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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR MABTHERA

International non-proprietary name/Common name: rituximab

Procedure No. EMEA/H/C/165/II/0060

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

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1. Introduction

Mabthera (rituximab) is a genetically engineered chimeric mouse/human monoclonal antibody which binds specifically to the transmembrane antigen, CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on hemopoietic stem cells, pro-B cells, normal plasma cells or other normal cells. The CD20 antigen is also expressed on >95% of all B cell NHL. After binding to the CD20 antigen on the cell surface, rituximab is believed to exert its therapeutic effect by promoting B cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and induction of apoptosis.

Mabthera is available in single-use vials containing 100 mg/10 ml and 500 mg/50 ml concentrate for solution for infusion. Mabthera (rituximab) was approved in the EU in June 1998 and is currently approved for a number of indications:

Non-Hodgkin's lymphoma (NHL)

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

Rheumatoid arthritis

MabThera 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 other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

This is a new indication concerning '**first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy'** and is based on one pivotal phase III study (ML 17102) and published data from phase II studies and retrospective studies.

Chronic lymphocytic leukaemia (CLL) is the most common form of adult leukaemia comprising 30% of all adult leukaemias. The incidence of CLL is around 3/100,000 inhabitants per year in the Western hemisphere and increases with age. The rate is almost 50/100,000 cases per year above the age of 70 years. The median age at first diagnosis is in the range of 65-70 years and men are affected more often than women. Over the years, the incidence has increased in younger patients and now about one-third of CLL patients are younger than 55 years at diagnosis.

CLL patients have an extremely variable clinical course and prognosis depending on disease stage and presence. The two clinical staging systems developed by Rai and Binet are widely used and are an accepted prognostic tool.

According to recently issued update of the guidelines of the National Cancer Institute Working Group (NCI-WG) newly diagnosed patients with asymptomatic early-stage disease (Binet A) should be monitored without therapy unless they have evidence of disease progression. However, therapy should be given to all patients with Binet stage C disease and to patients with symptomatic or progressive Binet stage B disease.

There is no universally accepted standard treatment for previously untreated patients with CLL. Single alkylating agents (chlorambucil, cyclophosphamide) are widely established; single purine-analogues such as fludarabine or cladribine may also be used. Despite initial response with single agent therapies, most patients progress and require further therapy within 1-2 years after single agent therapy.

Combination chemotherapy is widely used in order to induce longer progression-free/treatment free periods. Treatment with fludarabine and cyclophosphamide (FC) is considered by many CLL study groups worldwide as a standard treatment for previously untreated patients with CLL who can tolerate this regimen.

Based on synergistic activity between purine analogues, alkylating agents and monoclonal antibodies, new active combination therapies for CLL were introduced over the last years.

2. Clinical aspects

Study ML17102 was initiated in July 2003 as a national collaborative group study led by the German CLL Study Group (GCLLSG). The study was opened for international participation in 2004 and legal sponsorship was transferred to the Marketing Authorisation Holder (MAH), Roche.

Scientific advice was sought by the MAH at the level of the national agencies of the Rapporteurs (DK and NL) and two protocol amendments were implemented.

The pre-planned interim analysis of study ML17102 was performed with a clinical cut-off of July 4, 2007 and presented to the independent Data and Safety Monitoring Board (DSMB) in January 2008. The DSMB concluded that on the basis of these data, the primary objective of the study had been met and that the results demonstrated a statistically significant benefit for rituximab when added to FC (R-FC) versus FC alone as induction treatment for patients with previously untreated CLL. The DSMB considered the results to be statistically significant and clinically meaningful and recommended stopping the study and fully analyzing the study data.

Data from a series of published phase II studies were also provided and on the basis of these studies, in addition to the ML17102 study results.

Study ML17102 was conducted according to the guidelines of Good Clinical Practice (GCP). Nine study centres were audited, and the Collaborative Group had 2 system audits. All audits were conducted by the Roche Clinical Quality Assurance Group or designees. Significant non-compliance with GCP was observed which, in the opinion of the auditors, did not affect the validity of the data or patients' safety and/or rights. Appropriate corrective and preventive actions were undertaken.

2. 1. Clinical Efficacy

The proposed indication for rituximab in combination with chemotherapy in previously untreated patients with CLL is based on data from one randomized phase III pivotal study (ML17102 also known as study CLL-8). This study is supported by published data from phase II studies. Between them, these studies include a total of more than 900 patients with previously untreated CLL and more than 400 patients with relapsed/refractory disease, all treated with rituximab in combination with chemotherapy. Table 1 below is summarising the content of the application.

Table 1

Study	Title of Publication	Regimen	No and Type of Patients Included	Source Document
Previously Untreated Patients				
Study ML17102 (pivotal study)	A phase III trial of combined immunochemotherapy with R-FC versus chemotherapy with FC alone in patients with previously untreated CLL	FC ± R	Symptomatic previously untreated Binet stage B/C patients with CLL. 407 pts FC 403 pts R-FC	CSR
Tam et al.	Long term results of the fludarabine, cyclophosphamide and rituximab regimen as initial therapy of chronic lymphocytic leukaemia	R-FC	300 patients aged 18 years or older with previously untreated CLL and symptomatic or progressive disease	Publication
Byrd et al, 2003 Byrd et al., 2005	Randomized phase II study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with CLL: results from Cancer and Leukaemia Group B 9712 Addition of rituximab to fludarabine may prolong PFS and OS in patients with previously untreated CLL; an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011	R-F or F→R Patients with response ≥ SD were treated with an additional 4 cycles of R Historical cohort comparison	Symptomatic, previously untreated patients with CLL N=104 R-F (concurrent or sequential) N=178 F alone	Publication Publication
Faderl et al., 2007	Update of experience with fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline therapy for CLL	R-FCM (+ pegfilgrastim)	30 symptomatic, previously untreated patients with CLL	Conference abstract
Kay et al., 2007	Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukaemia	R-PC	64 previously untreated patients with CLL	Publication
Previously Treated Patients				
Wierda et al.	Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab for relapsed and refractory chronic lymphocytic leukaemia	R-FC	177 patients with recurrent/refractory CLL N=143 R-FC	Publication

Wierda et al.	A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukaemia treated with fludarabine-based regimens	F, FC or R-FC	(out of 177 patients from above) N=251 F N=111 FC	Publication
Hillmen et al., 2007	NCRI CLL201 trial: A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone with or without rituximab in previously treated CLL	FCM ± R	Previously treated patients with CLL N=23 FCM N=23 R-FCM	Conference abstract
Lamanna et al., 2006	Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukaemia	R-PC	46 previously treated patients with CLL (n=32) or other low grade B-cell neoplasms (n=14)	Publication
Lamanna et al., 2007	Pentostatin, cyclophosphamide, rituximab, and mitoxantrone: A new highly active regimen for patients with CLL previously treated with PCR or FCR	R-PCM	21 previously treated patients with CLL (n=17) or other low grade B-cell neoplasms (n=4)	Conference abstract
Robak et al., 2007	Rituximab plus cladribine with or without cyclophosphamide in patients with relapsed or refractory chronic lymphocytic leukaemia	R-Cl± C	Patients with relapsed/refractory CLL N=18 R-Cl N=28 R-ClC	Publication
Fischer et al., 2007	Bendamustine in combination with rituximab for patients with relapsed chronic lymphocytic leukaemia: A multicentre phase II trial of the German CLL Study Group (GCLLSG)	R-B	81 patients with relapsed/refractory patients	Conference abstract
Eichhorst et al., 2005	CHOP plus rituximab in fludarabine refractory CLL or CLL with autoimmune hemolytic anaemia or Richter's transformation: first interim analysis of a phase II trial of the German CLL Study Group (GCLLSG)	R-CHOP	34 patients refractory to F or with AIHA as well as in patients with Richter's transformation	Conference abstract

