The Differences between the log-normal and Gompertz estimates are probably caused by differences in the extrapolation at the end of clinical evidence, with the risk of progression using the Gompertz distribution flattening out after about 60 months (*Figure 42*).

As both curves provided a plausible fit to the observed data, the ICERs may be overestimated. However, as FL is usually considered as incurable, the Gompertz extrapolation might not be plausible.

S4: Varying the proportion of progression attributable to death The proportion of progression attributable to death in first-line induction was derived from the M39021 trial.[62,95,96] SAs were conducted assuming that no progressions are attributable to death or that the same proportion

TABLE 61 Sensitivity analysis: varying the time horizon

	Cost (£)		
Time horizon	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case (25 years)	7720	10,834	9316
5 years	20,998	33,975	24,366
10 years	11,287	16,650	13,598
Lifetime	7360	10,362	8963

TABLE 62 Sensitivity analysis: choice of parametric distribution

	Cost (£)		
Distribution	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
Weibull	8054	12,030	10,594
Gompertz	4174	3941	3146

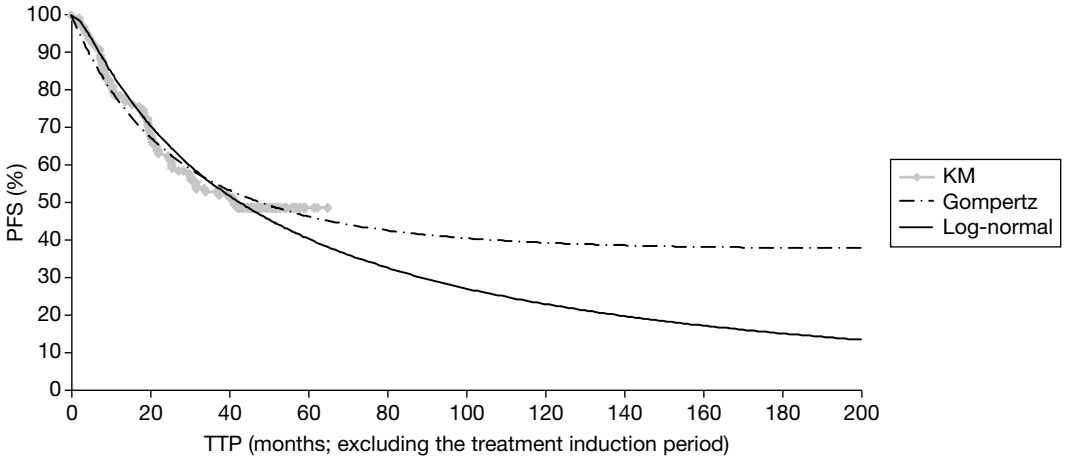


FIGURE 42 Comparison of the extrapolation using the log-normal and Gompertz distribution for responders to R-CVP. KM, Kaplan–Meier.

of progression is attributable to death in the two arms (*Table 63*). The impact on the ICER was minimal.

SA5: Examining the effect of resistance to rituximab in previously exposed patients As previously mentioned, the effect of rituximab resistance after retreatment with rituximab is unknown. In the base case, we assumed the same rate of progression after rituximab in combination with chemotherapy or salvage therapy in rituximab naive or rituximab pre-treated patients.

A SA was conducted exploring the potential impact of resistance among previously treated patients with rituximab. The resistance was modelled by reducing the rate of progression or death of rituximab in second line for patients previously treated with rituximab. A reduction up to 30% was examined in SAs to avoid the rate of progression/death in second line being higher for patients not receiving rituximab as part of the second-line treatment.

TABLE 63 Sensitivity analysis: Varying the rate of progression attributable to death

	Cost (£)		
Rate of progression	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case (5% for CVP, 3% for R-CVP)	7720	10,834	9316
None	8224	13,463	11,192
Using the rate from the CVP arm in both arms	7984	11,872	10,023
Using the rate from the R-CVP arm in both arms	8080	12,470	10,457

The ICER was very sensitive when a lower effectiveness was assumed in patients previously treated with rituximab (*Table 64*). For example, the ICER for R-CHOP against CHOP was > £20,000 per QALY gained if a reduction in effectiveness of > 20% was assumed (see *Table 64*).

Results of this SA have to be considered with caution, as the existence of a resistance effect is unknown and, if it does exist, how this would translate.

SA6: Examining the maximum time a patient can stay in PFS1 In the base case, a proportion of patients might not progress and remain in PFS1 during the entire simulation because of the parametric extrapolation. We examined a scenario in which we truncated the survival curves, assuming that patient can remain in PFS1 only for a maximum duration.

As expected, the ICER was very sensitive to this assumption. The ICER for the addition of rituximab to CHOP and MCP rose to > £20,000 per QALY gained if patients were assumed to be progression free in first line for a maximum duration of approximately 9 years (*Table 65*).

SA7: Increasing overall survival in patients receiving rituximab in addition to chemotherapy in second-line induction treatment In the base-case analysis, we assumed the same OS for patients treated with CHOP (FC) and R-CHOP (R-FC) in second-line induction after maintenance or observation. A SA was presented assuming an increase in the mean OS for patients receiving R-CHOP or R-FC in second-line induction treatment compared with CHOP or FC. As shown in *Table 66*, the impact on the cost per QALY was modest. This SA mainly effects the comparison between CVP against R-CVP as patients treated with CHOP or MCP regimens do not receive CHOP or R-CHOP in second-line induction treatment but only FC and R-FC if aged > 65 years.

The ICER increases as more patients treated with chemotherapy alone are expected to receive rituximab as part of their second line.

SA8: Health-state utility values There were uncertainties in the health-state utility values used in the economic model. In the base case, we assumed that the utility values in PFS1, PFS2 and progressive health state were 0.805, 0.805 and 0.7366, respectively.

A SA was conducted assuming the same utility values as in the MS[62] (0.880, 0.790 and 0.620) and resulted in an improvement in the ICER (*Table 67*). A SA was also performed using utility values estimated in Canada in a cohort of patients with different types of lymphoma (0.84, 0.81 and 0.74)[144] and showed a modest impact on the ICER (see *Table 67*).

TABLE 64 Sensitivity analysis: assuming a reduced effectiveness in second-line, in patients previously treated with rituximab

	Cost (£)		
Reduced effectiveness in previously treated rituximab patients	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
–10%	9379	13,843	11,718
–15%	10,616	16,328	13,632
–20%	12,328	20,163	16,494
–25%	14,870	26,939	21,253
–30%	19,102	42,361	30,902

TABLE 65 Sensitivity analysis: varying the maximum time a patient can stay in PFS1

	Cost (£)		
Maximum time that a patient can stay in PFS1	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
5 years	16,656	43,733	36,602
6 years	14,527	32,857	27,820
7 years	13,044	26,749	22,799
8 years	11,964	22,835	19,527
9 years	11,143	20,149	17,277
10 years	10,513	18,210	15,642
11 years	10,016	16,745	14,403
12 years	9613	15,607	13,437
13 years	9287	14,718	12,685
14 years	9018	13,999	12,074
15 years	8797	13,427	11,584
16 years	8616	12,963	11,188
17 years	8461	12,576	10,855
18 years	8331	12,256	10,579
19 years	8223	11,995	10,352

TABLE 66 Sensitivity analysis: assuming a higher survival in patients treated with rituximab in second line

Increase in mean OS	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
5%	8067	11,213	9620
10%	8441	11,588	9918
15%	8837	11,950	10,208
20%	9232	12,283	10,468
25%	9613	12,565	10,691

We examined a reduction in utility values ranging from 10% to 30%. Assuming a reduction in utility values of 30% had a modest impact on the ICER. A scenario is presented assuming that the utility in PFS1 is 10% higher compared with the utility values in PFS 2. The impact on the ICER was modest.

Finally, a range of SAs were conducted examining different assumptions about disutility owing to AEs. These had a minimal impact on the ICER.

SA9: Changes in the treatment pathway Changes in the treatment pathway were examined given the shortcoming in evidence available. Overall, using different evidence to model the effect of second-line treatment had a modest impact on the cost per QALY. Assuming that patients treated with CHOP or MCP regimens in first-line induction regimens received CHOP or R-CHOP in second line instead of HDT ± ASCT had a modest impact on the cost per QALY gained (*Table 68*). Similarly, we examined a scenario in which older patients received CHOP and R-CHOP in second-line induction instead of FC and R-FC. The impact on the cost per QALY was minimal (see *Table 68*).

The ICER was mainly sensitive whether the same treatment was given post-progression for patients previously treated with R-chemotherapy or chemotherapy alone.

SA10: Effectiveness of FC-containing regimens in older patients We also examined different assumptions about the effectiveness of FC-containing regimens in older patients assuming a reduced effectiveness compared with CHOP-containing regimens. The impact on the cost per QALY was minimal, with the ICER for R-CHOP against CHOP ranging from £10,019 (reduction

TABLE 67 Sensitivity analysis: varying health-state utilities

HS utility values	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
Utility values used in the MS[61]	6180	7167	6165
Utility values estimated in a mixed cohort of patients with lymphoma[143]	7147	9518	8186
Reduction in utility values by 10%	8578	12,038	10,352
Reduction in utility values by 20%	9650	13,543	11,646
Reduction in utility values by 30%	11,029	15,478	13,309
Assuming a 10% higher utility values in PFS1 compared with PFS2	6447	8019	6898
Assuming no disutility	7704	10,760	9291
Disutility of 10%	7715	10,809	9308
Disutility of 20%	7725	10,860	9325
Disutility of 30%	7736	10,910	9342

TABLE 68 Sensitivity analysis: varying the modelled treatment pathway

Modelled treatment pathway	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
Patients receive second-line after progression only	9230	10,945	10,125
Patients on R-CVP are not retreated with rituximab in second line if early relapse	8123	10,834	9316
Patients treated with an anthracycline regimen receive CHOP with or without rituximab in second line	7720	8058	7155
Older patients receive with or without rituximab in second line	7742	10,833	9232
Combination of the three previous scenarios	7841	7967	7035
All patients receive R-HDT	8506	8745	7574
All patients receive HDT	6159	6245	5604
All patients receive CHOP	7553	7714	6907
All patients receive R-CHOP	7742	7933	7041

in the rate of progression by 30%) to £11,268 (response rate reduced by 10% compared with CHOP/R-CHOP).

SA11: Assumption about response to high-dose therapy with or without rituximab, proportion of patients with successful harvest and cycles of high-dose therapy There were considerable uncertainties about the response rate for HDT, the proportion of patients with successful harvest and number of cycles of HDT.

In SAs we varied the response rate of HDT, assuming different success rates for harvest and assuming up to four cycles of HDT. The impact on the ICER was minimal with the ICER ranging from £9430 (assuming four cycles) to £11,221 (assuming the same response rate as CHOP/R-CHOP) per QALY gained for the comparison between R-CHOP and CHOP (see *Appendix 15*).

SA12: Adverse events Assumptions of the occurrence (assuming no AE) and management costs of AEs (±20%) had a minimal impact on the cost per QALY for all regimens (see *Appendix 15*).

SA13: Number of cycles for patients treated with CHOP/R-CHOP in first-line induction The ICER between R-CHOP and CHOP improved assuming that patients only receive six cycles (£5951 per QALY gained compared with £10,834 in the base case).

SA14: Management costs The ICER was not very sensitive to assumptions about management costs (*Table 69*).

SA15: Maximum age at transplant/aggressive therapies Varying the maximum age at which patients can receive aggressive therapies (60–80 years) had a small impact on the cost per QALY gained (*Table 70*).

SA16: Body surface area Finally, the impact in model results of varying the BSA was minimal (*Table 71*).

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

The AG explored a scenario in which first-line maintenance was incorporated into the treatment pathway. At the time of writing of the report, no guidance has been issued by NICE and, therefore, results are presented to help the Appraisal Committee in case a positive

TABLE 69 Sensitivity analysis: varying management costs

Management costs	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
Administration cost +20%	7724	10,859	9370
Administration cost –20%	7716	10,810	9263
Rx pharm (£35)	7847	11,089	9549
No monitoring	6475	9214	7600
Monitoring +20%	7969	11,159	9660
Monitoring –20%	7471	10,510	8973
No third-line cost	8427	10,921	9413
No palliative care	8715	13,744	12,228
No terminal care	8138	11,303	9773
No palliative or terminal care	9132	14,213	12,684

Rx pharm, rituximab pharmacy.

TABLE 70 Sensitivity analysis: varying the maximum age at which patients can receive aggressive therapies

Age to receive aggressive therapies	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
60 years	7690	9832	8528
70 years	7735	11,758	9973
75 years	7748	12,763	10,659
80 years	7747	13,377	11,099

TABLE 71 Sensitivity analysis: varying the BSA

BSA	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	7720	10,834	9316
1.6	6095	7384	6164
1.7	7192	9712	8289
1.8	7192	9712	8289
1.9	8318	12,094	10,469

recommendation is made by NICE for the use of rituximab monotherapy as a first-line maintenance treatment in patients responding to R-chemotherapy first-line induction.

Deterministic results incorporating first-line maintenance into the treatment pathway

The cost-effectiveness results for the scenario analysis incorporating first-line maintenance for responders to R-chemotherapy in first-line induction treatment are presented in *Tables 72–74*. Analyses indicate that the addition of rituximab to CVP leads to a gain of 1.25 discounted QALYs for an additional cost of about £18,727. The cost per QALY gained of CVP in combination with rituximab compared with CVP alone is £14,959 (see *Table 72*).

The addition of rituximab to CHOP leads to a gain of 0.88 QALYs for an additional cost of £19,150. The cost per QALY gained of CHOP in combination with rituximab compared with CHOP alone is £21,687 (see *Table 73*).

Finally, the addition of rituximab to MCP leads to a gain of 0.88 QALYs for an additional cost of about £17,976. The cost per QALY gained of MCP in combination with rituximab compared with MCP alone is £20,493 (see *Table 74*).

Details about the number of LYs, discounted QALY and costs by health states are presented in *Appendix 16*.

Probabilistic results for the scenario analysis incorporating first-line maintenance rituximab in responders to R-chemotherapy

The ICER in the PSA for the addition of rituximab to CVP, CHOP and MCP are estimated to be £15,017, £21,625 and £20,418, respectively (*Tables 75–77*). The probabilities of being cost-effective at different WTP thresholds are presented in *Figures 43–45* for R-CVP vs CVP, R-CHOP vs CHOP, R-MCP vs MCP, respectively.

The probabilities of the addition of rituximab to CVP being cost-effective compared with CVP alone are 95.60% and 100.00% assuming a WTP of £20,000 and £30,000 per QALY gained respectively (see *Table 75* and *Figure 43*).

TABLE 72 Scenario analysis: deterministic cost-effectiveness of the addition of rituximab to CVP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
CVP	9.86	30,793	5.99
R-CVP	12.03	49,520	7.25
Cost per QALY (£)			**14,959**

TABLE 73 Scenario analysis: deterministic cost-effectiveness of the addition of rituximab to CHOP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
CHOP	11.55	34,983	6.84
R-CHOP	13.02	54,134	7.72
Cost per QALY (£)			**21,687**

TABLE 74 Scenario analysis: deterministic cost-effectiveness of the addition of rituximab to MCP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY
MCP	11.45	36,103	6.79
R-MCP	12.89	54,079	7.67
Cost per QALY (£)			**20,493**

The probabilities of the addition of rituximab to CHOP being cost-effective compared with CHOP alone are 36.00% and 91.50% assuming a WTP of £20,000 and £30,000 per QALY gained, respectively (see *Table 76* and *Figure 44*).

The probabilities of the addition of rituximab to MCP being cost-effective compared with MCP alone are 44.90% and 91.90% assuming a WTP of £20,000 and £30,000 per QALY gained, respectively (see *Table 77* and *Figure 45*).

Univariate sensitivity analyses: impact of main model parameters in the scenario analysis incorporating first-line maintenance in responders to R-chemotherapy

A range of univariate SAs were undertaken to assess the impact of main model parameters and assumption on the cost per QALY gained. A limited number of SAs are presented in the main section of the report for readability. Full results of SAs performed are presented in *Appendix 15* for the comparison between R-CVP and CVP, R-CHOP and CHOP and R-MCP and MCP for the scenario analysis.

SA1: Varying the time horizon We explored different time horizons (5 years, 10 years and lifetime). 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 (*Table 78*).

SA2: Parametric distribution used to model the effectiveness in first-line Again, the ICER was very sensitive when a Gompertz distribution was used instead of a log-normal distribution (*Table 79*).

SA3: Assuming different assumption about the effect of first-line maintenance We also explored different assumptions about the effect of first-line maintenance, varying the HRs using the CIs (0.48 to 0.66) or varying the assumption of the treatment duration effect (36–72 months). Results are presented in *Table 80* and showed a modest impact on the cost per QALY gained.

TABLE 75 Scenario analysis: probabilistic cost-effectiveness of the addition of rituximab to CVP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at 20,000	Probability CE (%) at 30,000
CVP	9.91	30,651	6.02		
R-CVP	12.09	49,477	7.27		
Cost per QALY (£)			**15,017**	**95.60**	**100.00**

CE, cost-effectiveness.

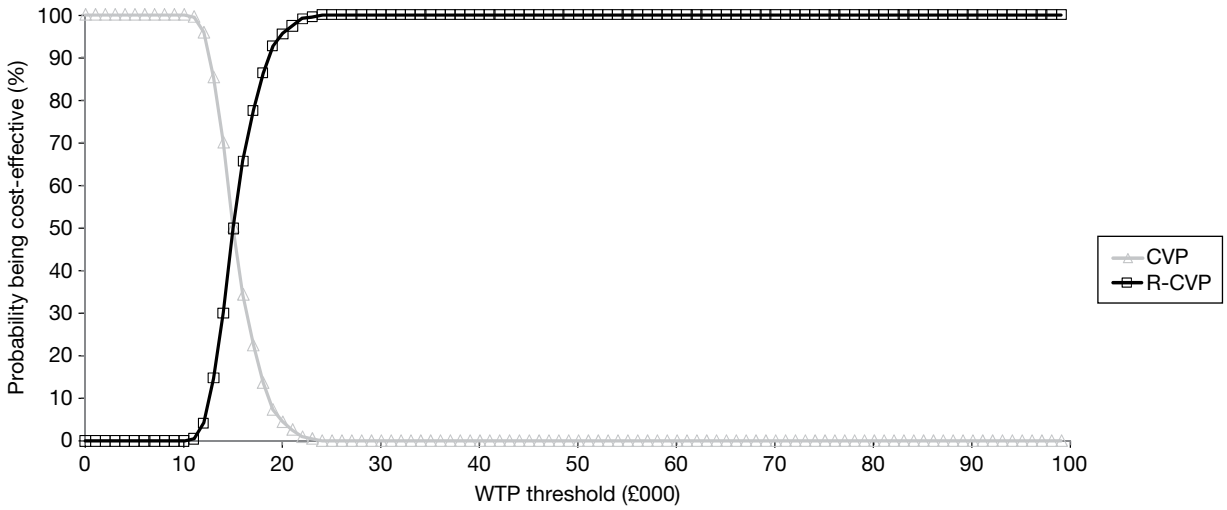


FIGURE 43 Scenario analysis: CEAC for R-CVP vs CVP alone.

TABLE 76 Scenario analysis: probabilistic cost-effectiveness of the addition of rituximab to CHOP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at £20,000	Probability CE (%) at £30,000
CHOP	11.60	34,881	6.85		
R-CHOP	12.94	54,063	7.74		
Cost per QALY (£)			**21,625**	**36.00**	**91.50**

CE, cost-effectiveness.

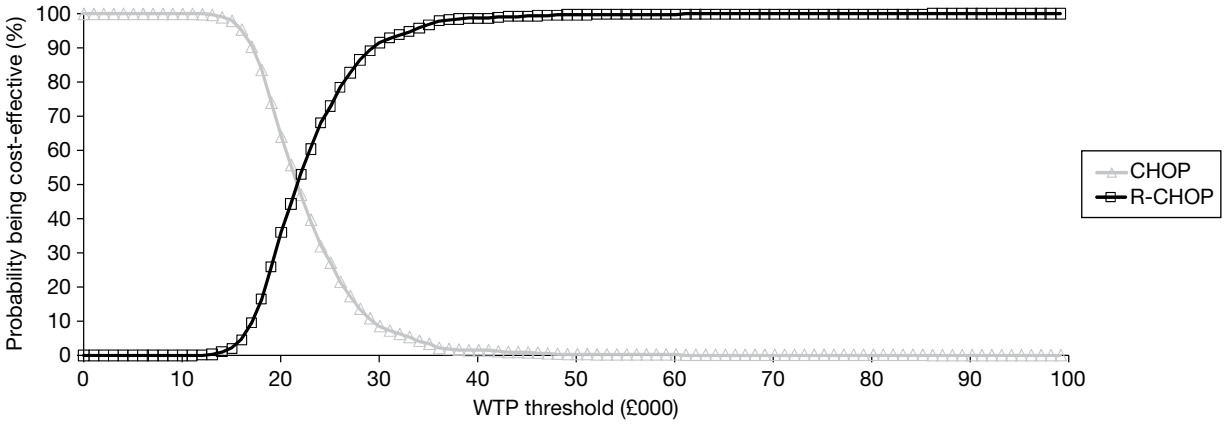


FIGURE 44 Scenario analysis: CEAC for R-CHOP vs CHOP alone.

TABLE 77 Scenario analysis: probabilistic cost-effectiveness of the addition of rituximab to MCP estimated by the AG

Regimen	Undiscounted LY	Discounted cost (£)	Discounted QALY	Probability CE (%) at £20,000	Probability CE (%) at £30,000
MCP	11.50	35,970	6.80		
R-MCP	12.90	54,004	7.69		
Cost per QALY (£)			**20,418**	**44.90**	**91.90**

CE, cost-effectiveness.

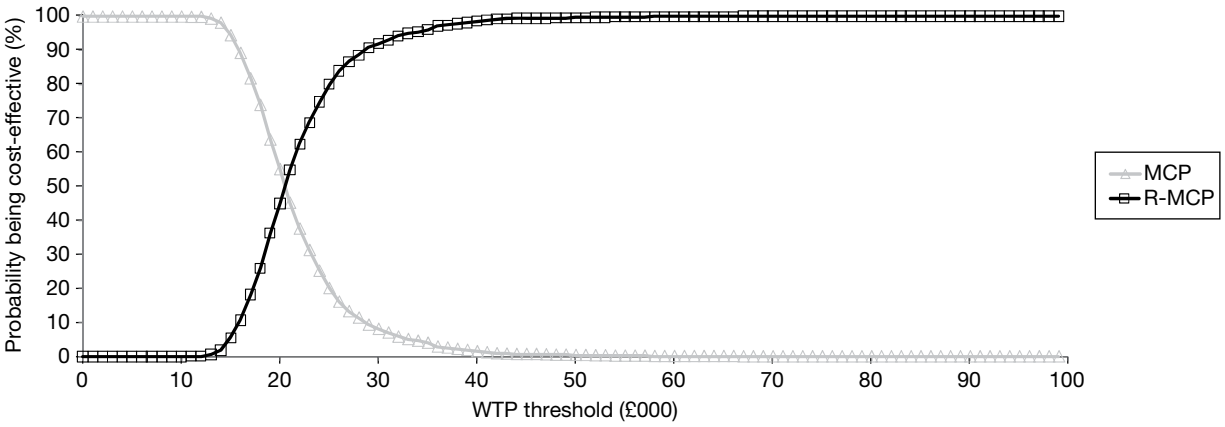


FIGURE 45 Scenario analysis: CEAC for R-MCP vs MCP alone.

SA4: Examining the effect of resistance to rituximab in previously exposed patients As previously mentioned, the effect of rituximab resistance after retreatment with rituximab is unknown. In the base case, we assumed the same rate of progression after rituximab in combination with chemotherapy or salvage therapy in rituximab-naive or rituximab pre-treated patients.

Again, the ICER was very sensitive when a lower effectiveness was assumed in patients previously treated with rituximab (*Table 81*).

SA5: Examining the maximum time a patient can stay in PFS1 In the base case, a proportion of patients might not progress and remain in PFS1 during the entire simulation because of the parametric extrapolation (*Table 82*). We examined a scenario in which we truncated the survival curves, assuming that patient can remain in PFS1 only for a maximum duration.

Again, the ICER was very sensitive to this assumption.

SA6: Changes in the treatment pathway Changes in the treatment pathway were examined given the shortcomings in evidence available. The ICER was sensitive when it was assumed that the same treatment post-progression was used in both arms (*Table 83*). In clinical practice, it is expected that patients not previously treated with rituximab are more likely to receive rituximab as part of the second-line treatment, and therefore would have a greater benefit in second line.

Comparison of the base-case cost-effectiveness for the addition of rituximab to chemotherapy estimated by Assessment Group and estimated by manufacturer

Only results for the base-case analysis are compared as the manufacturer[62] did not present a scenario analysis allowing responders to R-chemotherapy in first-line induction to receive

TABLE 78 Sensitivity analysis: varying the time horizon (scenario analysis)

Time horizon	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case (25 years)	14,959	21,687	20,493
5 years	54,094	91,356	80,497
10 years	24,126	36,367	33,482
Lifetime	14,125	20,533	19,510

TABLE 79 Sensitivity analysis: choice of parametric distribution (scenario analysis)

Distribution	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	14,959	21,687	20,493
Weibull	15,958	23,824	22,833
Gompertz	9419	12,490	11,653

TABLE 80 Sensitivity analysis: assumption about the effect of first-line maintenance rituximab (scenario analysis)

Length of first-line maintenance effect	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	14,959	21,687	20,493
36 months	15,469	22,703	21,436
48 months	14,524	20,827	19,712
60 months	13,828	19,478	18,470
72 months	13,305	18,495	17,547
HR: 0.48	14,205	20,051	19,063
HR: 0.66	16,210	24,628	23,044

TABLE 81 Sensitivity analysis: assuming a reduced effectiveness in second-line, in patients previously treated with rituximab (scenario analysis)

Reduced effectiveness in previously treated rituximab patients	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	14,959	21,687	20,493
–10%	16,851	24,447	23,067
–15%	18,100	26,301	24,788
–20%	19,650	28,629	26,946
–25%	21,624	31,646	29,731
–30%	24,234	35,734	33,489

first-line maintenance. Greater LYs were estimated by the AG compared with the manufacturer's estimate (*Figure 46*).

