



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Ltd

December 2011

TGA Health Safety
Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New Dosage Regimen
<i>Decision:</i>	Rejected but with Changes to the Product Information (PI)
<i>Date of Decision:</i>	18 July 2011
<i>Active ingredient(s):</i>	Rituximab
<i>Product Name(s):</i>	MabThera
<i>Sponsor's Name and Address:</i>	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2099
<i>Dose form(s):</i>	Concentrated solution
<i>Strength(s):</i>	10 mg of antibody/mL: 100 mg/10 mL and 500 mg/50 mL
<i>Container(s):</i>	Single use vials
<i>Pack size(s):</i>	100 mg/10 mL: pack of 2, 500 mg/50 mL: pack of 1
<i>Approved Therapeutic use:</i>	Approved indications are unchanged as a result of this submission – see PI for full details
<i>Route(s) of administration:</i>	Intravenous (IV) infusion
<i>Dosage:</i>	Complex – see PI
<i>ARTG Number (s):</i>	60318 and 60319

Product Background

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B and mature B-lymphocytes but not on haemopoietic stem cells, pro-B cells, normal plasma cells or other normal cells. Rituximab is believed to exert its therapeutic effect by promoting B-cell lysis. It binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity, antibody dependent cellular cytotoxicity and induction of apoptosis. It should be noted that CD20 antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHL).

It is currently registered for use in NHL in various settings as well as for the treatment of chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis.¹ The following indications are related to NHL:

- CD20+, previously untreated stage III/IV follicular, B-cell non-Hodgkin's lymphoma.
- CD20+, relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma.

¹ TGA. AusPAR for Rituximab, September 2010. Available at: <http://www.tga.gov.au/pdf/auspar/auspar-mabthera.pdf>

- CD20+, diffuse large B-cell non-Hodgkin's lymphoma in combination with chemotherapy.
- CD20+, chronic lymphocytic leukaemia in combination with chemotherapy.
- The current approved maintenance dosage regimen for MabThera in NHL is, "patients who have responded to induction treatment may receive maintenance therapy with MabThera given at 375mg/m² body surface area once every three months until disease progression or for a maximum period of two years".

The use of rituximab as maintenance therapy in NHL was approved by the TGA in May 2007 following consideration by the Australian Drug Evaluation Committee (ADEC) (which preceded the Advisory Committee on Prescription Medicines [ACPM]) at its March 2007 meeting. The pivotal study in that application (EORTC 20981) was conducted in patients with relapsed/refractory disease.² The dosage regimen used in that study (375 mg/m² every 3 months) was approved by the TGA for use in both the relapsed/refractory and previously untreated settings.

This AusPAR describes the evaluation of an application by Roche Products Pty Ltd (the sponsor) seeking approval for a new dosing regimen for maintenance therapy in patients with previously untreated follicular NHL. The current application is based upon the findings of a new pivotal study (the PRIMA trial) which specifically examined the efficacy of maintenance treatment in patients with previously untreated disease. This study used a different maintenance dosing regimen - 375 mg/m² every 2 months.

Regulatory Status

The product received initial ARTG Registration in 1998.

A similar application was approved in the US on 28 April 2010, Switzerland on 4 October 2010 and the European Union (EU) on 25 October 2010. The application was submitted to Canada on 6 August 2010 where it is under consideration.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

² Van Oers MHJ, Klasa R, Marcus RE et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. *Blood* 2006; 108: 3295-3301.

IV. Clinical Findings

Introduction

The current submission proposed to define maintenance dosing schedules for patients receiving MabThera as maintenance therapy for either previously untreated or relapsed refractory NHL. The dosage schedules proposed for patients with previously untreated NHL arise from the data from the pivotal study M018264 also known as the PRIMA study. Also included was a supportive study ECOG 1496.

On the basis of the data presented in relation to the two above trials it was proposed to revise the maintenance therapy instructions to:

1. Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m² body surface area once every two months until disease progression or for a maximum period of two years (12 infusions).
2. Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera given in 375 mg/m² body surface area once every three months until disease progression or for a maximum period of two years.

Also included in this submission was a population pharmacokinetic analysis of rituximab in patients with non-Hodgkin's lymphoma derived from six clinical studies involving pharmacokinetic evaluations.

The PRIMA study was developed on the basis of considering assessment of the role of maintenance therapy in patients with previously untreated B-cell follicular NHL, utilising European approaches to maintenance therapy, that is, infusion of 375 mg/m² once every 2-3 months.

The previous pivotal trial EORTC20981 in patients with relapsed refractory follicular NHL had utilised the three monthly schedule.² Since then a Phase II study was reported in which the effect of individualised pharmacokinetic dosing of rituximab was evaluated in patients with B-cell NHL who failed at least one prior therapy. Patients received four-weekly infusions of rituximab at a dose of 375 mg/m² as induction therapy and repeat rituximab bolus of 375 mg/m² given when serum levels fell to below 25 µg/ml. With this approach single infusions of rituximab had to be administered every 2-4 months to maintain drug levels above 25 µg/ml. Based on this information a more conservative schedule was therefore chosen for the PRIMA study to that used in the EORTC20981 study with a dose of rituximab to be given every two months during the maintenance phase.

Pharmacokinetics

Population Pharmacokinetic Analysis

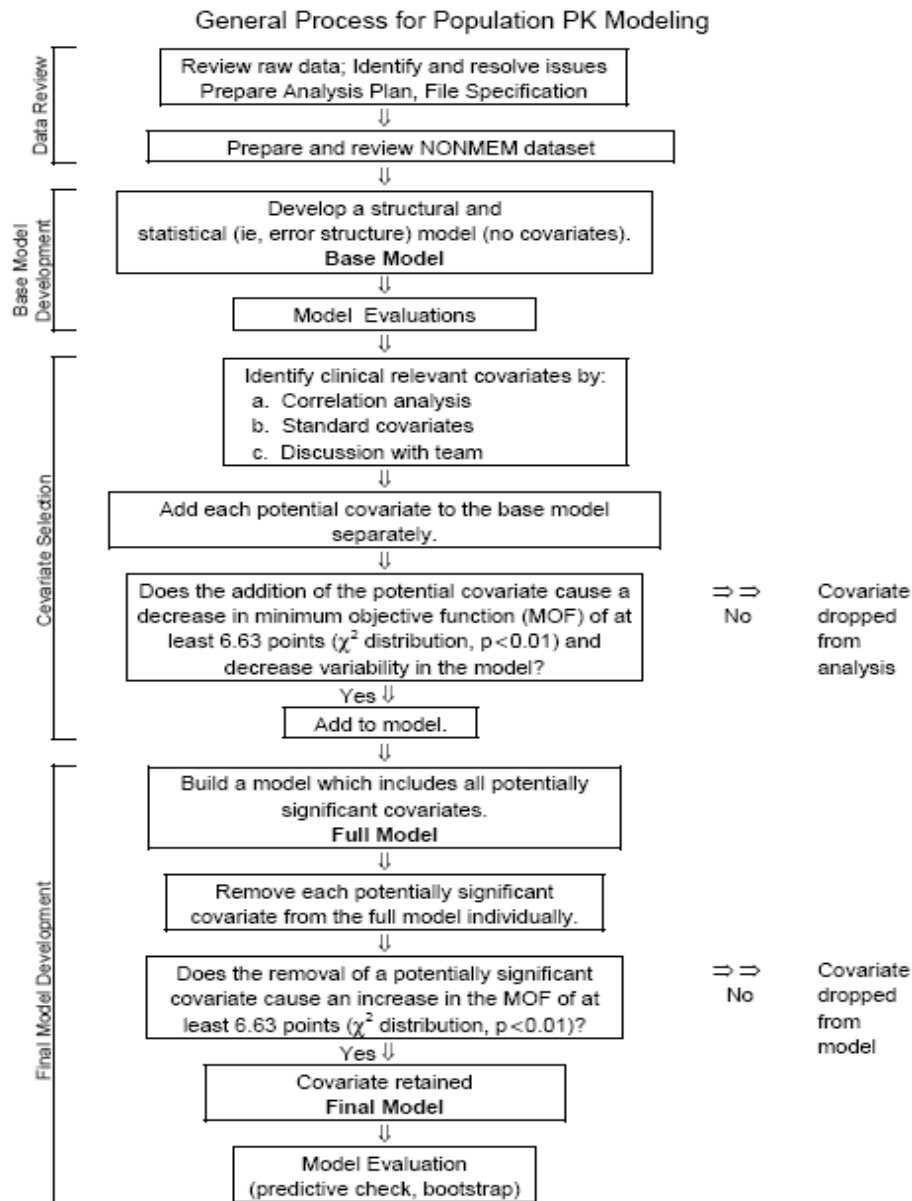
A single population of pharmacokinetic (PK) analysis was presented in the submission, which characterised the pharmacokinetics of rituximab based on the combined data from the six clinical studies in patients with NHL. Two of these were Phase I/II clinical trials (IDEC 102-01 and IDEC 102-2), two were Phase II clinical studies (IDEC 102-03 and IDEC 102-06) and two were Phase III clinical trials (IDEC 102-05 and U2035G). A total of 298 patients were enrolled in these six clinical trials. In all studies rituximab was administered as a single infusion or multiple infusions.

The objective of the analysis was:

1. to describe the pharmacokinetics of rituximab in patients with NHL using population pharmacokinetic modelling.
2. to estimate the effects of covariates such as demographics and clinical factors which may be important predictors of variability in rituximab PK parameters.
3. to determine the terminal half-life for rituximab in NHL patients.

The general process used for the population PK modelling is described in Figure 1.

Figure 1: Process for development of the PK model



After final formatting and cleaning the population PK database comprised 298 patients and 3739 concentration observations, which represented 84.1% of the overall available concentration records.

Covariates considered for the PK analysis included age, body surface area, sex, race, performance status by WHO criteria and laboratory determinations, that is, baseline CD19 cell counts and baseline sum of the product of perpendicular diameters (SPD) of measurable tumour lesions. With regards to the last parameter this could only be assessed in 161 patients in the pivotal study IDEC 102-05.

For a starting point for the analysis, a two compartment model, with zero order input (infusion) was used to describe the data from the six clinical studies. The basic model parameters were clearance (CL, mL/day), volume of distribution of the central compartment and peripheral compartment (V_1 , V_2 , mL) and inter-compartmental clearance (Q, mL/day). One and three compartment models were also evaluated. Reviewing the results, the population serum rituximab concentration/time relationship was displayed as a bi-exponential.

A two compartment model with time varying clearance was preferable to other models for describing the current time course of the rituximab concentrations as demonstrated by the visual inspection of goodness-of-fit plots, individual fit plots and change in minimum objective function.

Rituximab concentration data were best described by the two compartment model with time varying clearance parameterized in terms of systemic non-specific clearance (CL_1), systemic specific clearance at time zero (CL_2), apparent volume of distribution (V_1 and V_2), rate constant of the specific clearance decay (K_{des}) and distribution clearance between the central and peripheral compartments (Q). The population parameter estimates for the final covariate model using the pooled data from the six studies are summarised in Table 1.

Table 1: Parameter estimates for the final covariate model

Population Parameter Estimates (%SEE) for the Final Covariate Model

Parameter Description	Population Estimate (%SEE)	Between-Patient Variability (%SEE)
Non-specific clearance CL_1 (mL/day)	138 (4.28%)	42.8% (13.9%)
Specific clearance at time zero CL_2 (mL/day)	585 (8.58%)	102% (14.6%)
Volume of distribution in central compartment V_1 (mL)	2700 (1.96%)	29.8% (11.3%)
Influence of BSA on V_1	1.26 (13.1%)	
Volume of distribution in peripheral compartment V_2 (mL)	1500 (8.67%)	—
Rate of specific clearance decay K_{des} (day ⁻¹)	0.0459 (8.08%)	96.3% (14.8%)
Distribution clearance Q (mL/day)	522 (13.9%)	—
Proportional residual error		24.6% (2.11%)
Additive residual error (µg/mL)		0.674 (20.9%)

%SEE=percent standard error of estimation.

In order to assess the influence of concurrent CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine] and prednisone) therapy on rituximab disposition, the impact of the treatment on CL_1 and V_1 in patients receiving rituximab monotherapy (studies 1, 2, 5 and 6) were compared with that in patients receiving rituximab in combination with CHOP (studies 3 and U2035g). It was shown that

the use of concurrent CHOP therapy had no influence on CL_1 , but increased V_1 by 19% resulting in minimal change in the absolute objective of value. This increase in V_1 lies within the observed intra-patient variability or 24.6% and therefore changes in PK parameters due to concurrent CHOP therapy is not expected to be clinically relevant. Reviewing the effects of CD19 and SPD on population PK parameters from study 5 in which only the relevant data were available, revealed that after removing the SPD and CD19 covariates one at a time, both SPD and CD19 demonstrated a statistically significant influence on CL_2 as evidenced by increases in MOF by 26.1 and 9.07 points respectively.

Reviewing model evaluation results revealed that the fit of the model to observed data for six representative patients on the six studies indicates a good fit of the model to the observed data. Assessment of the boot strap of the final model revealed that the stratified non-parametric boot strap procedure resulted in 95% confidence intervals (CI) for population PK parameter estimates. This demonstrated that typical structure model parameters in random variance terms were estimated with good precision.

To evaluate whether the estimated fixed effect parameter has adequately described the data, simulation replicates of the original study 5 data were generated using the final population PK model. The entire set of original observations in study 5 was plotted vs time along with the summary statistics computed from the simulated data with 5th, 50th and 95th percentiles. The coincidence between the original data and simulated data were demonstrated in the predictive ability of fixed effects parameters in the final model.

In the final covariate model body surface area (BSA) was an important covariate for explaining inter-individual variability in V_1 . The change in rituximab V_1 for extreme BSA from 1.53 to 2.328/m² was up to 27.1% of the typical value. BSA explained 27.3% of the inter-individual variability in V_1 based on the final covariate model using pool data.

SPD and CD19 were the most significant covariates affecting CL_2 in study 5. Based on the final model SPD and CD19 explained 18.3% and 10.4% of the inter-individual variability in CL_2 respectively. There is large inter-individual variability in K_{des} in both the final and base models, 58.9% and 56.6% respectively. The SPD effect in the final model explained approximately 6.05% of the inter-individual variability in K_{des} . No covariate significantly influenced CL_1 .

Individual PK parameters (CL_1 , V_1 , CL_2 and K_{des}) of the 298 patients were also estimated with the final population PK model using pool data. The overall median of individual estimates of rituximab CL_1 and V_1 were 136 mL/day and 2706 mL respectively. The median serum half-life was 5.07 (range 2.03 – 14.5) days for treatment initiation and 22.4 (range of 6.14 – 51.9) days following prolonged rituximab treatment. The changing and wide range of half-lives may reflect the highly variable and decreased tumour burden in changes in B-cell population upon repeated rituximab administration.

Evaluator comment

This population pharmacokinetic analysis of rituximab in 298 patients with NHL was described by a two-compartment model with a constant non-specific clearance and a specific clearance which increases with increasing malignant B-cells or tumour burden.

The clinically relevant finding of the covariate analysis is that dose adjustment through tested covariates is not expected to result in a meaningful reduction in PK variability. Based on this population PK analysis, the median of individual estimates for rituximab terminal half-life is approximately 22.4 (range of 6.14 – 51.9) days.

Efficacy

Introduction

Information on the efficacy of rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma is provided from one pivotal Phase III trial (study M018264, also known as the PRIMA study) of rituximab maintenance therapy of patients responding to rituximab based induction chemo-immunotherapy and supported by data from the Phase III ECOG 1496 study of rituximab maintenance therapy following induction with combination chemotherapy.

Pivotal trial (PRIMA)

The PRIMA study was a multicentre Phase III open labelled randomised study in patients with advanced follicular lymphoma, evaluating the benefit of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with no maintenance therapy. The study was conducted in Europe, South America, Asia, Middle East and Australasia.

The study consisted of two treatment phases. During the non-randomised induction phase, patients with advanced follicular lymphoma were evaluated for response to one of three possible induction regimens, that is, R-CHOP (rituximab plus CHOP), R-CVP (rituximab plus fludarabine, cyclophosphamide and mitoxantrone or R-FCM (rituximab plus cyclophosphamide, vincristine and prednisone) chosen by the investigator as the standard regimen for participating patients at his/her centre. Most patients (75%) received R-CHOP induction therapy. In the maintenance observation phase, patients who responded to induction treatment with either a complete response (CR) or partial response (PR) were randomised to receive either rituximab maintenance therapy (one dose of 375 mg/m² every eight weeks for two years for a total of 12 doses) or observation (no further treatment for a total of 12 visits). Stratification of the maintenance/observation phase was based on induction regimen, centre and response to induction treatment. All randomised patients were to be treated or observed for two years and then followed up for five years.

During the two year maintenance/observation phase patients were assessed by physical examination, performance status, complete blood count every eight weeks, β -2 microglobulin, lactate dehydrogenase (LDH) and tumour lesion measurements by physical exam and radiographic images of the chest, abdomen and pelvis performed every six months. Patients with signs, symptoms or physical findings suggestive of progressive disease at any point during the study were required to have tumour assessments and a tumour biopsy if possible to confirm progression. Subsequent follow up was every three months for the next two years and every six months for the following three years.

The primary endpoint of these studies was progression free survival (PFS) defined as the time from randomisation to the first documented disease progression, relapse or death from any cause. The secondary endpoints were event free survival (EFS - defined as the time from randomisation to first documented progression, relapse, initiation of new anti-lymphoma treatment or death from any cause), overall survival (OS), time to next anti-lymphoma treatment (TTNLT), time to next chemotherapy treatment (TTNCT), response rates at the end of maintenance treatment, transformation rate at first relapse and quality of life.

An independent data and safety monitoring committee (DSMC) reviewed all safety and efficacy data as planned. In addition an independent review committee (IRC) assessed radiographic imaging data and reports of pertinent clinical findings including physical

exam and laboratory results for all patients who had a response and progression according to an independent review charter.

Of the 1217 patients registered, 1193 received induction therapy and 1078 of these patients responded to treatment with a CR or PR for an overall response rate of 90%. Around 1018 evaluable patients subsequently fulfilled the eligibility criteria for randomisation in the rituximab maintenance/observation phase of the study and are included in the primary efficacy analysis known as the maintenance intent to treat population (MITT). The demographic and disease characteristics of patients at registration were well balanced across the two arms and the two arms were also well balanced at the start of the randomised phase of the study with respect to baseline disease characteristics.

At the time of initial analysis for the clinical cut-off date of 14 January 2009, the median duration of follow up was 25 months. At the time of this analysis 174 patients (33.9%) in the observation arm and 93 patients (18.4%) in the rituximab arm had experienced a progression event, that is, disease progression/relapse or death since randomisation as indicated in Table 2.

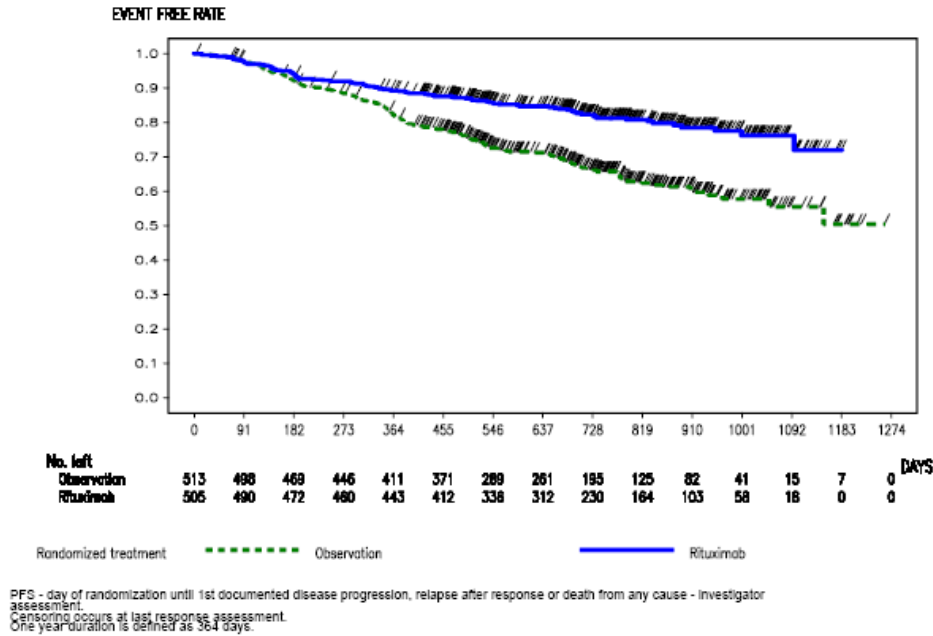
Table 2: Summary of progression free survival (PFS) (investigator assessment, MITT)

	Observation (N=513)	Rituximab (N=505)
Patients with event	174 (33.9 %)	93 (18.4 %)
Patients without events*	339 (66.1 %)	412 (81.6 %)
Time to event (days)		
Median#	.	.
95% CI for Median#	[1050;.]	[.;.]
25% and 75%-ile#	507;.]	1096;.]
Range##	3 to 1261	13 to 1182
p-Value (Log-Rank Test, stratified**)		<.0001
Hazard Ratio (stratified**)		0.50
95% CI		[0.39;0.64]
p-Value (Wald Test)		<.0001
1 year duration		
Number left	411	443
Event Free Rate#	0.82	0.89
95% CI for Rate#	[0.79;0.85]	[0.87;0.92]
Days To Event Or Censoring (PFS) (PFSTI) - Censoring: Event (PFS) (PFSCS)		
* censored		
** stratified by Induction Treatment and Derived Response To Induction (patients without CR, CRu or PR are included in the PR stratum)		
# Kaplan-Meier estimate		
## including censored observations		
PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.		
Censoring occurs at last response assessment.		
One year duration is defined as 364 days.		

