



European Medicines Agency

**ASSESSMENT REPORT  
FOR  
MABTHERA**

**International non-proprietary name/Common name:  
rituximab**

**Procedure No. EMEA/H/C/000165/II/0053**

**Variation Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.**

## 1. Introduction

Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20, a hydrophobic transmembrane protein which is present on the cell surface of pre-B- and mature B-lymphocytes, but not on hemopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. In particular, CD20 is present on malignant B-cells in most patients with mature B-cell lymphoma and leukemia. Rituximab binds to CD20 on B-lymphocytes and leads to elimination of these cells potentially via a number of different mechanisms (antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and apoptosis).

Mabthera (Rituximab) was first approved in 1998 in the European Union (EU) and has since received regulatory approval in 102 countries. It is currently approved in the EU for the following indications:

- for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy
- for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine, prednisone (CVP) chemotherapy
- as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab
- for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy
- in combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumor necrosis factor (TNF) inhibitor therapies.

Since the marketing authorization was granted for first-line treatment of patients with follicular lymphoma in combination with CVP chemotherapy in August 2004, data from a variety of recently published randomized clinical trials as well as meta-analyses and retrospective cohort studies have consistently demonstrated the efficacy of rituximab in combination with various chemotherapy regimens other than CVP for initial treatment of this disease.

Follicular lymphomas account for 20-25% of all lymphomas. The disease generally manifests with hypertrophy of peripheral and deep lymph nodes and splenomegaly, together with bone marrow infiltration.

Follicular lymphoma is characterized by an indolent course of disease. Treatment is usually associated with a high rate of initial response to various regimens, followed inevitably by relapse. Subsequent remissions occur but at a progressively lower rate and usually of shorter duration. Prognosis of patients with relapsed disease is poor. Even though remission can still be obtained with available salvage regimens, its duration is invariably shorter after each induction cycle. Median survival ranges between 6-10 years and the majority of patients eventually die from their disease. Histological transformation to more aggressive non-Hodgkin's lymphoma (NHL) with poor prognosis has been documented to occur in 20-80% of patients over time. Also, the likelihood of resistant lymphoma or occurrence of secondary malignancies such as myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) increases with time and with the number, choice and intensity of previous treatments.

A variety of different chemotherapy regimens are used for initial treatment and the choice of treatment is largely based on patient prognosis and physician preference. Generally accepted regimens include single-agent regimens (chlorambucil, cyclophosphamide, fludarabine) or combination regimens with or without anthracyclines (e.g. CHOP or CVP).

In August 2004, marketing authorization was granted for the use of rituximab in combination with CVP chemotherapy for treatment of previously untreated patients with follicular lymphoma. The approval was based on the results of study M39021 which demonstrated a large and clinically meaningful benefit for previously untreated patients with FL receiving rituximab in combination with CVP chemotherapy when compared to treatment with CVP alone. The overall response rate (ORR) was significantly improved with the addition of rituximab to CVP (81% vs. 57% for R-CVP and CVP, respectively [ $p < 0.0001$ ]) with a large difference in terms of complete response (CR) rates (41% vs. 11% for patients in the R-CVP and CVP arms, respectively). With a current median follow up of 53 months, median time to progression or death (TTP) was significantly increased from 14.7 months

with CVP alone to 33.6 months with R-CVP,  $p < 0.0001$ . The estimated overall survival (OS) showed a strong clinical benefit in favor of the R-CVP arm, and the two-sided significance level dropped below 0.05 ( $p = 0.029$ , log-rank test).

Due to the heterogeneity in the choice of first-line chemotherapy regimens for patients with FL, the use of rituximab as initial treatment in this setting was also evaluated in a number of trials using a variety of different chemotherapy regimens for combination. Chemotherapies evaluated in these studies included anthracycline-based (CHOP, CHVP-IFN, MCP) or fludarabine-based regimens (FCM, FND) depending on local standard practices. All of these trials have consistently demonstrated a significant improvement of progression-free survival (PFS) or time to treatment failure (TTF) and OS when rituximab was added to chemotherapy in this setting, regardless of the type of chemotherapy regimen chosen for combination with rituximab. Moreover, meta-analyses evaluating the role of rituximab in the treatment of FL as well as retrospective cohort comparisons in untreated patients with FL pooling data of rituximab in combination with a variety of chemotherapy regimens have confirmed the major clinical benefit provided by rituximab in the treatment of this disease.

Based on the overall strong evidence in these trials of a large and meaningful clinical benefit of rituximab regardless of the type of added chemotherapy, rituximab in combination with any chemotherapy has become the standard of care for first-line treatment of FL patients worldwide and has been widely adopted into clinical practice for the management of these patients. This is also reflected in several treatment guidelines worldwide for the management of patients with FL, which recommend the usage of rituximab for initial treatment of patients with FL in combination with chemotherapy without restriction to a specific chemotherapy regimen. In addition, rituximab-based combination therapy is the standard of care for initial therapy in a number of ongoing clinical trials evaluating new treatment strategies (e.g. maintenance therapy) or new compounds for the treatment of FL patients.

However, the current label in the EU for rituximab does not reflect current clinical practice as it restricts rituximab usage in this setting to combination with CVP chemotherapy only.

This application is based primarily on published data (either full text manuscripts or conference abstracts) from three key randomized studies conducted by European Cooperative Lymphoma Study Groups:

- The German Low-Grade Lymphoma Study Group trial (GLSG'00) comparing 6-8 cycles of frontline therapy with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (R-CHOP) with CHOP alone in previously untreated advanced-stage follicular lymphoma patients
- The German OSHO-39 (East German Study Group Hematology and Oncology) trial comparing 8 cycles of rituximab in combination with MCP (mitoxantrone, chlorambucil, prednisolone) chemotherapy (R-MCP) with MCP alone as first-line treatment for patients with low-grade lymphoma.
- The French FL2000 study conducted by the Groupe d'Études des Lymphomes de l'Adulte (GELA) in collaboration with the Groupe Ouest-Est d'Étude des Leucémies et Autres Maladies du Sang (GOELAMS) evaluating the efficacy of 6 cycles of rituximab in combination with CHVP-IFN (cyclophosphamide, doxorubicin, etoposide, prednisone, interferon- $\alpha$ ) for previously untreated patients with advanced stage follicular lymphoma.

