Rituximab for the first line treatment of stage III-IV follicular non-Hodgkin's lymphoma

ERG Report

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Abbreviations:

AE	Adverse events
ASCO	American Society of Clinical Oncology
CEC	Critical Events Committee
CHVP	Cyclophosphamide, doxorubicin, vindesine, prednisone
CI	Confidence interval
CNOP	Cyclophosphamide, mitoxantrone, vincristine and prednisolone
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRu	Unconfirmed complete response
CVP	Cyclophosphamide, vincristine and prednisolone
DFS	Disease free survival
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Clinical Oncology Group
ERG	Evidence review group
EMEA	European Medicines Evaluation Agency
FCM	Fludarabine, cyclophosphamide and mitoxantrone
FLIPI	Follicular Lymphoma International Prognostic Index
IPI	International Prognostic Index
ICER	Incremental cost effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan-Meier
LYG	Life years gained
MCP	Mitoxantrone, cholorambucil, and prednisolone
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Health and Clinical Excellence
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
RCT	Randomised controlled trial
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisolone
SA	Sensitivity analysis
SAE	Severe adverse event
SMC	Scottish Medicines Consortium
SNLG	Scottish and Newcastle Lymphoma Group
STA	Single technology appraisal
TTF	Time to treatment failure
TTP	Time to disease progression or death
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Definitions of terms:

Disease-free survival (Trial specific)	Time from randomisation to relapse or death in patients achieving a CR or CRu during or within 42 days of finishing study treatment
Duration of response	Time from documentation of response to treatment failure (as defined under TTF) in patients achieving PR, CR or CRu during the study treatment phase
Overall survival	Time from randomisation to death (from any cause)
Stable disease	Cancer that is not decreasing or increasing in scope or severity
Time to progressive disease	Time from randomisation to progressive disease
Time to treatment failure (Trial specific)	Time from randomisation to the first of: • Progressive disease/relapse after response • Death • Institution of a new antilymphoma treatment • Stable disease after cycle 4 treatment
Complete response	Disappearance of all lesions and /or radiologic or biologic abnormalities observed at diagnosis and absence of new lesions
Unconfirmed complete response	Complete response with the persistence of some radiological abnormalities, which had to have regressed in size by at least 75%
Partial response	Regression of all measurable lesions by more than 50%, disappearance of non-measurable lesions and absence of new lesions
Progressive disease	Appearance of any new lesion, any growth of the initial lesion by more than 25%, or growth of any measurable lesion that has regressed during treatment by more than 50% from its smallest dimensions
Progression free survival (Trial specific)	Within the health states valued in the included trial, progression free survival is defined as the amount of time patients have experienced a partial response, remission/full response and stable disease (i.e. disease free)

1 EXECUTIVE SUMMARY

1.1 Scope

This report presents the results of the assessment of the company report regarding the use of rituximab (within the context of the licensed indication) in combination with CVP (cyclophosphamide, vincristine and prednisolone) for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma. The report includes an assessment of both the clinical and cost effectiveness evidence submitted by the company (Roche Products Limited).

1.2 Summary of submitted clinical effectiveness evidence

The submitted clinical evidence includes one randomised controlled trial (RCT), M30921 study, comparing CVP chemotherapy alone with CVP in combination with rituximab, and involving a total study population of 322 patients with stage III or IV follicular lymphoma. The evidence from this trial suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the primary outcome of time to treatment failure and is reported as an increase from 6.6 months in patients receiving CVP to 27 months in patients in the R-CVP arm with a risk reduction of 66% (95% CI 55% to 74%).

Other positive outcomes were measured for disease progression, overall tumour response, duration of response and time to new lymphoma treatment. Overall survival was not estimable at 42 months and the 38% risk reduction had not reached statistical significance.

Adverse events are comparable between the two arms for the proportion of patients experiencing at least one adverse event, although the proportion experiencing an AE in the first 24 hours is greater for the R-CVP arm (51% vs. 71%). These are primarily represented by infusion related events. Similar numbers of patients in each arm experienced grade 3-4 haematological toxicity and infection except for neutropenia (14.5% CVP vs. 24.1% R-CVP).

1.3 Summary of submitted cost effectiveness evidence

The submitted review included 15 studies, only eight of which actually met the inclusion criteria established for the review. None of these studies however compares R-CVP versus CVP.

The data extraction of the economic literature undertaken by the company was lacking in depth, and provided no quality assessment of the included studies. However, given the fact that these studies do not compare the same healthcare technologies as the company's own economic evaluation, this is of limited importance.

The model submitted in support of the company submission is basic in design. It suffers from several serious design flaws and key parameter values are probably incompatible. The review team attempted to rectify the identified errors and limitations of the model, none of which increased the incremental cost effectiveness ratio (ICER) above the conventional threshold of £30,000.

However, due to design flaws within the model as outlined in this report it was impossible to simultaneously correct all of the errors and limitations within the model. Although the cost-effectiveness results obtained appear to be compelling in support of R-CVP compared to CVP, for the trial population it could be argued that the results would not be so convincing for a more representative population.

2 BACKGROUND

2.1 Introduction

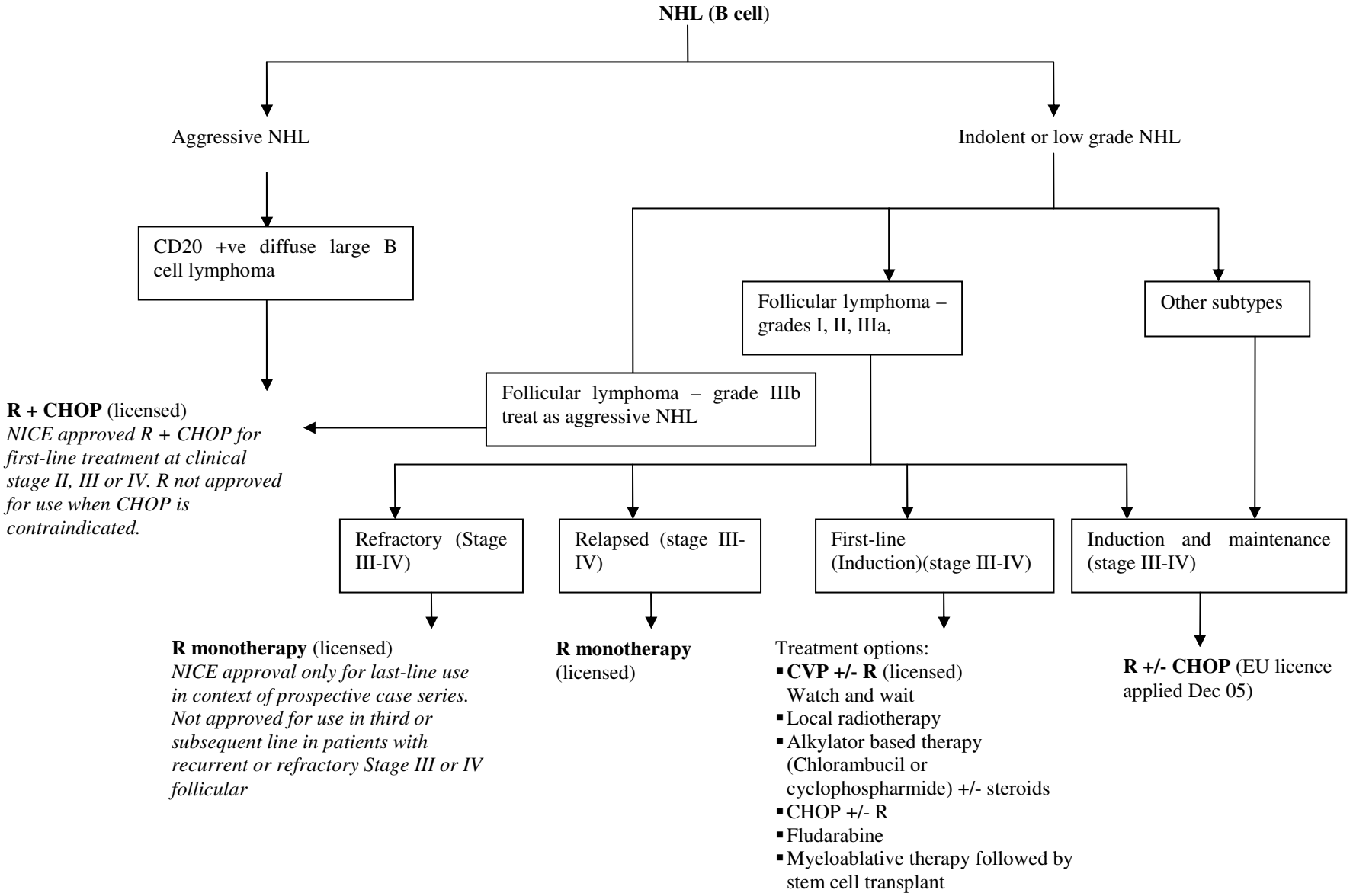
The title of this single technology appraisal (STA) is somewhat misleading. The diagnosis, grading, staging and treatment of non Hodgkin's lymphoma (NHL) are complex. Figure 1 represents the diagnostic categories as well as current guidance related to treatment of NHL and the role of this appraisal in the overall treatment regimen.