Maintenance therapy with rituximab in patients responding to induction therapy significantly reduced the risk of experiencing a progression event by 50% compared with no further treatment with a stratified hazard ratio (HR) of 0.5 ($p < 0.0001$). The Kaplan-Meier estimated median PFS times could not be calculated for either arm but over the 25th percentiles were calculated as 507 days or 16.7 months for patients on observation and 1096 days or 36 months for patients on rituximab maintenance with a $P < 0.0001$ by log rank test. A Kaplan-Meier plot of PFS is shown in Figure 2. Very similar findings were seen when the analysis of PFS was performed without stratification (sensitivity analysis) which showed a 51% reduction in risk of experiencing a progression event with rituximab maintenance treatment with an HR of 0.49 ($p < 0.0001$). The results were also supported by the analysis of PFS based on the maintenance per protocol population (MPPP). In the MPPP, 80/434 patients or 9.5% on rituximab maintenance treatment experienced a

progression event compared with 152/410 patients or 18% in the observation arm. Rituximab maintenance treatment significantly reduced the risk of experiencing a progression event by 55% compared with observation with an HR of 0.45 (p<0.0001).

Figure 2: Kaplan-Meier plot of PFS (investigator assessment, MITT)



Out of 1018 patients in the MITT, 887 patients were assessed for disease progression or death by the IRC (447 patients in the observation arm and 440 patients in the rituximab arm). In the data set of 887 patients of whom both reviews are available the IRC considered that 247 events had occurred with agreement between the IRC and investigator assessments recorded for 91% of patients. Based on the IRC assessments maintenance therapy with rituximab reduced the risk of disease progression by 46% with a hazard ratio (HR) of 0.54 (p<0.0001) compared with observation.

The benefit of rituximab maintenance therapy over no further treatment in reducing the risk of investigator assessed disease progression was demonstrated in all key subgroups evaluated. Similar results were obtained when subgroup analyses were performed using the IRC assessments.

Significant benefit from maintenance treatment with rituximab was also seen for the various secondary endpoints as indicated in Table 3.

Table 3: Summary of secondary efficacy assessments (investigator assessment, MITT)

Secondary Efficacy Parameter	Observation N=513	Rituximab N=505
Event-free survival		
No. of patients with event	179 (34.9%)	104 (20.6%)
No. of patients without event	334 (65.1%)	401 (79.4%)
Median time to event (days)	1150	NE
p value (log-rank test, stratified)	< 0.0001	
Hazard Ratio [95% CI]	0.54 [0.43, 0.69]	
Overall survival		
No. of patients with event	18 (3.5%)	16 (3.2%)
No. of patients without event	495 (96.5%)	489 (96.8%)
Median time to event	NE	NE
p value (log-rank test, stratified)	0.7246	
Hazard Ratio [95% CI]	0.89 [0.45, 1.74]	
Time to next anti-lymphoma treatment		
No. of patients with event	130 (25.3%)	82 (16.2%)
No. of patients without event	383 (74.7%)	423 (83.8%)
Median time to event	NE	NE
p value (log-rank test)	0.0003	
Hazard Ratio [95% CI]	0.61 [0.46, 0.80]	
Time to next chemotherapy treatment		
No. of patients with event	106 (20.7%)	65 (12.9%)
No. of patients without event	407 (79.3%)	440 (87.1%)
Median time to event	NE	NE
p value (log-rank test)	0.0011	
Hazard Ratio [95% CI]	0.60 [0.44, 0.82]	
Response rate at end of maintenance/observation phase^a	N=398	N=389
Responders (CR/CRu + PR)	219 (55.0%)	288 (74.0%)
Non-responders	179 (45.0%)	101 (26.0%)
Difference in Response Rate	19.01	
p value (χ -squared test)	< 0.0001	
Odds Ratio [95% CI]	2.33 [1.73, 3.15]	
No. of patients with:		
Complete Response (CR/CRu)	190 (47.7%)	260 (66.8%)
Partial Response (PR)	29 (7.3%)	28 (7.2%)
Stable Disease (SD)	1 (0.3%)	0 (0.0%)
Progressive Disease (PD)	162 (40.7%)	79 (20.3%)
Transformation rate		
Transformation	19 (3.7%)	11 (2.2%)
No transformation	494 (96.3%)	494 (97.8%)
Difference in Transformation Rate	-1.53	
p value (χ -squared test)	0.1502	
Odds Ratio [95% CI]	0.58 [0.27, 1.23]	

NE = not evaluable

* Unless otherwise specified.

At the time of the initial analysis there were only 18 deaths in the observation arm and 16 deaths in the rituximab arm which precluded statistical analysis. Therefore no definitive conclusions could be drawn from analysis of overall survival (OS).

The overall response rate at the end of the maintenance/observation phase was significantly higher in the rituximab arm (74% vs 55%) namely due to a higher complete response rate (66.8% vs 47.7%) and a lower rate of progressive disease (20.3% vs 40.7%).

At the time of the interim analysis the data were not mature enough to show a difference in transformation rate with transformation reported for 19 patients (3.7%) in the observation arm and 11 patients (2.2%) in the rituximab arm.

An updated analysis based on a later clinical cut-off (30 June 2009) was performed providing additional 5.5 months of follow up data. This analysis confirms the results of the earlier analysis indicating a significant benefit of rituximab maintenance therapy/observation for PFS with an HR of 0.51 ($p < 0.0001$). Too few additional events had occurred to draw any further conclusions about OS.

Evaluator comment

These data have shown in a robust trial that maintenance rituximab in patients with previously untreated follicular B-cell NHL achieve significant improvement in PFS. Insufficient follow up time was available to indicate potential improvement in OS. All secondary endpoints also demonstrated benefit for rituximab maintenance. This evidence of benefit is in accord with that also seen for rituximab maintenance in patients with relapsed/refractory follicular NHL from earlier studies.

Supportive Trial

The supportive ECOG 1496 study was a randomised Phase III trial in low grade lymphoma comparing maintenance anti-CD20 antibody vs observation following induction therapy. This was a Phase III randomised controlled multicentre National Cancer Institute (NCI) sponsored intergroup study of the efficacy and safety of rituximab as post induction therapy, compared with observation in previously untreated patients with Stage III/IV low grade CD20+ B-cell lymphoma following a cyclophosphamide/vincristine/prednisone (CVP) induction regimen. Induction therapy consisted of cyclophosphamide 1 g/m² on Day 1, vincristine 1.4 mg/m² on Day 1 and prednisone 100 mg/m² on Days 1-5.

Patients who achieved a complete response (CR), partial response (PR) or stable disease (SD) following induction therapy were randomised to rituximab maintenance in a dose of 375 mg/m² weekly for four weeks repeated at six monthly intervals for a total of four cycles or 16 doses total or observation.

A total of 401 patients received CVP induction therapy of whom 322 showed a response or stable disease and were randomised to receive rituximab maintenance (N=162) or observation (N=160). The maintenance randomisation was stratified by extent of residual disease and histology. A total of 305 patients (157 in the rituximab arm and 148 in the observation arm) were assessable for efficacy. Of these, 248 patients were considered to have follicular lymphoma including 125 in the rituximab maintenance arm and 123 in the observation arm.

The primary efficacy endpoint was duration of progression free survival (PFS). Secondary efficacy endpoints included duration of overall survival (OS) and response improvement within two years of maintenance randomisation.

Demographic and baseline disease characteristics for patients included in the primary analysis were generally similar across treatment arms. Slightly more patients randomised to rituximab maintenance treatment arm than the observation arm had PR as the best response induction therapy (69% vs 64%) but otherwise the two arms were well balanced.

Reviewing the results at the time of data transfer (8 November 2004) based on a median follow up of 27 months, where 133 patients had experienced a PFS event, 46 in the rituximab maintenance arm and 87 in the observation arm (Table 4).

Table 4: Summary of PFS

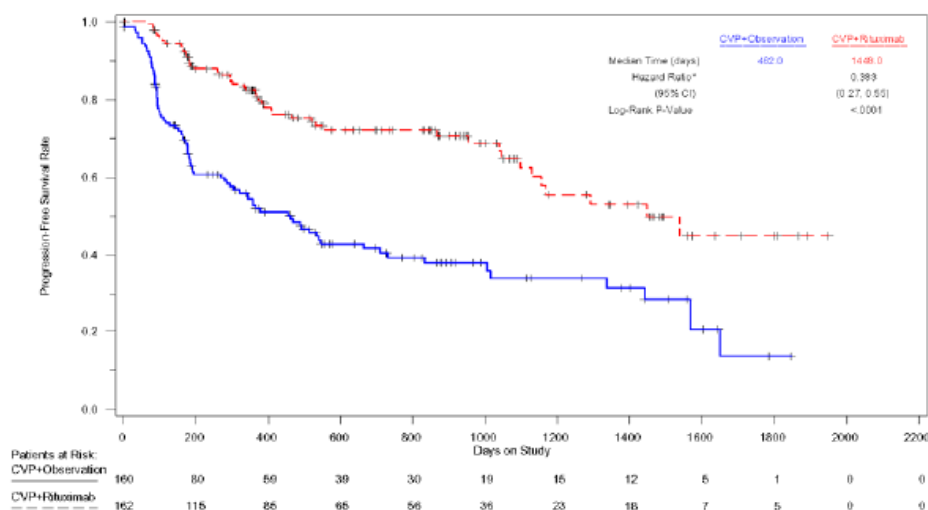
	All Patients		Follicular Lymphoma	
	Observation (N = 160)	Rituximab (N = 162)	Observation (N = 123)	Rituximab (N = 125)
No. (%) with an event	87 (54.4%)	46 (28.4%)	68 (55.3%)	34 (27.2%)
No. (%) observations	73 (45.6%)	116 (71.6%)	55 (44.7%)	91 (72.8%)
Duration of PFS (days)				
Median (95% CI) ^a	462 (294, 710)	1448 (1130, NE)	455	NE
Range	1 to 1846 ⁺	1 ⁺ to 1950 ⁺	NR	NR
p-value ^b	< 0.0001		< 0.0001	
Hazard ratio	0.36 (0.25-0.52)		0.37 (0.25 – 0.56)	
Event-free rate at:				
6 months	64.5	89.5		
1 year	52.8	82.5		NR
2 years	39.3	72.2		

NE = not estimable; + sign indicates a censored observation

NR = not reported

^a Kaplan-Meier estimates.^b Based on a stratified log-rank test

Figure 3 displays the Kaplan-Meier curve by trial treatment groups for the main analysis (PFS) demonstrating a statistically significant and clinically meaningful prolongation of PFS among patients receiving rituximab maintenance compared with those undergoing observation ($p < 0.0001$). The median duration of PFS was approximately 15 months for patients in the observation arm and approximately 48 months for patients in the rituximab maintenance arm. Based on this stratified analysis the HR of progression, relapse or death for patients in the rituximab maintenance arm relative to those in the observation arm was 0.36.

Figure 3: Kaplan-Meier curves for PFS

In those patients with follicular lymphoma, PFS was also seemingly prolonged in the rituximab arm with the median not being estimable vs 15 months in the observation arm with an HR of 0.37 ($p < 0.0001$). In the observation arm 68 patients (55.3%) were considered to have a progression event compared to 34 (27.2%) in the rituximab arm.

In general, subgroup analyses for baseline demographic and disease related characteristics demonstrated a consistent benefit for rituximab maintenance vs observation seen in the analysis of PFS in the overall patient group. Of note the benefit of rituximab maintenance was observed in all subgroups for patients including those with

disease characteristics thought to be associated with a poorer prognosis, for example, elevated LDH, age >60 years at baseline and gross residual disease post-induction.

In the initial analysis a total of 36 deaths were reported, 15 in the rituximab maintenance arm and 21 in the observation arm. The median duration of OS was not estimable for the patients in the observation arm and the estimate for the rituximab maintenance arm (approximately 69 months) was based on a single death when only two patients were at risk.

Of the 263 patients who had stable disease or partial response as the best response to induction, 129 patients were randomised to the observation arm and 134 patients randomised to the rituximab maintenance arm. The percentage of patients with SD or PR after induction, this response improved within two years following randomisation to rituximab maintenance or observation with 20.9% and 7% respectively with a difference being statistically significant ($p=0.001$).

An updated efficacy analysis was performed for the ECOG 1496 study based on a median follow-up of 67 months in the observation arm and 71 months for the rituximab maintenance arm. As of the clinical cut-off date (31 May 2008), a total of 282 patients had been followed for over three years (136 in the observation arm and 146 in the rituximab maintenance arm). Of these 212 patients had experienced a PFS event (124 patients in the observation arm and 88 patients in the rituximab maintenance arm). Again a statistically significant and clinically meaningful prolongation of PFS was observed with rituximab maintenance compared to observation with a stratified log rank $p<0.0001$. Median PFS was 15 months in the observation arm vs 55 months in the rituximab maintenance arm. After this extended follow up period, maintenance therapy of the rituximab was demonstrated to significantly reduce risk of progression by 56% compared with no further treatment with an HR of 0.436. Very similar results were seen for the subset of patients with follicular lymphoma after three years of follow up, with a median PFS of 4.3 years in the rituximab maintenance arm compared with 1.3 years in the observation arm with an HR of 0.4 ($p<0.0001$).

A total of 46 patients (29%) in the observation arm and 37 patients (23%) in the rituximab maintenance arm had died. The median overall survival time had not been reached and no statistically significant difference in overall survival was observed however the hazard ratio was in favour of rituximab maintenance therapy with an HR of 0.773 ($p=0.19$). The three year overall survival for the subset of patients with follicular lymphoma was 91% for rituximab maintenance vs 86% for the observation ($p = 0.08$). It is important to note that for patients on observation who relapsed, these patients subsequently received rituximab therapy which would therefore have an impact on the overall survival data.

Evaluator comment

The data from the supportive study ECOG 1496 have demonstrated significant benefit in relation to PFS for rituximab maintenance in patients with follicular NHL. Nevertheless it is important to note that the maintenance schedule utilised in this evaluation differs from that of the pivotal trial, namely maintenance therapy every two months for the PRIMA study vs four weeks of maintenance every six months for the ECOG 1496 study. Nevertheless the context of benefit for rituximab maintenance has been verified. The reviewer considered that there is good evidence supporting the role of rituximab maintenance therapy in patients with previously untreated follicular NHL.

Safety

Introduction

Assessment of safety in this evaluation was provided predominantly from the pivotal trial (PRIMA study). Supportive safety data were also provided from the ECOG 1496 study.

PRIMA study

During the maintenance/observation phase of the PRIMA trial, patients were assessed at each visit using a check list of pre-defined toxicities, for example, allergy, immunology, febrile neutropenia, gastrointestinal, cardiac, coagulation, vascular, metabolic/laboratory, neurology, dermatology/skin, pulmonary and renal/urinary toxicities. All toxicities encountered were graded according to NCI common terminology criteria.³ Additional information particularly for serious adverse events was documented with regards to intensity, duration, causality, action taken and outcome. All adverse events recorded between the start of the randomised phase of the rituximab maintenance/observation trial and the clinical cut-off date (14 January 2009) and subsequent review (30 June 2009) were included for analysis. All safety data collected during the course of study were reviewed by an independent data and safety monitoring committee (DSMC).

Laboratory assessment of haematology parameters, were performed at registration to completion of induction and at each maintenance visit during the follow up period. Biochemical parameters were assessed in full at registration and subsequently β 2 microglobulin, LDH, creatinine, sodium and potassium were assessed after completion of induction treatment and during the maintenance/observation phase. Laboratory abnormalities were defined based on local laboratory normal ranges.

Of the 1018 patients who entered the randomised maintenance/observation phase of the study, all apart from three had completed their induction therapy according to protocol. Nine other patients withdrew before the start of the observation/maintenance phase and the maintenance/observation phase safety analysis population (MSAP) comprised 1009 patients of which 508 was observation and 501 were rituximab treated patients.

At the clinical cut-off date (14 January 2009), 285 patients (57%) in the rituximab arm had received all 12 treatment cycles and completed the two years of rituximab maintenance therapy as indicated in Table 5. In comparison only 95 patients or 19% in the observation arm had completed all 12 observation visits. The median number of visits attended for patients from the observation arm was nine compared to 12 visits in the rituximab arm. The greater majority of patients on the rituximab arm (89.8%) received over 90% of their projected rituximab dose.

³ **Common Terminology Criteria (CTC)** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 – Life threatening, 5 – Death.

Table 5: Summary of treatment cycles/observation visits

No. of Treatment Cycles/ Observation Visits	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
1	17 (3.3)	8 (1.6)
2	18 (3.5)	12 (2.4)
3	26 (5.1)	12 (2.4)
4	39 (7.7)	14 (2.8)
5	33 (6.5)	5 (1.0)
6	43 (8.5)	14 (2.8)
7	32 (6.3)	11 (2.2)
8	43 (8.5)	27 (5.4)
9	55 (10.8)	46 (9.2)
10	46 (9.1)	37 (7.4)
11	61 (12.0)	30 (6.0)
12	95 (18.7)	285 (56.9)
Mean	8	10
Median	9	12
Range	1-12	1-12

An overview of safety parameters recorded during the maintenance/observation phase of the PRIMA study up to 14 January 2009 is indicated in Table 6. At the time of clinical cut-off the majority of patients in both arms had at least one toxicity recorded. As expected the incidence of adverse events, Grade III/IV adverse events and serious adverse events were higher in the rituximab arm than the observation arm. Of the pre-specified toxicities, 97% of patients in the rituximab arm and 90% in the observation arm experienced at least one episode of toxicity during the maintenance/observation phase and is indicated in Table 7.

Table 6: Overview of Adverse events and toxicities during the rituximab maintenance/observation phase (RMOP)

Safety Parameter	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
Toxicities ^a	459 (90)	485 (97)
Adverse Events ^b	179 (35)	263 (52)
Grade 3/4 AEs	81 (16)	114 (23)
Serious Adverse Events	63 (12)	95 (19)
Withdrawal from treatment due to toxicity	1 (<1)	10 (10)
AEs leading to treatment discontinuation	8 (2)	19 (4)
AEs leading to dose modification	–	27 (5)
AEs leading to death	2 (<1)	3 (<1)
Infection AEs (Grade ≥ 2)	114 (22)	184 (37)
Grade 3/4 infections	5 (<1)	22 (4)
AEs occurring within one day after treatment/observation visit	46 (9)	61 (12)
Total Deaths	18 (4)	13 (3)
Death due to cause other than lymphoma	6 (1)	3 (<1)

a Toxicities are based on the checklist CRF page (regardless of grade).

b Includes Grade 3–5 toxicities, Grade 2–5 infections, and SAEs regardless of grade, as recorded on the AE CRF pages.