Study GLSG'00 and study FL2000 were conducted independently by national lymphoma study groups in Germany and France, respectively. For study FL2000, the principal investigator provided confidential information on patient baseline demographics and safety data from the study manuscript that is currently in preparation. The Marketing Authorization Holder (MAH) has no access to the data from these two studies other than what is publicly available in the medical community in the format of full text publications and thus cannot provide any clinical study reports for these trials. Study OSHO-39 was conducted by the East German Study Group Hematology and Oncology and was sponsored by Hoffmann-La Roche AG, Germany. For this trial, the primary reference is a recent full text publication of the study results in the *Journal of Clinical Oncology* 2007. This reference presents the longest

follow up data that is currently available for this study. A final study report for this trial is expected to be available at the end of 2008.

In addition, efficacy and/or safety results of publications from different meta-analyses, retrospective cohort comparisons as well as a number of phase II studies exploring rituximab in combination with other cytotoxic agents such as chlorambucil or purine-analogue based regimens are supplied to support the application.

The decision to submit this variation application was based on:

- Strong evidence from several large, randomized phase III trials and supporting evidence from meta-analyses, retrospective cohort studies and phase II studies demonstrating that the addition of rituximab to any chemotherapy regimen provides a clinically meaningful benefit to previously untreated patients with FL.
- The observation that all data consistently demonstrated an improvement in overall survival when rituximab was added to chemotherapy compared to chemotherapy alone, regardless of chemotherapy regimen used for combination
- Follow-up periods in all studies presented in this dossier which were long enough to allow for clinically relevant and meaningful conclusions.
- Safety data showing that the safety profile overall of rituximab in combination with chemotherapy remains unchanged with no significant additional toxicity, regardless of the chemotherapy regimen combined with rituximab

Furthermore, section 4.2 was restructured in order to clarify posology and method of administration with regards to the numbers of chemotherapy cycles recommended for each chemotherapy combination option.

## **2. Clinical aspects**

The German Low-Grade Lymphoma Study Group trial (GLSG'00) was performed as a prospective, randomized, open-label multicenter phase 3 trial. It was approved by the Institutional Review Board of the Department of Medicine, University of Munich, Germany. The study was carried out in accordance with the modified Declaration of Helsinki. All patients gave their written informed consent after having been informed about the purpose and investigational nature of the trial. Before initiation the study received approval by the responsible ethics committee. Registration in a trials database, monitoring and institutional review are not mentioned in the publication.

The German OSHO-39 (East German Study Group Hematology and Oncology) trial was performed as a prospective, randomized, open-label multicenter phase 3 trial. The study complied with all of the requirements of the Declaration of Helsinki and its current amendments and was conducted in accordance with good clinical practice guidelines. All patients gave written informed consent. The protocol and accompanying materials were approved by an independent ethics committee and local ethics committees at each participating center. The study was registered at ClinicalTrials.gov under ID 00269113. Monitoring and institutional review are not mentioned in the publication.

The French FL2000 study conducted by the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) in collaboration with the Groupe Ouest-Est d'Étude des Leucémies et Autres Maladies du Sang (GOELAMS) was performed as a prospective, randomized, open-label multicenter phase 3 trial. The protocol was approved by the local or national ethics committees and the national regulatory agency according to the French and Belgium regulatory laws. Patients had to give their written informed consent prior to be randomized in the study. The study was registered on the National Institute of Health website (NCT00136552). Monitoring and institutional review are not mentioned in the manuscript.

All three pivotal trials seem to have been conducted in accordance with the principles of GCP.

## 2. 1. Clinical efficacy

### *Dose-response studies and main clinical studies*

There are no dose-response studies, as the dose used in the studies for the present application is the dose approved for other indications in lymphomas. There is no need for new dose response studies for the present application.

The three main studies for the present application are summarized in Table 1.

**Table 1: Treatment regimens and number of patients in treatment arms for the three pivotal randomized studies**

Study	No. pts. (-/+ R)	Treatment Regimens	Number of Cycles
<b>GLSG'00</b>	205/223	<i>CHOP:</i> Cyclophosphamide 750mg/m <sup>2</sup> i.v. on day 1, Doxorubicin 50mg/m <sup>2</sup> i.v. on day 1, Vincristine 1.4mg/m <sup>2</sup> (max. 2.0mg) iv on day 1 Prednisone 100mg/m <sup>2</sup> orally daily on days 1-5  <i>Rituximab:</i> 375mg/m <sup>2</sup> infusion on day 0	6 or 8 cycles Patients achieving a CR after 4 cycles were treated with a total of 6 cycles. All other patients received 8 cycles of treatment. Due to the low rate of complete remissions (overall 19%) the majority of patients were scheduled to complete 8 cycles of treatment. Responding patients underwent a second randomization to interferon- $\alpha$ maintenance treatment (3x5 Mio U/wk initial dose) or HDT/ASCT (patients <60 years) or to one of two interferon- $\alpha$ maintenance schedules (patients $\geq$ 60 years)
<b>OSHO-39</b>	96/105	<i>MCP:</i> Mitoxantrone 8mg/m <sup>2</sup> i.v. on days 1 and 2, Chlorambucil 3x3mg/m <sup>2</sup> p.o. on days 1-5 Prednisolone 25mg/m <sup>2</sup> p.o. on days 1-5  <i>Rituximab:</i> 375 mg/m <sup>2</sup> infusion two days prior to start of chemotherapy	Maximum of 8 cycles Patients with PD or SD after 2 cycles were to be withdrawn. Patients with a minimal response after 6 cycles (i.e. tumor remission <50%) were also to be withdrawn. Responding patients were planned to receive interferon- $\alpha$ maintenance treatment (3x4.5 Mio U/wk) until PD
<b>FL2000</b>	183/175	<i>CHVP-I:</i> Cyclophosphamide 600mg/m <sup>2</sup> i.v. on day 1, Doxorubicin 25mg/m <sup>2</sup> i.v. on day 1 Etoposide 100mg/m <sup>2</sup> i.v. on day 1 Prednisone 40mg/m <sup>2</sup> p.o. on days 1-5 Interferon- $\alpha$ 3x4.5 Mio U/wk s.c.  <i>Rituximab:</i> 375mg/m <sup>2</sup> infusion on days 1 and 8 (cycle 3 and 4) and on day 1 (cycle 5 and 6) = 6 cycles in total	<i>CHVP-I:</i> 12 cycles CHVP (6 monthly cycles followed by 6 bi-monthly cycles) + 18 months concurrent IFN- $\alpha$ 2b  <i>R-CHVP-I:</i> 6 monthly cycles CHVP + rituximab + 18 months concurrent IFN- $\alpha$ 2b

