

National Horizon Scanning Centre

Rituximab (MabThera) for chronic lymphocytic leukaemia

September 2007



This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

Rituximab (MabThera) for chronic lymphocytic leukaemia

Target group

- Chronic lymphocytic leukaemia^a (CLL) – newly diagnosed
- Chronic lymphocytic leukaemia – relapsed.

Technology description

Rituximab (MabThera) is a genetically engineered, humanised monoclonal anti-CD20 antibody, which is in phase III development as a first and subsequent line additive therapy for CLL. Rituximab causes lysis of B lymphocytes, and is administered by intravenous infusion. It is in regulatory trials as a course of six doses: first dose of 375 mg/m² followed by five doses of 500 mg/m².

Rituximab is currently licensed for:

- Combination therapy with standard cytotoxic chemotherapy for other blood cell malignancies, including diffuse large B-cell non-Hodgkin's lymphoma and follicular lymphoma.
- Combination therapy with methotrexate for severe rheumatoid arthritis.

Rituximab is in phase III clinical trials for:

- Multiple sclerosis
- Systemic lupus erythematosus
- Lupus nephritis.

Innovation and/or advantages

Rituximab would be the first immunotherapy agent licensed for first-line therapy in CLL. It would also provide another treatment option for people with relapsed and resistant disease.

Developer

Roche.

Place of use

- | | | |
|--|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis | <input type="checkbox"/> Community or residential care e.g. district nurses, physio | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses |
| <input checked="" type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter | <input type="checkbox"/> Other: | |

Availability, launch or marketing dates, and licensing plans:

Rituximab is in phase III clinical trials for these indications.

NHS or Government priority area:

- | | | |
|--|--|--|
| <input checked="" type="checkbox"/> Cancer | <input type="checkbox"/> Cardiovascular disease | <input type="checkbox"/> Children |
| <input type="checkbox"/> Diabetes | <input type="checkbox"/> Long term neurological conditions | <input type="checkbox"/> Mental health |
| <input type="checkbox"/> Older people | <input type="checkbox"/> Public health | <input type="checkbox"/> Renal disease |
| <input type="checkbox"/> Women's health | <input type="checkbox"/> None identified | <input type="checkbox"/> Other: |

^a Also known as B-cell chronic lymphocytic leukaemia (B-CLL).

This topic relates to the National Cancer Plan.

Relevant guidance

NICE technology appraisals on rituximab:

- Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. Expected publication Dec 2007.¹
- Rituximab for first-line stage III or IV follicular lymphoma. 2006.²
- Rituximab for aggressive non-Hodgkin's lymphoma. 2003.³
- Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. 2002.⁴
- Rituximab for rheumatoid arthritis (refractory). 2007.⁵

NICE technology appraisals on CLL:

- Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. 2007.⁶
- Fludarabine for the second-line treatment of B-cell chronic lymphocytic leukaemia. 2001.⁷

Other guidance:

- NICE Guidance on Cancer Services. Improving outcomes in haematological cancers. 2003.⁸
- Scottish Medicines Consortium. Advice on the restricted use of fludarabine for the treatment of B-cell chronic lymphocytic leukaemia. 2006.⁹
- British Committee for Standards in Haematology. Guideline on the diagnosis and management of chronic lymphocytic leukaemia. 2004.¹⁰

Clinical need and burden of disease

CLL is a chronic, life-threatening and incurable disease, and is the most common form of leukaemia in the Western World. It mainly affects older people, with 75% of diagnoses being made in people over the age of 60.

In England, 1,961 new cases of CLL were diagnosed in 2004¹¹ and in 2005 CLL caused 978 deaths.¹¹ Relative age-standardised 5-year survival rates for patients diagnosed with leukaemia in England and Wales between 1971-1999 were 43% for men and 39% for women.¹² There are two distinct genetic sub-types of CLL, one having a median survival of about 25 years and the other of about 8 years.¹³

Existing comparators and treatments

First-line chemotherapy:

- alkylating agents (usually chlorambucil or cyclophosphamide).
- fludarabine in combination with cyclophosphamide is widely used in UK clinical practice, especially for younger and/or fitter patients (although not currently recommended by NICE).

