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SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Assessment Report
For
MabThera
(rituximab)

Procedure No.: EMEA/H/C/000165/II/0069

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

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1. Scientific discussion

1.1 Introduction

Follicular lymphoma is generally a slow-growing form of non-Hodgkin's lymphoma (NHL) involving mature B lymphocytes, accounting for 11%–22% of all lymphoid malignancies and around 70% of indolent lymphomas. In Europe, there are around 74 800 new cases of NHL (all types) each year, including around 16 500 new cases of follicular lymphoma. The incidence of follicular lymphoma increases with age and it very rarely occurs in children**.** Most patients are over 50 years old, and the median age at diagnosis is 60 years. Men and women are about equally affected. Most patients (> 80%) with follicular lymphoma have widespread disease at diagnosis (Ann Arbor stage III/IV), including involvement of peripheral and central (abdominal and thoracic) lymph nodes and spleen. The bone marrow is involved in 50%-60% of patients. The disease is heterogeneous, and a number of prognostic factors have been identified, some of which are included in the widely used Follicular Lymphoma International Prognostic Index (FLIPI).
Follicular lymphoma generally follows an indolent course, although the majority of patients die of lymphoma after a series of relapses and remissions of decreasing duration. Although follicular lymphoma is usually very responsive to initial chemotherapy, the disease typically becomes increasingly resistant to cytotoxic agents. Around 30% of follicular lymphomas may eventually transform to intermediate or high-grade lymphomas, which are clinically more aggressive and have a poor outcome. Patients are also at risk of developing therapy related secondary malignancies, such as myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). The risk increases with time and depends on the number, intensity, and type of previous cytotoxic treatments. Overall, the 2-year survival rate of patients with follicular lymphoma is about 90%. Median survival has improved in recent years from around 6–10 years at the end of the 1990s to >10 years and as high as 18 years in one recent series.

Treatment options for patients with follicular lymphoma include ''watch and wait'', radiotherapy, and systemic treatments. Radiotherapy is the mainstay of treatment for patients with stage I/II disease, and in a subset of these patients this may sometimes be curative. Since the natural course of the disease is heterogeneous and spontaneous regressions may occur, initiation of chemotherapy is only recommended for patients with symptoms, haematopoietic impairment, bulky disease, or rapid lymphoma progression.

Chemotherapy and immunotherapy (with interferon-alpha [IFN-α] or rituximab) have both been evaluated as maintenance therapy in patients with follicular lymphoma. Rituximab is licensed in the EU as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction with chemotherapy, with or without rituximab.

MabThera (rituximab) is a chimeric murine/human monoclonal antibody that binds to CD20, a hydrophobic transmembrane protein which is present on the cell surface of pre-B- and mature B-lymphocytes, but not on hematopoietic stem cells, pro–B–cells, normal plasma cells or other normal tissues. Importantly, CD20 is present on the malignant B-cells in most patients with mature B-cell lymphomas and leukemias. Rituximab binds to CD20 on these cells and leads to their elimination via a number of different mechanisms, including antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and apoptosis.
Rituximab is administered by intravenous infusion.

Rituximab is currently approved in the EU for the following indications:
Non-Hodgkin's lymphoma
in combination with chemotherapy for the treatment of previously untreated patients with stage III–IV follicular lymphoma;
as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab;
for the treatment of patients with stage III–IV follicular lymphoma who are chemo resistant or are in their second or subsequent relapse after chemotherapy;
for the treatment of patients with CD20-positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.
Chronic lymphocytic leukaemia
in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and

safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy (further information is provided in section 5.1 of the EU SmPC).
Rheumatoid arthritis
in combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies.

This variation concerns an application for extension of the approved indications to include use of Mabthera as maintenance therapy in follicular lymphoma patients responding to induction therapy.

1.2 Clinical aspects

GCP
The MAH states that the PRIMA study was conducted in full conformance with the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the patient. The study adhered fully to the principles outlined in the "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with the local law, if it afforded greater protection to the patient.

Clinical efficacy
Main study
PRIMA study
The PRIMA study was a randomised (1:1), multicentre/multinational, open-label, comparative, parallel group, two-arm study comparing rituximab maintenance with observation, in patients with previously untreated follicular lymphoma who responded to induction therapy with a rituximab-based chemoimmunotherapy regimen [R-CHOP (rituximab- cyclophosphamide, doxorubicin, vincristine and prednisone, R-CVP (rituximab-cyclophosphamide, vincristine and prednisone) or R-FCM (rituximab-fludarabine, cyclophosphamide and mitoxantrone)].

METHODS

Study Participants
To be eligible for the study, patients had to have histologically-confirmed grade 1, 2 or 3a follicular lymphoma according to National Cancer Institute-Working Group (NCI-WG) criteria, and high tumour burden according to Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria, indicating a need to initiate treatment. Patients with high grade (3b) or transformed lymphomas or with central nervous system (CNS) involvement were not eligible.

Inclusion criteria, induction phase
• Histologically confirmed follicular lymphoma grade 1, 2, or 3a, with a lymph node biopsy performed within four months before study entry and with material available for central review.
• Patients with previously untreated follicular lymphoma (those on 'watch-and-wait' could enter the trial if a recent biopsy [obtained within the last four months] was available).
• Patients with at least one of the following high-tumour-burden GELF criteria requiring initiation of treatment:
– bulky disease defined as a nodal or extranodal (except spleen) mass > 7 cm in its greater diameter
– B symptoms
– elevated serum lactate dehydrogenase (LDH) or β2-microglobulin
– involvement of at least three nodal sites (each with a diameter greater than 3 cm)
– symptomatic splenic enlargement
– compressive syndrome
– pleural/peritoneal effusion.
• Age must be 18 years or over.
• Performance status ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale.
• Adequate haematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to registration, including haemoglobin ≥ 8.0 g/dL (5.0 mmol/L), absolute neutrophil count ≥ 1.5×109/L, and platelet count ≥ 100×109/L.
• Women: no breast-feeding, using effective contraception, not pregnant, and agreed not to become pregnant during participation in the trial and for 12 months thereafter. Men: agreed not to father a child during participation in the trial and for 12 months hereafter.
• Signed informed consent.

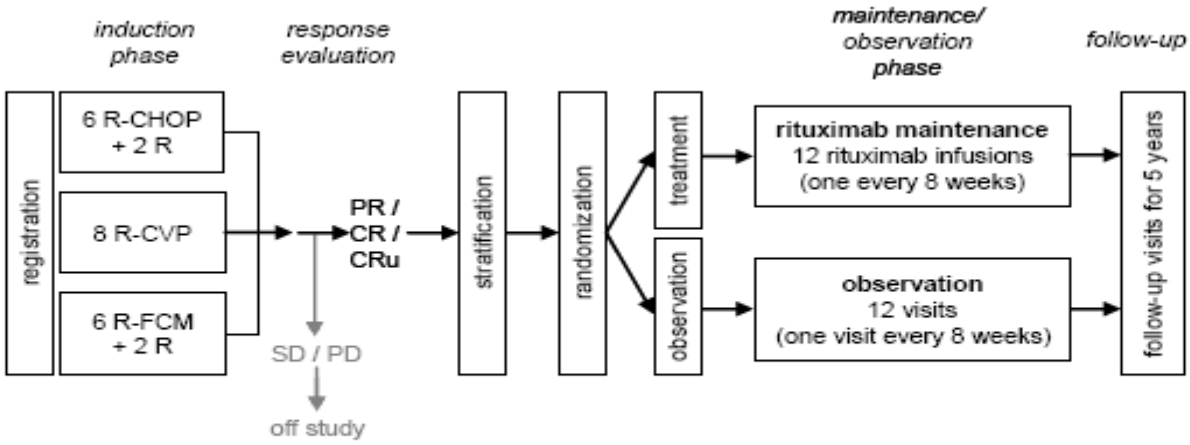
Inclusion criteria, maintenance/observation phase
To enter the maintenance/observation phase, patients had to meet the following criteria:
• Patients must have achieved a partial response (PR) or complete response/unconfirmed complete response (CR/CRu) at the end of induction treatment.
• All indicator lesions reported on the on-study form must have been re-evaluated.

Exclusion criteria, induction phase
Patients that met any of the following criteria were excluded from study entry:
• Transformation to high-grade lymphoma (secondary to 'low-grade' follicular lymphoma).
• Grade 3b follicular lymphoma.
• Presence or history of CNS disease (either CNS lymphoma or lymphomatous meningitis).
• Patients regularly taking corticosteroids during the four weeks prior to study entry, unless administered at a dose equivalent to ≤ 20 mg/day prednisone over that time.
• Patients with prior or concomitant malignancies except non-melanoma skin cancer or adequately treated in situ cervical cancer.
• Major surgery (excluding lymph node biopsy) within 28 days prior to registration.
• Poor renal function: serum creatinine > 2.0 mg/dL (197 µmol/L).
• Poor hepatic function: total bilirubin > 2.0 mg/dL (34 µmol/L), aspartate aminotransferase (AST) > 3 × Upper Limit Normal (ULN), unless these abnormalities were related to lymphoma.
• Known HIV infection or active hepatitis B or C infection within 28 days prior to registration. Testing for hepatitis B was not mandatory but recommended for all patients considered at high risk of infection and in endemic areas. Patients with any serological evidence of current or past hepatitis B exposure were excluded unless the findings were clearly due to vaccination.
• Serious underlying medical conditions that could impair the patient's ability to participate in the trial (eg, ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, or active autoimmune disease).
• Life expectancy of less than six months.
• Known sensitivity or allergy to murine products.
• Treatment within a clinical trial within 30 days prior to study entry.
• Any other co-existing medical or psychological condition that would preclude the patient's participation in the study or compromise their ability to give informed consent.
• Adult patients under tutelage (not competent to sign the informed consent form).

Exclusion criteria, maintenance/observation phase
Patients were excluded from the maintenance/observation phase of the study if they met any of the following criteria:
• Patients who had serious underlying medical conditions that could impair their ability to participate in the trial (eg, ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, or active autoimmune disease).
• Patients who could not complete all cycles of induction treatment due to toxicity or had not completed at least four cycles of R-CHOP + 2R, six cycles of R-CVP, or four cycles of R-FCM induction treatment.
• Patients who had a delay in treatment of more than 14 days following any cycle of induction chemotherapy.

Treatments
The study had two treatment phases:
Induction phase:
During the (non-randomised) induction phase, patients with advanced follicular lymphoma were evaluated for response to one of three possible induction regimens, R-CHOP, R-CVP, or R-FCM. Most patients (75%) received R-CHOP induction therapy. As the three induction regimens differed in the number of immunochemotherapy cycles usually administered for patients with follicular lymphoma (8 cycles of R-CVP, 6 cycles of R-CHOP, and 6 cycles of R-FCM), two additional infusions of rituximab (375 mg/m2) were added to the standard R-CHOP and R-FCM regimens for the PRIMA study. As a result, each patient in the induction phase would receive the same number of rituximab infusions (eight) prior to randomisation in the maintenance/observation phase, and the scheduled treatment phase would be 24 weeks for all three regimens.
Maintenance/observation phase:
Patients who responded to induction treatment with a CR/CRu or PR were randomised to receive either rituximab maintenance therapy (one dose of 375 mg/m^2 every eight weeks for two years, i.e., a total of 12 doses) or observation (no further treatment, one visit every 8 weeks, a total of 12 visits). All randomised patients were to be treated/observed for two years and then followed up for five years. The trial design is shown in Figure 1.

Figure 1. Trial design



R: rituximab; CVP: cyclophosphamide, vincristine, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; FCM: fludarabine, cyclophosphamide, and mitoxantrone. SD: stable disease; PD: progressive disease; PR: partial response; CR(u): complete response (unconfirmed).

Objectives
The primary objective of the PRIMA study was to evaluate the benefit of maintenance therapy with rituximab on progression-free survival (PFS) compared to no maintenance therapy (observation) after induction of response with chemotherapy plus rituximab in patients with high tumour-burden follicular lymphoma.

The secondary objectives were as follows:
To evaluate event-free survival (EFS), 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 (QoL) for three different chemotherapy regimens combined with rituximab, with or without maintenance rituximab, for first line treatment of high tumour burden follicular lymphoma.
To assess safety of rituximab maintenance therapy over 2 years as measured by the incidence of toxicity.

Outcomes/endpoints
The primary endpoint was PFS, defined as the time from randomisation to first documented disease progression, relapse, or death from any cause as evaluated by the investigator and by an Independent Review Committee (IRC).
Secondary endpoints were EFS (the time from randomisation to first documented progression, relapse, initiation of a new anti-lymphoma treatment or death from any cause), OS (the time from randomisation to death, regardless of cause), TTNLT [time from randomisation to first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy, radio immunotherapy, immunotherapy)], TTNCT (time from randomisation to first documented administration of new chemotherapy or new cytotoxic agent), response rates at the end of maintenance treatment, transformation rate at first relapse, QoL and overall safety.

