Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

ERG Report

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Contents:

Tables:

Figures:

Abbreviations:

AE(s)	Adverse events
BSC	Best supportive care
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisolone
CHOP>O	CHOP followed by observation
CHOP>R	CHOP followed by rituximab maintenance
CI	Confidence interval
CR	Complete response
CVP	Cyclophosphamide, vincristine and prednisolone
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence review group
EMEA	European Medicines Evaluation Agency
FCM	Fludarabine, cyclophosphamide and mitoxantrone
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FMD	Fludarabine, mitoxantrone and dexamethasone
GLSG	German Low Grade Lymphoma Study Group
IPI	International Prognostic Index
ICER	Incremental cost-effectiveness ratio
K-M	Kaplan-Meier
MS	Manufacturer's submission
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Not reached
NSAE(s)	Non-serious adverse event(s)
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
R-CHOP	Rituximab, CHOP
R-CHOP>O	Rituximab, CHOP followed by observation
R-CHOP>R	Rituximab, CHOP followed by rituximab maintenance
RCT	Randomised controlled trial
R-CVP	Rituximab, CVP
SA	Sensitivity analysis
SAE(s)	Serious adverse event(s)
SMC	Scottish Medicines Consortium
SR	Systematic review
STA	Single technology appraisal
TA	Technology appraisal
UK	United Kingdom
USA	United States of America
VBA	Visual Basic for Application
WHO	World Health Organisation
WTP	Willingness to pay

Definition of terms:

Chemotherapy intolerant	A patient who can be expected to suffer unacceptable treatment toxicity from the cytotoxic options that remain
Chemotherapy refractory	A patient who achieves no remission or a very short remission after their last chemotherapy and for whom no further obvious cytotoxic options remain
Complete response	EORTC trial - Not defined but LEXCOR[1] criteria used GLSG-FCM trial - Elimination of all lymphoma manifestations for at least 4 weeks
EORTC trial	Used in ERG report as abbreviation for EORTC 20981 trial
Maintenance	Maintenance of remission status
Minor response	Not defined but used in GLSG-FCM trial
Overall response rate	The total of complete and partial responses
Overall survival	EORTC trial - Induction phase: Time from first randomisation to death (all cause) Maintenance phase: Time from second randomisation to death from any cause Patients still alive or lost to follow-up were censored at the last date they were known to be alive (last contact date) GLSG-FCM - Induction: Time from enrolment on induction phase to death Maintenance: Time from enrolment on maintenance phase to death
Partial response	EORTC trial - not defined but LEXCOR[1] criteria used GLSG-FCM - Reduction of disease manifestations by at least 50% for more than 4 weeks
Progression-free survival	EORTC trial - Induction phase: The interval between the date of the first randomisation to the date of disease progression/relapse or death, whichever occurred first Maintenance phase: The interval between the date of the second randomisation and the date of disease progression/relapse or death, whichever occurred first. Otherwise patients were censored at the date they were assessed for response
Progressive disease	EORTC trial - Not defined but LEXCOR[1] criteria used GLSG-FCM - Appearance of new nodal or extra-nodal manifestations or the enlargement of pre-existing lymphoma manifestations by more than 25%
Response duration	GLSG-FCM - End of successful therapy to documentation of progressive disease
Stable disease	Cancer that is not decreasing or increasing in scope or severity

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from Roche in support of the use of rituximab for the treatment of relapsed/refractory follicular lymphoma (FL). The manufacturer's submission (MS) considers two ways of using rituximab: firstly, in conjunction with cytotoxic chemotherapy in order to induce remission in relapsed FL; secondly, as maintenance therapy after successful induction of remission, regardless of the chemotherapy used to induce remission. The MS claims that there is no new evidence for the use of rituximab in adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Therefore the MS presents no new case for the use of rituximab in this patient population.

1.2 Summary of submitted clinical-effectiveness evidence

The MS provides clinical evidence from two randomized controlled trials (EORTC and GLSG-FCM). Both trials were included in the systematic review (SR) and compare the clinical effects of chemotherapy with or without rituximab in the induction of remission at first or second relapse and the clinical benefits of rituximab maintenance therapy versus the NHS current clinical practice of observation for FL patients. Both trials had two points of randomisation. The induction phases included 465 and 147 patients with relapsed FL in EORTC and GLSG-FCM trials respectively. The maintenance phases included 395 and 176 patients who had responded to induction therapy in EORTC and GLSG-FCM trials respectively. Only 113 patients in the GLSG-FCM trial who received maintenance therapy or observation were FL patients.

Both trials showed that in patients with relapsed FL the addition of rituximab to chemotherapy induction treatment increased overall response rates (ORR); 72.3% (CHOP) versus 85.1% (R-CHOP) in the EORTC trial and 70% (FCM) versus 94% (R-FCM) in the GLSG-FCM trial. Furthermore, rituximab maintenance therapy increased the median length of remission when compared to observation only. In the EORTC trial, median progression-free survival (PFS) was 14.9 months for those on observation compared to 51.5 months for those receiving rituximab. In the GLSG-FCM trial for FL patients who received R-FCM, median PFS in the observation group was 26 months and for those receiving rituximab median PFS was not reached.

Safety data from the two trials showed that whilst the majority of patients reported some adverse events (AEs), the number of patients withdrawing from treatment in the EORTC trial was low: 3% in each group at induction and 4% in the rituximab group at maintenance (rates were not reported for the GLSG-FCM trial). The most commonly reported AEs were blood/bone marrow toxicity, skin rashes and allergies.

1.3 Summary of submitted cost-effectiveness evidence

The manufacturer conducted a SR of the available cost-effectiveness evidence. However, this review was limited and not linked to the de novo economic evaluations described in the MS.

The MS presents the results of two sets of economic evaluations. The first compares the use of rituximab maintenance (following response to an induction therapy) versus observation only (no treatment until relapse). This is referred to as the maintenance 2-arm model. A three state transition model (progression free, progressive disease (PD) and death) is used to capture the costs and benefits of relapsed/refractory FL.

The second model compares the use of rituximab maintenance therapy with observation only for patients responding to chemotherapy with or without rituximab and tests whether the use of rituximab as an induction therapy in addition to maintenance therapy is cost effective. This is referred to as the induction plus maintenance 4-arm model. A five state transition model (progression free in the induction setting, progression free in the maintenance setting, progression free but not in the induction or maintenance setting, PD and death) captures the costs and benefits of relapsed/refractory FL.

Evidence from the EORTC trial is the principal source of clinical data used in the economic evaluations. A half cycle correction is applied in both models. Patients in the economic evaluation are followed through the health states in monthly cycles over a period of 30 years in order to capture the entire lifetime costs and effects of the population. Patients only exit the model due to death.

In the MS, the 2-arm model is used to demonstrate that maintenance therapy with rituximab when compared to observation is cost effective against commonly applied thresholds. The manufacturer reports an incremental cost-effectiveness ratio (ICER) of £7,721 per quality adjusted life year (QALY) gained for this comparison. In the MS, when subject to extensive univariate and probabilistic sensitivity analysis (PSA), this ICER is shown to be robust.

In the MS, the 4-arm economic model illustrates that the greatest clinical effectiveness is achieved by R-CHOP followed by rituximab maintenance (R-CHOP>R). The MS concludes that R-CHOP>R is cost effective when compared to the second most clinically effective intervention of CHOP induction followed by rituximab maintenance therapy (CHOP>R); the

estimated ICER is £16,749 per QALY gained. Again, in the MS, this ICER is shown to be robust.

In summary, the ERG agrees that the use of rituximab for the treatment of FL is probably cost effective, but cannot confidently recommend either or both single use strategies over the dual use strategy from the data available. The ERG requested additional information from the manufacturer to enable full assessment of the cost effectiveness evidence described in the MS. The manufacturer did not provide these data.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The MS includes supporting clinical data from two randomized controlled trials (RCTs) both of which closed early due to interim analyses showing a significant clinical benefit for rituximab treatment as induction and/or maintenance therapy before enrolment was complete.

The two economic models submitted by the manufacturer are implemented to a generally high standard, clearly presented and with a large amount of source information included to aid traceability. The layouts of the various elements of the models are generally logical, and the formulae employed are straightforward.

1.4.2 Weaknesses

The SR reported in the MS does not clearly specify the inclusion and exclusion criteria employed, which results in ambiguity regarding reasons for the exclusion of some trials. In addition, the MS fails to describe adequately the existing clinical evidence for the use of rituximab monotherapy in the treatment of relapsed FL.

The GLSG-FCM trial includes FL, mantle cell and lymphocytoid lymphoma patients. Evidence to support the use of rituximab as maintenance from the GLSG-FCM trial is inconclusive due to missing clinical data for FL patients only.

From the available clinical evidence, the ERG concludes that the maintenance 2-arm economic model is too simplistic and therefore the ERG concentrates on the results generated by the induction plus maintenance 4-arm model.

1.4.3 Areas of uncertainty

NICE has requested clarification of the July 2006 marketing authorization for rituximab. The questions raised are: does the 2006 European Medicines Evaluation Agency (EMEA) marketing authorization confer a single licence for the use of rituximab as maintenance in patients responding to induction therapy? Or, does it confer **two** separate licences for (i) the

use of rituximab as maintenance therapy for responding patients and (ii) the use of rituximab in combination with chemotherapy as induction therapy at first or second relapse?

The clinical effectiveness of R-CHOP induction in patients previously treated with rituximab cannot be assessed from this STA as patients in the EORTC trial are rituximab naïve at entry. In 2006, R-CVP was approved by NICE[2] as a first-line treatment for patients with FL. It is therefore unlikely that future patients with relapsed FL in the NHS in England and Wales will be rituximab naïve.

The ERG raised some concerns about the modelling of the survival data. The ERG was unable to overcome such concerns (e.g. by conducting PSA) as the manufacturer did not provide the requested additional information on the disposition of patients in the EORTC trial and the mean time spent in each segment of the treatment pathway.

1.5 Key issues

Clinical:

- The MS fails to distinguish the methods and results of the SR of rituximab monotherapy from the overall results
- Exclusion of rituximab naïve patients from EORTC means that the clinical effect of rituximab induction and maintenance on patients who have had previous rituximab therapy is uncertain
- NICE has requested clarification of the July 2006 EMEA rituximab marketing authorization

Economics:

- What is the most appropriate approach to the modelling of survival data?
- How should post-progression treatment costs be included in the model?
- Incomplete data from the manufacturer means that the necessary PSA could not be undertaken by the ERG and therefore a full assessment of the cost-effectiveness evidence presented by the manufacturer was not possible

2 BACKGROUND

2.1 Manufacturer's description of underlying health problem

The remit of the ERG is to comment on the clinical and cost-effectiveness evidence submitted to NICE as part of the STA process. Evidence has been submitted to NICE from Roche in support of the use of rituximab for the treatment of relapsed FL for two separate clinical uses: firstly, as an induction therapy in combination with chemotherapy and secondly as a maintenance therapy (following response to an induction therapy).

A summary of the context section of the MS describing the underlying health problem and treatment pathways is provided in Box 1 and Box 2.

For an overview of non-Hodgkin's lymphoma (NHL) treatment options, see Figure 6-1 in Appendix 7.1.

Box 1: Summary of the manufacturer's description of the underlying health problem

- FL represents 22% of a group of diseases known collectively as non-Hodgkin's lymphomas - cancers arising from the lymphoid cells of the immune system.
- Survival for patients with FL is prolonged. Different figures for median survival have been reported, but 8-10 years from diagnosis is typical.[3, 4] However, these are likely to be underestimates since there is good evidence from recent large population-based[5] and single institution studies[6, 7] that survival is improving.[8] This is probably as a consequence of improved treatment, especially the introduction of rituximab, which is the first drug treatment for this disease to demonstrate an ability to improve overall survival in randomized clinical trials.[9]
- Prognosis is partly determined by the extent of disease at diagnosis, which is usually described using the Ann-Arbor staging system.
- Other factors besides disease stage have been identified as having prognostic significance. Five of these were incorporated into the International Prognostic Index (IPI) which allows a composite IPI score to be calculated.[10] This has been shown to be highly predictive of long-term survival. Although the IPI was formulated for aggressive lymphomas it was also applied to more indolent forms of the disease, like follicular lymphoma. More recently, the FL Prognostic Index (FLIPI) has been devised specifically for this type of lymphoma.[11]
- Although the FLIPI is well accepted as having prognostic significance, it is not routinely used to guide treatment, which is generally determined by disease stage plus clinician and patient preference for a particular chemotherapy regimen.

Box 2: Summary of the manufacturer's description of treatment pathways

- Approximately 15% of patients present with early-stage which can be managed by regional radiotherapy with excellent results.
- Treatment of patients who present with stage III/IV disease[12] is shaped by several important considerations:-
  - Whether stage III/IV disease has already disseminated and systemic therapy is required.
  - Whether patients are experiencing troublesome symptoms. If not, then a watch and wait policy is normally adopted.
  - The main aim of treatment is induction of remission. The ideal treatment will induce a prolonged remission, with acceptable acute toxicity and no significant chronic toxicity to impair quality of life during disease remission.
- Remission induction is of great value to patients. A recent study[13] found that patients valued time free of disease progression substantially more than life with progressive disease.
- Response, particularly complete response, to induction chemotherapy has repeatedly been reported to predict for better long-term outcomes including prolonged overall survival.[14-16]
- Prolonged remission defers the diagnosis of relapse, which in cancer management generally has been shown to be extremely traumatic – typically more so than the initial diagnosis of cancer.[17]
- Typically, a patient will require several episodes of treatment during the decade or more that they live with their disease. With each successive treatment the chances of remission are lower and the duration of the remissions achieved, shorter.[14, 18]

2.1.1 Critique of manufacturer's description of the underlying health problem

The manufacturer's description of the underlying health problem is detailed and generally accurate. However, more details on the epidemiology of FL and a description of the grading system used in the diagnosis of FL may be useful to the appraisal committee and are provided below. For completeness, the ERG also comments on statements made in the MS that require further discussion.

Epidemiology

NHL represents about 3% of all cancers diagnosed in the United Kingdom (UK). In 2002 there were 9,443 people diagnosed with NHL in the UK[19] with an incidence of 16 per 100,000 in England and 15.6 per 100,000 in Wales. The overall rate is increasing at 3% to 4% per year, which is greater than would be expected from simply a combination of the effects of an ageing population plus improved diagnostic techniques.[20] Follicular lymphoma is the second most common type of NHL (22%) with a UK incidence of approximately 4 per 100,000[21] and a prevalence of about 40 per 100,000.[20]

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 World Health Organisation (WHO) classification grades I, II, IIIa or IIIb.[21] 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.[21]

Overall survival (OS)

The MS argues, using studies by Swenson et al[5] and Marcus and Haegenbeek,[9] that there is good evidence from recent large population-based and single institution studies[6, 7, 22] that survival of FL patients is improving. The MS suggests that this is probably a consequence of improved treatment, especially the introduction of rituximab. However, the study by Swenson et al[5] does not attribute improved survival to the introduction of antibody based regimens. They performed an analysis of survival data truncated at 1996; the year in which rituximab was licensed in the United States of America (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[5] suggest that the clinical course of FL has altered, which coincides with 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.

In addition, the Marcus and Haegenbeek[9] review does conclude that the addition of rituximab to chemotherapy regimens improves OS. However, this was in all patients with NHL not only FL and Marcus and Hagenbeek[9] suggest that this improvement may be due to the interaction of rituximab and interferon which all patients in the three relevant trials were given concomitantly.

Remission

The MS states that "remission induction is of great value to patients. A recent study[13] found that patients valued time free of disease progression substantially more than life with PD"(MS p.27). The ERG acknowledges that the Wild study[13] did indeed find that patients in remission had a higher utility score than those with PD. However, the ERG points out that this study did not address the issue of whether patients would prefer longer survival with PD over a reduced survival with disease remission. As the Wild study[13] is available in abstract format only, it is difficult to critique fully.

2.2 Critique of manufacturer's overview of current service provision

A summary of the manufacturer's overview of current service provision for the currently approved therapeutic indications for rituximab in this patient population, the expected role of rituximab and relevant guidelines are provided in Box 3 to Box 7.

Box 3: First-line treatment options in Stage III/IV disease

- There is no universally accepted gold-standard regimen or treatment sequence for the treatment of NHL.[23]
- Most regimens are based on alkylating agents with or without a corticosteroid.[23]
- Roche's recent market research indicates that alkylator therapy +/- corticosteroids still dominates first-line chemotherapy and that there is still diversity of choice in this area, with some clinicians opting to add in either fludarabine or doxorubicin.
- Chemotherapy plus rituximab is now accepted as the standard of care in the first-line setting including the UK where both NICE and the Scottish Medicines Consortium (SMC) have endorsed the clinical and cost effectiveness of rituximab plus CVP chemotherapy.

Box 4: Treatment options in Stage III/IV disease after relapse

- For patients relapsing after first-line treatment, re-induction therapy is indicated.
- There is no standard treatment at this point and treatment is largely guided by previous lines of therapy and patients' and doctors' preferences.
- For patients who experienced a prolonged remission (at least 6 months) after initial alkylator therapy, an attempt may be made to reinduce using the same regimen.
- Typically, by the time patients have relapsed twice they will have received three lines of treatment starting with an alkylator-based regimen without fludarabine or an anthracycline, then either CHOP (the predominant doxorubicin containing regimen) or a fludarabine-based regimen at second-line then CHOP or a fludarabine-based regimen (whichever has not been used before) at third-line.
- There is attrition at each relapse with only a minority of patients receiving fourth and subsequent-line treatment.[24]
- Because of extensive trial evidence that rituximab enhances the efficacy of chemotherapy there is significant use of rituximab in conjunction with chemotherapy used to induce second and subsequent remissions.
- Many patients eventually reach a point where further cytotoxic chemotherapy is not an option because they have become chemotherapy refractory or intolerant.
- NICE allows the use of the 4 x weekly dose schedule of rituximab for chemotherapy refractory and resistant patients.[20]
- There continues to be low level usage of rituximab monotherapy rising from 2% of first-line induction treatment to 10% of fourth-line induction (down from 1.3% and 52.6% at fourth-line in 2004).[24]

Box 5: Treatment options in Stage III/IV disease during remission (maintenance therapy)

- There are limited data that maintenance with cytotoxic chemotherapy can extend remissions but not overall survival.[25]
- However, the toxicity of maintenance chemotherapy is such that it is not used in clinical practice.
- Although there is evidence from a meta-analysis of randomized trials[26] that use of interferon alfa may prolong remissions when used post-induction, this too suffers from poor tolerability[22, 26-28] and it is not used for this purpose in the UK.
- Market research evidence suggests that at present the use of rituximab maintenance for patients in remission after induction treatment is minimal, though it is significant in Scotland where the SMC has endorsed the use of rituximab in this way.

Box 6: Rituximab

- Within the scope of this appraisal, three uses of rituximab in the treatment of relapsed FL are under consideration:
  - Administration in conjunction with standard induction chemotherapy to increase the frequency and durability of disease remissions. This usage is already a well established part of clinical practice within the UK (based on Market Research).[24]
  - Roche estimates that around half of patients in first or second relapse receive rituximab in conjunction with chemotherapy for remission induction.
  - Administration as a maintenance therapy to patients whose disease is in remission after cytotoxic chemotherapy (+/- rituximab) with a view to extending the duration of the remission, keeping patients free of disease symptoms and the need for toxic re-induction therapy for longer. Patients in remission currently receive no active antilymphoma therapy.
  - Administration in order to induce disease remission in relapsed patients for whom further chemotherapy is not an option by reason of their disease being judged chemotherapy resistant or the patient being deemed unable to tolerate further cytotoxic treatment. This use of rituximab, as allowed by NICE[20] is already part of the standard treatment pathway in relapsed FL for this small group of patients.