2.2 Epidemiology

NHL represents about 3% of all cancers diagnosed in the UK. In 2002 there were 9,443 people diagnosed with NHL in the UK[1] with an incidence of 16 per 100,000 in England and 15.6 per 100,000 in Wales, giving an approximate health authority rate of 80 and 78 per 500,000, respectively. The overall rate is increasing at 3% to 4% per year, which is greater than would be expected from simply a combination of the ageing of the population and improved diagnostic techniques.[2]

Follicular lymphoma is the second most common type of NHL with a UK incidence of approximately 4 per 100,000[3] and a prevalence of about 40 per 100,000.[2]

Figure 1: Forms of non-Hodgkin's lymphoma (NHL) treatment options for stage III-IV NHL, current licensed status for rituximab (R) and relevant NICE guidelines



2.3 Grading and staging and prognosis of follicular lymphoma

The clinical course of follicular lymphoma differs considerably between individual patients. Grading and staging of the disease dictate treatment pathways.

Grading: Low grade or indolent disease is differentiated from high grade or aggressive disease by histology. Histological grading of the disease is determined by the WHO classification grades I, II, IIIa or IIIb.[3] The grade is determined by the number and size of abnormal cells taken from lymph node biopsies. There is a growing consensus that histological grade III and, in particular, grade IIIb disease should be classified as aggressive and treated as such rather than treated as indolent disease.[3]

Staging: Staging of disease generally determines treatment options and prognosis. Until recently, the Ann Arbor staging system,[3] based on anatomical extent of disease, was the major predictor of prognosis and determinant of therapy (Table 2.1). This system classifies disease according to anatomical site and extent of disease.

Table 2.1: Ann-Arbor staging system of non-Hodgkin's lymphoma

Stage I	Involvement of a single lymph node region (I), or localised involvement of a single extralymphatic organ or site (IE).
Stage II	Involvement of 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	Involvement of lymph node regions on both sides of the diaphragm (III), that 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 (nonregional) nodal involvement.

More recently, the International Prognostic Index (IPI) has been used to provide a predictive model for aggressive NHL, based on presenting features as well as extent of disease, however this index has been successfully applied to follicular NHL. The IPI takes into account various clinical and anatomical factors, which are used to predict prognosis.

Adverse prognostic factors include Ann Arbor stage (III or IV), age greater than 60, high serum lactate dehydrogenase level, reduced performance status and multiple extranodal sites of involvement.[3] Patients can be divided into four prognostic categories (low risk, low/intermediate risk, intermediate/high risk, high risk) based on number of risk factors, with more adverse factors indicating high risk for poor prognosis. This has been further refined for application to follicular lymphoma and is known as the Follicular Lymphoma International Prognostic Index (FLIPI).

In practice, the Ann Arbor staging system is still widely used in the UK rather than, or as well as the FLIPI index.

2.4 Aims of treatment

Follicular lymphoma is generally considered incurable and the aim of treatment is to induce periods of remission, increase the length of remission and to improve survival and quality of life.

Alkylating agents are useful palliative treatment options that can result in improved well being for most patients, often for long periods. Relatively recent studies have concluded that combinations of alkylator-based chemotherapy have not convincingly resulted in more frequent or longer periods of remission then monotherapy and that there is no proof that initial combination chemotherapy will prolong survival in comparison with single agent treatments.[4] However, this view is beginning to change as more evidence accumulates in this rapidly developing field. Recently published clinical guidelines[5] suggest trials have shown that combination or extended chemotherapy may result in more frequent and longer lasting remissions as well as improvement in quality of life. However, this does not automatically translate into a survival advantage owing to the continuous pattern of relapse and responsiveness to subsequent therapy.

2.5 Treatment options

There is no single accepted therapy for the first-line treatment of stage III/IV follicular lymphoma. A recent analysis of the first-line treatments in 662 patients with follicular lymphoma showed that there were 37 different regimens being used. (Scottish and Newcastle Lymphoma Group, 2004, Roche Submission to NICE)[6] Table 2.2 outlines current first-line chemotherapy treatment options for follicular lymphoma.

Table 2.2. Follicular lymphoma treatment options

NHL classification	*First-line chemotherapy treatment options*
Follicular lymphoma	• Alkylator based therapy (e.g. CVP, chlorambucil) • Anthracycline based therapy (CHOP, CNOP and MCP) • Fludarabine based therapy (FCM) • Rituximab + CVP

CVP: cyclophosphamide, vincristine and prednisolone; **CHOP**: cyclophosphamide, doxorubicin, vincristine and prednisolone; **CNOP**: cyclophosphamide, mitoxantrone, vincristine and prednisolone; MCP: mitoxantrone, cholorambucil, and prednisolone; **FCM**: fludarabine, cyclophosphamide and mitoxantrone

Alkylator based therapies such as CVP are standard treatments in follicular lymphoma grades I and II.[3]

CNOP and MCP are both mitoxantrone based regimens. Mitoxantrone is an anthracycline derivative and is structurally related to doxorubicin, which is more commonly used in the CHOP regimen. The British Committee for Standards in Haematology (BCSH) guidelines[3] suggest that chlorambucil or CVP should be first-line therapy for grades I and II lymphoma and CHOP for grade III lymphoma.

2.6 Rituximab

Rituximab (MabThera®) is a humanised monoclonal antibody (IgG) recognising the CD20 antigen found on mature B lymphocytes and is antineoplastic and an immunomodulator.

The European Medicines Evaluation Agency (EMEA) granted MabThera® an extension to its Marketing Authorisation in August 2004 stating that:

"MabThera® is indicated for the treatment of previously untreated patients with stage III/IV follicular lymphoma in combination with CVP chemotherapy."

For other uses of Rituximab in NHL see Figure 1.

2.7 Critique of company background

The company submission contains a generally accurate and thorough background section. However, there are several points that need further discussion.

> *"Remission induction is of great value to patients. Rituximab-induced remissions are associated with resolution of disease symptoms (Davis et al. 1999). In addition, a recent study (Oxford Outcomes, 2005) conducted amongst 219 patients with follicular lymphoma demonstrated that disease remission is associated with significantly better health-related quality of life (HRQoL) and lower levels of anxiety, depression and impairment in activity than progressive disease." (Page16)*

The Oxford Outcomes study is unpublished and was commissioned by the company, and therefore data have not been verified. We have found no other data that examine the health related quality of life of these patients.

> *"We are aware that guidelines on the treatment of follicular lymphoma from Europe (European Society for Medical Oncology, 2005), Canada (British Columbia Cancer Agency, 2005) and the USA (National Cancer Institute, 2005) all recommend the use of rituximab plus chemotherapy as first-line treatment for Stage III/IV follicular lymphoma" (Page10)*

The company submission indicates that rituximab plus chemotherapy combinations can be recommended as first-line treatment options. However, current guidelines are less directional, simply stating that these treatments can be considered.

> *"Although there are advocates of the universal inclusion of doxorubicin or fludarabine in first-line treatment regimens, both add significantly to treatment toxicity and there is a lack of evidence that either confers a survival benefit. Therefore, many UK clinicians reserve these agents for patients who have developed resistance to alkylating agents or for those previously untreated patients that they consider need more aggressive therapy or rapid cytoreduction. For example, those whose tumour histology shows characteristics of more aggressive lymphoma, those who have a high bulk of disease, and those whose tumour is compressing a vital structure." (Page 17)*

However, Roche has recently applied to the EU licensing authorities for use of rituximab for maintenance therapy for stage III-IV follicular NHL based on the results of the European Organization for Research and Treatment of Cancer (EORTC) study which showed that maintenance treatment with rituximab extended progression free

and overall survival in patients who already had a complete or partial response after induction with CHOP chemotherapy with or without rituximab.[7] In addition, in the US, an application has recently been submitted for the use of rituximab as first-line treatment of previously-untreated patients with follicular NHL in combination with CVP or CHOP chemotherapy or following CVP chemotherapy in those patients who achieved a response of stable disease or better.[8]

> *"Follicular lymphoma is generally considered incurable with current therapies and something to be lived with for a decade or more. Therefore, treatments which induce a high rate of durable remissions are very valuable. These minimise futile treatments from which patients experience treatment toxicity but no benefit and they maximise the time spent in remission and off treatment."(Page 9)*

It is not known which 'futile' treatments are referred to here, especially as there is little evidence for the most effective regimen i.e. those most likely to induce long lasting remission.

> *"Historically, extension of overall survival has not been a treatment goal in clinical practice. Conventional wisdom holds that the treatments used over the last 3 or 4 decades do not alter overall survival."(Page 16)*

> *"Recent studies have indicated that survival in this condition is increasing decade by decade (Swenson et al. 2005) and that this is a consequence of improved first-line treatments, notably the recent introduction of antibody-based regimens (Liu et al. 2003; Fisher et al. 2005; Dillman and Chico, 2005), specifically rituximab (Schulz et al. 2005)." (Page 17)*

Swenson *et* al does not attribute improved survival to introduction of antibody based regimens.[9] they performed an analysis of survival data truncated at 1996, the year rituximab was licensed in the USA. The results indicate that the survival advantage they describe was observed before the widespread use of rituximab; therefore if prolonged survival is attributed to improved treatment then it cannot be solely attributed to therapy with rituximab. Swenson *et* al[9] suggest that the clinical course of follicular lymphoma has altered, which coincides with the changes in the availability of management options. They speculate that the sequential application of effective therapies, coupled with improved supportive care, is responsible for the improvement in survival.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach

Key aspects of the methodological quality of the company's review of the clinical literature was quality assessed based on an accepted quality assessment tool[10] and the results are summarised in Table 3.3.1.