Abbreviations: F, fludarabine; C, cyclophosphamide; Cl, cladribine; R, rituximab; M, mitoxantrone; B, bendamustine; AIHA, autoimmune hemolytic anaemia

Dose-response studies and main clinical studies

Rituximab at the normal lymphoma dose and schedule (375 mg/m^2 iv. weekly) is not very effective for the treatment of small lymphocytic lymphoma (the non-leukaemic equivalent of CLL). Some investigators have found a convincing dose–response effect in patients with CLL using a dose-escalation strategy. A 75% response rate was observed in patients with CLL who received the

maximum rituximab monotherapy dose of 2250 mg/m^2 (six times the standard lymphoma dose) as compared to a response rate ranging from 10% to 45% with the standard regime. Others have tested a dose-intense schedule of three weekly rituximab infusions at standard dose levels and reported an improved response rate (45%) in previously treated patients with CLL/SLL.

Two phase II studies of rituximab at 500 mg/m^2 (375mg/m^2 for the first cycle) in combination with fludarabine (25 mg/m^2/day) and cyclophosphamide (250 mg/m^2/day) for 3 days were initiated in patients with untreated and relapsed/refractory CLL at the M.D. Anderson Cancer Center (MDACC). These studies demonstrated very high response rates and long PFS with this regimen. This regimen was subsequently chosen for testing in phase III clinical trials including study ML17102.

Pivotal study ML1702

Study ML17102 was a prospective, randomized, open-label multicenter phase III study. Study ML17102 included mainly previously untreated CD-20 positive CLL patients with symptomatic Binet stage B disease in need of therapy and Binet stage C disease (95% of the population).

Patients were planned to receive 6 treatment cycles of FC chemotherapy (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] i.v. on days 1, 2 and 3 of each cycle) at intervals of 28 days. Patients randomized to the R-FC arm received FC in combination with rituximab (375 mg/m^2 i.v. on day 0 of cycle 1, 500 mg/m^2 i.v. on day 1 of cycles 2-6).

The primary efficacy endpoint was progression-free survival. Secondary endpoints included Event-free survival, Overall survival, Disease-free survival, Duration of response, Time to new CLL treatment or death, Rates of molecular, complete and partial response, Response rates and survival times in biological subgroups.

The evaluation of the treatment outcome and disease progression was performed according to the updated criteria of the National Cancer Institute (NCI) Sponsored Working Group on CLL. These outcomes were assessed by the investigators. An independent assessment of the data was not performed. However, the absence of an independent review is not considered a major problem. CLL is a systemic disease with neoplastic cells in the peripheral blood and bone marrow that can be assessed objectively and the assessment of peripheral lymph nodes and hepatosplenomegaly is clinical. CT scans/ultra sound scans to document disease status are not considered necessary in the response evaluation of patients with CLL as their additional value has not been demonstrated in past clinical studies. Interim staging was performed after 3 cycles of therapy before starting the 4th cycle. All patients who showed at least a partial response (PR/CR) after the first 3 cycles, continued treatment according to the protocol for a total of 6 cycles of therapy. Patients who showed insufficient response (SD/PD) after the first 3 cycles of treatment were withdrawn from study treatment and were eligible to receive alternative treatment. However, all patients prematurely withdrawn from trial treatment were followed for disease progression (irrespective of new treatment), new treatment and survival as scheduled by the CLL-8 protocol.

The primary endpoint PFS was used to determine the sample size of the study. Based on data from the German CLL-4 trial , the median PFS was assumed to be 40 months in the FC arm (corresponding to a 66% PFS rate at 2 years) and 54 months in the R-FC arm. A median benefit of 35% corresponding to a hazard ratio of 0.741, was judged as both realistic and clinically relevant. Thus, the main analysis was triggered once 357 events (disease progression or death) were reached. With this number of events, it could also be possible to detect a median PFS benefit of 45% with a power of 80% at the overall alpha level of 1%.

Assuming a linear recruitment over 38 months resulting in 760 patients, a study duration of approximately 62 months was expected to reach the required 357 events which triggered the main analysis. An interim analysis was planned to be performed after 238 events have occurred (66.7% of 357). If the median in the FC arm was in truth 45 months (the benefit was still at 35% and the exponential assumption held), the study lasted approximately 5 months longer.

The efficacy analyses on PFS, OS, EFS, DFS, DR and TTNT were based on a non-stratified, two-sided Log-rank test. Response rates were compared applying a two-sided Chi-square test. For the primary endpoint PFS, the significance level's alpha was 0.012 at the interim analysis (after 2/3 of the events) to maintain an overall two-sided type I error of 5%. All tests on secondary endpoints were performed at a nominal significance level $\alpha = 0.05$ (2-sided). No adjustment for the multiplicity of testing was performed for the secondary parameters. No formal testing of safety endpoints was performed.

The first patient was randomized in the study on July 21, 2003 and the last patient was randomized on April 4, 2006. The cut-off date for the primary analysis presented in this report was July 4, 2007. A total of 817 patients were randomized in the study at 190 centres in 11 countries with each centre recruiting between 1 and 21 patients.
A pre-planned interim analysis of study ML17102 was performed with a clinical cut-off of July 4, 2007 and presented to the independent Data and Safety Monitoring Board (DSMB) in January 2008. At the time of interim analysis (clinical cut-off July 4th, 2007) there were 254 PFS events available. The DSMB concluded that on the basis of these data, the primary objective of the study had been met and that the results demonstrated a statistically significant benefit for rituximab when added to FC (R-FC) versus FC alone as induction treatment for patients with previously untreated CLL. The DSMB considered the results to be statistically significant and clinically meaningful and recommended stopping the study and fully analyzing the study data.

Demographics and disease characteristics assessed at baseline (BL) were well balanced between the two treatment arms. The median age was 61 years with a predominance of males (74%). Sixty-four percent of patients had Binet stage B disease at BL, 31% had Binet stage C and 5% had Binet stage A disease. A total of 58% of patients had lymphocyte counts >50 Giga/L at study entry, splenomegaly was present in 70%lactate dehydrogenase (LDH) was elevated in 41%, and the proportion of patients with B symptoms was around 45%. Prognostic biomarkers were balanced between the arms: del 11q was present in 25% of patients, del 17p in 8%, a complex karyotype (≥ 2 cytogenetic abnormalities) was found in 22% of patients with available data. Sixty-five percent of patients had un-mutated Give, 41% were ZAP-70+, and 46% were CD38+ at BL. Overall, the distribution of prognostic biomarkers was representative of a population of previously untreated CLL patients in need of therapy.