HDT, high dose therapy (DexaBEAM followed by TBI and HDT with cyclophosphamide); ASCT, autologous stem cell transplantation; NC, no change

In study GLSG'00, 630 previously untreated patients with advanced stage FL were randomized to a standard regimen of 6-8 cycles (2 cycles beyond CR) of CHOP chemotherapy or a combination of rituximab plus CHOP (R-CHOP). Responding patients underwent a second randomization to one of two different schedules; either interferon- $\alpha$  maintenance therapy (patients  $\geq$ 60 years) or interferon- $\alpha$  maintenance therapy vs. consolidation treatment with high-dose therapy and stem cell support (patients <60 years). The primary endpoint for the comparison of CHOP alone vs. R-CHOP was TTF, defined as the interval between the start of treatment and the documentation of resistance to initial therapy, progressive disease or death. The trial was stopped early after an interim analysis

demonstrated significant superiority for the primary endpoint TTF in favor of the R-CHOP arm ( $p < 0.001$ ) with 428 patients evaluable for analysis of efficacy and safety.

In study OSHO-39, 358 patients with indolent NHL or mantle cell lymphoma (MCL) were randomized to either 8 cycles of rituximab plus MCP-chemotherapy (mitoxantrone, chlorambucil, prednisolone) given every 4 weeks for a total of 8 cycles versus MCP alone. Responding patients with follicular histology were scheduled to continue on interferon- $\alpha$  maintenance treatment until PD. The primary efficacy analysis population in this study was the population of patients with follicular lymphoma ( $n=201$ ). The primary endpoint was the remission rate, defined as the rate of complete (CR) and partial (PR) remissions after induction therapy. Secondary efficacy parameters included progression-free survival (PFS; interval from randomization date to progression of disease or death from NHL), overall survival (OS; interval from randomization date to death from any cause), event-free survival (EFS; interval from randomization date to treatment failure (defined as PD after 2 cycles and failure to achieve at least PR at cycle 6, disease progression, relapse or death from any cause), duration of response (DR; interval from first assessment of CR/PR to disease progression), and time to next anti-lymphoma treatment (TTNT; interval from randomization date to the time when new treatment was initiated).

Study FL2000 recruited a total of 359 patients with previously untreated FL. Patients were randomized to either 12 courses of CHVP (cyclophosphamide, doxorubicin, etoposide, prednisolone) plus IFN- $\alpha 2b$  given over a period of 18 months (CHVP-IFN) or 6 courses of CHVP and rituximab combined with IFN- $\alpha 2b$  administered over 18 months (R-CHVP-IFN). The primary endpoint of the trial was EFS, defined as the interval between start of therapy and disease progression, initiation of new anti-lymphoma therapy or death due to any cause. A total of 358 patients were evaluable for efficacy.

The target population for recruitment into the studies included in this submission were patients with advanced stage (stage IIB-IV) follicular lymphoma (FL), with high tumor burden and symptomatic disease requiring therapy. The median age of patients enrolled in these three studies ranged between 54 and 61 years. Between 25% and 40% of patients had B-symptoms at study entry. More than 80% of the enrolled patients had intermediate to high risk disease according to the follicular lymphoma international prognostic index (FLIPI) and between 23% and 37% had elevated lactate dehydrogenase (LDH) levels. In 60%-74% of patients bone marrow involvement by lymphoma was present. A small fraction of patients (6%-9%) had an ECOG score  $> 1$ . Overall, the treatment groups in the three key randomized studies were comparable to the population of patients in the pivotal study M39021 (rituximab in combination with CVP which has already been approved) and generally representative for the overall population of patients with advanced stage follicular NHL in need of therapy. Within the individual studies, treatment groups were well balanced with respect to demographic parameters and baseline disease characteristics.

The key efficacy endpoints differed between the key studies as outlined in Table 2. For the definitions of time to event parameters, see also Table 3. Due to the different primary and secondary endpoints, a pooling of the data was not possible.

**Table 2: Primary Efficacy Endpoint and Follow-up in the three pivotal randomized studies**

Study	Primary Efficacy Endpoint	Median follow-up
GLSG'00	Time to treatment failure <sup>1)</sup>	18 months
OSHO-39	Overall response rate <sup>2)</sup>	47 months
FL2000	Event-free survival	42 months

<sup>1)</sup> Defined as the interval between the start of treatment and the documentation of resistance to initial therapy, progressive disease, or death. <sup>2)</sup> Defined as the rate of CR and PR after induction therapy.

**Results**

Overall, the addition of rituximab to chemotherapy compared with chemotherapy alone significantly improved the outcome of patients for all primary and secondary endpoints in all key studies:

- Overall response (OR) rates and complete remission rates were significantly increased for patients who had received rituximab plus chemotherapy compared to those who had received chemotherapy alone (table 3). ORR with R-chemo were 96% (R-CHOP), 92% (R-MCP), 94% (R-CHVP-I) and 81% (R-CVP) compared to ORRs with chemotherapy alone of 90% (CHOP), 75% (MCP), 85% (CHVP-I) and 57% (CVP). Complete response rates were up to quadrupled with the addition of rituximab to chemotherapy (CR rates 20-76% with R-chemo vs. 17-49% with chemotherapy alone).
- Time-to event parameters were significantly improved when rituximab was added to chemotherapy compared to chemotherapy alone with a risk reduction for experiencing disease progression or treatment failure of 50-60% across the trials.
- OS rates also significantly improved in all key trials when rituximab was combined with chemotherapy compared to chemotherapy alone despite a limited follow-up period (medians between 18-47 months).