Sample size
The primary endpoint of PFS was used to determine the final sample size of the study. To demonstrate a 45% increase in median PFS from the time of randomisation (six months after the start of induction therapy), for example, from 37.2 months to 54 months, 900 patients were required to be randomised in the maintenance/observation period. With an estimated response rate to induction immunochemotherapy of 75%, 1200 patients would need to be recruited in the induction period to ensure that 900 patients entered the maintenance/observation phase.
The sample size calculation was based on the following assumptions:
• Overall alpha = 5%
• Power = 80%
• 1:1 randomisation between the treatment arms
• A monthly hazard rate of 0.0186 in the observation group corresponding to a median PFS of 37.2 months

• A monthly hazard rate of 0.0186 within the first six months after randomisation (to mimic a possible lag in treatment effect) and 0.0121 thereafter for the maintenance arm (corresponding to a median PFS of 54 months)
• 900 patients would be randomised within 24 months (23 patients per month within the first 16 months, and 53 patients thereafter)
• One interim analysis would be performed after 75% of the total number of required PFS events. The alpha-spending function using the O'Brien–Fleming boundary was applied to maintain the overall two-sided Type I error of 0.05.

Randomisation
Patients who achieved a CR/CRu or PR after induction treatment and also fulfilled all other eligibility criteria were randomised in the maintenance/observation phase of the study. A stratified block randomisation procedure (block size: four) was used. Randomisation was stratified by induction regimen (R-CHOP, R-CVP, R-FCM), by response (CR/CRu, PR), by region GELA sites, Europe non-GELA, South America, Asia, Australia/New Zealand), and by centre (in countries other than France and Belgium, the country was considered as a single centre). Patients were allocated in a ratio of 1:1 to receive rituximab maintenance or no treatment (observation).

Blinding
The pivotal study was an open-label study.

Statistical methods
Four analysis populations were defined:
- Induction analysis population (IAP): all patients who received at least one component of the planned induction treatment regimen (R-CVP, R-CHOP, R-FCM).
- Maintenance intent-to-treat population (MITT): all randomised patients regardless of whether they received study treatment or not were included in this analysis population according to the maintenance therapy that they were randomised to receive.
- Maintenance per protocol population (PPP): all randomised patients who received at least six courses of maintenance treatment or completed at least six observation visits or who terminated treatment/observation because of progression or death and adhered to the protocol.
- Maintenance safety population (MSAP): all patients who received at least one dose of maintenance trial treatment/attended at least one observation visit and had at least one safety follow-up, whether withdrawn prematurely or not.

The statistical analysis for the primary and secondary endpoints are summarised in table 1:

Table 1. Statistical analysis of the primary and secondary endpoints

Endpoint[a]	Test	Stratification[b]/Adjustment[c]
Primary		
PFS (investigator and IRC assessments)	two-sided log-rank Cox regression	induction therapy, response to induction therapy[b]; non-stratified (sensitivity) adjusted for treatment effect and prognostic factors[c]
Secondary		
EFS, OS, TTNLT, TTNCT	two-sided log-rank Cox regression (OS only)	induction therapy, response to induction therapy[b] non-stratified (sensitivity) adjusted for treatment effect and prognostic factors[c]
response rate at end of maintenance/observation; transformation rate 1st relapse	χ^2 logistic regression (response rate only)	– prognostic factors[c] (exploratory)
quality of life (FACT-G and QLQ-C30 total score)	Cronbach's alpha ANCOVA[d]	– adjusted for baseline (ie, QoL total score at the end of induction treatment)

a. Details of all analyses are provided in the study DRAM

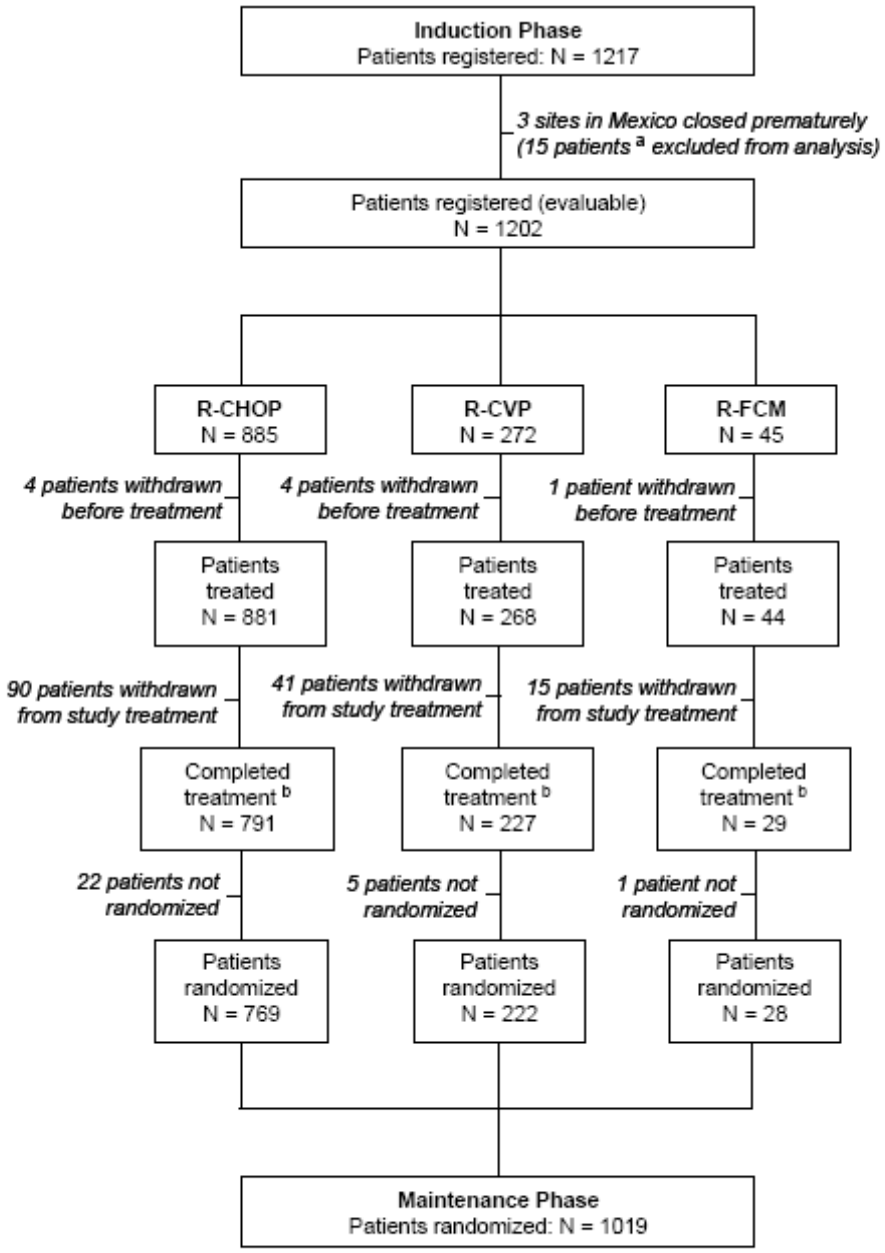
b. Induction therapy: R-CHOP, R-CVP, R-FCM; Response to induction therapy: CR/CRu or PR.
c. Prognostic factors: age, gender, FLIPI score, induction therapy, response to induction therapy.
d. ANCOVA: analysis of covariance.

RESULTS

Participant flow

The patient disposition in the induction and in the maintenance phase is presented in Figures 2 and 3 respectively.

Figure 2. Patient disposition in the induction phase

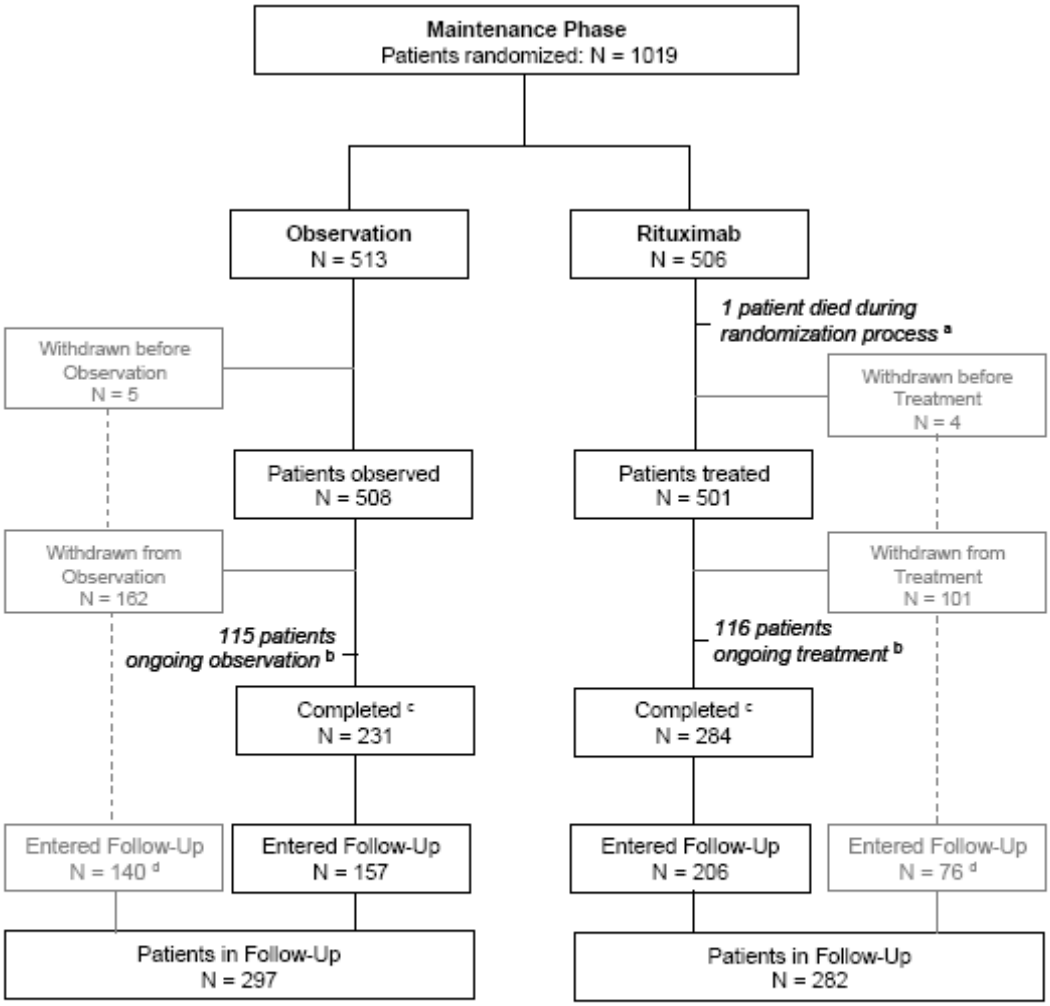


a Eleven of the 15 patients were randomized in the maintenance/observation phase (five to the observation arm, six to the rituximab arm) before the centers were closed.
b Defined as patients not withdrawn before completion of induction treatment and evaluated after completing induction treatment.

Of the 1202 patients registered, 1193 received a first course of induction treatment and are included in the induction analysis population (IAP). Nine patients withdrew from the study after registration but prior to receiving treatment and were excluded from the IAP. Of the 1193 patients treated, 1114

patients completed all eight cycles of induction treatment (ie, 6 R-CHOP + 2R, 8 R-CVP, or 6 R-FCM + 2R), with each additional rituximab injection for the R-CHOP and R-FCM regimens considered as a cycle. The proportion of patients completing eight cycles was over 95% in the R-CHOP group, about 90% in the R-CVP group, and 75% in the R-FCM group.

Figure 3. Patient disposition in the maintenance phase



a Patient 10164/1012 died one day before the date of randomization.
b At the time of clinical cut-off (January 14, 2009).
c Completed is defined as patients not withdrawn before completion of maintenance treatment/ observation and evaluated at end of treatment/observation.
d Includes one patient ongoing observation/two patients ongoing treatment entering follow-up.

A total of 1019 patients at 208 centres were randomised in the maintenance/observation phase of the PRIMA study: 506 patients were randomised to receive rituximab maintenance therapy, and 513 patients were randomised to the observation arm. The first patient was randomised on 5 July 2005, and the last patient was randomised on 22 November 2007.

Recruitment
A total of 1217 patients were enrolled in the PRIMA trial over a period of 29 months: the first patient was registered on 24 December 2004 and the last patient was registered on 11 April 2007. Three participating sites in Mexico were closed prematurely because of compliance issues and it was agreed by the Data and Safety Monitoring Committee (DSMC) that data for the 15 patients registered at those sites should be excluded from the main statistical analyses.

A total of 1202 patients were enrolled in the PRIMA trial from 220 centres in 24 countries, excluding the Mexican sites. France was the major recruiting country, enrolling over 50% of patients in the study.