Table 3.3.1: Quality assessment of the company's submission

Quality assessment checklist item	*Yes/No*
Did the review address a clearly focused research question?	✔
Was the search strategy adequate? (i.e. did the reviewers identify all relevant studies?)	✔/✖
Are the inclusion/exclusion criteria specified?	✔/✖
Did the review include the right type of studies?	✔
Is there a statement of completeness from the company?	✖
Did the reviewers assess the quality of the included studies?	✔/✖
Was the method of data extraction reported?	✖
Were appropriate measures of outcomes (as stated in the scope) used?	NA
If the results of the studies have been combined, was it reasonable to do so?	NA
Are appropriate sub-group analyses presented?	✔
Are the main results of the review reported? (e.g. numerical results included with the CIs)	✔
Are issues of generalisability addressed?	✔
Should the policy or practice change as a result of the evidence contained in this review?	✔

✓=yes, ✓/X=partially, X=no, NA=Not applicable

3.1.1 Search strategy

The literature search appears appropriate and comprehensive but insufficient detail was provided to allow the evidence review group (ERG) to replicate the search. We conducted searches which confirm the company's finding of only one relevant trial.

3.1.2 Inclusion and exclusion criteria used in the study selection

Details of inclusion and exclusion criteria used in the submission are summarised in Table 3.2.

Details of the process used to apply the inclusion criteria were not provided (e.g. the number of people involved in the process and whether this was done independently). It is stated that the titles and abstracts of all references retrieved through literature searches were reviewed and eliminated manually if they were not relevant to the review.

A flow diagram included in the submission indicates that of the 303 references identified in total, 293 were excluded. An additional two references that were known to the reviewers but not identified during electronic searching were included for consideration in the review.

3.1.3 Studies identified

Although the intervention under appraisal is rituximab plus CVP for the first-line treatment of follicular lymphoma, the submission considered other rituximab-chemotherapy combinations for further supporting evidence. It is, however, unclear exactly how many trials are 'included' in the review.

A total of 14 publications of five randomised controlled trials, available as fully published papers (n=2), conference abstracts (n=11) and one study report, were considered for inclusion in the review. Of these RCTs, one compares rituximab plus CVP versus CVP, one compares rituximab plus CHOP versus CHOP, one RCT compares rituximab versus CNOP versus rituximab plus CNOP, one compares rituximab plus MCP versus MCP, and one compares a combination of rituximab plus CHVP plus interferon alfa versus CHVP plus interferon alfa.

No further studies comparing CVP chemotherapy with or without rituximab were identified.

Table 3.2: Scope of the appraisal

	Clinical effectiveness	Cost-effectiveness
Population	Adults with stage III/IV non-Hodgkin's follicular lymphoma who have not received any previous treatment	
Intervention	Rituximab in combination with CVP (cyclophosphamide, vincristine and prednisolone)	
Comparators	• CVP • CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) • CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisolone) • MCP (mitoxantrone, cholorambucil, and prednisolone) • Chlorambucil	
Outcomes	• Time to treatment failure • Tumour response (complete response, unconfirmed complete response, partial response, progressive disease) • Duration of response • Overall survival • Disease-free survival • Adverse effects of treatment • Health related quality of life	• Incremental cost per quality adjusted life year *From the draft scope:* Details of the time horizon for the economic evaluation based on the time period over which costs and benefits can reasonably be expected given the progression of the disease.
Study design	RCT	Economic analyses
Inclusion criteria	• Main focus of follicular lymphoma • Clinical trial data publications	• Main focus of follicular lymphoma • Full economic evaluation
Exclusion criteria	• Clinical trials in previously-treated patients • Reviews • Animal studies or in vitro research work	• No attempt to synthesise costs and benefits • Letters, editorials, commentaries or methodological papers

3.1.4 Validity assessment of included studied

No formal methodological quality assessment of included trials was reported.

3.1.5 Data extraction

Details of the data extraction process (e.g. number of reviewers and whether data were extracted independently) are not provided in the submission.

3.1.6 Combination of studies

A meta-analysis was not undertaken by the company as there is only one trial included in the review. However, the submission reports preliminary results of a meta-analysis (conducted by Schulz and colleagues and available as a conference

abstract)[11] that compares survival in patients receiving chemotherapy with or without rituximab for the first-line treatment of follicular or mantle cell lymphoma.

3.2 Reported results

One multi-centre, open-label trial involving 322 patients was included in the review (one patient withdrew consent therefore not included in final analysis). Patients were enrolled during the period 2000-2002 and were given cyclophosphamide, vincristine, prednisone plus rituximab (R-CVP) or CVP alone. Results from this trial were reported in one peer-reviewed journal article, three conference abstracts, and one study report. A detailed summary of this trial is provided in the submission.

3.2.1 Quality assessment of included study

The company submission did not include a formal quality assessment, or discuss the methodological limitations of the trial. However, the submission provides information concerning certain aspects of the methodological quality of the included trial including the randomisation procedure and the adequacy of follow up.

Issues related to concealment of allocation are not directly addressed; but, as the randomisation process was performed centrally, it is likely that allocation concealment was adequate. Baseline characteristics (as reported in the published paper) were generally comparable in each treatment arm.

It is stated in the submission that the participants were not blinded to treatment allocation and that the nature of treatment made effective blinding of investigators impractical. However, a blinded and independent Critical Events Committee (CEC) was used to review the radiographic scans to avoid observer bias. The number of, and reasons for, withdrawals are reported in both sources.

3.2.2 Trial characteristics

Study characteristics are summarised in Table 3.3.

Table 3.3: Study characteristics

Study name	Interventions drug & dose, n	Data collection	Study design	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Follow-up
M39021	**Rituximab** (375 mg/m^2) ***and* CVP** **n=162** (137 completed 8 cycles) **CVP** (cyclophospahamide 750 mg/m^2 IV Day 1, vincristine 1.4 mg/m^2 IV Day 1, and prednisolone 40 mg/m^2 po days 1-5). **n=160** (159 received tx, 108 completed 8 cycles)	April 11, 2000- March 12, 2002	RCT, Open label	Primary outcomes: time to treatment failure (TTF) Secondary outcomes: response rate, tumour response (CR, CRu, PR, PD), overall survival, duration of response, disease-free survival, adverse events, time to disease progression or death, time to new lymphoma treatment or death	International, Multicentre, including 13 UK centres.	All of the following: stage III/IV follicular lymphoma, bi-dimensionally measurable lesion(s) in ≤1 site that had not been irradiated, no prior systemic lymphoma treatment, ECOG performance status 0-2, life expectancy >3 months, not in need of immediate intervention to treat life-threatening complications, Ann Arbor stage III/IV CD20-postive follicular lymphoma	One or more of the following: high grade or diffuse large B cell lymphoma, white blood count >25 x 10^9/L, disease involvement in the central nervous system, previous malignancy, previous systemic therapy for follicular lymphoma, severe cardiac disease, MI within 6 mo, ventricular tachyarrhythmia requiring treatment or ongoing angina pectoris, impairment of renal function or hepatic function not due to lymphoma, pregnancy or breast-feeding, child-bearing potential, major surgery ≤28 days, known infection with HBV, HCV or HIV	1223.6 days (median; range: 45-1801)

ECOG: The Eastern Cooperative Oncology Group

3.2.3 Participant characteristics

Information relating to the participant characteristics was reported in the published paper[12] but not in the submission.

Patient demographics were similar in both groups. Overall, 54% of patients were male, with a median age of 53 years in the CVP group, and 52 years in the R-CVP group. Fifty-seven percent of patients had an ECOG performance status of 0, and 39% had an ECOG score of I and 70% of patients had a stage IV follicular lymphoma. Nearly half of the patients (CVP: 47%, R-CVP: 44%) had high-risk disease according to the Follicular Lymphoma International Prognostic Index (FLIPI) score (scores 3-5).

3.2.4 Clinical results

Sixty-eight per cent of patients treated with CVP and 85% treated with R-CVP received eight cycles of chemotherapy.

The primary outcome measure used was "time to treatment failure". Stable disease (at cycle 4) was included in the definition of time to treatment failure at the request of the Data and Safety Monitoring Committee (DSMC) and was the subject of a protocol amendment in March 2002, prior to the first interim analysis being conducted. The reasons for this inclusion are outlined in the submission.

Secondary end points were "response rate" (complete response, unconfirmed complete response and partial response and progressive disease), "overall survival", "duration of response", "disease-free survival", "time from randomisation to next anti-lymphoma treatment or death" and "time from randomisation to disease progression or death". Adverse events and laboratory parameters were assessed according to the National Cancer Institute Common Toxicity Criteria grading system (version 2).[13]

The primary analysis in this trial was performed on all patients randomly assigned to treatment and who received the study drug and followed the intention-to-treat principle.

Key outcomes were extracted from the submission and the published paper and are presented in Table 3.4.

3.2.4.1 Time to treatment failure

At a median follow-up of 30 and 42 months, median time to treatment failure was 6.6 months in patients receiving CVP and 27 months in the R-CVP arm (P<0.0001) with a risk reduction of 66% (95% CI 55% to 74%). The risk reduction observed was further confirmed by an independent group of assessors (CEC) who were blind to treatment allocation.

Exploratory analyses of TTF in the patient subgroups (e.g. by age, number of extra-nodal sites, bone marrow involvement, lactate dehydrogenase levels (LDH), number of nodal sites) also indicated significantly consistent benefit from the addition of rituximab, with the exception of patients with low haemoglobin (n=66) who showed a risk reduction of 30% for TTF.