Table 7: Summary of toxicities by pre-specified terms during the RMOP

Body System/ Adverse Event	OBSERVATION	RITUXIMAB	TOTAL
	N = 508 No. (%)	N = 501 No. (%)	N = 1009 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	459 (90)	485 (97)	944 (94)
Total Number of AEs	1889	2680	4569
PRE-SPECIFIED IN CRF			
Total Pts With at Least one AE	434 (85)	472 (94)	906 (90)
CONSTITUTIONAL SYMPTOMS	155 (31)	203 (41)	358 (35)
LEUKOCYTES	140 (28)	201 (40)	341 (34)
INFECTION WITH NORMAL NEUTROPHILS	127 (25)	192 (38)	319 (32)
NEUROLOGY	143 (28)	145 (29)	288 (29)
GASTROINTESTINAL	114 (22)	165 (33)	279 (28)
NEUTROPHILS	93 (18)	150 (30)	243 (24)
AST / ALT	98 (19)	123 (25)	221 (22)
HEMOGLOBIN	72 (14)	136 (27)	208 (21)
PULMONARY	56 (11)	123 (25)	179 (18)
DERMATOLOGY / SKIN	75 (15)	97 (19)	172 (17)
PLATELETS	70 (14)	82 (16)	152 (15)
CREATININE	49 (10)	46 (9)	95 (9)
RENAL / GENITO-URINARY	30 (6)	40 (8)	70 (7)
CARDIAC GENERAL	28 (6)	41 (8)	69 (7)
VASCULAR	30 (6)	31 (6)	61 (6)
CARDIAC ARRHYTHMIA	14 (3)	26 (5)	40 (4)
ALLERGY / IMMUNOLOGY-OTHER	14 (3)	19 (4)	33 (3)
ALLERGY / IMMUNOLOGY-INFUSION	2 (<1)	11 (2)	13 (1)
RELATED REACTION			
INFECTION DOC. WITH NEUTROPHILS G3/4	2 (<1)	11 (2)	13 (1)
COAGULATION	2 (<1)	4 (<1)	6 (<1)
FEBRILE NEUTROPENIA	1 (<1)	1 (<1)	2 (<1)
Total Number of AEs	1315	1847	3162

Investigator text for Adverse Events encoded using MedDRA version 12.0.

Percentages are based on N.

Multiple occurrences of the same adverse event in one individual counted only once.

* Toxicities entered as free text under the "other" category on the toxicity CRF page by the investigator were encoded and are listed separately in the source table by system organ class and preferred term.

Toxicities which were more prevalent in the rituximab arm than on the observation arm included constitutional symptoms, decreases in leukocytes, neutrophils or haemoglobin, infection with normal neutrophils, gastrointestinal disorders, increase in hepatic transaminases and pulmonary disorders. The vast majority (>90%) of these toxicities were Grade I/II events. A summary of pre-specified toxicities occurring with a difference in incidence of 2% or higher in the rituximab arm compared with the observation arm is presented in Table 8.

Table 8: Summary of toxicities by pre-specified terms occurring with $\geq 2\%$ difference in incidence in the rituximab compared to the observation arm

Body System*/ Toxicity	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
All Body Systems		
Total Patients with at Least One AE	459 (90)	485 (97)
Prespecified in CRF		
Total Patients with at Least One AE	434 (85)	472 (94)
Constitutional Symptoms	155 (31)	203 (41)
Leukocytes	140 (28)	201 (40)
Infection with Normal Neutrophils	127 (25)	192 (38)
Gastrointestinal	114 (22)	165 (33)
Neutrophils	93 (18)	150 (30)
AST/ALT	98 (19)	123 (25)
Hemoglobin	72 (14)	136 (27)
Pulmonary	56 (11)	123 (25)
Dermatology/Skin	75 (15)	97 (19)
Platelets	70 (14)	82 (16)
Renal/Genito-urinary	30 (6)	40 (8)
Cardiac General	28 (6)	41 (8)
Cardiac Arrhythmia	14 (3)	26 (5)

The proportion of patients who experienced at least one adverse event >Grade II during the maintenance/observation phase was higher in the rituximab arm than the observation arm (52% vs 35%). This difference was mainly due to infections being 37% of patients in

the rituximab arm vs 22% in the observation arm. The most common system organ classes (SOCs) of adverse events were *Infections and Infestations*, mainly bronchitis, *Neoplasms*, mainly basal cell carcinoma, and *Blood and Lymphatic Systems Disorders*, mainly neutropenia. The incidence of other categories of adverse events was lower being <4% and similar in the two study arms. Adverse events in these three SOC categories which occurred in incidence of 1% or more in either arm are presented in Table 9. The majority of adverse events were Grade II in severity (61% in the observation arm and 63% in the rituximab arm) and the majority of these were Grade II infections (144 events in the observation arm and 248 events in rituximab arm). More patients in the rituximab arm than the observation arm experienced at least one Grade III or IV adverse event (23% vs 16%). This difference was mainly due to a higher incidence of Grade III or IV neutropenia (4% vs <1%) and infections (4% vs 1%) in the rituximab arm.

Table 9: Summary of adverse events by SOC occurring with an incidence of ≥1% in either arm

Body System/ Adverse Event	OBSERVATION	RITUXIMAB	TOTAL
	N = 508 No. (%)	N = 501 No. (%)	N = 1009 No. (%)
INFECTIONS AND INFESTATIONS			
BRONCHITIS	24 (5)	47 (9)	71 (7)
UPPER RESPIRATORY TRACT INFECTION	11 (2)	26 (5)	37 (4)
SINUSITIS	8 (2)	19 (4)	27 (3)
INFECTION	10 (2)	12 (2)	22 (2)
NASOPHARYNGITIS	14 (3)	8 (2)	22 (2)
URINARY TRACT INFECTION	8 (2)	13 (3)	21 (2)
ORAL HERPES	2 (<1)	10 (2)	12 (1)
RHINITIS	2 (<1)	10 (2)	12 (1)
LUNG INFECTION	4 (<1)	7 (1)	11 (1)
PHARYNGITIS	4 (<1)	7 (1)	11 (1)
PNEUMONIA	4 (<1)	7 (1)	11 (1)
RESPIRATORY TRACT INFECTION	3 (<1)	8 (2)	11 (1)
VIRAL INFECTION	3 (<1)	5 (<1)	8 (<1)
EAR INFECTION	1 (<1)	5 (<1)	6 (<1)
GASTROENTERITIS	1 (<1)	5 (<1)	6 (<1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	5 (<1)	19 (4)	24 (2)
LEUKOPENIA	1 (<1)	8 (2)	9 (<1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
BASAL CELL CARCINOMA	4 (<1)	5 (<1)	9 (<1)

Investigator text for Adverse Events encoded using MedDRA version 12.0.

Percentages are based on N.

Multiple occurrences of the same adverse event in one individual counted only once.

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Incidences of less than 1% are rounded to '<1'. However, those events with an incidence of close to 1% (ie ≥ 0.995%) are included in the table.

At the time of the data cut-off, a total of 31 patients from the safety population had died. The number of deaths was higher in the observation arm than the rituximab arm (18 vs 13). The most common cause of death was disease progression, which accounted for 12 deaths in the observation arm and 10 deaths in the rituximab arm. The incidence of non-lymphoma deaths was also higher in the observation arm (6 vs 3). Five of these nine deaths were considered to be the outcome of adverse events. Two fatal adverse events in the observation arm were the result of neoplasms (leukaemia which was considered possible related to trial treatment and metastatic neoplasm considered to be unrelated to treatment). The three recorded fatal adverse events on the rituximab arm resulted from a treatment unrelated disorder which was an unknown event, hepatitis B considered to be probably treatment related and pulmonary haemorrhage considered to be treatment unrelated. The four remaining deaths on the observation arm were due to acute myeloid leukaemia, coronary artery disease, myelodysplastic syndrome and sepsis.

A total of 193 serious adverse events (SAEs) were reported for 158 patients being 63 (12%) in the observation arm and 95 (19%) in the rituximab arm. No single type of SAE occurred with an incidence of 1% or more in either arm. The most common of these were neoplasms including basal cell carcinomas, colon cancer and breast cancer occurring in 39

events overall affecting 37 patients. The most common class of serious adverse events in the rituximab arm were *Infections and Infestations* involving 25 patients (5%) vs six patients (1%) in the observation arm. In the rituximab arm three patients had serious adverse events of pneumonia, two of diverticulitis and two of hepatitis B. Serious cardiac disorders were reported for two patients in the observation arm compared to 11 patients in the rituximab arm.

A total of 27 patients discontinued maintenance treatment/observation as a result of adverse events being eight patients (2%) in the observation arm and 19 patients (4%) in the rituximab arm. The most common adverse events leading to treatment discontinuation were neoplasms, which accounted for the withdrawal of six patients in the observation arm and five in the rituximab arm. Four patients in the rituximab arm were withdrawn as a result of infections including two with hepatitis and one each with endocarditis and microbacterial infections. One case of hepatitis B was considered to be unrelated to treatment and the other three infections were considered to be probably related to treatment. Five patients discontinued treatment after becoming pregnant.

A total of 30 patients had their dosing of rituximab dropped or modified as a result of an adverse event. The most common reasons for interrupting the dose schedule or for modifying the dose were *Infections and Infestations* which occurred in 12 patients and included bronchitis (3 cases) and upper respiratory tract infections (2) and *Blood and Lymphatic Disorders* which occurred in nine patients including 7 neutropenic events and 5 leukopenic events.

Analysis of adverse events by organ system or syndrome revealed that adverse events occurring within one day of a rituximab cycle or observation visit revealed more adverse events being reported in the rituximab arm than the observation arm, with 74 events in 61 patients (12%) vs 61 events in 46 patients (9%). The majority of these adverse events were infections, mainly upper respiratory tract infections and bronchitis. Typical infusion related adverse events of \geq Grade III severity such as chills, pyrexia, nausea and vomiting were not reported in the rituximab arm. It was noteworthy that constitutional symptoms were reported for 31% of patients in the observation arm and 41% of patients in the rituximab arm throughout the maintenance/observation phase. Most of these were Grade I or II in severity.

Review of infections during maintenance/observation revealed that more patients in the rituximab arm had an infection with a normal neutrophil count, being 192 patients (38%) vs 127 patients (25%). In addition 11 patients in the rituximab arm had an infection with Grade II/III neutropenia of whom nine were Grade II infections and two were Grade III infections. One additional patient had febrile neutropenia (Grade III).

Infections of at least Grade II severity were the most common class of adverse events recorded and more frequent on the rituximab arm than the observation arm being 37% vs 22% of patients. However most infections were Grade II in severity with the incidence of Grade III or IV infections being 4% in the rituximab arm and <1% in the observation arm. Similarly serious infections occurred in 25 patients in the rituximab arm and six in the observation arm. Four patients in the rituximab arm discontinued treatment and a further 12 patients had their rituximab dosing modified as a result of infection. One patient in the rituximab arm died of hepatitis B infection and one patient in the observation arm died of sepsis. While most infections had no causal organism documented, of those infections with identified organisms the most common pathogens were viral in 22 patients on observation and 28 in the rituximab arm followed by bacterial in 11 patients on the observation vs 22 on the rituximab and fungal in three patients on observation vs nine patients on rituximab.

Three patients had hepatitis B reported during the maintenance/observation phase of the study, two of which were reactivation of hepatitis B infection and one whose past hepatitis B status was unknown. It was noteworthy that at least three patients with a known history of hepatitis B infection who entered the study did not develop hepatitis B reactivation during treatment.

It was also noteworthy that two important events of progressive multifocal leukoencephalopathy were reported in the later follow up analysis (to 30 June 2009). One of these cases was a patient on the rituximab maintenance arm and the other on observation. Most of these patients also had progressive lymphoma.

Review of *Blood and Lymphatic System Disorders* revealed that more patients in the rituximab arm developed adverse events within this SOC, being 34 events in 26 patients vs nine events in seven patients. The majority of these events were neutropenia, being 19 patients on the rituximab arm vs five on the observation arm. Grade III or IV neutropenia were recorded for 18 patients on the rituximab arm compared with five patients on the observation arm. Two cases of febrile neutropenia, one in each study arm and two cases of neutropenia, one in each study arm were reported as serious adverse events. Seven patients on rituximab arm had their rituximab dosing modified or interrupted as a result of neutropenia.

Review of cardiac events revealed that cardiac adverse events were recorded for six patients in the observation arm and 16 patients on the rituximab arm. Of these, two patients in the observation arm and 11 in the rituximab arm experienced cardiac disorders reported to be serious adverse events as indicated in Table 10. Both these serious adverse events in the observation arm were considered to be unrelated to trial treatment whereas in the rituximab 3/4 serious adverse events of cardiac failure (probable), one of cardiac myopathy (possible) and one of myocardial infarction (remote) were related to trial treatment. It was noteworthy that all of these patients had received R-CHOP as part of their induction treatment and most of the patients had other risk factors of cardiac disease.

Table 10: Summary of cardiac SAEs

Body System/ Adverse Event	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
Cardiac Disorders		
<i>Total Patients with At Least One AE</i>	2 (<1)	11 (2)
Cardiac Failure	-	4 (<1)
Atrial Fibrillation	-	2 (<1)
Angina Pectoris	-	1 (<1)
Aortic Valve Disease	-	1 (<1)
Arrhythmia	1 (<1)	-
Cardiac Arrest	-	1 (<1)
Cardiomyopathy	-	1 (<1)
Myocardial Infarction	-	1 (<1)
Myocardial Ischaemia	1 (<1)	-
<i>Total Number of AEs</i>	2	11

An updated safety analysis as of 30 June 2009 revealed that there was slight increase in the number of patients in both arms who experienced an adverse event or serious adverse event. There was no change however in the overall safety profile for the study.

With regards to special group assessments, it was noteworthy that the overall incidence of *Infections and Infestations, Blood and Lymphatic System Disorders* and neutropenia showed no clear increase with age in either arm of study.

Review of clinical laboratory evaluations revealed that in relation to haematology and biochemistry parameters, these were very similar between the two arms during the

course of the maintenance/observation arm except for lymphocyte counts, which increased with time in the observation arm compared to the rituximab arm. This difference was probably due to B-cell recovery in the observation arm compared with continued B-cell suppression in the rituximab arm.

The majority of patients in both study arms showed no change in the grade of the laboratory test parameters between the maintenance/observation phase. In the rituximab arm a higher number of shifts to Grade III/IV values were observed for lymphopenia as well as leukopenia and neutropenia. There were very few shifts to Grade III/IV for blood chemistry parameters and there was little difference between the two study arms.

Patients on study sites in France underwent additional sampling for immunophenotyping of peripheral blood cells. Absolute levels of circulating B-cells (CD19+), T-cells (CD3+) and natural killer cells (CD16 or CD56+) were assessed before induction therapy, after induction therapy and every six months for the first three years after randomisation or until recovery.

In relation to B-cells the CD19+ lymphocyte subsets showed suppression of B-cells in both study arms at baseline prior to randomisation with continued suppression during the maintenance/observation arm for patients on rituximab, compared to those on observation who showed recovery of their B-cells. The mean B-cell count of the observation arm at the end of the maintenance/observation phase was $0.16 \times 10^9/L$ compared with undetectable counts in the rituximab arm.

The mean T-cell counts at baseline after completion of induction therapy in both arms were similar and within the standard reference range. Although the mean value increased slightly in the observation arm and decreased slightly in the rituximab arm at Visit 3 with a mean of $1.06 \times 10^9/L$ in observation arm and a mean of $0.86 \times 10^9/L$ in the rituximab arm, there was little difference between the two arms over subsequent visits and most patients on the two arms remained within the normal range throughout the maintenance/observation phase.

The mean count of natural killer cells (NK) at baseline in both arms were similar and then increased slightly during the course of the maintenance/observation phase but remained with the normal range.

Review of immunoglobulin data revealed that over the course of the maintenance/observation phase mean immunoglobulin (Ig) (IgG, IgA and IgM) values and 95% CI in both study arms remained within the normal range. Although the number of patients with available IgG data decreased during the maintenance/observation phase, the majority of evaluable patients in both arms continued to have IgG levels of 4 g/L or higher. At the end of maintenance/observation phase, 11 patients (26%) in the observation arm and 36 patients (47%) in the rituximab arm had IgG levels lower than 7 g/L. Only one patient in the observation arm and four in the rituximab arm had IgG levels lower than 4 g/L at the end of the maintenance/observation phase.

Evaluator comment

These data have shown that the safety profile for rituximab in the maintenance phase of treatment from the PRIMA trial is generally manageable and not commonly associated with serious sequelae. There were a relatively small number of patient withdrawals because of adverse events mainly related to neutropenia and only one death which appeared to be related to treatment (hepatitis B infection). Overall the safety profile for rituximab from the study is in line with that previously observed from other studies and reflects generally good tolerance for rituximab in maintenance treatment.

ECOG 1496

In relation to the supportive study ECOG 1496, documentation and categorisation of adverse events was similar to those reported for the PRIMA study. Review of drug exposure in this trial revealed that at the time of data transfer (8 November 2004), 83 of the 161 patients (52%) treated with rituximab maintenance had received a protocol specified maximum of 16 infusions and 42 patients (26%) were still in the study and continued to receive rituximab maintenance.

In terms of assessment of overall adverse events at the time of data transfer, 144 patients (89%) who received rituximab maintenance had experienced one or more adverse events during the maintenance/observation phase of study compared with 101 patients (63%) in the observation arm. The most common adverse events affecting between 30-45% of rituximab treated patients were haematological (leukopenia, anaemia), fatigue and peripheral sensory neuropathy. Other common events in the rituximab arm included *Infections and Infestations* and *Nervous System Disorders* (each 19%), lung disorder (18%) and liver and skin disorder (each 17%), which is illustrated in Table 11. No unexpected safety signals were observed among patients treated with rituximab maintenance during the ECOG 1496 study.

Table 11: Common adverse events (incidence ≥5%)

Adverse Event Preferred Term	Observation (N = 161)	Rituximab (N = 161)	Total (N = 322)
Any AE	101 (62.7%)	144 (89.4%)	245 (76.1%)
Leukopenia	28 (17.4%)	71 (44.1%)	99 (30.7%)
Anemia	32 (19.9%)	56 (34.8%)	88 (27.3%)
Fatigue	22 (13.7%)	62 (38.5%)	84 (26.1%)
Peripheral sensory neuropathy	29 (18.0%)	48 (29.8%)	77 (23.9%)
Lung disorder	16 (9.9%)	29 (18.0%)	45 (14.0%)
Infection	14 (8.7%)	30 (18.6%)	44 (13.7%)
Liver disorder	11 (6.8%)	27 (16.8%)	38 (11.8%)
Thrombocytopenia	18 (11.2%)	18 (11.2%)	36 (11.2%)
Skin disorder	8 (5.0%)	27 (16.8%)	35 (10.9%)
Nervous system disorder	4 (2.5%)	30 (18.6%)	34 (10.6%)
Pain	12 (7.5%)	20 (12.4%)	32 (9.9%)
Oedema	12 (7.5%)	17 (12.4%)	29 (9.0%)
Pyrexia	12 (7.5%)	17 (12.4%)	29 (9.0%)
Blood LDH increased	5 (3.1%)	23 (14.3%)	28 (8.7%)
Neuromyopathy	12 (7.5%)	16 (9.9%)	28 (8.7%)
Weight increased	7 (4.3%)	18 (11.2%)	25 (7.8%)
Arthralgia	4 (2.5%)	20 (12.4%)	24 (7.5%)
Shoulder pain	4 (2.5%)	20 (12.4%)	24 (7.5%)
Metabolic disorder	7 (4.3%)	16 (9.9%)	23 (7.1%)
Alopecia	4 (2.5%)	16 (9.9%)	20 (6.2%)
Granulocytopenia	4 (2.5%)	15 (9.3%)	19 (5.9%)
Nausea	4 (2.5%)	15 (9.3%)	19 (5.9%)
Drug toxicity	11 (6.8%)	8 (5.0%)	19 (5.9%)
Diarrhea	3 (1.9%)	14 (8.7%)	17 (5.3%)
Weight decreased	3 (1.9%)	14 (8.7%)	17 (5.3%)

Grade III or IV adverse events were recorded for 26 (16%) of the rituximab maintenance patients compared with 18 (11%) patients in the observation arm. The only Grade III or IV adverse event with a >2% higher frequency amongst patients in the rituximab maintenance arm was neutropenia, being 3.7% vs 0.6%. Grade III or IV cardiac events were slightly more frequent for rituximab involving four patients compared to one patient on observation.

At the cut-off date, 21 patients in the observation arm and 15 patients in the rituximab arm had died during the study. Of these, 10 patients in the observation arm and eight in the rituximab arm were considered to have died due to progressive disease. There was only one adverse event which resulted in death and this was a patient in the observation arm who died due to an infection. It was noted that one patient treated with rituximab maintenance therapy experienced extrasystoles, ventricular arrhythmia and ventricular tachycardia, all Grade IV. One patient in the observation arm experienced myocardial infarction and myocardial ischaemia, both of Grade IV severity.

No significant additional safety data were provided in the 67 month update.

Standard haematological and biochemical laboratory data were not collected during the ECOG 1496 study; however some immunological parameters were assessed. These included quantitative measurements of CD20+, CD8+ and CD4+ lymphocyte counts collected pre-study, prior to initiation of maintenance and every three months thereafter through 24 months or until recovery with lymphocyte counts. Also measurements of serum immunoglobulins were to be performed at baseline and every six months thereafter up to Month 24.

With relation to CD20+ cells, as might be expected, maintenance on rituximab led to a decrease in the CD20+ lymphocyte count relative to baseline. Mean CD8+ and CD4+ lymphocyte counts remained at or above their baseline values throughout the maintenance phase for patients in both arms of study. There were no consistent differences in the mean CD8+ and CD4+ lymphocyte count changes over time.