A total of 817 patients were randomized in the study (409 patients in the FC arm and 408 patients in the R-FC arm) at 190 centres in 11 countries. Although not specified in the protocol, but following the request of the Danish Medicines Agency (Rapporteur) at the pre-submission meeting of May 9, 2008, the main analysis of study ML17102 as presented in this dossier, was based on the ITT population and included all randomized patients (apart from those with missing informed consent), in order to comply with regulatory requirements. A total of 7 patients (2 patients on FC, 5 patients on R-FC) had a missing informed consent at the time of the main analysis and were excluded from all analyses. Therefore, the ITT population included a total of 810 patients (407 FC, 403 R-FC).

Results
At the time of the interim analysis (clinical cut-off July 4, 2007), a total of 254 patients (31%) had progressed or died. In the FC arm, 37% (152/407) of the patients had experienced an event compared to 25% (102/403 pts) in the R-FC arm.

As none of the study subjects were on active treatments at the time of clinical cut off, an additional follow up of 4.8 months was included, resulting in a total study duration of approximately 25 months. This is rather short for a disease with a mean course of several years and also the results are derived from an interim analysis. However, the MAH has satisfactorily explained the plans for updating the pivotal study, and is to submit the updated survival results from the pivotal study as a follow up measure when available.

The addition of rituximab to the FC regimen significantly prolonged PFS when compared to the FC regimen alone ($p < 0.0001$, Log-Rank test) (Figure 1) The Kaplan-Meier estimated median PFS was 32.2 months (981 days) with FC and 39.8 months (1212 days) with R-FC (Table 12). The risk of progression or death was reduced by 44% patients in the R-FC arm compared to patients in the FC

arm. This risk reduction was statistically significant (adjusted HR 0.56; p < 0001, Wald test). Sixty percent of patients in the FC arm and 77% in the R-FC arm had not progressed or died at two years.

Table 2 Summary of Progression-Free Survival (ITT)

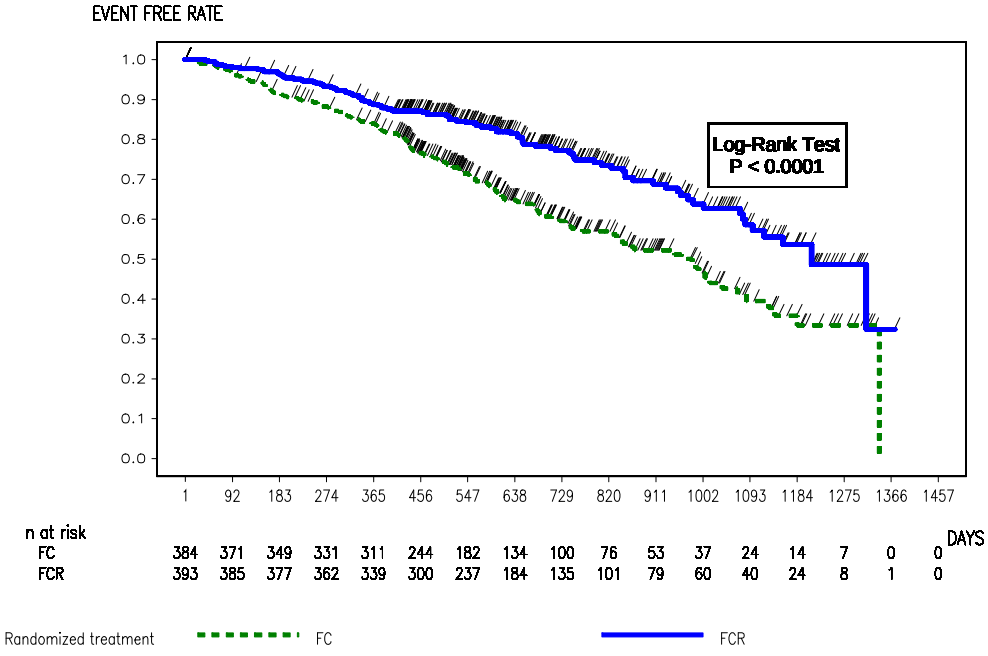
	FC (N=407)		R-FC (N=403)
Patients with event	152 (37.3 %)		102 (25.3 %)
Patients without events*	255 (62.7 %)		301 (74.7 %)
Time to event (days)			
Median#	981.0		1212.0
95% CI for Median#	[835;1069]		[1098;.]
25% and 75%-ile	491;1343		755;.
Range##	1 to 1343		1 to 1372
p-Value (Log-rank Test)		<.0001	
Hazard Ratio (adjusted$)		0.56	
95% CI		[0.43;0.72]	
p-Value (Wald Test)		<.0001	
2 year duration			
Patients remaining at risk	100		135
Event Free Rate	0.60		0.77
95% CI for Rate	[0.54;0.65]		[0.72;0.82]

Days from randomization to event or censoring (PFS) (TTPFS) - Censoring: Event (PFS) (CSPFS)
* censored $ Cox-regression adjusted by Age (years) at Randomization and Gender (Female/Male) and Binet Stage 3 (Binet A,B/Binet C) and Binet Stage 4 (Binet B,C/Binet A) and Time From 1st Diag. (6 -<12/not 6-<12) and Time From 1st Diag. (12-<24/not 12-<24) and Time From 1st Diag. (>=24/not >=24)
# Kaplan-Meier estimate ## including censored observations 2 year duration is defined as 730 days.
Program : $PROD/cd11899a/i17102a/et_pfssum.sas. Output : $PROD/cd11899a/i17102g/reports/et_pfssum_I.out

Figure 1 Kaplan-Meier Plot of Progression-free Survival in Study ML17102 (ITT Population)

eg_pfskm_I Kaplan-Meier Plot Of Progression-Free Survival (Censored Observations Shown)

Protocol(s): ML17102 (I17102G)
Analysis Population: Intent-To-Treat Population (N=810)
Snapshot Date: 08FEB2008 Cutoff Date: 04JUL2007