Box 7: Guidelines

- Within the UK there are no comprehensive management guidelines describing chemotherapy regimens for relapsed FL patients.
- NICE endorsed the use of rituximab for the last-line treatment of patients who are chemo-resistant or chemo-intolerant.[20]
- In November 2006 the SMC accepted rituximab for use within National Health Service (NHS) Scotland "as maintenance therapy for patients with relapsed/refractory FL responding to induction therapy with chemotherapy with or without rituximab".
- Globally there are many guidelines offering advice or guidance on different aspects of the treatment of follicular lymphoma. In many cases, such as the European Society for Medical Oncology Minimum Standards,[29] these cover only first-line treatment. However the National Cancer Institute in the USA does discuss the treatment of relapsed indolent lymphoma in its "physician data query" guidance, commenting on the value of rituximab used alone or in conjunction with chemotherapy as induction treatment and alone as maintenance therapy.[30]

The manufacturer's overview of current service provision is thorough and complete. The ERG is confident that all important issues have been discussed in the MS. No mention of the number of patients eligible for treatment with rituximab is made in the context section of the MS. However, in the budget impact section, the manufacturer estimates that within years one, two and three following a positive NICE endorsement, 268, 539 and 812 patients respectively will be treated with R-CHOP induction treatment at second-line. Of this patient pool, it is estimated that 183 patients in year one, 368 in year two and 555 in year three will go on to receive rituximab as a maintenance therapy.

3 CRITIQUE OF MANUFACTURER'S STATEMENT OF THE DECISION PROBLEM

The health care technology discussed in the MS is rituximab (MabThera) for the treatment of recurrent or refractory stage III or IV follicular (non-Hodgkin's) lymphoma.

The manufacturer presents clinical evidence to support the use of (i) rituximab plus chemotherapy (e.g. R-CHOP and R-FCM) in the induction phase and (ii) rituximab versus observation in the maintenance phase of treatment for FL patients. Only clinical evidence from the CHOP comparisons is used in the cost-effectiveness analyses.

The final scope issued by NICE and the manufacturer's statement of the decision problem are presented in Table 3-1.

Table 3-1: Final scope issued by NICE and manufacturer's statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the MS
Population	**For induction of remission** Adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy **For maintenance therapy** Adults with relapsed/refractory FL responding to induction therapy with chemotherapy with or without rituximab	**For induction of remission using rituximab monotherapy:** Adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy **For induction of remission using chemotherapy plus rituximab:** Adult patients with stage III-IV FL who are in relapse after previous chemotherapy, who are still suitable for chemotherapy **For maintenance therapy:** As scope. Responding meaning having achieved at least a partial response
Intervention	Rituximab as induction and as maintenance therapy	**For induction of remission in patients who are chemoresistant or in 2nd or subsequent relapse:** 4 weekly doses of rituximab alone **For induction of remission in relapsed FL patients in conjunction with chemotherapy:** 1 dose of rituximab with each chemotherapy cycle **For maintenance therapy**: 1 dose of rituximab every 3 months for 2 years
Comparator(s)	• Cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine), and prednisone (CHOP) • Fludarabine, as a single agent, or in combination with mitoxantrone and dexamethasone (FMD). • Cyclophosphamide, vincristine, and prednisone (CVP) • Chlorambucil • Best supportive care (BSC)	**For induction of remission using rituximab monotherapy:** BSC, other active treatment options having been exhausted. Chemotherapy would be an option according to Marketing Authorization but not within existing NICE guidance. With no new data this guidance should stand **Rituximab + chemotherapy for induction of remission in relapsed FL:** Chemotherapy alone. As will be explained in Section 4.1, CHOP and, fludarabine-containing chemotherapy are the dominant cytototoxic regimens used in relapsed FL and are the most appropriate comparators. These will be considered. Chlorambucil, BSC alone and CVP are little used in this setting and therefore will not be considered as comparators **Rituximab maintenance:** • No treatment (patients in remission currently get no treatment until relapse)

	Final scope issued by NICE	Decision problem addressed in the MS
Outcomes	The outcome measures to be considered include: • Partial/complete response rates • Duration of response/remission • Health related quality of life • Event-free survival • Time to new anti-lymphoma treatment/ time to progression • Overall survival • Adverse effects of treatment, including serious infection/ immunologic competence	The endpoints appropriate to rituximab use vary according to the way in which rituximab is employed: **All situations** • Health related quality of life (seldom collected in lymphoma interventional studies and dealt with by reference to general evidence of the quality of life benefit to patients of being in remission and off chemotherapy) • Adverse events of treatment **Rituximab maintenance after induction** • Event-free survival/progression-free survival/disease-free survival • Time to new anti-lymphoma treatment/progression • Overall survival **R-CHOP as part of induction therapy prior to maintenance** • Response rate • Event-free survival/progression-free survival/disease-free survival • Overall survival
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The time horizon for the economic evaluation should be based on life expectancy Costs should be considered from a NHS and Personal Social Services perspective	(i) Cost effectiveness of rituximab as a maintenance therapy only (following response to an induction therapy) compared to observation only (no treatment until relapse). (ii) Use of rituximab as an induction therapy in addition to maintenance therapy is cost effective The economic evaluation will estimate costs and consequences over the remaining life-time of each patient from the NHS perspective

3.1 Licensed indications

The MS explores the use of rituximab in relapsed/refractory FL patients. Within this remit, the MS considers that rituximab can be used as follows: (i) as monotherapy and (ii) as induction therapy (in combination with chemotherapy) followed by rituximab maintenance therapy.

3.1.1 Monotherapy (original indication)

In June 1998, rituximab received a pan-European marketing authorization for "the treatment of patients with stage III/IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy".[31] This indication for rituximab was appraised by NICE[20] which

concluded that the use of rituximab monotherapy for the induction of remission should be restricted to patients considered chemotherapy intolerant or chemotherapy refractory, i.e. for those patients in whom conventional cytotoxic chemotherapy was not an option.

Although the term monotherapy is not used in the EMEA licence or in the NICE guidance, it is assumed by all parties that the authorization is for rituximab monotherapy as there is no mention of its use in combination with any other drug.

The MS states that "…there is no new information in this area since its original review by NICE in Technology Appraisal (TA) 37. As such, no new case will be presented and the existing guidance should stand" (MS p.14). The manufacturer states that it will demonstrate, on the basis of a SR of the literature, that no new evidence on this use of rituximab in this setting is available. However, the ERG concludes that insufficient attention to detail has been paid by the manufacturer in their descriptions of the methods and results of the SR of the clinical evidence available regarding the use or rituximab monotherapy.

3.1.2 Induction followed by maintenance (new indication)

In July 2006, a pan-European marketing authorization was granted for "the use of rituximab as maintenance therapy for patients with relapsed/refractory FL responding to induction therapy with chemotherapy with or without MabThera."

The MS states that this marketing authorization covers two ways of using rituximab. Firstly, that rituximab can be used in conjunction with cytotoxic chemotherapy in order to induce remission in relapsed FL. Secondly, that rituximab can be used as maintenance therapy after successful induction of remission, regardless of the chemotherapy regimen used to induce remission (any chemotherapy regimen, with or without rituximab).

According to the EMEA scientific document on rituximab,[32] the manufacturer applied for an extension of the original indication to maintenance treatment of patients with FL responding to induction therapy. The application was based on the European Organisation for Research and Treatment of Cancer trial (EORTC 20981[33] - from now on referred to as the EORTC trial) comparing maintenance therapy with observation in the treatment of FL. The MS includes clinical and economic evidence to support the use of rituximab as maintenance treatment for patients with FL. However, the MS also includes clinical evidence from the EORTC trial to support the use of rituximab in combination with chemotherapy for FL patients at first or second relapse.

Currently there is no stand alone EMEA marketing authorization that recommends the use of rituximab in combination with chemotherapy for induction in patients at first or subsequent relapse after chemotherapy. The only mention of rituximab in combination with

chemotherapy for relapsed/refractory patients is that included in the July 2006 EMEA marketing authorization (i.e. rituximab is indicated as maintenance therapy for patients with relapsed/refractory FL responding to induction therapy with *chemotherapy with or without rituximab*).

Clarification is required. Does the 2006 EMEA marketing authorization confer a single licence for the use of rituximab as maintenance in patients responding to induction therapy? Or, does it confer two separate licences for (i) the use of rituximab as maintenance therapy for responding patients and (ii) the use of rituximab in combination with chemotherapy as induction therapy at first or second relapse?

The MS presents clinical and economic evidence to support the latter view that the 2006 EMEA marketing authorization covers two ways of using rituximab in relapsed FL. The ERG critiques all of the clinical and economic evidence presented by the manufacturer.

3.2 Population and interventions

The MS and the final scope issued by NICE differ in their descriptions of the relevant patient populations and therefore treatments. Differences are primarily due to the interpretation of the current EMEA marketing authorizations and have been discussed previously.

However, there is an additional issue related to the patient population in the EORTC trial that must be discussed. It is important to note that the inclusion criteria for the EORTC trial stated that only rituximab naïve patients could participate in the trial. At present, some patients with relapsed FL are rituximab naïve. However, as rituximab was approved by NICE[2] as a first-line treatment for FL in 2006 it is likely that "…in future most patients with FL will be treated with MabThera as primary treatment hence the number of patients fulfilling the criteria at relapse will decrease dramatically".[32] The MS discusses this difference in the trial and clinical practice populations in England and Wales (MS p.86-87).

As a result, the ERG notes that the clinical effectiveness of rituximab as induction and/or maintenance for patients who received rituximab as part of their first-line treatment is therefore currently unknown. Similar concerns were debated by the EMEA[32] who concluded that "a MabThera-containing first-line regimen given in median 3-4 years before disease progression would not impact on the efficacy of maintenance therapy at relapse, especially if the patient responds to re-induction therapy with MabThera and chemotherapy. It was recognized that the clinical evidence for maintenance treatment in the setting of MabThera pre-treated patients is very limited and the exact magnitude of the treatment effect of maintenance is not known. However, it was considered that the large efficacy benefit with MabThera maintenance therapy resulting in improved OS in relapsed FL with a favourable

safety profile demonstrated in various clinical settings strongly supports maintenance usage in the entire group of relapsed patients, including MabThera pre-treated patients".

3.3 Comparators

The manufacturer describes the comparators in relation to the relevant patient group and/or phase of treatment. The final scope issued by NICE describes a single list of comparators.

3.3.1 Rituximab as monotherapy

For the induction of remission using rituximab monotherapy, the MS cites BSC as a comparator. No new evidence is presented by the manufacturer for this comparison.

3.3.2 Rituximab as induction therapy

The MS and the final scope issued by NICE appear to differ in their descriptions of valid comparator therapies for induction of remission in relapsed FL. The manufacturer rejects the use of chlorambucil, BSC and CVP as comparators. The manufacturer argues that these three regimens are little used in this setting and are therefore not considered as comparators.

The key induction phase comparisons in the MS are R-CHOP versus CHOP and R-FCM versus FCM. The MS substantiates the comparison of R-CHOP and CHOP by stating that "CHOP is a predominant second-line treatment… no notable variations in clinical outcomes have been observed across the current alternative second-line induction therapies… therefore CHOP can be viewed as a reliable clinical proxy for other potential alternative comparators in the induction setting" (MS p.95). This view was confirmed to the ERG during discussions with clinical experts. However, the ERG notes that no clinical evidence is referenced in the main body of the MS to support the conclusion that second-line therapies are likely to be equally efficacious. Indeed, the MS states that using CHOP as a comparator is a conservative approach as the ORR for FL patients in the GLSG-FCM study[34, 35] are higher than those in the EORTC trial. The MS includes relevant clinical evidence from this trial (R-FCM versus FCM) to further support their argument for the use of rituximab in conjunction with chemotherapy to induce remissions in relapsed FL.

To summarise, for induction, the comparisons of interest to the manufacturer and extensively described in the MS are rituximab in combination with CHOP (R-CHOP) versus CHOP and rituximab in combination with FCM (R-FCM) versus FCM.

3.3.3 Maintenance therapy

In the maintenance phase, the manufacturer presents clinical evidence for rituximab compared with observation as is usual in current clinical practice.

3.4 Clinical outcomes

The manufacturer describes the outcomes of interest in relation to the relevant patient group and/or phase of treatment reflecting the single list of outcomes identified in the final scope.

The relevant outcomes used to measure clinical effectiveness in the induction and maintenance phases include: partial response (PR) and CR rates, duration of response/remission, health related quality of life, EFS, time to new anti-lymphoma treatment/time to progression, OS and AEs of treatment.

3.5 Economics

The MS generates two separate sets of cost-effectiveness results. Firstly, the cost effectiveness of rituximab as a maintenance therapy only (following response to an induction therapy) is compared to observation only (no treatment until relapse). Secondly, the cost effectiveness of rituximab as a maintenance therapy in addition to induction therapy is described.

The manufacturer's statement of the decision problem appropriately measures the cost effectiveness of rituximab in terms of incremental cost per QALY gained. The comparisons of interest in the economic evaluation section are CHOP based; for example in the 2-arm model, rituximab is compared with observation after prior CHOP +/- rituximab; for example in the 4-arm model, R-CHOP>R is compared with CHOP>R. The manufacturer's economic evaluations estimate costs and benefits over the remaining life time of each patient from the perspective of the NHS.

3.6 Summary

The manufacturer's statement of the decision problem does not wholly reflect the final scope issued by NICE. However, the ERG is confident that the manufacturer's statement of the decision problem identifies and describes the key points required of a single technology appraisal in this disease area. The main weakness of the statement of the decision problem is that the manufacturer does not explicitly report the results of the SR for rituximab monotherapy. Finally, the ERG notes that the relevance of much of the clinical and economic evidence submitted by the manufacturer is dependent on the way in which the 2006 EMEA marketing authorization is interpreted.

4 CLINICAL EFFECTIVENESS

The MS includes a SR of the clinical evidence available to assess the efficacy and safety of rituximab for the treatment of patients with relapsed/refractory FL, both as induction to remission and maintenance of remission. The MS also states that they will "demonstrate, on the basis of a SR of literature, that no new evidence has accrued on the use of rituximab monotherapy for the treatment of patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy (TA37)"[20] (MS p.10). However, the MS only describes the methods and results of a single SR. The ERG assumes that this single SR was designed to incorporate searches for all uses of rituximab in relapsed/refractory FL.

Key aspects of the methodological quality of the manufacturer's review of the clinical literature were assessed based on an accepted quality assessment tool[36] and the results are summarised in Table.

Table: Quality assessment of the clinical-effectiveness review

Quality assessment checklist item	Yes/No
Did the review address a clearly focused research question?	Yes
Was the search strategy adequate? (i.e. did the reviewers identify all relevant studies?)	No
Are the inclusion/exclusion criteria specified?	No
Did the review include the right type of studies?	Yes
Is there a statement of completeness from the manufacturer?	No
Did the reviewers assess the quality of the included studies?	Yes
Was the method of data extraction reported?	No
Were appropriate measures of outcomes used?	Partially
If the results of the studies have been combined, was it reasonable to do so?	N/A
Are appropriate subgroup analyses presented?	Yes
Are the main results of the review reported? (e.g. numerical results included with the CIs)	Yes
Are issues of generalisability addressed?	Yes

N/A =not applicable

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

Seven electronic databases were searched (Medline, Medline in process, Embase, Embase alerts, Biosys, Blood online, The Cochrane Library controlled trials database) covering the period 01/01/2000 to April/May 2007. The manufacturer also reviewed its original EMEA submission for additional relevant information.

All relevant databases were searched and, after clarification from the manufacturer, comprehensive and appropriate search strategies were provided to the ERG in order to make the searches reproducible.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion and exclusion criteria used in the study selection were not explicitly stated in the MS. However, a flow diagram of study selection shows reasons for exclusion of articles (Figure 4-1). The manufacturer does not state whether or not the inclusion/exclusion criteria used were predefined or how criteria were applied.

Figure 4-1: CONSORT flow chart for study selection process for SR

Publications identified	
Medline, EmBase, EmBase Alerts	58
ASH Abstracts via Biosys	55
Medline in process	9
Cochrane	32
EMEA submission	1
Total	155

Publications excluded on 1st screen (all RCTs versus rituximab in relapsed follicular/indolent lymphoma)	**No. excluded**
Based on title	41
Based on abstract	81
Based on publication	10
Publications excluded at 2nd stage as "irrelevant" to decision problem	
Based on abstract	10
Total publications excluded	**142**

Reasons for exclusion	**No. excluded (1st stage)**	**No. excluded (2nd stage)**
Duplicates	15	0
No rituximab used	6	0
Not Follicular lymphoma	5	0
Not relapsed patients	6	0
No non-rituximab arm	12	1
Not RCT	82	0
No clinical data	6	0
Unlicensed indication	0	2
Irrelevant comparator	0	7
Totals	**132**	**10**

Total included:
13 publications from 2 studies (includes 1 not identified during formal search) and 1 study report

4.1.3 What studies were included in the submission and what were excluded?

The MS presents 24 references for clinical papers from 5 trials (MS p.37, Table 4) that were examined in stage 2 of the inclusion process. Three of these trials (10 papers) were excluded due to non-licensed indication, no non-rituximab and inappropriate comparator. In the text there is also reference to a further study[37] that was excluded due to the use of non-licensed rituximab *maintenance* in a non-approved indication.

The MS notes that two RCTs[37, 38] excluded during the above process concerned the use of rituximab maintenance after induction of remission with rituximab *monotherapy*. Both these trials were excluded because they used non-licensed rituximab maintenance schedules in a non-approved indication.

In conclusion the MS identifies 13 publications and a clinical study report from two relevant clinical trials, EORTC and GLSG-FCM. Despite unclear information in the MS describing the exclusion and inclusion criteria used in the SR, the ERG is confident that all relevant trials have been identified by the manufacturer. The characteristics of these trials are shown in Table 4-1 and Table 4-2.

Both the EORTC and GLSG-FCM trials were open-label and included two phases; firstly, patients were randomized to induction of remission with chemotherapy treatment with or without rituximab and secondly, responders were randomized to maintenance of remission with either rituximab or observation only. Both trials were international studies but only the EORTC included UK treatment centres. Furthermore, whilst the EORTC trial only recruited patients with FL, the GLSG-FCM trial recruited patients with all types of indolent NHL including FL, mantle cell lymphoma and other subtypes of indolent NHL. It is important to note that the inclusion criteria for the EORTC trial stated that only rituximab naïve patients could participate in the trial. At present, some patients with relapsed/refractory FL are rituximab naïve. However, as rituximab was approved by NICE[2] as a first-line treatment for FL in 2006 it is likely that "…in future most patients with FL will be treated with MabThera as primary treatment hence the number of patients fulfilling the criteria at relapse will decrease dramatically".[32] The generalisability of the EORTC trial results is therefore uncertain.

4.1.4 Details of any relevant studies that were not included in the submission?

The ERG is confident that no relevant publicly available studies have been excluded from the MS.

