Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

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1. Title of the project:

Rituximab for the first-line treatment of stage III-IV follicular lymphoma (Review of TA 110)

2. TAR team

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3. Plain English Summary

Lymphomas are cancers of the lymphatic system, which is a system of tubes and glands in the body which filters body fluid and fights infection.[1] There are two main types of lymphoma: Hodgkin's and Non-Hodgkin's Lymphoma (NHL). NHL can be divided into low grade and high grade lymphomas, depending on how quickly they grow and spread. Follicular lymphoma (FL) is a type of NHL low-grade lymphoma of cells called B-lymphocytes.

Grading and staging of the disease informs treatment pathways. Staging of NHL refers to how many lymph nodes are affected by the disease and informs the treatment and prognosis of the disease. There are four stages of NHL. Stage I disease involves only one group of lymph nodes or lymphoma in one organ of the body is affected. Stage II refers to disease that has spread to two groups of lymph nodes or an organ and one or more group of lymph nodes, with a criteria being that these are on the same side of the diaphragm. Stage III and IV are more advanced disease. Stage III includes lymph nodes affected on both sides of the diaphragm, and stage IV disease indicates that the NHL has spread from the lymph nodes, for example, to the liver, bone marrow, or blood.[1]

Histological grading of the disease is determined by the WHO classification grades I, II, IIIa or IIIb,[2] which categorise disease into low grade/indolent disease or high grade/aggressive disease. There is consensus that grade IIIb disease should be classified as aggressive and treated as such.[2]

NHL accounts for approximately 4% of all cancers diagnosed in the UK, with 9703 new cases registered in England and Wales in 2007, and 3978 registered deaths in 2008.[3] FL accounts for 30% of all low grade lymphomas[1] and has a UK incidence of approximately 4 per 100,000.[2] The median age of patients with FL is around 60 years and approximately 50% of patients will present with bone marrow involvement (i.e. stage IV disease).[2] Over 70% of people with follicular lymphoma are still alive five years after the diagnosis,[4] with median survival of nine to ten years.[5]

Treatment of advanced (stage III or IV) FL is palliative; the aim of treatment being to prolong survival, achieve the longest possible remission and improve quality of life. Treatments are usually administered intermittently over a period of several years, with the expectation that the disease will relapse and remit during that time.[2]

Currently, rituximab (Mabthera®, Roche Products) in combination with cyclophosphamide, vincristine and prednisolone (CVP regimen) is recommended by NICE guidance (TA110) as a first-line treatment option for symptomatic stage III or IV follicular lymphoma.[6] However, the market authorisation has changed for rituximab, and it is now licensed for use for the treatment of previously untreated patients with symptomatic stage III-IV follicular lymphoma in combination with other chemotherapies in addition to CVP.[7]

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

4. Decision problem

4.1 Purpose of the decision to be made

This assessment will address the question: "What is the clinical and cost-effectiveness of rituximab (in its licensed indication) with chemotherapy for the first-line treatment of symptomatic stage III-IV follicular lymphoma".

4.2 Clear definition of the intervention

Rituximab (Mabthera®) is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy at a recommended dose of 375 mg/m^2 body surface area per cycle, for up to 8 cycles.[7] This assessment will include interventions where rituximab is given in combination with the following chemotherapy regimens:

- **CVP**: cyclophosphamide, vincristine and prednisolone
- **CHOP**: cyclophosphamide, doxorubicin, vincristine and prednisolone

- **CNOP**: cyclophosphamide, mitoxantrone, vincristine and prednisolone
- **CHVP:** cyclophosphamide, doxorubicin, vindesine, prednisolone
- **MCP:** mitoxantrone, cholorambucil, and prednisolone
- **FCM**: fludarabine, cyclophosphamide and mitoxantrone
- **FM**: fludarabine and mitoxantrone
- Bendamustine

If the TAR team become aware of another widely used chemotherapy regimen used in combination with rituximab, this will be searched for separately at that time. Note that due to the scope specifying the intervention as *rituximab given in combination with chemotherapy*, interventions including rituximab and radio-immunotherapy or bone marrow/stem cell transplant are not considered as an intervention for this appraisal.