The number of patients and centres (in parentheses) per country is: France 624 (74), Australia 132 (27), Belgium 75 (17), Spain 54 (19), Denmark 48 (9), Czech Republic 36 (9), New Zealand 26 (4), Finland 24 (4), The Netherlands 18 (10), Thailand 18 (3), UK 16 (9), Portugal 16 (1), Argentina 15 (4), India 14 (3), Brazil 13 (5), Colombia 11 (2), Peru 10 (2), Israel 9 (3), Serbia 9 (3), Venezuela 9 (1), China 8 (4), Turkey 7 (4), Croatia 7 (1), and Uruguay 3 (2).

Conduct of the study
Five amendments were made to the PRIMA study protocol. Key features of these amendments are described below:

• Amendment 1 (Protocol Version 3.1), dated 24 August 2005: This amendment applied to patients enrolled at French study sites only. It scheduled monitoring of serum immunoglobulins (IgG, IgA, and IgM) as well as levels of circulating B-cells (CD19-positive), T-cells (CD3-positive), and natural killer cells (CD16- or CD56-positive) every six months for three years after randomisation or until recovery to baseline if not reached by this time. Measurement of anti-tetanus toxoid antibodies was also scheduled at baseline, at the end of the induction phase, and at the end of the maintenance/observation phase.

• Amendment 2 (Protocol Version 3.2), dated 14 February 2006: This amendment increased the target enrolment from 640 patients (with 480 to be randomised in the maintenance/observation phase) to 900 patients (with 675 to be randomised in the maintenance/observation phase) to allow for more informative subgroup analyses within each induction immunochemotherapy group.

• Amendment 3 (Protocol Version 4.0), dated 16 August 2006: This amendment modified the primary endpoint of the study from EFS to PFS and increased the total number of study patients from 900 to 1200. The number of PFS events required for the final analysis was also modified, partly to account for a possible six-month lag inrituximab treatment benefit following randomisation. In line with these changes, the number of PFS events that would trigger interim efficacy analyses was also increased (from 100 and 150 events for the first and second interim analyses, respectively, to 172 and 258 events). The amendment also removed rituximab plus mitoxantrone, chlorambucil, and prednisone as a potential induction immunochemotherapy regimen (no patients had been treated with this induction regimen at the time), stipulated the minimum induction treatment required for randomisation, increased the duration of follow-up after completion of the maintenance/observation phase from three to five years, and introduced an independent, blinded review of lymphoma response and progression.

• Amendment 4 (Protocol Version 5.0), dated 22 February 2008: This amendment removed the first preplanned analysis which was scheduled to take place after 50% of events. This change was made following a recommendation by the DSMC who pointed out that at the expected time of the first interim analysis there would be limited follow-up of patients and a large proportion of patients would still be on active treatment. Therefore, regardless of the results of that first interim analysis, a recommendation to stop the study early would be highly unlikely since the results would be considered immature and would require confirmation with longer follow-up. Accordingly, the protocol was amended to include only one interim analysis after 75% of events occurred. The guidelines for completing and reporting serious adverse events (SAEs) were clarified to make it explicit that SAEs on both maintenance and observation arms were reportable. Prior to this amendment, SAE reporting in the observation arm was not clearly specified in the protocol. However, investigators and monitors were instructed to treat both arms equally with respect to the reporting of SAEs and the case report form gave the same instructions for both arms. The oversight in the protocol wording was corrected as part of this amendment.

• Amendment 5 (Protocol Version 5.1), dated 4 December 2008: (administrative change only).

Baseline data
Demographic and baseline disease characteristics of the patients in the pivotal study are presented in table 2.

Table 2.Summary of Demographic and Baseline Disease Characteristics at Registration (MITT)

	OBSERVATION N = 513	RITUXIMAB N = 505	TOTAL N = 1018
Sex			
MALE	263 (51%)	270 (53%)	533 (52%)
FEMALE	250 (49%)	235 (47%)	485 (48%)
n	513	505	1018
Age (years) At Registration			
Mean	54.9	56.0	55.5
SD	12.07	11.12	11.62
SEM	0.53	0.49	0.36
Median	55.0	57.0	56.0
Min-Max	22 - 84	26 - 79	22 - 84
n	513	505	1018
Bone Marrow Involvement			
INVOLVED	285 (56%)	275 (54%)	560 (55%)
NOT DONE	9 (2%)	5 (<1%)	14 (1%)
NOT INVOLVED	213 (42%)	217 (43%)	430 (42%)
UNSPECIFIED	6 (1%)	8 (2%)	14 (1%)
n	513	505	1018
Extra-Nodal Involvement			
<2 Extra-Nodal Sites	277 (54%)	290 (57%)	567 (56%)
>=2 Extra-Nodal Sites	236 (46%)	215 (43%)	451 (44%)
n	513	505	1018
ECOG			
0	341 (66%)	324 (64%)	665 (65%)
1	155 (30%)	162 (32%)	317 (31%)
2	17 (3%)	19 (4%)	36 (4%)
n	513	505	1018
Ann Arbor Stage			
I	7 (1%)	15 (3%)	22 (2%)
II	47 (9%)	31 (6%)	78 (8%)
III	97 (19%)	105 (21%)	202 (20%)
IV	362 (71%)	354 (70%)	716 (70%)
n	513	505	1018
FLIPI as reported on the CRF			
0	26 (5%)	17 (3%)	43 (4%)
1	84 (16%)	89 (18%)	173 (17%)
2	187 (36%)	183 (36%)	370 (36%)
3	151 (29%)	129 (26%)	280 (28%)
4	58 (11%)	72 (14%)	130 (13%)
5	7 (1%)	14 (3%)	21 (2%)
n	513	504	1017

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics.

The disease characteristics at randomisation to maintenance/observation (MITT) are presented in table 3.

Table 3. Summary of Baseline Disease Characteristics at Randomisation to Maintenance/Observation (MITT)

	OBSERVATION N = 513	RITUXIMAB N = 505	TOTAL N = 1018
Bone Marrow Involvement			
INVOLVED	29 (6%)	25 (5%)	54 (5%)
NOT DONE	233 (45%)	223 (44%)	456 (45%)
NOT INVOLVED	245 (48%)	249 (49%)	494 (49%)
UNSPECIFIED	6 (1%)	8 (2%)	14 (1%)
n	513	505	1018
B Symptoms			
NO	487 (99%)	477 (99%)	964 (99%)
YES	4 (<1%)	4 (<1%)	8 (<1%)
n	491	481	972
ECOG			
0	430 (84%)	403 (80%)	833 (82%)
1	71 (14%)	93 (19%)	164 (16%)
2	7 (1%)	5 (<1%)	12 (1%)
3	1 (<1%)	-	1 (<1%)
n	509	501	1010
Induction Treatment Received			
R-CHOP	386 (75%)	382 (76%)	768 (75%)
R-CVP	113 (22%)	109 (22%)	222 (22%)
R-FCM	14 (3%)	14 (3%)	28 (3%)
n	513	505	1018
Response At End Of Induction			
COMPLETE RESPONSE	195 (38%)	204 (40%)	399 (39%)
NOT EVALUATED	-	2 (<1%)	2 (<1%)
PARTIAL RESPONSE	151 (29%)	139 (28%)	290 (28%)
STABLE DISEASE	1 (<1%)	4 (<1%)	5 (<1%)
UNCONFIRMED COMPLETE RESPONSE	166 (32%)	156 (31%)	322 (32%)
n	513	505	1018

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics.

Numbers analysed

The primary population for the efficacy analyses was the MITT population comprising all patients who completed the randomisation process. The MITT population comprised 1018 patients: 513 patients in the observation arm and 505 patients in the rituximab arm. Based on all patients randomised, 5 patients in each arm were excluded from the MSAP as they did not receive study drug or did not attend an observation visit, respectively, after randomisation.

A total of 844 patients were included in the PPP. A higher proportion of patients in the observation arm (103 patients, 20%) than in the rituximab arm (72 patients, 14%) were excluded from the PPP. The main reason for this difference was inadequate maintenance treatment/observation visits (47 patients in the observation arm vs 11 patients in the rituximab arm).

Table 4. Overview of maintenance analysis population and reasons for exclusion (All patients randomised N=1019)

	Observation	Rituximab	Total
No. of Patients Randomized	513	506	1019
No. Included in MITT	513	505	1018
No. Excluded from MITT	0	1	1
Death before randomized	0	1	1
No. Included in MSAP	508	501	1009
No. Excluded from MSAP	5	5	10
No study drug received during the maintenance phase	5	5	10
Death before randomized	0	1	1
No. Included in PPP	410	434	844
No. Excluded from PPP	103	72	175
Inadequate diagnosis of follicular lymphoma	47	34	81
Inadequate maintenance treatment (except for early progression or death)	47	11	58
Inadequate disease assessment	16	24	40
Inadequate indicator lesions assessment at end of induction	7	4	11
Inadequate study treatment received with study randomized treatment	5	5	10
Inadequate response at end of induction	1	6	7
Death before randomized	0	1	1
Inadequate induction treatment	0	1	1

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Death before randomized corresponds to death during the randomization process.
Note: Inadequate diagnosis of FL refers to a diagnosis other than follicular lymphoma of grade 1, 2, or 3a, FL of undetermined grade, or FL with diffuse area.

Outcomes and estimation

The table 5 below presents the overview of the efficacy parameters.

Table 5. Overview of efficacy parameters (MITT)

Efficacy Parameter	Observation N = 513	Rituximab N = 505	HR / OR	p-value*
Primary Endpoint: PFS				
Investigator-Assessed PFS (Section 4.2.1.1) Median time to event 25th percentile One-year PFS rate [95% CI]	NE 507 days (16.7 months) 0.82 [0.79;0.85]	NE 1096 days (36.0 months) 0.89 [0.87;0.92]	HR = 0.50 [0.39;0.64]	p < 0.0001
IRC-Assessed PFS (Section 4.2.1.2) Median time to event 25th percentile One-year PFS rate [95% CI]	939 days (30.9 months) 458 days (15.0 months) 0.81 [0.78;0.85]	1130 days (37.1 months) 804 days (26.4 months) 0.87 [0.84;0.90]	HR = 0.54 [0.42;0.70]	p < 0.0001
Secondary Endpoints				
Event-free Survival (Section 4.2.2.1) Median time to event 25th percentile One-year event-free rate [95% CI]	1150 days (37.8 months) 496 days (16.3 months) 0.81 [0.78;0.84]	NE 890 days (29.2 months) 0.89 [0.86;0.92]	HR = 0.54 [0.43;0.69]	p < 0.0001
Overall Survival (Section 4.2.2.2) Median time to event 25th percentile One-year event-free rate [95% CI]	NE NE 0.99 [0.98;1.00]	NE NE 0.99 [0.98;1.00]	HR = 0.89 [0.45;1.74]	p = 0.7246
Time to Next Anti-Lymphoma Treatment (Section 4.2.2.3) Median time to event 25th percentile One-year event-free rate [95% CI]	NE 746 days (24.5 months) 0.89 [0.87;0.92]	NE 1135 days (37.3 months) 0.92 [0.89;0.94]	HR = 0.61 [0.46;0.80]	p = 0.0003
Time to Next Chemotherapy Treatment (Section 4.2.2.4) Median time to event 25th percentile One-year event-free rate [95% CI]	NE 884 days (29.0 months) 0.91 [0.89;0.94]	NE 1135 days (37.3 months) 0.92 [0.90;0.95]	HR = 0.60 [0.44;0.82]	p = 0.0011

Efficacy Parameter (Cont.)	Observation N = 513	Rituximab N = 505	HR / OR	p-value*
Secondary Endpoints (Cont.)				
Overall Response Rate at End of Maintenance/Observation (Section 4.2.2.6)				
N excluding patients still ongoing maintenance	N = 398	N = 389		
Responders (CR, CRu, PR)	219 (55%)	288 (74%)	Diff.: 19.01 [12.3;25.7]	p < 0.0001
Non-responders	179 (45%)	101 (26%)	OR = 2.33 [1.73;3.15]	
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%)		
progressive disease (PD)	162 (40.7%)	79 (20.3%)		
Transformation Rate at First Progression (Section 4.2.2.7)				
Patients with progression	173	91		
Transformation	19 (3.7%)	11 (2.2%)	Diff.: -1.53 [-3.7;0.6]	p = 0.1502
No transformation (no progression or missing)	494 (96.3%)	494 (97.8%)	OR = 0.58 [0.27;1.23]	

HR: hazard ratio; OR: odds ratio; Diff.: difference in rates; NE: not estimable.
* p-values and hazard ratios were calculated using the stratified log-rank test and stratified Cox regression for time-to-event endpoints, respectively. Stratification factors were induction treatment received and response to induction treatment. p-values for response rate were calculated using the χ_2 test, and odds ratios were calculated by using logistic regression (response rate analyses were unadjusted).