4.1.5 Description and critique of manufacturers approach to validity assessment

The MS provides completed validity assessments for the two included trials; no details on who conducted the validity assessment or how it was conducted are detailed. Both trials are considered to be high quality trials although it is noted both were open-label trials and it is unclear from the published papers[33-35, 39-47] whether assessors were aware of treatment allocation. The MS also highlights that the GLSG-FCM trial did not use an intention to treat

Table 4-1: Characteristics of EORTC trial

Study Name	Study intervention(s), comparator(s), drug, dose(s) and follow-up	Study design, location and enrolment	Study inclusion criteria	Study exclusion criteria	Study outcomes
EORTC 20981 Van Oers MHJ *et al 2002*[39] Van Oers, MHJ *et al 2004*[40] Van Oers MHJ *et al 2005*[41] **Van Oers MHJ *et al 2006*[33]** **Roche Study Report 1016350 December 2005**[48]	**Induction treatment N=466** **R-CHOP**: **(N=234)** Cyclophosphamide 750 mg/m^2 IV Day 1, doxorubicin 50 mg/m^2 IV Day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) IV Day 1; rituximab 375 mg/m^2 as a slow IV infusion Day 1, prednisolone 100 mg orally, Days 1 to 5 every 21 days. **CHOP (N=231)**: As R-CHOP without rituximab **Maintenance treatment**: **N= 395** **Rituximab (N=167)** Rituximab 375 mg/m^2 as a slow IV infusion once every 3 months for 8 doses (24 months) or until disease progression. **Observation (N=234)**	Open label randomized phase III trial Patients randomized to induction with 6 cycles of CHOP+/-R. Patients achieving PR/CR after 6 cycles randomized to 2 years of maintenance with rituximab or observation. International study (130 centres) including UK 37 UK study centres. Enrolment between: November 1998 and April 2004	**Induction phase** • Ann Arbor Stage III or IV FL • Relapsed disease after a maximum of one or two adequate non-anthracycline containing chemotherapy regimens • No prior treatment with anthracyclines, mitoxantrone or rituximab • Circulating tumour cells < 10 x 10^9/L • Remission to at least one of the prior chemotherapy regimens (modified in June 2000 to include patients with stable disease as their best prior response) • Response duration of 3 months or more to one prior chemotherapy (modified in June 2000 to at least 4 weeks) • CD20 positive FL according to the REAL classification • At least one bidimensionally measurable lesion • Age 18 years of age or older • WHO Performance status 0, 1, or 2 • Patient had given written informed consent (which covered both phases of the study) and was capable of and willing to meet the schedule of hospital appointments required by the study. **Maintenance phase** • Complete or partial remission (CR or PR) of at least 4 weeks duration after the last cycle of CHOP+/-R • For patients receiving rituximab during remission induction: no rituximab-related toxicity necessitating stopping rituximab. • Time interval since last cycle of CHOP+/-rituximab 4-8 weeks. • IgG levels <6g/L (reduced to 3g/L in June 2000) • No active infection.	**Induction phase** • Severe cardiac disease • Serum creatinine, BUN, alkaline phosphates or bilirubin =/> 2.5 times the upper limit of normal, unless clearly related to lymphoma • Pregnancy • Prior malignancy, except non-melanomatous skin cancers, cervical carcinoma *in situ* and cancers cured by surgical resection > 5 years ago. • HIV positivity • Uncontrolled asthma • IgG levels <6g/L (reduced to 3g/L in June 2000) • Prior stem cell transplantation • Planned peripheral blood stem cell collection using *chemotherapy* for mobilisation. **Maintenance phase** • Non stated	• Last tumour response rate (LEXCOR criteria) • Progression-free survival • Overall survival • Event-free survival • Time to new anti-lymphoma treatment or death • Disease-free survival • All AEs regardless of causality occurring during or up to 30 days after the last treatment cycle/observation period.

*N.B. Papers in bold are the key papers from which information was taken in the MS. BUN= **blood urea nitrogen** IgG= **Immunoglobulin G***

Table 4-2: Characteristics of GLSG-FCM trial

Study Name	Study intervention(s), comparator(s), drug, dose(s) and follow-up	Study design, location and enrolment	Study inclusion criteria	Study exclusion criteria	Study outcomes
GLSG-FCM Dreyling M et al 2003[42] Dreyling M et al. 2006[43] Dreyling M et al 2006b[43] Forstpointer R et al 2002[44] **Forstpointer et al. 2004[34]** **Forstpointer et al. 2006[35]** Hiddemann W et al 2001[45] Hiddemann W et al. 2003[46] Hiddemann W et al **2005[47]**	**Induction treatment N=147** **R-FCM (N=71)** Fludarabine 25 mg/m^2 IV Days 1-3, cyclophosphamide 200 mg/m^2 IV Days 1-3, mitoxantrone 8 mg/m^2 IV Day 1, rituximab 375 mg/m^2 as a short IV infusion Day -1 every 28 days. **FCM (N=66)** As R-FCM but without rituximab **Maintenance rituximab N=319** [1] Rituximab 375 mg/m^2 as a short IV infusion weekly x 4 at 3 months and 6 months after completion of induction therapy (total 8 doses).	Open label randomized phase III trial Patients randomized to induction with 4 cycles of FCM chemotherapy+/-R Patients achieving PR/CR after induction randomized to 8 further doses of rituximab delivered as 4 week blocks 3 months and 6 months after completion of induction International, multi centre trial, mainly conducted in Germany. No UK study centres. Enrolment between: November 1998 and June 2001[35]	**Induction phase** ***Inclusion:*** • Relapsed or refractory follicular, mantle cell or lymphocytoid lymphoma, with histology centrally confirmed • Not responding to or relapsing after at least 1 preceding chemotherapy regimen **Maintenance phase** ***Inclusion*** CR or PR after FCM+/R during induction phase	**Induction phase** ***Exclusion:*** • Pregnancy • Breast-feeding • Patients of child-bearing potential not using reliable contraception •	• Response rate (International working group criteria)[49] • Risk of relapse • Event-free survival • Time to progression • Overall survival • AEs (National Cancer Information Center Common Toxicity Criteria)

N.B. Papers in bold are the key papers from which information was taken in the MS. ***[1]An additional 172 patients who received R-FCM induction therapy after closure of the randomized induction phase were randomized in the maintenance phase***

analysis as stated, but rather 19 patients were excluded due to inadequate documentation or were withdrawn between randomisation and delivery of study treatment. Also, analysis of the clinical evidence from the GLSG-FCM maintenance phase is limited as it is unclear how many patients completed the maintenance treatment. The table of validity assessment provided in the MS is included in Appendix 7.2.

4.1.6 Description and critique of manufacturer's outcome selection

Table 4-3 shows the primary, secondary and exploratory outcomes as identified in the MS, for the two included trials.

EORTC

Specific definitions of each of the outcomes are provided by the manufacturer. In the induction phase, the primary endpoint is ORR, the secondary endpoints are event-free survival (EFS) and OS; survival outcomes are measured as time from first randomisation. The role of PFS in the MS is unclear; on p.55 it is not mentioned in the list of endpoints, on p.58 it is listed as an exploratory endpoint and on p.64 it is described as a secondary endpoint. Inspection of the protocol outlines EFS as a secondary outcome for the evaluation of induction therapy. However, EFS is not reported in the summary table of results on p.64. It is unclear from the MS why PFS is used instead of EFS.

In the maintenance phase, the primary endpoint is PFS and the secondary endpoint is OS; both are measured as time from second randomisation.

Outcomes were evaluated by physical examination, haematology and chemistry, CT scans and bone marrow biopsies where indicated. The outcomes were then evaluated according to the Lymphoma expert's confirmation of response (LEXCOR[1]) criteria.

GLSG-FCM

As stated by the manufacturer "…very limited data are available on study GLSG-FCM" (MS p.57). This also extends to descriptions of clinical outcomes. The manufacturer then states that outcomes are limited to response rates and risk of relapse (MS p.57); however, the MS tabulates results for response rates, PFS, OS and two year survival.

Outcomes were evaluated by physical examination, ultrasound of the abdomen, and CT scans of previously involved areas; where complete remission was indicated bone marrow biopsies were taken.[35] Outcomes were then assessed according to the International Working Group criteria.[49]

Table 4-3: Outcomes used in EORTC and GSLG-FCM trials

		Induction phase	Maintenance phase
EORTC	*Primary endpoint*	Last tumour response rate	Progression-free survival
	Secondary endpoints	Overall survival	Overall survival
		Event-free survival (not reported)	
	Exploratory endpoints	Progression-free survival	Time to new anti-lymphoma treatment or death
			Disease-free survival
	Safety in both phases	All AEs regardless of causality occurring during or up to 30 days after the last treatment cycle/observation period.	
GLSG-FCM	*Endpoints*	Response rate	
		Risk of relapse	
		Event-free survival	
		Time to progression	
		Overall survival	
	Safety in both phases	AEs (National Cancer Information Center Common Toxicity Criteria)	

4.1.7 Describe and critique the statistical approach used

The MS includes a thorough description of the statistical approaches used in the EORTC trial and the GLSG-FCM trial.

EORTC

The EORTC trial used a chi-square test for trend to examine response rates, with a significance threshold of P<0.001, with early stopping allowed if this threshold was crossed. For the secondary endpoints of EFS, OS and the exploratory endpoint PFS, a log-rank test using a two-sided alpha level of 5% was used. Kaplan-Meier (K-M) curves were produced to graphically display the unadjusted difference between the treatment arms. Results were presented as risk ratios with 95% confidence intervals (CIs) reported. In the maintenance phase, the primary endpoint of PFS was based on a log-rank test stratified according to induction treatment; secondary and exploratory endpoints were unstratified. For OS in the maintenance phase, an unstratified log-rank test using a two-sided alpha level of 5% was used for the primary analysis and secondary analyses were done by the Cox regression analysis and the results presented as risk ratios including 95% CIs.

Interim analyses were permitted after 50, 200, 400 and 600 patients were evaluable. The first interim analysis was conducted after 275 patients had been included in the induction phase. The second interim analysis was conducted after 461 patients had been included in the induction phase. This analysis demonstrated a significant difference between the two treatment arms above the threshold outlined to stop recruitment to the induction phase. Recruitment was stopped and, as protocol amendments were in the process of being produced, a third interim analysis was conducted that showed a significant benefit of rituximab maintenance therapy. The trial was therefore closed early.

The statistical approaches used in trial EORTC are generally appropriate. However, it is unclear as to why a significance threshold of $P<0.001$ was used instead of $P<0.05$ as is usually used when Haybittle-Peto's rule is applied. Furthermore, the trial protocol outlines that secondary analyses in the maintenance phase of the trial will use Cox regression analysis with adjustment for stratification factors and other potential prognostic factors and that the secondary endpoint of OS will be analysed with a log-rank test, stratified for the same factors as PFS. In the MS all analyses of secondary outcomes were unstratified; the reason for this deviation from the protocol is unclear. Finally, EFS results are not reported.

Whilst the EORTC trial allows comparison of the four alternative treatment strategies contained within the trial, as depicted by the 4-arm economic model, the trial was not powered or designed for this specific purpose.

GLSG-FCM

The GLSG-FCM trial used a 1-sided triangular sequential test with a significance level of 0.05, for both the induction and maintenance phases. Exploratory analyses were performed for histological subgroups, the PFS from the start of therapy and OS. The Fisher test was used for analyses of binary responses and the log-rank test and univariate Cox regression for time-censored analyses.

The statistical analyses performed in the GLSG-FCM trial appear to be appropriate. However, only limited results are available for FL patients.

4.1.8 Summary statement

The SR was adequately conducted by the manufacturer. The two trials included in the SR are of good quality and the primary outcome measures reported in the MS are considered to be appropriate. As specific clinical results for the FL patients in the GLSG-FCM trial are not fully reported in the published papers,[34, 35, 42-47] the value of the trial results is therefore limited, particularly for patients in the maintenance phase, as they are not focussed on the patient population of interest in this STA.

4.1.9 Summary of submitted clinical evidence

The two relevant RCTs included in the manufacturer's SR are the EORTC and GSLG-FCM trials. Both trials are phase III, multi-centre, randomized, open-label trials designed to evaluate the efficacy and safety of: (i) rituximab in combination with chemotherapy in inducing a remission in FL and (ii) rituximab as maintenance therapy for FL patients.

EORTC

In the induction phase of the EORTC trial, 474 patients were randomized (9 of whom were excluded due to missing consent forms) to either receive rituximab in combination with CHOP (R-CHOP, N=234) or CHOP alone (CHOP, N=231). 209 patients from the R-CHOP group and 186 patients from the CHOP group completed the prescribed six cycles of treatment.

Patients achieving a CR or PR to induction treatment of at least four weeks duration, after the last cycle of treatment, were approved to be enrolled on the maintenance phase of the trial and were randomized to either receive rituximab once every three months for eight doses (24 months) or until disease progression or to receive no further treatment until disease progression, as in normal clinical practice. A total of 334 of 366 responding patients were randomized in the maintenance phase, 145 from the original CHOP group and 189 patients from the R-CHOP group. Of the 167 patients randomized to rituximab maintenance, 56 withdrew before the end of the study; of the 167 patients randomized to observation, 91 patients withdrew before the end of the study.

GLSG-FCM

As highlighted by the manufacturer, the flow of patients in the GLSG-FCM trial is complicated due to patients having different types of indolent NHL, a change in protocol mid way through the induction phase which meant that all patients after June 2001 received R-FCM due to the superior clinical effectiveness of the regimen, and the unevaluable status of some patients.

In the GSLG-FCM trial, 319 patients were enrolled into the trial between November 1998 and April 2005. In June 2001, randomisation was halted after the enrolment of 147 patients as the applied 1-sided sequential test revealed a significant advantage for R-FCM over FCM alone; all subsequent patients received R-FCM. Seventy-two of the 147 randomized patients had FL. Due to incomplete documentation 10 patients were withdrawn from the study and not included in analyses. These 10 patients included 7 patients with FL thereby resulting in 65 evaluable patients with FL. At the end of the induction phase of the GLSG-FCM trial, patients

(randomized and non-randomized) achieving a CR or PR were eligible for randomisation in the maintenance phase.

One hundred and ninety-five patients were randomized to rituximab maintenance or observation only. Again, randomisation was stopped after statistical analyses showed a significant advantage for the rituximab maintenance arm. Of the 195 patients randomized, 113 patients had FL. The MS reports results for 105 FL patients in the maintenance phase.

4.1.10 Summary of clinical results

Data presented in this report have been primarily extracted from the MS (dated September 2005); however, some data were extracted from the primary published peer-reviewed clinical papers.[33-35] Additional information was provided by the manufacturer in clarification of questions raised by the ERG.

Details of baseline characteristics of patients in the two trials are presented in Table 4-4 and Table 4-5.

Table 4-4: Characteristics of patients randomized between CHOP and R-CHOP induction and between rituximab observation and maintenance in the EORTC trial

Characteristic	Induction Phase			Maintenance Phase*		
	CHOP N=231	R-CHOP N=234	All N=465	Obs N= 167	Maint N=167	All
Gender						
Male	118 (51%)	107 (46%)	225 (48%)	83 (50%)	78 (47%)	161 (48%)
Female	113 (49%)	127 (54%)	240 (52%)	84 (50%)	89 (53%)	173 (52%)
Age						
Median	54.0	54.0	54.0	55.0	53.0	54.0
Range	27-78	26-80	26-80	27-80	29-76	27-80
Ann Arbor stage						
I	1 (<1%)	4 (2%)	5 (1%)	3 (2%)	2 (1%)	5 (1%)
II	1 (<1%)	2 (<1%	3 (<1%)	2 (1%)	-	2 (<1%)
III	74 (32%)	73 (31%)	147 (32%)	56 (34%)	57 (34%)	113 (34%)
IV	155 (67%)	155 (66%)	310 (67%)	106 (63%)	108 (65%)	214 (64%)
Bulky disease						
No	200 (90%)	194 (85%)	394 (87%)	146 (88%)	143 (89%)	289 (89%)
Yes	22 (10%)	35 (15%)	57 (13%)	19 (12%)	18 (11%)	37 (11%)
WHO Performance status						
0	135 (58%)	134 (57%)	269 (58%)	99 (59%)	100 (60%)	199 (60%)
1	79 (34%)	84 (36%)	163 (35%)	61 (37%)	58 (35%)	119 (36%)
2	17 (7%)	15 (6%)	32 (7%)	7 (4%)	9 (5%)	16 (5%)
3	-	1 (<1%)	1 (<1%)	-	-	-
B-symptoms present						
No	168 (73%)	174 (74%)	342 (74%)	128 (77%)	125 (75%)	253 (76%)
Yes	62 (27%)	60 (26%)	122 (26%)	39 (23%)	41 (25%)	80 (24%)
Bone marrow involvement						
No	85 (39%)	96 (42%)	181 (41%)	74 (45%)	58 (36%)	132 (41%)
Yes	131 (61%)	132 (58%)	263 (59%)	89 (55%)	102 (64%)	191 (59%)
FLIPI prognostic score (derived)						
0	1 (<1%)	3 (1%)	4 (<1%)	3 (2%)	1 (<1%)	4 (1%)
1	67 (30%)	63 (28%)	130 (29%)	45 (28%)	56 (35%)	101 (31%)
2	73 (33%)	74 (33%)	147 (33%)	51 (32%)	56 (35%)	107 (33%)
3	52 (23%)	60 (27%)	112 (25%)	45 (28%)	40 (25%)	85 (26%)
4	28 (13%)	23 (10%)	51 (11%)	14 (9%)	9 (6%)	23 (7%)
5	3 (1%)	1 (<1%)	4 (<1%)	2 (1%)	-	2 (<1%)
Extra nodal disease sites						
0-1	219 (95%)	220 (94%)	439 (94%)	155 (93%)	161 (96%)	316 (95%)
>1	12 (5%)	14 (6%)	26 (6%)	12 (7%)	6 (4%)	18 (5%)
Number of prior chemotherapies						
1	189 (82%)	183 (78%)	372 (80%)	137 (82%)	138 (83%)	275 (82%)
2	41 (18%)	50 (21%)	91 (20%)	30 (18%)	29 (17%)	59 (18%)
3	1 (<1%)	1 (<1%)	2 (<1%)	-	-	-
Best response to prior therapy						
CR	72 (31%)	76 (32%)	148 (32%)	52 (31%)	62 (37%)	114 (34%)
PR	120 (52%)	120 (51%)	240 (52%)	86 (51%)	86 (51%)	172 (51%)
NC	26 (11%)	23 (10%)	49 (11%)	22 (13%)	11 (7%)	33 (10%)
PD	13 (6%)	15 (6%)	28 (6%)	7 (4%)	8 (5%)	15 (4%)
Time from initial diagnosis[1]						
<=2 years	48	50				
>2 years	52	50				

*FLIPI, Follicular Lymphoma International Prognostic Index; NC, no change; Obs, Observation; Maint, maintenance, * Characteristics recorded at time of study entry not at time of randomisation to maintenance/observation. [1]Taken from paper*

Table 4-5: Characteristics of patients with relapsed follicular lymphoma entered into the induction and maintenance phases of study GLSG-FCM

Characteristic	Induction		Maintenance	
	n=65*		n= 105**	
	FCM n=30	R-FCM n=35	Obs n=53	Maint n=52
Age				
Median	59.5	60	61	52[1]
Range	35-77	42-80	35-80	41-78
Gender, no. (%)				
Male	13 (43)	16 (46)	27 (51)	22 (42)
Female	17 (57)	19 (54)	26 (49)	30 (58)
No. of prior therapies, %				
1	53	66	73	67
2	30	23	17	27
More than 2	17	11	9	6
Previous PBCT, %	13	9	4	8
Remission to prior therapy %	90	86	89	94
Extranodal involvement, %				
Bone marrow	55	49	52	43
Liver	4	9	6	0
GI tract	0	9	4	2
Spleen	23	20	27	20
B-symptoms, %	30	29	28	21
LDH elevated, %	17	23	20	20
Initial therapy, no. (%)				
FCM	NA	NA	13 (25)	11 (21)
R-FCM	NA	NA	40 (75)	41 (79)

**Assessable patients **Intent-to-treat population, NA, not applicable; Obs, Observation; Maint, maintenance.* [1] *59 in paper*[35]

Information from both trials shows that, in general, patient characteristics are comparable with similar proportions of males and females and similar proportions of patients with B-symptoms. However, patients in trial GLSG-FCM are slightly older than those in the EORTC trial and have had more previous therapies (e.g. 17% of patients had received three prior therapies compared to only 1% of patients in the EORTC trial). This suggests that patients in the GLSG-FCM may have had FL for a longer time than patients in the EORTC trial or have been treated less aggressively.