Similarly, the mean discounted QALYs were usually higher in the AG model compared with the manufacturer's estimate (*Figure 47*).

On the other hand, the manufacturer's estimate of mean discounted management and treatment costs were greater compared with the costs estimated by the AG (*Figure 48*).

TABLE 82 Sensitivity analysis: varying the maximum time a patient can stay in PFS1 (scenario analysis)

Maximum time that a patient can stay in PFS1	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	14,959	21,687	20,493
5 years	31,354	61,115	60,170
6 years	27,043	49,043	47,647
7 years	24,178	41,756	40,277
8 years	22,151	36,904	35,414
9 years	20,651	33,528	32,065
10 years	19,516	31,050	29,618
11 years	18,645	29,166	27,766
12 years	17,951	27,698	26,330
13 years	17,394	26,544	25,206
14 years	16,944	25,615	24,305
15 years	16,577	24,869	23,580
16 years	16,274	24,252	22,984
17 years	16,023	23,746	22,496
18 years	15,815	23,326	22,089
19 years	15,642	22,985	21,758

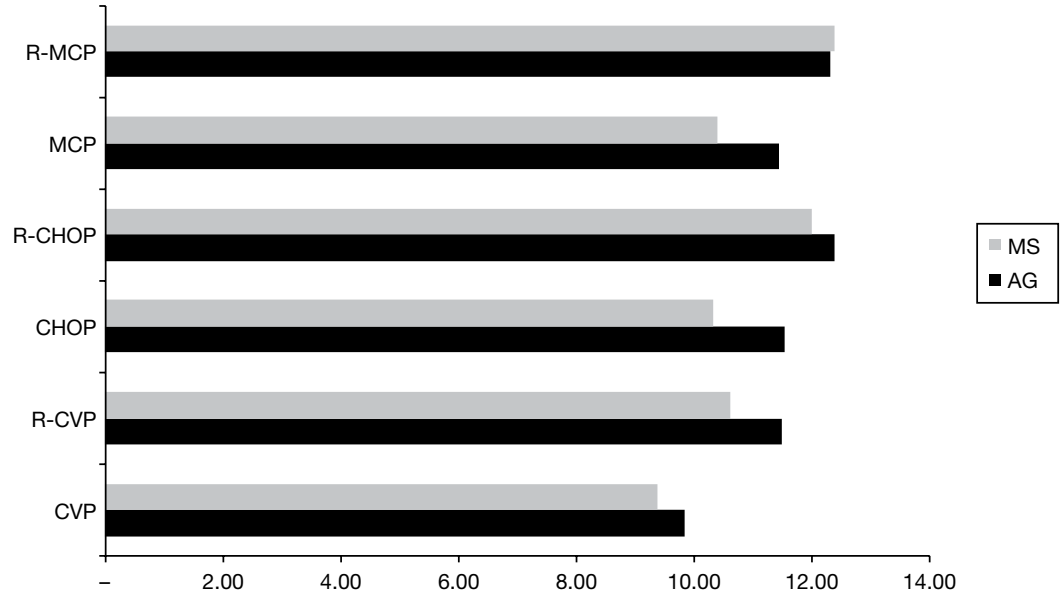
TABLE 83 Sensitivity analysis: varying the modelled treatment pathway (scenario analysis)

Modelled treatment pathway	R-CVP vs CVP	R-CHOP vs CHOP	R-MCP vs MCP
Base case	14,959	21,687	20,493
Patients receive second-line after progression only	16,828	21,576	20,944
Patients on R-CVP are not retreated with rituximab in second line if early relapse	15,816	21,687	20,493
Patients treated with an anthracycline regimen receive CHOP with or without rituximab in second line	14,959	16,517	15,261
Older patients receive with or without rituximab in second line	15,145	22,251	21,026
Combination of the three previous scenarios	15,919	16,750	15,452
All patients receive R-HDT	18,325	20,293	18,491
All patients receive HDT	11,273	12,153	11,227
All patients receive CHOP	14,127	15,337	14,146
All patients receive R-CHOP	15,034	16,436	15,111

Those differences translated into differences in the ICER estimated by the AG and included in the MS[62] (*Table 84*).

The AG believes that differences in results are explained by the following differences in the modelling approach and assumptions used:

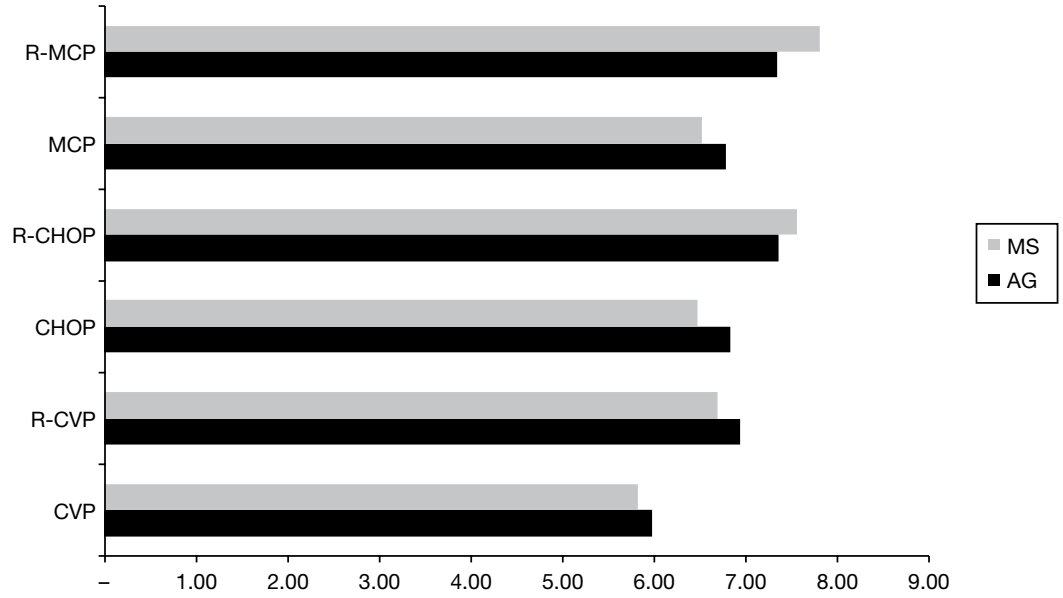
1. The MS[62] used time-to-event data from the GLSG-2000[91,92] and OSHO39 trials[93] to model the effectiveness of CHOP/R-CHOP and MCP/R-MCP in first-line induction. However, responders received subsequent therapies (maintenance interferon and SCT) in those trials and therefore the effectiveness is likely to be confounded. The AG used a more conservative approach combining data from the M39021 trial[95,96] but response rates from the trials.[91–93] A separate source indicated that median PFS was about 46.7 months in patients with FL treated with R-CHOP in first-line induction.[78] The modelled median PFS using the AG approach was close at about 43 months. The modelled median PFS using the MS[62] approach was about 64 months.



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
MS	9.39	10.63	10.34	12.02	10.42	12.42
AG	9.86	11.50	11.55	12.40	11.45	12.35

Discounted LYs

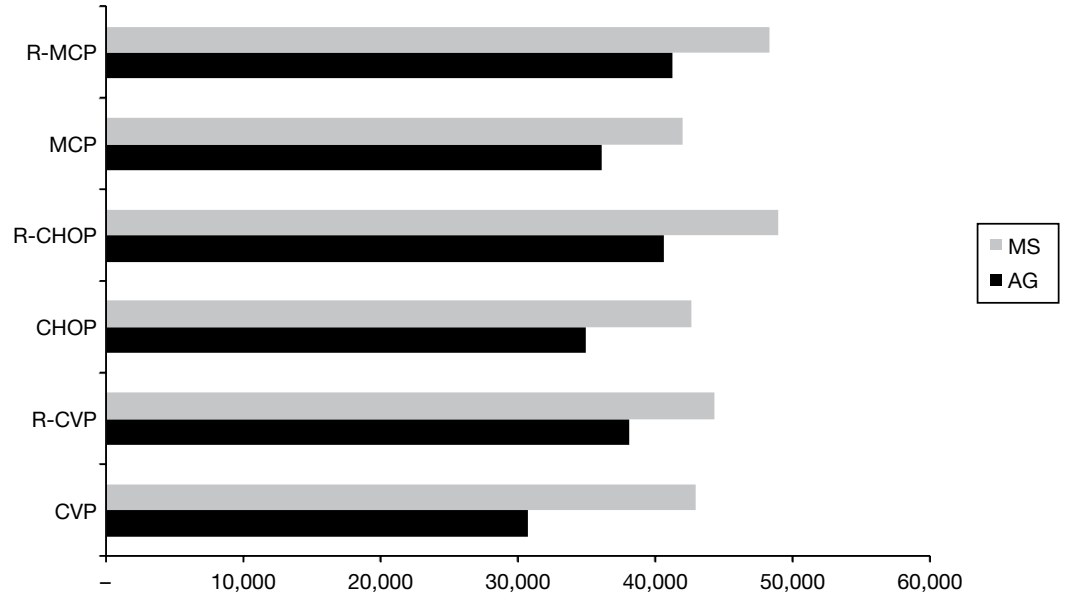
FIGURE 46 Comparison of the undiscounted LYs by treatment estimated by the MS[62] and AG.



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
MS	5.83	6.69	6.48	7.57	6.53	7.82
AG	5.99	6.95	6.84	7.37	6.79	7.36

Discounted QALY

FIGURE 47 Comparison of the discounted QALY by treatment estimated by the MS[62] and AG.



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
MS	43,061	44,386	42,717	49,029	42,072	48,340
AG	30,793	38,183	34,983	40,708	36,103	41,370

FIGURE 48 Comparison of discounted costs by treatment estimated by the MS[62] and AG.

TABLE 84 Comparison of the ICER produced by the MS[62] and AG model

R therapies vs non-R therapies	AG model	MS[61] model
R-CVP vs CVP	7720	1529
R-CHOP vs CHOP	10,834	5758
R-MCP vs MCP	9316	4861

2. There were differences in the modelled treatment pathway. The AG model provides a more detailed description of the treatment pathway in patients with FL owing to the flexibility in the model structure. The AG considered the use of salvage therapy (HDT) with or without rituximab in addition to ASCT in patients previously treated with an anthracycline regimen. The AG also considered the use of FC in second-line treatment for patients aged > 65 years. The economic model included in the MS[62] assumed that patients can only receive CHOP or R-CHOP in second-line induction. The source of effectiveness in second-line is different between the two economic evaluations.
3. As previously mentioned, there were some errors in the approach used by the manufacturer to model second-line treatment. This included:
   i. the derivation of the transition probability
   ii. the calculation of PPS
   iii. errors in the estimation of costs in second line.

More details are available in *Assessment of the manufacturer's submission*.

1. The manufacturer fitted exponential distributions to data in second line from the EORTC 20981 trial.[74,75] However, the distributions did not provide a reasonable fit to the data. The AG used log-normal distribution that provided a better fit to the data.

2. The economic model submitted by the manufacturer missed the time spend in second-line induction treatment. PFS and OS are calculated after induction treatment in second line. The AG model included the time spent at induction treatment. This was possible as the AG modelled the impact of maintenance more accurately by separating responders from non-responders.
3. The AG used a different approach to model the OS in second-line using direct Kaplan–Meier curves for OS. The manufacturer estimated OS derived from PFS and an estimated PPS. However, there were some concerns on the approach used to derived PPS.
4. The AG used different utility values (PFS1 0.805, PFS2 0.805; disease progression 0.7363) compared with the utility values included in the MS[61] (PFS1 0.88, PFS2 0.79; disease progression 0.62).
5. The model developed by the AG was also more flexible allowing to track patients over time, requiring less assumptions and therefore providing a more accurate description of outcomes over time.

Summary and conclusions to the cost-effectiveness section

The review of existing economic evaluations,[111–113,115] the manufacturer's model and the economic evaluation carried out by the AG suggests that the addition of rituximab to chemotherapy compared with chemotherapy alone has a cost per QALY gained < £20,000 assuming that responders to R-chemotherapy do not receive first-line maintenance. The ICERs estimated by the AG for the addition of rituximab to CVP, CHOP and MCP is £7720, £10,834 and £9316 per QALY gained, respectively, assuming no first-line maintenance for responders to R-chemotherapy.

The AG presented a scenario analysis incorporating first-line maintenance in responders to R-chemotherapy in first-line induction. The ICER estimated by the AG for the addition of rituximab to CVP, CHOP and MCP is £14,959, £21,687 and £20,493 per QALY gained, respectively, assuming that responders to R-chemotherapy receive first-line maintenance rituximab.

Results are not directly comparable across chemotherapies, as they are selected in clinical practice with regard to factors including age, performance status and disease aggressiveness.

A range of SAs were conducted and suggested that the ICER was sensitive to the assumptions about the time horizon (*Table 61* and *78*), the parametric extrapolation of evidence in first-line induction (*Tables 62* and *79*), resistance to rituximab in previously exposed patients (*Tables 64* and *81*), maximum time a patient can remain progression free after first-line induction (*Tables 65* and *82*) and the assumed treatment pathway (*Table 68* and *83*).

There were large uncertainties in the source of effectiveness in the absence of robust evidence. Therefore, the results presented should be interpreted with consideration of the assumption used.

Generalisability

There is no evidence to suggest that the results of the analysis cannot be generalised across all patients who have stage III/IV FL. However, it is noted that patients included in the trials were generally younger than those seen in clinical practice in the UK. Furthermore, despite the AG attempting to provide an accurate description of the treatment pathway in patients with FL, there were considerable uncertainties in the source of effectiveness of treatments used in second line, notably for the effect of salvage therapy in patients previously treated with an anthracycline regimen or the effectiveness in patients previously treated with rituximab in first-line induction. This assessment is based on data involving the following chemotherapeutic agents: CVP, CHOP and MCP. It is not certain that the results can be generalised to other R-chemotherapy regimens

and other second/subsequent lines of treatment.There are limitation in the pathway assumed within the model. Although SAs have been undertaken to provide an indication of the effect on the ICER when these assumptions are altered, not all possible second- and third-line therapies have been evaluated.

Strengths and limitations of analysis

The economic evaluation has several strengths compared with previous studies. The modelled treatment pathways in our model incorporates guidance issued by NICE[73] for the treatment of patients with FL and tried to provide an accurate description of the treatment pathway observed in clinical practice, whereas other models have not undertaken this in as great a detail. Notably, the economic model takes into account the fact that in clinical practice, patients previously treated with an anthracycline regimen (CHOP, MCP) would be offered alternative treatment with salvage therapy with or without rituximab in addition to ASCT if evidence of response and aged < 65 years and are sufficiently fit. Furthermore, the model evaluates the option that patients who are not in remission (complete or partial) at the end of first-line remission induction treatment with R-chemotherapy or chemotherapy alone are likely to be offered further treatment (second-line treatment) despite the absence of progression as observed in clinical practice.

The model also uses a continuous time method over a traditional Markov process. The continuous time approach confers numerous advantages over the Markov process used in previous cost-effectiveness models, notably in terms of flexibility. The rate of progression can be easily represented by distributions that are time dependent.

There was uncertainty regarding the effectiveness of CHOP and MCP with or without rituximab as first-line induction treatment owing to the confounding effect of maintenance therapy with interferon or SCT for responders in the main trials.[91–93] The AG used data from the M39021 trial[95,96] and the response rate from the appropriate trial[91–93] and showed that the median predicted PFS for R-CHOP was similar to the median PFS from a separate study.[78]

A range of SAs were also conducted. The model considered different assumptions regarding the risk of resistance and maximum time a patient can remain progression free in first-line induction. The model also incorporated the impact of AEs in terms of costs and impairment in quality of life. Although the implementation is simplistic, the conclusion was that these had a limited impact on the results.

Finally, a scenario analysis is also presented incorporating the impact of first-line maintenance among patients responding to first-line induction with rituximab in combination with chemotherapy.

There are several limitations of the study. There were considerable uncertainties in the effectiveness in first-line induction with CHOP, R-CHOP, MCP and R-MCP. The approach used by the AG provided a reasonable fit to R-CHOP when compared with a separate source,[78] although this was considered the best approach by the AG there is still uncertainty regarding the applicability of this assumption.

Another limitation relates to the data used to model the risk of progression after second-line treatment. We used data from the EORTC 20981 trial[74,75] to model the progression rate for patients treated in second line with CHOP and R-CHOP with or without maintenance rituximab. However, patients were rituximab naive (i.e. not previously treated with rituximab) and therefore results from this study might not be applicable to patients previously treated with rituximab. SAs have been conducted assuming a lower effectiveness for patients previously treated with

rituximab and showed that the results were highly sensitive to the assumption about the development of resistance.

Furthermore, we assumed that patients previously treated with an anthracycline regimen (CHOP, MCP) with or without rituximab would be eligible for salvage therapy with or with rituximab in addition to ASCT if there was evidence of response to chemotherapy. However, the effectiveness for patients treated with salvage therapy was extracted from a single study. Biases might have been introduced. The addition of rituximab to salvage therapy was associated with considerable benefit although it was unclear if the magnitude of the observed improvement was owing to the retrospective nature of the study.[134] The study was also conducted in a pre-rituximab era, and therefore patients were not previously exposed to rituximab. It is also unclear from the study the proportion of patients that responded to HDT, the proportion for whom the harvest was successful and the proportion of patients that received ASCT in both arms.

There were also uncertainties regarding the utility values used to describe health states in the economic model. Utility values have been extracted from a single unpublished study.[117,118] The study included 33% patients with stage I/II FL and utility values were presented according to the degree of response to therapy. The applicability of data to populate the economic model was limited because the health states in the economic model did not match health-state categories from the study. However, a range of SAs were conducted and showed a modest impact on the ICER.

Further potential limitation is the use of log-normal distribution to represent the risk of progression in first and second-line treatment. The log-normal distribution is non-monotonic and can have a long tail. In first-line treatment, the log-normal provided a plausible and reasonable fit to the data and was therefore used. The ICER was very sensitive, and became more favourable to rituximab if the Gompertz distribution was used. The AG believed that the log-normal distribution provided a more plausible long-term extrapolation (see *Figure 42*). The use of log-normal distribution in second-line treatment also hampered the uncertainty analysis, but this disadvantage was outweighed by the better fit of the log-normal distribution to the data compared with other distributions.

The inclusion of first-line maintenance in responders to R-chemotherapy in first-line induction was also modelled in a simplistic manner. The treatment pathway is unknown as not part yet of clinical practice.

Finally, our results are in line with findings from previous cost-effectiveness analyses; that the addition of rituximab to chemotherapy compared with chemotherapy alone (CVP, CHOP and MCP) is likely to have a cost per QALY gained of < £25,000.

Chapter 5

Assessment of factors relevant to the NHS and other parties

The Department of Health's updated cancer plan, issued in January 2011, has outlined the government's commitment to providing and expanding patient choice of treatment by 2013/14. This includes:

- when to have treatment
- where to have treatment (some treatments can be given in hospital or in the community)
- which organisation delivers treatment and care
- which team delivers the treatment, and
- what form of clinically appropriate treatment to have.

The paper also states that one of the NHS outcomes is to prevent people from dying prematurely and cancer is identified as a specific improvement area. One- and five-year cancer survival rates will be key indicators with regards to meeting this outcome.

No budget impact analysis was undertaken in this assessment report, as clinical experts and the evidence suggests that rituximab is already routinely used alongside CVP in the UK. The addition of rituximab to further chemotherapies is not expected to incur significant costs. There would be minimal additional staff or infrastructure costs.

Chapter 6

Discussion

Statement of principal findings

Four RCTs[91–96] comparing rituximab and chemotherapy with chemotherapy alone in untreated, symptomatic stage III–IV patients with FL were identified. Rituximab and chemotherapy compared with chemotherapy alone increased the likelihood of a response to treatment in all four trials, with additional toxicity of limited clinical relevance. In three trials, numbers of CRs were significantly greater in the R-chemotherapy arm when compared with the chemotherapy-alone arm. Over a follow-up period of 4–5 years, R-chemotherapy increased the OS rate compared with chemotherapy alone. Median OS values have not yet been reached in either the intervention or comparator arms in the trials; however, this is not unexpected given the median survival for patients with FL is 8–10 years.[29] The four trials[91–96] presented evidence that R-chemotherapy prolonged other clinical outcomes such as response duration, TTF, TTP, TTNT, EFS and DFS.

The ICERs for the addition of rituximab to CVP, CHOP and MCP are £7720, £10,834 and £9316 per QALY gained, respectively, when it was assumed that first-line rituximab maintenance was not used. When it was assumed that patients responding to first-line induction with R-chemotherapy receive first-line maintenance rituximab for up to 2 years, the ICERs increase to £14,959, £21,687 and £20,493 per QALY gained, respectively.

Sensitivity analyses indicated that the ICER was mostly sensitive to the assumptions 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, assumptions regarding resistance to rituximab and the modelled treatment pathway.

There were large uncertainties in the source of effectiveness in the absence of robust evidence. Therefore, the results presented should be interpreted with consideration of the assumption used. We have made assumptions, and the appraisal is based on a small set of trials with a great degree of heterogeneity in design and effectiveness. This may limit the generalisability of the findings.

Finally, results are not directly comparable across chemotherapies since they are selected in clinical practice with regard to factors including age, performance status and disease aggressiveness. This assessment is based on data involving the following chemotherapeutic agents: CVP, CHOP, MCP and CHVPi. It is not certain that the results can be generalised to other R-chemotherapy regimens.

Strengths and limitations of the assessment

This assessment provides a systematic review of RCTs comparing rituximab and chemotherapy with chemotherapy alone in the first-line treatment of untreated, symptomatic stage III–IV FL, using the most up-to-date data (more mature data from the GLSG-2000 trial using data from the Buske and Hoster[91] presentation at the ASH 2008 conference). We undertook comprehensive searches for trials and are confident that we have not missed any reports of RCTs or other systematic reviews of R-chemotherapy compared with chemotherapy alone.

Previous reviews have been carried out investigating the use of rituximab in FL but have included trials evaluating the use of R-chemotherapy compared with chemotherapy alone in both untreated and patients with relapsed FL.[146–148] These previous reviews present meta-analysed results for ORR, with findings in agreement with our own results, i.e. R-chemotherapy improves response rates when compared with chemotherapy alone. However, the AG believes the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens than meta-analysed response rates. This is owing to problems with the validity of the meta-analyses, namely the high level of statistical heterogeneity. Ideally, this high level of heterogeneity would be explored further and explained by estimating the predictive distribution of a new study. This was not undertaken in this assessment because of resource constraints.

Data for other outcomes such as OS are compromised in three studies owing to other trial treatments. Longer OS data follow-up would strengthen findings as median OS has not yet been reached in any of the trials.

This assessment provides an indication of the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP alone in the UK. The results of our model are consistent with the findings from previous cost-effectiveness analyses. The model developed by the AG extends the analysis undertaken in previous economic models in terms of a greater level of detail in the modelled treatment pathway. A wide range of assumptions have also been examined given the high uncertainty in model parameters. However, there are some limitations relating to the sources of data used for the effectiveness in first- and second-line and utility values. Assumptions have been made owing to the confounding effects of other trial treatments within two of the three trials in first-line induction. Data from a single trial have been used to represent the effectiveness for patients treated with salvage therapy with or without rituximab and studies reporting the effectiveness of treatment in second line were conducted in rituximab-naive patients. There were large uncertainties in the source of effectiveness in the absence of robust evidence. Therefore, the results presented should be interpreted with consideration of the assumption used.

Uncertainties

There was uncertainty regarding the effectiveness of CHOP and MCP with or without rituximab as first-line induction treatment owing to the confounding effect of maintenance therapy with interferon or SCT for responders in the main trials. There were also uncertainties about the inclusion of first-line maintenance in responders to R-chemotherapy in first-line induction as no guidance was issued by NICE at the time of writing of the report. Another uncertainty relates to the data used to model the risk of progression after second-line treatment. Furthermore, we also assumed that patients previously treated with an anthracycline regimen (CHOP, MCP) with or without rituximab would be eligible for salvage therapy with or with rituximab in addition to ASCT if there was evidence of response to chemotherapy. However, the effectiveness for patients treated with salvage therapy was extracted from a single study. Biases might have been introduced. Studies reporting the effectiveness of CHOP, R-CHOP and salvage therapy in second-line treatment were conducted in a pre-rituximab era and, therefore, patients were not previously exposed to rituximab. Therefore, results from these studies might not be applicable to patients previously treated with rituximab.

Other relevant factors

Other relevant factors to this assessment report include:

- The outcome of the NICE appraisal assessing the use of rituximab monotherapy as a first-line maintenance treatment in FL.
- Whether or not bendamustine becomes licensed for use as a first-line chemotherapy in FL and, if so, whether or not it is subsequently approved by NICE.