Primary Efficacy Endpoint: Progression Free Survival (PFS)

At the time of the analysis (clinical cut-off date 14 January 2009), the median duration of follow-up was 25 months. At the time of the analysis, 174/513 patients in the observation arm and 93/505 patients in the rituximab arm (33.9% vs 18.4%) had experienced a progression event (i.e., disease progression/relapse or death) since randomisation (Table 6). Maintenance therapy with rituximab in patients responding to induction therapy reduced the risk of experiencing a progression event by 50% compared with no further treatment (stratified HR 0.50, 95% CI [0.39;0.64], p < 0.0001). The Kaplan-Meier estimated median PFS times could not be calculated for either arm, however, the 25th percentile times were calculated as 507 days (16.7 months) for patients on observation and 1096 days (36 months) for patients on rituximab maintenance (p < 0.0001, log-rank test).

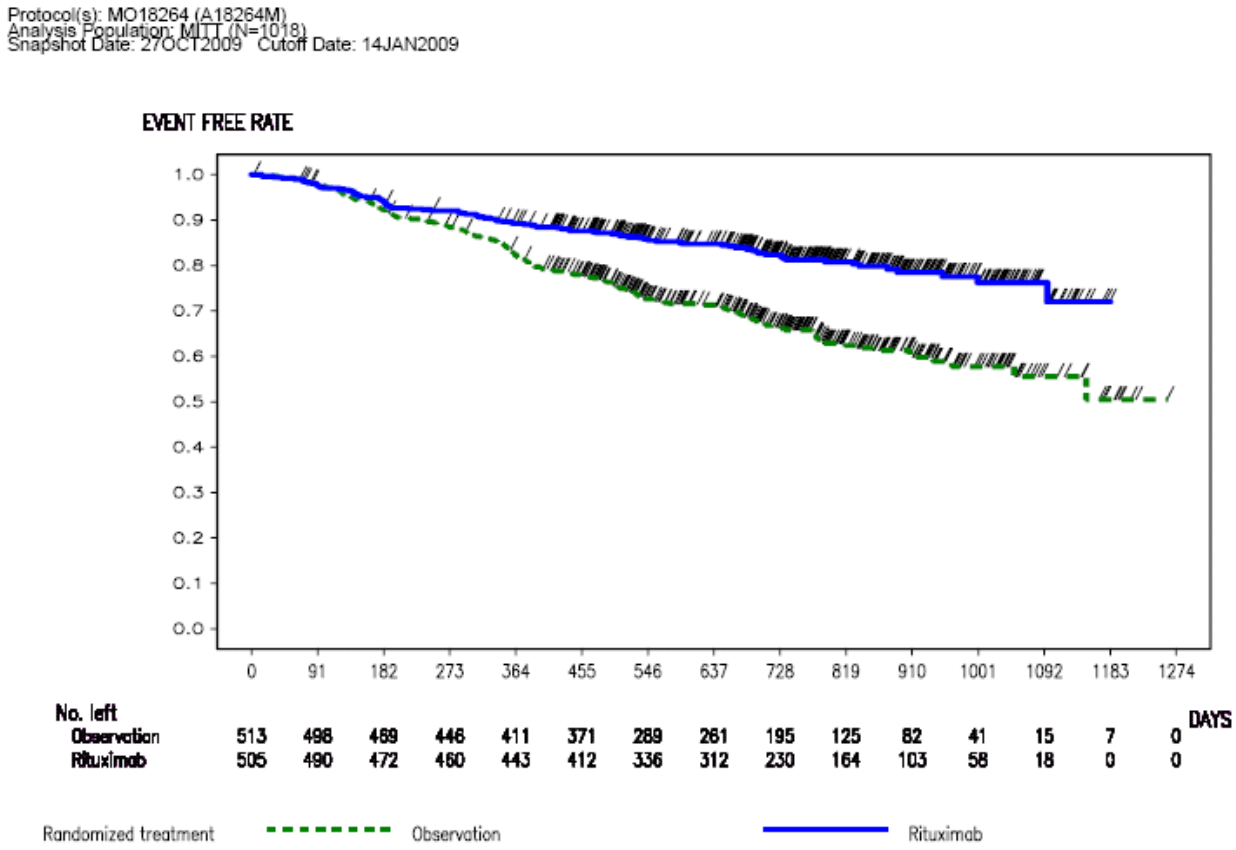
Table 6. Summary of Progression-Free Survival (Investigator Assessment) (MITT)

	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) (PFSTT) - 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

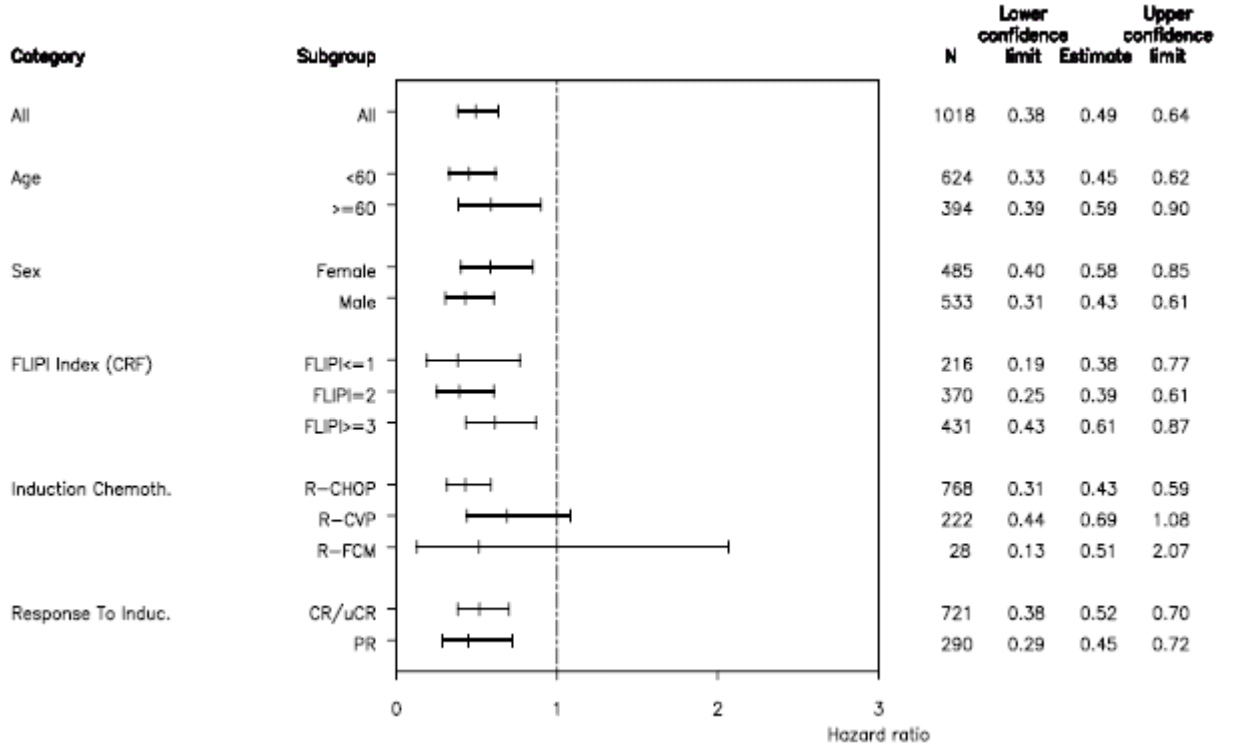
A Kaplan-Meier plot of PFS is shown in Figure 4.

Figure 4. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment) (MITT)



The results of subgroup (based on age, gender, Follicular Lymphoma International Prognostic Index (FLIPI) score at registration, induction treatment and response to induction treatment) analysis are presented in figure 5.

Figure 5. Subgroup Analysis of Progression-Free Survival (Investigator Assessment) (MITT)



Similar results for PFS were obtained from an Independent Review Committee (IRC, see table 5).

Secondary efficacy endpoints

The results of the secondary efficacy endpoints are presented in Table 7.

Table 7. 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.

[a] Based on patients who completed maintenance therapy/observation (N = 787).

Updated analysis

An updated analysis, based on a later clinical cut-off (30 June 2009), has been performed providing an additional 5.5 months of follow-up data. The results are presented in table 8.

Table 8. Overview of Efficacy Parameters (MITT)

Efficacy Parameter		**Observation** **N = 513**	**Rituximab** **N = 505**	**HR** [95%CI]	**p-value***
Clinical cut-off January 14, 2009					
Investigator-Assessed PFS	Median time to event 25th percentile One-year PFS rate [95% CI]	NE 16.7 months 0.82 [0.79;0.85]	NE 36.0 months 0.89 [0.87;0.92]	**0.50** [0.39;0.64]	p < 0.0001
Overall Survival	Median time to event	NE	NE	**0.89** [0.45;1.74]	
	25th percentile	NE	NE		p = 0.7246
	One-year OS rate [95% CI]	0.99 [0.98;1.00]	0.99 [0.98;1.00]		
Clinical cut-off June 30, 2009					
Investigator-Assessed PFS	Median time to event 25th percentile One-year PFS rate [95% CI]	42.8 months 16.9 months 0.82 [0.79;0.85]	NE 36.0 months 0.89 [0.87;0.92]	**0.51** [0.41;0.65]	p < 0.0001
Overall Survival	Median time to event 25th percentile One-year OS rate [95% CI]	NE NE 0.99 [0.98;1.00]	NE NE 0.99 [0.98;1.00]	**0.88** [0.48;1.61]	p = 0.6809

*p-values and hazard ratios (HRs) were calculated using the stratified log-rank test and stratified Cox regression, respectively. Stratification factors were induction treatment received and response to induction treatment.

Supportive study
ECOG 1496 trial
The ECOG 1496 study was a phase III, randomised, controlled, multicentre, intergroup study of the efficacy and safety of rituximab as post-induction therapy compared with observation.

METHODS
To be eligible for the study, patients had to have International Working Formulation (IWF) Grades A through C lymphoma (i.e., patients with marginal zone, lymphoplasmacytoid and small lymphocytic lymphoma were eligible, as well as patients with follicular lymphoma).

The main criteria for inclusion were previously untreated patients ≥18 years of age with Stage III or IV low-grade (IWF Grades A through C), CD20, B-cell lymphomas. An ECOG performance status of 0 or 1 was required.

The original protocol was designed to compare cyclophosphamide and fludarabine (CF) and CVP as induction regimens, but as a result of increased early mortality in the CF induction arm, the study was amended so that all further patients received CVP induction (cyclophosphamide 1 g/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1 and prednisone 100 mg/m^2 on days 1-5).

Patients who achieved a CR, PR, or SD following induction therapy (Stage 1) were randomised to rituximab maintenance (375 mg/m^2 weekly for 4 weeks, repeated at 6-month intervals for a total of four cycles [16 doses total]) or observation.

A total of 401 patients received CVP induction therapy (119 randomised to the CVP arm, and 282 assigned to CVP following the protocol amendment), of whom 322 showed a response or stable disease and were randomised to receive rituximab maintenance (n=162) or observation (n=160) in Stage 2 of the study. The maintenance randomisation was stratified by extent of residual disease post-induction (minimal or gross) and histology (follicular or other). 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 PFS, defined as the time from maintenance randomisation (Stage 2) to the first occurrence of disease progression, relapse, or death from any cause. Secondary efficacy endpoints included duration of OS (from maintenance randomisation) and response improvement within 2 years of maintenance randomisation.

RESULTS

Participant flow

A total of 401 patients received CVP induction therapy (119 randomised to the CVP arm, and 282 assigned to CVP following the protocol amendment). The overall response rate to induction therapy was 73% (13% CR; 60% PR) and 19% had SD; data based on induction population N=387 taken from Hochster et al, 2009 (Hochster H. et al (2009), JCO 27:1607-1614). In total, 322 of 401 patients showed a response or SD and were randomised to receive rituximab maintenance (n=162) or observation (n=160). These patients comprised the primary analysis population (PAP). Two hundred and forty eight (248) patients were considered to have follicular lymphoma, including 125 in the rituximab maintenance arm and 123 in the observation arm.

Baseline data

Demographic baseline characteristics of the patients are presented in table 9.

Table 9. Demographic Baseline characteristics (PAP)

	CVP+Observation (N=160)	CVP+Rituximab (N=162)
Age (years)		
Mean	55.4	57.4
SD	11.8	11.5
Median	55.0	58.0
Range	26–85	26–84
Distribution (%)		
≤60 years	105 (65.6%)	97 (59.9%)
61–65 years	17 (10.6%)	21 (13.0%)
66–70 years	19 (11.9%)	24 (14.8%)
71-75 years	13 (8.1%)	15 (9.3%)
>75 years	6 (3.8%)	5 (3.1%)
Sex		
Female	72 (45.0%)	73 (45.1%)
Male	88 (55.0%)	89 (54.9%)
Race/Ethnicity		
White	149 (93.1%)	151 (93.2%)
Black	7 (4.4%)	8 (4.9%)
Hispanic	1 (0.6%)	1 (0.6%)
American Indian/Alaskan Native	2 (1.3%)	0 (0.0%)
Asian	0 (0.0%)	1 (0.6%)
Other	1 (0.6%)	1 (0.6%)
Weight (kg)		
Mean	84.8	85.7
SD	20.6	19.3
Median	83.0	82.0
Range	43–198	48–148
Cooperative Group		
ECOG	141 (88.1%)	141 (87.0%)
CALGB	19 (11.9%)	21 (13.0%)

Baseline disease characteristics at pre- and post- induction phase are presented in tables 10 and 11.