3.2.4.2 Time to disease progression/ relapse or death

The addition of rituximab to the CVP arm more than doubled the time to disease progression/relapse after response or death (TTP), from 14.5 months to 33.6 months (P <0.0001) and the risk of progression/relapse or death was reduced by 58%.

3.2.4.3 Overall survival

Kaplan-Meier estimates for overall survival at 30 months were 85% for CVP arm and 89% for R-CVP arm. In the submission, the Kaplan-Meier (KM) estimates for survival at 36 months are reported as 81% and 89%, respectively, not reaching statistical significance. The rate of disease-specific deaths (i.e. death due to lymphoma) was significantly lower in the R-CVP arm compared to the CVP arm (p=0.02).

3.2.4.4 Disease-free survival

Disease-free survival or patients who achieved complete response (CR) or unconfirmed CR (CRu) during the study was 20.5 months in the CVP group compared with 44.8 months in the R-CVP group. The difference between the groups was significant (P=0.0005).

3.2.4.5 Response rates

The rate of overall tumour response at 42 months, defined as any patient who experienced a CR, CRu or partial response (PR), was 57% in the CVP group and 81%

in the R-CVP group (P<0.0001), with a duration of response of 13.5 months in the CVP arm, and 37.7 months in the R-CVP arm.

Table 3.4: Efficacy outcomes, ITT analysis at 42 months' median follow up (full population)

Outcomes	Time to event (median months)			Treatment effect*
	CVP	R-CVP	Log-Rank *p* value	
TTF	6.6	27.0	<0.0001	66%
Time to disease progression or death	14.5	33.6	<0.0001	58%
Overall survival	NE	NE	0.07	38%
Overall survival (KM estimates)**	85%	89%	0.22	NR
Overall tumour response	57%	81%	<0.0001	3.2
Duration of response	13.5	37.7	<0.0001	65%
Disease-free survival	20.5	44.8	0.0005	71%
Time to new lymphoma treatment or death	12.3	46.3	<0.0001	63%

NE: not estimable (Kaplan-Meier estimates of event-free rates were above 50% during the entire observation period). * Risk reduction except for tumour response rate where odds ratio was used. ** As reported at 30 months in the published trial paper.

3.2.4.6 Adverse events

Adverse events were evaluated according to National Cancer Institute's (NCI) Common Toxicity Criteria and reported in detail in the submission (see Table 3.5).

The proportion of patients experiencing at least one AE was comparable between the groups (95% in CVP, 97% in R-CVP arm). The incidence of adverse events within the 24 hours of an infusion with R-CVP was higher than that with CVP (71% versus 51%). These increases in the R-CVP arm were mostly attributable to the infusion reactions following rituximab administration. Severe adverse events (fatigue, neutropenia, and back pain) observed with R-CVP patients were more common (22%) compared with patients receiving CVP (16%). Of the 22% of patients experiencing severe adverse events in the R-CVP arm, 9% were due to severe or life threatening

infusion related rituximab reactions. This level is within the expected range of rituximab alone and indicates there was no interaction with CVP.

Table 3.5: Safety outcomes

Adverse event category	CVP (n=159)	R-CVP (n=162)	Difference
Pts with ≤1 SAE, n (%) **Total no of SAEs**	25 (16.0) 34	35 (22.0) 47	+6%
Pts with ≤1 AE, n (%) **Total no of AEs**	151 (95.0) 936	157 (96.9) 1170	+2%
Pts prematurely withdrawn owing to AEs, n (%)	6 (3.8)	5 (3.1)	-0.7%

Pts: Patients, SAE: Serious Adverse Events, ATs: Adverse Events

The incidence of grade 3/4 neutropenia with R-CVP was higher than that with CVP (24.1% versus 14.5%), with no difference between groups in the overall infection rate (Table 3.6).

Table 3.6: Patients experiencing grade 3/4 haematological toxicity and infection

No of pts experiencing (%)	CVP (n=159)	R-CVP (n=162)
Haemoglobin	3 (1.9)	1 (0.6)
Neutrophils	23 (14.5)	39 (24.1)
Platelets	0	2 (1.2)
Leucocytes	14 (8.8)	19 (11.7)
Infections	7 (4.4)	7 (4.3)

Pts: Patients

3.2.5 Indirect comparisons

Results from four RCTs exploring the impact of adding rituximab to chemotherapy regimes other than CVP are reported descriptively in the submission. None of these studies provide direct comparison to the technology being addressed in this appraisal Of note however, is that the company submission argues the importance of time to treatment failure as a primary outcome and this is reported in only one of the additional studies included in their submission.

Table 3.7 summarises the main results obtained from these trials.

Table 3.7: RCTs of mixed treatment comparisons (data extracted by evidence review group from original source)

Study name	Interventions, no of pts, follow up (mo)	Inclusion criteria	Response rates, %	CR Rates, %	Event-free survival, %	Time-to progression, mo	Overall-survival	Time to treatment failure (mo)
The German Low Grade Lymphoma Study Group (GLSG) Hiddemann *et al*[14]	R-CHOP 223 CHOP 205 Max of nearly 3 yrs	First-line, stage III/IV follicular lymphoma	R-CHOP 96 CHOP 90	R-CHOP 20 CHOP 17	Not reported	R-CHOP 50 CHOP 15	R-CHOP 95% CHOP 90% (Estimated probability of survival at 2 years)	R-CHOP not reached* CHOP 29**
Mexican Multicentric Hematology Study Group (MMHSG) Rivas-Vera *et al*[15]	R 62 CNOP 55 R-CNOP 66	First-line indolent lymphoma (**76% stage III/IV**)	R 84.9 CNOP 83.4 R-CNOP 90	Not reported	Disease free survival at 24 mo: R 68 CNOP 65 R-CNOP 70	Not reported	R 87% CNOP 84% R-CNOP 78%	Not reported
OSHO39 Herold *et al*[16]	R-MCP *vs.* MCP 358 pts (201 pts with follicular lymphoma, 157 pts with mantle-cell lymphoma) Median 30 mo	Patients with stage III/IV indolent lymphoma (**56% follicular, 44% mantle-cell**)	R-MCP 92.4 MCP 75 (Only those with follicular lymphoma)	R-MCP 49.5 MCP 25 (Only those with follicular lymphoma)	R-MCP 79.3 MCP 44.4 (Only those with follicular lymphoma)	Not reported	R-MCP 89.3 MCP 75.5 *PFS:* R-MCP 82.2 MCP 50.7 (Only those with follicular lymphoma)	Not reported
GELA-GOELAMS FL-2000 Salles *et al*[17]	R-CHVP+IFN vs CHVP+IFN Median 30 mo, n=359 pts	Follicular lymphoma (stage **II-IV**), **any grade**	Not analysed	R- CHVP +IFN 79 CHVP+IFN 63 (at 18 mo)	R-CHVP+IFN 78 CHVP+IFN 62 (estimated 30 mo)	Not reported	Not reported	Not reported

R: rituximab, **CHOP**: cyclophosphamide, doxorubicin, vincristine and prednisone, **MCP**: mitoxantrone, cholorambucil and prednisolone; **CHVP**: cyclophosphamide, vincristine, prednisone; **CNOP**: Cyclophosphamide, mitoxantrone, vincristine and prednisone. PFS: Progresion-free survival

* i.e. less than 50% of R-CHOP have had treatment failure by the end of the study.

** only for those aged:≥60 and an IPI Score 3-5

3.3 Summary of submitted evidence

3.3.1 Clinical outcome results

The submitted clinical evidence includes only one RCT (n=322) which investigates the use of rituximab in its licensed indication. The trial population appears to be representative of the UK population of patients treated for follicular lymphoma with the exception of a somewhat lower median age of trial participants (52 and 53 years, in the CVP and R-CVP arms, respectively). The evidence from this trial suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on all outcomes measured.

Rituximab in combination with CVP (R-CVP) shows a highly significant increase ($p<=0.0001$) in time to treatment failure (TTF), the primary endpoint, in the intention-to-treat (ITT) population. TTF is reported as an increase from 7 months in patients receiving CVP to 27 months in patients in the R-CVP arm with a risk reduction of 66% (95% CI 55%-74%).

The trial also reports positive results for time to disease progression or death ($p<0.0001$, 58% risk reduction), overall tumour response ($p<0.0001$, 3.2 odds ratio), duration of response ($p<0.0001$, 65% risk reduction), disease-free survival ($p<0.0005$, 71% risk reduction) and time to new lymphoma treatment or death ($p<0.0001$, 63% risk reduction). Overall survival was not estimable at 42 months and the 38% risk reduction had not reached statistical significance.

Adverse events are comparable between the two arms for the percentage of patients experiencing at least one adverse event, although compared to the CVP arm the percentage experiencing an AE in the first 24 hours is greater for the R-CVP arm (51% vs. 71%). Severe adverse events were experienced by 22% of those in the R-CVP arm compared to 16% in the CVP arm. The number of patients withdrawing from the study due to adverse events was similar in both groups (3.8% in CVP and 3.1% in R-CVP). Similar numbers of patients in each arm experienced grade 3/4 haematological toxicity and infection except for those experiencing neutropenia (14.5% CVP vs. 24.1% R-CVP).

3.3.2 Limitations

Choice of comparator

The first issue to be discussed relates to the choice of comparator. In the company submission the only comparator used is CVP alone. There is mention in the submission of other studies using a variety of treatments. However, no analyses were carried out comparing the results with R-CVP. Preliminary findings of a meta-analysis, available only as a conference abstract, are discussed descriptively.