In relation to immunoglobulins for patients on maintenance rituximab, initial increases in the mean IgG levels were noted at Month 3, gradually diminished for Month 6 to Months 24, whereas patients in the observation arm maintained their initial increase in mean IgG relative to the maintenance baseline. Similar trends were observed in the rituximab and observation arms for serum IgA. In the observation arm the mean change in serum IgM exhibited a positive trend, while in the rituximab arm, the mean change in serum IgM exhibited a slightly negative trend at all time points with the exception of Month 18.

Evaluator comment

These data from the supportive study ECOG 1496 are again in line with that reported from the PRIMA trial indicating generally reasonable tolerance for rituximab in the maintenance phase of treatment. It was noteworthy that the maintenance rituximab in this trial was according to a different schedule for that for the PRIMA trial.

Post marketing data

Since the first marketing authorisation of rituximab more than 2.1 million patients have been treated with this antibody. The majority of these patients had NHL. A total of 17 routine Periodic Safety Update Reports (PSURs) have been submitted since the first marketing authorisation of rituximab was granted in 1998. Product prescribing information for MabThera has been regularly updated with the latest safety information.

With the data cut-off date of 31 December 2009, a total of 44,681 adverse events have been reported with rituximab worldwide to the global safety data base. Of these 21,642 were classified as serious. The events were reported from spontaneous sources as well as sources from clinical trials in oncology. The most frequently reported events from the system organ classes were *General Disorders and Administration Site Conditions* (15.9%), *Infections and Infestations* (14%), *Blood and Lymphatic System Disorders* (10.4%) and *Respiratory, Thoracic and Mediastinal Disorders* (9.5%). No real differences in these events are noted when the patients with NHL are separated from the overall data base.

Evaluator comment

No evidence of new adverse events not previously documented in Product Information was observed from this updated safety data base.

Clinical Summary and Conclusions**Clinical Aspects**

A population pharmacokinetic analysis was provided in this submission with the purpose to update the rituximab PK data in the Product Information (PI). This involves categorising the pharmacokinetics of rituximab based on the combined data set from six clinical studies in patients with NHL. Two were Phase I/II clinical trials, two were Phase II clinical studies and two were Phase III clinical studies.

The main objectives of this analysis were to categorise the pharmacokinetics of rituximab in the NHL population, to estimate the effects of covariates as potential predictors of variability and to update the label. From the results of this analysis the median of individual estimates of the terminal half-life of rituximab was 22.4 (range of 6.1 to 51.9) days.

The clinical relevance of the final population PK model is that dose adjustment for tested covariants is not expected to result in a meaningful reduction in PK variability.

The clinical section of this application dealt with the assessment to update the current dosing recommendations for rituximab when used in maintenance therapy for the treatment of NHL. Current approved maintenance dosage regimen for rituximab in NHL patients who have responded to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m² body surface area once every three months until disease progression or for a maximum period of two years. This data is principally derived from the pivotal EORTC 20981 involving patients with relapsed/refractory NHL. In the current application the pivotal trial M018264 (PRIMA study) was undertaken in patients who have had previously untreated NHL. Following initial induction with chemotherapy combined with rituximab, patients were then randomised to receive either rituximab in a dose of 375 mg/m² once every two months or observation. The decision to utilise a two monthly schedule in this trial was based on earlier data suggesting that on pharmacokinetic evaluations plasma levels of rituximab declined below 25 ng/mL two months after administration of a single dose 375 mg/m².

Supporting data for assessment of maintenance of rituximab in patients with previously untreated NHL was also provided in this submission from the study ECOG 1496. In this trial, the maintenance rituximab administered in the randomised phase of study involved four weekly injections of rituximab of 350 mg/m² every six months.

The PRIMA study was a multicentre Phase III open labelled randomised trial in patients with advanced follicular lymphoma to evaluate the benefit of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with no maintenance treatment. The study involved 220 centres in 24 countries. The primary objective of the study was to evaluate the benefit from maintenance therapy with rituximab on PFS as compared to no maintenance therapy (observation) after induction response with chemotherapy therapy plus rituximab in previously untreated patients with high tumour burden follicular lymphoma.

Secondary objectives included comparison of the following parameters between the maintenance and observation arms (event free survival, overall survival, time to next anti-lymphoma treatment, time to next chemotherapy treatment, response rate at the end of

maintenance/observation, transformation rate at first relapse). The safety profile was also to be evaluated.

At the end of the induction phase 1078/1193 (90%) patients achieved a complete or partial response and 1019 patients were randomised to the maintenance /observation phase. Maintenance therapy of rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of PFS compared to no maintenance therapy. The investigator assessed PFS with a time to event at the 25th percentile was 16.7 months for patients on observation vs 36 months for patients receiving rituximab and the one year PFS rate was 0.82 on observation vs 0.89 for rituximab. The HR for the difference was 0.5 ($p < 0.0001$). This was supported by the independent review committee's assessment of PFS with a time to event at the 25th percentile of 15 months for patients on observation vs 26.4 months for patients on rituximab with the one year PFS rate of 0.81 vs 0.87 for patients on rituximab and an HR of 0.54 ($p < 0.0001$). This result was supported by improvements in all the secondary efficacy endpoints with the exception of overall survival and transformation rate. The additional 5.5 months of follow up to a clinical cut-off date of 30 June 2009 did not change these outcomes.

The supportive study was a randomised Phase III study in low-grade lymphoma comparing maintenance anti-CD20 antibody vs observation following induction therapy (ECOG 1496 study). This was a multicentre NCI sponsored intergroup study in which patients who had received initial induction chemotherapy with CVP and who achieved complete response, partial response or stable disease were subsequently randomised to receive maintenance rituximab in a dose of 375 mg/m² weekly for four weeks every six months or to observation. Treatment was to begin four weeks after completion of induction chemotherapy and repeated at six monthly intervals for a total of four cycles. Patients included in this study involved a histological or cytological diagnosis of NHL. Subsequent stratification for these patients was to follicular lymphoma vs other.

A total of 516 patients were initially enrolled on study and subsequently 322 patients were randomised to maintenance or observation. The primary endpoint of the study was duration of PFS with secondary endpoints including duration of overall survival and response improvement within two years after randomisation. Safety evaluation was also undertaken.

For patients who were progression free after induction with CVP chemotherapy, treatment with rituximab maintenance resulted in a statistically significant and clinically meaningful prolongation of PFS compared with observation with a stratified HR of 0.363 ($p < 0.0001$) with a median of four years vs 1.3 years for rituximab maintenance vs observation. Among the subset of 248 patients with follicular lymphoma, PFS was also significantly prolonged in the rituximab arm with an HR of 0.37 ($p < 0.0001$) and median PFS was non-estimable for patients on rituximab maintenance vs 1.2 years for those on observation. A subsequent analysis of the study based on a median follow up of 67 months for the observation arm and 71 months for the rituximab maintenance arm confirmed a statistically significant and clinically meaningful prolongation of PFS with rituximab maintenance with an HR of 0.436 ($p < 0.0001$) and median PFS 55 months vs 15 months. Updated results of follicular lymphoma revealed the difference in PFS between the rituximab maintenance/observation arms was maintained with the longer follow-up with an HR of 0.4 ($p < 0.0001$) and a median PFS of 4.3 years vs 1.3 years after a median follow up of 3.7 years. The subgroup analyses confirmed the benefit for rituximab maintenance for the various demographic and baseline disease characteristics.

Review of safety results from the PRIMA study revealed that during the maintenance/observation phase 97% of patients on rituximab arm and 90% of patients on the observation arm experienced at least one episode of toxicity as recorded on a

customised toxicity check list. Serious adverse events were more common on the rituximab arm than the observation arm (52% vs 35%) and the incidence of Grade II – IV infections was also higher in the rituximab arm than in the observation arm (37% vs 22%). However most infections were mild to moderate in severity and the incidence of Grade III to V infections was only 4% in the rituximab arm compared with <1.% in the observation arm. At the time of clinical cut-off a total of 31 patients had died, 18 on the observation arm and 13 on the rituximab arm. Disease progression accounted for the deaths of 22 patients and there were five fatal adverse events. Only one of these in relation to patients receiving rituximab maintenance therapy was considered directly related to treatment (hepatitis B infection). Two additional deaths from progressive multifocal leukoencephalopathy were reported one on each arm of trial. These were also associated with patients who had progressive lymphoma. Overall there were no unexpected safety findings in the PRIMA trial.

The effect of rituximab on lymphocyte subsets and immunoglobulins was also assessed during the study. Overall these data were consistent with the observed safety profile of maintenance rituximab and indicate manageable B-cell suppression during maintenance treatment with a slight adverse effect on IgG levels and neutrophil counts in a minority of patients.

Reviewing the safety data for the supportive study ECOG 1496, adverse events that occurred at a >5% frequency among patients who received maintenance rituximab included leukopenia, anaemia, neutropenia, diarrhoea, nausea, fatigue, asthenia, liver disorders, infections, lung disorders and nervous system events. These were consistent with the known toxicity profile of rituximab and most were mild to moderate in severity. Neutropenia was the only Grade III/IV adverse event with a frequency $\geq 2\%$ higher among patients in the maintenance rituximab arm compared with those under observation. Two patients experienced Grade IV cardiac events, one on each arm of study. The cardiac events for the patient on rituximab maintenance were severe cardiac arrhythmias, while for the patient on observation was a severe myocardial infarction. There was only one adverse event leading to death (an infection occurring in a patient randomised to observation).

Benefit Risk Assessment

The current approval for rituximab in the maintenance setting is for patients with previously untreated or relapsed/refractory follicular lymphoma after response to induction therapy with chemotherapy with or without rituximab. This approval was based on an earlier trial (EORTC 20981). The current data presented from the PRIMA trial in conjunction with the supportive data from ECOG 1496 has also shown that maintenance therapy is effective for previously untreated patients who have achieved response to induction chemo-immunotherapy. The observed benefit of rituximab maintenance in these two studies was consistent in magnitude resulting in a reduction risk of disease progression or death around 50% or more when compared to observation.

These data therefore have added to the evidence that rituximab is effective in both induction and maintenance phases of treatment for patients with follicular B-cell type non-NHL. This is irrespective of prior chemo-immunotherapy, regardless of the response to induction treatment be it either complete response or partial response and regardless of the maintenance schedule of rituximab. There are no new safety signals observed from the two studies. In general terms rituximab maintenance therapy is associated with a manageable toxicity profile.

The evaluator therefore considered that the benefits of rituximab maintenance in patients with previously untreated follicular NHL have been demonstrated and outweighs risks associated with the toxicity profile.

In view of the fact that the data provided from the PRIMA trial involved administration of maintenance rituximab at a dose of 375 mg/m² once every two months for patients with previously untreated follicular lymphoma, the PI should include a statement that previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m² body surface area once every two months until disease progression or for a maximum period of two years (12 infusions) is appropriate.

Furthermore, maintaining the earlier statement concerning rituximab maintenance that relapse/refractory patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m² body surface area once every three months until disease progression or for a maximum period of two years is appropriate.

V. Pharmacovigilance Findings

There was no requirement for a Risk Management Plan in a submission of this type.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Clinical evaluation

The clinical evaluator recommended approval of the application.

Pharmacokinetics

The submission included a new population PK analysis based on six previously submitted studies. The PK section of the PI has been updated based on these data. The data are not directly relevant to the proposed new dosage regimen.

Efficacy

The proposed new dosage regimen is supported by one pivotal randomised controlled trial (the PRIMA study). The trial has been published and the results presented in the published paper are more recent than those contained in the submitted study report.⁴

Subjects included in the trial had untreated follicular lymphoma with some evidence of a high tumour burden. All patients received induction treatment with rituximab in combination with one of three standard chemotherapy regimens. The specific induction

⁴ Salles G, Seymour JF, Offner F et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2010; 377: 42-51.

regimen used was chosen by individual study centres. Subjects who achieved a response following induction therapy were randomised to rituximab maintenance therapy (375 mg/m² every 8 weeks until disease progression or for a maximum of 2 years) or to observation.

The primary endpoint for the study was progression free survival (PFS) as assessed by the investigator. The TGA has adopted Appendix 2 to the EMA guideline on anticancer agents which provides guidance on the design of studies in haematological malignancies.⁵ This guidance recommends PFS as an appropriate endpoint for studies of low grade lymphoma. Disease progression and response were assessed using the 1999 International Workshop Response Criteria for NHL.

The results presented in the study report come from a planned interim analysis with a data cut-off of 14 January 2009. Updated efficacy and safety data from a later analysis with a cut-off date of 30 June 2009 were also included. The published version of the trial presented data with a cut-off of 15 January 2010.

Results for PFS are presented in Table 12. Maintenance therapy with rituximab was associated with an approximately 50% reduction in the risk of disease progression or death. Investigators were not blinded to treatment. However, an assessment of PFS by a blinded independent review committee gave similar results to the investigator assessment. A number of secondary endpoints were examined and these also demonstrated a significant benefit for rituximab maintenance therapy. Overall survival data were not mature with less than 5% of patients having died after a median follow up of 36 months. Quality of life results did not differ between the two treatment groups.

Table 12: Results for Progression-free survival – PRIMA study

Data cut-off	Median follow-up	Assessed by	PFS events (rituximab vs observation)	Hazard ratio (95% CI); p value
14 January 2009	25 months	Investigator	93 vs 174	0.50 (0.39 – 0.64); p < 0.0001
14 January 2009	25 months	IRC	96 vs 163	0.54 (0.42 – 0.70); p < 0.0001
30 June 2009	30.5 months	Investigator	110 vs 197	0.51 (0.41 – 0.65); p < 0.0001
15 January 2010	36 months	Investigator	135 vs 221	0.55 (0.44 – 0.68); p < 0.0001

The submission included a supportive phase III trial (ECOG 1496) of rituximab maintenance therapy in patients with previously untreated low grade CD20+ve B-cell lymphomas. The study used a maintenance dosage regimen (375 mg/m² every week for 4 weeks, repeated every 6 months for 2 years) which is not consistent with that being proposed in the current submission. The efficacy data from this study were therefore not considered relevant to the application.

⁵ EMA, Committee for Medicinal Products for Human Use (CHMP), 18 February 2010. Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies, EMA/CHMP/EWP/520088/2008.

Safety

In the PRIMA study, at the time of the interim analysis, 285 of 501 (57%) subjects in the rituximab arm had completed the planned 12 treatment cycles with 89.8% of subjects having received >90% of their planned dose.

Safety data were collected via the following two mechanisms:

- a checklist of pre-specified 'toxicities' was included on the case report form;
- 'adverse events' which included Grades III-V toxicities, Grades II-V infections and any serious adverse events were also recorded.

The overall safety profile of rituximab vs observation in the maintenance phase is shown in Table 6.

Rituximab treatment was associated with a modest increase in the incidence of toxicities, adverse events, serious adverse events and treatment discontinuations due to toxicity.

In terms of specific toxicities/adverse events, rituximab was associated with increased incidences of:

- infections
- leucopenia and neutropenia
- constitutional symptoms, GIT toxicity and pulmonary toxicity
- cardiac adverse events, including serious cardiac adverse events

These toxicities have been previously observed with rituximab and are described in the currently approved PI.

There was one death in the rituximab arm that was considered to be related to rituximab (hepatitis B infection).

The evaluator commented that the safety profile of the drug in the PRIMA study appeared manageable and was in line with that observed in previous studies.

In the supportive ECOG 1496 study, the safety profile of maintenance rituximab was generally consistent with that observed in the PRIMA study, with no unexpected safety signals observed.

Risk Management Plan

There was no requirement for a Risk Management Plan in a submission of this type.

Risk-Benefit Analysis

Delegate Considerations

Overall risk benefit

The pivotal study has demonstrated a clinically significant benefit for the new maintenance regimen, with an approximate 50% reduction in the risk of progression or death compared to observation. No new safety issues were identified and the level of toxicity produced by the new regimen was manageable and did not outweigh the efficacy benefit. The Delegate therefore considered that the risk benefit ratio for the new regimen was positive.

Appropriate dosage regimen

With the initial application for maintenance therapy considered by ADEC in 2007, the sponsor sought (and was granted) approval for use in both relapsed/refractory disease

and previously untreated disease, even though the maintenance regimen approved was studied only in the relapsed/refractory setting.

The proposed new maintenance dosage regimen for previously untreated disease results in an increased dose being delivered to the patient compared to the currently approved regimen (12 vs 8 doses of 375 mg/m² over 2 years). There were no efficacy and safety data to establish that the increase in dose results in improved outcomes for patients. In the absence of such data the Delegate did not consider an increase in dose can be justified and proposed to reject the application.

Conclusion

The Delegate proposed to reject the application on the grounds that the proposed increase in dose has not been demonstrated to be associated with improved outcomes for patients.

Response from Sponsor

The sponsor noted that the current dosing recommendation for maintenance therapy in NHL, as per the approved MabThera PI, is:

Patients who have responded to induction treatment may receive maintenance therapy with MabThera given at 375 mg/m² body surface area once every 3 months until disease progression or for a maximum period of two years.

This dosing recommendation does not distinguish between patients with relapsed/refractory or previously untreated NHL. With this current submission the sponsor proposed to define the maintenance dosing schedules for patients receiving MabThera as maintenance therapy for either previously untreated NHL or relapsed/refractory NHL, as follows:

Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/ m² body surface area once every 2 months until disease progression or for a maximum period of two years (12 infusions).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera given at 375 mg/ m² body surface area once every 3 months until disease progression or for a maximum period of two years.

Based upon the data submitted with the application, the clinical evaluator agreed that the proposed dosing change was appropriate since the data submitted support the change. The Delegate, however, proposed to reject this change on the basis that it has not been demonstrated that the increased dose (from a 3 monthly to a 2 monthly schedule for previously untreated patients) is associated with improved outcomes for patients.

The sponsor did not concur with the Delegate's proposal to reject the dosing change. The sponsor outlined reasons why the proposed dosing change was appropriate.

Choice of Dose Regimen

Three different maintenance regimens have been evaluated in patients with follicular lymphoma:

- In the PRIMA study (M018264), upon which this submission is based, single infusions were repeated every 2 months (a total of 12 doses) in patients with previously untreated disease;
- In the ECOG 1496 study, 4 weekly doses were repeated every 6 months (a total of 16 doses) in patients with previously untreated disease;
- And in the EORTC 20981 study, single infusions were repeated every 3 months (a total 8 of doses) in patients with relapsed/refractory disease.

These different schedules evolved over time, as a result of different treatment philosophies and emerging pharmacokinetic (PK) and clinical efficacy data.

The ECOG 1496 schedule was based on the concept of intermittent re-treatment as a means of preventing relapse. Preliminary data from one US trial of rituximab maintenance treatment, consisting of 4 weekly infusions every 6 months for 18 months following induction treatment with rituximab monotherapy, revealed a promising median PFS of 52 months in previously untreated patients with follicular lymphoma.⁶ Subsequently, another trial from the same group (the LYM-5 study) showed a prolongation of PFS using the same schedule of rituximab maintenance (median PFS 31.3 months vs 7.4 months for patients retreated at relapse; $p = 0.007$).⁷ Overall and complete response rates were also higher in the maintenance group than in the retreatment group and more patients in the maintenance group remained in continuous remission, and were still in remission, at the time the study was reported.

In the PRIMA and EORTC 20981 trials, the maintenance schedules were based on the hypothesis that continuous exposure to rituximab would be more effective than intermittent exposure in preventing relapse, as investigated by ECOG 1496. During the design of the PRIMA study, the 2 monthly schedule was selected instead of the schedule used in the EORTC 20981 study (375 mg/ m² every 3 months for 2 years) in relapsed/refractory follicular lymphoma because data available from a phase II PK study suggested at the time that a 2 monthly dosing schedule might be superior to a 3 monthly dosing schedule.⁸ These data were not available at the time the EORTC 20981 study was designed. The PK study referred to above investigated the effect of individualised pharmacokinetic dosing of rituximab in patients with B-cell lymphoproliferative disorders who had failed at least one prior therapy. Patients received 4 weekly infusions of rituximab (375 mg/m²) as induction therapy and a repeat rituximab dose (375 mg/m²), when serum levels fell to below 25 µg/mL. With this approach, single infusions of rituximab had to be administered every 2– 4 months to maintain levels above 25 µg/mL, a threshold previously shown to be associated with improved efficacy.