These results are in line with previously submitted data of patients with stage III-IV FL who had received rituximab in combination with CVP first-line (study M39021).

**Table 3 Summary of Efficacy Results from Randomized Studies**

Parameter	GLSG'00		OSHO-39		FL2000	
	CHOP N=205	R-CHOP N=223	MCP N=96	R-MCP N=105	CHVP-IFN N=183	R-CHVP-IFN N=175
<b>ORR</b>	90%	96%	<b>75%</b>	<b>92%</b>	86%	94%
p-value		0.011		0.0009		<0.0001
CR	17%	20%	25%	50%	49%	76%
PR	73%	77%	50%	42%	37%	18%
Median follow-up	18 months		47 months		42 months	
Median PFS			28.8 months	Not reached		
p-value			<0.0001			
Median TTF	<b>2.6</b>	Not reached				
p-value	<b>years</b>	<b>0.001</b>				
Median EFS*			26 months	Not reached	<b>36 months</b>	Not reached
p-value			<0.0001		<b>&lt;0.0001</b>	
3.5 yr EFS					<b>46%</b>	<b>67%</b>
					<b>p &lt; 0.0001</b>	
Median DR			35 months	Not reached		
p-value		0.001	<0.0001			
Median TNT			29.4 months	Not reached		
p-value		0.001	0.0002			
Overall Survival	90% <sup>1</sup>	95% <sup>1</sup>	74% <sup>2</sup>	87% <sup>2</sup>	84% <sup>3</sup>	91% <sup>3</sup>
p-value		0.016	0.0096		0.029	
Total No of deaths	17	6	25	15		
Lymphoma-related	9	1	17	7		

Numbers in bold reflect protocol-defined primary endpoints. \*EFS - OSHO'39 interval between randomization to treatment failure (defined as disease progression after two cycles and failure to achieve at least a PR at cycle 6, disease progression, relapse, or death from any cause). \*EFS in FL2000 interval between the start of therapy and disease progression, initiation of new anti-lymphoma therapy or death due to any cause. <sup>1</sup> Two-year overall survival rates. <sup>2</sup> Four-year overall survival rates. <sup>3</sup> Overall survival rates at 42 months (3.5 years). CR: complete response; DR: duration of response; EFS: event-free survival; ORR: overall response rate; PFS: progression-free survival; partial response: partial response; TNT: time to new therapy; TTF: time to treatment failure.

#### Clinical studies in special populations

Overall, the addition of rituximab to any chemotherapy regimen improved the clinical outcome in all subgroup populations analyzed [international prognostic index (IPI), FLIPI, age, quality of response to induction therapy].

- In study GLSG'00, the beneficial effects of R-CHOP compared to CHOP were seen in all subgroups analyzed according to the IPI (low/low-intermediate vs high-intermediate/high risk) or age (<60 years vs. ≥ 60 years) for the primary endpoint of time to treatment failure. The risk of treatment failure was reduced by 60%-70% for all subgroups. In the elderly population, R-CHOP also resulted in significantly improved PFS (p<0.0001) and OS (p=0.039) compared to CHOP treatment.
- Results from study OSHO-39 demonstrated that treatment with R-MCP significantly increased the 4-year PFS rate as well as prolonged the median time to disease progression or death in patients with intermediate (p=0.0016) as well as high risk (p=0.0011) disease according to the FLIPI score. Amongst patients with high risk disease, a significant improvement in overall survival was also seen amongst those treated with R-MCP compared with MCP (p=0.0096).
- In study FL2000, subgroup analysis were performed according to the FLIPI score and quality of response [CR/ complete response unconfirmed (CRu)] to induction therapy. The results demonstrated a significant improvement in the primary endpoint, event-free survival with R-CHVP-IFN compared with CHVP-IFN, for patients with low to intermediate risk (p = 0.0019) as well as for patients with high risk disease (p =0.0005). A significant benefit was also seen in the subgroup of patients who achieved a CR/CRu (p = 0.002).

*Analysis performed across trials (pooled analyses and meta-analysis)*

A Cochrane meta-analysis included a total of 1943 patients with indolent lymphoma (most commonly follicular lymphoma and mantle cell lymphoma) enrolled across seven controlled studies (including studies GLSG'00 and OSHO-39) which compared R-chemotherapy with chemotherapy alone. Of the seven listed trials, five were in previously untreated patients with stage III or IV disease and two trials included patients with relapsed/refractory disease. The chemotherapy regimens used for combination with rituximab included CHOP, CNOP, CVP, FCM, and MCP.

In the pooled population of studies, the ORR was 72% (673 of 935 patients) with chemotherapy-alone compared with 87% (854 of 979 patients) in the R-chemotherapy group. The relative risk for response with R-chemotherapy compared with chemotherapy-alone was 1.21 (95% confidence interval (CI): 1.16 to 1.27). Treatment with R-chemotherapy was associated with significantly more patients achieving a complete response (relative risk 2.03, 95% CI 1.71 to 2.40). Subgroup analyses by histology showed higher ORR and CR rates in the R-chemo group compared to the chemo-group for both FL and MCL patients.

Treatment with R-chemotherapy led to significantly superior disease control (defined as progression, relapse or death) compared with chemotherapy alone (HR: 0.62; 95% 0.55 to 0.71). These finding remained significant when the analysis was conducted according to the subgroup of patients with follicular lymphoma and MCL.

Overall survival data was available on all 1943 patients included in the meta-analysis. The hazard ratio for death from any cause was 0.65 (95% CI: 0.54-0.78) indicating a statistically significant better overall survival in the R-chemotherapy groups compared with the chemotherapy alone groups. Amongst the 1480 patients with follicular lymphoma, treatment with R-chemotherapy compared with chemotherapy-alone reduced the risk of death by 37% (HR: 0.63, 95% CI 0.51-0.79). Assuming a 2-year overall survival rate of 90% for patients with follicular lymphoma, it was estimated that approximately 28 patients had to be treated with R-chemotherapy to prevent one additional death in 2 years.