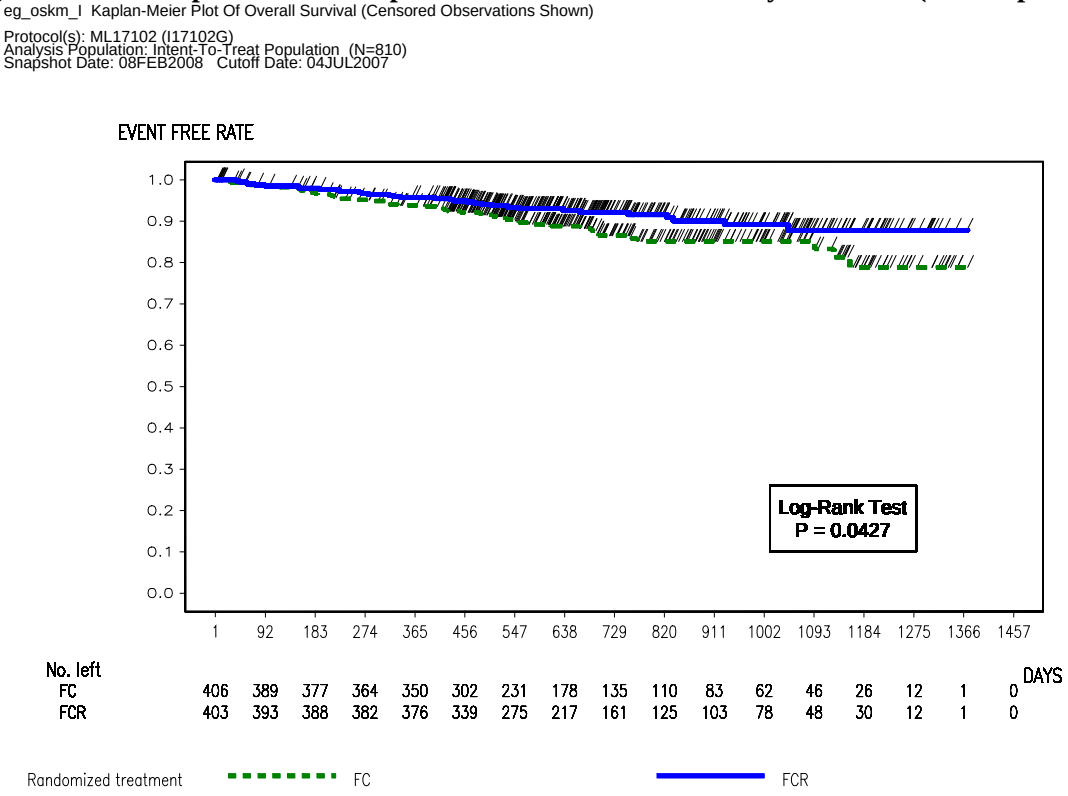


At the time of the main analysis (clinical cut-off July 4, 2007), a total of 81 patients had died: 48 patients (11.8%) in the FC arm and 33 patients (8.2%) in the R-FC arm. After a median follow-up time of 20.7 months and under a nominal significance level $\alpha = 0.05$ (2-sided), overall survival in the R-FC arm was significantly improved compared to the FC arm ($p = 0.0427$, Log-rank test). The median survival times could not be estimated for both treatment arms. Treatment with R-FC reduced the risk of death by 36% when compared to FC alone (adjusted HR 0.64; 95% CI [0.41; 1.00], $p = 0.0427$, Wald test). Eighty-six percent of patients (350/407) in the FC arm and 93% of patients

(376/403) in the R-FC arm were alive at 12 months, 2-year survival rates were 92% in the R-FC group compared to 87% in the FC group.
The additional analysis with 4.8 months longer follow-up (cut-off date of February 8, 2008) did not show a statistical significant effect, but confirmed overall the trend in favour of treatment with R-FC.

The Kaplan-Meier graph of overall survival is provided in Figure 2.

Figure 2 Kaplan-Meier Graph of Overall Survival in Study ML17102 (ITT Population)



In study ML17102, the proportion of patients with an objective response (CR + nPR + PR) was significantly higher in the R-FC arm (86.1%) compared to the FC arm (72.7%) ($p < 0.0001$, Chi-square test). The complete response rate was doubled in the R-FC arm compared to the FC arm (36.0% versus 17.2%) ($p < 0.0001$, Chi-square test).

The percentage of patients who achieved molecular remission (i.e., patients achieving a clinical remission [CR] without evidence of minimal residual disease [MRD] measured by flow cytometry) was higher in patients who received R-FC compared with patients who received FC.

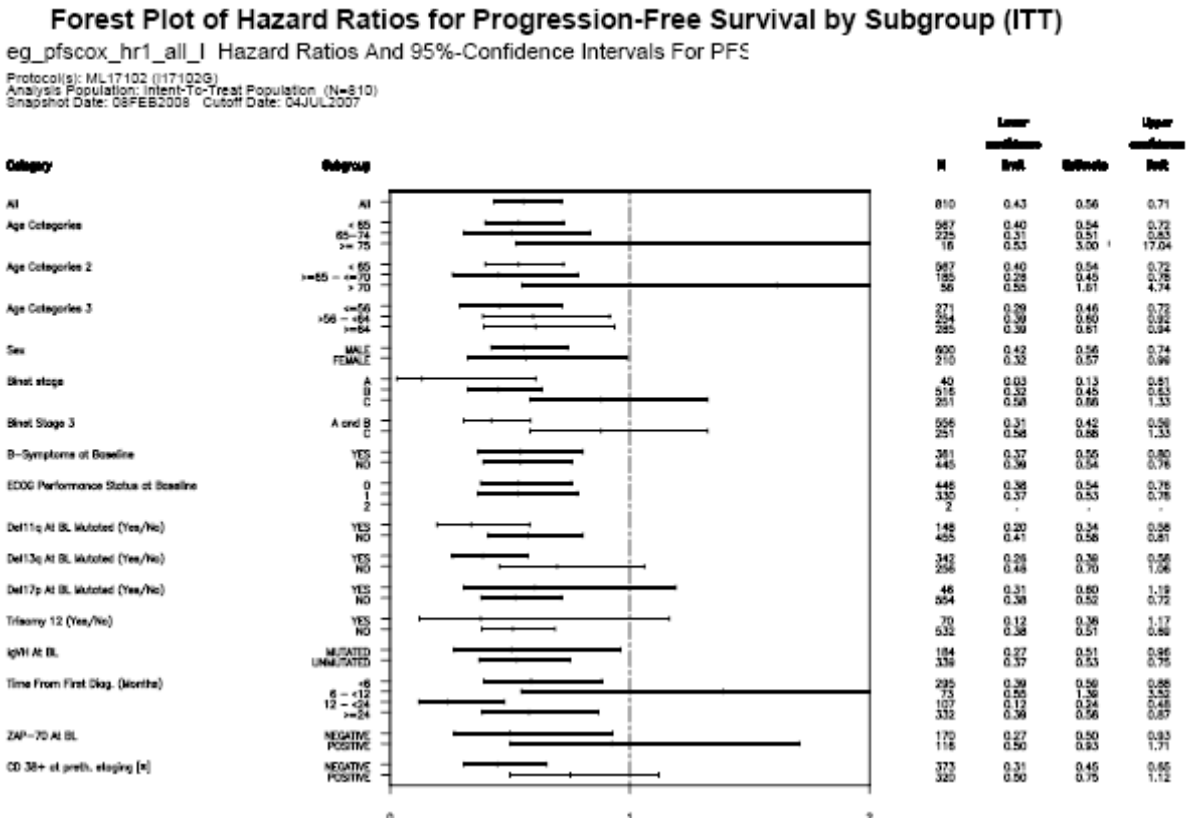
Secondary endpoints other than overall survival, response rates and duration of response are summarized below.