Table 4-6: Results from the induction and maintenance phases of the EORTC trial

		CHOP N=231	R-CHOP N=234	p-value	Risk reduction (95% CI)
Induction	**Primary**				
	ORR	72.30%	85.10%	<0.0001	-
	CR	15.60%	29.50%	0.0001	-
	PR	56.70%	55.60%	Non-sig	-
	SD[1]	10.40%	5.60%	-	-
	PD[1]	9.50%	2.60%	-	-
	Secondary				
	Median OS (months)	NR	NR	0.0508	32% (0%-54%)
	Median PFS	20.2	33.1	0.0003	35% (not reported)
	Three year OS	71.90%	82.5%	0.096	26% (not reported)
	Death				
	Toxicity/other[1]	0.90%	0.40%	-	-
	Non-assessable[1]	6.90%	6.40%	-	-
		Observation	**Rituximab**	**p-value (Log-Rank)**	**Risk reduction (95% CI)**
Maintenance	**Primary**				
	Median PFS (months)	14.9	51.5	<0.0001	60% (not reported)
	CHOP induction	11.6	42.2	<0.0001	70% (not reported)
	R-CHOP induction	23	51.8	0.0043	46% (not reported)
	CR after induction	14.3	52.8	0.0008	64% (33-81%)
	PR after induction	14.3	37.8	<0.0001	54% (33-69%)
	Risk of death	Reduction of 48%		0.011	-
		Observation	**Rituximab**	**p-value**	**Hazard ratio (95% CI)**
	Secondary (3 years OS)				
	Overall	77.10%	85.10%	0.011[1]	0.52 (not reported)
	CHOP induction	-	-	0.0743	0.498 (0.228-1.088)
	R-CHOP induction	-	-	0.0483	0.438 (0.188-1.101)

NR=not reached, 1Results taken from paper (Van Oers, 2006)[33]

Table 4-7: Results from the induction and maintenance phases GSLG-FCM trial for FL patients

		FCM	R-FCM	p-value
Induction	**No. evaluable**	**N=30**	**N=35**	
	Primary (response rates)			
	Complete response	23%	40%	-
	Partial response	47%	54%	-
	Minor response	7%	0%	-
	Stable disease	7%	0%	-
	Progressive disease	17%	3%	-
	Death	0%	3%	-
	Complete response + partial response	70%	94%	0.011
	Secondary			
	Median PFS (months)	21	NR	0.0139
	Median OS (months)	NR	NR	-
	2 year survival	70%	90%	0.0943
	Subgroup analyses (ORR) for all patients [1]			
	<2 prior therapies	71%	82%	-
	>=2 prior therapies	41%	74%	-
	Refractoriness against proceeding therapy	20%	62%	-
Maintenance (All patients)		**Observation**	**Rituximab**	**p-value (Log-Rank)**
	Median duration of response (months) after R-FCM induction (n=81)	17	NR	<0.001
	Three year OS	57%	77%	0.1

NR=not reached, [1]Taken from paper Forstpointner, 2006[35]

4.1.11 Induction therapy

EORTC

The primary outcome in the EORTC trial was ORR to treatment. In the CHOP arm 72.3% of patients attained a response; 15.6% a CR and 56.7% a PR. A higher percentage of patients in the R-CHOP arm showed a response to treatment (85.1%) with 29.5% achieving a CR and 55.6% a PR. The differences in ORR and CR were significantly different between the two arms with P<0.0001. As no difference was found between the proportions of patients achieving a PR, the difference in ORRs is entirely due to the number of patients achieving a CR in each arm. The most recently published analysis[33] also reports the rates of patients with stable disease, PD and death (Table 4-6).

The secondary outcome for the induction phase of the EORTC trial was median OS. However, median OS was not reached at the end of the trial. An exploratory outcome of median PFS in the induction phase showed a significant difference between the two arms (P=0.0003) with patients receiving CHOP having a PFS of 20.2 months and those receiving R-CHOP a PFS of 33.1 months (Table 4-6) at a median follow up of 39.4 months.

GLSG-FCM

The following primary and secondary outcome results are for FL patients only.

The primary outcome in the GLSG-FCM trial was also ORR. Again there was a significant difference between the two arms of the trial; 70% of patients receiving FCM responded to treatment compared to 94% of patients receiving R-FCM. A CR was achieved by 23% of patients receiving FCM and 40% of patients receiving R-FCM. A PR was achieved by 47% of patients in the FCM arm and 54% of patients in the R-FCM arm.

The secondary outcomes for GLSG-FCM were: median PFS, median OS and 2 year survival rates. Median PFS was not reached in the R-FCM group but was achieved in the FCM group (21 months). Median OS was not reached in either group and there was no statistical difference in 2 year survival between the two groups (Table 4-7).

For all trial patients, subgroup analyses were conducted to investigate the effect of R-FCM induction in patients who had received two or fewer prior treatments and those who had had more than two prior treatments. The results are shown in Table 4-7 but no P values are reported. Overall RR was also investigated for the subgroup of patients who had proved refractory to proceeding therapy; again P values are not reported.[35]

Both trials show that the addition of rituximab to chemotherapy increases the proportion of patients achieving a positive response to treatment; this is wholly due to a higher proportion of patients achieving a CR.

4.1.12 Maintenance therapy

EORTC

The second phase of the EORTC trial was designed to investigate the effect of rituximab treatment in maintaining a patient's remission. The control arm was observation only as usual clinical practice is no active treatment. Results of the maintenance phase of the trial are shown in Table 4-6. At the data cut off (December 2004) there was a median follow up of 33.3 months from the second randomization and 41 patients were still in the study.[33]

Of the 167 patients randomized to receive rituximab maintenance therapy, 61 (37%) had either progressed/relapsed or died at the point of data cut off compared to 103 patients (62%) in the observation group. The length of PFS for the rituximab group was nearly three times that of the observation group (51.5 months versus 14.9 months respectively) corresponding to a relative risk reduction of 60% (95% CIs not available). Figures for the three year OS showed 85.1% versus 77.1% of patients, treated with rituximab and observation respectively, were alive at three years (Table 4-6).

Due to the different induction treatments (CHOP and R-CHOP) received by the patients prior to second randomization in the maintenance phase of the trial, subgroup analyses were conducted for median PFS. However, it cannot be assumed with certainty that the clinical effects of maintenance rituximab on CHOP and R-CHOP patients will be exactly the same. The results of the subgroup analyses are therefore very important. These analyses show that all groups, regardless of induction therapy, significantly benefited from receiving rituximab in the maintenance phase (Table 4-6).

GLSG-FCM

The second phase of the GLSG-FCM trial investigated the effect of rituximab treatment in maintaining a patient's remission. As with the EORTC trial, the control arm was observation only. One hundred and sixty-seven of the 195 randomized patients were evaluable. After a median observation time of 26 months the median duration of response was not reached in patients treated with rituximab and was an estimated median of 17 months in the observation group. Of these 176 patients only 81 had FL and had also received R-FCM; in this patient population there was a significantly increased duration of response in the rituximab group compared with in the observation group (not reached in the rituximab group and an estimated 26 months in the observation group).

Overall, the three year OS was 57% for patients in the observation group and 77% in the rituximab group, this difference was not statistically different. Details on the OS of patients with FL were not reported separately from the overall trial population.

The ERG agrees with the manufacturer that "for the maintenance phase, it is unclear from published information how many patients finished the maintenance treatment" (MS p.52). The lack of reported results for FL patients in the GLSG-FCM trial is problematic and prevents meaningful interpretation of the clinical evidence available for the effectiveness of rituximab in the maintenance of remission.

4.1.13 Safety

EORTC

Results of the safety analysis of the EORTC trial are shown in Table 4-8 for both the induction and maintenance phases. In the induction phase, although the majority of patients in both arms reported AEs, they only resulted in 3% of patients in each arm withdrawing from the study. As reported in the MS, AEs that were experienced by at least 5% or more of patients receiving R-CHOP compared with those receiving CHOP included alopecia, rash/itch, other AEs, infections, allergies and neutropenia. Grade 3 and 4 AEs were experienced by 67% and 79% of patients (CHOP and R-CHOP respectively), with blood and

bone marrow toxicity being particularly dominant. Skin reactions and allergies, likely to be indicative of an infusion reaction, were reported in 17 cases in the CHOP group and 28 cases in the R-CHOP group.

In the maintenance period of the trial, patients receiving rituximab experienced more AEs than patients in the observation arm (90% versus 78% respectively). However, as shown in Table 4-8 these were mainly reported in the first three months of the maintenance period with 38% and 50% of patients receiving observation and rituximab respectively reporting AEs in the final three month period of the trial.

As with the induction phase of the trial, AEs affecting blood and bone marrow were higher in the rituximab group. Cardiovascular, infection, neurologic and gastrointestinal AEs were also more frequently reported in patients receiving rituximab compared to those in the observation group. In comparison, patients in the observation arm reported more neurological AEs and flu-like symptoms than those receiving rituximab.

The manufacturer commented that, when comparing the rates of AEs in patients assigned to maintenance rituximab or observation, two factors should be considered due to their possible bias against the rituximab group. Firstly, AE data are not collected after progression of disease and, as those on observation progress earlier, AE data are collected for this group for a shorter period. Secondly, as the studies were open-label this may result in under-reporting by health care professionals of non-serious adverse events (NSAEs) in the observation group. Finally, though not biasing either group, it is important to note that the maintenance period starts immediately after patients have completed induction chemotherapy and therefore many AEs will be related to chemotherapy and common to both groups. To illustrate this possibility, the MS includes details of the rates of AEs in the first and the eighth 3 month periods. Only 4% of patients receiving rituximab withdrew from treatment due to the AEs.

The ERG agrees that a shorter period of data collection of AEs was undertaken for the observation group but does not agree that the studies being open-label would necessarily result in bias against rituximab. A difficulty with open-label trials is that bias of reported AEs may occur, however this bias could possibly be in favour of rituximab, with AEs experienced by patients receiving rituximab being under reported compared to those in the observation group.

Table 4-8: Safety results for the induction and maintenance phases of the EORTC trial

		CHOP N=222 N (%)	R-CHOP N=234 N (%)
Induction	**All adverse events**	223 (98%)	233 (100%)
	Grade 3 and 4 adverse events	152 (67%)	185 (79%)
	Toxicity-related study withdrawals	6 (3%)	8 (3%)
	Deaths during induction therapy	2 (<1%)*	1 (<1%)**
	Grade 3 or 4 AEs experienced by ≥4% of R-CHOP group		
	Blood and bone marrow toxicity	(47%)	(55%)
	Skin reactions***	17[1](7%)	31[1] (14%)
	Allergies	0 (0%)	8 (4%)
Maintenance		**Observation N=166 N (%)**	**Rituximab N=166 N (%)**
	All adverse events	130 (78%)	149 (90%)
	First 3 month observation period	102 (62%)	119 (72%)
	Eighth 3 month observation period	61 (37%)	83 (50%)
	Treatment-related adverse events	91 (55%)	128 (77%)
	Toxicity related withdrawals	NA	6 (4%)
	Grade 3/4 adverse events (patients)	38 (23%)	61 (37%)
	Total number of adverse events	54	85
	Blood/bone marrow	12 (7)	22 (13)
	Cardiovascular	9 (5)	11 (7)
	Infection	3 (2)	17 (10)[2]
	Neurologic	9 (5)	7 (4)
	Gastrointestinal	5 (3)	10 (6)
	Flu-like symptoms	8 (5)	2 (1)
	Skin	2 (1)	3 (2)
	Bone	1 (<1)	3 (2)
	Pulmonary	-	1 (<1)
	Cancer related symptoms	1 (<1)	1 (<1)
	Genito-urinary	1 (<1)	1 (<1)
	Other	-	2 (1)
	Allergy	-	1 (<1)
	Coagulation	1 (<1)	-
	Endocrine	1 (<1)	-
	Hepatic	-	1 (<1)
	Metabolic	1 (<1)	-
	Weight	-	1 (<1)
	Deaths (not related to treatment)	3 (2%)	4 (2%)
	Deaths (related to treatment)	NA	0 (0%)

**1 sepsis, 1 respiratory distress syndrome **pneumonia ***No Grade 4 reported, [1]Taken from paper, [2]sig at P=0.009*

GLSG-FCM

Safety data from trial GLSG-FCM is reported in the key papers for all patients in the trial and not just those patients with FL. As the MS states, the addition of rituximab to FCM was well tolerated with reported AEs being predominantly asymptomatic lymphopenia (myelosupression and granulocytopenia). Forstpointer (2004)[34] reports that patients receiving rituximab in addition to FCM experienced lymphocotopenia significantly more frequently than those receiving FCM alone (P=0.006). Details of AEs experienced are shown in Table 4-9. Side effects related to the infusion of rituximab were observed in 8% of patients receiving rituximab as maintenance, and were mostly mild to moderate.[35]

As the AEs events most predominantly reported by patients receiving rituximab involved bone marrow/blood and infections, these are discussed in further detail in the MS alongside infusion reactions. The MS suggests that the higher incidence of blood and bone marrow AEs is due to residual toxicity from induction therapy and gradually resolves regardless of ongoing rituximab therapy. This is supported by the reduction of these AEs in the later months of therapy (Table 4-8). With regard to infection, the MS stresses that whilst infections were more commonly experienced by patients receiving rituximab maintenance therapy than those in the observation group they only resulted in four patients in the EORTC trial withdrawing from treatment. No patients in the GLSG-FCM trial reported serious or life threatening infections.

Finally, infusion reactions to rituximab are a known complication of rituximab therapy. However, as the MS states, the rates of infusion reactions in the two trials shown here are lower than those reported in trials where rituximab has been used as a monotherapy in the treatment of relapsed indolent lymphoma (unreferenced in the MS). The MS provides three possible explanations for the low frequency and modest severity of infusion reactions in the two trials. Firstly, as patients on CHOP induction receive high doses of steroids they may be less susceptible to infusion reactions; secondly, severe infusion reactions are more common in patients with high tumour burden and as all patients had received cytotoxic chemotherapy from the start of their rituximab therapy, their tumour bulk is likely to have reduced quickly. Finally, the majority of patients had received rituximab in the induction phase of the trial and infusion reactions are known to reduce with frequency of treatment.

Evidence from the trials included in the MS demonstrates that the AEs reported by patients in both studies were generally mild to moderate, generally did not significantly differ between the two groups and rarely resulted in withdrawal from the study.

Table 4-9: Safety results for the induction and maintenance phases of the GLSG-FCM trial

		FCM		R-FCM	
		Grades 1+2 %	Grades 3+4 %	Grades 1+2 %	Grades 3+4 %
Induction	Allergy	0.8	0	3.5	0.3
	Chill	0.5	0	5.7	0
	Exantheme	3.5	0	2.8	0
	Headache	2.2	0	5.3	0.3
	Granulocytes	14.3	40.6	18.7	39.6
	Haemoglobin	39.4	5.3	44.7	5.9
	Lymphocytes	3.9	39.4	10.3	51.2
	Thombocytes	33.3	11.3	30.8	11.7
	Leukocytes	16.9	55.6	23.5	53.6
	Infection	6.6	1.8	6.3	1.4
	Fever	2.3	0.5	1.1	1.1
	Nausea/vomiting	22.1	0	17.8	1.1
	Mucostitis	3.4	0	4.5	0.3
	Diahorea	0.5	0.5	3.9	0.6
	Cardiac dysfunction	0	0.9	0.3	0
	Neutotoxicity	1.1	0.1	0.8	0.2
	Liver	3.1	0	5.2	0
	Lactate dehydrogenase	6.2	0	6.3	0.3
	Alopecia	10.7	7.1	10.5	3.7
		Observation %		**Maintenance %**	
		Grades 1+2	Grades 3+4	Grades 1+2	Grades 3+4
Maintenance	Allergy	2	0	4	0
	Exantheme	5	0	6	0
	Headache	5	0	4	0
	Granulocyteopenia	14	6	18	13
	Anaemia	11	3	15	3
	Lymphocytopenia	10	16	3	22
	Thrombocytopenia	13	3	10	4
	Leukocytopenia	28	5	28	10
	Infection	16	3	24	4
	Fever	3	0	7	4
	Nausea/vomiting	5	0	8	0
	Mucostitis	2	02	2	0
	Diahorea	5	0	2	0
	Cardiac dysfunction	0	2	3	1
	Neutotoxicity	13	0	13	0
	Pulmonary toxicity	2	0	6	1
	Nephrotoxicity	0	0	1	0
	Alkaline phosphatise	2	0	6	0
	Alanine aminotransferase5	6	0	10	1
	Aspartate amino transfease	3	0	4	0
	Bilrubin	0	0	3	0
	LDH	13	0	18	0
	Alopecia	2	3	3	0

N.B Data extracted from Forstpointer 2004[34] and Forstpointer 2006[35]

4.1.14 Critique of submitted evidence syntheses

Although the MS includes two trials assessing the same clinical outcomes, the manufacturer states that differences between the trials, e.g. chemotherapy regimen, precludes a meta-analysis. Additionally, as there is head to head evidence for the two relevant comparators, no indirect comparisons are necessary. The ERG agrees with these two statements.

4.2 Summary of clinical evidence

4.2.1 Clinical results

EORTC trial: R-CHOP versus CHOP (induction)

- ORR was greater in the R-CHOP arm (85.1%) compared with the CHOP only arm (72.3%), P<0.0001; CRs were also higher in rituximab patients (29.5% versus 15.6%), P=0.0001
- Median PFS was increased in the rituximab arm (33.1 months versus 20.2 months), P=0.0003
- At three years, 82.5% of patients in the R-CHOP group were alive compared to 71.9% of patients receiving CHOP, P=0.096

EORTC trial: rituximab versus observation (maintenance)

- Median PFS was 51.5 months for those receiving rituximab versus 14.9 months for those on observation, P=<0.0001
- Subgroup analyses of entire patient group showed that all patients receiving rituximab at maintenance benefited from treatment regardless of induction therapy; level of response to induction did not affect the response to rituximab therapy

GLSG-FCM trial: R-FCM versus FCM (induction);

- Response rates were higher in the R-FCM arm (94%) compared with the FCM arm (70%), P=0.011; CRs were also higher in rituximab patients (40% versus 23%)
- Median PFS was 21 months in the FCM group and was not reached in the R-FCM group, P=0.0139
- At two years, OS (including non-FL patients) was higher in the rituximab group (90% versus 70%), P=0.0943

GLSG-FCM trial: rituximab versus observation (maintenance)

- FL patients who had received R-FCM at induction showed a significantly increased duration of response by rituximab maintenance compared with that by observation only
- Three year OS for all patients was 57% in the observation group and 77% in the rituximab group, P=0.1

EORTC trial and GLSG-FCM trial: adverse events

- AEs were reported for the majority of patients in both trials
- Numbers of patients withdrawing from treatment in the EORTC trial were low
- Blood/bone marrow toxicity, skin rashes and allergies were most commonly reported AEs

4.2.2 Clinical issues

- The MS fails to distinguish the methods and results of the SR of rituximab monotherapy from the overall results
- The majority of patients in clinical practice in England and Wales will not be rituximab naïve at relapse. The clinical effect of rituximab induction and maintenance on these patients is therefore uncertain
- NICE has requested clarification of the July 2006 EMEA rituximab marketing authorization

5 COST EFFECTIVENESS

5.1 Critique of cost-effectiveness review

The manufacturer conducted a SR of the published cost effectiveness evidence describing the use of rituximab in FL. The SR is not discussed in the main body of the MS.