Chapter 7

Conclusions

Implications for service provision

The addition of rituximab to CVP, CHOP and MCP is likely to be clinically effective in the first-line treatment of stage III–IV FL. The cost per QALY gained is estimated to be < £25,000 for all scenarios and is considerably lower if first-line rituximab maintenance is not assumed. The main uncertainties in terms of influencing the ICER relate to the effectiveness of rituximab retreatment (i.e. resistance) and the effect of salvage treatment in patients previously treated with anthracycline regimens. The context for care and the mode of delivery are very similar to the comparator therapy, thus there are no major implications that do not also apply to chemotherapy alone.

Suggested research priorities

Future research priorities include:

- effectiveness of rituximab retreatment (determination of resistance)
- trials comparing an R-chemotherapy with another R-chemotherapy in populations that are eligible to receive both therapies
- more studies are required assessing HRQoL in FL using the EQ-5D
- effectiveness of salvage treatment for patients previously treated with an anthracycline regimen
- non-confounded data for assessment of first-line treatment
- effectiveness of therapies in older patients (R-FC/FC)
- standardisation of time-to-event outcome measures.

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Declared competing interests of the clinical advisors/ peer reviewers

Dr Andrew McMillan, Consultant in Haematology (Clinical Advisor):

- Personal pecuniary interest:
  - financial support from Roche to attend conferences of the American Society of Haematology (ASH), the European Hematology Association (EHA) and the International Conference on Malignant Lymphoma (ICML) over the last years (5+)
  - honoraria from Roche Advisory Boards (5+)
  - honoraria from Roche for lectures, for example Satellite Symposia (3+)
  - honoraria from Napp pharmaceuticals for advisory board for bendamustine hydrochloride.

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- Personal non-pecuniary interest:
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Contributions of authors

Diana Papaioannou was the AG lead and undertook the clinical effectiveness review.

Rachid Rafia undertook the cost-effectiveness review and developed the cost-effectiveness model.

Matt Stevenson advised on the cost-effectiveness review and development of the cost-effectiveness model.

John Rathbone helped undertake the clinical effectiveness review.

Helen Buckley-Woods performed the literature searches.

John Stevens provided statistical advice.

About the School of Health and Related Research

The School of Health and Related Research (ScHARR) is one of the nine departments that constitute the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of the public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the NIHR Health Technology Assessment programme on behalf of a range of policy-makers, including NICE. ScHARR-TAG is part of a wider collaboration of five units from other regions. The other units are Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsula Technology Assessment Group (PenTAG), University of Exeter; and NHS CRD, University of York.

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Appendix 1

Incidence calculations and data sources for non-Hodgkin's lymphoma and follicular lymphoma

TABLE 85 Incidence of NHL and FL in England and Wales (2008)

Incidence	All	Male	Female
Total population[a]	54,454,800	26,782,800	27,672,000
NHL cases[b]	10,319	5534	4785
FL cases[b]	1869	879	990
Crude incidence rate NHL per 100,000 ((NHL cases/population) × 100,000)	18.9	20.7	17.3
Crude incidence rate FL per 100,000 ((FL cases/population) × 100,000)	3.4	3.3	3.6

a Mid-year population estimates 2008: 13 May 2010.[149]
b Data for England from the Office for National Statistics 2008[3] and data for Wales provided by the Welsh Cancer Intelligence & Surveillance Unit 2008.[16]

TABLE 86 Incidence of NHL and FL in England (2008)

Incidence	All	Male	Female
Total population[a]	51,464,700	25,323,500	26,141,200
NHL cases[b]	9676	5186	4490
FL cases[b]	1757	827	930
Crude incidence rate NHL per 100,000 ((NHL cases/population) × 100,000)	18.8	20.5	17.2
Crude incidence rate FL per 100,000 ((FL cases/population) × 100,000)	3.4	3.3	3.6

a Mid-year population estimates 2008: 13 May 2010.[149]
b Data from Office for National Statistics 2008.[3]

TABLE 87 Incidence of NHL and FL in Wales (2008)

Incidence	All	Male	Female
Total population[a]	2,990,100	1,459,300	1,530,800
NHL cases[b]	643	348	295
FL cases[b]	112	52	60
Crude incidence rate NHL per 100,000 ((NHL cases/population) × 100,000)	21.5	23.8	19.3
Crude incidence rate FL per 100,000 ((FL cases/population) × 100,000)	3.7	3.6	3.9

a Mid-year population estimates 2008: 13 May 2010.[149]
b Data provided by the Welsh Cancer Intelligence & Surveillance Unit 2008.[16]

Appendix 2

Ann Arbor staging system

The standard staging system used for FL is the same as that proposed for Hodgkin's disease at the Ann Arbor Conference in 1971. It classifies four stages of disease (*Table 88*).

Each stage of disease is divided into two subsets of patients according to the presence (A) or absence (B) of systemic symptoms. Fever of not evident cause, night sweats and weight loss of > 10% of body weight are considered to be systemic symptoms.

TABLE 88 Ann Arbor staging system

Stage I	One lymph node region (I), or localised involvement of a single extralymphatic organ or site (IE)
Stage II	Two or more lymph node regions on the same side of the diaphragm (II), or localised involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm (IIE)
Stage III	Lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localised involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE + S)
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement. Involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow)

Appendix 3

Eastern Cooperative Oncology Group performance status

TABLE 89 Eastern Cooperative Oncology Group performance status[150]

Grade	ECOG
0	You are fully active and more or less as you were before your illness
1	You cannot carry out heavy physical work but can do anything else
2	You are up and about more than half the day; you can look after yourself but are not well enough to work
3	You are in bed or sitting in a chair for more than half the day; you need some help in looking after yourself
4	You are in bed or a chair all the time and need a lot of looking after

Appendix 4

Deaths in England and Wales (including cancer and non-Hodgkin's lymphoma deaths)

TABLE 90 Deaths in England and Wales (including cancer and NHL deaths)

Deaths in England and Wales	No. of deaths
Cancer deaths in England and Wales in 2008	137,831
No. of deaths in England and Wales in 2008	509,090
No. of NHL deaths in England and Wales in 2008	3978

Source: Office for National Statistics. *Mortality statistics: cause. England and Wales 2008*. London: The Stationery Office; 2010.

Appendix 5

Literature search strategies

Sample search for clinical effectiveness evidence using a RCT filter in MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid):

1. Cyclophosphamide.af.
2. Cyclophosphamide/
3. 1 or 2
4. vincristine.af.
5. Vincristine/
6. 4 or 5
7. vindesine.af.
8. Vindesine/
9. 7 or 8
10. (prednisolone or prednisone).af.
11. Prednisolone/or Prednisone/
12. 10 or 11
13. doxorubicin.af.
14. Doxorubicin
15. 13 or 14
16. (mitoxantrone or mitozantrone).af.
17. Mitoxantrone/
18. 16 or 17
19. (cholorambucil or chlorambucil).af.
20. Chlorambucil/
21. 19 or 20
22. fludarabine.af.
23. Bendamustine.af.
24. 3 and 6 and 12
25. 3 and 15 and 6 and 12
26. 3 and 18 and 6 and 12
27. 3 and 15 and 9 and 12
28. 18 and 21 and 12
29. 22 and 3 and 18
30. 18 and 22
31. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 23
32. (CVP or CHOP or CNOP or CHVP or MCP or FCM or FM).af.
33. 31 or 32
34. (rituximab or mabthera or mab thera or rituxan or IDEC-102 or IDEC-C2B8 or Rituksimabi or Rituximabum or anti-CD20 or immunotherapy or 131I-rituximab or rituximab–alliinase conjugate or monoclonal antibod$).af.
35. Antibodies, Monoclonal/
36. 33 or 34 or 35
37. (follicular lymphoma or indolent lymphoma or low grade lymphoma or lymphoma or NHL).ti,ab.

38. (Lymphoma$adj5 non-hodgkin$).ti,ab.
39. (follic$adj5 (lymphocyte$or lymphoma$)).ti,ab.
40. Lymphoma, Follicular/
41. Lymphoma, Non-Hodgkin/
42. 37 or 38 or 39 or 40 or 41
43. 36 and 42
44. Randomized controlled trials as Topic/
45. Randomized controlled trial/
46. Random allocation/
47. Double blind method/
48. Single blind method/
49. Clinical trial/
50. exp Clinical Trials as Topic/
51. 44 or 45 or 46 or 47 or 48 or 49 or 50
52. (clinic$adj trial$1).tw.
53. ((singl$or doubl$or treb$or tripl$) adj (blind$3 or mask$3)).tw.
54. Placebos/
55. Placebo$.tw.
56. Randomly allocated.tw.
57. (allocated adj2 random).tw.
58. 52 or 53 or 54 or 55 or 56 or 57
59. 51 or 58
60. Case report.tw.
61. Letter/
62. Historical article/
63. Review of reported cases.pt.
64. Review, multicase.pt.
65. 60 or 61 or 62 or 63 or 64
66. 59 not 65
67. 43 and 66

In addition, searching was undertaken in October to November 2010 to identify literature on chlorambucil and fludarabine using the terms (cholorambucil or chlorambucil).af. or (Chlorambucil/) or (fludarabine).af.) combined with population terms (steps 37–42) and RCT terms (steps 44–66) (using Boolean AND).

Example of economics/cost-effectiveness filter

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw.

13. (economic$or pharmacoeconomic$or price$or pricing$).tw.
14. quality adjusted life years/
15. (qaly or qaly$).af.
16. or/1–15

Example of quality-of-life filter (combined with population terms only)

1. value of life/
2. quality adjusted life year/
3. quality adjusted life.tw
4. (qaly$or qald$or qale$or qtime$).tw
5. disability adjusted life.tw
6. daly$.tw
7. health status indicators/
8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw
9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw
10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw
11. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw
12. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw
13. (euroqol or euro qol or eq5d or eq 5d).tw
14. (hql or hqol or h qol or hrqol or hr qol).tw
15. (hye or hyes).tw
16. health$year$equivalent$.tw
17. health utilit$.tw
18. (hui or hui1 or hui2 or hui3).tw
19. disutili$.tw
20. rosser.tw
21. quality of wellbeing.tw
22. quality of wellbeing.tw
23. qwb.tw
24. willingness to pay.tw
25. standard gamble$.tw
26. time trade off.tw
27. time tradeoff.tw
28. tto.tw
29. or/1–28

Appendix 6

Response criteria for non-Hodgkin's lymphoma[89]

Complete response requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalisation of those biochemical abnormalities (e.g. LDH) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes of > 1.5 cm before therapy). Previously involved nodes that were 1.1–1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by > 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy owing to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥ 20-mm biopsy core).

Complete response/unconfirmed complete response includes those patients who fulfil criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass of > 1.5 cm in greatest transverse diameter that has regressed by > 75% in the SPD. Individual nodes that were previously confluent must have regressed by > 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytological or architectural atypical).

Partial response requires the following:

1. A decrease of ≥ 50% in the SPD of the six largest dominant nodes or nodal masses.
2. No increase in the size of the other nodes, liver or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, for example large-cell lymphoma or low-grade lymphoma (i.e. small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

Stable disease is defined as less than a PR but is not progressive disease.

Progressive disease requires the following:

1. An increase of ≥ 50% from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
2. Appearance of any new lesion during or at the end of therapy.

Appendix 7

List of unobtainable references

1. Agarwal, PK. Monoclonal antibody therapy for low grade follicular lymphoma: rituximab. *Ind J Hematol and Blood Transfus* 2000;**18**:71–4.
2. Bilgir O, Atesalan F, Cengiz E, Gediz F. The comparison of fludarabine and CHOP therapies for first line treatment in untreated low and intermediate grade non-Hodgkin lymphomas (NHL). *Blood* 2000;**96**:234b.
3. De Acquatella GS. Comparative study of the CHOP protocol versus COP-BLAM I. *Revista Inst Nac Cancerol* 1993;**39**:1867–79.
4. Herold M. Phase III randomised study of therapy for low grade non-Hodgkin's lymphoma in patients with advanced stage: chemotherapy versus chemotherapy plus rituximab. *Onkologie* 1999;**22**:4–6.
5. Herold M, Fiedler F, Pasold R, Knauf W, Freund M, Naumann R, *et al.* Efficacy and toxicity of rituximab plus mitoxantrone, chlorambucil, prednisolone (MCP) versus MCP alone in advanced indolent NHL: interim results of a clinical phase III study of the East German Study Group Hematology/Oncology (OSHO). *Blood* 2001;**98**: (Suppl 1): 601.
6. Li TS. Clinical observation of CHOP regimen and CHOEP regimen in the treatment of Non-Hodgkin's lymphoma. *Chin J Cancer Prev Treat* 2007;**14**:1019–20.
7. Lopez-Guillermo A, Garcia-Conde J, Alvarez-Carmona AM, Leon P, Maldonado J, Alcala A, *et al.* Comparison of chemotherapy CHOP vs CHOP/VIA in the treatment of aggressive non-Hodgkin's lymphoma: a randomized multicenter study of 132 patients. The PETHEMA group. Program for Study and Therapeutics of malignant hemopathies. Spanish Association of Hematology and Hemotherapy. *Med Clin-Barcelona* 1998;**110**:601–4.
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10. Moreno-Nogueira JA, Bezwoda WR, MacDonald MM, Moules IK, Akitt LM, Posner LE, *et al.* Phase III randomized multicenter trial comparing Cyclophosphamide, Adriamycin, Vincristin and Prednisone (CHOP) vs Cyclophosphamide, Mitoxantrone, Vincristin and Prednisone (CNOP) in the treatment of stage II-IV diffused non-Hodgkin and acute lymphomas. *Oncología* 1988;34.
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12. Prentice AG, Johnson SAN, Harper P, Hewins M, Hewins P, Tyrrell CJ, *et al.* A randomised, prospective trial of chlorambucil and prednisolone (CP) v mitozantrone, chlorambucil and prednisolone (MCP) in de novo, stage II or more advanced, low-grade non-Hodgkins lymphoma (LG-NHL). *B J Haematol* 1996;**93**:74.

13. Remy F, Ribrag V, Mounier N, Haioun C, Salles G, Golfier JB, *et al.* Preliminary evaluation of efficacy and toxicity of two doses schedules of bortezomib plus R-CHOP regimen in front-line B lymphoma patients. *Haematologica* 2006;**91:**68.

14. Solal-Celigny P, Brice P, Brousse N, Caspard H, Bastion Y, Haioun C, *et al.* Phase II trial of fludarabine monophosphate as first-line treatment in patients with advanced follicular lymphoma: a multicenter study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 1996;**14**:514–19.

15. Wendling, P. Bendamustine outshines CHOP in advanced lymphomas. *Oncol Rep* 2010;30.

Appendix 8

List of reports of four included studies

M39021 trial

1. Imrie K, Belch A, Pettengell R, Rueda A, McKendrick J, Solal Celigny P, *et al.* CVP plus rituximab compared to CVP alone in previously untreated patients with follicular lymphoma: impact of baseline prognostic factors. *Ann Oncol* 2005;**16**(Suppl. 5):109–10.
2. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, *et al.* An international multi-centre, randomized, open-label, phase III trial comparing rituximab added to CVP chemotherapy or CVP chemotherapy alone in untreated stage III/IV follicular non-Hodgkin's lymphoma. *Blood* 2003;**102**:28a.
3. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, *et al.* CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;**105**:1417–23.
4. Marcus R, Imrie K, Solal Celigny P, Catalano JV, Dmoszynska A, Raposo JC, *et al.* Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* 2008;**26**:4579–86.
5. Solal-Celigny P, Imrie K, Belch A, Robinson KS, Cunningham D, Rueda A, *et al.* Mabthera (Rituximab) plus CVP chemotherapy for first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma (NHL): confirmed efficacy with longer follow-up. *Blood* 2005;**106**:106A.

GLSG-2000 trial

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2. Buske C, Kneba M, Lengfelder E, Pfreundschuh M, Ludwig WD, Graeven U, *et al.* Front-line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Blood* 2006;**108**:146–7.
3. Buske C, Hoster E, Dreyling M, Forstpointner R, Kneba M, Schmitz N, *et al.* Rituximab in Combination with CHOP in patients with follicular lymphoma: analysis of treatment outcome of 552 patients treated in a randomized trial of the German Low Grade Lymphoma Study Group (GLSG) after a follow up of 58 months. *Blood* 2008;**112**:Abstract no. 2599.

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5. Buske C, Hoster E. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. *Blood* 2006;**108**:1504–8.
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OSHO-39 trial

1. Herold M, Dolken G, Fiedler F, Franke A, Freund M, Helbig W, *et al.* Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab. *Ann Hematol* 2003;**82**:77–9.
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3. Herold M, Haas A, Srock S, Neser S, Al-Ali K, Neubauer A, *et al.* Addition of Rituximab to First-Line MCP (Mitoxantrone, Chlorambucil, Prednisolone) Chemotherapy Prolongs Survival in Advanced Follicular Lymphoma 4 Year Follow-Up Results of a Phase III Trial of the East German Study Group Hematology and Oncology (OSHO39). *Blood* 2006;**108**:147.
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FL2000 trial

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2. Foussard C, Mounier N, Van Hoof A, Delwail V, Casasnovas O, Deconinck E, *et al. Update of the FL*2000 randomized trial combining rituximab to CHVP-Interferon in follicular lymphoma (FL) patients (pts). *J Clin Oncol: ASCO Annual Meeting Proceedings* 2006;**24**:424.
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Appendix 9

List of excluded studies

Excluded studies for head-to-head evidence review (*n* = 108)

1. No author. A phase III trial of CHOP vs CHOP + rituximab vs CHOP + 1–131 tositumomab for newly diagnosed follicular non-Hodgkin lymphoma. *Clin Adv Hematol Oncol* 2006;**4**:536–8.
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3. No author. Clinical studies for patients with indolent non-Hodgkin's lymphoma. *Lymphoma Today* 2000;**6**:10.
4. No author. Improved survival in aggressive NHL. *Eur J Cancer* 2001;**37**:1326.
5. No author. Low-grade malignant non-Hodgkin's lymphoma: initial treatment with the monoclonal antibody rituximab. *Deutsche Apotheker Zeitung* 2004;**144**:57–8.
6. No author. Positive results announced from pivotal study of bendamustine in non-Hodgkin's lymphoma. *Oncology* 2007;**21**:1496.
7. No author. Rituxan delays disease progression in indolent non-Hodgkin's lymphoma. *Oncology (Williston Park)* 2002;**16**:1472.
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18. Baltazar S, Tripp G, Baez E, Rivas S, Solis L, Ignacio G, *et al.* CNOP vs CNOP-rituximab vs rituximab alone as first line therapy for indolent non-Hodgkin lymphoma (INHL): preliminary disease-free/overall survival analysis. The Ninth Congress of the European Hematology Association, Geneva, Switzerland, 10–13 June 2004.

19. Baltazar S, Tripp G, Baez E, Rivas S, Solis L, Ignacio G, *et al.* CNOP vs CNOP-rituximab vs rituximab alone as first line therapy for indolent non-Hodgkin lymphoma (INHL): preliminary disease-free/overall survival analysis. *Hematology J* 2004;**5**:10.

20. Bassi S, Mancuso P, Gigli F, Antoniotti P, Bertazzoni P, Quarna J, *et al.* Lymphoid subpopulations and safety profile in untreated-follicular lymphoma receiving rituximab monotherapy as induction and maintenance therapy. *Blood* 2006;**108:**259.

21. Bjorkholm M, Andersson T, Ahlbom A, Osby E. CNOP (mitoxantrone) chemotherapy is inferior to CHOP (doxorubicin) in the treatment of patients with aggressive non-Hodgkin lymphoma (meta-analysis) (structured abstract). *Eur J Haematol* 2008;**80**:477–82.

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Appendix 10

List of excluded studies that met criteria for a network meta-analysis

1. Coiffier B, Stamatoullas A, Belanger C, Bouabdallah R, Haioun C, Neidhardt EM, *et al.* CHVP + interferon alpha 2b treatment is associated with a longer survival than fludarabine alone in elderly patients with high risk follicular lymphoma: a randomized study from the GELA. *Blood* 1998;**92**:486a.
2. Coiffier B, Neidhardt-Berard EM, Tilly H, Belanger C, Bouabdallah R, Haioun C, *et al.* Fludarabine alone compared to CHVP plus interferon in elderly patients with follicular lymphoma and adverse prognostic parameters: a GELA study. *Ann Oncol* 1999;**10**:1191–7.
3. Nickenig C, Dreyling MH, Schiegnitz E, Pfreundschuh M, Truemper LH, Reiser M, *et al.* CHOP Improves response rates but not overall survival in follicular and mantle cell lymphoma (MCL): results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Blood* 2004;**104**:176.
4. Nickenig C, Dreyling M, Schiegnitz E, Wandt H, Huber C, Trumper L, *et al.* CHOP significantly improves overall response and overall survival in patients with advanced follicular lymphoma: results of a randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *Onkologie* 2004;**27**:15.
5. Nickenig C, Dreyling M, Hoster E, Pfreundschuh M, Trumper L, Reiser M, *et al.* Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. *Cancer* 2006;**107**:1014–22.
6. Rummel MJ, von Gruenhagen U, Niederle N, Ballo H, Weidmann E, Welslau M, *et al.* Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: results of a randomized Phase III study of the Study Group Indolent Lymphomas (StiL). Abstract no. 2596. *Blood* 2008;**112**:900.
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Appendix 11

Data extraction tables

M39021 trial (Marcus *et al.*)[95,96]

Methods

Allocation: Randomised (1 : 1 ratio using stratification according to IPI scores).

Blinding: Open label.

Setting: Multicentre, 47 centres in Australia, Belgium, Brazil, Canada, France, Israel, Poland, Portugal, Spain, Switzerland and the UK.

Treatment duration: Treated every 21 days for a maximum of eight cycles.

Follow-up: Median 53 months (no range reported).

Design: Parallel group, ITT.

Power calculation: Yes.

Participants

Diagnosis: Follicular lymphoma, $n = 322$ (one CVP-enrolled patient withdrew consent).

Age: Median age – R-CVP 52 years, CVP = 53 years.

Gender: Males 174, females 148.

Inclusion criteria: Patients 18 years or older with untreated CD20-positive follicular lymphoma (NCI Working Formulation Groups B, C, D; WHO follicular lymphoma grades 1–3) confirmed by lymph node biopsy. All patients had to have stage III or IV disease, a performance status of 0–2 according to ECOG criteria, a life expectancy of > 3 months, and a need for therapy in the opinion of the participating clinician.

Exclusion criteria: Patients were ineligible if there was evidence of histological transformation to high-grade lymphoma or DLBCL, central nervous system (CNS) involvement, or a history of severe cardiac disease or previous malignancy other than in situ carcinoma of the cervix and basal cell carcinoma of the skin. Patients were also excluded if they had impaired renal or hepatic function.

Enrolment details and diagnosis

A total of 322 patients enrolled between 2000 and 2002 from 47 sites in Australia, Belgium, Brazil, Canada, France, Israel, Poland, Portugal, Spain, Switzerland and the UK. Patients diagnosed with CD20-positive follicular lymphoma (NCI) and were previously untreated.

Interventions

1. *CVP* Dose 750 mg/m^2 cyclophosphamide intravenously (i.v.) on day 1; 1.4 mg/m^2 vincristine, up to a maximal dose of 2 mg i.v., on day 1; and 40 mg/m^2 prednisone per day, orally, on days 1–5; $n = 159$.
2. *Rituximab + CVP* Dose 375 mg/m^2 rituximab i.v. on day 1 of eight therapy cycles; $n = 162$.

Patients in both groups were treated every 21 days for a maximum of eight cycles.

Maintenance therapy

None.

Tumour response and progression was determined using the guidelines by Cheson *et al.* Stable disease after cycle 4 was considered a 'treatment failure' event by the independent DSMC, who believed that patients with stable disease would be more likely to continue the same therapy in the R-CVP arm but would be more likely to start a new treatment in the CVP arm; these patients were withdrawn from treatment.

Time to progression was defined as the interval between randomisation and progression, relapse after response or death from any cause. Time to treatment failure (TTF) was defined as the time between randomisation and any one of the following events: progressive disease (PD), relapse after response, institution of new antilymphoma treatment (NLT), stable disease after cycle 4 (SD4) or death by any cause.

Disease-free survival was defined as the time between complete response and relapse or death (not specified).

Time to next antilymphoma treatment was defined as the time between randomisation and the date of next/new treatment or death (not specified).

Response duration was defined as the time between response and relapse or death (not specified).

Overall survival was defined as the time from randomisation to the date of death by any cause.