Based on this information, a more conservative schedule was chosen for the PRIMA study than that used in the EORTC 20981 study, with doses of rituximab given every 2 months during the maintenance phase. This schedule was supported by data from a trial conducted by the Swiss Group for Clinical Cancer Research (SAKK), in which one infusion of rituximab every 2 months for a period of 8 months significantly prolonged event free survival (EFS) (from a median of 19 months to 36 months) after induction using 4 weekly infusions of rituximab.⁹ PK data have since been published which provide further support for the 2 monthly regimen. In the ECOG 4402 (RESORT) trial in patients with low tumour burden indolent lymphoma, rituximab levels measured 12 weeks after rituximab induction (4 doses of 375 mg/m² at weekly intervals) were < 25 µg/mL in nearly half (47%) the patients (median 26.9 µg/mL). The investigators concluded that 3 monthly

⁶ Hainsworth JD, Litchy S, Greco FA. Scheduled rituximab maintenance therapy versus rituximab retreatment at progression in patients with indolent non-Hodgkin's lymphoma (NHL) responding to single-agent rituximab: a randomized trial of the Minnie Pearl Cancer Research Network. ASH 2003, abstract 231.

⁷ Hainsworth JD et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus retreatment at progression in patients with indolent non-Hodgkin's lymphoma—a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2005; 23: 1088-1095.

⁸ Gordan LN, Grow WB, Pusateri A, et al. A phase II trial of individualized pharmacokinetic dosing of rituximab maintenance for patients with CD20-positive lymphoproliferative disorders. *J Clin Oncol* 2005; 23: 1096–1102.

⁹ Ghielmini M et al. Prolonged treatment with Rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard Weekly X 4 Schedule. *Blood* 2004; 103: 4416-23.

schedule of administration would not be sufficient to maintain therapeutic levels (> 25 µg/mL) in a significant proportion of patients.¹⁰

Optimal Dose Regimen

Although the PK data described above clearly support the choice of 2 monthly dosing as a rational, PK based regimen for the PRIMA study, the sponsor acknowledged they do not confirm that the 2 monthly dosing regimen is superior to the 3 monthly regimen. To find out which rituximab maintenance regimen is superior would require a head-to-head comparison within the same patient population. The feasibility and desirability of such a large trial are questionable. If such a trial were to be performed, many investigators and patients would prefer it to answer more clinically important questions such as how to integrate new, potentially more effective agents into standard therapy.

The sponsor also acknowledged that there may be uncertainties about the optimal maintenance regimen for patients with follicular lymphoma and that the availability of more than one regimen might be considered scientifically unsatisfactory. Importantly however, the advent of the PRIMA data does not take away the positive results of the pivotal EORTC 20981 study in the relapsed/refractory setting and for this reason the sponsor was proposing that the 2 monthly regimen be added to the PI and specified for use in the first line setting only (the setting in which it was tested) rather than removing the 3 monthly regimen.

On the basis of the evidence provided by the PRIMA study, and given that the benefit risk assessment is considered positive, the sponsor believed it was appropriate to add to the MabThera PI the 2 monthly dosing schedule for maintenance treatment of previously untreated NHL patients, whilst retaining the current recommended 3 monthly (EORTC 20981-based) maintenance schedule for the treatment of relapsed/refractory NHL patients. Although PK data tend to support 2 monthly rather than 3 monthly administration of maintenance rituximab, there are insufficient clinical efficacy data to support a change to the current recommended 3 monthly regimen for patients with relapsed/refractory follicular lymphoma.

Overseas Approvals

The proposed 2 monthly dose regimen for previously untreated NHL patients was approved by the EMA on 25 October 2010, by the FDA on 28 April 2010 and by Swissmedic on 4 October 2010. These approvals were based upon the same dataset as was submitted to the TGA. No additional efficacy or safety data comparing the 2 monthly regimen to the 3 monthly regimen were provided to support these overseas approvals.

TGA approval of the initial application for maintenance therapy

During 2007 the sponsor was granted approval by the TGA for the 3 monthly maintenance dosing regimen for both relapsed/refractory disease and previously untreated disease, although the pivotal trial (EORTC 20981) supporting that registration only studied the 3 monthly regimen in relapsed/refractory patients. With this decision the TGA recognised the clinical need to provide maintenance treatment for both relapsed/refractory and previously untreated patients, a decision which the sponsor continued to support.

With this submission the sponsor was proposing to define the dosage regimen for previously untreated NHL patients since there were now substantial positive data from an

¹⁰ Kahl BS et al. Preliminary pharmacokinetic (PK) analysis of Eastern Cooperative Oncology Group Protocol E4402: rituximab extended schedule or re-treatment trial (RESORT). Blood (ASH). 2007; 110:Abstract 3420.

appropriate pivotal, Phase III trial in the pertinent patient group to support the dosing change. Such data were not available in 2007.

Conclusion

The PRIMA study is the first randomised Phase III study to show a significant improvement in PFS with rituximab maintenance therapy in previously untreated patients with follicular lymphoma who have responded to a rituximab containing induction regimen. The sponsor believed the efficacy results achieved in the PRIMA study utilising the 2 monthly dose regimen are exceptional.

After a median observation time of 25 months, rituximab maintenance significantly reduced the risk of disease progression or death by 50% compared with observation (stratified hazard ratio (HR) 0.50, 95% CI 0.39, 0.64, $p < 0.0001$). The median PFS was not reached in either arm but at the time of data cut-off 174 patients had progressed or died in the observation arm (33.9%) compared with 93 patients (18.4%) in the rituximab maintenance arm. Very similar results were obtained when IRC assessed disease progression was used to calculate PFS. According to the IRC assessments, rituximab maintenance significantly reduced the risk of disease progression or death by 46% (stratified HR 0.54, 95% CI [0.42, 0.70]).

The results of this primary analysis have since been confirmed by further updated analysis.

Safety data from the PRIMA study are consistent with the established safety profile of rituximab when used as maintenance treatment for up to 2 years and there were no new or unexpected findings. As expected, adverse events (including Grade III/IV, Grade II infections, and serious adverse events) were more common in the rituximab maintenance arm (52% vs 35% of patients), and the incidence of (Grade II-V) infections was also higher (37% vs 22% of patients). However, most infections were mild to moderate in severity: the incidence of Grade III-V infections was only 4% in the rituximab arm vs < 1% in the observation arm. One patient died of infection during the rituximab maintenance-observation phase, before initiation of second line treatment (a patient with fulminant hepatitis B reactivation). Two patients died of PML after initiation of subsequent therapy for progressive disease. As expected, blood and lymphatic adverse events (Grade III-IV) were also more common in the rituximab arm (5% vs 1%) during the maintenance/observation phase, but the difference was small.

In the interest of quality use of medicines, the sponsor believed the PI document should provide guidance to the prescriber on the basis of the available evidence. Australian patients with previously untreated NHL should be eligible to receive the 2 monthly regimen and realise the same benefits demonstrated by the PRIMA study. The sponsor has provided the necessary evidence to support the dosing change. The TGA agreed that the 2 monthly regimen is efficacious and no new safety issues were identified. The TGA agreed that the level of toxicity produced by the new regimen of 12 doses was manageable and did not outweigh the efficacy benefit. The evidence supports the use of the new dosing regimen and therefore the sponsor did not agree that the new regimen should not be approved

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the application.

It was noted that the pharmacokinetic data submitted for this application were not directly relevant and that the results in the published report of the single clinical trial submitted were more recent than those provided in the study report.

The previously evaluated dosage regimen approved in 2007 included this patient group. It was acknowledged that maintenance therapy with rituximab was associated with an approximately 50% reduction in the risk of disease progression or death. A number of secondary endpoints also demonstrated a significant benefit although treatment was associated with a modest increase in the incidence of toxicities, adverse events, serious adverse events and treatment discontinuations due to toxicity.

The ACPM agreed with the Delegate that the proposed new maintenance dosage regimen for previously untreated disease results in an increased dose being delivered to the patient compared to the currently approved regimen (12 compared to 8 doses of 375 mg/m² over 2 years). No efficacy and safety data were submitted to establish that the increase in dose results in improved outcomes for patients.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application to register a new dosage regimen for maintenance therapy in non-Hodgkin's lymphoma for rituximab (MabThera).

However, approval was given for a revised PI document based upon the data submitted with the application.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

MABTHERA[®]

Rituximab, recombinant for intravenous infusion (CAS registry number: 174722-31-7).

WARNING

Use of MABTHERA may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of MABTHERA should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. If a diagnosis of PML is confirmed MABTHERA must be permanently discontinued (see PRECAUTIONS).

DESCRIPTION

MABTHERA (rituximab) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG₁ kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Rituximab is composed of 1,328 amino acids and has an approximate molecular weight of 144 kD. Rituximab has a high binding affinity for the CD20 antigen of 5.2 to 11.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture in a nutrient medium containing 100 mg/mL of the antibiotic gentamicin. The antibiotic is not detectable in the final product. The anti-CD20 antibody is purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

MABTHERA is a sterile, clear, colourless, preservative-free, concentrated solution for intravenous infusion. MABTHERA is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide or hydrochloric acid.

PHARMACOLOGY

Pharmacodynamics

General: Rituximab binds specifically to the antigen CD20, a transmembrane molecule located on pre-B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas (NHL). CD20 (human B lymphocyte-restricted differentiation antigen, Bp35) is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD. This non-glycosylated phosphoprotein is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or

other normal tissues. CD20 regulates (an) early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 does not internalise upon antibody binding and is not shed from the cell surface. This antigen does not circulate in the plasma. Thus, free antigen does not compete for rituximab binding.

In rheumatoid arthritis (RA) the putative mechanism of action of rituximab involves the depletion of surface antigen-positive B lymphocytes from synovial tissue, with downstream effects potentially including reduced activation of T-cells and the associated release of pro-inflammatory cytokines.

In Vitro Mechanisms of Action: The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). The antibody also induces apoptosis in the DHL-4 human B-cell lymphoma line. Finally, *in vitro* studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Binding specificity: In human tissue, the expression of the CD20 antigen is highly restricted; rituximab binding to CD20 was found only on lymphoid cells in the thymus, the white pulp of the spleen and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no non-specific binding was observed.

In Vivo: In cynomolgus monkeys, four or eight weekly doses of 269 mg/m² of rituximab resulted in plasma concentrations of 161 to 386 ng/mL, approximately 24 hours after the first dose. Two weeks after the last dose, rituximab was still detected in the plasma of 3/6 monkeys treated for four weeks and in 4/6 monkeys treated for eight weeks.

B lymphocyte numbers were reduced by 99% or more in comparison with pre-test values in the peripheral blood of all monkeys, approximately 24 hours after the first dose. Two weeks after the last dose, B lymphocyte numbers were still reduced by more than 99% in 3/6 monkeys dosed for four weeks and in 4/6 monkeys dosed for eight weeks, and B lymphocyte numbers were also depleted in the mandibular lymph nodes and femoral bone marrow. A partial recovery of B lymphocyte numbers in the peripheral blood of some monkeys in both dose groups was correlated with the development of antibodies against rituximab.

Human Pharmacodynamics: A marked decline in median peripheral blood B-cell counts was seen beginning after the first dose of MABTHERA.

In patients treated for haematological malignancies, B-cell recovery began at approximately six months following the completion of treatment. B-cell levels returned to normal between nine and twelve months following completion of treatment.

In patients with RA, the duration of peripheral B cell depletion was variable. The majority of patients who received further treatment did so prior to full B cell recovery.

Pharmacokinetics

Non-Hodgkin's Lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m² as an intravenous (IV) infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2 . However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. The variability in V_1 caused by the range in BSA (1.53 to 2.32 m²) and concurrent CHOP therapy was relatively small (27.1% and 19% respectively). Age, gender, race, and WHO (World Health Organisation) performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mL (range 77.5 - 996.6 µg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.

Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Rituximab at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Chronic Lymphocytic Leukaemia (CLL)

Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m² increased to 500 mg/m² each cycle for a further 5 doses in combination with fludarabine and cyclophosphamide (FC) in CLL patients. The mean C_{max} (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m² infusion.

Rheumatoid Arthritis

Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar

mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender-related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 $\mu\text{g/mL}$ for 2 x 500 mg dose and ranged from 298 to 341 $\mu\text{g/mL}$ for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 $\mu\text{g/mL}$ for the 2 x 500 mg dose and ranged from 355 to 404 $\mu\text{g/mL}$ for the 2 x 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 x 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

Upon re-treatment with a second course the pharmacokinetics of rituximab were again assessed following two IV doses of 500 mg and 1000 mg. Mean C_{max} for serum rituximab following first infusion was 170 to 175 $\mu\text{g/mL}$ for 2 x 500 mg dose and 317 to 370 $\mu\text{g/mL}$ for 2 x 1000 mg dose. C_{max} following second infusion, was 207 $\mu\text{g/mL}$ for the 2 x 500 mg dose and ranged from 377 to 386 $\mu\text{g/mL}$ for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

CLINICAL TRIALS

Non-Hodgkin's Lymphoma

Relapsed/Refractory Low Grade or Follicular non-Hodgkin's Lymphoma

Monotherapy

In the pivotal study, an open label, single arm trial of 166 patients with relapsed or refractory low-grade or follicular B-cell NHL, subjects received 375 mg/m^2 of MABTHERA as an IV infusion once a week for four weeks (4 doses). The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% (CI_{95%} 41% – 56%), comprising a 6% complete response (CR) and 42% partial response (PR). The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was significantly higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs 12%) and in patients with prior autologous bone marrow transplantation (ABMT) compared to those with no prior ABMT (78% vs 43%). Age, sex, lymphoma grade, years since initial diagnosis, presence or absence of bulky disease, normal or high LDH, or presence of extranodal disease did not have a significant effect (Fisher's exact test) on response to MABTHERA.

ORR was also significantly higher in patients with no bone marrow involvement compared to those with bone marrow involvement (59% vs 40%). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as

prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Re-treatment

In a multicentre, single-arm study, 58 patients with relapsed or refractory low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MABTHERA, were re-treated with 375 mg/m² of MABTHERA as IV infusion weekly for four doses. Three of the patients had received two courses of MABTHERA before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CR 10% and PR 28%) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MABTHERA 12.4 months.

Bulky Disease

In pooled data from three studies, 39 patients with relapsed or refractory, bulky disease (single lesion ≥ 10cm in diameter), low-grade or follicular B-cell NHL received 375 mg/m² of MABTHERA given as an IV infusion once weekly for four doses). The overall response rate (ORR) was 36% (CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Clinical Laboratory Findings

Molecular Genetic Markers: Results from the exploratory analysis of the bcl-2 gene rearrangement showed that samples of peripheral blood obtained at baseline were positive for the bcl-2 rearrangement (bcl-2 positive) by nested Polymerase Chain Reaction (PCR) in 70 (42%) of the 166 enrolled patients. Of these 70 patients, 55 patients had a follow-up blood sample at 3 months and more than 60% showed a conversion to negative bcl-2 gene rearrangement.

With regard to bone marrow assessment, of 71 (45%) of the 166 enrolled patients who were bcl-2 positive in marrow at baseline, 22 were assessed for bcl-2 rearrangement at 3 months. Of these, 12 (55%) were bcl-2 negative at three months.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 patients evaluated for HACA, 1.1% (4 patients) were positive.

Previously Untreated Follicular non-Hodgkin's Lymphoma

Combination with chemotherapy

In an open-label randomised study (M39021), a total of 322 previously untreated Stage III or IV follicular B cell NHL patients were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m²/day on days 1 –5) every 3 weeks for 8 cycles or MABTHERA 375 mg/m² in combination with CVP (R-CVP). MABTHERA was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy.

The median follow-up of patients was 53 months. Addition of MABTHERA to CVP significantly increased time to treatment failure (the primary endpoint), tumour response, progression-free survival (PFS) and overall survival (OS) (Table 1).

Table 1 Summary of key results from study M39021

	CVP (N=159)	R-CVP (N=162)	Hazard Ratio [95% CI] log-rank p
Median Time to Treatment Failure (months)	6.6	27.0	0.34 [0.26, 0.44] p<0.0001
Median Progression-free Survival (months)	14.7	33.6	0.44 [0.33, 0.57] p<0.001
Overall Tumour Response¹ (%)	57	81	-
Overall Survival (%)	71	81	0.60 [0.38, 0.95] p=0.029 ²

¹Tumour response = CR (complete response), CRu (complete response unconfirmed) and PR (partial response)

²Stratified by centre

Results from three other randomised studies using MABTHERA in combination with chemotherapy regimens other than CVP (CHOP, MCP, CHVP/interferon-alfa 2a) have also demonstrated significant improvements in response rates, time dependent parameters as well as in overall survival (Table 2).

Table 2 Summary of key results from three phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, n	Median follow up, months	ORR, %	CR, %	Outcome¹ (months)	OS rates, %
GLSG'00	CHOP, 205	18	90	17	Median TTF: 31.2	90
	R-CHOP, 223		96	20	Not reached p<0.001	95 p=0.016
OSHO-39	MCP, 96	47	75	25	Median PFS: 28.8	74
	R-MCP, 105		92	50	Not reached p<0.0001	87 p=0.0096
FL2000	CHVP-IFN, 183	42	85	49	Median EFS: 36	84
	R-CHVP-IFN, 175		94	76	Not reached p<0.0001	91 p=0.029

Abbreviations: ORR – overall response rate; CR – complete response; OS rates – overall survival rates at the time of the analyses; R – MABTHERA; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone ; IFN – interferon-alfa 2a.

¹GLSG'00 outcome: TTF (time to treatment failure); OSHO-39: PFS (progression free survival); FL2000 outcome: EFS (event free survival)

Maintenance Therapy

Relapsed/Refractory follicular NHL

In a prospective, open label, international, multicentre, Phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MABTHERA plus CHOP (R-CHOP, n=234), one dose of rituximab combined with each cycle of chemotherapy. The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MABTHERA maintenance therapy (n=167) or observation (n=167). MABTHERA maintenance treatment consisted of a single infusion of MABTHERA at 375 mg/m² body surface area given every 3 months until disease progression or for a maximum period of two years. Patients with hypogammaglobulinaemia (IgG <3g/L) or known HIV infection were excluded from the trial.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 3).

Table 3 Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction ¹⁾
Primary Efficacy				
ORR ²⁾	74%	87%	0.0003	NA
CR ²⁾	16%	29%	0.0005	NA
PR ²⁾	58%	58%	0.9449	NA
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS (median)	19.4 mo.	33.2 mo.	0.0001	38%

¹⁾ Estimates were calculated by hazard ratios

²⁾ Last tumour response as assessed by the investigator. The “primary” statistical test for “response” was the trend test of CR versus PR versus non-response (p < 0.0001)

Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS : overall survival ; PFS : progression free survival

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with MABTHERA led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone (p < 0.0001 log-rank test). The median PFS was 42.2 months in the MABTHERA maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with MABTHERA maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the MABTHERA maintenance group vs 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MABTHERA maintenance over observation (p=0.0039 log-rank test). MABTHERA maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

The median time to new anti-lymphoma treatment was significantly longer with MABTHERA maintenance treatment than with observation (38.8 months vs. 20.1 months, p < 0.0001 log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI;

30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, MABTHERA maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, $p=0.0003$) log-rank test (Table 4). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 4 Maintenance phase: overview of efficacy results MABTHERA vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction (95% CI)
	Observation (N=167)	MabThera (N=167)	Log-Rank p value	
Progression-free survival (PFS)	14.3	42.2	<0.0001	61% (45-72%)
Overall Survival	NR	NR	0.0039	56% (22-75%)
Time to new lymphoma treatment	20.1	38.8	<0.0001	50% (30-64%)
Disease-free survival ^a	16.5	53.7	0.0003	67% (39-82%)
Subgroup Analysis				
<u>PFS</u>				
CHOP	11.6	37.5	<0.0001	71% (54-82%)
R-CHOP	22.1	51.9	0.0071	46% (15-65%)
CR	14.3	52.8	0.0008	64% (33-81%)
PR	14.3	37.8	<0.0001	54% (33-69%)
<u>OS</u>				
CHOP	NR	NR	0.0348	55% (4-79%)
R-CHOP	NR	NR	0.0482	56% (-2-81%)

NR: not reached; ^a: only applicable to patients achieving a CR

The benefit of MABTHERA maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 5). MABTHERA maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, $p<0.0001$) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, $p=0.0071$). Although analysed subgroups were small, and the median survival had not been reached after an overall median observation period of 47.2 months, a clinically meaningful benefit in terms of overall survival was observed for patients receiving MABTHERA maintenance treatment when compared to observation, in the overall population.

MABTHERA maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 versus > 0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus > 1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), haemoglobin (< 12 g/dL versus ≥ 12 g/dL), β_2 -microglobulin (< 3 mg/L versus ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Previously untreated follicular NHL

In a prospective, open label, international, multi-centre, Phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to MABTHERA maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MABTHERA maintenance treatment consisted of a single infusion of MABTHERA at 375 mg/m² body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomisation, maintenance therapy with MABTHERA resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to no maintenance therapy in patients with previously untreated follicular NHL (Table 5). This improvement in PFS was confirmed by an independent review committee (IRC) (Table 5).