The meta-analysis contains 7 randomized trials, 2 of the trials are the first 2 trials submitted by the MAH for the present application, 1 of the trials is the pivotal trial for the approved indication for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy, 2 of the trials are trials of patients relapsing after previous therapy, 1 of the trials is for patients with mantle cell lymphoma only, and 1 of the trials does not specify the type of indolent lymphomas included in the trial. Hence, the meta-analysis does not in fact contribute significant new



information with regard to efficacy for the present application. The results of the meta-analysis are, as expected, in accordance with the results of the three pivotal trials.

### Supportive studies

- In a retrospective cohort study, five consecutive cohorts involving 580 patients with stage IV FL treated at the M.D. Anderson Cancer Center between 1972 and 2002 were analyzed for OS, failure-free survival and survival after first relapse in order to assess the impact of new treatment strategies on the response of FL patients over time. Treatment regimens included were CHOP-Bleomycin (CHOP-Bleo), CHOP-Bleo followed by interferon- $\alpha$ , a rotation of three regimens followed by interferon- $\alpha$  (alternating triple therapy – ATT); fludarabine, mitoxantrone, dexamethasone followed by interferon- $\alpha$  (FND) and FND plus delayed or concurrent rituximab followed by interferon- $\alpha$  (R-FND). Median follow-up times of survivors for the five cohorts were 23.7 years, 17.5 years, 12 years, 8.2 years, and 3.3 years respectively. The results showed a steady increase in 5-year OS rates over time from 64% with CHOP-Bleo to 95% with R-FND ( $p < 0.0001$ ). Notable increments in OS occurred with the incorporation of interferon- $\alpha$  in 1982 and rituximab in 1997 ( $p \leq 0.05$ ). Like the data on OS, the failure-free survival (FFS) showed a stepwise improvement with the more recent studies from a median FFS of 2.8 years with CHOP-Bleo to the median not being reached with R-FND. These observations held true after controlling for differences in prognostic factors among the cohorts.
- The GLSG analyzed two consecutive study generations covering a ten year period for remission rates, time to treatment failure (TTF) and OS in order to identify treatment modalities leading to improvements in overall survival for patients with advanced stage follicular lymphoma. The analysis was adjusted for risk factors according to the FLIPI and the type of induction regimen (including rituximab or not). A total of 1332 patients with complete data sets were collected between 1996 and 2005. Therapies included CHOP and MCP in GLSG Study'96 and CHOP and R-CHOP in GLSG Study'00. CHOP was superior to MCP in terms of OR rates, but did not improve TTF or OS compared to MCP. Although the entry criteria and the distribution of risk factors were nearly identical in both study generations, patients in study GLSG'00 had a significantly higher OR rate (94% vs. 88%, odds ratio 0.47;  $p = 0.0002$ ), a longer TTF (median 48 months vs. 32 months, relative risk 0.66;  $p < 0.0001$ ) and a longer OS (4-year OS 89% vs. 78%, relative risk 0.42;  $p < 0.0001$ ) when compared to patients in study GLSG'96. Multiple Cox-regression analysis identified rituximab as being the determinant parameter for the differences in ORR (adjusted odds ratio 0.45,  $p < 0.0001$ ), TTF (adjusted relative risk 0.39,  $p < 0.0001$ ) and OS (adjusted relative risk 0.44,  $p = 0.0064$ ). Hence, rituximab was identified as the essential treatment modality that underlies the improvement in short and long term outcome of patients with advanced stage FL.
- In a retrospective cohort study from the Gruppo Italiano Studio Linfomi (GISL), 438 patients with advanced stage, histologically confirmed diagnosis of follicular lymphoma who met the defined eligibility criteria were included in the analysis. Of these, 307 previously untreated patients were treated with one of the following regimens: ProMECE-CytaBOM (36 patients, group 1), bleomycin, epidoxorubicin, cyclophosphamide, vincristine, prednisone (BACOP; 66 patients, group 2), BACOP/FND (144 patients, group 3) or BACOP/F in combination with rituximab (61 patients, group 4). One hundred and thirty-one patients with recurring disease were treated with CHOP or FC (52 patients, group 5), or with CHOP or FC in combination with rituximab (79 patients, group 6).

The median FFS improved stepwise with evolving treatments from group 1 to group 4 which was the group of patients receiving treatment with rituximab. This significant improvement over time was confirmed by a Cox regression analysis adjusted for FLIPI scores and radiotherapy. Of note, improvements in FFS were particularly evident in cohort 4 patients treated with rituximab. The relative risk reduction for FFS with the rituximab-chemotherapy regimen in cohort 4 compared with cohort 1 was 76% (95% CI: 49% to 89%) and compared with cohort 3 was 51%. Amongst treatment-naïve patients, the 4-yr overall survival was 76%, 87%, 82% and 97% in groups 1, 2, 3 and 4, respectively, although the overall p-value (for the comparison of survival curves between the studies) was not significant. However, after adjusting for the FLIPI score in the Cox

regression model, there was a significant reduction in the hazard ratio from group 1 to 4. Of note, the relative risk reduction for mortality with the rituximab-chemotherapy regimen in group 4 compared with group 1 was 91% (95% CI: 30% to 98%) and 71% compared to group 3.

The impact of rituximab used as part of salvage therapy was investigated by an analysis of survival after recurrence (SAR) in 131 relapsed patients. The 5-year estimate of SAR was significantly longer for patients who received rituximab in combination with chemotherapy (group 6) compared with patients who received chemotherapy alone at the time of relapse (group 5) (74% versus 57%,  $p=0.032$ ). This statistically significant difference in SAR was maintained after the analysis was adjusted for age and duration of the previous remission ( $p=0.014$ ).