A wide range of treatment options are used in the UK for the treatment of follicular lymphoma but currently there is no consensus on the most effective treatment. These include alkylator-based regimens (e.g. CVP, chlorambucil) or anthracycline-based regimens (e.g. CHOP, CNOP, MCP) used either alone or in combination with rituximab.

Clinical guidelines however note a lack of data directly comparing outcomes with alternative therapeutic strategies. Comparative studies of other rituximab chemotherapy combinations are therefore warranted.

Outcomes

The second issue relates to the rationale for the outcomes used including an explanation of the reasons for using "time to treatment failure" as the primary outcome instead of "overall survival" as is usual for oncology clinical trials.

The main reason for using "time to treatment failure" is that follicular lymphoma is generally considered incurable with current therapies and therefore ideal treatment will induce a prolonged remission and a high rate of durable remissions. The submission also outlines that historically "overall survival" has not been a treatment goal in clinical practice and that conventional wisdom holds that the treatments used over the last three or four decades do not alter overall survival. However, the submission disputes this, referencing several papers which indicate that survival is increasing decade by decade and that this is a consequence of improved first-line treatments, especially with the introduction of antibody-based regimens, specifically rituximab.

The duration of survival is another factor in determining what measurable outcomes are: with a median survival of 8-10 years from diagnosis, measuring overall survival

would require a long follow up period, and is not an outcome which can be reasonably expected in the trial at this point.

The use of tumour response as an outcome depends on its ability to predict an improvement in overall survival and/or quality of life. Though an increase in overall survival is desirable, disease-free, progression free or event free survival are also important measures and should be represented in more than one manner e.g. percent surviving or median survival.

Whilst overall survival is a preferred outcome measure, in the case of follicular lymphoma the submission presents a persuasive rationale for the use of "time to treatment failure". Clinical advice on this matter also highlights that overall survival does not denote progression free survival, and in the case of an incurable cancer with a relatively long life expectancy with the disease, progression free survival is an important factor in determining quality of life. It is important to note that in due course the overall survival of patients will be estimable and the relationship between time to treatment failure and overall survival can be investigated.

In addition, inclusion of 'death' in combined outcomes in the M30921 trial (e.g. time to progression or death, time to new lymphoma treatment or death) where the results are statistically significantly in favour of the combination arm, may be misleading as the trial reports no significant differences between treatment groups in overall survival. It may therefore be better to report these outcomes separately; however, it is unlikely that this would make a significant difference to the findings.

4 ECONOMIC EVALUATION

4.1 Summary of published cost-effectiveness studies identified in the submission

4.1.1 Identification and description of studies

Insufficient detail of the search strategy as reported in the submission meant that we were unable to replicate the economic literature search. However, key terms used and databases searched were described. In addition, the number of papers initially found, and the number of papers excluded, were not reported.

Stated inclusion criteria were:

- **Date of publication**
  Studies published after January 1st 1996 were included.

- **Language of publication**
  Only studies published in English or where English translations were available were included in the systematic review. One exception to this is a French paper by Malliti.[18]

- **Type of study and outcome measure**
  Studies were included if they described an economic evaluation quantifying both costs and benefits (full economic evaluation).

- **Intervention**
  Studies that evaluated the first line treatment of follicular lymphoma with rituximab were included. However, considering that this is a new treatment option and due to the lack of available evidence, studies that evaluated the use of rituximab in relapsed or recurrent follicular lymphoma were also included as well as some studies on aggressive lymphoma.

- **Subjects**
  Studies examining patients with stage III/IV, relapsed and recurrent follicular lymphoma as well as some studies that examined aggressive lymphoma were included. No restrictions were placed on the age or gender of patients included in the analysis. Economic evaluations conducted on patients with different

levels of disease severity were also included if they assessed cost-effectiveness in a subgroup of patients with early disease.

Using these inclusion criteria the company identified 15 papers for inclusion and subsequent data extraction. However, upon closer inspection we found that only eight of the 15 studies fulfilled the inclusion criteria of assessing both costs and benefits (see Table 4.1). Furthermore, both the Edelman[19] and Tolley[20] studies did not include rituximab either alone or in combination. This conflicts with the company's inclusion criteria. It is also worth noting that none of the 15 studies were of R-CVP versus CVP. Although this fact does not conflict with the inclusion/exclusion criteria outlined in the review, it does limit its relevance.

4.1.2 Data extraction

The company extracted data from the 15 papers included in the review. Aim of the study, study results, and relevance to decision making in England and Wales were reported. This data extraction is simplistic and does not go into sufficient depth and the data extraction tables were not accompanied by a commentary. However, given that none of the papers compared R-CVP to CVP these studies are not directly comparable with the economic evaluation presented in the company submission.

4.1.3 Quality assessment

The submission states that descriptions of any shortcomings in the included papers will be reported. However, it is not clear from the data extraction table if this has been carried out. No formal quality assessment of the included papers appears to have been conducted.

4.1.4 Summary and conclusions

No economic evaluations are available for R-CVP versus CVP, although this is not explicitly stated by the company. Only eight of the included studies actually met the criteria of full economic analysis (i.e. including both costs and benefits).

The data extraction of the economic literature undertaken by the company was lacking in depth, and provided no quality assessment of the included studies. However, given the fact that these studies do not compare the same healthcare technologies as the company's own economic evaluation, this is of limited importance.

Table 4.1: Inclusion and exclusion criteria as applied by the review team to each paper reported in the company submission

Paper	Date	Language	Full economic evaluation	Intervention	Subjects
Best[21]	✓	✓	✓	✓	✓
Edelman[19]	✓	✓	X	X	✓
Groot [22]	✓	✓	✓	✓	✓
Hamblin [23]	✓	✓	✓	✓	✓
Herold [24]	✓	✓	X	✓	✓
Hieke [25]	✓	✓	X	✓	✓
Hornberger[26]	✓	✓	✓	✓	✓
Klish [27]	✓	✓	✓	✓	✓
Knight [28]	✓	✓	✓	✓	✓
Malliti [18]	✓	X	X	✓	✓
Mathieu-Boue [29]	✓	✓	✓	✓	✓
Sweetenham [30]	✓	✓	✓	✓	✓
Tolley [20]	✓	✓	X	X	✓
Van Agthoven[31]	✓	✓	X	✓	✓
Wake[32]	✓	✓	X	✓	✓

4.2 Overview of company's economic evaluation

4.2.1 Description of company model

The model is a three-state Markov model, with the health states being defined as:

- "Progression free survival"
- "Progressed" in which patients have relapsed.
- "Death" which is an absorbing state.

Patients begin in the PFS state and at the end of each cycle (cycle length 1 month) can either stay within this health state or move to the progressed health state or death state. Once in the progressed health state patients either move to the death state or continue in the progressed health state. But once in the progressed health state they cannot return to PFS (see Figure 4.1). However, the progressed state has been adjusted (in terms of utility) to account for periods of PFS (see Table 21 of company submission).

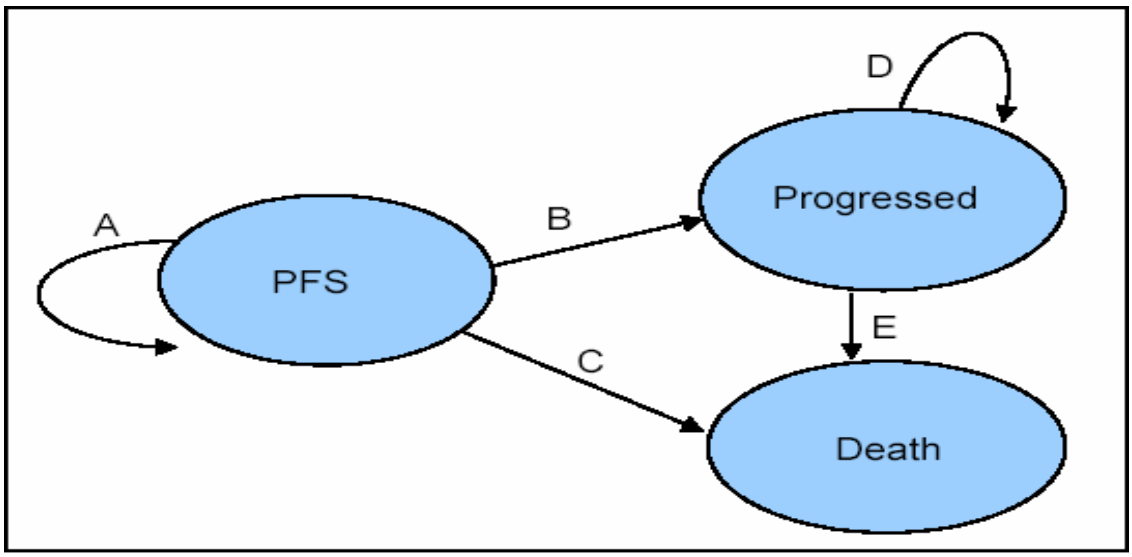


Figure 4.1: Structure of the Markov model (adapted from company submission)

Movement between health states is governed by transition probabilities (see Table 4.2). The probabilities applied to the PFS health state vary over time, but are generally similar between the two arms. The probabilities applied to the progressed health state are constant, and do not differ between the two arms.

The submitted model generates results for a cohort of patients with an initial age of 53, and makes no distinction between men and women.

