

Roche Submission Executive summary

Background

In 2008ⁱ, the licence for MabThera (rituximab) in the treatment of previously untreated follicular lymphoma was broadened to allow the use of **any** suitable chemotherapy partner, not just the combination of cyclophosphamide, vincristine and prednisolone (CVP) as specified previously. This was based on the results of three additional randomised Phase III studies (GLSG'00^{ii,iii}, OSHO-39^{iv} and FL-2000^{v,vi,vii,viii}).

This change has increased the opportunity for physicians to select the most appropriate chemotherapy regimen in accordance with the specific needs and characteristics of their patients, and provides much greater flexibility when considering the best tailored care for first-line follicular lymphoma patients requiring systemic treatment.

Clinical Practice

Approximately 93% of all eligible previously untreated stage III-IV follicular lymphoma patients in the UK currently receive rituximab in combination with chemotherapy as standard treatment^{ix}. Of these patients, in accordance with the current NICE guidance (TA110) approx 67% are treated with rituximab plus CVP. A further 16% are treated with R-CHOP, with the remainder receiving rituximab combined with other chemotherapies^{ix}.

There is no one single combination chemotherapy regimen that has emerged as the preferred partner for rituximab in this setting, which is likely driven by several factors, including:

1. The **clinical heterogeneity** in patients presenting with follicular lymphoma requiring treatment;
2. **Patient choice**; acceptability of alopecia, tolerance of side effects, age and geographical residence relative to the treating unit;

3. A **breadth of data** from several randomised trials and a meta-analysis^{iii,iv,vii,x} demonstrating that the clinical benefit associated with the addition of rituximab to chemotherapy is independent of the chemotherapy backbone. It was these data that formed the core of a filing package submitted to the EMA by Roche that lead to a broadened R-chemotherapy licence for rituximab in January 2008 for patients with previously untreated follicular lymphoma.
4. Demonstrated **cost effectiveness** of R-chemotherapy^{xi}
5. **No directly comparative, randomised trial data** exists to show that the addition of doxorubicin to rituximab-based upfront immunochemotherapy improves clinical outcomes (ie no head-to-head data directly comparing R-CHOP vs R-CVP); and a recent meta-analysis which demonstrated that both regimens have a clinical utility when used in appropriate patients.^{xii}
6. Individual preference amongst haematologists as to whether to spare patients from anthracycline-related toxicities up front and reserve R-CHOP for when a patient's disease relapses or transforms, or treat more aggressively upfront so as decrease the risk of disease transformation.

Clinical Effectiveness

The data from all the studies presented in this submission consistently demonstrate that rituximab significantly improves the outcome of patients with advanced stage FL when given first-line in addition to any chemotherapy regimen. Specifically, the addition of rituximab to chemotherapy significantly improves response rates and long-term outcomes for patients with advanced stage FL receiving:

- six to eight cycles of R-CHOP (GLSG'00)
- eight cycles of R-MCP (study OSHO-39)
- six cycles of R-CHVP-I (study FL2000)

Additional evidence from meta-analyses, retrospective cohort studies and a number of phase II trials supports a consistent clinical benefit including improved overall survival when rituximab is added to any chemotherapy regimen.

All these results are in line with the improved clinical outcome seen in patients who received eight cycles of CVP in combination with rituximab in the pivotal study M39021. The key results for all 4 studies are summarized in the table below.

Table 1: Summary of main efficacy findings from four key RCTs

<i>Parameter</i>	M39021 Error! Bookmark not defined. Error! Bookmark not defined.		GLSG'00 ^{ii,iii}		OSHO-39 ^{iv}		FL2000 ^{v,vi,vii,viii}	
	CVP	R-CVP	CHOP	R-CHOP	MCP	R-MCP	CHVP-IFN	R-CHVP-IFN
<i>Median follow up</i>	53 months		56 months		47 months		60 months	
<i>Median Months</i>	7 ⁺	27 [*]	35 ⁺	Not reached ⁺	28.8 ⁺	Not reached ⁺	35 [^]	Not reached [^]
<i>p-value</i>	<0.0001		<0.0001		<0.0001		0.0004	
<i>OS rates</i>	77%	83%	84% ^b	90% ^b	74 ^c	87 ^c	79 ^b	84 ^b
<i>p-value</i>	0.029		0.0493		0.0096		0.1552	

⁺ TTF, time to treatment failure; ^{*} PFS, progression free survival; [^] EFS, event free survival; ^bFive-year OS rates; ^cFour-year OS rates

Across all studies, no new safety signals were observed and rituximab did not add to the toxicity of chemotherapy.