The retrospective cohort analyzes present data from patients treated at the M.D. Anderson Cancer Center over a 25-year period, by the German Low Grade Lymphoma Study Group over a 10-year period, and by the Gruppo Italiano Studio Linfomi over a 16-year period. None of these analyzes contain patients randomized in trials relevant to the present application. Comparisons of treatments with and without Rituximab are retrospective and bias cannot be excluded. The results of these analyzes are in accordance with the findings of the three randomized trials. They do not, however, by themselves contribute significantly with regard to efficacy for the present application.

Data from five uncontrolled phase II studies provide additional supportive evidence of the efficacy of rituximab when added to various chemotherapy regimens (single agent or combinations). Although the majority of studies were in the first-line setting, the protocols of two studies also allowed recruitment of relapsed patients (table 1).

The ORR across the studies was very high and in the range 89% to 100% with a complete response rate of between 55% and 96%. The median duration of follow-up ranged between 2.8 and 9 years. The most impressive results were seen in the study by Czuczman et al using the R-CHOP regimen; with a median follow-up of 9 years, the median time to progression and the median duration of response were nearly 7 years.

**Table 1: Summary of Efficacy Results from Supportive Studies**

Lead Investigator	Czuczman et al	Fayad et al	Czuczman et al	Hainsworth et al	Martinelli et al
Regimen	<b>R-CHOP</b>	<b>R-CHOP</b>	<b>R-fludarabine</b>	<b>R-CVP or R-CHOP</b>	<b>R-chlorambucil</b>
Number of Pts	<b>N=38</b>	<b>N=45</b>	<b>N=40</b>	<b>N=86</b>	<b>N=27</b>
Study Phase	II	II	II	II	II
Patients	Untreated or relapsed	Histologic grade 3 FL	Low grade or FL	Grade 1 or 2 FL	Untreated or relapsed
ORR	100%	100%	90%	93%	89%
CR	87%	96%	80%	55%	63%
Median duration of follow-up	9 years	33 month	44 months	42 months	Not reported
Median TTP	82.3 months	Not reported	Not reached	Not reported	Not reported
Median DR	83.5 months	Not reported	61% at 44 months	Not reported	Not reported
3 year - FFS	Not reported	73%	Not reported	Not reported	Not reported
3 year PFS	Not reported	Not reported	Not reported	71%	Not reported
3 year OS	Not reported	97%	85% at 44 months	95%	Not reported

DR, duration of response; ORR, overall response rate; CR, complete response; OS, overall survival; TTP, time to progression; FFS, failure free survival; PFS, progression-free survival

The results of these phase II studies do not yield significant information regarding the value of the addition of rituximab to chemotherapy, but their results are in accordance with the findings of the pivotal studies.

## 2. 2. Clinical safety

### Patient exposure

The overall evaluation of the safety of rituximab in combination with any chemotherapy (R-Chemo) is mainly derived from safety information available from three key randomized studies including a total of 987 patients. Additional evidence about the safety profile of rituximab in combination with different chemotherapy regimens comes from the Cochrane meta-analysis and multiple phase II studies. For the purpose of the discussion, safety data of the pivotal study M39021 (CVP or R-CVP in patients with advanced stage follicular lymphoma) are presented alongside safety results of the three key randomized studies.

In study OSHO-39, all eight cycles of treatment were administered to 88% of patients in the R-MCP arm and to 67% of patients in the MCP arm. This difference in exposure was mainly accounted for by more patients withdrawing from the MCP than from the R-MCP arm due to treatment failure during therapy: failures due to progressive disease (PD) after 2 cycles occurred in 3 (R-MCP) and 10 (MCP) patients and failure to achieve at least PR after 6 cycles occurred in 7 (R-MCP) and 22 (MCP) patients. Mean doses of study drug administered were as follows: rituximab, 660–680 mg/cycle; mitoxantrone, 24–28 mg/cycle; chlorambucil, 68–81 mg/cycle and prednisolone, 226–231 mg/cycle. Dose intensity of the chemotherapy did not differ between treatment arms. Interferon-alpha maintenance treatment (3 x 4.5 million units per week until disease progression) was initiated in 97% and 92% of responding patients in the R-MCP group and the MCP group, respectively. To date, the median duration of interferon maintenance treatment is 15.5 months in the R-MCP group and 9.5 months in the MCP group with the difference being due to earlier disease progression in the MCP group.

In study FL2000, 94% of patients in the CHVP-IFN arm and 95% of patients in the R-CHVP-IFN arm received the initial six cycles of treatment. Of those patients who did not progress during therapy, 153 (98%) and 161 (98%) patients on CHVP-IFN and R-CHVP-IFN, respectively, completed the planned chemotherapy induction courses during the first 6 months. In the CHVP-IFN arm, 116 (89%) of the patients not experiencing disease progression received the 6 planned bi-monthly cycles of chemotherapy consolidation following induction treatment. In total, 237 (66%) patients received interferon-alpha treatment according to the protocol: dose modifications occurred in 45 patients and short (less than 4 weeks) interruptions occurred in 55 patients without significant differences between the two study arms. Interferon-alpha treatment was stopped due to disease progression in 50 patients (CHVP-IFN arm 31 cases; R-CHVP-IFN arm 19 cases). Dose interruptions for more than one month or stopping of interferon-alpha treatment were reported in 47 patients (26%) in the CHVP-IFN arm and 41 patients (23 %) in the R-CHVP-IFN arm.

### Adverse events

Overall, the safety profile of rituximab in combination with chemotherapy (R-Chemo) as described in the key studies in this submission is consistent with the safety profile of rituximab in combination with CHOP or CVP chemotherapy as reported in studies M39021 (R-CVP, untreated FL), M39022 (R-CHOP, relapsed/refractory FL), BO16368 (R-CHOP in elderly patients with DLBCL) and M39045 (R-Chemo in younger patients with DLBCL). An increase in all grade AEs was observed in the rituximab containing arms of all key studies compared to chemotherapy alone, which was mainly due to a higher incidence of leukopenia and/or neutropenia, infection and allergy. Importantly, although the incidence of infections of all grades was usually slightly increased with rituximab added to chemotherapy, none of the studies reported a significant increase in the incidence of grade 3/4 infections. There were no new or unexpected toxicities observed.