Table 10. Baseline (Pre-Induction) Disease Characteristics (PAP)

	Observation (N = 160)	**Rituximab (N = 162)**
Age (years)		
Median	55.0	58.0
Sex		
Female	72 (45.0%)	73 (45.1%)
Male	88 (55.0%)	89 (54.9%)
Ann Arbor Stage at study entry		
n	160	160
Stage I	0 (0.0%)	1 (0.6%)

Stage III	47 (29.4%)	49 (30.6%)
Stage IV	113 (70.6%)	110 (68.8%)
No. extranodal sites		
0	24 (15.0%)	30 (18.5%)
1	69 (43.1%)	84 (51.9%)
≥ 2	67 (41.9%)	48 (29.6%)
Bone Marrow Involvement		
Yes	114 (71.3%)	111 (68.5%)
Bulky Disease [a]		
n	160	161
Yes	38 (23.8%)	31 (19.3%)
Initial Tumor Burden		
High [b]	109 (68.1%)	100 (61.7%)
Low	51 (31.9%)	62 (38.3%)
ECOG Performance Score		
0	96 (60.0%)	117 (72.2%)
1	64 (40.0%)	45 (27.8%)
B symptoms		
n	159	162
Yes	46 (28.9%)	35 (21.6%)
Elevated LDH		
n	121	121
Yes (> 1 × normal)	25 (20.7%)	29 (24.0%)
CRF-derived IPI score [c]		
0	2 (1.3%)	2 (1.2%)
1	56 (35.0%)	60 (37.0%)
2	68 (42.5%)	66 (40.7%)
3	28 (17.5%)	32 (19.8%)
4	6 (3.8%)	2 (1.2%)

Note: n represents the number of patients contributing to the summary statistics, if < 160 (Observation) or < 162 (Rituximab). Percentages are based on n.

[a] Defined as the presence of tumour with diameter > 10 cm

[b] High tumour burden was defined as the presence of one or more of the following: nodal or extranodal mass ≥ 7 cm, three or more nodal masses each > 3 cm, the presence of systemic or B symptoms and splenomegaly > 16 cm by CT scan

[c] The IPI score, which ranged from 0 to 5, was derived by assigning 1 point for each of the following risk factors: age > 60 years, Ann Arbor Stage III or IV, extranodal disease involvement at > 1 site, ECOG performance status ≥ 2, and elevated LDH

Table 11. Baseline Disease Characteristics at Maintenance Randomisation (Post-Induction) (PAP)

Disease Characteristics	Observation (N = 160)	Rituximab N = 162)
Residual Disease Post-Induction		
Minimal [a]	89 (55.6%)	91 (56.2%)
Gross	71 (44.4%)	71 (43.8%)
Best response to Induction (Stage 1)		
CR	25 (15.6%)	23 (14.2%)
PR	102 (63.8%)	112 (69.1%)
SD	27 (16.9%)	22 (13.6%)
Lymphoma Histopathology		
Follicular	123 (76.9%)	125 (77.2%)
Other	37 (23.1%)	37 (22.8%)

[a] Minimal residual disease was defined as either no evidence of disease or all lesions reduced to < 2 cm in maximal diameter, decreased by > 75% in cross-sectional area and bone marrow involvement reduced to < 10%.

Outcomes and estimation

Primary Efficacy Endpoint: Progression Free Survival (PFS)

At the time of data transfer (November 8, 2004) based on a median follow up of 27 months, 133 patients had experienced a PFS event, 46 in the rituximab maintenance arm and 87 in the observation arm. Based on the stratified analysis, the hazard ratio of progression, relapse, or death for patients in the rituximab maintenance arm relative to those in the observation arm was 0.36 (95% CI: 0.25, 0.52).

In the subset of patients with follicular lymphoma, in the observation arm, 68/123 patients (55.3%) were considered to have a progression event compared to 34/125 patients (27.2%) in the rituximab. The hazard ratio of progression, relapse, or death for patients in the rituximab maintenance arm relative to those in the observation arm was 0.37 (95% CI: 0.25, 0.56) (Table 12).

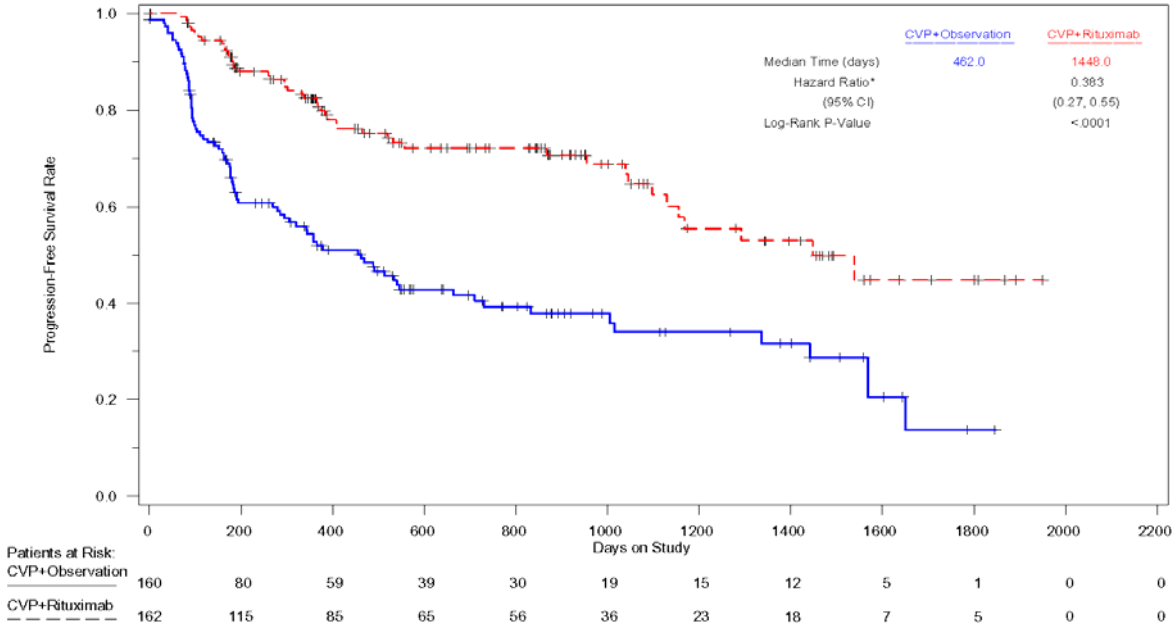
Table 12. Summary of PFS (PAP)

	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 6 displays the Kaplan-Meier curve by trial treatment group for the main analysis of PFS.

Figure 6. Kaplan-Meier Curves for PFS (All Patients in PAP)



Secondary Efficacy Endpoints

Overall Survival

A total of 36 deaths were reported, 15 in the rituximab maintenance arm and 21 in the observation arm (Table 13). The median duration of overall survival was not estimable for 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.

Table 13. Summary of Overall Survival

	Observation (N = 160)	Rituximab (N = 162)
No. (%) of patients who died	21 (13.1%)	15 (9.3%)
No. (%) of patients with censored observations	139 (86.9%)	147 (90.7%)
Duration of overall survival (days)		
Median [a] (95% CI)	NE (NE, NE)	2115 (NE, NE)
Range	3^+ to 2030^+	1^+ to 2115
p-value [b]	0.1496	
Percentage of patients alive at:		
6 months	98.7	99.4
1 year	96.7	98.7
2 years	91.3	95.5

NE = not estimable; $^+$ indicates a censored value.[a] Kaplan-Meier estimates.[b] Based on a stratified log-rank test

Updated analysis

An updated efficacy analysis has been performed for the ECOG 1496 study, based on a median follow-up of 67 months for the observation arm and 71 months for the rituximab maintenance arm. As of the clinical cut-off date of 31 May, 2008, a total of 282 patients had been followed for over 3 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). Median PFS was 15 months in the observation arm versus 55 months in the rituximab maintenance arm. After this extended follow-up period, maintenance therapy with rituximab reduced the risk of progression by 56% compared with no further treatment (HR 0.436, 95% CI [0.330, 0.576]). For the subset of patients with follicular lymphoma after 3 years follow-up the results were as follows: median PFS 4.3 years in the rituximab maintenance arm compared with 1.3 years for observation patients (HR 0.4, 95% CI [0.3, 0.6]).

At the clinical cut-off for the final analysis of the ECOG 1496 study, 46 patients (29%) in the observation arm and 37 patients (23%) in the rituximab maintenance arm had died. The median OS time had not been reached and no statistically significant difference in OS was observed. The hazard ratio for OS for the maintenance rituximab arm relative to the observation arm was 0.773 (95% CI [0.501, 1.193], p = 0.19). The 3-year OS for the subset of patients with follicular lymphoma was 91% for rituximab maintenance versus 86% for observation (HR 0.6; 95% CI, 0.3 to 1.2; p = 0.08).

Response Improvements during the rituximab maintenance/observation phase

Of the 263 patients who had SD or PR as their best response to induction, 129 patients were randomised to the observation arm and 134 patients were randomised to the rituximab maintenance arm. The percentage of patients with SD or PR after induction whose response improved within 2 years following randomisation to rituximab maintenance or observation was 20.9% and 7.0%, respectively. The difference between the arms of 13.9% was statistically significant (95% CI: [5.6%, 22.6%]; p = 0.001) (Table 14).

Table 14. Post-induction Response Improvement within Two Years after Maintenance Randomisation

	Observation N = 160	Rituximab N = 162
No. of patients with SD/PR as best response post-induction	129	134
No (%) of patients with improvement from SD/PR to PR/CR	9 (7.0%)	28 (20.9%)
95% CI [a]	(3.5%, 12.4%)	(14.7%, 28.4%)
Between-arm difference in improvement percentage [b]	NA	13.9%
95% CI [c]	NA	(5.6%, 22.6%)
p-value [d]	NA	0.001

NA = not applicable; CI = confidence interval; [a] Calculated using the method of Casella**.**
[b] CVP + rituximab relative to CVP + observation.[c] Calculated using the method of Agresti and Min**.**
[d] Exact 2-sided p-value for H_0: Common Odds Ratio is 1, based on "horizontal line" method for stratified 2 x 2 tables (StatXact PROCS for SAS Users, Version 6).

Comparison and Analyses of Results Across Studies

Study Populations

A comparison of the key baseline demographic and disease characteristics is presented in Table 15.

Table 15. Summary of Baseline Demographic and Disease Characteristics Populations Across Studies

	PRIMA Study		ECOG 1496 Study	
	Observation N=513	Rituximab N=505	Observation N = 160	Rituximab N = 162
At Study Entry:				
Age (years)				
Median	55.0	57.0	55.0	58.0
n	513	505	160	162
Sex				
Female	263 (51%)	270 (53%)	72 (45%)	73 (45.)
Male	250 (49%)	235 (47%)	88 (55%)	89 (55%)
n	513	505	160	162
Ann Arbor Stage				
Stage I	7 (1%)	15 (3%)	-	1 (< 1%)
Stage II	47 (9%)	31 (6%)	-	-
Stage III	97 (19%)	105 (21%)	47 (29%)	49 (31%)
Stage IV	362 (71%)	354 (70%)	113 (71%)	110 (69%)
n	513	505	160	162
No. of extra-nodal sites				
< 2	277 (54%)	290 (57%)	93 (58%)	114 (70%)
≥ 2	236 (46%)	215 (43%)	67 (42%)	48 (30%)
n	513	505	160	162
Bone Marrow Involvement				
Involved	285 (56%)	275 (54%)	114 (71%)	111 (69%)
Not Involved	213 (42%)	217 (43%)	46 (29%)	51 (31%)
Not Done/Unspecified	15 (3%)	13 (3%)	-	-
n	513	505	160	162
ECOG Performance Score				
0	341 (66%)	324 (64%)	96 (60.0%)	117 (72%)
1	155 (30%)	162 (32%)	64 (40.0%)	45 (28%)
2	17 (3%)	19 (4%)	-	-
n	513	505	160	162
B symptoms				
No	357 (70%)	345 (68%)	113 (71%)	127 (78%)
Yes	156 (30%)	160 (32%)	46 (29%)	35 (22%)
n	513	505	159	162
CRF-derived IPI score				
0	26 (5%)	17 (3%)	2 (1.3%)	2 (1.2%)
1	84 (16%)	89 (18%)	56 (35.0%)	60 (37.0%)
2	187 (36%)	183 (36%)	68 (42.5%)	66 (40.7%)
3	151 (29%)	129 (26%)	28 (17.5%)	32 (19.8%)
4	58 (11%)	72 (14%)	6 (3.8%)	2 (1.2%)
5	7 (1%)	14 (3%)	-	-
n	513	505	160	162
At Randomisation:				
Response to Induction				
CR	195 (38%)	204 (40%)	25 (16%)	23 (14%)
CRu	166 (32%)	156 (31%)	-	-
PR	151 (29%)	139 (28%)	102 (63.8%)	112 (69.1%)
SD	1 (< 1%)	4 (< 1%)	27 (16.9%)	22 (13.6%)
Not evaluated	-	2 (< 1%)	-	-
n	513	505	160	162

- **Discussion on clinical efficacy**

After a median follow up-time of 25 months the results from the pivotal study showed that the 25th percentile PFS for patients on observation was 16.7 months and for patients on rituximab maintenance it was 36 months, with a Hazard Ratio of 0.5 (CI 0.39; 0.64).
The increase of PFS was seen in the total group as well as in the sub-group of patients treated with induction R-CHOP. In the sub-groups treated with induction R-CVP or R-FCM a trend for PFS increase was observed, however the difference was not statistically significant. This could possibly be explained by the low percentage of patients receiving these induction therapies and experiencing an event, resulting in wide CI.
There is no head-to-head comparison of the efficacy of R-CVP vs. R-CHOP in patients with follicular lymphoma . In a meta-analysis concerning this issue, it was concluded that both R-CHOP and R-CVP can achieve excellent overall responses, by which the response rates for R-CHOP were slightly higher. The PFS of follicular lymphoma patients who were treated with R-CHOP as induction therapy, proved to be significantly increased after rituximab maintenance in comparison to observation (no maintenance). There is no rationale to assume a different effect of rituximab maintenance treatment after various induction regimes (R-CVP or R-CHOP).