Baseline characteristics of M39021 trial[95,96]

Baseline characteristics	R-CVP, no. (%) ($n = 162$)	CVP, no. (%) ($n = 159$)
Age/gender		
Median age (years)	52	53
< 40 years	24 (15)	16 (10)
40–50 years	48 (30)	45 (28)
51–60 years	49 (30)	54 (34)
≥ 60 years	41 (25)	44 (28)
Male sex	88 (54)	85 (54)
Performance status (ECOG score)[a]		
0	93 (57)	90 (57)
1	65 (40)	60 (38)
> 1	4 (3)	8 (5)
Not evaluable/missing	0	1 (1)
Histology class (IWF classification): local review		
A (CLL)	0	2 (1)
B (FL grade 1)	59 (36)	53 (33)

Baseline characteristics of M39021 trial[95,96] (*continued*)

Baseline characteristics	R-CVP, no. (%) (*n* = 162)	CVP, no. (%) (*n* = 159)
C (FL grade 2)	87(54)	89 (56)
D (FL grade 3)	14 (9)	13 (8)
Other	1 (1)	1 (1)
Not evaluable/missing	1 (1)	1 (1)
Histology class (IWF classification): central review		
A (CLL)	0	2 (1)
B (FL grade 1)	38 (23)	46 (29)
C (FL grade 2)	82 (51)	69 (43)
D (FL grade 3)	19 (12)	19 (12)
Other	7 (4)	6 (2)
Not evaluable/missing	16 (10)	17 (11)
Stage (Ann Arbor)		
II	2 (1)	2 (1)
III-1[b]	5 (3)	4 (3)
III-2[c]	40 (25)	41 (26)
IV	114 (70)	112 (70)
Not evaluable/missing	1 (1)	0
IPI score[d]		
0	1 (1)	1 (1)
1	72 (44)	69 (43)
2	57 (35)	57 (36)
3	19 (12)	21 (13)
4	2 (1)	3 (2)
Not evaluable/missing	11 (7)	8 (5)
FLIPI score[d]		
0–2	80 (49)	75 (47)
3–5	71 (44)	75 (47)
Not evaluable/missing	11 (7)	9 (6)
One or more B symptoms[e]	65 (40)	51 (32)
Bulky disease[f]	63 (39)	73 (46)
Bone marrow involvement	103 (64)	102 (64)
One or more extranodal sites	28 (17)	27 (17)
Elevated LDH[g]	39 (26)	39 (26)

IWF, International Working Formulation.

a Performance status was defined according to the criteria of ECOG. A higher score indicates poorer performance status.

b Stage III-1: Involvement of lymph nodes on both sides of diaphragm. Abdominal disease limited to the upper abdomen (i.e. spleen, splenic hilar nodes, celiac nodes, porta hepatica node).

c Stage III-2: Involvement of lymph nodes on both sides of diaphragm. Abdominal disease including para-aortic, mesenteric, and iliac involvement with or without disease in the upper abdomen.

d Higher scores indicate a greater risk of death.

e Symptoms were defined as fever, weight loss and night sweats.

f Bulky disease is defined as nodal or extranodal mass of >7 cm at its greater diameter.

g The percentage calculation was not based on the 159 and 162 patients in the CVP and R-CVP groups, respectively, because LDH normal values were unavailable for seven patients in the CVP group and 10 patients in the R-CVP group.

Note: percentages based on evaluable patients.

Baseline characteristics used to determine patients in need of treatment in M39021 trial[95,96]

Parameter	R-CVP, no. (%) (*n* = 162)[a]	CVP, no. (%) (*n* = 159)[a]
Method of selecting patients		
BNLI criteria	45 (27.8)	46 (28.9)
Not BNLI criteria	117 (72.2)	113 (71.1)
B symptoms[b]		
At least one present	65 (40.1)	51 (32.1)
All absent	97 (59.9)	108 (67.9)
Bulky disease[c]		
Yes	63 (38.9)	73 (45.9)
No	99 (61.1)	86 (54.1)
More than three nodal sites with diameters > 3 cm		
Yes	44 (27.2)	32 (20.1)
No	118 (72.8)	127 (79.9)
Baseline haemoglobin (R-CVP = 161, CVP = 158)		
< 100 g/l (%)	7 (4.3)	7 (4.4)
≥ 100 g/l (%)	154 (95.7)	151 (95.6)
Baseline WBC (R-CVP = 161, CVP = 158)		
$< 3.0 \times 10^9$/l	1 (0.6)	1 (0.6)
3.0×10^9/l	160 (99.4)	157 (99.4)
Baseline neutrophils (R-CVP = 160, CVP = 155)		
$< 1.5 \times 10^9$/l	1 (0.6)	3 (1.9)
$\geq 1.5 \times 10^9$/l	159 (99.4)	152 (98.1)
Baseline platelets (R-CVP = 161, CVP = 158)		
$< 100 \times 10^9$/l	5 (3.1)	6 (3.8)
$\geq 100 \times 10^9$/l	156 (96.9)	152 (96.2)
Baseline β_2-microglobulin (R-CVP = 147, CVP = 141)		
< 3 mg/dl	1 (0.7)	0
≥ 3 mg/dl	146 (99.3)	141 (100)
Baseline LDH (R-CVP = 152, CVP = 152)		
< 2 ULN	39 (25.7)	39 (25.7)
≥ 2 ULN	113 (74.3)	113 (74.3)
Baseline performance status ECOG (R-CVP = 162, CVP = 158)		
< 1	4 (2.5)	8 (5.1)
≥ 1	158 (97.5)	150 (94.9)
Macroscopic liver involvement (R-CVP = 162, CVP = 159)		
Yes	10 (6.2)	9 (5.7)
No	152 (93.8)	150 (94.3)
Macroscopic renal involvement (R-CVP = 162, CVP = 159)		
Yes	4 (2.5)	2 (1.3)
No	158 (97.5)	157 (98.7)
At least one symptom	132 (81.5)	125 (78.6)

BNLI, British Lymphoma Investigation Group; ULN, upper limit of normal; WBC, white blood cell.

a Number per group unless otherwise stated.

b Symptoms were defined as fever, weight loss and night sweats.

c Bulky disease is defined as nodal or extranodal mass of > 7 cm at its greater diameter.

Outcomes in M39021 trial[95,96]

	M39021,[95,96] median follow-up = 53 months	
Parameter	**R-CVP (*n* = 162)**	**CVP (*n* = 159)**
Overall response: no. (%)	131 (81) (95% CI 74% to 87%)	90 (57) (95% CI 49% to 64%)
p-value	< 0.0001	
CR (includes CRu): no. (%)	66 (41) (95% CI 33% to 49%)	16 (10) (95% CI 6% to 16%)
p-value	< 0.0001	
PR: no. (%)	65 (40)	74 (47)
	No *p*-value reported	
Stable disease	12 (7)	33 (21)
p-value	No *p*-value reported	
Progressive disease	17 (11)	31 (20)
p-value	No *p*-value reported	
OS rate (% alive using Kaplan–Meier estimate at 4 years)	83 (95% CI 77 to 89)	77 (95% CI 70 to 83)
p-value	< 0.0290	
Median OS	Not reached	Not reached
No. of deaths (42-month follow-up) (%)[101]	23 (14)	35 (22)
p-value	No *p*-value reported	
Deaths owing to lymphoma: no. (%)	13 (8)	22 (14)
Median TTF	27 months (95% CI 25 to 37)	7 months (95% CI 6 to 9)
p-value	< 0.0001	
Median response duration	38 months (95% CI 28 to NE)	14 months (95% CI 9 to 18)
p-value	< 0.0001	
Median time to next treatment, months	49 (32 to NE)	12 (10–18)
p-value	< 0.0001	
Median DFS, months	Not reached (35 to NE)	21 (14–38)
p-value	0.0001	
Median TTP, months	34 (27–48)	15 (12–18)
p-value	< 0.0001	

NE, not estimable.

Adverse events and treatment exposure reported in M39021 trial[95,96]

	M39021[95,96]	
AEs (grade 3/4)	**R-CVP, *n* = 162**	**CVP, *n* = 159**
Neutropenia	39 (24)	22 (14)
Leucopenia taken from MS[61] (could not be confirmed in manuscripts)	19 (12)	14 (9)
Experiencing at least one AE	157 (97)	153 (96)
Experiencing an AE with 24 hours of infusion	115 (71)	81 (51)
Experiencing a total of six life-threatening AEs	5(3)	0
Grade 3 or 4 rituximab infusion-related reaction	14 (9)	Not applicable
Leaving study before completing four cycles	6 (4)	13 (8%)
Leaving study early before completing eight cycles	25 (15)	51 (32)
Treatment-related deaths	0 (0)	0 (0)

Number of treatment cycles and dose administered in M39021 trial[95,96]

R-CVP ($n=162$)	CVP ($n=159$)
Eight cycles administered to $n=144$ (89%)	**Eight cycles administered to $n=103$ (65%)**

Ninety per cent of patients received the planned dose of prednisolone and vincristine at each administered cycle and this was similar between the R-CVP and CVP arms. The proportion of patients who received >90% of cyclophosphamide was higher in the CVP group (>94%) than the R-CVP group (>85%). Ninety-six per cent of patients received >90% of the planned dose of rituximab at each administered cycle

Subgroup analyses

Multivariate analysis assessed the prognostic value of various parameters (BNLI criteria, age, extranodal sites, LDH, FLIPI, IPI, bone marrow involvement, elevated B_2-microglobulin, B symptoms, bulky disease, nodal areas, haemoglobin level) on outcome in terms of TTP in the presence of the trial treatment effect. Only the FLIPI (categorised as 0–2 vs 3–5 in the analysis) was a significant prognostic parameter for TTP in addition to the trial treatment. Patients with a FLIPI score of 0–2, who received R-CVP, had the longest TTP. No other prognostic factor improved the predictive power. In two further multivariate analyses (one utilising IPI instead of FLIPI, the other considering neither of the composite factors FLIPI and IPI), only haemoglobin level and number of nodal areas were found to be statistically significant predictors of TTP in addition to trial treatment

BNLI, British Lymphoma Investigation Group.

Subgroup analyses of efficacy data in M39021 trial[95,96]

	R-CVP ($n=162$)			CVP ($n=159$)			
Prognostic factor	**No.**	**Median TTP (months)**	**95% CI**	**No.**	**Median TTP (months)**	**95% CI**	***p*-value**
FLIPI score							
0–1	28	Not reached	38 to NE	23	22	16 to 40	0.0085
2	62	37	28 to NE	56	17	13 to 25	0.0003
3–5	61	26	16 to 34	71	11	10 to 15	0.0004
IPI score							
0–1	73	44	30 to NE	70	20	13 to 26	<0.0001
2	57	27	20 to 39	57	14	10 to 17	0.0003
3–4	21	40	11 to NE	24	12	8 to 25	0.0333
Histology at central review (IWF)							
Class B	38	34	27 to NE	46	17	11 to 24	0.0037
Class C	82	35	26 to NE	69	15	10 to 21	<0.0001
Class D	19	Not reached	30 to NE	19	14	7 to 24	<0.0046
B symptoms							
≥1	65	32	22 to NE	51	17	12 to 23	0.0014
All absent	97	37	26 to 48	108	14	11 to 20	<0.0001
Bulky disease							
Yes	63	38	25 to 48	73	13	11 to 21	<0.0001
No	99	32	26 to NE	86	16	13 to 21	<0.0001
Haemoglobin (g/dl)							
≥12	132	39	31 to NE	121	17	13 to 22	<0.0001
<12	29	11	9 to 28	35	12	10 to 16	0.3941

IWF, International Waling Formulation; NE, not estimable.

Median TTP (months) according to baseline FLIPI scores (univariate analysis)

FLIPI	R-CVP ($n=162$)	CVP ($n=159$)
FLIPI 0–1 (good prognosis)	Not reached	22
FLIPI 2 (intermediate prognosis)	37	17
FLIPI 3–5 (poor prognosis)	26	11

GLSG-2000 trial[91,92]

Methods

Allocation: Randomised (computer generated, in blocks stratified).

Blinding: Open label.

Setting: Germany, multicentre.

Treatment duration: Six to eight cycles (up to 24 weeks).

Follow-up: Median 58 months.

Design: Parallel group, ITT analysis.

Power calculation: Yes.

Participants

Diagnosis: Follicular lymphoma (advance stage III–IV), untreated, grades I and II (WHO) classification.

Number: 630 enrolled (not reported how many randomised).

Age: Median age 57 years (range 21–90 years).

Gender: 266 males and 291 females.

Inclusion criteria: Patients 18 years of age and older previously untreated, advanced-stage FL grades 1 and 2 according to the WHO classification, Stage III or IV disease and a requirement for therapeutic intervention as defined by the presence of B symptoms (night sweats, fever or weight loss), bulky disease (mediastinal lymphomas of > 7.5 cm or other lymphomas of > 5 cm in maximal diameter), impairment of normal hematopoiesis with haemoglobin levels of < 100 g/l, granulocyte count of $< 1.5 \times 10^9$/l, thrombocyte count of $< 100 \times 10^9$/l, or rapidly progressive disease.

Exclusion criteria: Patients were ineligible if they had FL grade III, were pregnant or lactating, or were women of childbearing potential and not using a reliable method of contraception.

Interventions

1. *CHOP* Dose: 750 mg/m^2 cyclophosphamide; 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine: all given i.v. on day 1. Prednisolone given 100 mg/m^2 daily on days 1–5 orally; $n = 278$.
2. *Rituximab + CHOP* Dose rituximab: 375 mg/m^2 the day before the respective R-CHOP course; $n = 279$.

Patients achieving CR after four cycles were treated with a total of six cycles only, whereas all other patients received eight courses of CHOP or R-CHOP.

Treatment cycles Every 3 weeks for a total of six to eight cycles; number of cycles, patients achieving CR after four cycles were treated with a total of six cycles; all other patients received eight cycles. Patients with progressive disease at anytime during R-CHOP or CHOP therapy were withdrawn from treatment.

Maintenance therapy

Patients aged < 60 years achieving CR or PR after CHOP or R-CHOP were offered a second randomisation for treatment in remission to either intensification by the Dexa-BEAM regimen consisting of dexamethasone 3 × 8 mg/day orally on days 1–10, bischloroethylnitrosourea (BCNU) 60 mg/m^2 daily on day 2, melphalan 20 mg/m^2 daily i.v. on day 3, etoposide 75 mg/m^2 daily i.v. on days 4–7, and cytosine arabinoside 2 × 100 mg/m^2 every 12 hours i.v. on days 4–7 with subsequent stem cell harvest followed by myeloablative radiochemotherapy with total body irradiation (12 Gy) and cyclophosphamide 60 mg/kg daily for 2 days and stem cell retransfusion or long-term interferon-alpha maintenance initiated at a dose of 3 × 5 million international units (MIU)/week and reduced according to observed adverse effects. Interferon maintenance therapy was given until lymphoma progression or the development of intolerable adverse effects. Second randomisation stratified for type of initial therapy (R-CHOP or CHOP) and the response (CR or PR). Only 25 patients did not receive either of these options.

Enrolment details and diagnosis

A total of 630 patients enrolled from 200 institutions between May 2000 and August 2003. In June 2003, significantly longer TTF was recorded for the R-CHOP arm ($p = 0.001$) and randomisation stopped according to the protocol in August 2003. Grade 1 or 2 histological diagnosis for 390 patients confirmed by a central pathology review, 38 patients' results still pending.

Evaluation response and definitions

Tumour response and progression was determined using the guidelines by Cheson *et al.*[89] Response to therapy assessed every two cycles and 4 weeks after completion of last course, and consisted of:

- physical examination – every 3 months
- blood count and LDH level – every 3 months
- ultrasound of abdomen – every 3 months
- CT scan of previously involved areas – every 6 months
- patients fulfilling CR criteria had bone marrow biopsy – every 3 months.

Time to treatment failure was defined as the interval between the start of treatment and the documentation of resistance to initial therapy, disease progression or death. Response duration was defined as the interval from the end of successful induction therapy to the documentation of disease progression or death. Overall survival was defined as the interval between start of treatment and death. Time to next antilymphoma treatment was not defined.

Baseline characteristics in GLSG-2000 trial[92]

Characteristic	R-CHOP ($n=279$)		CHOP ($n=278$)		p-value
Median age (years), min.–max.	57	27–90	57	21–81	0.79
Male	120	43%	146	53%	0.027
Ann Arbor stage IV	194	70%	191	69%	0.85
Bone marrow involved	180	65%	179	64%	1.00
B symptoms	108	39%	113	41%	0.60
Elevated LDH	73	26%	66	24%	0.56
Hb < 120 g/l	54	20%	56	20%	0.83
ECOG performance status 0	97	36%	88	32%	0.82
ECOG performance status 1	155	57%	167	61%	NR
ECOG performance status > 2	18	7%	19	7%	NR
FLIPI low risk	39	14%	31	11%	0.61
FLIPI intermediate risk	114	41%	119	44%	NR
FLIPI high risk	123	45%	123	45%	NR

max., maximum; min., minimum.

Outcomes in the GLSG-2000 trial[91,92]

	GLSG-2000 trial[91,92] (median follow-up = 56 months)	
Outcome	R-CHOP ($n=279$)	CHOP ($n=278$)
OR: no. (%)	271 (97) (no CI reported)	253 (91) (no CI reported)
p-value reported in study	0.0046	
CR: no. (%)	53 (20)	47 (17)
p-value reported in study	No p-value reported	
PR (includes CRus): no. (%)	215 (77)	187 (74)
	No p-value reported	
Stable disease including minor response	6 (2)	17 (6)
p-value reported in study	No p-value reported	
Progressive disease	3 (1)	6 (2)
p-value reported in study	No p-value reported	
OS 5-year rate %	90 (no CI reported)	84 (no CI reported)
p-value reported in study	0.0493	
Median OS	Not reached	Not reached
No. of deaths reported at 3 years[92]	6	17
p-value reported in study	= 0.016	
Median TTF	Not reached	35 months
p-value	< 0.0001	
Duration of response at 5 years	66%	35%
p-value reported in study	$p < 0.0001$	
Median time to next antilymphoma treatment (reported at 18-month follow-up)[92]	NR	NR
p-value reported in study	0.001	

NR, not reported.

Adverse events

Deaths reported in GLSG-2000 trial[92]

Cause of death/time of death	R-CHOP ($n=223$)	CHOP ($n=205$)
Death owing to lymphoma	1 (0)	9 (4)
Death owing to infection	4 (2)	4 (2)
Death owing to cardiac failure	0	1 (0)
Apoplectic insult	0	1 (0)
Death owing to GVHD after ASCT	0	1 (0)
Death cause unknown	1 (0)	1 (0)
Death by 18 months	2 (1)	2 (1)
Death by 36 months	6 (3)	17 (8)
	($p=0.016$)	

GVHD, graft-versus-host disease.

Adverse events reported in GLSG-2000 trial[92]

	Grade 1 and 2		Grade 3		Grade 4	
AE	R-CHOP ($n=223$)	CHO ($n=205$)	R-CHOP ($n=223$)	CHOP ($n=205$)	R-CHOP ($n=223$)	CHOP ($n=205$)
Haemoglobin level	112 (50)	100 (49)	18 (8)	18 (9)	2 (1)	2 (1)
Leucocyte	54 (24)	57 (28)	96 (43)	78 (38)	58 (26)	47 (23)
Granulocyte	42 (19)	41 (20)	49 (22)	47 (23)	91 (41)	62 (30)
Platelets count	38 (17)	33 (16)	9 (4)	10 (5)	4 (2)	6 (3)
Infection	74 (33)	59 (29)	11 (5)	12(6)	0 (0)	2 (1)
Bleeding	9 (4)	6 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	100 (45)	90 (44)	9 (4)	12(6)	0 (0)	0 (0)
Stomatitis	58 (26)	59 (29)	2 (1)	4 (2)	0 (0)	0 (0)
Obstipation	33 (15)	27 (13)	4 (2)	2 (1)	0 (0)	0 (0)
Diarrhoea	25 (11)	23 (11)	4 (2)	6 (3)	0 (0)	0 (0)
Fever	65 (29)	45 (22)	0 (0)	2 (1)	0 (0)	0 (0)
Cardiac dysfunction	7 (3)	8 (4)	4 (2)	2 (1)	2 (1)	0 (0)
Alopecia	42 (19)	51 (25)	140 (63)	115 (56)	9 (4)	10 (5)
Cardiac arrhythmia	13 (6)	8 (4)	2 (1)	0 (0)	2 (1)	0 (0)
Neurotoxicity	76 (34)	86 (42)	2 (1)	4 (2)	0 (0)	0 (0)
CNS toxicity	4 (2)	4 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Allergy	13 (6)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
	R-CHOP ($n=223$)		CHOP ($n=205$)			
Infections including fevers of unknown origin	11 (5)		14 (7)			
Stopped treatment due to AEs	2 (1)		0 (0)			
Early cessation of rituximab AEs (%)	2 (1)		0 (0)			

Number of treatment cycles and dose administered: not reported

Subgroup analyses in GSLG-2000 trial,[92] TTF and OS

Subgroup	Result
Age, years	
< 60	Median TTF not reached for CHOP (p-value for Cox regression = 0.003). Estimated RR for TTF for R-CHOP: 0.417 (95% CI 0.233 to 0.747)
≥ 60	Median TTF 29 months for CHOP (p-value for Cox regression = 0.004). Estimated RR for TTF for R-CHOP: 0.354 (95% CI 0.175 to 0.715)
IPI score	
1–2	Median not reached (p-value for Cox regression = 0.001). Estimated RR for TTF for R-CHOP 0.412 (95% CI 0.242 to 0.701)
3–5	29 months (p-value for Cox regression = 0.009). Estimated RR for TTF for R-CHOP 0.33 (95% CI 0.144 to 0.761)
Elderly patients	
	Estimated 4 years' PFS was 62.2% for R-CHOP (n = 109) vs 27.9 % after CHOP (n = 112) (log-rank test: p < 0.0001). R-CHOP (n = 109) prolonged OS in elderly patients with an estimated 4 years' OS of 90% after immunochemotherapy vs 81% after CHOP (n = 112) alone (log-rank test: p = 0.039)
FLIPI score	
Low-risk group	R-CHOP prolonged 5 years' TTF: R-CHOP 84% vs 46% CHOP (p = 0.0021)
Intermediate-risk group	TTF prolonged 5 years' R-CHOP 73% vs 37% CHOP (p < 0.0001)
High-risk group	TTF prolonged 5 years' R-CHOP 49% vs CHOP 23% (p < 0.0001)

OSHO-39 trial (Herold *et al.*)[93]

Methods

Allocation: Randomised (random number list).

Blinding: Open label.

Setting: Germany, 34 centres.

Treatment duration: Total of 32 weeks consisting of eight treatment cycles of rituximab.

Follow up: Median 49 months for R-MCP, 42 months MCP (no range reported).

Design: Parallel group, ITT analysis.

Power calculation: Yes (using primary popaulton of follicular lymphoma).

Participants

Diagnosis: Follicular lymphoma.

Number: 358 total (201 with FL).

Age: Median age, MCP arm = 57 years (range 31–75 years), R-MCP arm = 60 years (33–78 years).

Gender: 89 males and 112 females.

Inclusion criteria: Age 18–75 years, untreated, histologically confirmed, CD20 indolent NHL (FL, grade 1 and 2 only; lymphoplasmacytic lymphoma) and MCL. Stage III or IV disease according to the Ann Arbor classification General performance status of ≤ 2 according to the ECOG scale. Needing treatment for either, B symptoms or extranodal manifestation, haematopoietic insufficiency, rapid tumour growth, bulky disease [lymphoma of > 7.5 cm in diameter, mediastinal tumor one-third of thorax diameter at thoracic vertebra 5/6, or immunohaematological phenomena (e.g. haemolytic anemia or immune thrombocytopenia)].

Exclusion criteria: Patients with concomitant diseases and/or restricted organ function not caused by lymphoma or patients with HIV infection were excluded from the study.

Interventions

1. *MCP* Dose mitoxantrone 8 mg/m^2 i.v. on days 3 and 4, chlorambucil (3 × 3mg/m^2 orally) on days 3–7, and prednisolone (25 mg/m^2 orally) on days 3–7; $n = 96$.
2. *Rituximab-MCP* Dose rituximab 375 mg/m^2 i.v. on day 1 of each therapy cycle, followed by mitoxantrone (8 mg/m^2 i.v.) on days 3 and 4, chlorambucil (3 × 3mg/m^2 orally) on days 3–7, and prednisolone (25 mg/m^2 orally) on days 3–7; $n = 105$.

Maintenance

Maintenance therapy with interferon alpha-2a (4.5 MIU three times per week until relapse) was planned in all study patients with FL who had achieved PR or CR and was initiated within 4–8 weeks after treatment completion; thus 3 × 4.5 MIU per week until disease progression was initiated in 97% ($n = 102$) and 92% ($n = 88$) of planned patients in the R-MCP group and MCP group, respectively.

Enrolment details and diagnosis

Enrolment occurred between October 1998 and September 2003 at 34 centres in Germany. Follicular lymphoma was confirmed histologically by a designated reference pathologist.

Evaluation response and definitions

After completion of induction treatment, patients were observed every 8 weeks during the first year, at 3-month intervals during the second year, and then every 6 months from the third year onward. Tumour responses were assessed after two treatment cycles, after six treatment cycles, and 4 weeks after completion of study treatment. Response assessment included all diagnostic measures used in the pre-therapeutic staging (including CT scans of neck, chest, abdomen and pelvis, and bone marrow biopsy).

Patients with disease progression after two cycles of therapy were prematurely withdrawn from study treatment and were considered as having treatment failure in the analysis of EFS. Patients who had not reached a PR or CR after six cycles of therapy were also classified as experiencing treatment failure in the EFS analysis. Patients with a CR or a PR after six cycles of chemotherapy or immunochemotherapy, respectively, received a further two consolidation cycles of MCP or R-MCP for a total of eight treatment cycles.

Progression-free survival was defined as randomisation to disease progression or death from NHL. Overall survival was defined as the time from randomisation to the date of death by any cause. Response duration was defined as the time between response to treatment and disease progression or death by any cause. EFS was defined as the time between randomisation and relapse, disease progression or disease progression after two cycles or PR after six cycles. Time to next antilymphoma treatment was defined as time between randomisation and date of next/new treatment.