The most common ( $\geq 10\%$  in at least one treatment group) reported AEs of any grade reported in studies GLSG'00 and OSHO-39 included blood and bone marrow disorders, gastrointestinal disorders, skin toxicities, neurological disorders, infections, fever bone pain and other.

The higher incidence of AEs of all grades in the rituximab containing arms was mainly due to a higher incidence of blood and bone marrow disorders (leukopenia and/or neutropenia) and allergy (including rash) as well as more gastrointestinal disorders in study OSHO-39. Other AEs that were observed at a

higher frequency ( $\geq 2\%$  difference in all grade AEs in the rituximab containing arms) in at least one of the studies included infections, fever, cardiac arrhythmia, neurological disorders and bone pain.

The most common grade 3/4 adverse events included blood and bone marrow disorders, and alopecia. A higher incidence of grade 3/4 AEs in the rituximab containing arms was observed for blood and bone marrow disorders in studies GLSG'00 and OSHO-39. Other grade 3/4 AEs that were observed at a higher frequency ( $\geq 2\%$  difference in grade 3/4 AEs in the rituximab containing arms) in at least one of the studies included alopecia, infection, cardiac disorders and bone pain.

Of note, in study GLSG'00 there was a slight increase in grade 3/4 cardiac events (cardiac dysfunction and cardiac arrhythmia) in the rituximab containing arm (1% of patients on CHOP versus 5% of patients on R-CHOP with a cardiac event). However, no difference in the incidence of grade 3/4 cardiac events was observed in study FL2000.

Adverse events related to the infusion of rituximab occurred in 7% of courses during the first infusion in one particular key study (GLSG'00); early cessation of rituximab therapy was required in 2 patients. The overall safety profile of rituximab combined with different chemotherapy regimen as described in the key studies is similar to the safety profile observed in the pivotal study M39021 comparing CVP with R-CVP. In this study, an increase in all grade and grade 3/4 AEs was observed in the R-CVP arm. In most of the cases, AEs with a higher incidence in the R-CVP group were those already recognized as belonging to the safety profile of rituximab, mostly typical of infusion-related reactions (IRRs). In addition, the incidence of grade 3 or 4 neutropenia was higher for patients in the R-CVP arm than for patients on CVP treatment (24% versus 14%). However, this was not associated with an increased rate of grade 3/4 infections.

#### Blood and Lymphatic System Disorders

As observed in previous studies (M39021, table 5), a higher frequency of leukopenia and/or granulocytopenia of all grades and grades 3/4 was observed after treatment with R-Chemo in studies GLSG'00, and OSHO-39. In contrast to these two studies, grade 3/4 neutropenia occurred at a higher incidence in the chemotherapy alone arm (62% with CHVP-IFN vs 59% with R-CHVP-IFN) in study FL2000. This difference is due to the different number of treatment cycles for the CHVP regimen in the study arms: in the chemotherapy alone arm, 12 cycles of CHVP given over a period of 12 months were administered in combination with interferon- $\alpha$ , whereas in the rituximab-containing arm only 6 cycles of CHVP were given over a period of 6 months in combination with rituximab and interferon- $\alpha$ .

**Table 5 Overview of Grade 3 and 4 Blood and Lymphatic System Disorders in Studies GLSG'00, OSHO-39, FL2000 and M39021**

	GLSG'00		OSHO-39		FL2000		M39021	
	CHOP (N=205)	R-CHOP (N=222)	MCP (N=96)	R-MCP (N=105)	CHVP- IFN (N=183)	R-CHVP- IFN (N=175)	CVP (N=159)	R-CVP (N=162)
Grade 3/4 Leukopenia	61%	69%	58%	72%	n.r.	n.r.	9%	12%
Grade 3/4 Neutropenia	53%	63%	n.r.	n.r.	62%	59%	13%	24%

n.r., not reported

Overall, grade 3/4 granulocytopenia was more frequently encountered after rituximab treatment in combination with CHOP (63%) than after treatment in combination with CVP (24%) or CHVP-I (59%). However, clinically relevant infections (grade 3/4) were not significantly different between the rituximab-containing and the chemotherapy alone arms in any of the studies described.

#### Infections and Infestations

Overall, between 36% and 49% of patients in studies GLSG'00 and OSHO-39 experienced an infection. The incidence of infections of all grade was slightly higher in the rituximab-containing treatment arm: 36% with CHOP vs. 38% with R-CHOP in study GLSG'00, 43% with MCP vs. 49%

with R-MCP in study OSHO-39. For study FL2000, no rates for patients experiencing an infection of any grade were provided.

Importantly, although the incidence of all grades infection was usually higher in the rituximab-containing treatment arms of the studies conducted, the incidence of grade 3/4 infections was always comparable between R-chemo and chemotherapy alone: 7% after CHOP vs. 5% after R-CHOP (GLSG'00), 8% after MCP vs. 7% after R-MCP (OSHO-39) and 0% after CHVP-I vs 2% after R-CHVP-I.

These rates of all grade and grade 3/4 infections reported in the key studies above are in line with previously reported incidences of infections in patients with FL or DLBCL from other randomized trials.

#### *Safety Results of the Cochrane Meta-analysis*

Safety data is available from the meta-analysis performed by the Cochrane Hematological Malignancies Group. In summary, the analysis confirmed the observations from the three key randomized studies: patients treated with R-Chemo experienced significantly more leukopenia and fever than patients with chemotherapy alone, but there were no significant differences in the incidence of infections or thrombocytopenia between the groups.

#### *Post Marketing Surveillance*

Post-marketing surveillance data collected in the global rituximab safety database with a data cut-off of April 30, 2007 are consistent with the safety profile in the three key studies and the supportive safety information from the meta-analysis.

In the global database with over 10,000 AEs reported, the most frequently reported events were infection and infestation (15%), blood and lymphatic system disorders (14%), general disorders and administration site conditions (11%) and respiratory, thoracic and mediastinal disorders (10%). Where data on chemotherapy regimens combined with rituximab is available, the most frequently reported AEs in any rituximab-chemotherapy combination were blood and lymphatic system disorders, infections and infestations, respiratory disorders, general disorders and gastrointestinal disorders, apart from R-CVP where the order is slightly different: respiratory, general, blood and lymphatic, infections and infestations, investigations and gastrointestinal disorders.