Bendamustine is not currently licensed as a first-line treatment with rituximab within this population but is included as a combination chemotherapy agent (with rituximab) as the anticipated date of licensing is not known and could occur within the time scales of the appraisal.

Rituximab (Mabthera®) is also licensed for treatment of follicular lymphoma at other stages within the treatment pathway, other types of NHL (and has indications for treatment of chronic lymphocytic leukaemia and rheumatoid arthritis). These indications for use are not included within the final scope but are included below for completeness:

- Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without Mabthera.
- Rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.[7]

4.3 Place of the intervention in the treatment pathway

The review will focus on the use of rituximab (in its licensed indication) in combination with chemotherapy as first-line treatment of symptomatic stage III-IV follicular lymphoma.

4.4 Relevant comparators

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

- **CVP:** cyclophosphamide, vincristine and prednisolone
- **CHOP:** cyclophosphamide, doxorubicin, vincristine and prednisolone
- **CNOP:** cyclophosphamide, mitoxantrone, vincristine and prednisolone
- **CHVP:** cyclophosphamide, doxorubicin, vindesine, prednisolone
- **MCP:** mitoxantrone, cholorambucil, and prednisolone
- **FCM:** fludarabine, cyclophosphamide and mitoxantrone
- **FM:** fludarabine and mitoxantrone
- Bendamustine

In addition, each intervention will be compared against each other.

4.5 Population and relevant sub-groups

The population will comprise adults with symptomatic stage III-IV follicular lymphoma (a Non-Hodgkin's lymphoma) who have not received any previous treatment. If the evidence allows, subgroup analyses by type of chemotherapy regimen received will be considered, although initial clinical advice indicates that there are no relevant sub-groups within the population that need to be addressed.

4.6 Key factors to be addressed

This review will aim to evaluate the following objectives:

- Evaluate the clinical effectiveness of rituximab in combination with chemotherapy as first-line treatment in terms of overall survival, progression-free survival, response rates, duration of disease remission, and health-related quality of life.
- Evaluate the adverse effect profile and toxicity.

- Evaluate the cost-effectiveness of rituximab in combination with other chemotherapy in terms of incremental cost per quality-adjusted life year.
- Estimate the possible overall cost in England and Wales.

4.7 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment

There was no scoping workshop for this appraisal.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care[8] and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).[9]

5.1. Search strategy

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature pertaining to rituximab for the treatment of follicular lymphoma.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

5.1.1. Electronic searches

Search strategies will be used to identify relevant trials (as specified under the inclusion criteria, below) and systematic reviews/meta-analyses (for identification of additional trials). Searches will not be restricted by language or publication date. An example of the Medline search strategy is shown in Appendix 1. This will be adapted for other databases. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager© software.

5.1.2. Databases

The following electronic databases will be searched from inception: MEDLINE including Medline in process (Ovid); CINAHL; EMBASE; The Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI); NIHR Clinical Research Network Portfolio; National Research Register (NRR) archive 2000-2007; Current Controlled Trials; Clinical Trials.gov.; BIOSIS. Relevant conference proceedings will be searched, for example the American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), American Society of Hematology (ASH) and the British Society for Haematology (BSH) will be searched.

5.2 Inclusion/Exclusion criteria

5.2.1 Population

The population will comprise adults with symptomatic stage III-IV follicular lymphoma (a non-Hodgkin's lymphoma) who have not received any previous treatment.

5.2.2 Interventions

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

5.3. Comparators

The comparator will be chemotherapy without Rituximab, which for this review are considered to be one of the following: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM or bendamustine. In addition, the interventions will be compared against each other.