Baseline characteristics of OSHO-39 trial[93]

Characteristic	R-MCP ($n=105$), no. (%)	MCP ($n=96$), no. (%)
Age, median (range)	57 (31–75)	60 (33–79)
Males	36 (37)	53 (50)
Ann Arbor stage III	22 (23)	30 (29)
Ann Arbor stage IV	74 (77)	75 (71)
ECOG performance status 0	54 (56)	69 (65)
ECOG performance status 1	36 (39)	29 (29)
ECOG performance status 2	6 (6)	7 (7)
LDH > normal	30 (31)	31 (30)
Bone marrow infiltrate	71 (74)	73 (70)
B symptoms: nightly sweating	34 (35)	46 (44)
B symptoms: fever > 38ºC	2 (2)	4 (4)
B symptoms: weight loss > 10% within 6 months	20 (21)	16 (15)
FLIPI low (0–1)	6 (6)	9 (9)
FLIPI intermediate (2)	37 (39)	39 (36)
FLIPI high (3–5)	53 (55)	59 (56)

Outcomes in OSHO-39 trial[93]

	OSHO-39[93] (median follow-up)	
Outcome	**R-MCP (*n* = 105)**	**MCP (*n* = 96)**
OR: no. (%)	97 (92) (no CI reported)	72 (75) (no CI reported)
p-value reported in study	0.0009	
CR: no. (%)	52 (50)	24 (25)
p-value reported in study	0.0004	
PR (includes CRus): no. (%)	45 (43)	48 (50)
	No *p*-value reported	
Stable disease	NR[a]	NR[a]
p-value reported in study	No *p*-value reported	
Progressive disease	3 (3)	10 (10)
	(after two cycles]	(after two cycles)
p-value reported in study	No *p*-value reported	
OS rate at 4 years (%)	87 (CI NR)	74 (CI NR)
p-value reported in study	0.0096	
Median OS	Not reached	Not reached
No. of deaths at 4 years	15	25
p-value reported in study	No *p*-value reported	
Median PFS, months	Not reached	28.8
p-value reported in study	< 0.0001	
No. of events, *n* (%)	30 (29)	50 (52)
% PFS at 4 years	71	40
Median EFS, months	Not reached	26
p-value	< 0.0001	
Median response duration, months	Not reached	35
p-value	< 0.0001	
Median TTNT, months	Not reached	29.4
p-value	0.0002	

NR, not reported.
a Stable disease not reported but '< PR' reported at cycle 6 (R-MCP = 7 and MCP = 22) and at cycle 8 (R-MCP = 8 and MCP = 24).

Deaths reported in OSHO-39 trial[93]

Cause of death	**R-MCP (*n* = 105)**	**MCP (*n* = 96)**
Death cause unknown	15 (14)	25 (26) 0
Cause-specific deaths ($p = 0.0159$)	7 (7)	17 (18)

Adverse events (no., %) reported in the OSHO-39 trial[93]

	Grade 1 or 2		Grade 3		Grade 4	
AE	R-MCP (*n* = 105)	MCP (*n* = 96)	R-MCP (*n* = 105)	MCP (*n* = 96)	R-MCP (*n* = 105)	MCP (*n* = 96)
Haemoglobin level	18 (17)	18 (19)	2 (2)	3 (3)	1 (1)	1 (1)
Leucocyte/WBC	3 (3)	8 (8)	25 (24)	21 (22)	50 (48)	35 (36)
Platelets count	31 (30)	32 (33)	4 (4)	6 (6)	0 (0)	1 (1)
Infection	44 (42)	34 (35)	6 (6)	7 (7)	1 (1)	1 (1)
Nausea/vomiting	25 (24)	14 (14)	1 (1)	6 (6)	0 (0)	0 (0)
Stomatitis	11 (10)	7 (7)	1 (1)	1 (1)	0 (0)	0 (0)
Diarrhoea	11 (10)	4 (4)	2 (2)	0 (0)	0 (0)	2 (2)
Rash	16 (15)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Heartburn	15 (14)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Insomnia	15 (14)	7 (7)	0 (0)	0 (0)	0 (0)	0 (0)
Bone pain	10 (10)	10 (10)	2 (2)	0 (0)	0 (0)	0 (0)
Gastrointestinal	9 (9)	5 (5)	2 (2)	1 (1)	0 (0)	1 (1)
Other (not specified)	11 (10)	8 (8)	0 (0)	1 (1)	0 (0)	1 (1)

WBC, white blood cell.

Number of treatment cycles and dose administered in OSHO-39 trial[93]

R-MCP (*n* = 105)	MCP (*n* = 96)
Eight cycles administered to *n* = 92 (88%)	**Eight cycles administered to *n* = 64 (67%)**
The mean dose of study drugs administered in the OHSO–39 trial[93] were rituximab, 660–680 mg/cycle; mitoxantrone, 24–28 mg/cycle; chlorambucil, 68–81 mg/cycle and prednisolone, 226–231 mg/cycle. The authors stated that the dose intensity of the chemotherapy did not differ between treatment arms[93]	
Interferon-alpha maintenance treatment (3 x 4.5 MIU per week until disease progression) was initiated in 97% and 92% of responding patients in the R-MCP and MCP arms, respectively	

Subgroup analyses

None.

FL2000 trial (Salles *et al.*)[94]

Methods

Allocation: Randomised (methods not specified).

Blinding: Open label.

Setting: France and Belgium, 54 centres.

Treatment duration: 72 weeks.

Follow up: Median 5 years (range: 0.2–6.4 years).

Design: Parallel, ITT anlayses.

Power calculation: Yes.

Participants

Diagnosis: Follicular lymphoma.

Number: = 60 (358 analysed; one patient withdrew consent after registration; one patient had a major inclusion violation, which was registered at relapse).

Age: Median 61 years (range 25–75 years).

Gender: 178 males and 180 females.

Inclusion criteria: Untreated patients 18–75 years of age; histological diagnosis of FL grade 1, 2, 3a performed in last 3 months on lymph node biopsy (pathologic review by panel of three expert pathologists) stage II–IV (Ann Arbor); fulfil any one of following criteria for high tumour burden: (1) presence of a bulk tumour defined by either one of the following: tumour lesion with a largest diameter of ≥ 7 cm, spleen enlargement with a craniocaudal diameter of >20 cm, existence of three lymph nodes in three distinct nodal areas with a diameter of > 3 cm, pleural effusion, ascites, or symptomatic compressive syndrome; (2) presence of B symptoms (fever, night sweats, or weight loss); (3) a performance status on the ECOG scale > 1; (4) elevated serum levels of LDH (above normal values) or β_2-microglobulin (≥ 30 mg/dl).

Exclusion criteria: Patients with contraindications to anthracyclines, interferon, or rituximab, with known positivity for HIV or active viral hepatitis, or with a previous malignancy were not eligible for the study.

Interventions

1. *CHVPi* Twelve courses: six courses every 28 days, six courses every 56 days: 600 mg/m^2 cyclophosphamide i.v. on day 1, 25 mg/m^2 adriamycin/doxorubicin intravenously on day 1, 100 mg/m^2 etoposide i.v. on day 1, 40 mg/m^2 predisolone orally from days 1–5. Interferon-alpha2a s.c. during 18 months, three times a week at an initial dose of 4.5 MIU per injection for patients of < 70 years or 3 MU per injection for patients aged > 70 years; *n* = 183.
2. *Rituximab + CHVPi* Doses as per comparator arm on same days of cycle. Rituximab = 375 mg/m^2, six cycles every 28 days; however, cycles 1 and 2 CHVPi only; cycles 3 and 4 R-CHVP-I (plus extra rituximab on day 8 of cycle); cycles 5 and 6 RCHVP-I: and cycles 7–12 interferon only every 56 days; *n* = 175.

Maintenance therapy

None.

Evaluation and response and outcomes definitions

- Evaluation of response performed after six chemotherapy courses (6 months) and at the end of the whole treatment (18 months).
- Disease evaluation for response assessments was recommended in the International Workshop criteria: CR, disappearance of all lesions and of radiological or biological abnormalities observed at diagnosis and the absence of new lesions; CRu, CR with persistence of some radiologic abnormalities, which had to have regressed in size by at least 75%; PR, regression of all measurable lesions by > 50%, the disappearance of non-measurable lesions, and the absence of new lesions and 'stable disease', regression of any measurable lesion by ≤ 50% or no change in the non-measurable lesions, but without growth of existing lesions or the appearance of new lesions.
- Progressive disease – appearance of a new lesion, any growth of the initial lesion by > 25%, or growth of any measurable lesion that had regressed during treatment by > 50% from its smallest dimensions.
- Responding patients with previous bone marrow involvement for which bone marrow evaluation was missing at evaluation were considered has having a PR even if they met the criteria of CRu or CR. Any residual marrow infiltrate that could not be demonstrated to be a reactive infiltrate using immunostaining was considered as a positive bone marrow biopsy, and the response, if other criteria were met, as a PR.
- Patients who completed their treatment had a complete clinical examination every 3 months for the first year and then every 6 months for 5 years. A CT scan was performed yearly, and a new bone marrow biopsy was performed 18 months after treatment completion or when clinically indicated.

Overall survival was defined as the time from randomisation to the date of death by any cause. EFS was defined as time from randomisation to disease progression, death any cause, relapse or new antilymphoma treatment. Response duration was defined as the time from response to disease progression, death from any cause, or relapse.

Enrolment details and diagnosis

Patients were enrolled between May 2000 and May 2002. Histological diagnosis of FL grades 1, 2 and 3a performed in last 3 months on lymph node biopsy (pathological review by panel of three expert pathologists for 344 patients, four diagnoses of FL could not be formally confirmed because of technical problems, 12 cases were classified as non-FL subtypes), according to WHO criteria.

Baseline characteristics of the FL2000 trial[94]

Patient characteristics	R-CHVPi (*n*, %)	CHVPi (*n*, %)	Missing values
ECOG performance status >1	11 (6)	16 (9)	0
B symptoms presence	38 (22)	52 (29)	1
Ann Arbor stage III or IV	152 (87)	165 (91)	2
No. of nodal sites involved >4	86 (49)	78 (43)	0
Bone marrow involvement:	108 (62)	121 (67)	4
Extranodal sites >1	60 (35)	73 (40)	3
LDH more than upper normal value	64 (37)	66 (36)	5
Haemoglobin <12 g/dl	37 (21)	30 (17)	2
β_2-microglobulin >3 mg/l	62 (38)	56 (33)	28
IPI score >2	60 (36)	71 (39)	10
FLIPI 0–1 factors	28 (16)	37 (21)	9
FLIPI 2 factors	63 (37)	59 (33)	9
FLIPI 3 factors or more	79 (46)	83 (46)	9

Outcomes in the FL2000 trial (median follow-up = 60 months)[94]

	6-month follow-up data		18-month follow-up data (response rate only)	
Outcome	R-CHVPi (*n* = 175)	CHVPi (*n* = 183)	R-CHVPi (*n* = 175)	CHVPi (*n* = 183)
OR: no. (%) (no CI reported)	164 (94)	156 (85)	142 (81)	131 (72)
p-value reported in study	NR	NR	NR	NR
CR: no. (%)	63(36)	29(16)	90 (51)	71 (39)
p-value reported in study	<0.001[a]		0.035[a]	
PR[d]: no. (%)	101(58)	127 (69)	52 (30)	60 (33)
	<0.001[a]		0.035[a]	
Stable disease	2 (1)	9 (5)	1 (1)	3 (2)
p-value reported in study	<0.001[a]		0.035[a]	
Progressive disease	8 (5)	18 (10)	31 (18)	47 (26)
p-value reported in study	<0.001[a]		0.035[a]	
OS rate at 5 years, %	84, (95% CI 78 to 84)		79, (95% CI 72 to 84)	
p-value reported in study	0.1552			
Median OS	NR			
No. of deaths at 18 months	1 (1)		2 (1)	
p-value reported in study	No *p*-value reported			
Median EFS, months	Not reached		35	
p-value reported in study	0.0004			
5-year EFS	53% (95% CI 45% to 60%)		37% (95% CI 29% to 44%)	
p-value reported in study	0.001			
Duration of response at 4 years	64%[b] (95% CI 55% to 72%)		37% (95% CI 29% to 44%)	
p-value reported in study	0.012			

NR, not reported.
a *p*-values calculated by Salles *et al.*[94] using a global chi-squared test for all strata.

Adverse events (grade 3 and 4 combined) in the FL2000 trial[94]

	Induction (6 months of treatment)		Consolidation additional (12 months of treatment)	
AE	R-CHVPi ($n=175$)	CHVPi ($n=183$)	R-CHVPi ($n=175$)	CHVPi ($n=183$)
Haemoglobin level	6 (3)	9 (5)	1 (1)	4 (2)
Neutrophil	103 (59)	114 (62)	11 (6)[a]	69 (38)
Platelet count	5 (3)	6 (3)	2 (2)	4 (2)
Fever	2 (1)	2 (1)	0 (0)	1 (1)
Infection	4 (2)	0 (0)	2 (1)	2 (1)
Cardiac dysfunction	2 (1)	3 (2)	0 (0)	1 (1)

a Significant difference between two treatment arms, $p<0.001$.

Numbers of cycles administered

- In total, 95% of patients in the R-CHVPi arm and 94% of patients in the CHVPi arm received the initial six cycles of treatment.
- Among patients who did not progress during therapy, 161 (98%) and 153 (98%) of the patients received the planned chemotherapy courses during the first 6 months in the R-CHVPi and CHVPi arms, respectively.
- In the CHVPi arm, 116 (87%) of 134 patients without death or progression received the six planned cycles of chemotherapy consolidation.
- A total of 237 (66%) patients followed the interferon treatment according to the protocol, with dose adaptation (45 patients) or short (< 4 weeks) interruptions (55 patients), without significant differences in adaptation between the two study arms.
- Interferon treatment was stopped in 50 patients resulting from disease progression (R-CHVPi arm, 19 cases; CHVPi arm, 31 cases, respectively) and was interrupted either for > 1 month (16 cases) or definitively (72 cases) resulting from toxicity. These major interruptions were observed in 41 patients in the RCHVPi arm and 47 patients in the CHVPi arm.

Subgroup analyses

Because the FL2000 trial[94] was not stratified by the FLIPI, checked for effects of prognostic factors on outcome resulting from sampling fluctuation in the treatment groups using multivariate analysis of survival. The Cox regression model included FLIPI and treatment as explanatory variables. The interactions between risk factors and treatment were also included in the model.

Results

Significantly different outcomes for each group both for 5-year EFS and OS ($p<0.001$ for each). When the low- and intermediate-risk groups were considered together and compared with the high-risk group, this index was also able to discriminate risk groups for patients in each treatment arm. When considering together the 187 patients who presented either a low or an intermediate FLIPI score, no significant difference in outcome was observed according to each treatment arm. However, the outcome of the 162 patients with the highest FLIPI score (three to five adverse prognostic factors) was found to be significantly different both for 5-year EFS ($p=0.001$) and OS ($p=0.025$) between the CHVPi- and R-CHVPi-treated patients. Five-year OS probability for patients in the FL2000[94] in the different FLIPI prognostic subgroups (low, intermediate, and high) was found to be 95%, 89% and 70% as opposed to 91%, 78% and 53%, respectively.

Appendix 12

Outcomes definitions for time-to-event data

Note that the definitions do not include OS or PFS.

TABLE 91 Definitions used in the trials for response duration

From when response (complete or partial) achieved to:

Trial	Death not specified	Relapse	Disease progression	Death any cause
M39021[95,96]	✓	✓		
GLSG-2000[91,92]			✓	✓
OSHO-39[93]			✓	
FL2000[94]		✓	✓	✓

a It was unclear how relapsed was defined and how this differed from disease progression.

TABLE 92 Definitions used in the trials for TTF

Trial	Resistance to initial therapy	Disease progression	Death any cause	Death not specified	Relapse after response	New antilymphoma treatment	Stable disease after cycle 4
M39021[95,96] From randomisation			✓		✓	✓	✓
GLSG-2000[91,92] From start of treatment	✓	✓		✓			

TABLE 93 Definitions used in the trials for TTNT

From randomisation to:

Trial	Date of next/new treatment	Death not specified
M39021[95,96]	✓	✓
GLSG2000[91,92]	Not defined	
OSHO-39[93]	✓	

TABLE 94 Definitions used in the trials for EFS

From randomisation to

Trial	Disease progression after two cycles or PR at six cycles	Disease progression	Death any cause	Relapse	New antilymphoma treatment
FL2000[94]		✓	✓	✓	✓
[a]OSHO-39[93]	✓	✓		✓	

a All counted as a 'treatment failure' by Herold *et al.*[93]

TABLE 95 Definitions used in the trials for other outcomes reported

Outcome	Study	Definition
TTP	M39021[95,96]	Randomisation to disease progression, relapse after response, death by any cause
DFS	M39021[95,96]	CR to relapse or death (not specified)

Appendix 13

Chi-squared test analysis for response rate data

TABLE 96 R-CVP vs CVP, chi-squared test

	Observed		Expected	
Outcome	**R-CVP**	**CVP**	**R-CVP**	**CVP**
CR	49	12	30.8	30.2
PR (includes CRu)	82	78	80.7	79.3
Stable disease	12	33	22.7	22.3
Disease progression	17	31	24.2	23.8
Death	2	5	3.5	3.5
Treatment arm totals	162	159	162.0	159.0
p-value	< 0.001			

TABLE 97 R-CVP vs CVP (combining disease progression and death categories), chi-squared test

	Observed		Expected	
Outcome	**R-CVP**	**CVP**	**R-CVP**	**CVP**
CR	49	12	30.8	30.2
PR (includes CRu)	82	78	80.7	79.3
Stable disease	12	33	22.7	22.3
Disease progression + dead	19	36	27.8	27.2
Treatment arm totals	162	159	162.0	159.0
p-value	< 0.001			

TABLE 98 R-CHOP vs CHOP, chi-squared test

	Observed		Expected	
Outcome	**R-CHOP**	**CHOP**	**R-CHOP**	**CHOP**
CR	53	47	50.1	49.9
PR (includes CRu)	215	206	210.9	210.1
Stable disease (includes 'minor response' as well)	6	17	11.5	11.5
Disease progression	3	6	4.5	4.5
Dead	2	2	2.0	2.0
Treatment arm totals	279	278	279	278
p-value	0.15			

TABLE 99 R-CHOP vs CHOP (combining disease progression and death), chi-squared test

	Observed		Expected	
Outcome	**R-CHOP**	**CHOP**	**R-CHOP**	**CHOP**
CR	53	47	50.1	49.9
PR (includes CRu)	215	206	210.9	210.1
Stable disease (includes 'minor response' as well)	6	17	11.5	11.5
Disease progression + dead	5	8	6.5	6.5
Treatment arm totals	279	278	279.0	278.0
p-value	0.09			

TABLE 100 R-MCP vs MCP, chi-squared test

	Observed		Expected	
Outcome	**R-MCP**	**MCP**	**R-MCP**	**MCP**
CR	52	24	39.7	36.3
PR	45	48	48.6	44.4
< PR + disease progression	8	24	16.7	15.3
Treatment arm totals	105	96	105	96
p-value	< 0.001			

TABLE 101 R-CHVPi vs CHVPi (6 months' data), chi-squared test

	Observed		Expected	
Outcome	**R-CHVPi**	**CHVPi**	**R-CHVPi**	**CHVPi**
CR	63	29	45.0	47.0
PR (includes CRu)	101	127	111.5	116.5
Stable disease	2	9	5.4	5.6
Disease progression	8	18	12.7	13.3
Dead	1	0	0.5	0.5
Treatment arm totals	175	183	175.0	183.0
p-value	< 0.001			

TABLE 102 R-CHVPi vs CHVPi (6 months' data): combining categories stable disease + disease progression + death, chi-squared test

	Observed		Expected	
Outcome	**R-CHVPi**	**CHVPi**	**R-CHVPi**	**CHVPi**
CR	63	29	45.0	47.0
PR (includes CRu)	101	127	111.5	116.5
Stable disease + disease progression + dead	11	27	18.6	19.4
Treatment arm totals	175	183	175.0	183.0
p-value	< 0.001			

TABLE 103 R-CHVPi vs CHVPi (18 months' data) chi-squared test

	Observed		Expected	
Outcome	**R-CHVPi**	**CHVPi**	**R-CHVPi**	**CHVPi**
CR	90	71	78.70112	82.29888268
PR (includes CRu)	52	60	54.7486	57.25139665
Stable disease	1	3	1.955307	2.044692737
Disease progression	31	47	38.12849	39.87150838
Dead	1	2	1.46648	1.533519553
Treatment arm totals	175	183	175	183
p-value	0.123063805			

TABLE 104 R-CHVPi vs CHVPi (18 months' data) combining categories stable disease + disease progression + death

	Observed		Expected	
Outcome	**R-CHVPi**	**CHVPi**	**R-CHVPi**	**CHVPi**
CR	90	71	78.70112	82.29888268
PR (includes CRu)	52	60	54.7486	57.25139665
Stable disease + disease progression + dead	33	52	41.55028	43.44972067
Treatment arm totals	175	183	175	183
p-value	0.031978375			

Appendix 14

Exploratory meta-analyses

Three exploratory meta-analyses were conducted to explore the results of synthesising the ORR, CR and PR from the four trials.

There were several problems with the validity of these analyses. First, the level of statistical heterogeneity calculated in RevMan using the I^2-statistic was very high (range $I^2 = 56–88\%$). The I^2-value describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance),[106] and an I^2-value of > 50% is considered to be a high enough level of heterogeneity to suggest that meta-analysis is not appropriate. Ideally, this high level of heterogeneity would be explored further and explained by estimating the predictive distribution of a new study. This was not undertaken owing to resource constraints.

Reasons for the high level of heterogeneity could be because of differences in treatment effects in the four trials. Examination of the CIs for the results from the individual trials showed that there was little overlap in the meta-analyses for CR, and to a lesser extent for PR, indicating evidence for heterogeneity of intervention effects. Indeed, the GLSG-2000[91,92] trial observed much higher ORR (a combination of CR and PR) for both the R-chemotherapy and chemotherapy-alone arms in comparison with the other studies. This was mostly accounted for by an increase in the numbers of PR (20% CR and 77% PR in the R-CHOP arm), whereas in the OSHO-39 trial[93] there was a more even split between the CR/PR categories (50% CR and 43% PR in the R-MCP arm). As well as evidence for different intervention effects in the four trials, there are other possible explanations for the high level of heterogeneity. First, each study administered a different therapeutic intervention with respect to the chemotherapy regimen used: this included different chemotherapeutic agents (CVP, CHOP, MCP and CHVPi) and different regimens of treatment (3-weekly vs 4-weekly cycles; six cycles of treatment vs eight cycles of treatment). Second, there was a difference in the sample sizes of the studies, for example the GLSG-2000 trial[91,92] was the largest trial with an ITT population of $n = 557$ patients, whereas the OSHO-39 trial[93] was substantially smaller ($n = 201$).

The AG also notes that the choice of chemotherapeutic regimen is not solely determined by clinical efficacy. For example, R-CHOP is less likely to be given to patients who are elderly or unfit, but more likely to be given to treat aggressive or bulky disease, which may impact on the perceived efficacy. Additionally, the analyses assume that rituximab has no synergistic interaction with the chemotherapeutic component of a regimen for the treatment effect. The AG also comment that the analyses of ORR, CR and PR are not independent analyses given that the same patients are counted in more than one analysis.

The AG therefore believes the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens. These are subsequently used in the decision model (see *Chapter 4*) rather than meta-analysed response rates. The findings from the meta-analyses are presented below for completeness, but the use of these is strongly cautioned against.

Overall response rate

The addition of rituximab to chemotherapy showed a significant improvement in ORR compared with chemotherapy alone when the four trials were combined, with a RR of 1.18 (95% CI 1.04 to 1.33, $p = 0.01$) (*Figure 49*). This translated as an 18% increased likelihood of being a responder (complete or partial) to treatment if receiving R-chemotherapy compared with chemotherapy alone.

Complete response rate

The addition of rituximab to chemotherapy showed a significant improvement in CR compared with chemotherapy alone when the four trials were combined, with a RR of 2.05 (95% CI 1.27 to 3.30, $p = 0.003$) (*Figure 50*). This translated as a 105% (i.e. over double) increased likelihood of being a CR to treatment if receiving R-chemotherapy compared with chemotherapy alone.

Partial response rate

The meta-analysis of PR incorporated the results from three trials (M39021 trial[95,96] not being directly comparable: see *Chapter 3*, *Summary of trials*, for further details). For PR, the addition of rituximab to chemotherapy did not show a significant improvement in PR compared with chemotherapy; the RR calculated as 0.95 (95% CI 0.83 to 1.08, $p = 0.44$); this translated as a 5% decreased likelihood of being a PR if receiving R-chemotherapy compared with chemotherapy alone (*Figure 51*).

The meta-analysed PR appears counterintuitive when compared with the meta-analysed results for ORR and CR. However, this might be explained by the way in which the rituximab–chemotherapy combination affects the movement of the number of patients within each response category ('non-responder', 'partial responder' and 'complete responder'). It is plausible that the rituximab–chemotherapy combination might 'shift' more non-responders to PRs relative to the chemotherapy alone group, thus increasing the numbers within the PR group. However, at the same time the rituximab–chemotherapy combination appears to have an effect in patients who would otherwise be PRs and 'shift' such patients to 'complete responders'. This effect of shifting PRs to CRs would thus reduce the numbers within the PR group, negating the increase in numbers with the PR group as a result of the 'non-responder' to 'PR' conversion. These two effects may result in the number of PRs in the R-chemotherapy arm being similar to the number of PRs in the chemotherapy alone group.