The overall conclusion from post-marketing experience is that the safety profile and the benefit/risk assessment for rituximab in combination with any chemotherapy regimen remain favorable for patients with advanced stage (stage III-IV) FL.

#### *Serious adverse events and deaths*

In the randomized studies with information on deaths, a higher number of death cases were reported for the chemotherapy alone arms compared to the R-Chemo arms. A total of 23 deaths (17 CHOP and 6 R-CHOP) and 40 deaths (25 MCP and 15 R-MCP) occurred in study GLSG'00 and study OSHO-39, respectively. This increase in death cases in the chemotherapy arms was predominantly due to progression of disease (9 versus 1 patient in study GLSG'00 and 17 versus 7 patients in study OSHO-39). Eight and 5 patients (on CHOP and R-CHOP, respectively) in study GLSG'00 and 8 patients in each treatment arm in study OSHO-39 died due to lymphoma-unrelated causes. In study FL2000, a total of 45 patients had died at the time of the analysis at 42 months (29 on CHVP-IFN and 16 on R-CHVP-IFN). No information was available on the cause of death from this study. These data do not indicate any increase in deaths due to toxicity of rituximab.

#### *Laboratory findings*

No information on clinical laboratory evaluations was available from the studies presented in this application. Extensive data are available from previous applications for the now approved indications, and from post-marketing data.

#### *Safety in special populations*

Except for results on an elderly population in study GLSG'00, no safety information was available on special groups and situations from the studies presented in this application.

In study GLSG'00, no new, unexpected safety signals were detected in the elderly population ( $\geq 60$  years of age,  $n=221$ ). In line with the analysis on the full safety population, the most common AEs of any grade included blood and bone marrow disorders, gastrointestinal disorders, skin toxicities, neurological disorders, cardiac disorders, infections and fever. Most of the AEs were mild to moderate in intensity except for alopecia, leukopenia and neutropenia, which were mainly of grade 3/4 in intensity.

#### *Immunological events*

No specific information on immunological events is presented, except for the listed numbers of blood and lymphatic system disorders and immune system disorders.

#### *Discontinuation due to AES*

In the GLSG'00 trial early discontinuation of rituximab was required in 2 patients. No early discontinuations were reported in the OSHO-39 trial and the FL2000.

### **3. Overall Discussion and Benefit- Risk assessment**

A number of clinical trials evaluated the efficacy of rituximab in combination with various different chemotherapy regimens. The results from the three key randomized trials, plus the pivotal study M39021, using rituximab in combination with either CVP, CHOP, CHVP or MCP as the chemotherapy backbone consistently demonstrated significant superiority in terms of PFS and/or EFS. More importantly, all studies also showed a significant improvement in terms of overall survival for any of the four chemotherapy regimens combined with rituximab when compared to chemotherapy alone.

These findings in randomized clinical trials were further confirmed in subsequent meta-analyses incorporating key studies including the 4 randomized trials mentioned, in retrospective cohort studies and in other studies evaluating fludarabine-based regimens in combination with rituximab. In addition, a number of phase II studies where longer follow-up was available suggested that combining rituximab with regimens such as fludarabine, CHOP or chlorambucil was effective and induced long-lasting responses.

In conclusion, the published efficacy results from different clinical trials strongly support the use of rituximab in combination with various chemotherapy regimens without restriction to the CVP regimen.

The overall safety profile of rituximab in combination with different chemotherapy regimens as presented in this Clinical Overview is similar to that observed in previous clinical experience. Overall, adding rituximab to different chemotherapy regimens increases the incidence of neutropenia and/or leucopenia, allergy or infusion-related reactions as well as infections. An increase in grade 3/4 neutropenia usually did not translate into an increase in grade 3/4 infection. No significant new safety concerns have been observed in the three key studies and the Cochrane meta-analysis, in which a number of different concomitant chemotherapy regimens have been used. In summary, the addition of rituximab to various different chemotherapy regimens did not significantly increase the toxicity of chemotherapy.

The data from all the studies presented in this dossier 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. These beneficial effects were seen in all patient subgroups analyzed according to disease risk (FLIPI) or age (GLSL'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.
- Across all studies, no new safety signals were observed and rituximab did not add to the toxicity of chemotherapy.

All studies consistently demonstrated significant superiority in terms of PFS and/or EFS for combined immunochemotherapy. The addition of rituximab to chemotherapy significantly reduced the risk for disease progression or treatment failure by 40-60% across the trials. More importantly, all studies have also shown a significant improvement in overall survival for all of the four chemotherapy regimens combined with rituximab when compared to chemotherapy alone. Overall survival is considered the most important endpoint in clinical trials evaluating follicular lymphoma and is a robust and unbiased endpoint, which is not affected by differences in study design such as schedule and methodology of assessment of tumor response. In those trials where hazard ratios for OS were available, the risk of death was reduced by 40-50% when patients were treated with immunochemotherapy compared to chemotherapy alone.

A higher incidence of infusion-related reactions/allergy, blood and bone marrow disorders (neutropenia) and infections have been described in association with rituximab treatment in previous studies. Increases in all grade and grade 3/4 leukopenia/neutropenia and infections were also observed in the key studies supplied in this application. These toxicities were manageable and did not change the risk-benefit assessment of previous studies. No new or unexpected toxicities were reported in the submitted three key randomized studies. In summary, the overall safety profile of rituximab in combination with any chemotherapy reported in the key studies supporting this application is consistent with the safety profile as previously described in other trials.

Since the indication is an enlargement of the existing one, the submission of a Risk Management Plan was not considered necessary.

In conclusion, the data from the key publications in this submission, along with data from supportive published studies, provide enough evidence justifying the use of rituximab in combination with any chemotherapy for the treatment of patients with advanced stage follicular lymphoma.

The overall Benefit/Risk of rituximab is positive if administered in combination with chemotherapy in combination treatment of previously untreated patients with stage III-IV follicular lymphoma.