Relapsed or refractory disease:

- single alkylating agent.
- monotherapy with fludarabine where an alkylating agent alone has proved inadequate.
- fludarabine plus cyclophosphamide (FC).
- alemtuzumab (MabCampath), which also causes lysis of B lymphocytes, is licensed for patients who have failed to respond to an alkylating agent or fludarabine.

Efficacy and safety

Several uncontrolled case series studies have been published.^{14,15,16,17}

Trial name	CLL-8 (ML17102) Phase III Rituximab plus FC versus FC alone – first-line	REACH (BO17072E) Phase III Rituximab plus FC versus FC alone – previously treated	Data comparison from (i) CALGB9712 rituximab plus fludarabine and (ii) CALGB-9011 fludarabine alone – first-line
Sponsor	German CLL Study Group, Roche	Roche	National Cancer Research Institute and other research foundations. ^b
Status	Ongoing (recruitment completed March 2007).	Ongoing (recruitment expected to complete Q3 2007).	Published ^{18,19,20}
Location	Multicentre	Multicentre	Multicentre
Design	Randomised, open label.	Randomised, open label.	Retrospective comparison of data from 2 randomised [(i) phase II and (ii) phase III] clinical trials, using multivariate analysis of patient outcome data.
Participants and trial schedule	n=320; aged 18-75 years; with a life-expectancy of >6 months. <u>Arm A</u> (n=160) fludarabine 25 mg/m ² on days 1-3 and cyclophosphamide 250 mg/m ² on days 1-3. Repeated every 28 days for up to 6 cycles. <u>Arm B</u> (n=160) FC as above plus: ○ first cycle: rituximab 375 mg/m ² on day 1, then ○ subsequent cycles: rituximab 500 mg/m ² on day 1.	n=624; aged over 18; with a life expectancy >6 months; previously treated with: chlorambucil +/- prednisolone; fludarabine, and/or other nucleoside analogue only, and/or alkylating agent combination therapy. <u>Arm A</u> (n=312) FC chemotherapy. <u>Arm B</u> (n=312) FCR immunotherapy. Treatment regimes were as for the CLL-8 study.	Stage III/IV or I/II CLL, with no prior therapy. <u>Trial (i)</u> n=104. Compared treatment with fludarabine plus rituximab concurrently versus sequentially. <u>Trial (ii)</u> n=178. Patients enrolled in the fludarabine arm of a trial comparing fludarabine versus chlorambucil versus both.
Follow-up	Two years from completion of treatment.	Eight years after entry of the last patient.	Median (i) 43 months and (ii) 13 years.
Primary outcome	Event-free survival	Progression-free survival	Progression-free survival and overall survival.
Secondary outcomes	Overall survival; progression-free survival; time to treatment failure; response rate; pharmacoeconomics; and quality of life.	Event-free survival; duration of response; response rate; overall survival; medical resource utilisation; quality of life.	
Results			Fludarabine plus rituximab groups had significantly better progression-free survival (p<0.0001) and

^b Sidney Kimmel Cancer research Foundation, Leukemia and Lymphoma Society of America, D Warren Brown Foundation, Peter Jay Sharp Foundation, and Joel Finkelstein Cancer Foundation.

			overall survival (p=0.0006) than fludarabine alone. Infectious toxicity was similar in the 2 groups.
--	--	--	--

Estimated cost and cost impact

Based on the treatment schedule used in regulatory trials, each course of rituximab (given in 6 doses) costs £9,081.^c Although administered at the same time as the other chemotherapy agents, rituximab is infused over several hours, requiring longer clinic visits, with nursing observation throughout, as well as preparation of the infusion fluid. There are also minor costs associated with the use of steroid and antihistamine pre-medications to prevent rituximab infusion reactions.