Overall, the conduct of the literature review of economic evidence in the MS is weak. In particular, the MS does not state the objective of the literature review; nor does it provide any discussion or conclusions related to the data extracted from the included studies. The methods used in the literature review are unclear. The review is only described in appendices with the results of different database searches in four separate electronic files. There is no summary statement describing the number of studies identified, excluded or included in the review. Nor is there a summary statement stating the inclusion/exclusion criteria used.

5.1.1 Identification and description of studies

The databases used in the electronic searches were identified in the MS as Medline, Medline in process, Embase, Embase alerts, Biosys, NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluation Database (HEED). Blood online was also searched for abstracts. Key search terms were stated but no original search strategy was provided. The term "rituxan" is cited as a key search term; however, it is not clear from the manufacturer's description why the term "MabThera" was not also used. One of the studies in the review has a publication date of 1999, yet the search period stated is 2000 to May 2007. From the results described, it appears that the Wake study[50] (identified as study 5 and study 69 in the MS) has been excluded for two different reasons: NICE document and clinical paper. Finally, the MS did not include an economic evaluation search flow diagram.

The ERG's review of the inclusion and exclusion file in appendix 10 of the MS reveals that from a total of 73 identified studies, nine were included in the review. The ERG concludes that reasons for exclusion are as follows: not indication of interest (n=26); NICE document (n=4); NICE guidance (n=2); clinical (n=21); not disease area of interest (n=4); not treatment of interest (n=2); patients who are refractory to rituximab (n=2); same model as presented in the submission using Canadian costs (n=1); looking at indirect costs (n=2).

5.1.2 Data extraction and quality assessment

The manufacturer presented summary details of the nine studies included in the review in a table which included the following categories: study, aims, methods, results and relevance to decision-making in England and Wales. It is unknown whether or not a second reviewer

conducted independent data abstraction or how any discrepancies were discussed. The manufacturer did not state whether quality assessment of the included studies had been undertaken.

5.1.3 Summary of cost-effectiveness evidence identified

The manufacturer presented summary details of the nine included studies. The studies were published during the period 1999-2006. Seven of the studies were cost analyses. Only the cost-effectiveness study by Leppa and colleagues[51] included rituximab maintenance as a comparator (rituximab maintenance versus autologous stem cell transplant). In the cost-minimisation analysis by Sweetenham,[52] the authors assumed that there was no significant difference between the treatments in terms of response rates and disease duration yet went on to describe differences in the incidence and severity of drug-related AEs. Only two of the nine included studies were conducted in the UK (Sweetenham[52] and Hutchison[53]).

5.2 Conclusions

The systematic literature review of the economic evidence conducted by the manufacturer was poor. The ERG concludes that direct or meaningful comparison of the included studies was not possible due to the fact that the economic analyses were very different. In particular, the studies were heterogeneous in terms of the comparators, approaches to costing and country of origin.

5.3 Overview of manufacturer economic evaluation

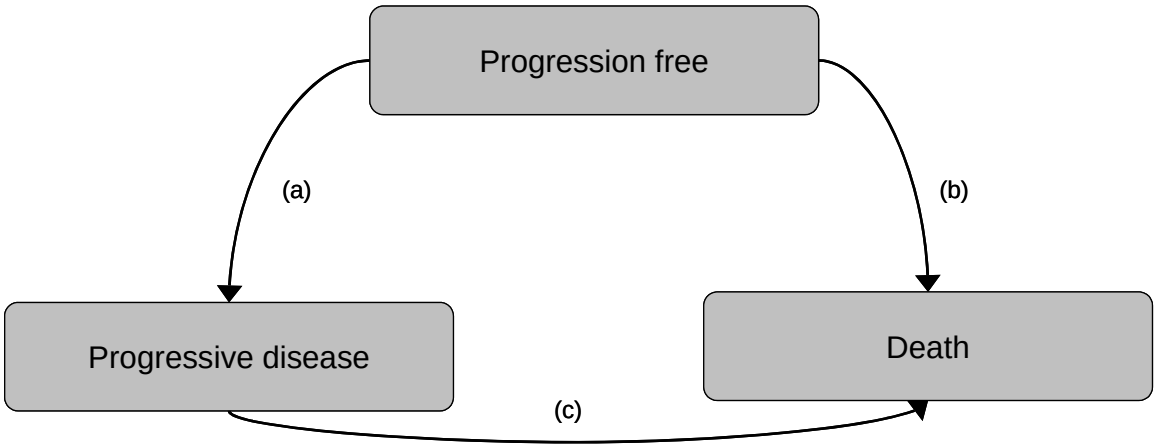
The economic evaluation includes two distinct models, which are described in this section. The choice of model designs reflects the nature of the EORTC trial which has both a first and second randomisation element. A half cycle correction is applied in both models.

In the clinical section, the MS also includes details of the GLSG-FCM trial which compares R-FCM versus FCM in the induction phase and rituximab versus observation in the maintenance phase. Data from this trial are not used to inform the economic evaluations conducted by the manufacturer.

5.3.1 Maintenance model

The pharmacoeconomic evaluation has been designed by the manufacturer to evaluate the cost effectiveness of rituximab as a maintenance therapy only (following response to an induction therapy) compared to observation only (no treatment until relapse). This is referred to as the maintenance 2-arm model.

A health state transition model with three health states was used to model costs and effects of rituximab compared to observation alone. Patients enter the economic model following a response to second-line CHOP induction therapy with or without rituximab. On entering the model patients will either receive treatment with maintenance rituximab until disease progression or for a maximum of two years or will be observed until disease progression. Patients will only exit the model due to death. The three health states of the model are PFS, PD and death, as defined in the EORTC trial. Patients in the economic evaluation are followed through the three health states in monthly cycles over a period of 30 years in order to capture the entire lifetime costs and effects of the population. Figure 5-1 shows the structure of the health state transition model.



Key:

a) The transition from progression free to progressive disease is derived from the PFS observed in EORTC and the corresponding Weibull parametric extrapolation

b) The transition from progression free to death is based on the overall survival observed in EORTC and the corresponding Weibull parametric extrapolation

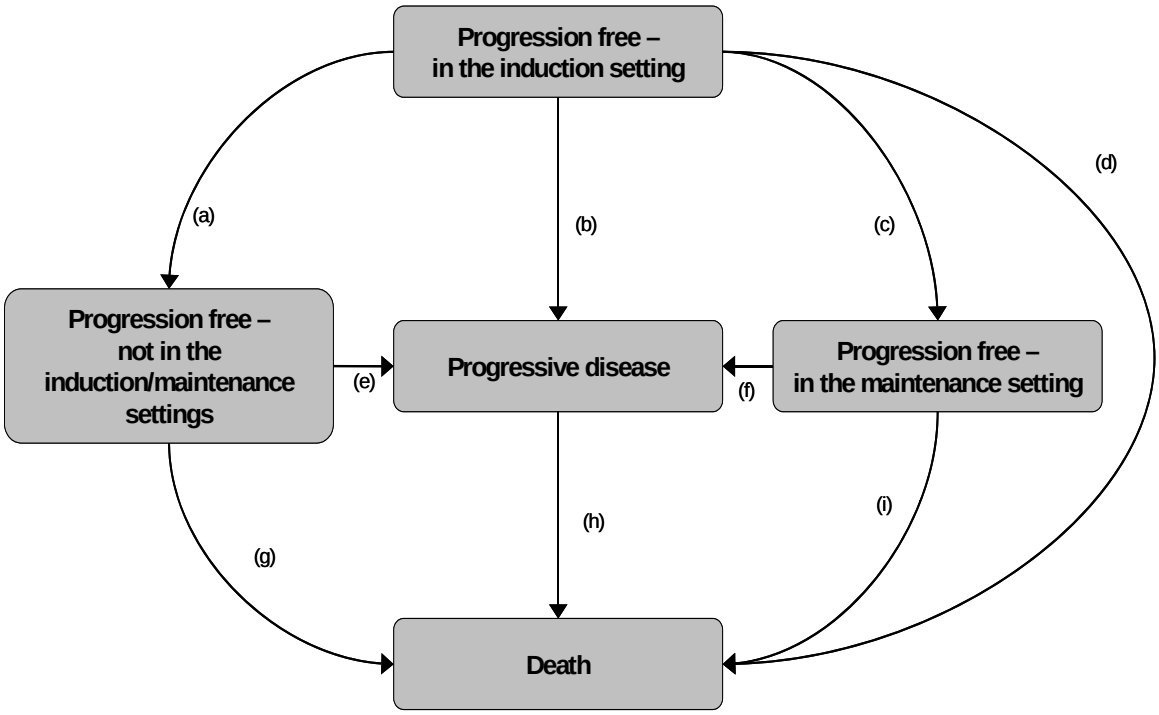
c) The transition from progressive disease to death is based on the overall survival observed in EORTC and the corresponding Weibull parametric extrapolation

Figure 5-1: Structure of the three health state transition model

5.3.2 Induction plus maintenance model

A further version of the model was developed by the manufacturer to evaluate whether the use of rituximab as an induction therapy in addition to maintenance therapy was cost effective. This is referred to as the induction plus maintenance model (4-arm model). Patients enter the economic model upon commencement of second-line treatment with CHOP with or without rituximab. Responders to second-line treatment will then go on to receive maintenance treatment with rituximab until relapse or for a maximum of two years or will be observed until disease progression. Patients will exit the model only due to death.

A health state transition model with five different health states was used to model costs and effects of the four different treatment strategies; these health states are described as progression-free survival in the induction setting (PFSI), progression-free survival in the maintenance setting (PFSM); progression-free survival but not in the induction or maintenance setting (PFSNIM), PD and death. The structure of the model and possible transitions between the health states is presented in Figure 5-2.



***Key**:*

- *(a) The transition from the induction setting to "progression free – not in the induction/maintenance settings" is based on results of EORTC. Those patients who complete induction therapy without progressive disease but who did not qualify for maintenance therapy according to the EORTC protocol will enter this health state*
- *(b) The transition to progressive disease is based on the PFS and OS observed in EORTC*
- *(c) The transition from the induction setting to "progression free –in the maintenance setting" is based on results of EORTC. Those patients who qualified for maintenance therapy according to the EORTC protocol will enter this health state*
- *(d) The transition to death is based on the overall survival observed in EORTC*
- *(e) The transition to progressive disease is based on the PFS and OS observed in EORTC*
- *(f) The transition to progressive disease is based on the PFS and OS observed in EORTC*
- *(g) The transition to death is based on the overall survival observed in EORTC*
- *(h) The transition to death is based on the overall survival observed in EORTC*
- *(i) The transition to death is based on the overall survival observed in EORTC*

Figure 5-2: Structure of the five health state transition model

5.3.3 Key assumptions in the models

Table 5-1: Key model assumptions

Assumption	Maintenance model	Induction plus maintenance model
Survival	0-24 months: data from EORTC trial used +24 months: PD and mortality hazards from parametric curve fitting used Hazards for PD and death for the rituximab maintenance group are assumed to be equivalent to those in the observation group after 5 years.	0-24 months: data from EORTC trial used +24 months: PD and mortality hazards from parametric curve fitting used Hazards for PD and death for the rituximab maintenance group are assumed to be equivalent to those in the CHOP>O group after 5 years.
Quality of life	Utility scores reported for PFS and PD are applied directly to health states and are not assumed to vary	Utility scores reported for PFS and PD are applied directly to health states and are not assumed to vary
Drug utilisation	Rituximab patients received 5.93 cycles as observed in the EORTC study. Excludes censored patients. Includes 134 patients who either completed all 8 cycles or stopped taking rituximab medication for other reasons.	
Clinical evidence	Patients would relapse and receive treatment every two years; patients with progression free disease would attend hospital for routine management/surveillance every 3 months; patients with PD attend hospital for routine management/surveillance every month (based on expert clinical opinion).	

Survival

The median length of follow-up of the EORTC trial dataset that was utilised in the economic evaluation was 31 months. To estimate the lifetime health benefits and associated costs of receiving induction chemotherapy with or without rituximab followed by maintenance rituximab, the manufacturer makes several assumptions about future disease progression and survival of patients.

The manufacturer extrapolates the K-M data (truncated at 1500 days) for progression free and OS from the EORTC trial. This was performed for the survival curves following (i) second randomisation in the EORTC trial (2-arm model) and (ii) first randomisation in the EORTC trial (4-arm model). For both models, the OS and PFS data used in the economic evaluations for each of the treatment groups are based on the fitted Weibull distributions. The Weibull curve was selected by the manufacturer on the basis of a series of good fit evaluations. The parametric curve fitting for each of the treatment groups implies different hazards across the treatment groups for the life time of the model. This is considered an unrealistic assumption by the manufacturer and so in the 2-arm model the hazards for the rituximab maintenance group are assumed to be equivalent to those in the observation group after 5 years and in the 4-arm model the hazards for the rituximab maintenance group are assumed to be equivalent to those in the CHOP>O group after 5 years.

5.3.4 Parameters and values

Table 5-2: Model parameters and values (2-arm model)

Model Variable	Value	Source
Drug costs		
Rituximab drug costs per dose	£1,325	Economic model sheet
Mean cost per administration	£86	NHS Reference costs 2004, (TOPS FU 303)[54]
Mean number of rituximab doses per patient	5.93	EORTC
Total rituximab drug costs per patient	£7,739	Economic model sheet
Total rituximab administration costs per patient	£502	Economic model sheet
Serious adverse events (SAEs)		
Patients experiencing SAEs – Rituximab	0.180	EORTC
Patients experiencing SAEs – Observation	0.006	EORTC
Unit cost per SAE – Rituximab	£1,051	Economic model sheet
Unit cost per SAE - Observation	£1,177	Economic model sheet
Expected cost of SAEs - Rituximab	£188.90	Economic model sheet
Expected cost of SAEs - Observation	£7.05	Economic model sheet
Non-serious adverse events (NSAEs)		
Number of NSAEs per patient - Rituximab	1.605	EORTC
Number of NSAEs per patient - Observation	1.443	EORTC
Unit cost per NSAE – Both tx groups	£86	NHS Reference costs 2004,(TOPS FU 303)[54]
Expected cost of NSAEs - Rituximab	£138.01	Economic model sheet
Expected cost of NSAEs - Observation	£124.11	Economic model sheet
Treatment costs upon relapse		
Expected cost per treatment received upon relapse – Rituximab	£6,870.57	Economic model sheet
Expected cost per treatment received upon relapse – Observation	£6,858.44	Economic model sheet
Frequency of treatment received upon relapse		
Number of years between each line of therapy whilst in the PD health state – Rituximab & Observation	2 (years)	Assumption
Average post protocol treatment costs upon relapse per cycle of the health state transition model in the PD health state		
Rituximab	£286.27	Economic model sheet
Observation	£285.77	Economic model sheet
Cost of non-drug resources (routine management / surveillance) by health state		
Cost per month Rituximab - Progression free	£28.67	Economic model sheet
Cost per month Observation - Progression free	£28.67	Economic model sheet
Cost per month in PD health state	£86	Economic model sheet
Cost per month whilst Dead	£0	Assumption

Table 5-3: Additional model parameters and values used in the 4-arm model

Model Variable	Value	Source
Response rates		
Patients eligible for maintenance therapy - R-CHOP	80.8%	EORTC
Patients eligible for maintenance therapy - CHOP	62.8%	EORTC
Induction drug costs per dose		
Rituximab	£1,325	Economic model
Cyclophosphamide	£9.47	Economic model
Doxorubicin	£186	Economic model
Prednisone	£3.45	Economic model
Regimen drug costs per dose R-CHOP	£1,545	Economic model
Regimen drug costs per dose R-CHOP	£220	Economic model

Number of induction doses per patient		
R-CHOP	5.6838	EORTC
CHOP	5.4474	EORTC
Total drug and administration costs per patient		
R-CHOP	£9,272	Economic model sheet
CHOP	£1,699	Economic model sheet
Rituximab maintenance drug costs		
Rituximab drug costs per dose	£1,325	Economic model sheet
Mean number of rituximab doses per patient	5.9254	EORTC
Total rituximab drug and administration costs per patient	£8,241	Economic model sheet
R-CHOP (I), R (M) Expected cost of maintenance	£6,656.28	Economic model sheet
CHOP (I), R (M) Expected cost of maintenance	£5,172.99	Economic model sheet
Cost of serious adverse events (SAEs)		
R-CHOP (I), R (M)Expected cost of SAEs (I)	£528	Economic model sheet
R-CHOP (I), R (M) Expected cost of SAEs (M)	£191	Economic model sheet
R-CHOP (I), O (M) Expected cost of SAEs(I)	£427	Economic model sheet
R-CHOP (I), O (M) Expected cost of SAEs(M)	£0	Economic model sheet
CHOP (I), R (M) Expected cost of SAEs (I)	£376	Economic model sheet
CHOP (I), R (M) Expected cost of SAEs (M)	£186	Economic model sheet
CHOP (I), O (M) Expected cost of SAEs (I)	£301	Economic model sheet
CHOP (I), O (M) Expected cost of SAEs (M)	£17	Economic model sheet
R-CHOP (I), Not eligible (M) Expected cost of SAEs (I)	£744.25	Economic model sheet
CHOP (I), Not eligible (M) Expected cost of SAEs (I)	£604.96	Economic model sheet
Cost of non-serious adverse events by outcome of induction (NSAEs)		
Cost per non-serious AE	£86	Economic model sheet
R-CHOP (I), R (M) Expected cost of NSAEs (I)	£188	Economic model sheet
R-CHOP (I), R (M) Expected cost of NSAEs (M)	£133	Economic model sheet
R-CHOP (I), O (M) Expected cost of NSAEs (I)	£176	Economic model sheet
R-CHOP (I), O (M) Expected cost of NSAEs (M)	£106	Economic model sheet
CHOP (I), R (M) Expected cost of NSAEs (I)	£173	Economic model sheet
CHOP (I), R (M) Expected cost of NSAEs (M)	£144	Economic model sheet
CHOP (I), O (M) Expected cost of NSAEs (I)	£172	Economic model sheet
CHOP (I), O (M) Expected cost of NSAEs (M)	£150	Economic model sheet
R-CHOP (I), Not eligible (M) Expected cost of NSAEs (I)	£290	Economic model sheet
CHOP (I), Not eligible (M) Expected cost of NSAEs (I)	£189	Economic model sheet
Expected cost of treatments received upon relapse		
R-CHOP (I), R (M)	£5,837	Economic model sheet
R-CHOP (I), O (M)	£6770	Economic model sheet
CHOP (I), R (M)	£8,195	Economic model sheet
CHOP (I), O (M)	£6,943	Economic model sheet
Frequency of treatments received upon relapse		
R-CHOP (I), R (M) R-CHOP (I), O (M) CHOP (I), R (M) CHOP (I), O (M)	2 (years)	Assumption
Treatment costs upon relapse per cycle in the PD health state		
R-CHOP (I), R (M)	£243	Economic model sheet
R-CHOP (I), O (M)	£282	Economic model sheet
CHOP (I), R (M)	£341	Economic model sheet
CHOP (I), O (M)	£289	Economic model sheet
Cost of non-drug resources (routine management/surveillance) by health state		
R-CHOP (I), R (M) Cost per month in PF	£28.67	Economic model sheet
R-CHOP (I), O (M) Cost per month in PF	£28.67	Economic model sheet
CHOP (I), R (M) Cost per month in PF	£28.67	Economic model sheet
CHOP (I), O (M) Cost per month in PF	£28.67	Economic model sheet
Cost per month in PD health state	£86	Economic model sheet
Cost per month whilst dead	£0	Assumption

5.3.5 Population

The economic evaluation is based on the EORTC trial. Therefore the population in the economic evaluation is reflected by the population enrolled and randomized in the induction and maintenance phases of the EORTC trial. The manufacturer considers that the (intention-to treat) population is relevant for the economic evaluation because it accurately reflects the patient population likely to present for induction and subsequently maintenance therapy in the clinical setting in the UK. The economic evaluation was not carried out for any patient subgroups.