Significant benefit from maintenance treatment with MABTHERA was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (Table 5).

Table 5 Overview of efficacy results for maintenance MABTHERA vs. observation (25 months median observation time)

Efficacy Parameter	Observation (N=513)	MABTHERA (N=505)	Log Rank P value	Risk reduction
Primary Efficacy				
PFS (median)	NE	NE	<0.0001	50%
Secondary Efficacy				
PFS (median)*	30.9 months	37.1 months	<0.0001	46%
EFS (median)	37.8 months	NE	< 0.0001	46%
OS (median)	NE	NE	0.7246	-
TNLT (median)	NE	NE	0.0003	39%
TNCT (median)	NE	NE	0.0011	40%
ORR**	55.0%	74.0%	< 0.0001	[Odds ratio = 2.33]
Complete Response (CR/CRu) rate**	47.7%	66.8%	< 0.0001	[Odds ratio = 2.21]

*As assessed by an independent review committee (IRC)

**At end of maintenance/observation; PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: Time to next chemotherapy treatment

NE: Not estimable at time of clinical cut-off

MABTHERA maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, ≥ 60 years), FLIPI score (1, 2 or 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR or PR).

There are currently no data to support superior efficacy for maintenance treatment given every 2 months over maintenance therapy given every 3 months, in either the relapsed/refractory or previously untreated setting.

Diffuse Large B-cell non-Hodgkin's Lymphoma

In a randomised, Phase III, open-label trial, a total of 399 previously untreated elderly ambulatory patients (age 60 to 80 years, ECOG performance status 0-2) with moderate to advanced (Ann Arbor stage II-IV) diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisone 40 mg/m²/day on days 1-5) every 3 weeks for eight cycles, or MABTHERA 375 mg/m² administered as an intravenous infusion plus CHOP (R-CHOP). MABTHERA was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 38 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0094), representing a risk reduction of 33%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively, although the benefit with R-CHOP was not always statistically significant.

A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

Chronic Lymphocytic Leukaemia (CLL)

In two open-label randomised studies, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either fludarabine and cyclophosphamide (FC) chemotherapy (fludarabine 25 mg/m², cyclophosphamide 250 mg/m², days 1-3) every 4 weeks for 6 cycles or MABTHERA in combination with FC (R-FC). MABTHERA was administered at a dosage of 375 mg/m² during the first cycle one day prior

to chemotherapy and at a dosage of 500 mg/m² on day 1 of cycles 2-6. A total of 810 patients (403 R-FC, 407 FC) from the first-line study (Table 6) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 7) were analysed for efficacy.

In the first-line study, the primary endpoint of progression-free survival (PFS) was a median of 40 months in the R-FC group and a median of 32 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm ($p = 0.0427$), however longer follow-up is needed to confirm this observation. The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline.

Table 6 First-line treatment of Chronic Lymphocytic Leukaemia - overview of efficacy results for MABTHERA plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio R-FC vs FC [95% CI]
	FC (N=407)	R-FC (N=403)	Log-Rank p value	
Progression-free survival	32.2	39.8	<0.0001	0.56 [0.43, 0.72]
Overall Survival	NR	NR	0.0427	0.64 [0.41, 1.00]
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	NA
CR rates	17.2%	36.0%	<0.0001	NA

Response rate and CR rates analysed using Chi-squared Test.

Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached

Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

In a case series of 30 previously untreated patients with CLL, an overall response rate of 97% was achieved with MABTHERA in combination with fludarabine, cyclophosphamide and mitoxantrone (FCM). Survival was not reported. In another case series of 64 previously untreated patients with CLL, an overall response rate of 91% and a median progression-free survival of 32.6 months were achieved with MABTHERA in combination with pentostatin and cyclophosphamide (PC).

In the relapsed/refractory study, the median PFS (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group ($p = 0.0002$, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A non-significant trend towards improvement in overall survival was reported in the R-FC arm compared to the FC arm.

Table 7 Treatment of relapsed/refractory Chronic Lymphocytic Leukaemia – overview of efficacy results for MABTHERA plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio R-FC vs FC [95% CI]
	FC (N=276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival	20.6	30.6	0.0002	0.65 [0.51, 0.82]
Overall Survival	51.9	NR	0.2874	0.83 [0.59, 1.17]
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	NA
CR rates	13.0%	24.3%	0.0007	NA

Response rate and CR rates analysed using Chi-squared Test.

Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached

Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

In relapsed/refractory CLL patients, response rates of 70% or greater have been reported in small studies of the following chemotherapy regimens with MABTHERA: FCM (fludarabine, cyclophosphamide, mitoxantrone), PC (pentostatin, cyclophosphamide), PCM (pentostatin, cyclophosphamide, mitoxantrone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), bendamustine and cladribine.

Rheumatoid Arthritis

The efficacy and safety of MABTHERA in alleviating the symptoms and signs of RA was demonstrated in three randomised, controlled, double-blind, multicentre studies.

Study 1, WA17042 (REFLEX), was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active RA, diagnosed according to the criteria of the American College of Rheumatology (ACR). The study population was comprised of adult patients aged ≥ 18 years with RA for at least 6 months who had experienced an inadequate response to previous treatment with an anti-TNF therapy. The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received 2 x 1000 mg IV infusions of MABTHERA, each following an IV infusion of 100 mg methylprednisone and separated by an interval of 15 days. All patients received concomitant oral methotrexate (MTX) (10-25 mg/week) and 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks. During this time patients could receive further courses of MABTHERA under an open label extension study protocol (see Radiographic Response).

Study 2, WA17043 (DANCER), was a randomised, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of MABTHERA (2 x 1000 mg or 2 x 500 mg) given with or without one of two corticosteroid infusion regimens in combination with weekly MTX. All patients received concomitant oral methotrexate. The primary endpoint was the proportion of RF (Rheumatoid Factor) positive patients with an ACR20 response at week 24. The study population was comprised of adult patients aged ≥ 18

years with RA who had previously failed 1-5 DMARDs and who currently had an inadequate response to MTX.

Study 3 was a double-blind, double-dummy, controlled study evaluating MABTHERA monotherapy, and MABTHERA in combination with either cyclophosphamide or MTX in patients with active RA who had not responded to one or more prior DMARDs. The primary endpoint was the proportion of patients with an ACR50 response at week 24. The study population was comprised of adult patients aged ≥ 21 years with RA who had failed 1-5 DMARDs, were RF seropositive at screening, and who currently had a partial clinical response to MTX monotherapy.

An ACR20 response was defined as at least a 20% improvement, compared to baseline, in both swollen and tender joint counts (SJC and TJC), as well as in 3 out of 5 additional parameters: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and C-reactive protein (CRP).

The comparator drug in all three studies was weekly MTX (10-25 mg weekly).

Disease Activity Outcomes

In all three studies, MABTHERA 2 x 1000 mg + MTX significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with MTX alone (Table 8). The treatment effect was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and CRP (mg/dL).

Table 8 Cross-study comparison of ACR responses at Week 24 (ITT Population)

	ACR Response	Placebo+MTX	MABTHERA +MTX
Study 1 REFLEX		(N=201)	(N=298)
	ACR20	36 (18%)	153 (51%) ¹
	ACR50	11 (5%)	80 (27%) ¹
	ACR70	3 (1%)	37 (12%) ¹
Study 2 DANCER		(N=143)	(N=185)
	ACR20	45 (31%)	96 (52%) ²
	ACR50	19 (13%)	61 (33%) ²
	ACR70	6 (4%)	28 (15%) ²
Study 3		(N= 40)	(N= 40)
	ACR20	15 (38%)	28 (70%) ³
	ACR50	5 (13%)	17 (43%) ³
	ACR70	2 (5%)	9 (23%) ³

¹ p \leq 0.0001; ² p \leq 0.001; ³ p < 0.05

MABTHERA + MTX treated patients had a significantly greater reduction in disease activity score (DAS28) than patients treated with MTX alone. A good to moderate EULAR response

was achieved by significantly more MABTHERA + MTX treated patients compared to patients treated with MTX alone (Table 9).

Table 9 Cross-Study Comparison of DAS and EULAR Responses at Week 24 (ITT Population)

	Placebo+MTX	MABTHERA +MTX 2 × 1g
Study 1	(N=201)	(N=298)
Change in DAS28 [Mean (SD)]	-0.4 (1.2)	-1.9 (1.6)*
EULAR Response (%)		
None	78%	35%
Moderate	20%	50%*
Good	2%	15%
Study 2	(N= 143)	(N=185)
Mean change in DAS28 (SD)	-0.8 (1.4)	-2.0 (1.6)
EULAR response		
None	61%	37%
Moderate	35%	40%
Good	4%	23%
Study 3	(N=40)	(N=40)
Change in DAS [Mean (SD)]	-1.3 (1.2)	-2.6 (1.3)
EULAR response		
None	50%	18%
Moderate	45%	63%
Good	5%	20%

*p value <0.0001. p values not calculated for studies 2 and 3.

Radiographic Response

In Study WA17042 (REFLEX), structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. MABTHERA + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year (Table 10). 70% of patients initially randomised to MABTHERA + MTX and 72% of patients initially randomised to placebo + MTX were evaluated radiographically at year 2. Progression of structural damage in MABTHERA + MTX patients was further reduced in the second year of treatment (Table 10).

Table 10 Mean radiographic change from baseline to 104 weeks

Inadequate Response to TNF Antagonists				
Parameter	MABTHERA + MTX ^b (2 x 1000 mg)	Placebo + MTX ^c	Treatment Difference (Placebo – MABTHERA)	95% CI
<u>Change during first year</u>				
TSS	0.66	1.78	1.12	(0.48, 1.76)
ES	0.44	1.19	0.75	(0.32, 1.18)
JSN score	0.22	0.59	0.37	(0.11, 0.63)
<u>Change during second year^a</u>				
TSS	0.48	1.04	-	-
ES	0.28	0.62	-	-

JSN score	0.20	0.42	-	-
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^a Based on radiographic scoring following 104 weeks of observation

^b Patients received up to 2 years of treatment with MABTHERA + MTX

^c Patients receiving placebo + MTX could receive retreatment with MABTHERA + MTX from week 16 onwards

Following 2 years of treatment with MABTHERA + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of MABTHERA + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with MABTHERA + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the MABTHERA + MTX treated patients who had no progression in the first year also had no progression in the second year.

Quality of life outcomes

MABTHERA + MTX treated patients reported an improvement in all patient-reported outcomes such as Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Short Form-36 (SF-36) questionnaires. Significant reductions in disability index (HAQ-DI), fatigue (FACIT-F) (Table 11), and improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36 were observed in patients treated with MABTHERA + MTX compared to patients treated with MTX alone.

Table 11 Physical Function and Quality of Life Outcomes at Week 24 in Study 1

	Outcome	Placebo + MTX	MABTHERA + MTX (2 x 1000 mg)
WA17042 (REFLEX; TNF-IR)			
		n=201	n=298
	Mean change in HAQ-DI	-0.1	-0.4***
	% HAQ-DI MCID	20%	51%
	Mean change in FACIT-F	-0.5	-9.1***
		n=197	n=294
	Mean Change in SF-36 PHS	0.9	5.8***
	% SF-36 PHS MCID	13%	48%***
	Mean Change in SF-36 MHS	1.3	4.7**
	% SF-36 MHS MCID	20%	38%**

Significant difference from placebo at the primary time point: **p ≤ 0.001 ***p ≤ 0.0001

MCID (minimum clinically important difference): HAQ-DI ≥ 0.22, SF-36 PHS > 5.42, SF-36 MHS > 6.33

At week 24, in all three studies, the proportion of MABTHERA + MTX treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of > 0.25) was higher than among patients receiving MTX alone.

Laboratory evaluations

Approximately 10% of patients with RA tested positive for HACA (Human Anti-Chimeric Antibody) in clinical studies. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic

reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

In Study 1 WA17042 (REFLEX), 15/308 (4.8%) MABTHERA + MTX treated patients and 8/209 (3.8%) patients treated with MTX alone were anti-nuclear antibody (ANA) negative at day 1 and became ANA positive at week 16 and/or week 24. The adverse event profile in these patients did not provide any evidence of new onset autoimmune disease.

In RF positive patients, marked decreases were observed in RF concentrations following treatment with MABTHERA in all three studies (range 45-64%).

Hyperuricaemia (Grade 3/4) occurred in 143/950 (15%) patients, with the majority post-infusion on days 1 and/or 15. It was not associated with any clinical symptoms, and none of these patients developed evidence of renal disease. Increases in serum uric acid are often associated with the catabolism of DNA. This finding is consistent with the destruction of B cells resulting from MABTHERA therapy.

Hypophosphataemia (Grade 3) occurred in 193/950 (21%) patients. There was also one case of Grade 4 hypophosphataemia. Most cases occurred post-infusion, where patients received oral and/or IV corticosteroids. Low phosphate levels are associated with corticosteroid treatment and osteoporosis.

Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following MABTHERA treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Lymphopenia (Grade 3/4) was experienced by 679/1003 (68%) of patients compared to 52%-54% of patients who experienced Grade 3 lymphopenia and 1%-3% of patients who experienced Grade 4 lymphopenia in the 24-week double-blind populations. Most cases occurred immediately after the first infusion, consistent with peripheral B-cell depletion, and lymphocyte numbers recovered thereafter. The majority of the Grade 4 cases were transient though 6 patients had more persistent Grade 4 lymphopenia, one of whom had a serious infection (2 occurrences of pneumonia in a diabetic patient; both cases resolved). All 6 patients had low lymphocyte counts before exposure to MABTHERA, including 2 patients who experienced up to Grade 4 lymphopenia whilst on placebo. A total of 17 non serious infections were reported all of which resolved without sequelae.

Titres of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MABTHERA in RA patients.

The effect of MABTHERA on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of MABTHERA on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-CCP immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP)]. MABTHERA treatment, whether as monotherapy or in combination with MTX or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to MTX alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the MABTHERA + MTX groups compared to MTX alone.

Multiple Course Therapy

Following completion of the 24-week double blind comparative study period, patients were permitted to enrol into an open-label long term follow up study. Patients received subsequent courses of MABTHERA as needed according to the treating clinician's assessment of disease activity and irrespective of the peripheral B lymphocyte count.

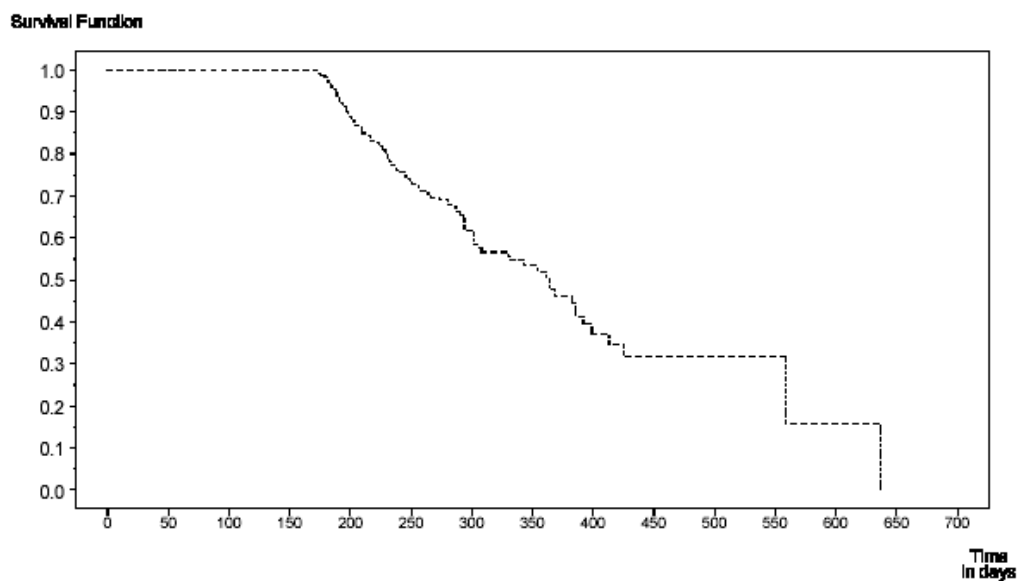
The all exposure population in the three double blind controlled trials (one Phase III and two Phase II trials) was 990 patients. Of these, 301 patients received a second course of MABTHERA 2 x 1000 mg + MTX, and 46 patients received a third course of MABTHERA 2 x 1000 mg + MTX.

At the point of data cut-off, 24.7% (193/781) of patients who had enrolled in the MABTHERA 2 x 1000 mg + MTX arms of the Phase II and Phase III studies had been retreated (point of data cut-off was defined as the time when all patients had been followed up for at least 24 weeks). Also at the data cut-off point, the majority of patients from the double blind comparative study period had received one course of treatment in the year. Kaplan-Meier analysis of time to second treatment course (censoring patients who did not receive a second treatment course or who withdrew from the study) shows an estimated median time for retreatment in the prior anti-TNF population of 364 days (interquartile range: 245-559 days), Figure 1, and 547 days (interquartile range: 302-889 days) in the no prior anti-TNF population, Figure 2.

The time interval between courses was variable. The majority of patients, who had two treatment courses at the time of cut-off, received their second course of treatment 6 to 12 months after the first treatment course. Some patients required even less frequent retreatment. The response to further therapy was at least the same magnitude as that following the initial treatment course, as evidenced by the change from baseline DAS28 (Figure 3).

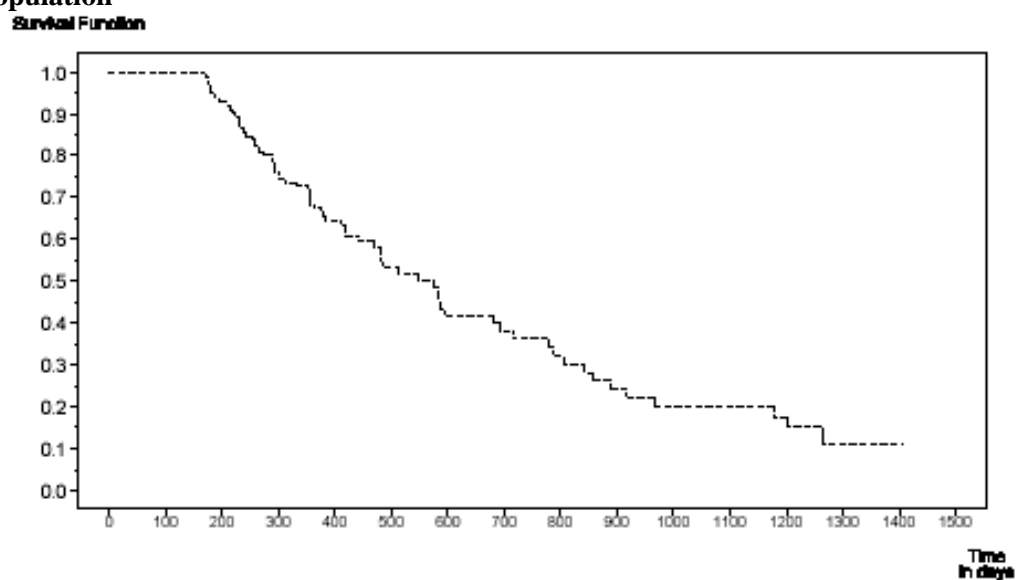
Since many patients in the prior anti-TNF population remain in the studies after a single course of treatment with MABTHERA + MTX, these results are subject to change as the observation period increases.