Cost Effectiveness

The improved effectiveness and increased costs of R-chemotherapy relative to chemotherapy alone results in ICERs consistently below £10,000 irrespective of which chemotherapy rituximab was added to. In addition probabilistic sensitivity

analysis illustrated the probability of R-chemotherapy being costs effective at a threshold of £20,000 to be exceptionally high for all of the comparisons (range 98% to 100%).

Table 2: ICERs of Each Pair-wise Comparison (£'s)

Comparison	R-CVP	R-CVP OLS	R-CHOP	R-MCP	R-CHVP
Incremental Cost	1,325	2,486	6,312	6,268	6,247
Incremental QALY	0.867	0.443	1.096	1.289	0.675
ICER (£ per QALY)	1,529	5,611	5,758	4,861	9,251

Whilst there is certainty of the economic result within each comparison, care should be taken in attempting to compare cost and QALYs across the results of the economic models as this is fraught with the same generic issues faced by any naive indirect comparison across trials. Differences in trial populations and design can have a large confounding effect on the outcomes.

Budget Impact

Since the majority of patients receiving first-line treatment for stage III/IV follicular lymphoma already receive rituximab plus chemotherapy in England and Wales, this proposed change in the NICE guidance is expected to have little net impact on the amount of rituximab used and thus the budget impact is also expected to be negligible.

Conclusion

In summary this evaluation reaffirms the clinical and cost effectiveness of rituximab when added to CVP. In addition the results demonstrate that adding rituximab to alternative chemotherapy regimens is consistently both clinically and cost effective. The sensitivity analysis demonstrated that there is a very high degree of certainty in the cost effectiveness of rituximab therapy at the lowest of the willingness to pay thresholds typically used by NICE (£20,000).

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- ⁱ MabThera Summary of Product Characteristics. January 2008 – Roche data on file.
- ⁱⁱ Hiddemann W, Kneba M, Dreyling M *et al.* Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*, 2005;106: 3752-3732
- ⁱⁱⁱ Buske C, Hoster E, Dreyling M *et al.* Rituximab in Combination with CHOP in Patients with Follicular Lymphoma: Analysis of Treatment Outcome of 557 Patients Treated in a Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG) after a Follow up of 58 Months. *Blood*, 2008 112: Abstract 2259
- ^{iv} Herold M, Haas A, Srock S *et al.* Rituximab Added to First-Line Mitoxantrone, Chlorambucil, and Prednisolone Chemotherapy Followed by Interferon Maintenance Prolongs Survival in Patients with Advanced Follicular Lymphoma: An East German Study Group Hematology and Oncology Study. *J Clin Oncol.* 2007; 15: 1986-1992
- ^v Salles GA, Foussard C, Mounier N *et al.* Rituximab Added to αIFN+CHVP Improves the Outcome of Follicular Lymphoma Patients with s High Tumor Burden: First Analysis of the GELA-GOELAMS FL-2000 Randomized Trial in 359 Patients. *Blood.* 2004; 104: abstract 160
- ^{vi} Foussard C, Mounier A, Van Hoof V *et al.* Update of the FL2000 randomized trial combining rituximab to CHVP-Interferon in follicular lymphoma (FL) patients (pts). *J. Clin. Oncol* 2006; 24,18S: Abstract 7508
- ^{vii} Salles GA, Mounier N, de Guibert S *et al.* Rituximab Combined with Chemotherapy and Interferon in Follicular Lymphoma Patients: Final Analysis of the GELA-GOELAMS FL2000 Study with a 5-Year Follow-Up. *Blood*, 2007; 110: abstract 792
- ^{viii} Salles G, Mounier N, de Guibert S, *et al.* High Numbers of Tumor-Associated Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood.* 2008; 112: 4824-31.

^{ix} Genactis, patient record survey, Q2 2010 (base = 143 FL patient records; 50 haematologists)

^x Schulz H, Bohlius JF, Trelle S *et al.* Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *JNCI*. 2007; 99(9):706-714.

^{xi} Ray J, Carr E, Lewis G, *et al.* An Evaluation of the Cost-Effectiveness of Rituximab in Combination with Chemotherapy for the First-Line Treatment of Follicular Non-Hodgkin's Lymphoma in the UK. *Value Health*. 2010; 13(4): 346–357.

^{xii} Ganguly S. and Patel V., R-CHOP versus R-CVP in the treatment of follicular lymphoma: a meta-analysis and critical appraisal of current literature. *Journal of Hematology and Oncology*, 2009; 2: 14-20.