5.3.6 Perspective and time horizon

In the MS, the perspective taken when estimating costs within the economic evaluations is that of the NHS in England and Wales. All relevant direct healthcare costs are evaluated. A lifetime time horizon of 30 years has been used in both analyses, thereby capturing the lifetime costs and health outcomes of patients in each of the treatment groups. The MS states that a time horizon of less than the life-time of the patient population would not be sufficient to capture the total costs and total benefit consequences of the treatments under evaluation.

5.3.7 Comparator

The comparator assumed in the 2-arm economic model is the same as that in the maintenance phase of the EORTC trial; rituximab maintenance is compared with observation alone in responding patients until relapse.

In the 4-arm economic model, there are four distinct treatments available resulting in six potential treatment comparisons (Table 5-4).

Table 5-4 Possible treatment comparisons

Comparisons
R-CHOP>R vs CHOP>R
R-CHOP>R vs R-CHOP>O
R-CHOP>R vs CHOP>O
CHOP>R vs R-CHOP>O
CHOP>R vs CHOP>O
R-CHOP>O vs CHOP>O

5.3.8 Efficacy

The data set used in the MS is from the regulatory submission with a median follow up of 31 months.

Efficacy data are taken directly from the EORTC trial. The transition probabilities used in the models (PFS to progression, progression to death and PFS to death) are 0-24 month values. Values from 24 months have been extrapolated out for 30 years and are time dependent based on Weibull extrapolations of the PFS and OS curves.

5.3.9 Health benefits and utilities

The health effects of AEs were not included in the economic evaluations as it was considered that (i) there was no clinically significant difference between the rate or severity of AEs observed in both arms of the clinical trial and (ii) the impact of an AE, on a patient's quality of life, over the lifetime of the patient would be negligible.

Health benefits for patients were measured using quality adjusted life years (QALYs). Utility scores were taken from the Oxford Outcomes Study[55] commissioned by the manufacturer for PFS (0.805) and progressed disease (0.618) health states.

5.3.10 Resources and costs

There were four major types of costs included in the 2-arm and 4-arm economic models:

1. Study drug costs, including costs of administration

Study drug costs were based on rituximab usage during the EORTC trial. The total study drug cost included the costs of administration incurred in an oncology outpatient setting.

2. Adverse events

Adverse events costs were split into SAEs and NSAEs cost categories. Only those AEs which required medical intervention were included in the economic analyses. The incidence rates of SAEs and NSAEs were as reported in the EORTC trial. Serious AEs were categorised according to ICD-10 coding and the ICD-10 code was mapped to a UK NHS Healthcare Resource Group (HRG) to obtain a unit cost. Non-serious AEs were described as those AEs that can be managed in the outpatient setting.

3. Treatment costs upon relapse

The MS includes treatment costs upon relapse for patients in order to reflect the therapies that this patient group receives upon disease progression and continues to receive for the remainder of their lives. Post-protocol therapies received by patients are based on data collected during the EORTC trial. It is assumed that patients in each group will receive a line of treatment upon relapse every two years; this assumption is based on the approximate time to first progression observed in EORTC.

4. Cost of routine management/surveillance

Patients incurred routine management/surveillance costs during each cycle of the health state transition models. Patients in the PD health state were assigned the cost of an outpatient visit ever month whilst patients in the PFS health state were assigned the cost of an outpatient visit every three months.

5.3.11 Discounting

In both models, health benefits and costs were discounted at 3.5% in line with current NICE guidance.[56]

5.4 Cost-effectiveness results

The main results of the manufacturer economic evaluations are shown in Table 5-5 and Table 5-6. In terms of cost per QALY, the manufacturer concludes that rituximab can be considered a cost-effective treatment option in FL for both sets of comparisons (2-arm model/maintenance and 4-arm model/induction plus maintenance).

Table 5-5: Incremental cost effectiveness of rituximab maintenance compared to observation

Treatment group	Total costs	QALYs gained	Incremental cost per QALY gained
Rituximab	£21,608	4.2250	
'Observation'	£14,722	3.3331	
Incremental	£6,886	0.8919	£7,721

In the 4-arm model, R-CHOP followed by rituximab (R-CHOP>R) is considered to be the most effective intervention. The next most effective intervention is considered to be CHOP followed by rituximab (CHOP>R). This comparison produces an ICER of £16,749 per QALY gained.

Table 5-6: Incremental cost effectiveness of a treatment strategy of R-CHOP>R versus a treatment strategy of CHOP>R in patients presenting for induction therapy

Treatment and comparator groups	Costs	QALYs gained	Incremental cost per QALY gained
R-CHOP>R	£28,585	4.0906	
CHOP>R	£22,389	3.7207	
Incremental	£6,196	0.3699	£16,749

It is noted that the comparison of CHOP followed by rituximab (CHOP>R) compared with CHOP followed by observation (CHOP>O) yields an ICER of £9,076.

Finally, the MS considers different scenarios in the 4-arm model and the wide range of cost-effectiveness results are presented in Table 5-7.

Table 5-7: Scenario analysis (4-arm model)

Scenario	Response rate	Cost per QALY
1	Response to chemotherapy – 70% (Rituximab incremental advantage – 10.8%)	R-CHOP>R vs CHOP>R £21,262
2	Response to chemotherapy – 75% (Rituximab incremental advantage – 5.8%)	R-CHOP>R vs CHOP>R £27,612
3	Response to chemotherapy – 77% (Rituximab incremental advantage – 3.8%)	R-CHOP>R vs CHOP>R £31,962
Scenario	**Cost of alternative chemotherapy regimen**	**Cost per QALY**
4	FCM	R-CHOP>R vs CHOP>R £9,414 R-CHOP>O vs CHOP>O £6,860
5	CVP	R-CHOP>R vs CHOP>R £15,052 R-CHOP>O vs CHOP>O £10,746
6	Chlorambucil	R-CHOP>R vs CHOP>R £17,342 R-CHOP>O vs CHOP>O £12,324

5.4.1 Sensitivity analysis

Univariate sensitivity analysis (SA) and PSA were conducted by the manufacturer. The results of the SA are presented in Table 5-8 and Table 5-9. Both the 2-arm model and the 4-arm model were most sensitive to the duration of treatment benefit, the unit cost per line and frequency of treatment upon relapse and the duration of follow up.

Table 5-8: Sensitivity results: maintenance (2-arm model)

Variables	Assumptions (Low and high)	Result (Cost per QALY gained)
Extrapolation	Weibull (Base case)	£7,721
	Log logistic	£6,040
Duration of treatment benefit	2 years	£18,124
	30 years	£6,270
Unit cost non-severe AEs	£43	£7,713
	£172	£7,736
Cost of AEs excluded	£0	£7,501
Unit cost per line of treatment upon relapse	Double costs in observation arm	Rituximab dominant
	Double costs in both arms	£18,016
Frequency of treatment upon relapse	Double frequency in observation arm	Rituximab dominant
	Double frequency in both arms	£18,016
Cost or routine management/surveillance per cycle	Cost in PD health state equal to cost in PFS health state	£8,079
	Cost in PFS health state equal to cost in PD health state	£8,850
Utility values for PFS	Utility value equal to PD	£11,141
	Utility value equal to PFS	£8,553
Duration of follow-up	4 years	£15,933
	50 years	£7,721
Discount rate for costs and outcomes	undiscounted	£6,960
Discount rate for costs	Costs undiscounted	£8,103
Discount rate for outcomes	Outcomes undiscounted	£6,632

Table 5-9: Sensitivity analysis results: induction plus maintenance (4-arm model)

Variables	Assumptions (low and High)	Result (Cost per QALY) R-CHOP>R vs CHOP>R	Result (Cost per QALY) R-CHOP>R vs R-CHOP>O	Result (Cost per QALY) R-CHOP>R vs CHOP>O
R-CHOP and CHOP response rates (CHOP response rate kept constant)	Lower 95% CI of difference between the groups	£21,004	£11,654	£12,491
	Upper 95% CI of difference between the groups	£14,541	£12,108	£11,452
Extrapolation	Log logistic	£9,835	£8,606	£8,528
Duration of treatment benefit	2 years	£36,497	£91,373	£28,400
	30 years	£8,907	£6,765	£8,052
Unit cost non-severe AEs	£43	£16,686	£11,870	£11,889
	£172	£16,874	£11,971	£11,953
Cost of AEs excluded	£0	£16,228	£11,328	£11,568
Unit cost of non-serious adverse events	£43	£16,686	£11,870	£11,889
	£172	£16,874	£11,971	£11,953
Unit cost per line of treatment upon relapse	Double costs in R-CHOP>R arm only	£37,868	£28,719	£19,712
	Double costs in all arms	£8,022	£8,614	£9,105
Frequency of treatment upon relapse	Double frequency in R-CHOP>R arm	£37,868	£28,719	£19,712
	Double frequency in all arms	£8,022	£8,614	£9,105
Administration costs	£0 (CHOP only arm)	£18,015	£11,904	£12,378
Utility values for PFS	Utility value equal to PD	£22,009	£16,037	£16,707
	Utility value equal to PFS	£16,896	£12,312	£12,826
Duration of follow-up	4 years	£48,116	£41,171	£25,278
	50 years	£16,749	£11,904	£11,910
Discount rate for costs and outcomes	undiscounted	£14,425	£10,001	£10,279

For the PSA, scatter plots and cost-effectiveness acceptability curves (CEACs) were calculated. For the 2-arm model, these are shown in Figure 5-3 and Figure 5-4. The CEAC for the 2-arm model illustrates that rituximab is most likely to be cost-effective even at very low levels of willingness to pay (WTP) for an additional QALY.

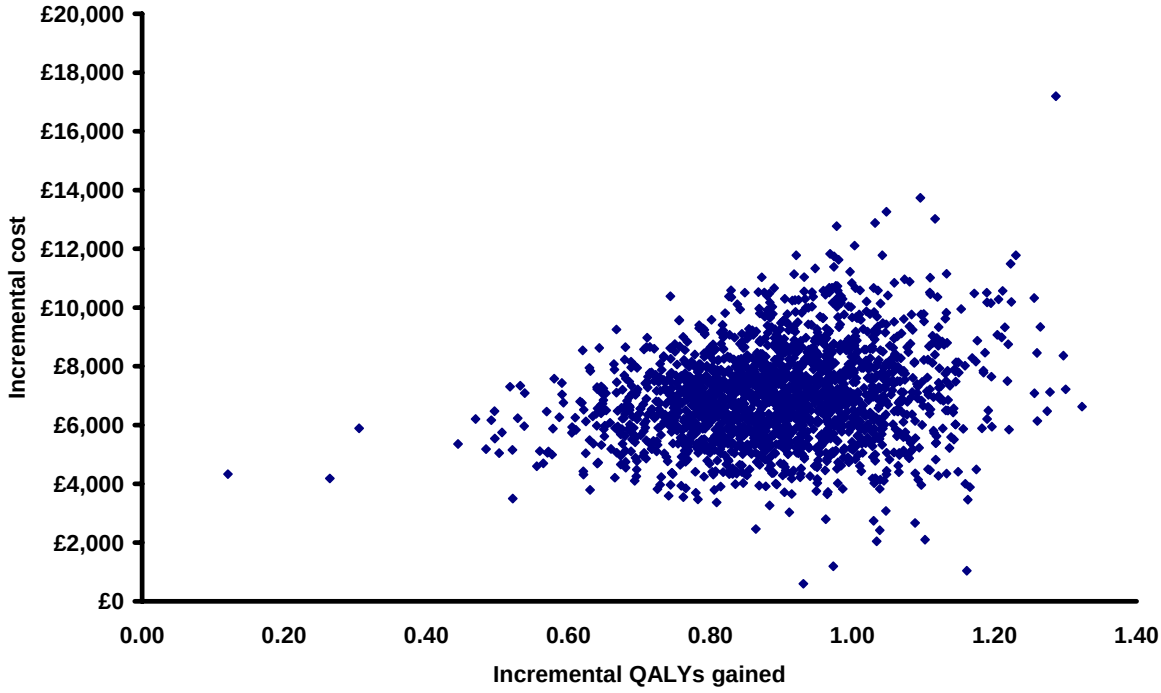


Figure 5-3: Scatter plot showing incremental cost and effect of maintenance therapy over observation across 2000 simulations of the economic model

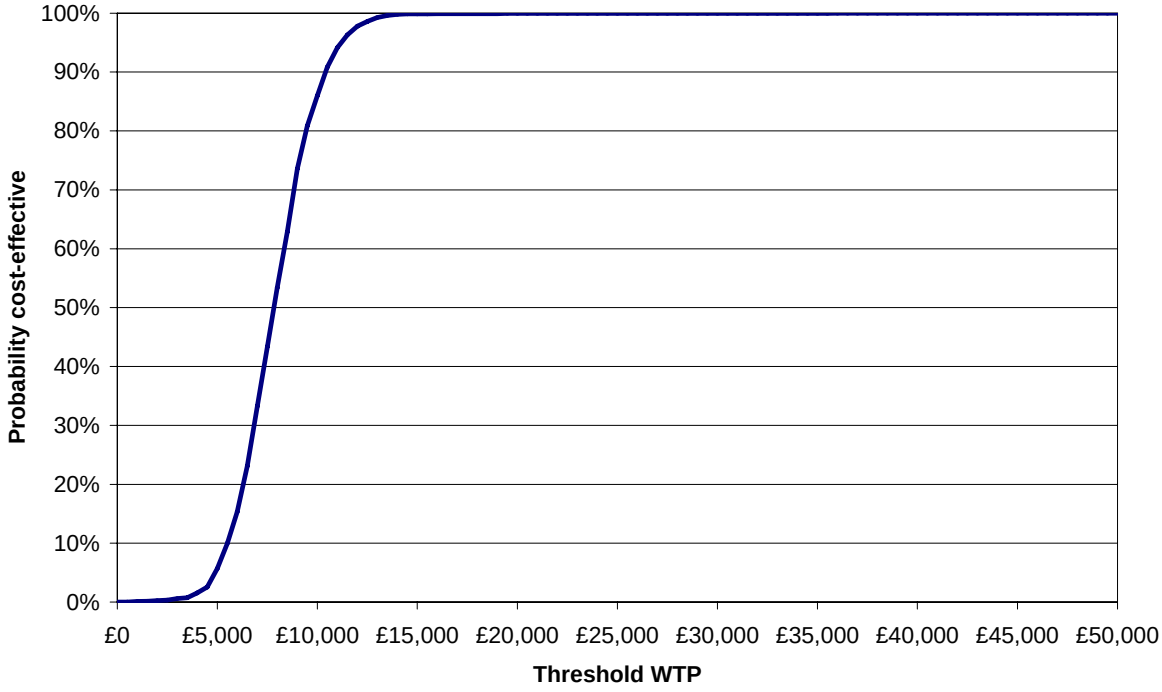


Figure 5-4: Cost-effectiveness acceptability curve – probability that the incremental cost of rituximab maintenance over observation meets a WTP threshold

For the 4-arm model, the manufacturer presents a scatter plot to illustrate the considerable overlap of costs and QALYs across the four treatment groups (Figure 5-5). The CEAC shows that at a WTP for a QALY of approximately £18,000 or greater, the R-CHOP>R treatment strategy had the greatest probability of being cost effective (Figure 5-6).

Figure 5-5: Scatter plot showing incremental cost and effect of maintenance therapy over CHOP>observation across 2000 simulations of the economic model

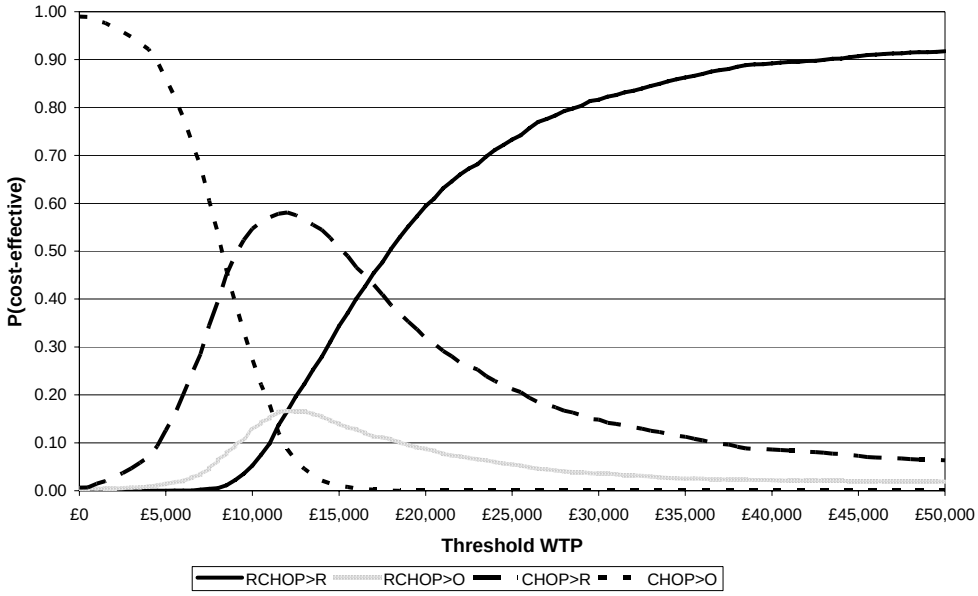


Figure 5-6: Cost effectiveness acceptability curve –probability that each treatment practice is cost-effective at a given WTP threshold

5.4.2 Model validation reported within the submission

The model was validated by an external agency which checked for calculation errors, errors in structure as well as the plausibility of assumptions and data. The face validity of the model was checked by the same agency's oncologists. The economic model assumptions were also validated by external UK clinicians at a UK Roche advisory board.

5.4.3 Budget impact analysis

Assuming a staggered uptake of 20% per annum over the next five years, the estimated budget impact of R-CHOP induction therapy followed by maintenance rituximab is £2,764,931 in the first year following its introduction; £6,453,512 in the second year; and £10,626,912 in the third year. The budget impact for using rituximab maintenance alone, with no rituximab and chemotherapy induction would cost £896,002 in the first year, £2,696,966 in the second year and £3,601,928 in the third year. According to the manufacturer, the budget impact estimates presented represent the maximum possible cost to the NHS during the first three years following positive NICE guidance.

5.5 Critique of manufacturer's economic model

5.5.1 General observations

The design of the two submitted models is very similar, using common methods throughout, adapted only as necessary to accommodate the requirements of the different decision problems. In this section any comments apply equally to both models except where differences between the models are specifically identified.

The economic models submitted by the manufacturer are implemented to a generally high standard, clearly presented and with a large amount of source information included to aid traceability. The layouts of the various elements of the model are generally logical, and the formulae employed are straightforward. Some internal validation checks are built into the main health state transition worksheets.

The VBA used to generate PSA results is very simple and robust. It is perhaps unfortunate that it does not allow any disaggregation of results below the level of total costs and total outcomes, which would aid an understanding of the main sources of uncertainty.