Table 4.2: Model transition probabilities

Transition Probabilities	Value	Source
A From PFS to PFS	Range 0.9617-0.9998	Time dependent based upon log logistic extrapolation of PFS trial curves. Marcus[12]
B From PFS to Progressed	Range R-CVP 0.0042-0.018 Range CVP 0.0042-0.0387	Marcus[12]
C From PFS to Death	Range 0.0003-0.0041	Age-specific UK mortality www.mortality.org
D From Progressed to Progressed	0.9830	Scottish And Newcastle Lymphoma Group (SNLG) Vanguard database
E From Progressed to Death	0.0170	SNLG Vanguard database[6]

4.2.2 Health benefits

Health benefits within the model were estimated using the quality adjusted life year (QALY). QALYs encompass both gains in quality of life (utility), and survival differences (life years gained).

4.2.3 Utilities

Utility values were taken from a quality of life study (Oxford outcomes and quality of life study[6]) in which an EQ-5D dataset had been obtained for 215 patients. Fifty of the 215 patients were newly diagnosed and were therefore excluded from the analysis. The utility values were then grouped by disease stage and subsequently by model health states using a pooling approach (see Table 4.3).

Utility values were not assumed to change over time so that any patient is assumed to have the utility of ***CIC information removed*** during PFS regardless of initial age, or elapsed time.

Table 4.3: Utility values for each health state

Health states	N	Mean (SE)	Reference
Progression free survival	132	***CIC information removed***	Oxford outcomes quality of life study. Mean estimate based on responses from patients with partial response to therapy (n=39), remission/full response to therapy (n=66), and disease-free patients (n=27)
Progression	33	***CIC information removed***	Oxford outcomes quality of life study. Mean value based on 33 relapsed patients
Weighted Progression		***CIC information removed***	To allow for periods of remission the utility values were adjusted. See table 21 of company submission

4.2.4 Survival

Within the model survival is estimated according to progression free survival, and progressed survival. Progression free survival was estimated by fitting a log-logistic curve to the M39021 trial data. Survival in the progressed state was estimated by fitting an exponential curve to the Scotland and Newcastle Lymphoma Group (SNLG) registry data on survival from second line chemotherapy (see Figure 4.2). The SNLG database since 1994 has captured comprehensive treatment and outcomes data on more than 95% of lymphomas presenting in a population of 8.5 million across northern England and Scotland.[6]

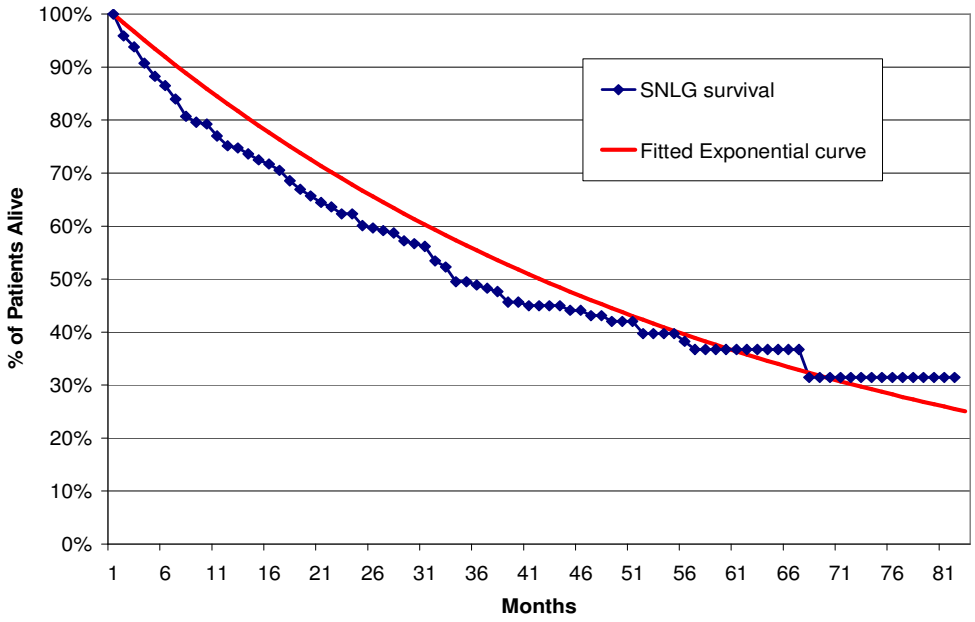


Figure 4.2: Survival in the progressed health state using an exponential curve

4.2.5 Resources and costs

In the model costs and resources are assigned according to health states (see Table 4.4). Patients in the PFS health state are costed at £32.33 per monthly cycle spent in remission, regardless of treatment. This cycle cost is based on what the company call "surveillance" costs, which is founded on the assumption of four oncology visits annually whilst in remission.

In addition, during the first monthly cycle spent in the PFS health state it is assumed that patients will incur the full costs of eight cycles of therapy. In the R-CVP arm this is £10,110.24, in the CVP arm this is £330.96. Also included during the first monthly cycle is an £800 administration cost for rituximab.

For patients in the progressed health state the monthly cycle cost is estimated at £193.33, irrespective of treatment arm. This value is taken from Tolley[20] and subsequently inflated to 2006 prices and adjusted to estimate the monthly cycle drug cost.

Table 4.4: Costs according to health states

Health states	Initial treatment costs (1st month only)	Monthly cost	Source
Progression free survival	Drug costs: R-CVP £10,110.24 CVP £330.96 Admin: R-CVP £800	Surveillance: £32.33	Initial treatment costs are based on 8 cycles of chemotherapy. The monthly costs are based on four annual oncology visits at a cost of £97 per visit, based on Edelman[19] and expert opinion.
Progression		Drug cost: £193.33	Estimated lifetime drug costs taken from Tolley[20] (£13,145), and uplifted to 2006 prices (£15,774). This value is subsequently divided by the expected lifetime survival of follicular lymphoma patients which the company estimate to be 6.8 years (£2,320 annually)

4.2.6 Discounting

Both health outcomes and costs were discounted by 3.5%, which is in line with current NICE guidance on the methods of technology appraisal.

4.2.7 Results

The results of the company model are shown in Table 4.5. In terms of cost per QALY the ICER of £8,290 is well below conventional 'willingness to pay' thresholds.

Table 4.5 : Results of base case using point estimates (discounted)

Timeframe	10 years	25 years
Total CVP Costs	**8,474**	**£9,977**
PFS Costs	1,143	£1,222
Progressed Costs	7,331	£8,755
Total R-CVP Costs	**18,195**	**£20,347**
PFS Costs	12,305	£12,540
Progressed Costs	5,891	£7,807
Incremental Cost	**9,721**	**£10,370**
Total CVP Life Years	**5.253**	**6.070**
PFS Life Years	2.093	2.296
Progressed Life Years	3.160	3.774
Total R-CVP Life Years	**6.133**	**7.566**
PFS Life Years	3.594	4.201
Progressed Life Years	2.539	3.365
Incremental Life Years	**1.501**	**1.497**
PFS Utility	***CIC information removed***	***CIC information removed***
Progressed Utility	***CIC information removed***	***CIC information removed***
Total CVP QALYs	**3.872**	**4.460**
PFS QALYs	1.685	1.848
Progressed QALYs	2.187	2.612
Total R-CVP QALYs	**4.650**	**5.711**
PFS QALYs	2.893	3.382
Progressed QALYs	1.757	2.329
Incremental QALYs	**0.779**	**1.251**
Cost per LYG	**11,047**	**£6,929**
Cost per QALY	**12,486**	**£8,290**

4.2.8 Sensitivity analysis

One way sensitivity analysis together with probabilistic sensitivity analysis (PSA) was conducted (Roche Submission, Page 92).[6] The results of one-way SA are shown in Table 4.6. As can be seen, the key issues are the time frame of the analysis and whether the incremental benefit of R-CVP compared to CVP extends beyond the trial.

Table 4.6: One-way sensitivity analysis included in company submission

Variables	Assumptions	Result company
Base case		£8,290
Monthly cost of PFS health state		
Low	-50%	£7,994
High	50%	£8,585
Monthly cost of progressed health state		
Low	-50%	£8,669
High	50%	£7,911
Utility of PFS health state		
Low	***CIC information removed***	£15,483
High	***CIC information removed***	£6,790
Utility of progressed health state		
Low	***CIC information removed***	£7,348
High	***CIC information removed***	£8,608
Mortality rate for progressed health state		
Low	-50%	£9,413
High	50%	£7,964
Drug administration cost of Rituximab		
Low	-50%	£7,970
High	50%	£8,610
Discount rate costs		
Low	1.5%	£8,478
High	6%	£8,132
Discount rate QALYs		
Low	1.5%	£6,885
High	6%	£10,226
Time horizon		
	10 years	£12,801
	5 years	£26,602
Parametric function		
Weibull parametric function for R-CVP and CVP PFS	25 year Time	£9,029
Incremental benefit		
No incremental benefit of R-CVP compared to CVP beyond trial follow-up	Equivalent PFS and OS after 42 months	£21,430

The results of the company's PSA suggest that the model is robust (see Table 4.7). Allowing parameters to vary according to a designated probability distribution did not significantly alter the ICER. The cost-effectiveness acceptability curve (see Figure

4.3) indicates that at a threshold of £30,000 there is 100% probability that R-CVP is cost-effective compared with CVP.