Table 3 Summary of Other Efficacy Parameters in Study ML17102

	FC N=407	**R-FC N=403**
Event-free survival		
Median	31.1	39.8
95% CI	(25.3, 35.1)	(36.1, n.r.)
p-value (Log-rank)	<0.0001	
Hazard ratio (adjusted)	0.55	
95% CI	(0.43, 0.7)	
Overall Response Rate	296 (72.7%)	347 (86.1%)
p-value (Chi square)	<0.0001	
CR	70 (17.2%)	145 (36.0%)
PR	226 (55.5%)	202 (50.1%)
Molecular Response		
MRD-negative ORR	8% (*n=110*)	18% (*n=74*)
MRD-negative CR	7% (*n=15*)	25% (*n=24*)
MRD-negative PR[1]	8% (*n=95*)	14% (*n=50*)
Duration of Response	*296*	*347*
n		
Median (months)	34.7	40.2
95% CI	(29.5, 40.8)	(35.4, n.r.)
p-value (Log-rank)	0.0040	
Hazard ratio (adjusted)	0.61	
95% CI	(0.43, 0.85)	
Disease-free Survival	*91*	*186*
n		
Median (months)	n.r.	n.r.
95% CI	(n.r., n.r.)	(30.9, n.r.)
p-value (Log-rank)	0.7882	
Hazard ratio (adjusted)	0.93	
95% CI	(0.44, 1.96)	
Time to new treatment		
Median (months)	n.r.	n.r.
95% CI	(n.r., n.r.)	(n.r., n.r.)
p-value (Log-rank)	0.0052	
Hazard ratio (adjusted)	0.65	
95% CI	(0.47, 0.90)	

CI, confidence interval; EFS, event-free survival; CR, complete response; PR, partial response; TTNT, time to new (CLL) treatment; MRD, minimal residual disease. [1] includes nodular partial responses (nPR)

In order to assess the impact of potential prognostic factors on the treatment effect, baseline characteristics were analyzed. Risk ratios with 95% CI (R-FC vs. FC) for patient subgroups based on baseline factors are shown for progression-free survival in Figure 7. Overall, the results of the PFS subgroup analyses were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the R-FC arm compared to the FC arm in most of the subgroups analyzed, except for patients older than 70 years and those who were diagnosed 6-< 12 months before study entry.



Of particular interest were subgroups of patients based on Binet stage at baseline (stratification factor) and more detailed analyses on these subgroups are shown below. Of note, in general the study was not powered to show significant differences in subgroups. In all subgroups analyzed according to Binet stage, the risk of disease progression or death was decreased by the addition of rituximab to FC when compared to FC alone. The effect was most pronounced in the group of patients with stage A disease (not adjusted HR 0.13, 95% CI [0.03; 0.61]; p = 0.0093) and stage B disease (HR 0.46, 95% CI [0.32;0.63]; p < 0.0001), whereas the risk reduction in patients in stage C disease was less pronounced (not adjusted HR 0.88, 95% CI [0.58; 1.33]; p = 0.5406). A potential explanation for the lower treatment effect observed in the subgroup of Binet stage C patients when compared to the Binet stage A or B patients may be the observation that certain prognostic biomarkers, mainly IgVH mutational status and ZAP-70 expression, were imbalanced between treatment arms in the Binet C subgroup with more patients on the R-FC arm expressing these adverse prognostic factors, whereas most of the biomarkers were relatively balanced in subgroups of patients with Binet stage A or B disease. In Binet stage C patients, more patients in the R-FC group had un-mutated IgVH (46% FC, 59% R-FC) or were ZAP-70+ (33% FC, 41% R-FC) compared to the FC arm (i.e. had worse prognostic features than patients in the FC arm. As the subgroup analysis shows that Binet stage C patients did not benefit statistically significantly from the addition of rituximab to chemotherapy (R-FC), and also since patients with Binet stage C experienced more safety problems due to rituximab, the risk balance in this sub group I doubtful. Thus adequate information with respect to treatment of patients with Binet stage C with rituximab in combination with chemotherapy has been requested to be put into the SPC.

Supportive studies
As shown in the table in the start of the clinical section rituximab has been investigated in combination with other chemotherapies in both previously untreated and treated patients with CLL. Given the fact that most of these studies are conducted by independent investigators and are provided as publications only the most important findings is summarized here. These trials are phase II studies and some of them retrospective series. The studies are summarised in the Clinical AR and the data can only be supportive. Median PFS in previously untreated patients ranged from around 32 months to 40 months. Median duration of response for previously untreated, responding patients ranged from 34 to 80 months, and for relapsed/refractory, responding patients from 12 to 36 months. The wide range of median PFS and duration of response (DR) results across studies may be due to the different nature of the studies (e.g. different durations of follow up, different baseline characteristics and different patient populations). Overall response rates for rituximab in combination with chemotherapy in previously untreated patients were high and consistent across studies and ranged from 77% (sequential administration of rituximab after fludarabine) to 97% (rituximab in combination with FCM). Complete response rates ranged from 15% (sequential fludarabine followed by rituximab) to 77% (rituximab in combination with FCM). In previously treated patients, overall response rates were similarly high and ranged from 65% (rituximab in combination with bendamustine) to 94% (rituximab in combination with PCM). In the retrospective analysis by Wierda et althea overall response rate was significantly higher for patients who had received R-FC compared with patients who had received F ($p=0.008$), but not compared to patients who received FC. However, the proportion of CRs was significantly higher in patients in the R-FC cohort compared to patients in the F and FC cohorts ($p<0.05$).
In conclusion, rituximab in combination with chemotherapy seems to produce high response rates and PFS comparable to the results of the pivotal phase III study.

2. 2. Clinical safety

The evaluation of safety information for the proposed indication in CLL is mainly based on data from the phase III study ML17102 sponsored by Roche and conducted in collaboration with the German CLL Study Group. The 11 investigator sponsored studies have reported limited safety information.

Patient exposure
In study ML17102 a total of 397 patients with CLL received at least one treatment cycle of rituximab (in combination with fludarabine and cyclophosphamide). Supplementary safety data in CLL patients is available from several phase II trials of rituximab in combination with FC or other chemotherapy treatment regimens. The total number of patients treated with rituximab in these phase II studies was 498 previously untreated patients (who required therapy) and 411 previously treated patients.

ML17102 is main safety database. In the R-FC arm, more patients received six cycles of therapy (i.e., at least one component of cycle treatment) compared to the FC arm (75% [299/397] vs. 69% [273/396]). This difference was mainly due to a higher number of patients in the FC arm with insufficient response at interim staging or withdrawals for administrative reasons. Of those patients treated with R-FC, 75% received all six doses of rituximab. Most patients in the R-FC arm received at least 90% of the planned dose of rituximab (at each cycle between 82% and 95% of patients).

Adverse events
At the time of the clinical cut-off July 4, 2007, the incidence of grade 3 or 4 AEs and SAEs was higher in the R-FC arm, ´Table 8, while the number of all deaths was higher in the FC arm. AEs leading to dose modifications were more frequent in the R-FC arm than the FC arm. However, AEs leading to treatment discontinuation occurred with the same frequency in both arms (18%). Importantly, there was no difference in the rate of deaths considered related to therapy. Overall, the safety profile of rituximab in CLL was consistent with the known safety profile of rituximab used in combination with chemotherapy in other indications. No new safety signals related to rituximab appeared in this study.