5.5.2 Model structure

Despite the complexity of the EORTC trial, the two submitted models have been constructed on a very simple basis involving only two health states (progression free and PD). The ERG has concerns that this may not adequately reflect the differences between patients following

different treatment/disease pathways, and in particular may not provide a suitable framework for identifying and evaluating the important policy decisions.

Health state modelling is founded on strong assumptions about homogeneity for patients within a state with respect to all relevant variables - resource use, unit costs, prior history, baseline characteristics, transition probabilities and prognosis. The 2-arm model of rituximab maintenance therapy is particularly vulnerable in this respect, since no attempt is made to distinguish patients at the second randomisation by their previous treatment history (i.e. first randomisation treatment). With differential response rates in the initial phase of the trial, the patients in the second phase will be a mixture of those with response to rituximab plus CHOP (R-CHOP) induction treatment and those achieving response with CHOP. It cannot be assumed that the effects of maintenance rituximab on the two groups of patients will be the same, and therefore it is inappropriate to draw any conclusion on the cost effectiveness for either discrete treatment strategy from the results of this combined but heterogeneous analysis. It seems more appropriate to use the relevant separate pathways in the 4-arm model instead, which do not suffer from this problem. For completeness, ICERs generated from the 2-arm model are presented for illustration only.

By contrast the 4-arm model concentrates on six comparisons between the four possible strategies from combining initiation and maintenance options for rituximab use. This appears reasonable, since it allows flexibility to address a variety of different ways of formulating the decision problem. For this reason the ERG has chosen to concentrate attention on the 4-arm model in considering the cost effectiveness of rituximab in both modes of use.

Another important issue to consider is the modifying role of subsequent treatments offered to patients. Since each treatment is liable to have a different mode of action and particular response profile, it cannot be concluded that parametric survival models calibrated only on the basis of within-trial data will remain valid when new regimens are introduced. This therefore calls into question the interpretation of long-term projections of benefit based on survival models. A more credible approach may involve limiting apparent gains only to the observation period prior to initiation of later treatments, though this is also not unambiguous in respect to inferences that can be drawn as to the relationship between observed improvements in PFS and potential gains in OS. It is quite possible for apparent gains in OS to be offset by later accelerated mortality in subsequent treatment phases.

5.5.3 Discounting and half-cycle correction

Although both discounting and a half-cycle correction have been implemented correctly in most instances, there is a minor anomaly in the model coding which affects estimates of both costs and outcomes. It relates to those 30-day model periods which are just before and after a

year-end. In these cases, the submitted model applies the half-cycle correction before discounting so that costs and outcomes attributable to separate accounting periods are combined and discounted at the rate appropriate to the later year. The impact of this error on the submitted cost-effectiveness ratios (as shown in Table 5-10) is found to be very small, and is unlikely to be important in decision-making. In all cases the correction favours the rituximab arm.

Table 5-10: Effect of half-cycle / discounting logic correction on cost-effectiveness ratios in submitted 4-arm model

	Incremental cost/QALY	
Comparison	**Submitted base case**	**With correction**
R-CHOP>R vs CHOP>R	£16,749	£16,706
R-CHOP>R vs R-CHOP>O	£11,904	£11,865
R-CHOP>R vs CHOP>O	£11,910	£11,881
CHOP>R vs R-CHOP>O	Dominant	Dominant
CHOP>R vs CHOP>O	£9,076	£9,056
R-CHOP>O vs CHOP>O	£11,916	£11,895

5.5.4 Estimation of costs

Acquisition costs: The acquisition costs of rituximab and the component agents of the CHOP regimen are correctly costed using the distribution of body surface area recorded in the EORTC trial. No reduction of drug wastage (from unused vials) is assumed on the basis of vial sharing. The average number of treatment cycles/doses is estimated directly from the trial data, using only patients who had completed their 8 maintenance doses or were withdrawn from the trial, to avoid potential bias from censored observations. The estimated acquisition costs of interventions and comparators therefore appear to have been accurately estimated.

Administration costs: In the submitted model it is assumed that all courses are given in an outpatient setting and are therefore costed as outpatient follow up visits (£86 per cycle). This is clearly inappropriate with such demanding regimens as CHOP. Such chemotherapy is routinely given within a day case setting and costed appropriately. Two NHS Reference Costs 2005/6 HRG codes are available which may be used in coding the cost of administration for FL patients:

- *Day Cases* 'Chemotherapy with a Haematology, Infectious Disease, Poisoning, or Non-specific Primary Diagnosis' (S98) £408.07 per event

- *Patient Treatment Attendances* 'Lymphoma Non Solid Tumour Cancer Chemotherapy: All Drugs' (XY99LYM) £603.86 per event

Since the total number of events in the NHS Reference Costs database is very similar for the two codes (69,000 and 66,000) it is appropriate to adopt the weighted average cost per event of £504.04 in place of the outpatient visit cost.

This parameter alteration leads to important changes in the cost-effectiveness results in both submitted models as shown in Table 5-11.

Table 5-11: Effect of using day case/chemotherapy administration costs in the submitted models

	Incremental cost/QALY gained			
Comparison	**Submitted base case 2 ARM model**	**With alteration**	**Submitted base case 4 ARM model**	**With alteration**
R-CHOP>R vs CHOP>R	-	-	£16,749	£18,204
R-CHOP>R vs R-CHOP>O	-	-	£11,904	£16,149
R-CHOP>R vs CHOP>O	-	-	£11,910	£13,978
CHOP>R vs R-CHOP>O	-	-	Dominant	£8,119
CHOP>R vs CHOP>O	-	-	£9,076	£11,503
R-CHOP>O vs CHOP>O	-	-	£11,916	£12,100
Maintenance vs Observation	£7,721	£10,458	-	-

Adverse event costs: The models categorise AEs into two types - serious and NSAEs (Grades 3 & 4) are all assumed to involve hospitalisation, and a relevant HRG code is assigned to each event in the EORTC trial to allow direct costing. The calculated average cost per patient for the different patient subgroups is very similar. NSAEs are assigned a nominal additional outpatient follow up attendance, and costed accordingly. This approach does not recognise that AE are commonly reported during routine out-patient appointments, nor does it account for the additional costs of prescribed treatments (usually drugs) for the reported problems. However, since these omissions operate in opposite directions (over-estimating additional outpatient visits, but under-estimating treatment costs), it is likely that any bias would be small enough to have little influence on the overall cost-effectiveness results.

Post-progression treatment costs: Once patients have suffered PD, it is assumed that they will incur additional periods of active treatment at regular intervals (assumed to be two years on average). Although additional costs are included in the model, there is no opportunity for these treatments to have any effect on patient health outcomes, which are wholly determined by the survival models estimated from within-trial data. This might not be too great a problem if it were clear that the case-mix of patients suffering PD in the different treatment arms were equivalent (and therefore had similar prognoses). Unfortunately this is not the case, and therefore appears to be a modelling shortcoming, in that both cost and outcome effects of additional treatments are not estimated.

The assumed interval between treatments corresponds approximately to the median progression free period for the whole trial dataset. However, the estimated weighted mean interval based on the manufacturer preferred Weibull models is in fact 3.00 years.

For each treatment strategy, an average cost of post-progression treatments is calculated directly from the EORTC trial evidence of the distribution of treatments between ten regimens. Because the unit costs of individual treatments vary widely (from zero to £41,700), and the proportions of each are derived from very small numbers in the majority of cells, this approach to costing is liable to generate unwarranted apparent differences between strategies.

An alternative method is to aggregate events into a small number of meaningful categories, and estimate joint averages where there is no strong evidence of significant differences. In this case, the largest category is 'chemotherapy'. For all patient groups, the post-progression use of chemotherapy appears to be inversely related to the use of regimens involving rituximab. Aggregating the latter into a single group, and creating an 'other treatments' group for all remaining events, a clear pattern emerges in which subsequent use of chemotherapy is greater for patients receiving rituximab (initiation and/or maintenance) during the trial, while the use of other treatments remains constant. We therefore assume that 25% of further therapy is attributable to 'other treatments' for all strategies. The remaining 75% is split between chemotherapy and rituximab-based treatments.

Table 5-12 shows that 55% of patients not previously given rituximab will receive it post-progression whilst 45% will receive chemotherapy, falling to 25% of those previously given rituximab either for initiation or for maintenance (75% will receive chemotherapy), and 10% of those given rituximab in both trial phases (90% will receive chemotherapy).

Weighted average unit costs were calculated directly for the three categories of therapy, and these were applied to the estimated proportions of therapies to generate an alternative set of average costs for each of the four treatment strategies.

Table 5-12details the derivation of revised costs for the 4-arm model.

Table 5-13 shows the changes in cost effectiveness obtained with these values.

Table 5-12: Calculation of alternative post-progression treatment costs in the 4-arm model

		Post-progression therapies: proportions by treatment strategy							
Treatment strategy		Actual			Adopted			Model cost per treatment	
Induction	Maintenance	Chemotherapy	Rituximab based	Other	Chemotherapy[1]	Rituximab based	Other	ERG estimates	Submitted model
R-CHOP	Rituximab	68.5%	8.2%	23.3%	67.5%	7.5%	25.0%	£5,809.06	£5,836.31
R-CHOP	Observation	51.4%	17.4%	31.2%	56.3%	18.8%	25.0%	£6,532.28	£6,770.27
CHOP	Rituximab	56.1%	15.8%	28.1%	56.3%	18.8%	25.0%	£6,532.28	£8,195.16
CHOP	Observation	36.3%	45.1%	18.6%	33.8%	41.3%	25.0%	£7,993.72	£6,943.49
		Average cost per treatment			£3,232.47	£9,705.55	£11,596.90		

1 To illustrate, 67.5/75*100 = 90%

Table 5-13: Effect of using alternative post-progression treatment costs in the submitted models

Comparison	Incremental cost/QALY gained			
	Submitted base case 2 ARM model	With alteration	Submitted base case 4 ARM model	With alteration
R-CHOP>R vs CHOP>R	-	-	£16,749	£22,688
R-CHOP>R vs R-CHOP>O	-	-	£11,904	£12,518
R-CHOP>R vs CHOP>O	-	-	£11,910	£10,269
CHOP>R vs R-CHOP>O	-	-	Dominant	Dominant
CHOP>R vs CHOP>O	-	-	£9,076	£2,999
R-CHOP>O vs CHOP>O	-	-	£11,916	£8,323
Maintenance vs Observation	£7,721	£5,775	-	-

Clearly, from Table 5-13 it can be seen that use of the ERG's post-progression treatment assumptions substantially increases the ICER for the R-CHOP>R versus CHOP>R comparison and decreases the ICER for the CHOP>R vs CHOP>O comparison.

Routine management costs: It is assumed that, whilst in the progression free condition, patients are seen routinely in an outpatient clinic every three months. This is increased to monthly visits in the PD state. It is not clear whether this reflects the true level of related healthcare resource use, since it omits any primary care contacts or prescribed medications.

Terminal care costs: The submitted model does not include any costs associated with the terminal phase of the disease, when most health care costs typically escalate during the last few months of life. Although these costs are incurred for all patients dying directly from FL, the timing of death (i.e. differential survival) can have an important bearing on cost effectiveness when these costs have been discounted. The ERG knows of no reliable published source for the size of these terminal care costs, but experience from analysis of patient data relating to another haematological cancer suggests that an estimate of around £5,000 would be reasonable to illustrate the potential impact on cost effectiveness. With this ERG modification, the ICERs for all patient groups are reduced slightly as shown in Table 5-14.

Table 5-14: Effect of adding terminal care costs of £5,000 per patient to the submitted 4-arm model

Comparison	Incremental cost/QALY	
	Submitted base case 4 ARM model	With alteration
RCHOP>R v CHOP>R	£16,749	£16,534
RCHOP>R v RCHOP>O	£11,904	£11,698
RCHOP>R v CHOP>O	£11,910	£11,713
CHOP>R v RCHOP>O	Dominant	Dominant
CHOP>R v CHOP>O	£9,076	£8,889
RCHOP>O v CHOP>O	£11,916	£11,726

5.5.5 Estimation of outcomes

Utility estimates: Two estimates of health-related utility are used in the model corresponding to the two health states. These are derived from a study carried out for the manufacturer by Oxford Outcomes,[55] which uses the EQ-5D quality of life instrument. The pre-progression value (0.805) is obtained by combining results for 132 patients in the categories "Partial response", "Remission-Full response" and "Disease free". For the post-progression state the responses from 33 patients described as experiencing "Active disease-Relapsed" were used. For the larger group, the sample appears to be reasonable and probably representative. However, the small size of the post-progression group is worrying, particularly as it is likely that the sample would not include the more seriously affected patients in the later stages of the disease. This would imply that the true mean utility may be somewhat lower than 0.618.

Another concern is that the models include additional costs of subsequent treatment episodes, but do not allow any adjustment to outcomes, including mean utility values. Given that some proportion of subsequent treatments can be expected to result in full or partial response for some patients, it would be expected that the mean utility value should be improved somewhat to reflect these benefits.

Taken together it is not clear whether the post-progression utility value used in the models should be considered optimistic or pessimistic. In view of the greater uncertainty involved in this parameter, it should be subject to wide SA. Table 5-15 illustrates the impact of a wide variation in values for this parameter; it appears that even substantial changes in post-progression utility do not have a major impact on cost-effectiveness ratios.

Table 5-15: Sensitivity of cost-effectiveness results to post-progression utility value in the submitted models

	Incremental cost/QALY					
Comparison	**Submitted[1] base case 2 ARM model**	**Utilities: 0.805/ 0.805**	**Utilities: 0.805/ 0.4**	**Submitted[1] base case 4 ARM model**	**Utilities: 0.805/ 0.805**	**Utilities: 0.805/ 0.4**
R-CHOP>R vs CHOP>R	-	-	-	£16,749	£16,896	£16,580
R-CHOP>R vs R-CHOP>O	-	-	-	£11,904	£12,312	£11,462
R-CHOP>R vs CHOP>O	-	-	-	£11,910	£12,826	£10,995
C-HOP>R vs R-CHOP>O	-	-	-	Dominant	Dominant	Dominant
CHOP>R vs CHOP>O	-	-	-	£9,076	£10,176	£8,060
R-CHOP>O vs CHOP>O	-	-	-	£11,916	£13,307	£10,621
Maintenance vs Observation	£7,721	£8,553	£6,934	-	-	-

1 In the submitted models, the utilities used are 0.805 (pre-progression) and 0.618 (post progression)

Survival analysis: The submitted models depend on the results of parametric survival modelling as the basis for estimating lifetime benefits from use of rituximab. The outcome gains shown in the submitted models are very sensitive to the way this modelling of the trial data is performed. There are several reasons to question the approach taken by the modellers:

1) It is assumed that trend lines for PFS and OS based on trial observations will **continue unchanged** until all patients die. In view of the relatively long expected lifetime of this group of patients (7-10 years median survival from diagnosis), this seems to be a brave suggestion. In addition, the modellers acknowledge that after relapse, patients will undergo a series of further treatments, each of which may modify the prognosis of patients in different ways.

2) The MS provides **'goodness of fit'** measures for a range of different types of statistical model, and selects Weibull as the base case function with Log-logistic as an alternative. However, it is far from clear that this choice can be justified from the analysis which suggests that other functions may be preferable for most of the comparisons being analysed.

3) All the fitted survival models assume that non-zero hazards occur in all comparisons immediately after randomization. This is true for patients who do not achieve a response to treatment where lack of response justifies exclusion from the second randomisation. However, for the other four groups, this assumption is false because the groups are selected on the basis of achieving a response to treatment which justifies their inclusion in the second randomization i.e. they are still alive and have not experienced disease progression when assessed for phase 2 of the trial. Thus for these four groups there is a **protocol driven event-free period** equivalent to the time it takes to undergo six cycles of chemotherapy and a formal assessment prior to randomization of at least 126 days (the true mean duration of this period can only be obtained from analysis of patient level data). The impact of the omission of this factor on the estimation of survival model parameters is profound - it alters the shape of the hazard function (changing the relative 'goodness of fit' of different statistical models) and also substantially alters the long-term estimated survival.

4) In estimating model parameter values from the trial data, the modellers have calibrated groups of patients in pairs and assume that the treatments share common parameters, except for a 'treatment effect' parameter which is added to one of the common parameters to capture the influence of rituximab maintenance therapy. Thus they estimate **only three parameters**, instead of the four required to fit the two functions independently. This approach is justified on the grounds of making a proportional hazards assumption, but this assumption has not been substantiated by reference to the trial evidence. The ERG believes there are good grounds for questioning this strong assumption, which has the effect of over-riding potentially

important differences in response patterns, and may exaggerate the long-term size of the apparent outcome benefits of rituximab.

In view of all these problems, and because of the importance of survival modelling to the economic evaluation of rituximab, the ERG requested further information from the manufacturer about the disposition of patients and the mean time spent in each segment of the treatment pathway. In addition, the ERG requested access to a limited anonymized extract of patient level outcome data from the trial in order to allow the ERG to explore alternative approaches to survival modelling which might overcome these difficulties. The manufacturer did not respond positively to either request.

In the absence of other evidence, the ERG considers that it is prudent to give preference to the observed and reported evidence on PFS and OS, rather than to the manufacturer's projections. The ERG assumes that the observed effects are real and sustainable, but that no additional benefits accrue beyond the chosen cut-off point; for this we have used the same 1500 day limit as used by manufacturer's analysts.

In Table 5-16 the PFS and OS model projections for the six patient subgroups in the 4-arm model are compared to the undiscounted and discounted K-M estimates limited to 1500 days post-randomization. Although in general the K-M estimates are lower than the projections, the pairwise differences (rows 1 vs. 2, 3 vs. 4 and 5 vs. 6) are reduced to a much greater extent, illustrating the influence of joint parameter estimation on projection-based outcome gain results.

Table 5-16: Overall survival and progression-free survival estimated from K-M plots up to 1500 days from first randomization, compared to model lifetime projections

	Progression-free survival (years)			Overall survival (years)		
Treatment subgroup	**Model estimate**	**K-M undiscounted**	**K-M discounted**	**Model estimate**	**K-M undiscounted**	**K-M discounted**
CHOP>ineligible	1.401	1.392	1.355	4.355	2.870	2.745
RCHOP>ineligible	1.926	1.873	1.806	4.500	2.844	2.720
CHOP>O	1.500	1.698	1.654	5.270	3.435	3.275
CHOP>R	3.330	2.987	2.858	6.573	3.782	3.598
R-CHOP>O	2.538	2.452	2.361	5.872	3.662	3.488
R-CHOP>R	3.406	3.071	2.933	6.701	3.853	3.661

The ERG has used the submitted 4-arm model to obtain cost-effectiveness results employing the K-M 1500-day outcome estimates, making appropriate adjustments to care costs (for routine maintenance and post-progression treatment). Table 5-17 compares these to the submitted manufacturer's base case results: in all cases the cost-effectiveness of use (or greater use) of rituximab worsens, though to different degrees, so that some strategies no longer appear to be cost effective.