Table 4.7: Results of PSA

Timeframe	10 years	25 years
Total CVP Costs	**8,510**	**10,138**
PFS Costs	1,139	1,228
Progressed Costs	7,371	8,910
Total R-CVP Costs	**18,204**	**20,485**
PFS Costs	12,304	12,548
Progressed Costs	5,900	7,937
Incremental Cost	**9,694**	**10,347**
Total CVP Life Years	**5.278**	**6.164**
PFS Life Years	2.081	2.303
Progressed Life Years	3.197	3.862
Total R-CVP Life Years	**6.151**	**7.639**
PFS Life Years	3.592	4.199
Progressed Life Years	2.559	3.441
Incremental Life Years	**0.873**	**1.475**
PFS Utility	*CIC information removed*	*CIC information removed*
Progressed Utility	*CIC information removed*	*CIC information removed*
Total CVP QALYs	**3.635**	**4.237**
PFS QALYs	1.619	1.780
Progressed QALYs	2.016	2.457
Total R-CVP QALYs	**4.407**	**5.436**
PFS QALYs	2.794	3.247
Progressed QALYs	1.614	2.189
Incremental QALYs	**0.772**	**1.198**
Cost per LYG	**11,108**	**7,016**
Cost per QALY	**12,555**	**8,633**

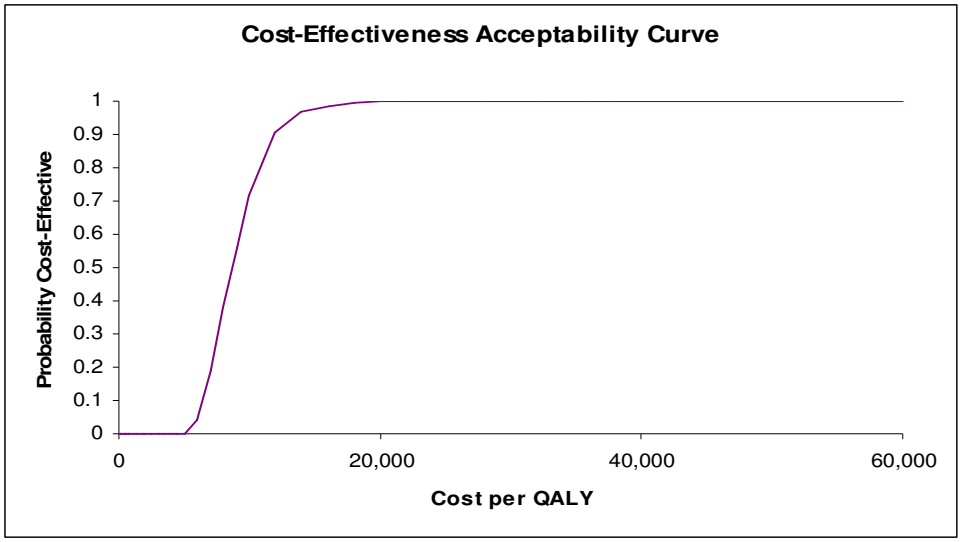


Figure 4.3: Cost-effectiveness acceptability curve for R-CVP versus CVP

4.2.9 Model validation reported within the submission

For validation purposes the company claims to have re-run the model using Treeage, and had similar results to using Excel. However the ERG was not supplied with a copy of the Treeage model and hence could not confirm this claim.

4.2.10 Budget impact analysis

Estimates of five year annual and cumulative budget impact of adding rituximab to CVP are provided in Table 32 in the company submission. However, the calculations do not include the administration costs of a rituximab infusion. The company submission states that the total incremental administration cost of R-CVP compared to CVP is assumed to be £800 per patient. In order to estimate the true budget impact of R-CVP compared to CVP, the administration costs should have been included. Table 4.8 estimates the five year annual budget impact of adding rituximab to CVP including the marginal administration costs of a rituximab infusion.

Table 4.8: Budget impact

Costs	Year 1	Year 2	Year 3	Year 4	Year 5
Number of stage III/IV follicular NHL patients *	1,525	1,537	1,537	1,546	1,552
CVP drug costs*	£504,714	£506,700	£508,686	£511,664	£513,650
Rituximab drug costs*	£15,418,116	£15,478,777	£15,539,439	£15,630,431	£15,691,092
Rituximab admin cost	£1,220,000	£1,224,800	£1,229,600	£1,236,800	£1,241,600
Budget impact of adding rituximab (including admin costs) to CVP	£16,133,402	£16,196,877	£16,260,353	£16,355,567	£16,419,042

* Values are taken from the company submission. Costs of 8 cycles of chemotherapy are estimated to be £10,110.24 for R-CVP, and £331 for CVP. NB Cost of R-CVP at the bottom of Table 31 of the company submission is incorrectly stated as £10,107. The ERG assume that this is a typographical error as it is not used in the model or the budget impact calculations.

4.3 Critique of company's economic evaluation

4.3.1 Model errors and design flaws

A number of errors have been identified in the submitted model and are discussed below. Some are relatively minor mistakes which can be readily corrected, but others raise questions about the design of the model and its reliability.

***Therapy costs**:* The manner of calculation of active therapy costs is simplistic and unduly conservative. A full eight cycles of treatment in either arm is applied in the first month to all patients, irrespective of their progression status, or indeed whether they are alive or dead. Clearly this must overstate costs for both arms, nor does this allow for early discontinuation of therapy due to adverse events or other non-clinical reasons. The ERG has corrected these errors in the assessment of the submitted model.

Life-years gained (LYG): Simple formula errors led to comparing accumulated life years after 25 years in the R-CVP arm with accumulated life years after 10 years in the CVP arm, thus seriously underestimating the PFS life-years gained. In addition, all results were found to relate to an additional month of both costs and outcomes beyond the 25 years stated.

Costs in the progressed health state: Although surveillance costs are included in the model for patients in the PFS health state (estimated as £32.33), no such costs are included for patients in the progressed health state. The ERG has subsequently corrected this within the model.

In addition, reliance on a single source[20] for the estimation of the average drug costs in the progressed health state means that the total costs in this health state may be underestimated. The submission fails to account for on-going routine care and monitoring costs.

None of the above errors has a significant effect upon the cost-effectiveness results; once they are corrected in the base case, cost per QALY decreases from £8,290 to £8,251, and the cost per LYG decreases from £6,929 to £6,897.

Mortality estimation: The adopted structure of the submitted model incorporates all-cause mortality in the general population as an implicit component of monthly progression risk. This is a basic flaw in design, since it is inevitable that at some point

the total number of patients progressing per month will be less than the number expected to die from general (non-lymphoma) causes. This anomaly leads to the inclusion of negative deaths from general causes from a certain age onwards, which artificially inflates the apparent total life years. In the base case results, this effect is not obvious, since for 53 year olds, negative deaths do not occur until more than 25 years have elapsed. However, if the initial age in the model were increased (e.g. 63 years of age) to reflect real world patients, this problem would arise at an earlier time point. This problem betrays a superficial appreciation of the limitations of Markov modelling, and of the importance of structuring such a model with death as the primary risk, and all other events as conditional.

A corollary of this observation is that it calls into question the applicability of the long-term projective models of PFS (e.g. log-logistic) if they are unable to generate results which are compatible with mortality risks in the general population. A more appropriate analysis would be to model progression and death within a competing risks framework, ideally distinguishing between non-Hodgkin's lymphoma deaths and all other causes of death. This would ensure that survival cannot be accidentally over-estimated when projected to the end of life. It has not been possible for the ERG to correct these errors in the model so the size of the effect on the cost/QALY ratio is unknown.

Costing incompatibility: A further error was found in the company's comparison of chlorambucil with R-CVP. The company state that they assume equivalent efficacy between chlorambucil and R-CVP, hence the only difference is the costs. Chlorambucil is costed at £84.27 for 8 cycles (rather than the £331 for CVP), and R-CVP drug administration costs are estimated at £1715 rather than £800. Making these changes in the model leads to an ICER of £9,219 rather than the £9,752 reported in the submission. This is only a minor matter and does not seriously bias the analysis, but does raise issues over model cross-checking and validation.

4.3.2 Key issues for economic evaluation

Progression free survival and overall survival: A strong implicit assumption within the submitted model is that estimated progression free survival gains can be equated with equivalent overall survival benefits. From our own reading of the clinical literature, there is little evidence available in follicular lymphoma to support this

hypothesis. The company's own submission states that there was no statistically significant overall survival benefit (demonstrated by the M39201 RCT), but a statistically significant benefit in terms of PFS. It may be that future longer term studies will not show an overall survival benefit for patients receiving R-CVP compared to CVP, or may show only a reduced benefit.

In other cancers, there is conflicting evidence on the correlation between PFS and OS. Colorectal cancer studies indicate that PFS is correlated with overall survival,[33, 34] but that each incremental month in PFS leads to only 0.68 month of additional OS. Evidence from ovarian cancer suggests that although progression free survival is improved, overall survival may not be affected.[35]

A recent study on chronic lymphocytic leukaemia (CLL) patients treated with rituximab and fludarabine versus fludarabine alone, showed that both progression free survival and overall survival did improve.[36] However, for follow-up periods of 2-4 years only 30-40% of the estimated PFS gain was translated into OS gain. This is a more comparable haematological cancer with a similar treatment regimen, and therefore supports the suspicion that it would not be appropriate to infer that PFS benefit automatically confers OS benefit.