Using the FL2000 18-month response rate data

The 6-month response rate data from the FL2000 trial[94] were considered most appropriate for the meta-analysis of response rates, as the intervention and comparator treatment arms up until that time point were comparable with the other three trials. The trial participants went on to receive a further 12 months of treatment, which consisted of interferon only for both treatment arms and bimonthly CHVP for the comparator arm. The results are presented in *Figures 52–54*. The use of the 18-month response rate data did not materially affect the results, with the exception of reducing the median RR by 0.4 for CR and reducing statistically heterogeneity considerably in the analysis of PR.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	164	175	156	183	27.5%	1.10 (1.02 to 1.18)
GLSG-2000[91,92]	268	279	253	278	29.2%	1.06 (1.01 to 1.10)
M39021[95,96]	131	162	90	159	20.4%	1.43 (1.22 to 1.67)
OSHO-39[93]	97	105	72	96	22.8%	1.23 (1.08 to 1.40)
Total (95% CI)		**721**		**716**	**100.0%**	**1.18 (1.04 to 1.33)**
Total events	660		571			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 24.65$, df = 3 ($p < 0.0001$); $I^2 = 88\%$

Test for overall effect: $z = 2.59$ ($p = 0.010$)

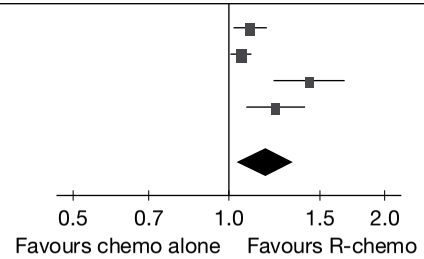


FIGURE 49 Forest plot for meta-analysis of ORR of the four trials. Chemo, chemotherapy.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	63	175	29	183	26.1%	2.27 (1.54 to 3.35)
GLSG-2000[91,92]	53	279	47	278	26.8%	1.12 (0.79 to 1.60)
M39021[95,96]	49	162	12	159	21.2%	4.01 (2.22 to 7.25)
OSHO-39[93]	52	105	24	96	25.9%	1.98 (1.33 to 2.95)
Total (95% CI)		**721**		**716**	**100.0%**	**2.05 (1.27 to 3.30)**
Total events	217		112			

Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 15.37$, df = 3 ($p = 0.002$); $I^2 = 80\%$

Test for overall effect: $z = 2.95$ ($p = 0.003$)

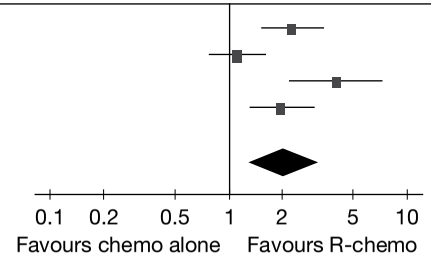


FIGURE 50 Forest plot for meta-analysis of CR rate of the four trials. Chemo, chemotherapy.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	101	175	127	183	27.9%	0.83 (0.71 to 0.98)
GLSG-2000[91,92]	215	279	206	278	38.0%	1.04 (0.95 to 1.14)
M39021[95,96]	82	162	78	159	20.4%	1.03 (0.83 to 1.29)
OSHO-39[93]	45	105	48	96	13.8%	0.86 (0.64 to 1.15)
Total (95% CI)		**721**		**716**	**100.0%**	**0.95 (0.83 to 1.08)**
Total events	443		459			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.79$, df = 3 ($p = 0.08$); $I^2 = 56\%$
Test for overall effect: $z = 0.77$ ($p = 0.44$)

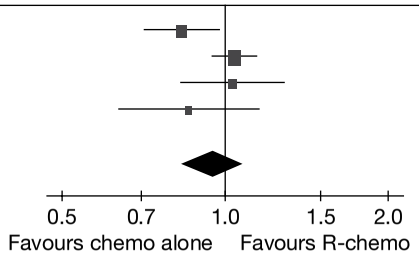


FIGURE 51 Forest plot for meta-analysis of PR rate of the four trials. Chemo, chemotherapy.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	142	175	131	183	24.9%	1.13 (1.01 to 1.27)
GLSG-2000[91,92]	268	279	253	278	28.6%	1.06 (1.01 to 1.10)
M39021[95,96]	131	162	90	159	22.3%	1.43 (1.22 to 1.67)
OSHO-39[93]	97	105	72	96	24.2%	1.23 (1.08 to 1.40)
Total (95% CI)		**721**		**716**	**100.0%**	**1.19 (1.03 to 1.39)**
Total events	638		546			

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 25.60$, df = 3 ($p < 0.0001$); $I^2 = 88\%$
Test for overall effect: $z = 2.30$ ($p = 0.02$)

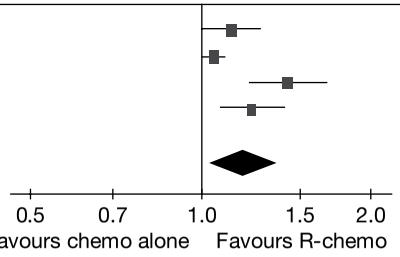


FIGURE 52 Forest plot for meta-analysis of ORR using the FL2000[94] 18-month response rates. Chemo, chemotherapy.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	90	175	71	183	29.0%	1.33 (1.05 to 1.67)
GLSG-2000[91,92]	53	279	47	278	26.1%	1.12 (0.79 to 1.60)
M39021[95,96]	49	162	12	159	19.9%	4.01 (2.22 to 7.25)
OSHO-39[93]	52	105	24	96	25.0%	1.98 (1.33 to 2.95)
Total (95% CI)		**721**		**716**	**100.0%**	**1.75 (1.14 to 2.69)**
Total events	244		154			
Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 16.48$, df = 3 ($p = 0.0009$); $I^2 = 82\%$						
Test for overall effect: $z = 2.54$ ($p = 0.01$)						

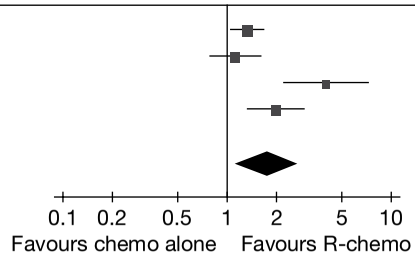


FIGURE 53 Forest plot for meta-analysis of CR rate using the FL2000[94] 18-month response rates. Chemo, chemotherapy.

Study or subgroup	R-chemo Events	R-chemo Total	Chemo Events	Chemo Total	Weight	Risk ratio M–H, Random, 95% CI
FL2000[94]	52	175	60	183	6.8%	0.91 (0.67 to 1.23)
GLSG-2000[91,92]	215	279	206	278	72.5%	1.04 (0.95 to 1.14)
M39021[95,96]	82	162	78	159	13.4%	1.03 (0.83 to 1.29)
OSHO-39[93]	45	105	48	96	7.3%	0.86 (0.64 to 1.15)
Total (95% CI)		**721**		**716**	**100.0%**	**1.01 (0.94 to 1.10)**
Total events	394		392			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.26$, df = 3 ($p = 0.52$); $I^2 = 0\%$						
Test for overall effect: $z = 0.36$ ($p = 0.72$)						

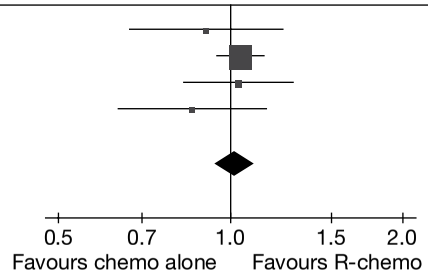


FIGURE 54 Forest plot for meta-analysis of PR using the FL2000[94] 18-month response rates. Chemo, chemotherapy.

Appendix 15

Full results of sensitivity analyses

TABLE 105 Sensitivity analyses for R-CVP vs CVP

	CVP			R-CVP (base case)			R-CVP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Base case	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Time horizon											
5 years	4.06	2.98	23,278	4.37	3.22	28,360	4.43	3.27	38,683	20,998	54,094
10 years	6.57	4.51	27,472	7.38	5.07	33,813	7.60	5.22	44,673	11,287	24,126
Lifetime	10.80	6.24	31,278	12.69	7.26	38,795	13.30	7.57	50,186	7360	14,125
Discounting											
0% costs, 0% benefits	9.86	7.73	35,632	11.50	9.09	44,002	12.03	9.52	56,241	6147	11,469
0% costs, 3.5% benefits	9.86	5.99	35,632	11.50	6.95	44,002	12.03	7.25	56,241	8745	16,463
3.5% costs, 0% benefits	9.86	7.73	30,793	11.50	9.09	38,183	12.03	9.52	49,520	5426	10,421
Parametric distribution											
Weibull	9.76	5.94	31,041	11.37	6.89	38,669	11.81	7.15	50,199	8054	15,958
Gompertz	9.97	6.05	30,279	12.18	7.26	35,349	12.91	7.66	45,421	4174	9419
Death event in PFS											
None	10.30	6.25	32,058	11.72	7.07	38,766	12.22	7.35	50,046	8224	16,386
CVP arm	9.86	5.99	30,793	11.35	6.87	37,759	11.89	7.17	49,139	7984	15,599
R-CVP arm	10.04	6.10	31,327	11.50	6.95	38,183	12.03	7.25	49,520	8080	15,914
Resistance to rituximab (%)											
–10	9.86	5.99	30,793	11.19	6.79	38,229	11.76	7.11	49,565	9379	16,851
–15	9.86	5.99	30,793	11.01	6.70	38,246	11.61	7.03	49,579	10,616	18,100
–20	9.86	5.99	30,793	10.82	6.60	38,249	11.45	6.95	49,586	12,328	19,650
–25	9.86	5.99	30,793	10.62	6.50	38,235	11.28	6.86	49,580	14,870	21,624
–30	9.86	5.99	30,793	10.41	6.38	38,210	11.09	6.77	49,563	19,102	24,234

	CVP			R-CVP (base case)			R-CVP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Utility values											
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	9.86	5.81	30,793	11.50	7.01	38,183	12.03	7.39	49,520	6180	11,862
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	9.86	6.08	30,793	11.50	7.11	38,183	12.03	7.43	49,520	7147	13,804
–10%	9.86	5.40	30,793	11.50	6.26	38,183	12.03	6.52	49,520	8578	16,621
–20%	9.86	4.80	30,793	11.50	5.56	38,183	12.03	5.80	49,520	9650	18,699
–30%	9.86	4.20	30,793	11.50	4.87	38,183	12.03	5.07	49,520	11,029	21,370
Higher in PFS1 (+10%)	9.86	6.12	30,793	11.50	7.27	38,183	12.03	7.63	49,520	6447	12,395
No disutility	9.86	6.00	30,793	11.50	6.96	38,183	12.03	7.25	49,520	7704	14,928
Disutility = –10%	9.86	6.00	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7715	14,949
Disutility = –20%	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.24	49,520	7725	14,969
Disutility = –30%	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.24	49,520	7736	14,990
Treatment pathway											
Second line after progression	10.14	6.17	30,228	11.60	7.01	37,977	12.13	7.31	49,315	9230	16,828
R-CVP no retreatment if early relapse	9.86	5.99	30,793	11.31	6.83	37,550	11.87	7.15	49,026	8123	15,816
Patients receive CHOP and R-CHOP instead of salvage HDT and R-HDT	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Patients receive CHOP and R-CHOP instead of FC and R-FC	10.11	6.14	31,913	11.73	7.08	39,172	12.24	7.36	50,394	7742	15,145
Last three scenarios	10.11	6.14	31,913	11.52	6.94	38,193	12.07	7.25	49,636	7841	15,919
All patients receive salvage with rituximab	12.14	7.14	38,358	13.36	7.86	44,421	13.72	8.07	55,262	8506	18,325
All patients receive salvage without rituximab	6.99	4.45	28,838	9.18	5.74	36,776	9.96	6.18	48,402	6159	11,273
All patients receive CHOP	9.36	5.67	28,377	11.11	6.71	36,174	11.71	7.05	47,764	7553	14,127
All patients receive R-CHOP	10.11	6.14	31,913	11.73	7.08	39,172	12.27	7.38	50,519	7742	15,034
Effectiveness of FC											
No loss of response	10.10	6.14	31,188	11.73	7.08	38,530	12.24	7.36	49,834	7827	15,271
Response 10% lower than CHOP regimens	9.98	6.07	30,990	11.62	7.01	38,358	12.13	7.30	49,679	7776	15,114
Response 30% lower than CHOP regimens	9.74	5.93	30,598	11.39	6.89	38,010	11.93	7.19	49,362	7676	14,832
Response 40% lower than CHOP regimens	9.61	5.85	30,400	11.28	6.83	37,840	11.82	7.14	49,204	7615	14,673
Response 50% lower than CHOP regimens	9.49	5.78	30,212	11.17	6.77	37,676	11.72	7.08	49,056	7565	14,523
PFS reduction –10%	9.72	5.92	30,835	11.39	6.89	38,223	11.92	7.19	49,559	7625	14,754
PFS reduction –20%	9.57	5.83	30,870	11.25	6.81	38,259	11.79	7.12	49,593	7520	14,525
PFS reduction –30%	9.39	5.73	30,875	11.09	6.73	38,270	11.64	7.04	49,608	7409	14,282

continued

TABLE 105 Sensitivity analyses for R-CVP vs CVP (*continued*)

	CVP			R-CVP (base case)			R-CVP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Costing of salvage therapy											
Response rate same as CHOP regimens	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Response rate 20% greater than CHOP regimens	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Response rate 30% greater than CHOP regimens	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
No. of cycles of ESHAP = 3	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
No. of cycles of ESHAP = 4	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Harvest success rate: 1	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Harvest success rate: 0.95	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Harvest success rate: 0.90	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Harvest success rate: 0.85	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Harvest success rate: 0.75	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Only one administration	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
One additional administration	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
AEs											
No AEs	9.86	6.00	30,337	11.50	6.96	37,390	12.03	7.25	48,637	7353	14,588
Costs +20%	9.86	5.99	30,884	11.50	6.95	38,341	12.03	7.25	49,697	7791	15,027
Costs –20%	9.86	5.99	30,702	11.50	6.95	38,024	12.03	7.25	49,344	7650	14,891
No. of cycles											
Six cycles for CHOP	9.86	5.99	30,793	11.50	6.95	38,183	12.03	7.25	49,520	7720	14,959
Six cycles for FC	9.87	6.01	32,540	11.52	6.96	39,728	12.04	7.26	50,926	7521	14,714
Management costs											
Cost +20%	9.86	5.99	31,730	11.50	6.95	39,123	12.03	7.25	50,962	7724	15,362
Cost –20%	9.86	5.99	29,856	11.50	6.95	37,242	12.03	7.25	48,078	7716	14,556
Cost pharmacy = 35	9.86	5.99	30,948	11.50	6.95	38,459	12.03	7.25	49,951	7847	15,179
No monitoring costs	9.86	5.99	28,037	11.50	6.95	34,234	12.03	7.25	46,450	6475	14,708
Monitoring cost +20%	9.86	5.99	31,344	11.50	6.95	38,972	12.03	7.25	50,134	7969	15,009
Monitoring cost –20%	9.86	5.99	30,242	11.50	6.95	37,393	12.03	7.25	48,906	7471	14,909
No third-line treatment costs	9.86	5.99	26,933	11.50	6.95	34,999	12.03	7.25	46,495	8427	15,626
No cost palliative care	9.86	5.99	26,223	11.50	6.95	34,564	12.03	7.25	46,232	8715	15,984
No terminal care costs	9.86	5.99	29,000	11.50	6.95	36,789	12.03	7.25	48,253	8138	15,379
No terminal or palliative care costs	9.86	5.99	24,429	11.50	6.95	33,170	12.03	7.25	44,965	9132	16,404

Parameters	CVP			R-CVP (base case)			R-CVP (scenario)			ICER – cost per QALY gained	
	LY	QALY	Cost	LY	QALY	Cost	LY	QALY	Cost	Base case	Scenario
Maximum age (years) at which aggressive therapy is given											
60	9.75	5.93	30,441	11.41	6.90	37,903	11.95	7.21	49,281	7690	14,821
70	9.95	6.05	31,118	11.59	7.00	38,465	12.10	7.29	49,764	7735	15,040
75	10.02	6.09	31,419	11.65	7.03	38,724	12.17	7.32	49,993	7748	15,117
80	10.07	6.12	31,653	11.70	7.06	38,929	12.21	7.34	50,172	7747	15,149
BSA (m^2)											
1.6	9.86	5.99	28,432	11.50	6.95	34,266	12.03	7.25	43,586	6095	12,105
1.7	9.86	5.99	30,110	11.50	6.95	36,994	12.03	7.25	47,684	7192	14,038
1.8	9.86	5.99	30,110	11.50	6.95	36,994	12.03	7.25	47,684	7192	14,038
1.9	9.86	5.99	31,550	11.50	6.95	39,512	12.03	7.25	51,584	8318	16,003
Maximum time (years) in PFS1											
5	9.68	5.90	31,256	10.60	6.48	40,882	10.79	6.60	53,183	16,656	31,354
6	9.72	5.92	31,170	10.74	6.56	40,500	10.99	6.72	52,669	14,527	27,043
7	9.74	5.94	31,103	10.86	6.63	40,182	11.16	6.81	52,240	13,044	24,178
8	9.77	5.95	31,051	10.97	6.69	39,911	11.30	6.89	51,873	11,964	22,151
9	9.78	5.96	31,009	11.05	6.74	39,682	11.41	6.95	51,564	11,143	20,651
10	9.80	5.97	30,975	11.13	6.78	39,490	11.52	7.01	51,301	10,513	19,516
11	9.81	5.97	30,948	11.19	6.81	39,326	11.60	7.05	51,080	10,016	18,645
12	9.82	5.98	30,926	11.25	6.84	39,183	11.68	7.09	50,885	9613	17,951
13	9.82	5.98	30,906	11.29	6.86	39,058	11.74	7.12	50,717	9287	17,394
14	9.83	5.98	30,890	11.33	6.88	38,948	11.79	7.15	50,568	9018	16,944
15	9.84	5.99	30,876	11.37	6.89	38,854	11.84	7.17	50,439	8797	16,577
16	9.84	5.99	30,864	11.40	6.91	38,774	11.88	7.18	50,329	8616	16,274
17	9.84	5.99	30,855	11.42	6.92	38,701	11.91	7.20	50,230	8461	16,023
18	9.85	5.99	30,846	11.44	6.93	38,635	11.94	7.21	50,141	8331	15,815
19	9.85	5.99	30,838	11.46	6.93	38,576	11.97	7.22	50,063	8223	15,642

continued

TABLE 105 Sensitivity analyses for R-CVP vs CVP (*continued*)

	CVP			R-CVP (base case)			R-CVP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Greater OS (%) for R-CHOP compared with CHOP											
5	10.41	6.26	31,444	11.95	7.16	38,677	12.41	7.42	49,930	8067	15,969
10	10.94	6.51	32,043	12.37	7.35	39,130	12.76	7.58	50,307	8441	17,080
15	11.42	6.73	32,572	12.74	7.52	39,531	13.08	7.72	50,638	8837	18,263
20	11.85	6.92	33,033	13.07	7.66	39,878	13.36	7.84	50,924	9232	19,489
25	12.21	7.09	33,424	13.36	7.79	40,170	13.60	7.94	51,163	9613	20,696
Maintenance duration effect (months)											
36	9.86	5.99	30,793	11.50	6.95	38,183	11.97	7.22	49,684	7720	15,469
48	9.86	5.99	30,793	11.50	6.95	38,183	12.08	7.27	49,373	7720	14,524
60	9.86	5.99	30,793	11.50	6.95	38,183	12.17	7.32	49,115	7720	13,828
72	9.86	5.99	30,793	11.50	6.95	38,183	12.24	7.36	48,896	7720	13,305
HR maintenance											
0.48	9.86	5.99	30,793	11.50	6.95	38,183	12.13	7.31	49,411	7720	14,205
0.66	9.86	5.99	30,793	11.50	6.95	38,183	11.88	7.16	49,676	7720	16,210

TABLE 106 Sensitivity analyses for R-CHOP vs CHOP

	CHOP			R-CHOP (base case)			R-CHOP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Base case	11.55	6.84	34,983	12.40	7.37	40,708	13.02	7.72	54,134	**10,834**	**21,687**
Time horizon											
5 years	4.28	3.13	25,929	4.44	3.25	30,003	4.52	3.31	42,241	**33,975**	**91,356**
10 years	7.19	4.90	30,458	7.63	5.21	35,660	7.90	5.40	48,618	**16,650**	**36,367**
Lifetime	13.15	7.23	35,994	14.07	7.78	41,705	14.79	8.16	55,183	**10,362**	**20,533**
Discounting											
0% costs, 0% benefits	11.55	9.01	40,994	12.40	9.76	47,222	13.02	10.28	61,687	**8306**	**16,295**
0% costs, 3.5% benefits	11.55	6.84	40,994	12.40	7.37	47,222	13.02	7.72	61,687	**11,788**	**23,434**
3.5% costs, 0% benefits	11.55	9.01	34,983	12.40	9.76	40,708	13.02	10.28	54,134	**7634**	**15,081**
Parametric distribution											
Weibull	11.43	6.77	35,483	12.16	7.25	41,186	12.75	7.59	55,009	**12,030**	**23,824**
Gompertz	11.72	6.92	34,115	12.87	7.58	36,733	13.80	8.09	48,766	**3941**	**12,490**
Death event in PFS											
None	12.04	7.11	36,344	12.61	7.48	41,296	13.21	7.82	54,651	**13,463**	**25,867**
CVP arm	11.55	6.84	34,983	12.25	7.28	40,281	12.88	7.65	53,759	**11,872**	**23,141**
R-CVP arm	11.76	6.95	35,559	12.40	7.37	40,708	13.02	7.72	54,134	**12,470**	**24,200**
Resistance to rituximab											
–10%	11.55	6.84	34,983	12.18	7.25	40,769	12.82	7.62	54,194	**13,843**	**24,447**
–15%	11.55	6.84	34,983	12.06	7.19	40,796	12.71	7.57	54,220	**16,328**	**26,301**
–20%	11.55	6.84	34,983	11.93	7.13	40,814	12.59	7.51	54,239	**20,163**	**28,629**
–25%	11.55	6.84	34,983	11.78	7.05	40,822	12.46	7.45	54,252	**26,939**	**31,646**
–30%	11.55	6.84	34,983	11.62	6.97	40,826	12.32	7.38	54,260	**42,361**	**35,734**

continued

TABLE 106 Sensitivity analyses for R-CHOP vs CHOP (*continued*)

	CHOP			R-CHOP (base case)			R-CHOP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Utility values											
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	11.55	6.66	34,983	12.40	7.45	40,708	13.02	7.92	54,134	**7167**	**15,113**
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	11.55	6.95	34,983	12.40	7.55	40,708	13.02	7.94	54,134	**9518**	**19,354**
–10%	11.55	6.15	34,983	12.40	6.63	40,708	13.02	6.95	54,134	**12,038**	**24,097**
–20%	11.55	5.47	34,983	12.40	5.89	40,708	13.02	6.18	54,134	**13,543**	**27,109**
–30%	11.55	4.79	34,983	12.40	5.16	40,708	13.02	5.40	54,134	**15,478**	**30,982**
Higher in PFS1 (+10%)	11.55	7.02	34,983	12.40	7.73	40,708	13.02	8.17	54,134	**8019**	**16,628**
No disutility	11.55	6.87	34,983	12.40	7.40	40,708	13.02	7.75	54,134	**10,760**	**21,580**
Disutility = –10%	11.55	6.85	34,983	12.40	7.38	40,708	13.02	7.73	54,134	**10,809**	**21,651**
Disutility = –20%	11.55	6.83	34,983	12.40	7.35	40,708	13.02	7.71	54,134	**10,860**	**21,724**
Disutility = –30%	11.55	6.81	34,983	12.40	7.33	40,708	13.02	7.69	54,134	**10,910**	**21,796**
Treatment pathway											
Second line after progression	11.60	6.87	34,821	12.48	7.41	40,765	13.10	7.76	54,190	**10,945**	**21,576**
R-CVP no retreatment if early relapse	11.55	6.84	34,983	12.40	7.37	40,708	13.02	7.72	54,134	**10,834**	**21,687**
Patients receive CHOP and R-CHOP instead of salvage HDT and R-HDT	10.30	6.25	31,905	11.83	7.12	38,928	12.51	7.50	52,598	**8058**	**16,517**
Patients receive CHOP and R-CHOP instead of FC and R-FC	11.80	6.98	36,067	12.61	7.48	41,493	13.22	7.82	54,882	**10,833**	**22,251**
Last three scenarios	10.54	6.39	32,989	12.04	7.23	39,713	12.70	7.60	53,346	**7967**	**16,750**
All patients receive salvage with rituximab	12.45	7.32	39,045	13.63	8.00	45,002	14.06	8.25	57,917	**8745**	**20,293**
All patients receive salvage without rituximab	7.60	4.81	30,140	9.76	6.06	37,961	10.68	6.59	51,809	**6245**	**12,153**
All patients receive CHOP	9.83	5.95	29,624	11.56	6.95	37,321	12.27	7.35	51,130	**7714**	**15,337**
All patients receive R-CHOP	10.54	6.39	32,989	12.13	7.29	40,137	12.77	7.65	53,656	**7933**	**16,436**
Effectiveness of FC											
No loss of response	11.80	6.97	35,363	12.61	7.48	41,013	13.21	7.82	54,415	**11,268**	**22,509**
Response 10% lower than CHOP regimens	11.67	6.91	35,174	12.50	7.42	40,861	13.11	7.77	54,274	**11,045**	**22,098**
Response 30% lower than CHOP regimens	11.44	6.77	34,790	12.30	7.31	40,548	12.92	7.67	53,986	**10,669**	**21,348**
Response 40% lower than CHOP regimens	11.31	6.70	34,599	12.19	7.25	40,390	12.82	7.62	53,840	**10,489**	**20,980**
Response 50% lower than CHOP regimens	11.20	6.63	34,420	12.09	7.20	40,237	12.73	7.57	53,706	**10,331**	**20,622**
PFS reduction –10%	11.42	6.76	35,026	12.29	7.30	40,744	12.91	7.66	54,170	**10,582**	**21,233**
PFS reduction –20%	11.27	6.68	35,061	12.15	7.23	40,774	12.79	7.60	54,200	**10,310**	**20,733**
PFS reduction –30%	11.10	6.58	35,071	12.00	7.15	40,784	12.65	7.53	54,216	**10,019**	**20,199**