Table 4 Overview of Adverse Events in Study ML17102 (SAP)

	Number of Patients (%)	
	FC	**R-FC**
	N = 396	**N = 397**
Grade 3 or 4 AE	246 (62%)	304 (77%)
Serious AE	162 (41%)	182 (46%)
AE leading to treatment discontinuation	70 (18%)	71 (18%)
AE leading to dose modification/interruption	80 (20%)	133 (34%)
Treatment-related death	8 (2%)	6 (2%)

Safety information from the phase II studies of rituximab in combination with a variety of chemotherapy regimens as described in journal articles or conference abstracts. The publications mainly focus on the most commonly reported events such as severe infections, neutropenia, anaemia and thrompocytopenia.
Overall, the proportion of patients reporting a grade 3 or 4 adverse event in study ML17102 was higher in the R-FC arm (77%) compared to the FC arm (62%).
The most common system organ classes for grade 3 or 4 AEs were 'blood and lymphatic system disorders' and 'infections and infestations' (each ≥ 10% incidence).

Table 5 Grade 3 or 4 AEs that occurred with an at least 2% higher incidence in one of the treatment arms were:

Higher incidence in the R-FC arm versus the FC arm:	
– Neutropenia:	19% and 30% in the FC arm and R-FC arm, respectively
– Leukopenia:	12% and 23%
– Febrile neutropenia:	6% and 9%
– Pancytopenia:	1% and 3%
Higher incidence in the FC arm versus the R-FC arm:	
– Thrombocytopenia:	10% and 7% in the FC arm and R-FC arm, respectively
– Anaemia:	7% and 4%
– Pyrexia:	5% and 3%

The proportion of patients reported as having at least one grade 3 or 4 infection or infestation was balanced between treatment arms (17% in the FC arm vs. 18% in the R-FC arm). Infection AEs with an incidence of at least 1% were pneumonia, herpes zoster, sepsis, bronchitis, infection, sinusitis and neutropenic infection.

The overall incidence of grade 3 or 4 cardiac disorders was balanced between treatment arms (3% vs. 4%), however, more patients in the R-FC arm (six patients [2%]) experienced grade 3 or 4 angina pectoris compared to the FC arm (one patient). One additional FC patient had a grade 2 SAE of angina pectoris. All eight patients the event resolved without sequelae.

In the FC arm, only one patient experienced an immune system disorder (grade 4 SAE of hypersensitivity) compared to 12 patients (3%) in the R-FC arm. These 12 patients experienced hypersensitivity (six patients, all with grade 3 events, three were serious), anaphylactic reactions (one grade 3 AE and one grade 4 SAE), drug hypersensitivity (two patients with grade 3 SAEs), allergic oedema (one patient, grade 3) and cytokine release syndrome (one patient, grade 4 SAE). In seven of the 12 patients these events occurred during or within 24 hours of a rituximab infusion. All patients with immune system disorders received treatment for the events, all of which resolved without sequelae. The patients all continued in the study.

In both arms the overall incidence of grade 3 or 4 AEs per treatment cycle was highest during cycle 1 and then decreased to the lowest incidence during cycle 6.

Serious adverse events and deaths
At the time of the data cut, 80/793 patients in the safety population (10%) had died. There were more deaths in the FC arm (47/396 [12%]) compared to the R-FC arm (33/397 [8%]). The most common

causes of death were infections (19 patients [5%] vs. 12 patients [3%]) and neoplasms (14 patients [4%] vs. 10 patients [3%], including CLL and related disorders). Five patients in the FC arm and three patients in the R-FC arm (approximately 1%) died due to a cardiac disorder. The underlying cause of death was considered to be progressive disease in 42 patients (25 [6.3%] in the FC arm and 17 [4.2%] in the R-FC arm). In these patients the investigator reported the (underlying) cause of death from infection or others causes to be CLL, CLL transformation, disease progression, neoplasm progression, acute myeloid leukaemia, metastases to the central nervous system, Hodgkin's disease, lymphoma, non-Hodgkin's lymphoma, or B-cell small lymphocytic leukaemia. Most of those patients whose death was related to progressive disease developed an infection and died (13 patients in the FC arm and eight in the R-FC arm).

Of the 38 patients who died due to causes not related to disease progression, eight FC patients and six R-FC patients died from infections. The most common infection adverse events resulting in death were sepsis (five patients in each arm, including bacterial sepsis, pulmonary sepsis and septic shock).

In 8/396 FC patients (2%) and 6/397 R-FC patients (2%), the investigator judged the death to be related to study treatment. However, one of these, died on study day 658 after starting second line therapy (R-CHOP). The investigator reported an AE of lung infection remotely related to (second line) treatment. With the exception of sepsis/septic shock (two patients in each arm), the treatment-related fatal events were single occurrences.

A total of 550 SAEs in 344 patients were reported across the two arms. A slightly higher incidence of serious adverse events was observed in the R-FC arm (46%) compared to the FC arm (41%). This difference was driven by more events in the following body systems: infections and infestations (15% in the FC arm vs. 18% in the R-FC arm), blood and lymphatic system disorders (11% vs. 17%), gastrointestinal disorders (2% vs. 4%) and immune system disorders (one patient vs. seven patients [2%]). In other body systems, no meaningful imbalance was evident.

Although blood and lymphatic system disorders were overall the most commonly reported grade 3 or 4 AEs in both arms), the majority of these events were not serious. In the FC arm, the overall incidence of grade 3 or 4 AEs reported in this system organ class was 41%, while the incidence of serious events was 11%. In the R-FC arm, 57% of patients experienced grade 3 or 4 blood and lymphatic system disorders, but only 17% had a serious event. The most common serious blood and lymphatic system event was febrile neutropenia (reported in 6% and 8% of patients in the FC arm and R-FC arm, respectively).

Most reported infection AEs, on the other hand, were considered serious. Seventeen percent of FC patients had a grade 3 or 4 infection during the study, and 15% had a serious infection. In the R-FC arm 73 patients (18%) had a grade 3 or 4 infection, and 71 patients (18%) had a serious infection. A total of 68 serious infection events were reported in the FC arm compared to 91 serious infection events in the R-FC arm. The difference between the treatment arms could not be attributed to a specific cluster of infections, but events were distributed across various groups of underlying agents, Other system organ classes where SAEs were reported with an at least 2 percentage points higher incidence in the R-FC arm compared to the FC arm included gastrointestinal disorders (2% in the FC arm vs. 4% in the R-FC arm) and immune system disorders (one patient vs. seven patients [2%]). The seven R-FC patients with immune system disorders experienced hypersensitivity (three patients), drug hypersensitivity (two patients), anaphylactic reaction and cytokine release syndrome (one patient each).

Laboratory findings

Overall, more patients in the R-FC group experienced blood and lymphatic system AEs. Consistent with this, the most common grade 3 and 4 haematological laboratory abnormalities reported were neutropenia (65% FC; 78% R-FC), lymphocytopenia (73% FC; 87% R-FC), and leukopenia (57% FC; 81% R-FC). However, thrombocytopenia (15% FC; 12% R-FC) was less frequent in the R-FC arm and anaemia was about the same in the two arms (10% FC, 12% R-FC). These findings are consistent with the incidence of grade 3 and 4 neutropenia and febrile neutropenia reported as AEs. However,

these cytopenias were not associated with an increase in grade 3 or 4 infections in the R-FC arm (18%) compared to the FC arm (17%).