5.4. Outcomes

- overall survival
- progression free survival
- response rates
- duration of disease remission
- adverse effects of treatment
- health related quality of life

5.5 Sub-groups to be examined

If the evidence allows, subgroup analyses by type of chemotherapy regimen received will be considered.

5.6 Inclusion criteria

According to the accepted hierarchy of evidence, randomised controlled trials (RCTs) will be included for clinical effectiveness, as they provide the most authoritative form of evidence. If insufficient data are not available from RCTs, observational studies or clinical trials may be considered. Studies published as abstracts or conference presentations will only be included if sufficient details represented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be used as sources of references.

5.7 Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound will be excluded from the review as well as the following publication types: non-randomised studies (except for adverse events); animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers and reports where insufficient methodological details are reported to allow critical appraisal of study quality.

5.8 Data extraction strategy

Studies will be selected for inclusion through a two-stage process according to the above inclusion/exclusion criteria. Titles and abstracts will be examined for inclusion by one reviewer. Screening will be checked by a second reviewer on ten percent of citations and a kappa coefficient will be calculated to measure inter-rater reliability. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Full manuscripts of selected citations will be retrieved and assessed by one reviewer against the inclusion/exclusion criteria. Data will be extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study

5.9 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, according to (adapted) criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials (RCTs).[8] (See Appendix 2).

Consideration of study quality to assess RCTs will include the following factors: method of randomisation, allocation concealment, blinding of patients, outcome assessors and data-analysts, numbers of participants randomised, baseline comparability between groups, specification of eligibility criteria, whether intent to

treat analysis is performed, completeness of follow up and whether study power calculations are performed and reported.

5.10 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate (i.e. populations, interventions and outcomes are comparable), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed or random effects models, using the Cochrane Collaboration Review Manager© Software (version 5.0).[10] Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

It is anticipated that the work will require a network meta-analysis to be undertaken to determine efficacy. This will be populated with all identified trials involving an intervention or a comparator. It is noted that the network meta-analysis could potentially be strengthened by the inclusion of RCTs involving two pharmaceuticals that were neither interventions nor comparators, provided there were RCTs comparing these pharmaceuticals with an intervention or a comparator. However, literature searches for all RCTs from these pharmaceuticals will not be conducted as they are likely to have little impact on the results of interest and would have significant resource implications.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the cost-effectiveness associated with rituximab in combination with chemotherapy will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1; this economic search filter is presented in Appendix 1. Relevant studies identified and included in the manufacturer's submission will also be included. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal[11] checklist for economic evaluations together with the Eddy checklist on mathematical model[12]

6.2 Systematic literature search for other data related to cost-effectiveness

A search of the broader literature on follicular lymphoma will be undertaken to identify the evidence base on HRQoL (i.e. health state values). The literature search will identify relevant values for appropriate health states. Primary data collection will not be undertaken.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper produced by InterTASC (January 2005).

6.3 Methods for estimating costs and cost-effectiveness

Where appropriate a mathematical model will be constructed by adapting an existing model or developing a new model using available evidence. The model developed will estimate the cost per QALY gained for rituximab and chemotherapy. It is hoped that suitable quality of life data will be identified from the literature, in the absence of quality of life data; the model may use indirect evidence on quality of life from alternative sources. The model will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. Uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA), where uncertainty of all input variables is modelled with probability distribution of their value. The information derived from PSA will be summarised graphically using cost effectiveness acceptability curves.

The time horizon of the analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both cost and QALY will be discounted at 3.5%.

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 20 December 2010. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in blue in the assessment report (followed by an indication of the relevant company name e.g. in brackets).Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

Dr Andrew McMillan has attended Roche Advisory Boards (and received Honoraria) and received sponsorship from Roche to attend International meetings.