Table 5-17: Effect of using restricted K-M outcome estimates on modelled cost-effectiveness

	Model projections			K-M estimates		
Comparison	**IC**	**IQ**	**ICER**	**IC**	**IQ**	**ICER**
R-CHOP>R vs CHOP>R	£6,196	0.3699	£16,749	£7,398	0.2015	£36,718
R-CHOP>R vs R-CHOP>O	£5,531	0.4646	£11,904	£5,298	0.1728	£30,665
R-CHOP>R vs CHOP>O	£11,927	1.0014	£11,910	£11,101	0.4580	£23,721
CHOP>R vs R-CHOP>O	- £665	0.0947	Dominant	- £2,100	- 0.0287	£73,140
CHOP>R vs CHOP>O	£5,731	0.6315	£9,076	£3,703	0.2665	£13,895
R-CHOP>O vs CHOP>O	£6,396	0.5368	£11,916	£5,803	0.2952	£19,657

IC = Incremental discounted cost per patient, IQ = Incremental discounted QALYs per patient, ICER = Incremental cost per QALY gained

5.6 Revised cost-effectiveness results and uncertainty

The combined effect of the corrections and amendments suggested above by the ERG are shown in Table 5-18. It is evident from this table that the assumptions made about the estimation of outcome gains are most influential on the point estimates of cost effectiveness.

It is clear that the treatment strategies involving only the single use of rituximab, i.e. for induction of remission or for maintenance of remission, are the most cost-effective options (£16,488 per QALY gained and £13,122 per QALY gained respectively). Moreover, direct comparison of these two options involves relatively small differences in both costs and QALYs which means the estimated ICER is subject to much uncertainty. A comparison of dual use of rituximab with no use also appears to be moderately cost effective when considered in isolation (£25,978 per QALY gained).

However, a different picture emerges if we consider sequential decision-making. To illustrate, if the first decision is to give rituximab once compared to never i.e. as induction or as maintenance, then the next decision is conditional i.e. would it be cost effective to then prefer dual (R-CHOP>R) use of rituximab to single use? Following this approach, it appears that the additional benefits of dual use do not warrant the additional costs incurred. Compared to both single use strategies, dual use rituximab is associated with ICERs above £42,000 per QALY gained, and would not normally be considered cost effective. Yet, because the R-CHOP>R comparison with 'no use' also appears to be moderately cost effective, the simple reasoning based on point estimates cannot be considered decisive.

The more appropriate approach in this instance is to use the results of a comprehensive PSA in the form of a combined cost-effectiveness acceptability probability plot, to indicate which of the four strategies has the highest probability of being preferred across a range of WTP thresholds. This would yield an updated version of Figure 29 in the MS (MS p.173). Unfortunately, it is not possible to carry out this analysis using the information available to the ERG, primarily because without information on the standard error of K-M estimates of OS and PFS it is not possible to incorporate uncertainty in outcomes into the PSA. This

would require access to the requested extract of patient level data, or to the requested details of patient disposition and K-M mean durations which were not provided by the manufacturer. It is not possible to make approximate adjustments to the submitted PSA which could be relied upon in this instance, because the alterations to outcome benefits are both very large and very influential.

It therefore appears that some use of rituximab in the treatment of FL is probably cost-effective. However, it is impossible for the ERG to be confident in preferring either or both single use strategies over the dual use strategy, all of which could be shown to have the highest probability of being cost effective were the necessary information available.

Table 5-18: Combined effect on cost effectiveness of applying ERG modifications to the submitted 4-arm model

	Model projections			ERG modifications[1] but using original outcome projections			ERG modifications including K-M outcome estimates		
Comparison	**IC**	**IQ**	**ICER**	**IC**	**IQ**	**ICER**	**IC**	**IQ**	**ICER**
R-CHOP>R vs CHOP>R	£6,196	0.3699	£16,749	£8,849	0.3705	£23,882	£8,660	0.2015	£42,982
R-CHOP>R vs R-CHOP>O	£5,531	0.4646	£11,904	£7,686	0.4656	£16,509	£7,289	0.1728	£42,192
R-CHOP>R vs CHOP>O	£11,927	1.0014	£11,910	£12,149	1.0034	£12,108	£12,157	0.4680	£25,978
CHOP>R vs R-CHOP>O	- £665	0.0947	Dominant	- £1,163	0.0951	- £12,232	- £1,371	- 0.0287	£47,734
CHOP>R vs CHOP>O	£5,731	0.6315	£9,076	£3,300	0.6329	£5,214	£3,497	0.2665	£13,122
R-CHOP>O vs CHOP>O	£6,396	0.5368	£11,916	£4,463	0.5378	£8,298	£4,867	0.2952	£16,488

IC = Incremental discounted cost per patient, IQ = Incremental discounted QALYs per patient, ICER = Incremental cost per QALY gained

[1]ERG modifications:
- amended discounting logic
- increased cost of drug administration
- revised calculation of relapsed treatment costs
- inclusion of £5,000 per patient terminal care costs
- replace projected overall and progression-free survival estimates with K-M estimates at 1500 days (right-hand section of table only)

5.7 Summary of cost-effectiveness evidence

5.7.1 Economic evaluation results

Base case: manufacturer

- The manufacturer reports a range of ICERs for the six possible combinations of the four treatment strategies. The comparison of R-CHOP>R versus R-CHOP yields an ICER of £16,749 per QALY gained
- Results of PSA conducted by the manufacturer suggest that, based on the assumptions made and the evidence available, that R-CHOP>R compared with CHOP>R has a high probability of being cost-effective at the WTP threshold of £30,000 per QALY

Base case: ERG

- The ERG substitutes different values for several of the parameters in the 4-arm economic model. The most influential changes made to costs include: increasing the costs of chemotherapy administration and re-calculating post-progression treatment costs. Both changes increase the ICER for the R-CHOP>R versus CHOP>R comparison to £18,204 and £22,688 per QALY gained respectively
- The most influential change made by the ERG is to the analysis of survival data. The ERG used the observed and reported PFS and OS values rather than the manufacturer's projections to calculate relevant ICERs.
- The cumulative effect of all of the ERG changes, including the K-M outcome estimates, increases the ICER for the R-CHOP>R versus CHOP>R comparison from £16,749 to £42,982
- Single use of rituximab (i.e. induction of remission or maintenance of remission) appears to be cost effective. Dual use of rituximab compared to no use appears to be cost effective. However, it is impossible to recommend either or both single uses of rituximab or dual use of rituximab due to limited data

5.7.2 Economic issues and uncertainties

- What is the most appropriate approach to the modelling of survival data?
- How should post-progression treatment costs be included in the model?
- Incomplete data from the manufacturer means that the necessary PSA could not be undertaken by the ERG and therefore currently decision-making in this area cannot be fully informed

6 Discussion

The MS presents a case for the use of rituximab (MabThera) for the treatment of relapsed/refractory FL. The current marketing authorization for rituximab is for "adults with relapsed/refractory FL responding to induction therapy with chemotherapy with or without rituximab". NICE is currently pursuing clarification of this authorization with both the manufacturer and the EMEA. The key question is whether or not this marketing authorization confers a **single** licence for the use of rituximab as maintenance in patients responding to induction therapy. Or, whether it confers **two separate** licences for (i) the use of rituximab as maintenance therapy for responding patients and (ii) the use of rituximab in combination with chemotherapy as induction therapy at first or second relapse. In the MS, the manufacturer presents clinical and economic evidence to support the use of rituximab in both settings. The ERG critiques all of the evidence contained in the MS.

The SR performed by the manufacturer appropriately identified two clinical trials (EORTC and GLSG-FCM) for inclusion in their SR. Results from the EORTC trial furnish the principal clinical evidence presented in the MS. The EORTC trial is a well-conducted RCT, the results of which demonstrate that the ORR is superior for patients when rituximab is used in combination with chemotherapy (R-CHOP) as an induction therapy after first or second relapse compared to chemotherapy alone. The trial also demonstrates that rituximab maintenance therapy is more clinically effective than observation in patients who have responded to previous induction therapy with or without rituximab. All groups, regardless of induction therapy, significantly benefited from receiving rituximab in the maintenance phase.

However, the EORTC trial only included rituximab naïve patients. Consideration must therefore be given to the generalisability of these results to future NHS patients in England and Wales following the recommendation by NICE[2] that all patients with FL should receive rituximab as first-line therapy.

Clinical evidence from the GLSG-FCM trial is cited as supporting evidence for the use of rituximab. Again, the RCT evidence appears to demonstrate that patients who receive rituximab in combination with FCM in the induction phase have improved outcomes compared to patients who receive FCM alone. In the maintenance phase, rituximab improved patient outcomes compared with observation alone. However, only 65 of the 147 randomised patients in the maintenance phase were FL patients and the number of FL patients who completed the treatment cycles is unknown.

The cost-effectiveness section of the MS describes two distinct but related economic models. The maintenance 2-arm model was designed to evaluate the cost effectiveness of rituximab as

a maintenance therapy only (following response to an induction therapy) compared to observation only (no treatment until relapse). The induction plus maintenance 4-arm model was designed to evaluate whether the use of rituximab as an induction therapy in addition to maintenance therapy was cost effective. In the 4-arm model there are six different treatment comparisons derived from the four possible treatment strategies combining induction and maintenance options. Both models are based on clinical data from the EORTC trial and the ERG believes it to be appropriate to focus on the results of the 4-arm model due to the availability of key clinical data for relevant subgroups of patients. Based on the 4-arm model, the ICERs, using the model projections as set out in the MS, show that the use of rituximab in all combinations is likely to be cost effective. The comparison of R-CHOP>R versus CHOP>R yields an ICER of £16,749 and is the primary focus of the MS.

The ERG acknowledges that the economic models submitted by the manufacturer are implemented to a generally high standard, clearly presented and with a large amount of source information included to aid traceability. The layouts of the various elements of the models are generally logical, and the formulae employed are straightforward.

On detailed examination of the models, the ERG identified a minor anomaly in the model coding which affected estimates of both costs and outcomes. Correction of this anomaly favoured the rituximab patients. In terms of costs, the ERG made two adjustments which increased the R-CHOP>R versus CHOP>R ICER. Firstly, the outpatient cost (£86) is replaced by a chemotherapy administration cost (£504) in order to reflect that demanding chemotherapy regimens are typically given within a day-case setting and the ICER increases from £16,749 to £18,204. Secondly, the calculation of alternative post-progression treatment costs by the ERG also increases the ICER from £16,749 to £22,688.

In terms of utilities, changing the post-progression utility values does not have a major impact on the ICERs. However, the preferred approach to survival modelling does impact on the size of the ICER for every possible combination in the 4-arm model. The ERG identifies four areas of concern regarding the manufacturer's estimation of lifetime benefits from use of rituximab. In order to overcome such concerns, the ERG requested additional information from the manufacturer about the disposition of patients and the mean time spent in each segment of the treatment pathway. The manufacturer declined to provide this information. Consequently, the ERG used the observed and reported evidence on PFS and OS from the EORTC trial rather than the manufacturer's projections. In doing so, the ICERs for the six possible combinations now range from £13,895 to £73,140.

The ERG calculated the cumulative effect of all of the changes on the ICERs. It is clear that the single use strategies are the most cost effective options i.e. use of rituximab for induction

of remission (£13,122 per QALY gained) or for maintenance of remission (£16,488 per QALY gained). Dual use strategies compared to single use strategies are the least cost effective options at around £42,000 per QALY gained. A comparison of dual use of rituximab with no use of rituximab also appears to be moderately cost effective (£26,000/QALY gained). However, in order to fully inform decision-making about the preferred use of rituximab for FL, a comprehensive PSA in the form of a cost-effectiveness acceptability plot is required. However, as all of the necessary data were not available to the ERG, it was not possible to carry out this assessment.

In summary, the ERG agrees that the use of rituximab for the treatment of FL is probably cost-effective, but cannot confidently recommend either or both single use strategies over the dual use strategy based on the available data.

6.1 Implications for future research

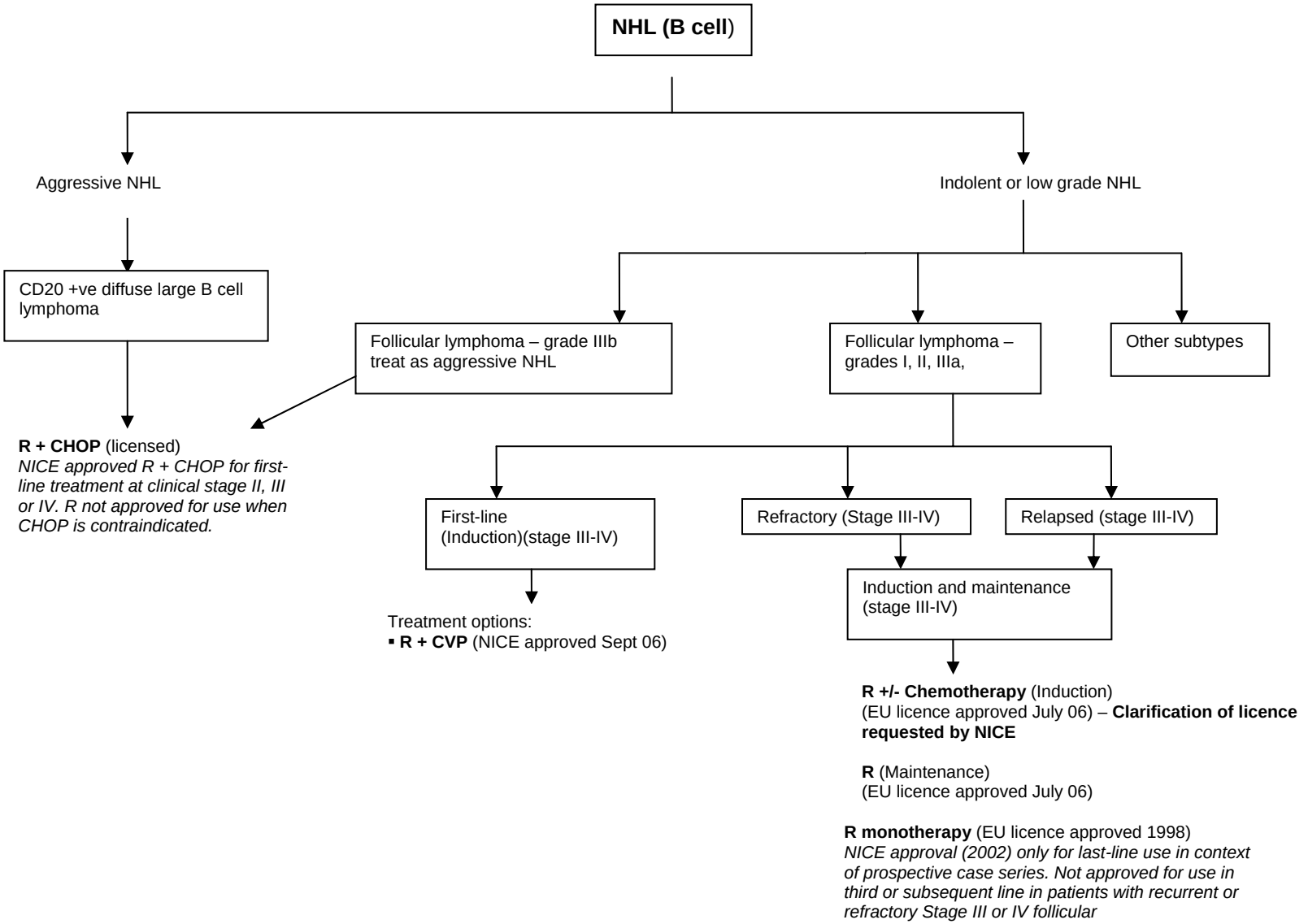
There is substantial uncertainty around the clinical effectiveness of rituximab in combination with chemotherapy for patients at first or second relapse who have previously received rituximab as part of their first-line treatment. Also, there is substantial uncertainty around the clinical effectiveness of rituximab maintenance for patients who have previously received rituximab in combination with chemotherapy at relapse **and** rituximab as part of their first-line treatment The GLSG-FCM trial, which only includes a small number of non-rituximab naïve FL patients, is the only source of clinical trial evidence for the real population of interest to the NHS in England and Wales.

In addition, to inform NHS decision-making, future trials need to include relevant treatment comparisons where the primary outcomes are powered to ensure that any differences in outcomes are clinically and statistically significant (e.g. R-CHOP>R versus CHOP>R, R-CHOP>R versus CHOP>O).

Finally, close monitoring and long-term surveillance of all FL patients in receipt of rituximab are necessary.

6.2 Appendix 1: Treatment options for NHL

Figure 6-1: Forms of non-Hodgkin's lymphoma (NHL) treatment options for stage III-IV, current licensed status for rituximab (R) and relevant NICE guidelines



6.3 Appendix 2: Critical appraisal of included RCTs

Table 6-1: Critical appraisal of RCTs included in this review

Criterion	EORTC	GLSG-FCM
Concealment of allocation	Open-label study. Placebo control for a study involving IV rituximab administration and oral and IV pre-medication would been very difficult and probably considered unethical during maintenance/observation Endpoints are fairly objective and placebo effect not likely to be a major problem	Open-label study As EORTC
Randomisation technique	An appropriate technique was used: centralised using minimisation approach of Pocock and Simon	An appropriate technique was used: centralised using permutated block approach
Sample size justified adequately?	Yes. Though given there was no data on which to base any assumption on the efficacy of rituximab maintenance at the time of protocol development	Yes Comment as for EORTC
Adequate follow-up	Yes Closure of first- and second-randomisations was mandated by independent monitoring given highly statistically significant differences in outcomes, making further follow-up very unlikely to change outcomes materially. Follow up appropriate to trajectory of disease with follow-up being longer than the median PFS after induction therapy	Yes Statistical design mandated that study end was determined by adequate events for statistical certainty so follow-up was self correcting. Again, follow-up appropriate to trajectory of disease with follow-up being longer than the median PFS after induction therapy
Assessors aware of treatment allocation?	Unclear Although no reference made to blinding of assessors it is likely that scan results which would determine response/progression would, in most cases, be reported by radiologists with no interest in the study	As EORTC
Parallel group/cross-over	Parallel-group Primary endpoints in both parts of study not influenced by post-study treatment	Parallel-group Primary endpoints in both parts of study not influenced by post-study treatment
Carried out in UK?	International study including UK There were 37 UK study centres who recruited 102 of the 465 patients randomized. Indicating that UK clinicians found this study pertinent to their practice and had plenty of patients fitting the study entry criteria within their clinical population. As explained in Section 4.1 the control treatment in this study (induction with CHOP followed by no further treatment until relapse) is used in routine clinical practice in the UK	No However there are no obvious differences between the study population and non-trial patients requiring treatment for relapsed FL in the UK, except, perhaps that the study patients are slightly younger . However, disproportionate recruitment of younger patients is a general problem in oncology clinical trials – the study had no upper age limit for participation. As explained in Section 4.1 the control treatment in this study (induction with fludarabine-based chemotherapy followed by no further treatment until relapse) is used in routine clinical practice in the UK

Dosage regimen	For both induction and maintenance portions of the trial dosage regimens accord with SmPC recommendations	The SmPC does not make specific recommendations on the combination of FMD and rituximab, but the use of 1 dose per cycle is consistent with all other recommendations for the use of rituximab given concomitantly with cytotoxic chemotherapy The maintenance schedule (8 doses of rituximab delivered in 2 block of 4 weekly doses 3 and 6 months after completion of induction therapy) is not consistent with the SmPC, which recommends 8 x 3-monthly doses, but does deliver the same total dose of rituximab as maintenance
Study groups comparable?	Yes See Section 5.3.2	Yes See Section 5.3.2
Appropriate statistical tests?	Yes. See Section 5.3.5. Note that statistical analysis in this study has been subjected to both peer-review for publication and EMEA scrutiny	Yes. See Section 5.3.5. Note that statistical analysis in this study has been subjected to peer-review for publication
ITT analysis?	Yes for both induction and maintenance portions of study	No for induction phase. Although investigators report that analysis was done on an intention to treat basis, they excluded 10 patients from the original published analysis on the basis of inadequate documentation and 9 who were withdrawn between randomisation and receiving any study treatment Yes for maintenance portion, though in 19 patients documentation was not available at the time of analysis

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