The increased incidence of lymphopenia in the R-FC arm was entirely expected and related to the mechanism of action of rituximab – B-cell depletion, which is a desirable effect in patients with CLL. Leukopenia and neutropenia were also expected to be more frequent in the R-FC arm compared to the FC arm, since this is well recognized in patients treated with rituximab in combination with chemotherapy for NHL. The slight differences in incidence of anaemia and thrombocytopenia between the two arms are probably due to chance although the lower rate of thrombocytopenia in patients treated with R-FC could be related to improved disease control.

No significant changes in biochemistry parameters were detected in this study.

In both treatment arms, median levels of IgG and IgA at BL were above the lower limit of normal (7 g/L and 0.7 g/L, respectively) and remained so during and after treatment.
The median levels of IgM at baseline were slightly lower than normal in both arms (0.36 g/L for FC, 0.36 g/L for R-FC; LLN = 0.4 g/L) at BL. In the FC arm, the median IgM levels increased to above the LLN (0.4 g/L) during treatment, whereas in the R-FC arm median levels remained stable and slightly below the LLN.

Safety in special populations
Safety analyses were performed on subgroups based on patient age, creatinine clearance, Binet stage at BL, Cumulative Illness Rating Scale (CIRS) score at BL, and lymphocyte counts. As expected, the proportion of patients experiencing a grade 3 or 4 AE increased with age in both arms. As in the overall safety population, the incidence of grade 3 or 4 events was higher in the R-FC arm compared to the FC arm for all age categories. The proportion of patients experiencing at least one serious AE in the R-FC arm increased with age (from 43% for patients <65 years to 52% for those ≥65 to 70 years and 53% for those >70 years), whereas in the FC arm the proportion was approximately 40% in all age groups. Surprisingly, the incidence of SAEs of the blood and lymphatic system actually declined in the FC control arm with increasing age, so that the difference between the two arms appeared to become more marked with increasing age. This difference between treatment arms was mostly due to a higher rate of serious infections and serious blood and lymphatic system disorders in R-FC patients above 65 years of age. The rate of deaths from infections did not increase with age.

There was no relevant difference in the death rate in patient subgroups by age.

In Binet B and C patients, the rates of grade 3 or 4 AEs were higher in the R-FC arm compared to the FC arm. In both arms, the rate of grade 3 or 4 AEs slightly increased from patients with Binet stage B to those with Binet stage C (Binet B: 57% FC vs. 74% R-FC; Binet C: 71% FC vs. 83% R-FC), but the difference between the treatment arms remained stable.
The rate of SAEs increased with more advanced disease stage in the FC group, but not in the R-FC group, in which SAEs rates remained relatively constant across all subgroups according to Binet stage.
However, adequate information and possible restrictions and conditions has been requested to be put into the SPC section 5.1 with respect to treatment of Binet stage C patients.

Discontinuation due to AES
The proportion of patients who discontinued study treatment due to AEs was the same in both treatment arms (70 patients [18%] in the FC arm, 71 patients [18%] in the R-FC arm). Almost all of these events were of grade 3 or 4 intensity. Consistent with the overall pattern of adverse events, the most common AEs that led to treatment discontinuation were blood and lymphatic system disorders (10% vs. 12%), such as neutropenia (2% vs. 4%), thrombocytopenia (3% vs. 2%), leukopenia (< 1% vs. 2%) and related terms (two patients and three patients in the FC arm and R-FC arm, respectively, with events of neutrophil count decreased, white blood cell count/white blood cell count decreased or platelet count/platelet count decreased).

Risk Management Plan
The applicant has provided an adequate updated RMP covering the current and planned safety risk management activities for rituximab (MabThera®) in rheumatoid arthritis (RA), non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL).

Table 6 Summary of the EU Risk Management Plan

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
RA – identified risks		
(Serious) Infections	Routine + Pharmacoepidemiology studies	As described in section 4.4 of the SmPC: **4.4 Special warnings and precautions for use** Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active and/or severe infection (eg. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (eg. in hypogammaglobulinemia or 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 (see section 4.8). Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.
Acute Infusion Related Reactions	Routine + Pharmacoepidemiology studies	As described in sections 4.2 and 4.4 of the SmPC: **4.2 Posology and method of administration** Method of Administration Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. …
Impaired immunisation Response	Routine + Pharmacoepidemiology studies	
Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
RA – potential risks		
Infections (including serious viral and opportunistic infections)	Routine + Pharmacoepidemiology studies	As above

Malignancies	Routine + Pharmacoepidemiology studies	As described in section 4.4 of the SmPC: **4.4 Special warnings and precautions for use** Malignancy Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see section 4.8) 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.
Pregnancy/lactation	Routine + Pharmacoepidemiology studies	As described in section 4.6 of the SmPC: **4.6 Pregnancy and lactation** <u>Pregnancy</u> … Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy. … <u>Lactation</u> Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.
Impact on cardiovascular disease	Routine + Pharmacoepidemiology studies	As described in section 4.4 of the SmPC: **4.4 Special warnings and precautions for use** There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic 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.
Gastrointestinal perforation	Routine + Pharmacoepidemiology studies	GI perforations in patients treated in autoimmune indications will continue to be monitored by the MAH.
RA – missing information		
Immunogenicity and autoimmune disease	Routine	N/A

Acute infusion related reactions	Routine	As above
Infections	Routine	As above
Neutropenia	Routine + planned analysis of prolonged neutropenia in ML17102/CLL8 study	As described in section 4.4 of the SmPC **4.4 Special warnings and precautions for use** 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 (cyclophosphamide, vincristine, and prednisone) chemotherapy, regular full blood counts should be performed according to usual medical practice.
HBV reactivation	Routine + possible implementation of guidelines for screening trial patients at baseline	As described in section 4.4 of the SmPC: ***4.4 Special warnings and precautions for use*** *Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy.*
Tumour lysis syndrome	Routine + results of the BO17072/REACH study (expected 2009)	See Acute infusion related reactions recommendations above. Maintenance of adequate hydration and urine output are crucial in preventing TLS. Allopurinol and/or rasburicase are also recommended depending on the risk group. Patients at low-risk of TLS may require no additional treatment other than hydration. Those with intermediate risk require allopurinol with the addition of rasburicase if hyperuricaemia still develops. Vigorous hydration is recommended for all patients in the middle-to-high risk groups and for those with diagnosed TLS. Rasburicase is recommended for patients with hyperuricaemia associated with a diagnosis of TLS or in the initial management of high risk paediatric patients.
PML	Routine + continued expedited reporting of new cases/questionnaire used to better characterise all such reports (all indications).	Please refer to section 4.4 of the SmPC ***4.4 Special warnings and precautions for use*** *Progressive Multifocal Leukoencephalopathy* *Use of MabThera maybe associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. ..*
Serious viral infection	Routine	See Infections recommendations above
GI perforation	Routine	Routine: There are no known ways of preventing GI perforation in patients receiving rituximab for haematological malignancies.
Prolonged B cell depletion	Routine + results of PRIMA (MO18264) study (expected 2010 or 2011)	B Cell depletion is the expected therapeutic outcome with rituximab. Prolonged B-cell depletion/delayed B-cell recovery is currently not listed as a potential risk in the rituximab SmPC but detailed information on B-cell and