9. Appendices

Appendix 1: Draft clinical effectiveness search strategy

1. Cyclophosphamide.af.
2. Cyclophosphamide/
3. 1 or 2
4. vincristine.af.
5. Vincristine/
6. 4 or 5
7. vindesine.af.
8. Vindesine/
9. 7 or 8
10. (prednisolone or prednisone).af.
11. Prednisolone/ or Prednisone/
12. 10 or 11
13. doxorubicin.af.
14. Doxorubicin/
15. 13 or 14
16. (mitoxantrone or mitozantrone).af.
17. Mitoxantrone/
18. 16 or 17
19. (cholorambucil or chlorambucil).af.
20. Chlorambucil/
21. 19 or 20
22. fludarabine.af.
23. Bendamustine.af.
24. 3 and 6 and 12
25. 3 and 15 and 6 and 12
26. 3 and 18 and 6 and 12
27. 3 and 15 and 9 and 12
28. 18 and 21 and 12
29. 22 and 3 and 18
30. 18 and 22
31. 24 or 25 or 26 or 27 or 28 or 29 or 23
32. (CVP or CHOP or CNOP or CHVP or MCP or FCM or FM).af.
33. 30 or 31
34. (rituximab or mabthera or mab thera or rituxan or IDEC-102 or IDEC-C2B8 or Rituksimabi or Rituximabum or anti-CD20 or immunotherapy or 131I-rituximab or rituximab-alliinase conjugate or monoclonal antibod$).af.
35. Antibodies, Monoclonal/
36. 32 or 33 or 34
37. (follicular lymphoma or indolent lymphoma or low grade lymphoma or lymphoma or NHL).ti,ab.
38. (Lymphoma$ adj5 non-hodgkin$).ti,ab.
39. (follic$ adj5 (lymphocyte$ or lymphoma$)).ti,ab.
40. Lymphoma, Follicular/
41. Lymphoma, Non-Hodgkin/
42. 36 or 37 or 38 or 39 or 40

43. 35 and 41
44. Randomized controlled trials as Topic/
45. Randomized controlled trial/
46. Random allocation/
47. Double blind method/
48. Single blind method/
49. Clinical trial/
50. exp Clinical Trials as Topic/
51. 43 or 44 or 45 or 46 or 47 or 48 or 49
52. (clinic$ adj trial$1).tw.
53. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
54. Placebos/
55. Placebo$.tw.
56. Randomly allocated.tw.
57. (allocated adj2 random).tw.
58. 51 or 52 or 53 or 54 or 55 or 56
59. 50 or 57
60. Case report.tw.
61. Letter/
62. Historical article/
63. Review of reported cases.pt.
64. Review, multicase.pt.
65. 59 or 60 or 61 or 62 or 63
66. 58 not 64
67. 42 and 65

Economics filter

1. Economics/
2. exp "Costs and Cost Analysis"/
3. economic value of life/
4. exp economics hospital/
5. exp economics medical/
6. economics nursing/
7. exp models economic/
8. Economics, Pharmaceutical/
9. exp "Fees and Charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw.
13. (economic$ or pharmacoeconomic$ or price$ or pricing$).tw.
14. quality adjusted life years/
15. (qaly or qaly$).af.
16. or/1-15

Appendix 2: Draft quality assessment scale

Was the method used to assign participants to the treatment groups really random?
What method of assignment was used?
Was the allocation of treatment concealed?
What method was used to conceal treatment allocation?
Was the number of participants who were randomised stated?
Were details of baseline comparability presented?
Was baseline comparability achieved?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocations?
Were the individuals who administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?
Were the reasons for withdrawal stated?
Was an intention-to-treat analysis included?

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal[11] checklist for economic evaluation together with the Eddy checklist[12] on mathematical models employed in technology assessments.

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

Additional information that is needed by NCCHTA and NICE.

Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

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Timetable/milestones

Milestone	**Date**
Draft protocol	02 July 2010
Final protocol	13 September 2010
Progress report (to NETSCC)	5 January 2011
Draft assessment report	04 March 2011
Assessment report (simultaneously to NICE and NETSCC)	04 April 2011

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