Parameters	CHOP			R-CHOP (base case)			R-CHOP (scenario)			ICER – cost per QALY gained	
	LY	QALY	Cost	LY	QALY	Cost	LY	QALY	Cost	Base case	Scenario
Costing of salvage therapy											
Response rate same as CHOP regimens	11.55	6.84	34,216	12.40	7.37	40,145	13.02	7.72	53,652	**11,221**	**22,011**
Response rate 20% greater than CHOP regimens	11.55	6.84	35,750	12.40	7.37	41,271	13.02	7.72	54,615	**10,448**	**21,364**
Response rate 30% greater than CHOP regimens	11.55	6.84	36,043	12.40	7.37	41,534	13.02	7.72	54,834	**10,393**	**21,281**
No. of cycles of ESHAP = 3	11.55	6.84	36,271	12.40	7.37	41,624	13.02	7.72	54,921	**10,132**	**21,121**
No. of cycles of ESHAP = 4	11.55	6.84	37,558	12.40	7.37	42,540	13.02	7.72	55,708	**9430**	**20,555**
Harvest success rate: 1	11.55	6.84	37,093	12.40	7.37	42,255	13.02	7.72	55,457	**9771**	**20,798**
Harvest success rate: 0.95	11.55	6.84	36,565	12.40	7.37	41,869	13.02	7.72	55,126	**10,037**	**21,020**
Harvest success rate: 0.90	11.55	6.84	36,038	12.40	7.37	41,482	13.02	7.72	54,796	**10,303**	**21,243**
Harvest success rate: 0.85	11.55	6.84	35,511	12.40	7.37	41,095	13.02	7.72	54,465	**10,569**	**21,465**
Harvest success rate: 0.75	11.55	6.84	34,456	12.40	7.37	40,321	13.02	7.72	53,803	**11,100**	**21,910**
Only one administration	11.55	6.84	34,349	12.40	7.37	40,224	13.02	7.72	53,722	**11,119**	**21,940**
One additional administration	11.55	6.84	34,561	12.40	7.37	40,385	13.02	7.72	53,859	**11,024**	**21,856**
AEs											
No AEs	11.55	6.87	34,028	12.40	7.40	39,604	13.02	7.75	52,920	**10,479**	**21,288**
Costs +20%	11.55	6.84	35,174	12.40	7.37	40,929	13.02	7.72	54,376	**10,891**	**21,746**
Costs –20%	11.55	6.84	34,792	12.40	7.37	40,487	13.02	7.72	53,891	**10,778**	**21,629**
No. of cycles											
Six cycles for CHOP	11.51	6.81	34,234	12.27	7.29	37,122	12.93	7.67	50,718	**5951**	**19,092**
Six cycles for FC	11.57	6.85	36,680	12.42	7.37	42,054	13.03	7.73	55,398	**10,206**	**21,261**
Management costs											
Cost +20%	11.55	6.84	35,813	12.40	7.37	41,550	13.02	7.72	55,591	**10,859**	**22,398**
Cost –20%	11.55	6.84	34,154	12.40	7.37	39,865	13.02	7.72	52,677	**10,810**	**20,977**
Cost pharmacy = 35	11.55	6.84	35,062	12.40	7.37	40,921	13.02	7.72	54,545	**11,089**	**22,064**
No monitoring costs	11.55	6.84	31,292	12.40	7.37	36,160	13.02	7.72	50,627	**9214**	**21,897**
Monitoring cost +20%	11.55	6.84	35,722	12.40	7.37	41,617	13.02	7.72	54,835	**11,159**	**21,646**
Monitoring cost –20%	11.55	6.84	34,245	12.40	7.37	39,798	13.02	7.72	53,432	**10,510**	**21,729**
No third-line treatment costs	11.55	6.84	33,111	12.40	7.37	38,881	13.02	7.72	52,501	**10,921**	**21,960**
No cost palliative care	11.55	6.84	29,502	12.40	7.37	36,764	13.02	7.72	50,769	**13,744**	**24,085**
No terminal care costs	11.55	6.84	33,549	12.40	7.37	39,521	13.02	7.72	53,100	**11,303**	**22,141**
No terminal or palliative care costs	11.55	6.84	28,067	12.40	7.37	35,577	13.02	7.72	49,735	**14,213**	**24,538**

continued

TABLE 106 Sensitivity analyses for R-CHOP vs CHOP (*continued*)

	CHOP			R-CHOP (base case)			R-CHOP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Maximum age (years) at which aggressive therapy is given											
60	11.13	6.63	33,780	12.16	7.25	39,946	12.81	7.62	53,470	**9832**	**19,745**
70	11.90	7.02	36,129	12.63	7.47	41,530	13.24	7.82	54,886	**11,758**	**23,230**
75	12.17	7.16	37,152	12.80	7.56	42,270	13.40	7.90	55,592	**12,763**	**24,704**
80	12.33	7.25	37,973	12.91	7.61	42,906	13.52	7.96	56,187	**13,377**	**25,559**
BSA (m^2)											
1.6	11.55	6.84	33,716	12.40	7.37	37,617	13.02	7.72	48,435	**7384**	**16,669**
1.7	11.55	6.84	34,665	12.40	7.37	39,796	13.02	7.72	52,385	**9712**	**20,067**
1.8	11.55	6.84	34,665	12.40	7.37	39,796	13.02	7.72	52,385	**9712**	**20,067**
1.9	11.55	6.84	35,378	12.40	7.37	41,768	13.02	7.72	56,143	**12,094**	**23,517**
Maximum time (years) in PFS1											
5	11.33	6.71	35,877	11.56	6.91	44,464	11.86	7.09	59,233	**43,733**	**61,115**
6	11.37	6.74	35,698	11.69	6.99	43,896	12.03	7.20	58,465	**32,857**	**49,043**
7	11.41	6.76	35,567	11.79	7.05	43,429	12.18	7.29	57,834	**26,749**	**41,756**
8	11.43	6.78	35,462	11.88	7.11	43,038	12.31	7.37	57,300	**22,835**	**36,904**
9	11.45	6.79	35,379	11.96	7.15	42,708	12.42	7.43	56,854	**20,149**	**33,528**
10	11.47	6.80	35,312	12.03	7.19	42,428	12.51	7.48	56,474	**18,210**	**31,050**
11	11.49	6.81	35,262	12.09	7.22	42,202	12.59	7.52	56,167	**16,745**	**29,166**
12	11.50	6.81	35,220	12.14	7.25	42,006	12.66	7.56	55,900	**15,607**	**27,698**
13	11.51	6.82	35,184	12.19	7.27	41,837	12.72	7.59	55,673	**14,718**	**26,544**
14	11.52	6.82	35,153	12.23	7.29	41,686	12.78	7.61	55,470	**13,999**	**25,615**
15	11.53	6.82	35,128	12.26	7.30	41,559	12.82	7.64	55,298	**13,427**	**24,869**
16	11.53	6.83	35,106	12.29	7.32	41,454	12.86	7.65	55,152	**12,963**	**24,252**
17	11.54	6.83	35,089	12.31	7.33	41,359	12.90	7.67	55,024	**12,576**	**23,746**
18	11.54	6.83	35,074	12.34	7.34	41,275	12.93	7.68	54,910	**12,256**	**23,326**
19	11.55	6.83	35,060	12.35	7.35	41,201	12.95	7.69	54,811	**11,995**	**22,985**

	CHOP			R-CHOP (base case)			R-CHOP (scenario)			ICER – cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Greater OS (%) for R-CHOP compared with CHOP											
5	11.71	6.91	35,155	12.52	7.42	40,825	13.13	7.77	54,241	**11,213**	**22,292**
10	11.85	6.98	35,308	12.62	7.47	40,930	13.23	7.81	54,337	**11,588**	**22,876**
15	11.97	7.04	35,439	12.71	7.51	41,022	13.31	7.85	54,420	**11,950**	**23,415**
20	12.08	7.09	35,553	12.79	7.54	41,099	13.39	7.89	54,490	**12,283**	**23,910**
25	12.17	7.14	35,645	12.86	7.57	41,164	13.45	7.91	54,549	**12,565**	**24,323**
Maintenance duration effect (months)											
36	11.55	6.84	34,983	12.40	7.37	40,708	12.97	7.69	54,364	**10,834**	**22,703**
48	11.55	6.84	34,983	12.40	7.37	40,708	13.07	7.75	53,931	**10,834**	**20,827**
60	11.55	6.84	34,983	12.40	7.37	40,708	13.15	7.79	53,572	**10,834**	**19,478**
72	11.55	6.84	34,983	12.40	7.37	40,708	13.22	7.83	53,276	**10,834**	**18,495**
HR maintenance											
0.48	11.55	6.84	34,983	12.40	7.37	40,708	13.13	7.78	53,961	**10,834**	**20,051**
0.66	11.55	6.84	34,983	12.40	7.37	40,708	12.85	7.62	54,390	**10,834**	**24,628**

TABLE 107 Sensitivity analyses for R-MCP vs MCP

	MCP			R-MCP (base case)			R-MCP (scenario)			ICER– cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Base case	11.45	6.79	36,103	12.35	7.36	41,370	12.89	7.67	54,079	**9316**	**20,493**
Time horizon											
5 years	4.25	3.12	27,233	4.43	3.26	30,660	4.49	3.31	42,324	**24,366**	**80,497**
10 years	7.12	4.87	31,621	7.61	5.22	36,341	7.84	5.38	48,633	**13,598**	**33,482**
Lifetime	13.04	7.18	37,112	13.99	7.76	42,361	14.63	8.10	55,109	**8963**	**19,510**
Discounting											
0% costs, 0% benefits	11.45	8.94	42,032	12.35	9.73	47,913	12.89	10.19	61,663	**7416**	**15,677**
0% costs, 3.5% benefits	11.45	6.79	42,032	12.35	7.36	47,913	12.89	7.67	61,663	**10,401**	**22,379**
3.5% costs, 0% benefits	11.45	8.94	36,103	12.35	9.73	41,370	12.89	10.19	54,079	**6643**	**14,356**
Parametric distribution											
Weibull	11.35	6.74	36,499	12.11	7.24	41,822	12.63	7.54	54,903	**10,594**	**22,833**
Gompertz	11.59	6.85	35,367	12.82	7.57	37,623	13.64	8.02	48,991	**3146**	**11,653**
Death event in PFS											
None	11.95	7.07	37,490	12.56	7.47	41,961	13.08	7.77	54,602	**11,192**	**24,562**
CVP arm	11.45	6.79	36,103	12.19	7.27	40,942	12.75	7.60	53,702	**10,023**	**21,849**
R-CVP arm	11.67	6.91	36,690	12.35	7.36	41,370	12.89	7.67	54,079	**10,457**	**22,899**
Resistance to rituximab (%)											
–10	11.45	6.79	36,103	12.13	7.24	41,432	12.70	7.57	54,140	**11,718**	**23,067**
–15	11.45	6.79	36,103	12.00	7.18	41,457	12.59	7.52	54,165	**13,632**	**24,788**
–20	11.45	6.79	36,103	11.87	7.12	41,476	12.47	7.46	54,184	**16,494**	**26,946**
–25	11.45	6.79	36,103	11.73	7.04	41,483	12.34	7.40	54,195	**21,253**	**29,731**
–30	11.45	6.79	36,103	11.57	6.96	41,485	12.20	7.33	54,203	**30,902**	**33,489**

Parameters	MCP			R-MCP (base case)			R-MCP (scenario)			ICER– cost per QALY gained	
	LY	QALY	Cost	LY	QALY	Cost	LY	QALY	Cost	Base case	Scenario
Utility values											
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	11.45	6.59	36,103	12.35	7.44	41,370	12.89	7.86	54,079	**6165**	**14,092**
PFS1 = 0.805; PFS2 = 0.805; disease progression = 0.7363	11.45	6.89	36,103	12.35	7.54	41,370	12.89	7.88	54,079	**8186**	**18,216**
–10%	11.45	6.11	36,103	12.35	6.62	41,370	12.89	6.90	54,079	**10,352**	**22,770**
–20%	11.45	5.43	36,103	12.35	5.88	41,370	12.89	6.13	54,079	**11,646**	**25,616**
–30%	11.45	4.75	36,103	12.35	5.15	41,370	12.89	5.37	54,079	**13,309**	**29,275**
Higher in PFS1 (+10%)	11.45	6.96	36,103	12.35	7.72	41,370	12.89	8.11	54,079	**6898**	**15,572**
No disutility	11.45	6.80	36,103	12.35	7.37	41,370	12.89	7.68	54,079	**9291**	**20,440**
Disutility = –10%	11.45	6.79	36,103	12.35	7.36	41,370	12.89	7.67	54,079	**9308**	**20,475**
Disutility = –20%	11.45	6.79	36,103	12.35	7.35	41,370	12.89	7.66	54,079	**9325**	**20,510**
Disutility = –30%	11.45	6.78	36,103	12.35	7.34	41,370	12.89	7.65	54,079	**9342**	**20,546**
Treatment pathway											
Second line after progression	11.57	6.86	35,693	12.49	7.44	41,475	13.03	7.75	54,184	**10,125**	**20,944**
R-CVP no retreatment if early relapse	11.45	6.79	36,103	12.35	7.36	41,370	12.89	7.67	54,079	**9316**	**20,493**
Patients receive CHOP and R-CHOP instead of salvage HDT and R-HDT	10.16	6.18	32,938	11.79	7.11	39,588	12.42	7.47	52,589	**7155**	**15,261**
Patients receive CHOP and R-CHOP instead of FC and R-FC	11.70	6.93	37,204	12.56	7.47	42,157	13.08	7.77	54,811	**9232**	**21,026**
Last three scenarios	10.41	6.33	34,038	12.00	7.23	40,374	12.62	7.57	53,321	**7035**	**15,452**
All patients receive salvage with rituximab	12.36	7.28	40,209	13.61	8.00	45,717	14.02	8.24	58,020	**7574**	**18,491**
All patients receive salvage without rituximab	7.41	4.71	31,113	9.70	6.05	38,621	10.59	6.55	51,811	**5604**	**11,227**
All patients receive CHOP	9.69	5.88	30,613	11.52	6.95	37,990	12.19	7.33	51,144	**6907**	**14,146**
All patients receive R-CHOP	10.41	6.33	34,038	12.10	7.29	40,820	12.70	7.63	53,697	**7041**	**15,111**
Effectiveness of FC											
No loss of response	11.70	6.93	36,492	12.56	7.47	41,678	13.08	7.77	54,360	**9655**	**21,314**
Response 10% lower than CHOP regimens	11.58	6.86	36,299	12.45	7.41	41,525	12.98	7.72	54,218	**9487**	**20,916**
Response 30% lower than CHOP regimens	11.34	6.72	35,911	12.24	7.30	41,213	12.79	7.62	53,935	**9188**	**20,156**
Response 40% lower than CHOP regimens	11.21	6.65	35,717	12.14	7.24	41,055	12.69	7.56	53,789	**9027**	**19,783**
Response 50% lower than CHOP regimens	11.09	6.58	35,535	12.03	7.19	40,903	12.60	7.52	53,653	**8896**	**19,442**
PFS reduction –10%	11.32	6.72	36,146	12.23	7.29	41,409	12.78	7.61	54,117	**9101**	**20,050**
PFS reduction –20%	11.17	6.63	36,182	12.10	7.22	41,438	12.66	7.55	54,145	**8865**	**19,558**
PFS reduction –30%	10.99	6.53	36,192	11.95	7.14	41,447	12.52	7.47	54,159	**8608**	**19,031**

continued

TABLE 107 Sensitivity analyses for R-MCP vs MCP (*continued*)

	MCP			R-MCP (base case)			R-MCP (scenario)			ICER– cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Costing of salvage therapy											
Response rate same as CHOP regimens	11.45	6.79	35,317	12.35	7.36	40,803	12.89	7.67	53,591	**9704**	**20,833**
Response rate 20% greater than CHOP regimens	11.45	6.79	36,890	12.35	7.36	41,938	12.89	7.67	54,567	**8929**	**20,152**
Response rate 30% greater than CHOP regimens	11.45	6.79	37,189	12.35	7.36	42,206	12.89	7.67	54,798	**8874**	**20,074**
No. of cycles of ESHAP = 3	11.45	6.79	37,423	12.35	7.36	42,293	12.89	7.67	54,872	**8613**	**19,892**
No. of cycles of ESHAP = 4	11.45	6.79	38,743	12.35	7.36	43,215	12.89	7.67	55,665	**7910**	**19,292**
Harvest success rate: 1	11.45	6.79	38,266	12.35	7.36	42,931	12.89	7.67	55,421	**8251**	**19,557**
Harvest success rate: 0.95	11.45	6.79	37,725	12.35	7.36	42,541	12.89	7.67	55,086	**8517**	**19,791**
Harvest success rate: 0.90	11.45	6.79	37,184	12.35	7.36	42,151	12.89	7.67	54,750	**8784**	**20,025**
Harvest success rate: 0.85	11.45	6.79	36,644	12.35	7.36	41,761	12.89	7.67	54,415	**9050**	**20,259**
Harvest success rate: 0.75	11.45	6.79	35,562	12.35	7.36	40,980	12.89	7.67	53,744	**9583**	**20,727**
Only one administration	11.45	6.79	35,453	12.35	7.36	40,882	12.89	7.67	53,659	**9601**	**20,755**
One additional administration	11.45	6.79	35,670	12.35	7.36	41,045	12.89	7.67	53,799	**9506**	**20,667**
AEs											
No AEs	11.45	6.80	35,996	12.35	7.37	41,287	12.89	7.68	53,892	**9331**	**20,348**
Costs +20%	11.45	6.79	36,124	12.35	7.36	41,387	12.89	7.67	54,117	**9308**	**20,511**
Costs –20%	11.45	6.79	36,082	12.35	7.36	41,354	12.89	7.67	54,042	**9324**	**20,474**
No. of cycles											
Six cycles for CHOP	11.45	6.79	36,103	12.35	7.36	41,370	12.89	7.67	54,079	**9316**	**20,493**
Six cycles for FC	11.47	6.80	37,814	12.36	7.36	42,718	12.90	7.68	55,334	**8704**	**20,036**
Management costs											
Cost +20%	11.45	6.79	37,328	12.35	7.36	42,626	12.89	7.67	55,919	**9370**	**21,194**
Cost –20%	11.45	6.79	34,878	12.35	7.36	40,115	12.89	7.67	52,239	**9263**	**19,792**
Cost pharmacy = 35	11.45	6.79	36,182	12.35	7.36	41,581	12.89	7.67	54,478	**9549**	**20,856**
No monitoring costs	11.45	6.79	32,666	12.35	7.36	36,963	12.89	7.67	50,675	**7600**	**20,529**
Monitoring cost +20%	11.45	6.79	36,790	12.35	7.36	42,252	12.89	7.67	54,760	**9660**	**20,485**
Monitoring cost –20%	11.45	6.79	35,416	12.35	7.36	40,489	12.89	7.67	53,398	**8973**	**20,500**
No third-line treatment costs	11.45	6.79	34,209	12.35	7.36	39,531	12.89	7.67	52,404	**9413**	**20,742**
No cost palliative care	11.45	6.79	30,484	12.35	7.36	37,397	12.89	7.67	50,677	**12,228**	**23,020**
No terminal care costs	11.45	6.79	34645	12.35	7.36	40,170	12.89	7.67	53,016	**9773**	**20,944**
No terminal or palliative care costs	11.45	6.79	29,025	12.35	7.36	36,197	12.89	7.67	49,614	**12,684**	**23,471**

	MCP			R-MCP (base case)			R-MCP (scenario)			ICER– cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Maximum age (years) at which aggressive therapy is given											
60	11.02	6.57	34,868	12.12	7.25	40,617	12.69	7.58	53,433	**8528**	**18,492**
70	11.81	6.97	37,258	12.58	7.47	42,200	13.10	7.77	54,815	**9973**	**22,116**
75	12.08	7.11	38,306	12.75	7.55	42,941	13.26	7.84	55,512	**10,659**	**23,667**
80	12.24	7.21	39,134	12.86	7.61	43,574	13.37	7.89	56,099	**11,099**	**24,650**
BSA (m^2)											
1.6	11.45	6.79	35,051	12.35	7.36	38,536	12.89	7.67	48,769	**6164**	**15,638**
1.7	11.45	6.79	35,855	12.35	7.36	40,541	12.89	7.67	52,455	**8289**	**18,925**
1.8	11.45	6.79	35,855	12.35	7.36	40,541	12.89	7.67	52,455	**8289**	**18,925**
1.9	11.45	6.79	36,427	12.35	7.36	42,346	12.89	7.67	55,957	**10,469**	**22,264**
Maximum time (years) in PFS1											
5	11.26	6.68	36,843	11.52	6.91	45,008	11.75	7.05	59,088	**36,602**	**60,170**
6	11.30	6.71	36,694	11.64	6.99	44,454	11.92	7.16	58,329	**27,820**	**47,647**
7	11.33	6.72	36,585	11.75	7.05	44,001	12.07	7.25	57,706	**22,799**	**40,277**
8	11.35	6.74	36,497	11.84	7.10	43,621	12.20	7.32	57,181	**19,527**	**35,414**
9	11.37	6.75	36,429	11.92	7.15	43,302	12.30	7.38	56,742	**17,277**	**32,065**
10	11.39	6.76	36,375	11.98	7.18	43,032	12.39	7.43	56,369	**15,642**	**29,618**
11	11.40	6.76	36,333	12.04	7.21	42,813	12.47	7.47	56,066	**14,403**	**27,766**
12	11.41	6.77	36,299	12.09	7.24	42,623	12.54	7.51	55,804	**13,437**	**26,330**
13	11.42	6.77	36,268	12.14	7.26	42,461	12.60	7.54	55,582	**12,685**	**25,206**
14	11.43	6.78	36,243	12.18	7.28	42,316	12.65	7.56	55,383	**12,074**	**24,305**
15	11.43	6.78	36,221	12.21	7.30	42,194	12.70	7.59	55,216	**11,584**	**23,580**
16	11.44	6.78	36,204	12.24	7.31	42,092	12.74	7.60	55,072	**11,188**	**22,984**
17	11.44	6.78	36,190	12.26	7.32	42,001	12.77	7.62	54,947	**10,855**	**22,496**
18	11.44	6.79	36,177	12.28	7.33	41,919	12.80	7.63	54,836	**10,579**	**22,089**
19	11.45	6.79	36,167	12.30	7.34	41,849	12.82	7.64	54,740	**10,352**	**21,758**

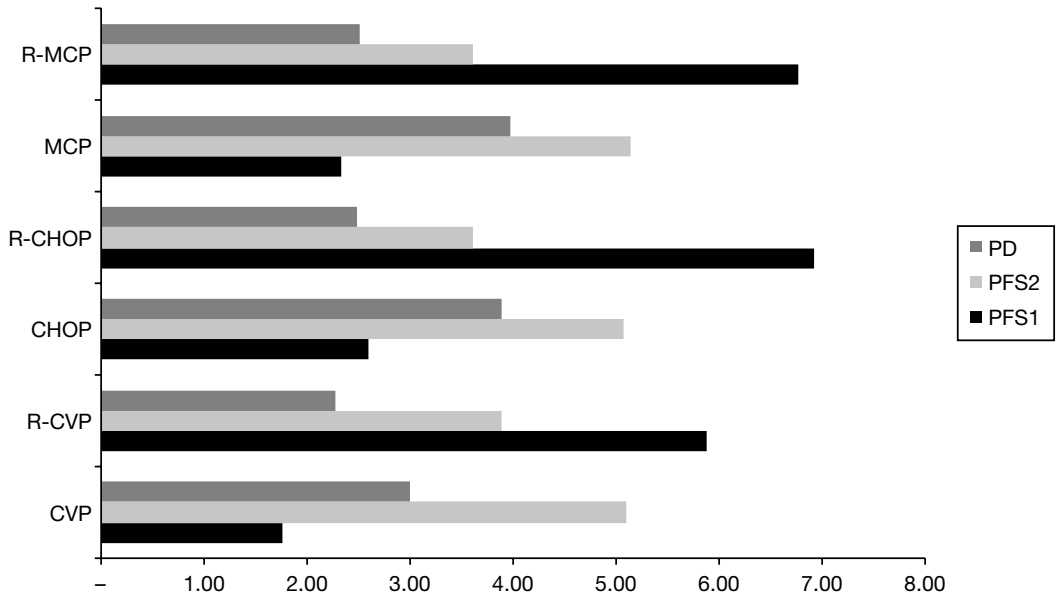
continued

TABLE 107 Sensitivity analyses for R-MCP vs MCP (*continued*)

	MCP			R-MCP (base case)			R-MCP (scenario)			ICER– cost per QALY gained	
Parameters	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**LY**	**QALY**	**Cost**	**Base case**	**Scenario**
Greater OS (%) for R-CHOP compared with CHOP											
5	11.61	6.87	36,277	12.46	7.41	41,489	12.99	7.72	54,185	**9620**	**21,106**
10	11.75	6.94	36,433	12.57	7.46	41,594	13.09	7.76	54,280	**9918**	**21,704**
15	11.88	7.00	36,565	12.66	7.50	41,686	13.18	7.80	54,361	**10,208**	**22,261**
20	11.99	7.05	36,680	12.74	7.54	41,764	13.25	7.83	54,431	**10,468**	**22,766**
25	12.08	7.09	36,773	12.81	7.57	41,830	13.31	7.86	54,488	**10,691**	**23,191**
Maintenance duration effect (months)											
36	11.45	6.79	36,103	12.35	7.36	41,370	12.84	7.64	54,299	**9316**	**21,436**
48	11.45	6.79	36,103	12.35	7.36	41,370	12.93	7.69	53,884	**9316**	**19,712**
60	11.45	6.79	36,103	12.35	7.36	41,370	13.01	7.73	53,546	**9316**	**18,470**
72	11.45	6.79	36,103	12.35	7.36	41,370	13.08	7.77	53,263	**9316**	**17,547**
HR maintenance											
0.48	11.45	6.79	36,103	12.35	7.36	41,370	12.99	7.72	53,898	**9316**	**19,063**
0.66	11.45	6.79	36,103	12.35	7.36	41,370	12.74	7.58	54,338	**9316**	**23,044**