		immunoglobulin changes is provided.
Impaired immunisation response	Routine	As described in section 4.4 of the SmPC. ***4.4 Special warnings and precautions for use*** *The safety of immunization with any vaccine, particularly live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.*
Grade 3/4 and serious blood and lymphatic AEs in patients > 70 years with CLL	Routine + results of the BO17072/REACH study (expected 2009)	The SmPC already includes information on blood and bone marrow system disorders (without reference to age categories): ***4.4 Special warnings and precautions for use*** *Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/l and/or platelet counts < 75 x 10^9/l as clinical experience in this population is limited. MabThera has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.*
Opportunistic infections	Routine	See recommendations for infections above
AML/MDS	Routine	There are no known ways of reducing the risk of treatment-related secondary AML/MDS, other than by reducing exposure to chemotherapy and radiotherapy and/or by substituting a less DNA-damaging agent, if possible (e.g. substitution of ABVD for MOPP chemotherapy in Hodgkin's lymphoma
NHL/CLL – missing information		
Prolonged neutropenia	See neutropenia above	See neutropenia above
Prolonged B-cell depletion	See under potential risk above	See under potential risk above

The two ongoing studies in CLL patients evaluating the prolonged B-cell depletion should be added in a next RMP revision.

Apart from the changes resulting from the new indication in CLL additional risk minimisation measures related to the risk of Progressive Multifocal Leucoencephalopathy (PML) -such as a patient alert card- as recommended by the CHMP during the review of variation II/62 have been proposed. The MAH proposed to implement a patient alert card. The patient's and doctor's name as well as the dates of MabThera treatment can be listed and the card provides information regarding symptoms of PML. The MAH proposes to verify the success of this activity by monitoring the occurrence of PML through MAH's routine pharmacovigilance system.

Table 7 Patient Alert Card Text

MABTHERA in RA Patient Alert Card This alert card contains important safety information that you need to be aware of before you are given MABTHERA and during treatment with MABTHERA. • Show this card to any doctor involved in your treatment, not just your prescribing specialist physician **Infections** MABTHERA may increase the risk of getting infections. Prior to MABTHERA treatment • You should not be treated with MABTHERA if you have an active infection or serious problem with your immune system. • TELL YOUR DOCTOR IF YOU ARE TAKING OR HAVE PREVIOUSLY TAKEN MEDICINES WHICH MAY AFFECT YOUR IMMUNE SYSTEM, SUCH AS CHEMOTHERAPY OR IMMUNOSUPPRESSIVE AGENTS During or after treatment with MABTHERA If you develop symptoms suggestive of infections, such as fever, persistent cough, weight loss, or listlessness, seek medical attention immediately. Very rarely, some patients taking MabThera have had a serious brain infection called Progressive Multifocal leukoencephalopathy (PML) which has been fatal. Symptoms of PML include memory loss, trouble thinking, difficulty with walking and/or loss of vision. You should **tell your doctor immediately if you experience any of these symptoms.**	**Dates of MABTHERA Treatment**: Start: _____ Most recent: _____ • See the MABTHERA package leaflet for more information. • Please make sure you also have a list of all your other medicines with you at any visit to a health care professional. Patient's Name: _____ Doctor's Name: _____ Doctor's Phone: _____ • AS THE IMMUNOSUPRESSION CAUSED BY MABTHERA CAN LAST FOR SEVERAL MONTHS, SIDE EFFECTS MAY OCCUR EVEN AFTER YOU HAVE STOPPED TREATMENT. PLEASE THEREFORE KEEP THIS CARD WITH YOU FOR 24 MONTHS AFTER THE LAST DOSE OF MABTHERA,

BENEFIT RISK ASSESSMENT

The MAH has provided a large well-designed phase III clinical study comparing FC with FC+rituximab in a population of patients with CD20-positive B-CLL. A pre-planned interim analysis showed superior efficacy for the primary endpoint PFS demonstrated in favour of the rituximab containing combination. Overall survival benefit is rarely observed in CLL clinical trials, however a positive effect on OS was also been shown for the FC-R regimen. Thus the DSMB concluded that the interim analysis was adequate to provide sufficient evidence demonstrating the effect of the rituximab combination treatment
This clinical trial is itself sufficient documentation for clinical benefit and pivotal for approval of the extended indication for MabThera.

The median observation time of 20.7 months for the pivotal trial ML17102 is fairly short for a CLL population. Data from an additional 'snapshot' analysis (based on a clinical cut-off February 8, 2008) adding 4.8 months to the median observation time show persistence of the efficacy in terms of PFS and OS. The applicant has committed to provide annual updates for the primary endpoint of study ML17072, progression-free survival (PFS), and for the secondary endpoint overall survival (OS) in the 4th quarter of 2009 and in the 4th quarter of 2010 which is considered appropriate.

Subgroup analyses on the primary endpoint of Binet stages demonstrate benefit in all stages, however, the outcome in patients with Binet stage C did not reach statistical significance and the clinical benefit was less compared to stage B (Stage B: unadjusted HR 0.45, 95% CI [0.32; 0.63]; Stage C: unadjusted HR 0.88, 95% CI [0.58;1.33]) The study was not powered to show significant differences in subgroups. Of note, in this subgroup, there was a higher proportion of patients (difference of 8-13% between the two arms) with unfavorable prognostic biomarkers such as unmutated IgVH and ZAP70-positivity in the R-FC arm than in the FC arm. However, adequate information was included into the SPC section 5.1.

Similar positive benefits were seen for rituximab added to a range of other cytotoxic chemotherapy regimens in patients with CLL. These data were mainly presented as publications but in the CHMP opinion is sufficient evidence to support the broad indication "***MabThera is indicated for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.***"

Overall, the risks of rituximab in CLL patients were comparable to known safety profiles of rituximab used in approved indications in combination with other cytotoxic chemotherapy regimens and marketed experience for more than 10 years. In particular, higher incidences of neutropenia, leukopenia, febrile neutropenia and pancytopenia were also seen in patients treated with rituximab for NHL. There were no new safety signals observed in both the pivotal trial and the supportive studies. The addition of rituximab did not increase the rate of treatment discontinuations or the incidence of treatment related deaths compared to FC alone.
There are no safety concerns against an approval of the extended indication.

Based on the data from three large randomized trials, FC chemotherapy is now considered by many CLL study groups worldwide as a standard treatment for previously untreated patients with CLL who can tolerate this regimen. In this application the MAH has demonstrated significant improvement of this standard therapy by adding rituximab to chemotherapy in terms of a clinically important prolongation of PFS, improved overall response rate and a trend towards improved survival. The benefit has been obtained without increased toxicity except from the expected rituximab-related side effects consisting mainly of infusion-related events.

In conclusion the overall Benefit /Risk of MabThera as an add-on to chemotherapy for the first-line therapy of patients with CD-20 positive B-cell chronic lymphocytic leukaemia is positive.

A prolonged follow-up for survival is of major clinical interest and is requested to be provided by the MAH as part of the follow-up measures.