Hence, the question of how much (if any) of the progression free survival (seen in the M39021 trial of NHL patients treated with rituximab and CVP versus CVP monotherapy) will translate into a survival gain remains unanswered. The submitted model does not address this issue, but assumes that the improvement in PFS automatically leads to a survival gain; this is because the mortality rates for progressed patients are identical for both arms. In the base case results this implies that 79% of PFS gain is translated into OS gain. Thus the gain in PFS is ameliorated only by differential mortality attrition as patients' progress at different times in the arms.

Age and sex: The submitted model generates results for a cohort of patients with an initial age of 53, and making no distinction between men and women. Using USA incidence rates for non-Hodgkin's lymphoma combined with the UK population structure for 2004 we are able to estimate the likely proportion of incident cases (see Table 4.9).

Table 4.9: Incidence rates for non-Hodgkin's lymphoma

Age-group	Males	Females	Combined
20-54	12%	7%	20%
55-64	11%	9%	19%
65-74	15%	12%	27%
75+	16%	18%	34%
Overall	54%	46%	100%

This suggests that the initial age of 53 used in the model is not a particularly representative age for patients receiving first-line therapy. Due to important differences in life expectancy by sex and advancing age it is important to consider these subgroups in the cost-effectiveness analysis.

Utility values: In the submitted model the utility values assigned to patients pre- and post-progression do not change over time regardless of a patient's age. Since advancing age is known to be associated with increasing co-morbidity and disability, it is very likely that utility values will show a general decrease over time. This will have the effect of reducing the calculated QALY gains especially for patients with extended survival. It is also a cause for concern that the calculations on which utility gains are based are founded largely on a small subset (n=33) of the EQ-5D data collected in Oxford. Given the non-linear nature of these data, the estimated standard error may give an over-optimistic assessment of the reliability of the estimated utility value for patients in the progressed health state.

Survival and costs in the progressed health state: The long-term survival of patients in the progressed health state is governed in the model by a single parameter (probability E in the model see Table 4.2), derived from the SNLG database involving 295 patients followed for 83 months. In Figure 12 of the company's submission the combined Kaplan-Meier plot is displayed together with a fitted exponential function used to model post-progression survival. The fit of this model to the data is particularly poor, which is surprising considering the great effort put into modelling alternative functional forms for PFS. A suitable alternative model would be the Weibull function, which is commonly compatible with long-term survival in incurable

cancers. The chart below shows how a Weibull model provides an excellent representation of the data.

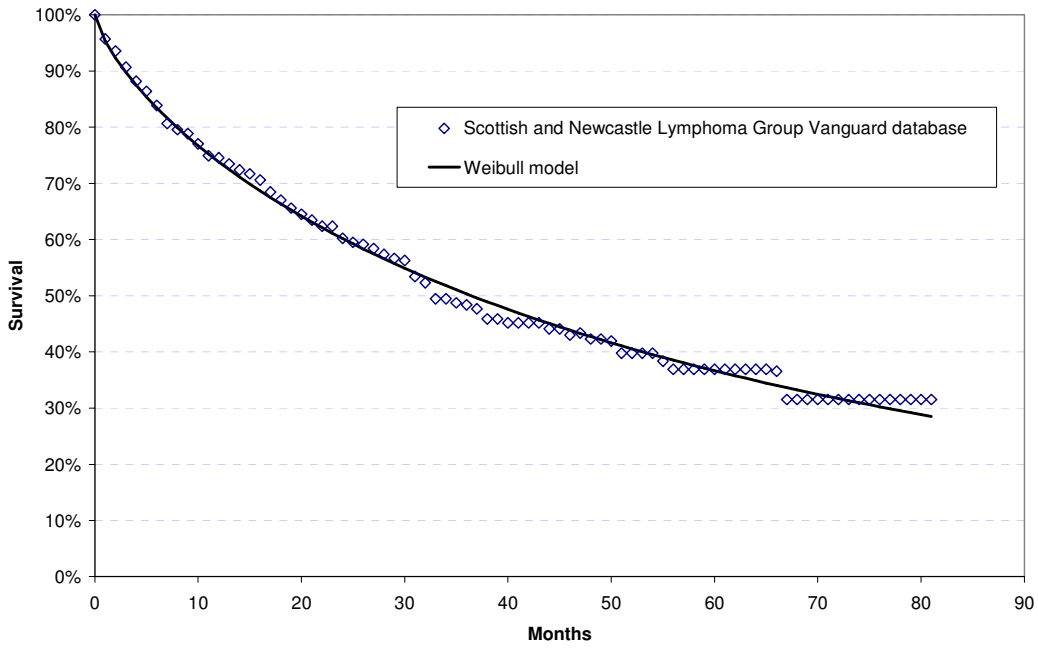


Figure 4: The long-term survival of patients in the progressed health state derived from the SNLG database and the plotted Weibell model

The exponential projection in submitted model yields a lifetime expected mean survival of 59.3 months, whereas the Weibull model projects a value of 71.6 months. This alteration has the effect of reducing the apparent survival benefit between R-CVP and CVP, and also reduces the incremental cost of R-CVP versus CVP. Consequently, the ICER is increased, but is still below the £30,000 threshold.

No information describing the characteristics of the SNLG patients used in the company submission is provided. This is of critical importance because the modelled population is so unrepresentative (by age group) of the normal incident population, implying that the mortality parameters in different parts of the model are almost certainly incompatible. It is not possible to correct the mortality rates applied to progressed patients for such age differences.

The costs of the progressed health state were based on Tolley's estimates of lifetime chemotherapy costs. These costs include first-line chemotherapy costs, which will therefore have been double counted in the model. Since this will inflate costs

disproportionately in the CVP arm it is likely that it will bias the analysis in favour of R-CVP. However, it is not possible to correct for this effect consistently in the model.

Adverse events: Adverse event costs were omitted completely from the submitted model, despite evidence within the company submission of increased serious adverse events in the R-CVP arm (see page 51 of company submission). Such SAEs could result in hospital admissions, which need to be costed accordingly in the economic analysis. Excluding the costs of such adverse events may bias the economic analysis in favour of R-CVP, but cannot easily be estimated without access to more detailed information from the clinical trial.

Comparators: Only one other comparator (chlorambucil) was compared with R-CVP. It would have been helpful if a wider range of potential comparators had been considered.

4.3.3 Economic results

In order to explore the likely impact of these issues on the size of the cost-effectiveness ratios within the model, the following modifications have been made:

- the three modelling errors described above (therapy costs, life-years gained and costs in the progressed health state) have been corrected

- a simple facility has been added to the model to allow adjustment of the proportion of PFS gain which results in OS gain, together with a corresponding adjustment of incremental costs

- the fitted Weibull model mortality rates for progressed patients has been substituted for the exponential rates in the submitted model.

With these changes implemented, the base case ICER becomes £9,015 per QALY gained, with about 64% of PFS gain resulting in OS gain. If no OS gain is obtained at all, the ICER becomes £20,593 per QALY gained. If 30% and 50% of PFS results in an OS gain, the ICER becomes £11,188 and £9,645 respectively.

It is clear that with older patients the results would be significantly worse, but it is not possible to estimate the size of this effect, due to the inherent flaws in the model design and assumed parameters.

4.3.4 Economic summary

The model submitted in support of the company submission is very basic in design. It suffers from several serious design flaws and some of the key parameter values are probably incompatible. The ERG attempted to rectify the identified errors and limitations of the model, none of which increased the ICER above the conventional threshold of £30,000. However, it was impossible to simultaneously correct all of the errors and limitations within the model, due to design flaws within the model as outlined in this report. Although the cost-effectiveness results obtained appear to be compelling in support of R-CVP compared to CVP, it could be argued that the results would not be so convincing for a more representative population.

5 Conclusions

The submitted clinical evidence includes one randomised controlled trial (RCT), M30921 study, comparing CVP chemotherapy alone with CVP in combination with rituximab, and involving a total study population of 322 patients with stage III or IV follicular lymphoma. The evidence from this trial suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the primary outcome of time to treatment failure and is reported as an increase from 7 months in patients receiving CVP to 27 months in patients in the R-CVP arm with a risk reduction of 66% (95% CI 55%-74%).

Other positive outcomes were measured for disease progression, overall tumour response, duration of response and time to new lymphoma treatment Overall survival was not estimable at 42 months and the 38% risk reduction had not reached statistical significance.

Adverse events are comparable between the two arms for the percentage of patients experiencing at least one adverse event, although the percentage experiencing an AE in the first 24 hours is greater for the R-CVP arm (51% vs. 71%). These are primarily represented by infusion related events. Similar numbers of patients in each arm experienced grade 3-4 haematological toxicity and infection except from those experiencing neutropenia (14.5% CVP vs. 24.1% R-CVP).

The submitted economic literature review included 15 studies, only eight of which actually met the inclusion criteria established for the review. None of these studies however compares R-CVP versus CVP.

The data extraction of the economic literature undertaken by the company was lacking in depth, and provided no quality assessment of the included studies. However, given the fact that these studies do not compare the same healthcare technologies as the company's own economic evaluation, this is of limited importance.

The model submitted in support of the company submission is very basic in design. It suffers from several serious design flaws and some of the key parameter values are probably incompatible. The ERG attempted to rectify the identified errors and limitations of the model, none of which increased the ICER above the conventional threshold of £30,000.

However, due to design flaws within the model as outlined in the report it was impossible to simultaneously correct all of the errors and limitations within the model. Although the cost-effectiveness results obtained appear to be compelling in support of R-CVP compared to CVP, for the trial population it could be argued that the results would not be so convincing for a more representative population.

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