Potential or intended impact – speculative

Patients

- | | | |
|---|---|---|
| <input checked="" type="checkbox"/> Reduced morbidity | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Services

- | | | |
|---|--|---|
| <input checked="" type="checkbox"/> Increased use: longer day-case chemotherapy treatment sessions, infusion preparation, and nursing observation needed. | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input checked="" type="checkbox"/> Decreased use: longer progression-free survival would defer/reduce the need for repeat chemotherapy. | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Costs

- | | | |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs: drug costs plus premedication costs, and some additional administration costs | <input type="checkbox"/> Savings: | <input type="checkbox"/> Other: |

References

- ¹ NICE technology appraisal. Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma (in preparation) Expected publication Dec 2007.
- ² NICE technology appraisal. Rituximab for the treatment of follicular lymphoma. TA110 2006.
- ³ NICE technology appraisal. Rituximab for aggressive Non-Hodgkin's lymphoma. TA65 2003.
- ⁴ NICE technology appraisal. Guidance on the use of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. TA37 2002.
- ⁵ NICE technology appraisal. Rituximab for the treatment of rheumatoid arthritis (refractory). TA126 August 2007.
- ⁶ NICE technology appraisal. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. TA119 2007.
- ⁷ NICE technology appraisal. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. TA29 2001.
- ⁸ NICE guidance on cancer services. Improving outcomes in haematological cancers. 2004.

^c Cost (assuming wastage) based on an average body surface area of 1.7 m² and prices from BNF 53, March 2007.

- ⁹ Scottish Medicines Consortium. Advice for NHS Scotland on the restricted use of fludarabine phosphate (Fludara) for the treatment of B-cell chronic lymphocytic leukaemia (10 mg tablet and 50 mg for injection or infusion). No. 176-05 2006.
- ¹⁰ British Committee for Standards in Haematology (BCSH). Diagnosis and management of chronic lymphocytic leukaemia - a guideline. 2004.
- ¹¹ Office of National Statistics, Cancer Statistics series MB1 no. 35. <http://www.statistics.gov.uk>
- ¹² Cancer Research UK website <http://info.cancerresearchuk.org/cancerstats/survival> accessed 8/8/2007.
- ¹³ Montillo M et al. Chronic lymphocytic leukemia: novel prognostic factors and their relevance for risk adapted therapeutic strategies. *Haematologica* 2005; 90: 391-399.
- ¹⁴ Wierda W, O'Brien S, Wen S et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukaemia. *J Clin Oncol* 2005; 23: 4070-4078.
- ¹⁵ Wierda W, O'Brien S, Faderl S et al. A retrospective comparison of three sequential groups with recurrent/refractory chronic lymphocytic leukaemia with fludarabine-based regimens. *Cancer* 2006; 106: 337-345.
- ¹⁶ Keating MJ, O'Brien S, Albitar M et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukaemia. *J Clin Oncol* 2005; 23: 4079-4088.
- ¹⁷ Keating MJ, O'Brien S, Albitar M et al. Extended follow-up of a chemo-immunotherapy regimen FCR (fludarabine, cyclophosphamide and rituximab) as initial therapy for chronic lymphocytic leukemia (CLL). *Blood* 2005; 106: abstract 2118.
- ¹⁸ Bryd JC, Rai K & Peterson BL. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously treated chronic lymphocytic leukaemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. *Blood* 2005; 105: 49-53.
- ¹⁹ Bryd JC, Peterson BL, Morrison VA et al. Randomised phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukaemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood* 2003; 101: 6-14.
- ²⁰ Rai KR, Peterson BL, Appelbaum FR et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukaemia. *N Engl J Med* 2000; 343: 1750-1757.

The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.

The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, Edgbaston, Birmingham, B15 2TT, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.pcpoh.bham.ac.uk/publichealth/horizon