Figure 1 Kaplan-Meier Analysis of Time to Second Treatment Course, Prior Anti-TNF Population



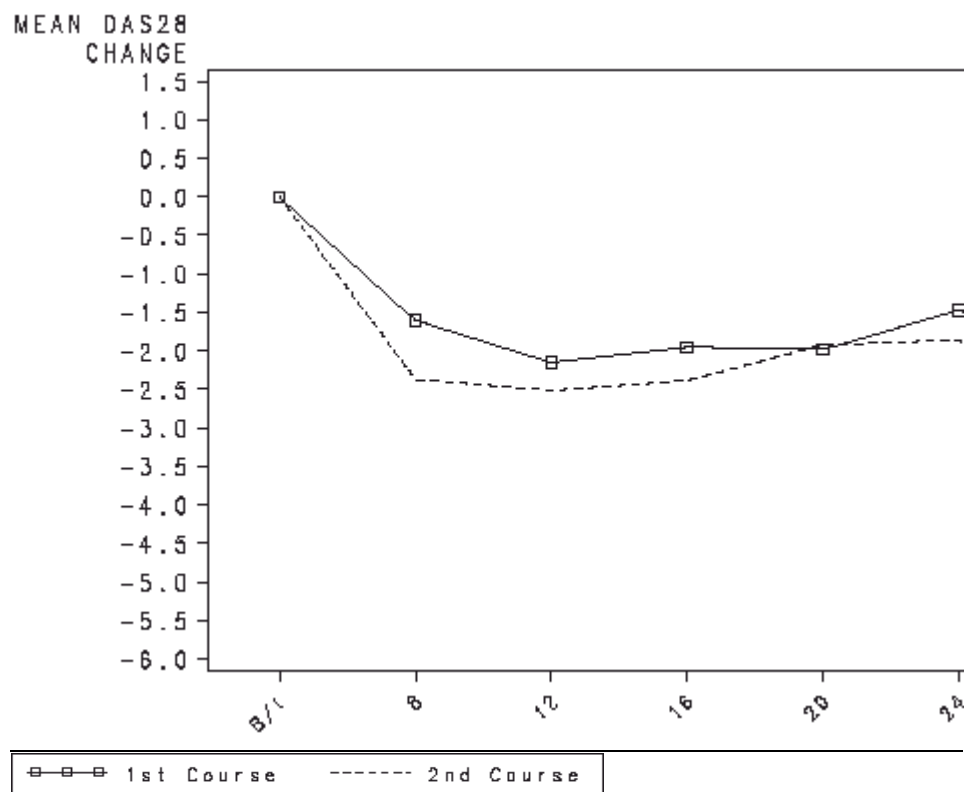
Survival function = Probability of not switching to re-treatment
n = 525

Figure 2 Kaplan-Meier Analysis of Time to Second Treatment Course, No Prior Anti-TNF Population



Survival function = Probability of not switching to re-treatment
n = 256

Figure 3 Mean Change in DAS28 Over Time Following First and Second Course Therapy (Prior anti-TNF population)



INDICATIONS

Non-Hodgkin's Lymphoma

MABTHERA is indicated for treatment of patients with:

- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic Lymphocytic Leukaemia

MABTHERA is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

MABTHERA (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.

MABTHERA has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

CONTRAINDICATIONS

MABTHERA is contraindicated in patients with known hypersensitivity to murine proteins or to any component of the product.

PRECAUTIONS

Progressive multifocal leukoencephalopathy (PML)

Use of MABTHERA may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of MABTHERA should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of MABTHERA may resume.

If a diagnosis of PML is confirmed MABTHERA must be permanently discontinued. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

Infusion-related reactions

MABTHERA is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Severe infusion-related reactions might be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe reactions usually manifested within 30 minutes to 2 hours after starting the first MABTHERA infusion, were characterised by *pulmonary events* and included, in some cases, *rapid tumour lysis* and *features of tumour lysis syndrome* in addition to fever, chills, rigors, hypotension, urticaria, angio-oedema and other symptoms. Patients with a high tumour burden or with a high number ($>25 \times 10^9/L$) of circulating malignant cells such as patients with chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma may be at higher risk of developing severe infusion-related reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol (acetaminophen) is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of MABTHERA therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in

repeated severe infusion-related reactions. Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to MABTHERA.

Patients with a high number ($>25 \times 10^9/L$) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still $>25 \times 10^9/L$.

Pulmonary events

Pulmonary events have included hypoxia, pulmonary infiltrates, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until the pulmonary event has resolved.

Rapid tumour lysis

MABTHERA mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MABTHERA infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number ($>25 \times 10^9/L$) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent MABTHERA therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular

Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MABTHERA infusion. Angina pectoris or cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MABTHERA. Therefore patients with a history of cardiac disease should be monitored closely. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias.

Monitoring of Blood Counts

Although MABTHERA is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of $<1.5 \times 10^9/L$ and/or platelet counts of $<75 \times 10^9/L$, as clinical experience with such patients is limited. MABTHERA has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MABTHERA. When MABTHERA is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

MABTHERA treatment should not be initiated in patients with severe active infections.

Cases of Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death have been reported in some patients with haematologic malignancies treated with MABTHERA. The majority of patients received MABTHERA in combination with chemotherapy. Isolated cases have been reported in patients who either had evidence of antibodies against Hepatitis B surface antigen before treatment or did not have any such antibodies. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of MABTHERA and approximately one month after the last dose.

Persons at high risk of HBV infection should always be screened before initiation of MABTHERA. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, non-Hodgkin's lymphoma of itself may be an independent risk factor for HBV reactivation. Carriers of hepatitis B, and patients with evidence of having recovered from hepatitis B, should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following therapy with MABTHERA.

In patients who develop reactivation of viral hepatitis B, MABTHERA and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming therapy with MABTHERA in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of MABTHERA and have resulted in death.

Immunisation

The safety of immunisation with live viral vaccines, following MABTHERA therapy has not been studied and vaccination with live virus vaccines is not recommended.

Patients treated with MABTHERA may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received MABTHERA monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs 69% when assessed for > 2-fold increase in antibody titer).

Mean pre-therapeutic antibody titers against a panel of antigens (*Streptococcus pneumoniae*, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MABTHERA.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of MABTHERA in NHL and CLL. The majority of patients had received MABTHERA in combination with chemotherapy or as part of a haematopoietic stem cell transplant. (See BOXED WARNING, ADVERSE EFFECTS and *Post-Marketing Experience*.)

Rheumatoid Arthritis

Methotrexate (MTX) naïve populations

The use of MABTHERA is not recommended in MTX-naïve patients since a favourable benefit-risk relationship has not been established.

Infusion-related Reactions

MABTHERA is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/antipyretic drug and an antihistamine drug should always be administered before each infusion of MABTHERA. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events.

Most infusion events reported were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the post-marketing setting (see *Post-Marketing Experience – Rheumatoid Arthritis*). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MABTHERA infusions were better tolerated by patients than the initial infusion. Fewer than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see Adverse Effects - *Experience from Rheumatoid Arthritis Clinical Trials*). The reactions reported were usually reversible with a reduction in rate, or interruption, of MABTHERA infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids if required. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue MABTHERA. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., adrenaline, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MABTHERA. The presence of HACA may be associated with worsening infusion or allergic reactions after the second infusion of subsequent courses.

Infections

Serious infections, including fatalities, can occur during therapy with MABTHERA. Based on the mechanism of action of MABTHERA and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MABTHERA therapy. MABTHERA should not be administered to patients with an active infection or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MABTHERA in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients who develop infection following MABTHERA therapy should be promptly evaluated and treated appropriately.

Cases of reactivation of hepatitis B infection, including those with a fatal outcome, have been reported in RA patients receiving MABTHERA.

Hepatitis B virus (HBV) screening should always be performed in high risk patients before initiation of treatment with MABTHERA. Carriers of hepatitis B and patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during and for several months following MABTHERA therapy.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported following use of MABTHERA for the treatment of autoimmune diseases including RA. Several but not all of the reported cases involved patients with recognised risk factors for PML, including the underlying disease and long term immunosuppressive therapy or chemotherapy. (See BOXED WARNING and PRECAUTIONS.) The efficacy and safety of MABTHERA for the treatment of autoimmune diseases other than RA has not been established.

Immunisation

Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to treatment with MABTHERA. Vaccination should be completed at least 4 weeks prior to first administration of MABTHERA.

The safety of immunisation with live viral vaccines following MABTHERA therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MABTHERA or whilst peripherally B cell depleted.

Patients treated with MABTHERA may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised study, patients with RA treated with MABTHERA and MTX had comparable response rates to tetanus recall antigen (39% vs 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs 93%), when given at least 6 months after MABTHERA as compared to patients only receiving MTX. Should non-live

vaccinations be required whilst receiving MABTHERA therapy, these should be completed at least 4 weeks prior to commencing the next course of MABTHERA.

In the overall experience of MABTHERA repeat treatment over one year, the proportions of patients with positive antibody titers against *S. pneumoniae*, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Cardiovascular Events

Patients with a history of cardiac disease should be monitored closely during infusions. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias (see Precautions for Cardiovascular Events under *Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia* section). There are no data on the safety of MABTHERA in patients with moderate or severe heart failure (NYHA class III or IV) or severe, uncontrolled cardiovascular disease. In patients treated with MABTHERA, the occurrence of pre-existing ischaemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MABTHERA and patients closely monitored during administration. Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MABTHERA infusion.

Concomitant/Sequential Use of Other DMARDs

The concomitant use of MABTHERA and antirheumatic therapies other than those specified under the RA indication and dosing is not recommended.

Limited data are available on the safety of the use of biologic agents or DMARDs other than MTX in patients exhibiting peripheral B cell depletion following treatment with MABTHERA. If biologic agents and/or DMARDs are used following MABTHERA therapy, patients should be observed for signs of infection.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MABTHERA in RA patients (see 'ADVERSE EFFECTS - *Experience from Rheumatoid Arthritis Clinical Trials*') a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.

Patients with Renal or Hepatic Impairment

The safety and effectiveness of MABTHERA in patients with renal or hepatic impairment has not been established. MTX is contraindicated in such patients and since MABTHERA is given in combination with MTX these patients were not included in the clinical studies for RA.

General Precautions

Carcinogenicity, Mutagenicity and Impairment of Fertility

No animal studies have been performed to establish the carcinogenic or mutagenic potential of MABTHERA, or to determine its effects on fertility in males or females.

Use in Pregnancy (Category C)

It is not known whether MABTHERA can cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab. In clinical studies in patients with RA, three pregnancies occurred following exposure to MABTHERA + MTX with two resulting in spontaneous abortions and the third ongoing at the time. Rituximab has been shown to cause B-cell depletion in the monkey foetus. MABTHERA should not be given to a pregnant woman, unless the potential benefit outweighs the potential risk.

Individuals of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months following MABTHERA therapy.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero at relative exposure levels (AUC) similar to that anticipated clinically. New born offspring of maternal animals exposed to MABTHERA during lactation and/or gestation showed no untoward toxicity except for depleted B cell populations during the post-natal phase at the same relative exposure. B cell levels in human neonates following maternal exposure to MABTHERA have not been studied.

Use in Lactation

It is not known whether MABTHERA is excreted in human milk. In monkey studies, rituximab was excreted in the milk and was detected in the serum of breast-fed infants. Reversible B-cell depletion was observed in all monkey infants exposed to rituximab via maternal transfer during lactation and/or gestation. It is recommended that a nursing woman discontinue breast-feeding whilst undergoing treatment with MABTHERA.

Use in Children

The safety and effectiveness of MABTHERA in children have not been established.

Driving and Operating Machinery

It is not known whether MABTHERA has an effect on the ability to drive and operate machines, though the pharmacologic activity and adverse events reported to date do not indicate that such an effect is to be expected.

Drug /Laboratory Interactions

Currently, there are limited data on possible drug interactions with MABTHERA.

In CLL patients, co-administration with MABTHERA did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MABTHERA.

Co-administration with MTX had no effect on the pharmacokinetics of MABTHERA in RA patients.

Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

The tolerability of simultaneously or sequential combination of MABTHERA with chemotherapy other than CHOP or CVP, or agents which are liable to cause depletion of normal B cells is not well defined.

In a small cohort of patients with RA, 110 patients received subsequent therapy with other DMARDs (including biologicals). Patients received subsequent DMARDs 4-6 months following therapy with MABTHERA and generally while peripherally B cell depleted. The rate of clinically relevant infections was 7.8 per 100 patient years.

ADVERSE EFFECTS

Experience from Clinical Trials in Haemato-Oncology

The most common adverse reactions of MABTHERA (incidence $\geq 25\%$) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia and lymphopenia. The most important serious adverse reactions of MABTHERA are infusion reactions, tumour lysis syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

The frequencies of adverse drug reactions (ADRs) reported with MABTHERA alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common $\geq 1/10$ ($\geq 10\%$), common $\geq 1/100$ to $< 1/10$ ($\geq 1\%$ to $< 10\%$) and uncommon $\geq 1/1,000$ to $< 1/100$ ($\geq 0.1\%$ to $< 1\%$).

MABTHERA monotherapy/maintenance therapy

The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MABTHERA weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma up to 4 weeks in most patients and from 25 patients who received doses other than 375 mg/m² for four doses and up to 500 mg/m² single dose in the Phase I setting (see CLINICAL TRIALS). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MABTHERA as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see CLINICAL TRIALS). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MABTHERA maintenance.

Table 12 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving MABTHERA monotherapy (N = 356) or MABTHERA maintenance treatment (N = 671) in clinical trials

System Organ Class	Very Common ($\geq 10\%$)	Common ($\geq 1\%$ - $< 10\%$)	Uncommon ($\geq 0.1\%$ - $< 1\%$)
Infections and infestations	bacterial infections, viral infections	sepsis, ⁺ pneumonia, ⁺ febrile infection, ⁺ herpes zoster, ⁺ respiratory tract infection, fungal infections, infections of	

		unknown aetiology	
Blood and the lymphatic system disorders	neutropenia , leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		⁺ myocardial infarction, arrhythmia, ⁺ atrial fibrillation, tachycardia, ⁺ cardiac disorder	⁺ left ventricular failure, ⁺ supraventricular tachycardia, ⁺ ventricular tachycardia, ⁺ angina, ⁺ myocardial ischaemia, bradycardia
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm , respiratory disease, chest pain, dyspnoea , cough , rhinitis	asthma , bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain , dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement
Skin and subcutaneous tissue disorders	pruritis , rash	urticaria , ⁺ alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia, back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	pain at the infusion site
Investigations	decreased IgG levels		

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (\geq Grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.

MABTHERA in combination with chemotherapy in NHL and CLL

The ADRs listed in the table below are based on rituximab-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively, and from 397 previously untreated CLL patients and 274

relapsed/refractory CLL patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) (see CLINICAL TRIALS).

The safety information of MABTHERA in combination with certain chemotherapy regimens is limited. When MABTHERA is used with other chemotherapy medicines, prescribers are advised to consider the adverse reaction profile of the component medicine(s).

Table 13 Summary of severe ADRs reported in patients receiving R-CHOP in DLBCL (N=202), R-CHOP in follicular lymphoma (N=234), R-CVP in follicular lymphoma (N=162) and R-FC in previously untreated (N=397) or relapsed/refractory (N=274) CLL

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis, hepatitis B*
Blood and the lymphatic system disorders	febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions	-	fatigue, shivering

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
Frequency count was based on only severe reactions defined in clinical trials as ≥ Grade 3 NCI common toxicity criteria. Only the highest frequency observed in any trial is reported.

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MABTHERA-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrhoea, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

Further information on selected, serious adverse drug reactions

Infusion-related reactions

Monotherapy – 4 weeks treatment

Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with MABTHERA infusion as part of an infusion-related symptom complex. Such infusion-related symptoms occurred in the majority of patients during the first MABTHERA infusion (see PRECAUTIONS). The incidence of infusion-related symptoms decreased from 77% (7% Grade 3/4) with the first infusion to approximately 30% (2% Grade 3/4) with the fourth infusion and to 14% (no Grade 3/4 events) with the eighth infusion.

Maintenance Treatment (NHL) up to 2 years

Non-serious signs and symptoms suggestive of an infusion-related reaction were reported in 41% of patients for general disorders (mainly asthenia, pyrexia, influenza like illness, pain) and in 7% of patients for immune system disorders (hypersensitivity). Serious infusion-related reactions (defined as serious adverse events starting during or within one day of a rituximab infusion) occurred in < 1% of patients treated with MABTHERA maintenance.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

Severe infusion-related reactions occurred in up to 12% of all patients at the time of the first treatment cycle with rituximab in combination with chemotherapy. The incidence of Grade 3 or 4 infusion-related reactions decreased to less than 1% by the eighth cycle of therapy. The signs and symptoms were consistent with those observed during monotherapy (see PRECAUTIONS), but also included dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-chemotherapy were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Infections*Monotherapy – 4 weeks treatment*

MABTHERA induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in only a minority of patients. Infectious events, irrespective of causal assessment, occurred in 30.3% of 356 patients: 18.8% of patients had bacterial infections, 10.4% had viral infections, 1.4% had fungal infections, and 5.9% had infections of unknown aetiology. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients; in 1.4% during the treatment period and in 2.5% during the follow-up period.

Maintenance Treatment (NHL) up to 2 years

The proportion of patients with Grade 1 to 4 infections was 25% in the observation group and 45% in the MABTHERA group with Grade 3 or 4 infections in 3% of patients on observation and 11% receiving MABTHERA maintenance treatment. Grade 3 to 4 infections reported in $\geq 1\%$ of patients in the MABTHERA arm were pneumonia (2%), respiratory tract infection (2%), febrile infection (1%) and herpes zoster (1%). In a large proportion of infections (all grades), the infectious agent was not specified or isolated, however, where an infectious agent was specified, the most frequently reported underlying agents were bacterial (observation 2%, MABTHERA 10%), viruses (observation 7%, MABTHERA 11%) and fungi (observation 2%, MABTHERA 4%). There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from a phase III clinical trial included 2 cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see BOXED WARNING and PRECAUTIONS).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

In the R-CVP study the overall proportion of patients with infections or infestations during treatment and for 28 days after trial treatment end was comparable between the treatment groups (33% R-CVP, 32% CVP). The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP; most of these infections were nasopharyngitis. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life threatening infections were reported during this study.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs 2.6% in the CHOP group); this difference was due to a higher incidence of localised *Candida* infections during the treatment period. The incidence

of Grade 2 to 4 herpes zoster, including ophthalmic herpes zoster, was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%), with 7 of a total of 9 cases in the R-CHOP group occurring during the treatment phase. The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was reported only during the treatment period, in 20.8% in the R-CHOP group and 15.3% in the CHOP group.

In patients with CLL, the overall incidence of Grade 3 or 4 infections during treatment and for 28 days after the end of trial treatment was comparable between the treatment groups both in the first-line (18% R-FC vs 17% FC) and in the relapsed/refractory setting (19% R-FC vs 18% FC). The incidence of Grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% FC.

Haematologic Events

Monotherapy – 4 weeks treatment

Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anaemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients. A single occurrence of transient aplastic anaemia (pure red cell aplasia) and two occurrences of haemolytic anaemia following MABTHERA therapy were reported.

Maintenance Treatment (NHL) up to 2 years

Leucopenia (all grades) occurred in 26% of patients on observation vs 31% of patients in the MABTHERA arm, and neutropenia was reported in 13% of patients on observation and in 25% of patients on MABTHERA. There was a higher incidence of Grade 3-4 neutropenia (observation 5%, MABTHERA 11%) and leucopenia (observation 2%, MABTHERA 5%) in the MABTHERA arm compared to the observation arm. The incidence of Grade 3 to 4 thrombocytopenia (observation 1%, MABTHERA < 1%) was low.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

Severe (Grade 3 or 4) Neutropenia: There was a higher incidence of Grade 3 or 4 neutropenia in the MABTHERA containing study arms compared to the chemotherapy arms. In the R-CVP study, the incidence of neutropenia was 24% in the R-CVP arm versus 14% of patients in the CVP arm. These laboratory findings were reported as adverse events and resulted in medical intervention in 3.1% of patients on R-CVP and 0.6% of patients on CVP. The higher incidence of neutropenia in the R-CVP group was not associated with a higher incidence of infections and infestations. In patients with previously untreated CLL, Grade 3 or 4 neutropenia was reported as an adverse event in 30% of patients in the R-FC arm and in 19% of patients in the FC arm. In patients with relapsed/refractory CLL, the incidence of Grade 3 or 4 neutropenia adverse events was slightly higher in the R-FC arm (42% R-FC) compared to FC arm (40%).

Severe (Grade 3 or 4) Leucopenia: In the R-CHOP study, the incidence of severe leucopenia was 88% in the R-CHOP arm versus 79% in the CHOP arm. In CLL first-line, more patients receiving R-FC experienced Grade 3 or 4 leucopenia (23%) compared with patients receiving FC (12%). In patients with relapsed/refractory CLL, the overall incidence of Grade 3 or 4 leucopenia adverse events was comparable between the treatment arms (4% R-FC vs 3% FC).

Severe (Grade 3 or 4) Anaemia and Thrombocytopenia: No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia for

the R-CHOP and R-CVP studies. In the R-CVP study, the incidence of anaemia was 0.6% in the R-CVP arm versus 1.9% in the CVP arm. The incidence of thrombocytopenia was 1.2% in the R-CVP arm versus 0% in the CVP arm. In the R-CHOP study, the incidence of anaemia was 14% in the R-CHOP arm versus 19% in the CHOP arm. The incidence of thrombocytopenia was 15% in the R-CHOP arm versus 16% in the CHOP arm. The time to recovery from all haematological abnormalities was comparable in the two treatment groups. In the CLL first-line study, Grade 3 or 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 or 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 or 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 or 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Events

Monotherapy – 4 weeks treatment

Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Two patients (0.6%) experienced Grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during a MABTHERA infusion and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Maintenance Treatment (NHL) up to 2 years

The incidence of Grade 3 to 4 cardiac disorders was comparable between the two treatment groups (4% in observation, 5% in MABTHERA). Cardiac events were reported as serious adverse event in < 1 % of patients on observation and in 3% of patients on MABTHERA: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (< 1%), myocardial ischaemia (< 1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

In the R-CVP study the overall incidence of cardiac disorders in the safety population was low (4% R-CVP, 5% CVP), with no relevant differences between the treatment groups.