The results of the secondary endpoints, EFS, Time to next anti-lymphoma treatment, time to next chemotherapy treatment, response rate at end of maintenance/observation phase, were consistent and in line with the increase in PFS and suggest a benefit for rituximab maintenance treatment at first remission.
However the improvement of PFS didn't translate into a significant increase in OS, (HR of 0.89 with a CI 0.42; 1.74). The lack of a significant improvement of OS could be explained by the low number of deaths recorded (18 deaths in the observation arm and 16 deaths in the rituximab maintenance arm) at the time of analysis (after a median follow up time of 25 months), resulting in a wide CI. Another explanation could be that the results are diluted by the efficacy of any next line (possibly rituximab-containing) therapy at progression.
After updated analysis, based on a later clinical cut-off (June 30, 2009), no statistical significant OS benefit could be determined either, as too few additional events had occurred.

Patients will be followed until 5 years after completion of the 2-year maintenance/observation period for PFS and OS. The OS data to be obtained after completion of the follow-up period must be considered important to assess the safety of rituximab maintenance after first remission induction. Results must be submitted as a FUM.

The result from the supportive study concerning the increase in PFS in response to rituximab maintenance is in agreement with the results obtained in the pivotal study. Concerning PFS benefit, a HR of 0.37 in favour of rituximab maintenance therapy was reported. In the supportive study, rituximab maintenance seems to be even more beneficial, however the effect can be exaggerated by the fact that none of the patients were treated with rituximab during the induction phase and therefore the patients in the observational arm never had the benefit of any rituximab treatment during this trial. Like in the pivotal study, the OS is not significantly increased after rituximab maintenance at first remission when compared with OS in the observation arm.
Nevertheless, the percentage of patients (including patients with follicular lymphoma or other lymphoma) who improved from SD/PR to PR/CR two years after randomisation was significantly higher in the rituximab maintenance arm vs. observation (20.9% vs. 7.0%). In the setting of the supportive study, this observation further attests to the clinical benefit of rituximab maintenance therapy.

Clinical safety
PRIMA study
- Patient exposure

Induction Phase
Of the 1018 patients who entered the randomised maintenance/observation phase of the study, all but three had completed their induction therapy according to the protocol. One patient in each of the rituximab maintenance and observation arms completed only 6 of the eight rituximab/chemotherapy induction cycles, while an additional patient in the rituximab maintenance arm received 7 out of the eight induction treatment cycles. Nine of the 1018 patients withdrew before the start of observation or maintenance treatment, and finally the rituximab maintenance/observation phase safety analysis population (MSAP) comprised 1009 patients (508 observation, 501 rituximab).

Maintenance/observation phase
At the clinical cut-off of January 14 2009, 285 patients (57%) in the rituximab arm had received all 12 treatment cycles and completed the 2 years of rituximab maintenance therapy (Table 16). In comparison, 95 patients (19%) in the observation arm had completed all 12 observation visits. The median number of visits attended for patients in the observation arm was 9, compared to 12 visits attended (cycles received) in the rituximab arm.

Table 16. Summary of Treatment Cycles/Observation Visits (MSAP) PRIMA

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

The majority of patients in the rituximab arm (89.8%) received over 90% of their projected rituximab dose (Table 17).

Table 17. Summary of Extent of Exposure to maintenance Rituximab (MITT) PRIMA

	Rituximab (N=501)
Treatment Duration (WEEKS)	
Mean	83.67
SD	24.321
SEM	1.087
Median	96.00
Min	8.0
Max	116.0
n	501
Percentage Projected Dose Intensity (%)	
Mean	96.67
SD	5.479
SEM	0.245
Median	97.66
Min	65.7
Max	116.4
n	501
0% - 60%	0
>60% - 80%	6 (1.2%)
>80% - 90%	45 (9.0%)
>90%	450 (89.8%)

- Adverse Events

The proportion of patients who experienced at least one adverse event (including Grade 3–5 toxicities, Grade 2–5 infections, and SAEs) during the maintenance/observation phase was 52% in the rituximab arm vs 35% in the observation arm. The most common categories of AEs were infections and infestations (mainly bronchitis), neoplasms (mainly basal cell carcinoma), and blood and lymphatic system disorders (mainly neutropenia). The incidence of other categories of AEs was < 4% and similar in the two study arms. AEs which occurred with an incidence of 1% or more in either arm are presented in Table 18.

Table 18. Summary of Adverse Events by Body System Occurring with an Incidence of ≥ 1% in Either Arm (MSAP) PRIMA

Body System/ Adverse Event	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL 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.
AE13 19JAN2010:14:15:35

* AEs with an incidence of less than 1% in both arms are also displayed in this table due to rounding-up of crude rates ≥ 0.995% to 1%.

The majority of AEs were Grade 2 in severity (165/269 [61%] in the observation arm; 291/459 [63%] in the rituximab arm), and the majority (85%) of those events were Grade 2 infections (144 events in the observation arm, and 248 events in the rituximab arm).

More patients in the rituximab arm than in the observation arm experienced at least one Grade 3 or 4 adverse event (23% vs 16%). This difference was mainly due to a higher incidence of Grade 3 or 4 neutropenia (4% vs <1%) and infections (4% vs <1%) in the rituximab arm than in the observation arm, respectively.
There were five Grade 5 (fatal) AEs.

- Other serious adverse events (SAEs)

A total of 193 SAEs were reported for 158 patients (63 [12%] in the observation arm, and 95 [19%] in the rituximab arm) during the maintenance/observation phase (Table 19). No single type of SAE occurred with an incidence of 1% or more in either arm. The most common class of SAEs overall was neoplasms (39 events overall affecting 37 patients), including basal cell carcinoma (2 patients in the observation arm vs 4 patients in the rituximab arm), colon cancer (three patients in the rituximab arm) and breast cancer (two patients in the rituximab arm). The most common class of SAE in the rituximab arm was infections and infestations (25 patients [5%] vs 6 patients [1%] in the observation arm). In the rituximab arm, 3 patients had SAEs of pneumonia, 2 patients had diverticulitis, and two patients had hepatitis B. In the observation arm, 3 patients had SAEs of urinary tract infections. Other serious infections were reported by 1 patient in each case. Serious cardiac disorders were reported for 2 patients in the observation arm compared with 11 patients in the rituximab arm.

Table 19. Summary of Serious Adverse Events with an Incidence of ≥ 1% by Body System* in Either Arm (MSAP)

Body System	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
All Body Systems		
Total Patients with at Least One AE	63 (12)	95 (19)
Neoplasms Benign, Malignant and Unspecified	17 (3)	20 (4)
Infections and Infestations	6 (1)	25 (5)
Nervous System Disorders	8 (2)	10 (2)
Cardiac Disorders	2 (<1)	11 (2)
Gastrointestinal Disorders	3 (<1)	10 (2)
Injury, Poisoning and Procedural Complications	8 (2)	3 (<1)
Psychiatric Disorders	6 (1)	5 (<1)
Musculoskeletal and Connective Tissue Disorders	3 (<1)	6 (1)

* The total number of patients with at least one AE is provided for each body system.

- Deaths

At the time of data cut-off (January 14, 2009), a total of 31 patients in the safety population (MSAP) had died (Table 20). The number of deaths was higher in the observation arm than in the rituximab arm (18 patients vs 13 patients). The most common cause of death was disease progression (lymphoma), which accounted for 12 deaths in the observation arm and 10 deaths in the rituximab arm. The incidence of non-lymphoma deaths was: 6 patients in the observation arm vs 3 patients in the rituximab arm.

Five of the 9 remaining deaths were considered to be outcome of AEs (Table 21). Two fatal AEs in the observation arm were a result of neoplasms: leukaemia considered as possibly related to trial treatment and metastatic neoplasm considered to be treatment-unrelated. The 3 recorded fatal AEs in the rituximab arm resulted from a treatment-unrelated disorder (unknown/unevaluable event), hepatitis B considered to be probably treatment-related and pulmonary haemorrhage considered to be treatment-unrelated.

The remaining 4 deaths (not due to lymphoma or reported as AEs) were all in the observation arm and were due to acute myeloid leukaemia, coronary artery disease, myelodysplastic syndrome, and sepsis.

Table 20. Summary of Deaths during the maintenance/observation phase (MSAP)

Cause of Death	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL N = 1009 No. (%)
Total No. of Deaths	18 (4)	13 (3)	31 (3)
LYMPHOMA	12 (2)	10 (2)	22 (2)
ACUTE MYELOID LEUKAEMIA	1 (<1)	-	1 (<1)
CORONARY ARTERY DISEASE	1 (<1)	-	1 (<1)
HEPATITIS B	-	1 (<1)	1 (<1)
LEUKAEMIA	1 (<1)	-	1 (<1)
METASTATIC NEOPLASM	1 (<1)	-	1 (<1)
MYELODYSPLASTIC SYNDROME	1 (<1)	-	1 (<1)
PULMONARY HAEMORRHAGE	-	1 (<1)	1 (<1)
SEPSIS	1 (<1)	-	1 (<1)
UNEVALUABLE EVENT	-	1 (<1)	1 (<1)

Table 21. Summary of Adverse Events Leading to Death (MSAP)

Body System/ Adverse Event	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL N = 1009 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	2 (<1)	3 (<1)	5 (<1)
Total Number of AEs	2	3	5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total Pts With at Least one AE	2 (<1)	-	2 (<1)
LEUKAEMIA	1 (<1)	-	1 (<1)
METASTASES TO ADRENALS	1 (<1)	-	1 (<1)
Total Number of AEs	2	-	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
DEATH	-	1 (<1)	1 (<1)
Total Number of AEs	-	1	1
HEPATOBILIARY DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
HEPATITIS FULMINANT	-	1 (<1)	1 (<1)
Total Number of AEs	-	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
PULMONARY HAEMORRHAGE	-	1 (<1)	1 (<1)
Total Number of AEs	-	1	1

- Laboratory findings

Haematology and Biochemistry

Haematology and biochemistry parameters were very similar between the two arms during the course of the maintenance/observation phase, except for lymphocyte counts, which increased with time in the observation arm compared with 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 NCI-CTC grade for any laboratory test parameter during the maintenance/observation phase. In the rituximab arm, a higher number of shifts to Grade 3/4 values was observed for lymphopenia as well as leucopenia and neutropenia. There were very few shifts to Grade 3/4 for blood chemistry parameters, and for these parameters there was little difference between the two study arms.

In the rituximab arm, 8% of patients recorded newly occurring Grade 3 or 4 neutropenia based on laboratory counts, while 4% of patients recorded AEs of neutropenia. Similarly, 10% of patients recorded newly occurring Grade 3 or 4 lymphopenia based on laboratory data, while less than 1% of patients recorded adverse events of lymphopenia.

Additional Laboratory Parameters

Differential Lymphocyte Counts

Patients at study sites in France underwent additional sampling for immunophenotyping of peripheral blood cells. Absolute levels of circulating B-cells (CD19-positive), T-cells (CD3-positive), and natural killer cells (CD16- or CD56-positive) were assessed before induction therapy, after induction therapy (baseline), and every six months for the first three years after randomisation or until recovery if not reached at this time.