Appendix 16

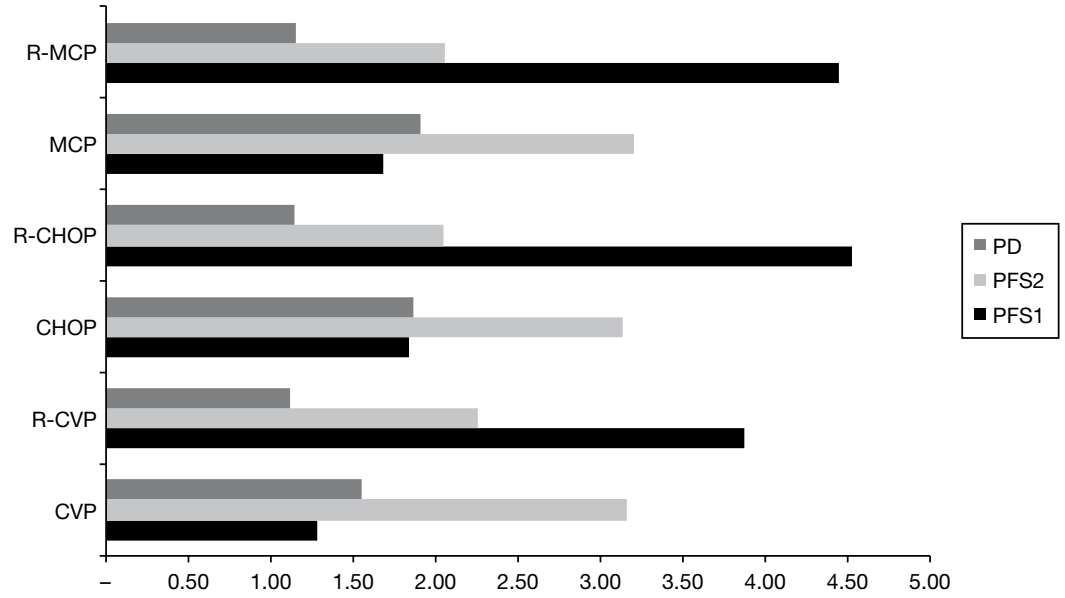
Additional results for the scenario analysis incorporating first-line maintenance



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
PD	3.00	2.27	3.89	2.49	3.98	2.51
PFS2	5.09	3.88	5.07	3.61	5.15	3.61
PFS1	1.77	5.87	2.59	6.92	2.33	6.77

Undiscounted LYs

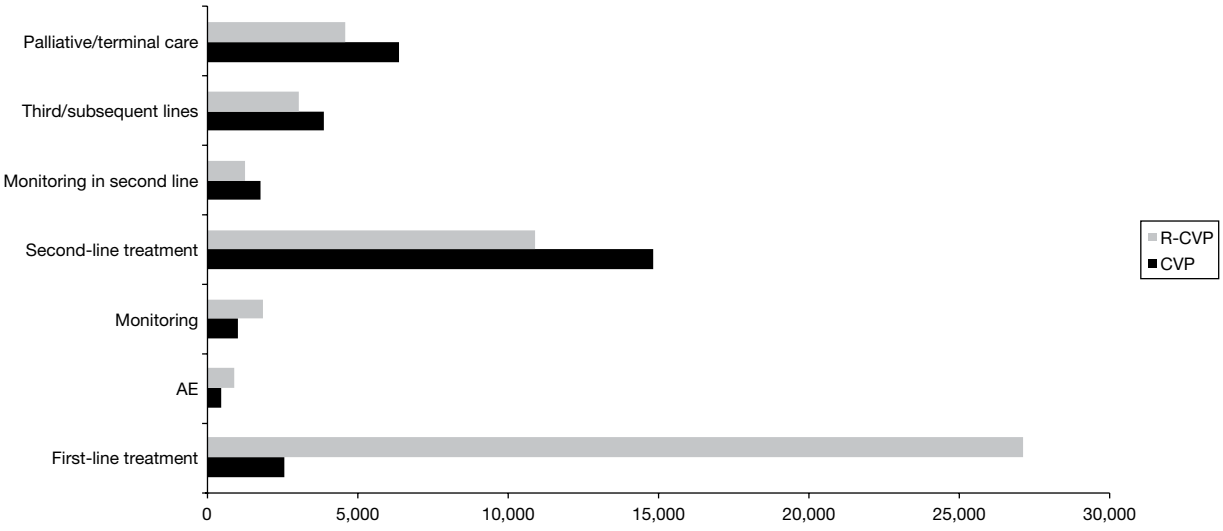
FIGURE 55 Scenario analysis: undiscounted LYs. PD, progression.



	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP
PD	1.55	1.12	1.86	1.14	1.91	1.16
PFS2	3.16	2.26	3.14	2.05	3.20	2.06
PFS1	1.28	3.87	1.84	4.53	1.68	4.45

Discounted QALYs

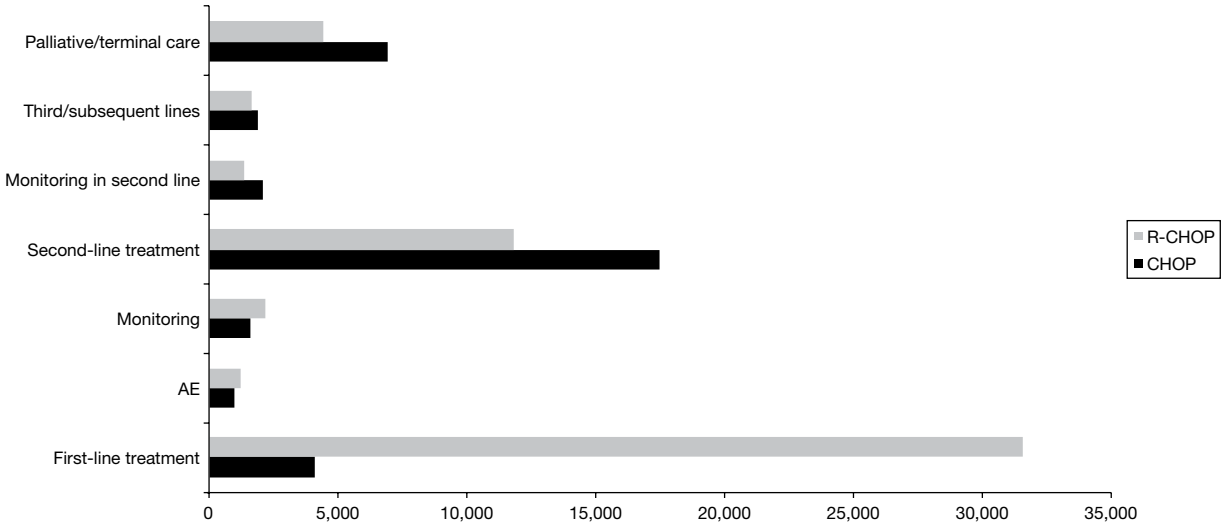
FIGURE 56 Scenario analysis: discounted QALYs. PD, progression.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-CVP	27,103	885	1822	10,883	1248	3025	4555
CVP	2544	456	997	14,812	1759	3860	6364

Discounted costs (£)

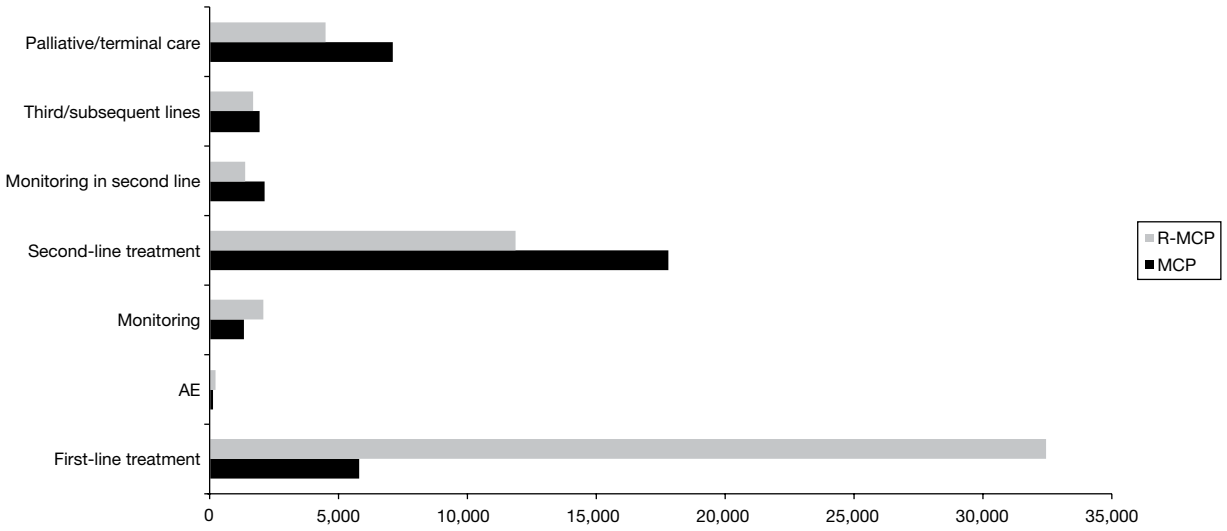
FIGURE 57 Scenario analysis: management and treatment costs for patients treated with CVP in first-line induction with or without rituximab.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-CHOP	31,588	1216	2172	11,795	1335	1632	4399
CHOP	4096	955	1610	17,452	2081	1873	6916

Discounted costs (£)

FIGURE 58 Scenario analysis: management and treatment costs for patients treated with CHOP in first-line induction with or without rituximab.



	First-line treatment	AE	Monitoring	Second-line treatment	Monitoring in second line	Third/subsequent lines	Palliative/terminal care
R-MCP	32,483	190	2065	11,863	1339	1676	4465
MCP	5791	107	1311	17,797	2125	1894	7078

Discounted costs (£)

FIGURE 59 Scenario analysis: management and treatment costs for patients treated with MCP in first-line induction with or without rituximab.

Appendix 17

Protocol

Technology Assessment Report commissioned by the NIHR HTA programme on behalf of the National Institute for Health and Clinical Excellence

Reference no: 09/141/01 (Batch 10).

Title of the project:

Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of TA110).

TAR team

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Plain English summary

Lymphomas are cancers of the lymphatic system, which is a system of tubes and glands in the body which filters body fluid and fights infection.[1] There are two main types of lymphoma: Hodgkin's and Non-Hodgkin's Lymphoma (NHL). NHL can be divided into low-grade and high-grade lymphomas, depending on how quickly they grow and spread. Follicular lymphoma (FL) is a type of NHL low-grade lymphoma of cells called B-lymphocytes.

Grading and staging of the disease informs treatment pathways. Staging of NHL refers to how many lymph nodes are affected by the disease and informs the treatment and prognosis of the disease. There are four stages of NHL. Stage I disease involves only one group of lymph nodes or lymphoma in one organ of the body is affected. Stage II refers to disease that has spread to two groups of lymph nodes or an organ and one or more group of lymph nodes, with a criteria being that these are on the same side of the diaphragm. Stages III and IV are more advanced disease. Stage III includes lymph nodes affected on both sides of the diaphragm, and stage IV disease indicates that the NHL has spread from the lymph nodes, for example to the liver, bone marrow, or blood.[1]

Histological grading of the disease is determined by the WHO classification grades I, II, IIIa or IIIb,[2] which categorise disease into low-grade/indolent disease or high-grade/aggressive disease. There is consensus that grade IIIb disease should be classified as aggressive and treated as such.[2]

NHL accounts for approximately 4% of all cancers diagnosed in the UK, with 9703 new cases registered in England and Wales in 2007, and 3978 registered deaths in 2008.[3] FL accounts for 30% of all low grade lymphomas[1] and has a UK incidence

of approximately 4 per 100,000.[2] The median age of patients with FL is around 60 years and approximately 50% of patients will present with bone marrow involvement (i.e. stage IV disease).[2] Over 70% of people with follicular lymphoma are still alive five years after the diagnosis,[4] with median survival of nine to ten years.[5]

Treatment of advanced (stage III or IV) FL is palliative; the aim of treatment being to prolong survival, achieve the longest possible remission and improve quality of life. Treatments are usually administered intermittently over a period of several years, with the expectation that the disease will relapse and remit during that time.[2]

Currently, rituximab (Mabthera®, Roche Products) in combination with cyclophosphamide, vincristine and prednisolone (CVP regimen) is recommended by NICE guidance (TA110) as a first-line treatment option for symptomatic stage III or IV follicular lymphoma.[6] However, the market authorisation has changed for rituximab, and it is now licensed for use for the treatment of previously untreated patients with symptomatic stage III-IV follicular lymphoma in combination with other chemotherapies in addition to CVP.[7]

The aim of this review is to systematically evaluate and appraise the clinical and cost-effectiveness of rituximab (in its licensed indication) in combination with chemotherapy compared with non-rituximab-containing chemotherapy, for the first-line treatment of symptomatic stage III-IV follicular lymphoma.

Decision problem

Purpose of the decision to be made

This assessment will address the question: 'What is the clinical and cost-effectiveness of rituximab (in its licensed indication) with chemotherapy for the first-line treatment of symptomatic stage III-IV follicular lymphoma'.

Clear definition of the intervention

Rituximab (Mabthera®) is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy at a recommended dose of 375 mg/m^2 BSA per cycle, for up to eight cycles.[7] This assessment will include interventions where rituximab is given in combination with the following chemotherapy regimens:

- **CVP**: cyclophosphamide, vincristine and prednisolone
- **CHOP**: cyclophosphamide, doxorubicin, vincristine and prednisolone
- **CNOP**: cyclophosphamide, mitoxantrone, vincristine and prednisolone
- **CHVP:** cyclophosphamide, doxorubicin, vindesine, prednisolone
- **MCP:** mitoxantrone, cholorambucil, and prednisolone
- **FCM**: fludarabine, cyclophosphamide and mitoxantrone
- **FM**: fludarabine and mitoxantrone
- Bendamustine.

If the TAR team become aware of another widely used chemotherapy regimen used in combination with rituximab, this will be searched for separately at that time. Note that due to the scope specifying the intervention as *rituximab given in combination with chemotherapy*, interventions including rituximab and radio-immunotherapy or bone marrow/stem cell transplant are not considered as an intervention for this appraisal.

Bendamustine is not currently licensed as a first-line treatment with rituximab within this population but is included as a combination chemotherapy agent (with rituximab) as the anticipated date of licensing is not known and could occur within the time scales of the appraisal.

Rituximab (Mabthera®) is also licensed for treatment of follicular lymphoma at other stages within the treatment pathway, other types of NHL (and has indications for treatment of CLL and rheumatoid arthritis). These indications for use are not included within the final scope but are included below for completeness:

- Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without Mabthera.
- Rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- Rituximab is indicated for the treatment of patients with CD20-positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.[7]

Place of the intervention in the treatment pathway

The review will focus on the use of rituximab (in its licensed indication) in combination with chemotherapy as first-line treatment of symptomatic stage III-IV follicular lymphoma.

Relevant comparators

Non-rituximab-containing chemotherapies are the relevant comparators, and for this assessment the following comparators are considered:

- **CVP:** cyclophosphamide, vincristine and prednisolone
- **CHOP:** cyclophosphamide, doxorubicin, vincristine and prednisolone
- **CNOP:** cyclophosphamide, mitoxantrone, vincristine and prednisolone
- **CHVP:** cyclophosphamide, doxorubicin, vindesine, prednisolone
- **MCP:** mitoxantrone, cholorambucil, and prednisolone
- **FCM:** fludarabine, cyclophosphamide and mitoxantrone
- **FM:** fludarabine and mitoxantrone
- Bendamustine.

In addition, each intervention will be compared against each other.

Population and relevant subgroups

The population will comprise adults with symptomatic stage III-IV follicular lymphoma (a non-Hodgkin's lymphoma) who have not received any previous treatment. If the evidence allows, subgroup analyses by type of chemotherapy regimen received will be considered, although initial clinical advice indicates that there are no relevant subgroups within the population that need to be addressed.

Key factors to be addressed

This review will aim to evaluate the following objectives:

- Evaluate the clinical effectiveness of rituximab in combination with chemotherapy as first-line treatment in terms of overall survival, progression-free survival, response rates, duration of disease remission, and health-related quality of life.
- Evaluate the adverse effect profile and toxicity.
- Evaluate the cost-effectiveness of rituximab in combination with other.
- chemotherapy in terms of incremental cost per quality-adjusted life year.
- Estimate the possible overall cost in England and Wales.

Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment

There was no scoping workshop for this appraisal.

Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care[8] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[9]

Search strategy

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature pertaining to rituximab for the treatment of follicular lymphoma.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

Electronic searches

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria, below) and systematic reviews/meta-analyses (for identification of additional trials). Searches will not be restricted by language or publication date. An example of the Medline search strategy is shown in Appendix 1. This will be adapted for other databases. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager© software.

Databases

The following electronic databases will be searched from inception: MEDLINE including Medline in process (Ovid); CINAHL; EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI); NIHR Clinical Research Network Portfolio; National Research Register (NRR) archive 2000-2007; Current Controlled Trials; Clinical Trials.gov.; BIOSIS. Relevant conference proceedings will be searched, for example the American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), American Society of Hematology (ASH) and the British Society for Haematology (BSH) will be searched.

Inclusion/exclusion criteria

Population

The population will comprise adults with symptomatic stage III-IV follicular lymphoma (a non-Hodgkin's lymphoma) who have not received any previous treatment.

Interventions

Rituximab in combination with any of the following chemotherapy regimens: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM and bendamustine.

Comparators

The comparator will be chemotherapy without Rituximab, which for this review are considered to be one of the following: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM or bendamustine. In addition, the interventions will be compared against each other.

Outcomes

- overall survival
- progression free survival
- response rates
- duration of disease remission
- adverse effects of treatment
- health related quality of life.

Subgroups to be examined

If the evidence allows, subgroup analyses by type of chemotherapy regimen received will be considered.

Inclusion criteria

According to the accepted hierarchy of evidence, randomised controlled trials (RCTs) will be included for clinical effectiveness, as they provide the most authoritative form of evidence. If insufficient data are not available from RCTs, observational studies or clinical trials may be considered. Studies published as abstracts or conference presentations will only be included if sufficient details represented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be used as sources of references.

Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound will be excluded from the review as well as the following publication types: non-randomised studies (except for adverse events); animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English-language papers and reports where insufficient methodological details are reported to allow critical appraisal of study quality.

Data extraction strategy

Studies will be selected for inclusion through a two-stage process according to the above inclusion/exclusion criteria. Titles and abstracts will be examined for inclusion by one reviewer. Screening will be checked by a second reviewer on ten per cent of citations and a kappa coefficient will be calculated to measure inter-rater reliability. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion/exclusion criteria. Data will be extracted by one reviewer using a standardised data extraction form and checked

by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study

Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, according to (adapted) criteria based on those proposed by the NHS CRD for randomised controlled trials (RCTs).[8] (See Appendix 2.)

Consideration of study quality to assess RCTs will include the following factors: method of randomisation, allocation concealment, blinding of patients, outcome assessors and data-analysts, numbers of participants randomised, baseline comparability between groups, specification of eligibility criteria, whether intent to treat analysis is performed, completeness of follow up and whether study power calculations are performed and reported.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate (i.e. populations, interventions and outcomes are comparable), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on ITT analyses.

Meta-analysis will be carried out using fixed or random effects models, using the Cochrane Collaboration Review Manager© Software (version 5.0).[10] Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

It is anticipated that the work will require a network meta-analysis to be undertaken to determine efficacy. This will be populated with all identified trials involving an intervention or a comparator. It is noted that the network meta-analysis could potentially be strengthened by the inclusion of RCTs involving two pharmaceuticals that were neither interventions nor comparators, provided there were RCTs comparing these pharmaceuticals with an intervention or a comparator. However, literature searches for all RCTs from these pharmaceuticals will not be conducted as they are likely to have little impact on the results of interest and would have significant resource implications.

Report methods for synthesising evidence of cost-effectiveness

Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the cost-effectiveness associated with rituximab in combination with chemotherapy will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1; this economic search filter is presented in Appendix 1. Relevant studies identified and included in the manufacturer's submission will also be included. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal[11] checklist for economic evaluations together with the Eddy checklist on mathematical model[12]

Systematic literature search for other data related to cost-effectiveness

A search of the broader literature on follicular lymphoma will be undertaken to identify the evidence base on HRQoL (i.e. health state values). The literature search will identify relevant values for appropriate health states. Primary data collection will not be undertaken.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper produced by InterTASC (January 2005).

Methods for estimating costs and cost-effectiveness

Where appropriate a mathematical model will be constructed by adapting an existing model or developing a new model using available evidence. The model developed will estimate the cost per QALY gained for rituximab and chemotherapy. It is hoped that suitable quality of life data will be identified from the literature, in the absence of quality of life data; the model may use indirect evidence on quality of life from alternative sources. The model will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. Uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA), where uncertainty of all input variables is modelled with probability distribution of their value. The information derived from PSA will be summarised graphically using cost effectiveness acceptability curves.

The time horizon of the analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and PSS. Both cost and QALY will be discounted at 3.5%.

Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 20 December 2010. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in blue in the assessment report (followed by an indication of the relevant company name e.g. in brackets).Any academic in confidence data will be underlined and highlighted in yellow.

Competing interests of authors

Dr Andrew McMillan has attended Roche Advisory Boards (and received Honoraria) and received sponsorship from Roche to attend International meetings.

Appendix 1: Draft clinical effectiveness search strategy

1. Cyclophosphamide.af.
2. Cyclophosphamide/
3. 1 or 2
4. vincristine.af.
5. Vincristine/
6. 4 or 5
7. vindesine.af.
8. Vindesine/
9. 7 or 8
10. (prednisolone or prednisone).af.
11. Prednisolone/ or Prednisone/
12. 10 or 11
13. doxorubicin.af.
14. Doxorubicin/
15. 13 or 14
16. (mitoxantrone or mitozantrone).af.
17. Mitoxantrone/
18. 16 or 17
19. (cholorambucil or chlorambucil).af.
20. Chlorambucil/
21. 19 or 20
22. fludarabine.af.
23. Bendamustine.af.
24. 3 and 6 and 12
25. 3 and 15 and 6 and 12
26. 3 and 18 and 6 and 12
27. 3 and 15 and 9 and 12
28. 18 and 21 and 12
29. 22 and 3 and 18
30. 18 and 22
31. 24 or 25 or 26 or 27 or 28 or 29 or 23
32. (CVP or CHOP or CNOP or CHVP or MCP or FCM or FM).af.
33. 30 or 31
34. (rituximab or mabthera or mab thera or rituxan or IDEC-102 or IDEC-C2B8 or Rituksimabi or Rituximabum or anti-CD20 or immunotherapy or 131I-rituximab or rituximab-alliinase conjugate or monoclonal antibod$).af.
35. Antibodies, Monoclonal/
36. 32 or 33 or 34
37. (follicular lymphoma or indolent lymphoma or low grade lymphoma or lymphoma or NHL).ti,ab.
38. (Lymphoma$ adj5 non-hodgkin$).ti,ab.
39. (follic$ adj5 (lymphocyte$ or lymphoma$)).ti,ab.
40. Lymphoma, Follicular/
41. Lymphoma, Non-Hodgkin/

42. 36 or 37 or 38 or 39 or 40
43. 35 and 41
44. Randomized controlled trials as Topic/
45. Randomized controlled trial/
46. Random allocation/
47. Double blind method/
48. Single blind method/
49. Clinical trial/
50. exp Clinical Trials as Topic/
51. 43 or 44 or 45 or 46 or 47 or 48 or 49
52. (clinic$ adj trial$1).tw.
53. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
54. Placebos/
55. Placebo$.tw.
56. Randomly allocated.tw.
57. (allocated adj2 random).tw.
58. 51 or 52 or 53 or 54 or 55 or 56
59. 50 or 57
60. Case report.tw.
61. Letter/
62. Historical article/
63. Review of reported cases.pt.
64. Review, multicase.pt.
65. 59 or 60 or 61 or 62 or 63
66. 58 not 64
67. 42 and 65

Economics filter

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw.
13. (economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
14. quality adjusted life years/
15. (qaly or qaly$).af.
16. or/1-15

Appendix 2: Draft quality assessment scale

Was the method used to assign participants to the treatment groups really random?
What method of assignment was used?
Was the allocation of treatment concealed?
What method was used to conceal treatment allocation?
Was the number of participants who were randomised stated?
Were details of baseline comparability presented?
Was baseline comparability achieved?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocations?
Were the individuals who administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?
Were the reasons for withdrawal stated?
Was an ITT analysis included?

Y – item addressed; N – no; ? – not enough information or not clear; NA – not applicable.

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal[11] checklist for economic evaluation together with the Eddy checklist[12] on mathematical models employed in technology assessments

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies;	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n = number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses: unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including: concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis.	

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We look forward to hearing from you.

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