In the R-CHOP study the incidence of Grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MABTHERA infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of Grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC vs 3% FC) and in the relapsed/refractory study (4% R-FC vs 4% FC).

IgG Levels

Maintenance Treatment (NHL) up to 2 years

After induction treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) in both the observation and the MABTHERA groups. In the observation group, the

median IgG level subsequently increased to above the LLN, but remained constant during MABTHERA treatment. The proportion of patients with IgG levels below the LLN was about 60% in the MABTHERA group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). Monitoring of IgG levels should be considered for patients treated with MABTHERA. IV Ig substitution may be indicated for patients with decreased IgG levels.

Neurologic Events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

During the treatment period, four patients (2%) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC vs 4% FC) and in the relapsed/refractory study (3% R-FC vs 3% FC).

Subpopulations

The adverse events described below are only those considered by the investigator to be related to treatment with MABTHERA.

Elderly patients (³ 65 years)

Monotherapy – 4 weeks treatment: The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (N=94) and younger (N=237) patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for Grade 3 and 4 ADR).

Combination Therapy: The incidence of Grade 3 or 4 blood and lymphatic adverse events was higher in elderly patients (\geq 65 years of age) compared to younger patients, with previously untreated or relapsed/refractory CLL.

Bulky disease: Patients with bulky disease (N=39) had a higher incidence of Grade 3 and 4 ADRs than patients without bulky disease (N=195; 25.6% versus 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease versus 89.2% in non-bulky disease).

Re-treatment: The percentage of patients reporting any adverse event and Grade 3 and 4 ADRs upon re-treatment (N=60) with further courses of MABTHERA was similar to the percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon initial exposure (N=203; 95.0% versus 89.7% for any ADR and 13.3% versus 14.8% for Grade 3 and 4 ADRs).

Experience from Clinical Trials in Rheumatoid Arthritis

The clinical efficacy of MABTHERA, given together with methotrexate, was studied in three double blind controlled clinical trials (one Phase III and two Phase II trials) in patients with rheumatoid arthritis. 1039 patients received at least one treatment course, 570 patients received two or more courses of treatment during the follow up period, 191 patients three or more courses, 40 patients four or more courses and 3 patients received 5 or more courses

during the follow up period. So far 839 patients have been followed for more than a year, 139 for more than 2 years and 89 for more than 3 years post MABTHERA treatment.

In clinical trials patients received 2 x 1000 mg of MABTHERA separated by an interval of two weeks; in addition to MTX (10-25 mg/week) (see DOSAGE AND ADMINISTRATION – *Rheumatoid Arthritis*). MABTHERA infusions were administered after an IV infusion of 100 mg methylprednisolone; the majority of patients also received treatment with oral prednisone for 15 days. ADRs, which occurred with at least a 2% difference compared to the control arm and more frequently by patients who had received at least one infusion of MABTHERA than among patients that had received placebo in the Phase III trial and the combined population included in Phase II studies, are listed in the table below. Frequencies are defined as very common ($\geq 10\%$) and common ($\geq 1\%$ to $< 10\%$).

The most frequent ADRs considered due to receipt of 2 x 1000 mg MABTHERA in Phase II and III studies were acute infusion reactions. Infusion reactions occurred in 15% patients following the first infusion of MABTHERA and 5% in placebo patients. Infusion reactions decreased to 2% following the second infusion in both MABTHERA and placebo groups.

Table 14 Summary of Adverse Reactions Occurring in Patients with Rheumatoid Arthritis receiving MABTHERA during Phase II and III Clinical Studies †

	Phase II Study Population		Phase III Study Population	
	Very Common ($\geq 10\%$)	Common ($\geq 1\%$ - $< 10\%$)	Very Common ($\geq 10\%$)	Common ($\geq 1\%$ - $< 10\%$)
Acute Infusion reactions*		hypertension, rash, pruritus, chills, pyrexia, rhinitis, throat irritation		hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension
Gastrointestinal disorders		dyspepsia		dyspepsia
Infections and Infestations	any infection	urinary tract infections	any infection, upper respiratory tract infection	
Metabolism and Nutritional disorders				hypercholesterolemia
Musculo skeletal disorders		arthralgia/ musculoskeletal pain		arthralgia/ musculoskeletal pain, osteoarthritis
Nervous System disorders		migraine		paraesthesia

† This table include all events with an incidence difference of $\geq 2\%$ for rituximab compared to placebo

* Reactions occurring during or within 24 hours of infusion

The following adverse events were reported at a frequency between 1% and 2% greater in the MABTHERA-arms compared to control arms: lower respiratory tract infections/pneumonia, abdominal pain upper, muscle spasms, asthenia.

In addition to the events tabulated above, medically significant events reported rarely in the MABTHERA treated population and considered potential reactions to treatment include the following:

General Disorders:	Generalised oedema
Respiratory Disorders:	Bronchospasm, wheezing, laryngeal oedema
Skin and Subcutaneous Disorders:	Angioneurotic oedema, generalised pruritis

Immune system Disorders: Anaphylaxis, anaphylactoid reaction.

Multiple Courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. However, worsening of infusion or allergic reactions and failure to B cell deplete following rituximab cannot be excluded in HACA positive patients after repeated exposure to rituximab on the basis of the available data. The incidence of acute infusion reactions following subsequent treatment courses was generally lower than the incidence following the first infusion of MABTHERA.

Laboratory Abnormalities

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with MABTHERA.

Events of neutropenia associated with MABTHERA treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MABTHERA.

Further information on selected, serious adverse drug reactions

Infusion-related Reactions (IRRs)

Symptoms suggesting an acute infusion reaction (pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 79/540 (15%) patients following their first exposure to MABTHERA. In a study comparing the effect of glucocorticoid regimen, these events were observed in 5/149 (3%) of patients following their first placebo infusion and 42/192 (22%) of patients receiving their first infusion of 1000 mg MABTHERA. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see PRECAUTIONS – *Rheumatoid Arthritis*). Of the patients who received 1000 mg MABTHERA without premedication with glucocorticoids, 18/65 (28%) experienced an acute infusion reaction, compared with 24/127 (19%) in patients given IV glucocorticoid premedication, respectively.

In Study 1 (REFLEX) 5/308 (1.6%) patients from the MABTHERA + MTX group and no patients from the placebo + MTX group withdrew from the study due to acute infusion reactions. A reduced number of acute infusion reactions occurred during the second infusion, and none resulted in withdrawal of a patient.

In Study 2 (DANCER) 5/192 (3%) patients in the 2 x 1000 mg MABTHERA + MTX group were withdrawn due to acute infusion reactions. No patients in the placebo or 2 x 500 mg MABTHERA groups withdrew from treatment.

In Study 3 one patient in the 2 x 1000 mg MABTHERA group withdrew due to an acute infusion reaction.

Infections

The rate of infection was approximately 0.9 per patient year in MABTHERA treated patients. The infections consisted mostly of upper respiratory tract infections and urinary tract infections. Clinically significant infections (defined as those which were reported as serious

and/or were treated with IV antibiotics) were observed in 68/1039 (7%) of patients treated with MABTHERA compared to 3/107 (3%) of patients treated with only placebo. The rate of clinically significant infection was 0.05 per patient year in MABTHERA treated patients. Clinically significant infections predominantly included those of the lower respiratory, urinary and gastrointestinal tracts. Three clinically significant infections resulted in fatal outcomes, one was considered related to MABTHERA (septic shock) and two unrelated (neutropenic sepsis and bronchopneumonia).

Malignancies

The observed incidence of malignancies following exposure to rituximab (1.6 per 100 person years) lies within the range expected for a population with similar age and gender profile. A total of 26 malignancies have been reported in 22/1039 (2%) patients treated with MABTHERA. The most common types were skin cancer (basal cell carcinoma squamous cell cancer, or melanoma) and breast cancer. Four malignancies (thyroid gland cancer, oligodendroglioma, basal cell carcinoma and malignant melanoma) were assessed by the investigator as being related to trial treatment.

Latency of onset was variable, ranging from 35 to 1324 days. There was no evidence that the incidence of malignancies altered over time, with fourteen malignancies occurring following the first course of MABTHERA, ten following the second course, and two following the third course. Malignancies were reported mainly in patients aged ≥ 60 years (mean 60 years; range 37-80 years).

Additional all exposure data from combined approved and unapproved RA indications

The following all exposure data is sourced from RA studies relating to both approved and unapproved uses of MABTHERA in RA. The registered indication (in severe RA) is supported primarily by data from the REFLEX phase III pivotal study and additionally by data from the DANCER and WA16291 studies. The data presented below is taken from pooled all exposure analyses which included the 3 studies supporting the approved indication, as well as data from their respective open label extension studies, namely WA17531 (REFLEX extension) and WA16855 (DANCER/WA16291 extension). The all exposure analyses also included data from SERENE, SUNRISE, MIRROR, SIERRA and IMAGE studies, all of which support RA indications (early RA or moderate to severe RA) not registered in Australia.

In clinical trials 3095 patients were treated with MABTHERA for RA providing 7198 patient years of observation, with up to > 8 years follow-up and up to 13 courses of MABTHERA received (one patient had received the 1st infusion of the 13th course at the time of data cut-off). Over 750 patients had been followed for > 3 years and 225 patients for > 5 years with 2365, 1581, 1038 and 497 patients receiving ≥ 2 , ≥ 3 , ≥ 4 and ≥ 5 courses, respectively. (The patient figures refer to the number of patients receiving at least one infusion or part of an infusion for any given course.) Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of ADRs reported for subsequent courses of MABTHERA were similar to rates and types seen for a single course of MABTHERA.

Hypophosphataemia and hyperuricaemia

In the overall RA clinical trial programme hypophosphatemia (< 2.0 mg/dl) was observed in 22% patients (688/3083), and hyperuricemia (> 10 mg/dL) in 13.0% (400/3083) patients. In

the majority of cases, hypophosphataemia and hyperuricaemia were transient, occurring at the time of infusion.

Infusion-related Reactions (IRRs)

The most frequent ADRs following receipt of MABTHERA in clinical studies were IRRs. Among the 3095 patients treated with MABTHERA (for up to 13 courses), 1077 (35%) experienced at least one IRR. The vast majority of IRRs were Grade 1 or 2. Less than 1% (14/3095 patients) of patients with RA who received an infusion of MABTHERA at any dose experienced a serious infusion-related reaction. There were no Grade 4 IRRs and no deaths due to IRRs in the clinical studies (see *Post-Marketing Experience – Rheumatoid Arthritis*). The proportion of Grade 3 events and IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and symptoms suggesting an IRR (nausea, pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following first infusion of the first exposure to MABTHERA. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see PRECAUTIONS – *Rheumatoid Arthritis*).

Infections

The overall rate of infection was approximately 97 per 100 patient years in MABTHERA treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The rate of serious infections was 4.25 per 100 patient years. The most common serious infections were pneumonia or lower respiratory tract infections, cellulitis, urinary tract infections, gastroenteritis and bronchitis. Fatal serious infections included pneumonia, sepsis, colitis and PML.

In 240 MABTHERA-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Sixteen serious infections were observed in 262.4 patient years (6.10 per 100 patient years) prior to exposure and 12 were observed in 246.5 patient years (4.87 per 100 patient years) after exposure.

Malignancies

The incidence of malignancy (excluding non-melanoma skin cancer) following exposure to MABTHERA in clinical studies (0.8 per 100 patient years) lies within the range expected for an age and gender matched population. A total of 60 confirmed malignancies (excluding non-melanoma skin cancers) have been reported in 59/3095 (2%) patients treated with MABTHERA. The most common types were breast cancer and thyroid cancer.

Latency of onset was variable, ranging from 32 to 1561 days. There was no evidence that the rate of malignancies altered over time or with multiple courses of MABTHERA.

Cardiovascular Events

In clinical trials the rate of serious cardiac reactions was 1.71 per 100 patient years. The most common serious cardiac event was myocardial infarction (MI) with a rate of 0.56 per 100 patient years. Rates did not increase over multiple courses of MABTHERA, and were consistent with those observed in epidemiologic studies of RA patients. Since patients with RA are at increased risk for cardiovascular events compared with the general population,

patients with RA should be monitored throughout the infusion and MABTHERA should be discontinued in the event of a serious or life threatening cardiac event (see PRECAUTIONS – *Rheumatoid Arthritis*).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralising antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to MABTHERA with the incidence of antibodies to other products may be misleading.

A total of 392/3095 (12.7%) patients with RA tested positive for HACA at any time after receiving MABTHERA. HACA positivity was not associated with increased infusion reactions or other adverse reactions. Upon further treatment, the proportions of patients with infusion reactions were similar between HACA positive and negative patients, and most reactions were mild to moderate. Two HACA positive patients had serious infusion reactions after developing HACA. The clinical relevance of HACA formation in MABTHERA-treated patients is unclear.

Post-Marketing Experience

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of MABTHERA.

As part of the continuing post-marketing surveillance of MABTHERA safety, the following serious adverse reactions have been observed:

- *Cardiovascular system*: Severe including fatal cardiac events, such as heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion-related reactions. Vasculitis, predominantly cutaneous, such as leucocytoclastic vasculitis, has been reported very rarely.
- *Blood and lymphatic system*: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MABTHERA. Cases of infusion-related acute reversible thrombocytopenia have been reported.
- *In post-marketing*: Studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

- *Respiratory system*: Fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis) have been reported. Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.
- *Skin and appendages*: Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis have been reported rarely.
- *Nervous system*: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MABTHERA therapy.
- *Body as a whole*: Serum sickness-like reactions have been reported rarely.
- *Infections and infestations*: Cases of hepatitis B reactivation have been reported in subjects receiving MABTHERA in combination with cytotoxic chemotherapy (see PRECAUTIONS). Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) see BOXED WARNING) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV (Human Immunodeficiency Virus)-positive.
- *Gastro-intestinal system*: Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy for non-Hodgkin's lymphoma.
- *Renal and urinary system*: Renal failure has been reported.

Rheumatoid Arthritis

In addition to ADRs seen in RA clinical trials for MABTHERA (see ADVERSE EFFECTS - *Experience from Clinical Trials in Rheumatoid Arthritis*), progressive multifocal leukoencephalopathy (PML), serum sickness-like reaction, reactivation of hepatitis B and severe IRRs with fatal outcome infection have been reported during post-marketing experience. Neutropenic events, including severe late onset and persistent neutropenia, have been reported rarely in the post-marketing setting, some of which were associated with fatal infections.

DOSAGE AND ADMINISTRATION

MABTHERA may be administered in an outpatient setting. MABTHERA should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

Dosage

Non-Hodgkin's Lymphoma

Premedication, consisting of an analgesic/antipyretic such as paracetamol and an antihistamine such as diphenhydramine should always be administered 30 to 60 minutes before each infusion of MABTHERA. Premedication with glucocorticoids should also be considered, particularly if MABTHERA is not given in combination with steroid-containing chemotherapy.

Relapsed or refractory Low Grade or Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA when used in monotherapy is 375 mg/m² administered as an intravenous infusion once weekly for four weeks.

The recommended dosage of MABTHERA when used in combination with CHOP chemotherapy is 375 mg/m² administered on day 1 of each chemotherapy cycle (6 cycles).

Previously untreated stage III/IV Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m² administered on day 1 of each chemotherapy cycle for up to 8 cycles as induction therapy.

MABTHERA should be administered prior to the administration of chemotherapy. Any infusion related reactions should have settled before chemotherapy is instituted.

Maintenance treatment

Patients who have responded to induction treatment may receive maintenance therapy with MABTHERA given at 375 mg/m² body surface area once every 3 months until disease progression or for a maximum period of two years.

Diffuse large B-cell non-Hodgkin's lymphoma

The recommended dosage for MABTHERA in combination with CHOP chemotherapy is 375 mg/m², administered as an intravenous infusion on day 1 of each chemotherapy cycle, for up to 8 cycles.

Chronic Lymphocytic Leukaemia

Premedication, consisting of an analgesic/antipyretic such as paracetamol and an antihistamine such as diphenhydramine should always be administered 30 to 60 minutes before each infusion of MABTHERA. Premedication with glucocorticoids should also be considered, particularly if MABTHERA is not given in combination with steroid-containing chemotherapy.

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m² administered on day 1 of the first treatment cycle followed by 500 mg/m² administered on day 1 of each subsequent cycle, for a total of 6 cycles (see CLINICAL TRIALS). The chemotherapy should be given after the infusion of MABTHERA.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to the start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are $>25 \times 10^9/L$ it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with MABTHERA to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

Dosage adjustments during treatment

No dose reductions of MABTHERA are recommended. When MABTHERA is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.

First Infusion: The recommended initial rate of infusion is 50 mg/h. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see PRECAUTIONS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent MABTHERA infusions can be administered at an initial rate of 100 mg/h and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.

Rheumatoid Arthritis

Premedication consisting of an analgesic/antipyretic such as paracetamol and an antihistamine such as diphenhydramine should always be administered 30 to 60 minutes before each infusion of MABTHERA. Premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of IRRs. Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each MABTHERA infusion (see PRECAUTIONS – *Rheumatoid Arthritis*).

A course of MABTHERA consists of two 1000 mg IV infusions. The recommended dosage of MABTHERA is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later. The course of MABTHERA is given concomitantly with the dose of MTX tolerated by the patient. The minimal effective dose is not yet known.

Background therapy with glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with MABTHERA.

Disease activity should be regularly monitored. Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of MABTHERA treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients who received additional courses doing so 6 -12 months after the previous course. Some patients required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course.

Human anti chimeric antibodies (HACA) develop in some patients after the first course of MABTHERA. The presence of HACA may be associated with the worsening of infusion or allergic reactions after the second infusion of subsequent course. Furthermore, in one case with HACA, failure to deplete B-cells after receipt of further treatment courses has been

observed. Thus, the benefit/risk balance of therapy with MABTHERA should be carefully considered before administering subsequent courses of MABTHERA. If a repeat course of treatment is considered it should not be given at an interval less than 16 weeks.

First infusion of each course: The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Second infusion of each course: Subsequent doses of MABTHERA can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minutes intervals, to a maximum of 400 mg/h.

Special Populations

Elderly: No dose adjustment is required in elderly patients (aged > 65 years).

Preparation

MABTHERA vials do not contain an antimicrobial agent or preservative; therefore, care must be taken to ensure the sterility of the vials and prepared solution. Each vial should be used once only and any residue discarded.

Aseptically withdraw the necessary amount of MABTHERA and dilute to a calculated concentration between 1 mg/mL to 4 mg/mL of rituximab into an infusion bag containing either 0.9% sodium chloride or 5% dextrose in water. To mix the solution, gently invert the bag to avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

To reduce microbiological hazard, prepared infusion solutions of MABTHERA should be used as soon as practicable after dilution. If necessary, the prepared solutions may be stored in the refrigerator (2°C to 8°C) for up to 24 hours. This timeframe allows for the temporary interruption of the infusion and subsequent recommencement if the patient has an infusion reaction (see *Administration* below).

No incompatibilities between MABTHERA and polyvinyl chloride or polyethylene bags have been observed.

Administration

The MABTHERA solution for infusion should be administered intravenously through a dedicated line.

As with all parenteral products, appropriate aseptic technique should be used during the administration of MABTHERA. Do not administer as an intravenous push or bolus. Hypersensitivity reactions may occur whenever protein solutions such as MABTHERA are administered (see PRECAUTIONS).

OVERDOSAGE

There has been no experience of overdosage in human clinical trials. Single doses higher than 1000 mg have not been tested in controlled clinical trials. The highest dose tested to date is 5 g in patients with CLL. No additional safety signals were identified. Patients who experience

overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

Treatment of overdose should also consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE

Packs of 2:

- Single-use vials containing concentrated solution for dilution and intravenous infusion 100 mg/10 mL

Pack of 1:

- Single-use vial containing concentrated solution for dilution and intravenous infusion 500 mg/50 mL

Rituximab 100 mg (10 mL) or 500 mg (50 mL) is formulated in a 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide and/or hydrochloric acid.

Storage

MABTHERA vials must be refrigerated between 2°C to 8°C. Do not freeze MABTHERA vials. MABTHERA vials must be protected from direct sunlight. Do not use beyond the expiry date stamped on the carton/vial. MABTHERA vials should be used once only and any unused portion left in the vials should be discarded.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE

Prescription only medicine- Schedule 4

SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer Enquires: 1800 233 950

Date of TGA approval: 15 August 2011

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