B-Cells

Analysis of CD19-positive lymphocyte subsets showed suppression of B-cells in both study arms at baseline (after completion of induction therapy) and continued B-cell suppression during the maintenance/observation phase for patients in the rituximab arm. In comparison, patients in the observation arm showed recovery of B-cells during the maintenance/observation phase, with the mean value returning to within the normal range by visit 6 (ie, approximately one year after completing induction therapy). The mean B-cell count in the observation arm at the end of the

maintenance/observation phase was 0.16×10^9/L (compared with undetectable counts in the rituximab arm.

T-Cells
The mean T-cell counts at baseline (after completion of induction therapy) was 0.90×10^9/L in the observation arm vs 0.91×10^9/L in the rituximab arm (both within the standard reference range). Although the mean values increased to 1.06×10^9/L in the observation arm and decreased to 0.86×10^9/L in the rituximab arm at visit 3), there was little difference between the two arms over subsequent visits and most patients in the two arms remained within the normal range throughout the maintenance/observation phase.

Natural Killer Cells
The mean counts of natural killer (NK) cells at baseline (after completion of induction therapy) were 0.17×10^9/L in the observation arm vs 0.17×10^9/L in the rituximab arm. These values increased slightly during the course of the maintenance/observation phase, and remained within the normal range throughout the maintenance/observation phase. At visit 12, the mean counts were 0.24×10^9/L in the observation arm and 0.23×10^9/L in the rituximab arm.

Immunoglobulins
Over the course of the maintenance/observation phase, mean Ig (IgG, IgA and IgM) values and 95% confidence intervals in both study arms remained within the normal range.

Although the numbers 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 the 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. One patient (2%) in the observation arm and 4 patients (5%) in the rituximab arm had IgG levels lower than 4 g/L at the end of the maintenance/observation phase.

Recovery of IgG levels during the maintenance/observation phase was observed for 5 of the 11 patients who had IgG levels at the end of induction lower than the LLN and lower than the value at screening (1/5 patients [20%] in the observation arm, and 4/6 patients [67%] in the rituximab arm). Of 7 patients with IgA concentrations below LLN and their screening value after induction, none showed recovery. During the maintenance period, 9/11 patients showed recovery of IgM concentrations in the observation arm vs 2 /16 patients in the rituximab arm.

- Safety in special populations

Adverse Events by Age
Table 22 presents the AEs occurring in patients aged under 65 years, from 65 to 74 years inclusive, and 75 years and over.

Table 22. Summary of AEs by Age Group (MSAP)

Age Group (years)	**Observation N = 508** n (%)	**Rituximab N = 501** n (%)
< 65	n = 387	n = 379
Total patients with at least one AE	*122 (32)*	*204 (54)*
Total patients with Infection & Infestations AEs	82 (21)	142 (37)
Total patients with Blood & Lymphatic System AEs	6 (2)	17 (4)
Total patients with neutropenia AEs	4 (1)	11 (3)
65–74 inclusive	n = 97	n = 99
Total patients with at least one AE	*45 (46)*	*47 (47)*
Total patients with Infection & Infestations AEs	28 (29)	34 (34)
Total patients with Blood & Lymphatic System AEs	–	7 (7)
Total patients with neutropenia AEs	–	6 (6)
≥ **75**	n = 24	n = 23
Total patients with at least one AE	*12 (50)*	*12 (52)*
Total patients with Infection & Infestations AEs	4 (17)	8 (35)
Total patients with Blood & Lymphatic System AEs	1 (4)	2 (9)
Total patients with neutropenia AEs	1 (4)	2 (9)

Infections were the most commonly occurring AEs in all three age categories. For patients under 65 years, the incidence of AEs was 54% in the rituximab arm vs 32% the observation arm. For patients aged 65–74 years, the overall incidence of AEs was 47% in the rituximab arm vs 46% in the observation arm. In the ≥ 75 year age group, the incidence of AEs was 52% in the rituximab arm vs 50% in the observation arm.

Use in Pregnancy and Lactation
Nine pregnancies were reported in the PRIMA trial, including 2 pregnancies in the female partners of male patients. Two pregnancies occurred during the induction phase, and 7 pregnancies occurred during the maintenance/observation phase. Of the 6 patients who became pregnant during the maintenance/observation phase, 3 patients were in the observation arm and 3 patients were in the rituximab arm. The 3 women in the observation arm received 4, 6, and 7 doses of rituximab, respectively, and all delivered normal babies, 1 baby delivered at 35th gestational week, the 2 others probably both at full term.

- Safety related to drug-drug interactions and other interactions

No new information is available

- Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation
A total of 27 patients discontinued maintenance treatment/observation as a result of AEs (8 patients [2%] in the observation arm, and 19 patients [4%] in the rituximab arm). The most common AEs that led to treatment discontinuation were neoplasms, which accounted for the withdrawal of 6 patients in the observation arm and 5 patients in the rituximab arm. Four patients in the rituximab arm were withdrawn as a result of infections: hepatitis B (2 patients), endocarditis, and mycobacterial infection. One case of hepatitis B was considered to be unrelated to trial treatment, and the other 3 infections were considered as being probably treatment-related. Five patients discontinued treatment after becoming pregnant.

Adverse Events Leading to Dose Interruptions or Modifications
A total of 30 patients had their dosing of rituximab interrupted or modified as a result of an AE. The most common reasons for interrupting the dose schedule or for modifying the rituximab dose were infections and infestations (12 patients) including three bronchitis events and two upper respiratory tract infections, and blood and lymphatic disorders (9 patients) including seven neutropenia events and five leucopenia events.

- Post marketing experience

Since the first marketing authorisation of rituximab, more than 2.1 million patients have been treated with this antibody. The majority of these were patients with NHL.
With a data cut-off date of 31 December 2009, a total of 44,681 AEs have been reported with rituximab worldwide to the global safety database. Of these reported AEs, 21,642 were classified as serious. The events were reported from spontaneous sources (post-marketing experience). Other sources include clinical trials in oncology and rheumatoid arthritis (company-sponsored and investigator-sponsored trials). A summary of all AEs in the global safety database for rituximab as of 31 December 2009 is shown in the table 23. The most frequently reported events were from the system organ classes (SOCs) 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%).

Table 23. Summary of All Adverse Events in the Global Rituximab Safety Database as of 31 December 2009 (All Sources and Indications)

System Organ Class	Serious Adverse Events	% Serious Adverse Events	Total Adverse Events	% Total Adverse Events
Blood and lymphatic system disorders	2834	13.09	4649	10.40
Cardiac disorders	1207	5.58	1891	4.23
Congenital, familial and genetic disorders	30	0.14	43	0.10
Ear and labyrinth disorders	61	0.28	136	0.30
Endocrine disorders	31	0.14	47	0.11
Eye disorders	139	0.64	411	0.92
Gastrointestinal disorders	1225	5.66	2996	6.71
General disorders and administration site conditions	1847	8.53	7116	15.93
Hepatobiliary disorders	327	1.51	461	1.03
Immune system disorders	836	3.86	1148	2.57
Infections and infestations	4320	19.96	6296	14.09
Injury, poisoning and procedural complications	461	2.13	984	2.20
Investigations	732	3.38	1947	4.36
Metabolism and nutrition disorders	374	1.73	709	1.59
Musculoskeletal and connective tissue disorders	752	3.47	1872	4.19
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	999	4.62	1283	2.87
Nervous system disorders	1088	5.03	2380	5.33
Pregnancy, puerperium and perinatal conditions	55	0.25	132	0.30
Psychiatric disorders	149	0.69	428	0.96
Renal and urinary disorders	371	1.71	626	1.40
Reproductive system and breast disorders	64	0.30	129	0.29
Respiratory, thoracic and mediastinal disorders	2155	9.96	4222	9.45
Skin and subcutaneous tissue disorders	536	2.48	2609	5.84
Social circumstances	11	0.05	25	0.06
Surgical and medical procedures	116	0.54	161	0.36
Vascular disorders	783	3.62	1765	3.95
(blank)	139	0.64	215	0.48
Grand total	**21642**	**100**	**44681**	**100**

ECOG 1496 trial

- Patient Exposure

Patients in the ECOG 1496 study were to receive a minimum of 6 cycles and a maximum of 8 cycles of CVP induction therapy. Of the patients that proceeded to the rituximab maintenance/observation phase of the study, a total of 96% (309/322) received between 6 and 8 cycles of induction CVP (157/161 patients [97.5%] were subsequently treated with rituximab maintenance and 152/161 patients [94.4%] who then underwent observation).

At the time of data transfer (November 8, 2004), 52% (83/161) of patients treated with rituximab maintenance had received the protocol-specified maximum of 16 infusions, and 42 patients (26%) were still in the study and continuing to receive rituximab maintenance.

- Adverse events

At the time of data transfer (November 8, 2004), 144 patients (89%) who received rituximab maintenance had experienced one or more AEs during the rituximab maintenance/observation phase of the study compared with 101 patients (63%) in the observation arm. The most common AEs, affecting between 30-45% of rituximab-treated patients, were haematological (leucopenia, anaemia), fatigue, and peripheral sensory neuropathy. Other common events in the rituximab arm included infections and

nervous system disorder (each 19%), lung disorder (18%) and liver and skin disorder (each 17%), all of which had a higher frequency with rituximab than with observation.
All AEs for which there was at least a 2% higher frequency among patients in the rituximab maintenance arm compared with those in the observation arm beginning from the time of randomisation to the rituximab maintenance/observation phase are summarized in Table 25.

Table 24. Common Adverse Events (Incidence ≥ 5%) (PAP, as Treated)

Adverse Event Preferred Term	Observation (N = 161)	Rituximab (N = 161)	Total (N = 322)
Any AE	**101 (62.7%)**	**144 (89.4%)**	**245 (76.1%)**
Leucopenia	28 (17.4%)	71 (44.1%)	99 (30.7%)
Anaemia	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%)
Diarrhoea	3 (1.9%)	14 (8.7%)	17 (5.3%)
Weight decreased	3 (1.9%)	14 (8.7%)	17 (5.3%)

Table 25. Adverse Events with a ≥ 2% Higher Incidence in the Rituximab Arm Compared with the Observation Arm During Maintenance/Observation Phase (PAP, as Treated)

Adverse Event Preferred Term	Observation (N = 161)	Rituximab (N = 161)	Total (N = 322)
Blood			
Leucopenia	28 (17.4%)	71 (44.1%)	99 (30.7%)
Anaemia	32 (19.9%)	56 (34.8%)	88 (27.3%)
Granulocytopenia	4 (2.5%)	15 (9.3%)	19 (5.9%)
Cardiac			
Cardiac	2 (1.2%)	7 (4.3%)	9 (2.8%)
GI			
Nausea	4 (2.5%)	15 (9.3%)	19 (5.9%)
Diarrhoea	3 (1.9%)	14 (8.7%)	17 (5.3%)
Vomiting	3 (1.9%)	7 (4.3%)	10 (3.1%)
Stomatitis	1 (0.6%)	5 (3.1%)	6 (1.9%)
General			
Fatigue	22 (13.7%)	62 (38.5%)	84 (26.1%)
Pain			
Oedema	12 (7.5%)	17 (12.4%)	29 (9.0%)
Pyrexia	12 (7.5%)	17 (12.4%)	29 (9.0%)
Asthenia	2 (1.2%)	12 (7.5%)	14 (4.3%)
Chills	2 (1.2%)	9 (5.6%)	11 (3.4%)
Liver			
Liver disorder	11 (6.8%)	27 (16.8%)	38 (11.8%)
Immune			
Hypersensitivity	1 (0.6%)	7 (4.3%)	8 (2.5%)
Infections			
Infection	14 (8.7%)	30 (18.6%)	44 (13.7%)
Investigations			
Blood LDH increased	5 (3.1%)	23 (14.3%)	28 (8.7%)
Weight increased	7 (4.3%)	18 (11.2%)	25 (7.8%)
Weight decreased	3 (1.9%)	14 (8.7%)	17 (5.3%)
Metabolic			
Metabolic disorder	7 (4.3%)	16 (9.9%)	23 (7.1%)
Anorexia	1 (0.6%)	5 (3.1%)	6 (1.9%)
Musculoskeletal			
Arthralgia	4 (2.5%)	20 (12.4%)	24 (7.5%)
Shoulder pain	4 (2.5%)	20 (12.4%)	24 (7.5%)
Muscle spasms	2 (1.2%)	12 (7.5%)	14 (4.3%)
Muscular weakness	2 (1.2%)	12 (7.5%)	14 (4.3%)
Myalgia	2 (1.2%)	12 (7.5%)	14 (4.3%)
Myopathy	2 (1.2%)	12 (7.5%)	14 (4.3%)
Nervous system			
Peripheral sensory neuropathy	29 (18.0%)	48 (29.8%)	77 (23.9%)
Neuromyopathy	12 (7.5%)	16 (9.9%)	28 (8.7%)
Nervous system disorder	4 (2.5%)	30 (18.6%)	34 (10.6%)
Respiratory system			
Lung disorder	16 (9.9%)	29 (18.0%)	45 (14.0%)
Skin			
Skin disorder	8 (5.0%)	27 (16.8%)	35 (10.9%)
Alopecia	4 (2.5%)	16 (9.9%)	20 (6.2%)
Hyperhydrosis	3 (1.9%)	12 (7.5%)	15 (4.7%)
Vascular			
Haemorrhage	1 (0.6%)	5 (3.1%)	6 (1.9%)
Hypotension	1 (0.6%)	5 (3.1%)	6 (1.9%)

Grade 3 or 4 adverse events were recorded for 26 (16.1%) of the rituximab maintenance patients compared with 18 (11.2%) patients in the observation arm. The Grade 3 or 4 AE with a ≥ 2% higher frequency amongst patients in the rituximab maintenance arm compared with those in the observation arm was granulocytopenia (3.7% vs. 0.6%). Grade 3 or 4 cardiac events were more frequent with rituximab (4 patients [2.5%] vs 1 patient [0.6%]).

Table 26. Summary of Grade ≥ 3 Adverse Events (PAP, as Treated)

Adverse Event Preferred Term	Observation (N = 161)	Rituximab (N = 161)	Total (N = 322)
Any grade 3 or 4 AE	**18 (11.2%)**	**26 (16.1%)**	**44 (13.7%)**
Blood			
Leucopenia	2 (1.2%)	4 (2.5%)	6 (1.9%)
Anaemia	1 (0.6%)	1 (0.6%)	2 (0.6%)
Granulocytopenia	1 (0.6%)	6 (3.7%)	7 (2.2%)
Cardiac			
Cardiac	1 (0.6%)	4 (2.5%)	5 (1.6%)
GI			
Nausea	1 (0.6%)	0	1 (0.3%)
Vomiting	1 (0.6%)	0	1 (0.3%)
Abdominal pain	1 (0.6%)	0	1 (0.3%)
General			
Fatigue	0	2 (1.2%)	2 (0.6%)
Pain	1 (0.6%)	1 (0.6%)	2 (0.6%)
Pyrexia	1 (0.6%)	0	1 (0.3%)
Asthenia	1 (0.6%)	0	1 (0.3%)
Hepatobilliary disorders			
Liver disorder	0	2 (1.2%)	2 (0.6%)
Infections			
Infection	2 (1.2%)	3 (1.9%)	5 (1.6%)
Injury, poisoning …			
Drug toxicity	5 (3.1%)	2 (1.2%)	7 (2.2%)
Investigations			
Weight increased	0	1 (0.6%)	1 (0.3%)
Metabolic			
Metabolic disorder	1 (0.6%)	3 (1.9%)	4 (1.2%)
Musculoskeletal			
Muscle spasms	1 (0.6%)	0	1 (0.3%)
Muscular weakness	1 (0.6%)	0	1 (0.3%)
Myalgia	1 (0.6%)	0	1 (0.3%)
Myopathy	1 (0.6%)	0	1 (0.3%)
Nervous system			
Nervous system disorder	0	1 (0.6%)	1 (0.3%)
Neuromyopathy	2 (1.2%)	1 (0.6%)	3 (0.9%)
Cerebrovascular accident	1 (0.6%)	0	1 (0.3%)
Intracranial haemorrhage	1 (0.6%)	0	1 (0.3%)
Respiratory system			
Lung disorder	0	1 (0.6%)	1 (0.3%)
Vascular			
Haemorrhage	0	1 (0.6%)	1 (0.3%)
Hypertension	1 (0.6%)	0	1 (0.3%)
Hypotension	0	1 (0.6%)	1 (0.3%)

At the cut-off date, 21 patients (13.1%) in the observation arm and 15 patients (9.3%) in the rituximab arm had died during the study. Of these, 10 patients in the observation arm and 8 patients in the rituximab arm were considered to have died due to progressive disease. There was one AE that resulted in death: one patient in the observation arm died due to an infection. The cause of death was recorded as "not treatment- or disease-related" for 7 patients in the observation arm and 3 patients in the rituximab arm and as "missing/unknown for 4 patients in each arm.

A total of 5 expedited AEs, all cardiac in nature, were recorded in 2 patients during Stage 2 (maintenance phase) of the study. One patient treated with rituximab maintenance therapy experienced extrasystoles, ventricular arrhythmia and ventricular tachycardia (all Grade 4), while 1 patient in the observation arm experienced myocardial infarction and myocardial ischemia (both Grade 4).

In reply to CHMP concerns the MAH submitted a summary of all adverse events presented in Table 27.

Table 27. Summary of Related Summary Of Related Adverse Events (Incidence Proportion) By Maintenance Trial Treatment And Body System (MSAP)

Body System/ Adverse Event	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL N = 1009 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	48 (9)	147 (29)	195 (19)
Total Number of AEs	60	229	289
INFECTIONS AND INFESTATIONS			
Total Pts With at Least one AE	30 (6)	107 (21)	137 (14)
BRONCHITIS	6 (1)	26 (5)	32 (3)
UPPER RESPIRATORY TRACT INFECTION	5 (<1)	17 (3)	22 (2)
SINUSITIS	1 (<1)	11 (2)	12 (1)
ORAL HERPES	1 (<1)	7 (1)	8 (<1)
PNEUMONIA	2 (<1)	6 (1)	8 (<1)
URINARY TRACT INFECTION	1 (<1)	7 (1)	8 (<1)
INFECTION	1 (<1)	6 (1)	7 (<1)
NASOPHARYNGITIS	3 (<1)	4 (<1)	7 (<1)
HERPES ZOSTER	2 (<1)	4 (<1)	6 (<1)
RHINITIS	1 (<1)	4 (<1)	5 (<1)
VIRAL INFECTION	1 (<1)	4 (<1)	5 (<1)
HAEMOPHILUS INFECTION	-	4 (<1)	4 (<1)
INFLUENZA	-	4 (<1)	4 (<1)
LUNG INFECTION	1 (<1)	3 (<1)	4 (<1)
PHARYNGITIS	-	4 (<1)	4 (<1)
FOLLICULITIS	1 (<1)	2 (<1)	3 (<1)
RESPIRATORY TRACT INFECTION	-	3 (<1)	3 (<1)
CELLULITIS	-	2 (<1)	2 (<1)
EAR INFECTION	-	2 (<1)	2 (<1)
ESCHERICHIA URINARY TRACT INFECTION	1 (<1)	1 (<1)	2 (<1)
HERPES VIRUS INFECTION	1 (<1)	1 (<1)	2 (<1)
ORAL CANDIDIASIS	-	2 (<1)	2 (<1)
SKIN INFECTION	-	2 (<1)	2 (<1)
TOOTH ABSCESS	-	2 (<1)	2 (<1)
VIRAL PHARYNGITIS	-	2 (<1)	2 (<1)
BRONCHOPNEUMONIA	-	1 (<1)	1 (<1)
CAMPYLOBACTER INFECTION	1 (<1)	-	1 (<1)
CAMPYLOBACTER INTESTINAL INFECTION	-	1 (<1)	1 (<1)
DIVERTICULITIS	-	1 (<1)	1 (<1)
ENDOCARDITIS	-	1 (<1)	1 (<1)
ERYSIPELAS	-	1 (<1)	1 (<1)
GASTRIC INFECTION	-	1 (<1)	1 (<1)
GASTROINTESTINAL INFECTION	1 (<1)	-	1 (<1)
HEPATITIS B	-	1 (<1)	1 (<1)
HERPES OPHTHALMIC	-	1 (<1)	1 (<1)
HERPES SIMPLEX	1 (<1)	-	1 (<1)
KLEBSIELLA INFECTION	1 (<1)	-	1 (<1)
MENINGITIS	-	1 (<1)	1 (<1)
MYCOBACTERIAL INFECTION	-	1 (<1)	1 (<1)
NEUTROPENIC INFECTION	-	1 (<1)	1 (<1)
ONYCHOMYCOSIS	-	1 (<1)	1 (<1)
ORAL FUNGAL INFECTION	-	1 (<1)	1 (<1)
PULMONARY TUBERCULOSIS	-	1 (<1)	1 (<1)
PYELONEPHRITIS	1 (<1)	-	1 (<1)
SERRATIA INFECTION	-	1 (<1)	1 (<1)
SKIN BACTERIAL INFECTION	-	1 (<1)	1 (<1)
SKIN CANDIDA	-	1 (<1)	1 (<1)
STREPTOCOCCAL BACTERAEMIA	-	1 (<1)	1 (<1)
TRACHEITIS	-	1 (<1)	1 (<1)
UPPER AERODIGESTIVE TRACT INFECTION	-	1 (<1)	1 (<1)
VAGINITIS BACTERIAL	-	1 (<1)	1 (<1)
VIRAL UPPER RESPIRATORY TRACT INFECTION	-	1 (<1)	1 (<1)
VULVOVAGINAL CANDIDIASIS	-	1 (<1)	1 (<1)
VULVOVAGINAL MYCOTIC INFECTION	-	1 (<1)	1 (<1)
Total Number of AEs	33	154	187

BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total Pts With at Least one AE	5 (<1)	24 (5)	29 (3)
NEUTROPENIA	4 (<1)	17 (3)	21 (2)
LEUKOPENIA	1 (<1)	8 (2)	9 (<1)
LYMPHOPENIA	-	4 (<1)	4 (<1)
FEBRILE NEUTROPENIA	1 (<1)	1 (<1)	2 (<1)
THROMBOCYTOPENIA	-	2 (<1)	2 (<1)
ANAEMIA	1 (<1)	-	1 (<1)
Total Number of AEs	7	32	39
CARDIAC DISORDERS			
Total Pts With at Least one AE	1 (<1)	8 (2)	9 (<1)
CARDIAC FAILURE	-	3 (<1)	3 (<1)
ATRIAL FLUTTER	-	1 (<1)	1 (<1)
CARDIOMYOPATHY	-	1 (<1)	1 (<1)
CONGESTIVE CARDIOMYOPATHY	-	1 (<1)	1 (<1)
LEFT VENTRICULAR DYSFUNCTION	1 (<1)	-	1 (<1)
MYOCARDIAL INFARCTION	-	1 (<1)	1 (<1)
VENTRICULAR EXTRASYSTOLES	-	1 (<1)	1 (<1)
Total Number of AEs	1	8	9
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total Pts With at Least one AE	4 (<1)	4 (<1)	8 (<1)
BASAL CELL CARCINOMA	1 (<1)	1 (<1)	2 (<1)
ACUTE MYELOID LEUKAEMIA	-	1 (<1)	1 (<1)
BOWEN'S DISEASE	1 (<1)	-	1 (<1)
BREAST CANCER	-	1 (<1)	1 (<1)
COLON CANCER	-	1 (<1)	1 (<1)
EPSTEIN-BARR VIRUS ASSOCIATED LYMPHOPROLIFERATIVE DISORDER	1 (<1)	-	1 (<1)
LEUKAEMIA	1 (<1)	-	1 (<1)
SQUAMOUS CELL CARCINOMA OF SKIN	-	1 (<1)	1 (<1)
Total Number of AEs	4	5	9
INVESTIGATIONS			
Total Pts With at Least one AE	4 (<1)	4 (<1)	8 (<1)
NEUTROPHIL COUNT DECREASED	2 (<1)	2 (<1)	4 (<1)
ASPARTATE AMINOTRANSFERASE INCREASED	-	1 (<1)	1 (<1)
BLOOD URIC ACID INCREASED	1 (<1)	-	1 (<1)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	-	1 (<1)	1 (<1)
PLATELET COUNT DECREASED	1 (<1)	-	1 (<1)
Total Number of AEs	4	4	8
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	1 (<1)	4 (<1)	5 (<1)
LUNG DISORDER	-	2 (<1)	2 (<1)
OROPHARYNGEAL PAIN	1 (<1)	1 (<1)	2 (<1)
ASTHMA	-	1 (<1)	1 (<1)
Total Number of AEs	1	4	5
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total Pts With at Least one AE	-	4 (<1)	4 (<1)
ARTHRALGIA	-	2 (<1)	2 (<1)
CREST SYNDROME	-	1 (<1)	1 (<1)
MYALGIA	-	1 (<1)	1 (<1)
NECK PAIN	-	1 (<1)	1 (<1)
Total Number of AEs	-	5	5
EYE DISORDERS			
Total Pts With at Least one AE	2 (<1)	2 (<1)	4 (<1)
CONJUNCTIVITIS	1 (<1)	1 (<1)	2 (<1)
GLAUCOMA	1 (<1)	1 (<1)	2 (<1)
Total Number of AEs	2	2	4
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	1 (<1)	3 (<1)	4 (<1)
DIARRHOEA	1 (<1)	-	1 (<1)
INTESTINAL OBSTRUCTION	-	1 (<1)	1 (<1)
JEJUNAL PERFORATION	-	1 (<1)	1 (<1)
PAROTID GLAND ENLARGEMENT	-	1 (<1)	1 (<1)
Total Number of AEs	1	3	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	1 (<1)	3 (<1)	4 (<1)
PYREXIA	1 (<1)	1 (<1)	2 (<1)
ASTHENIA	-	1 (<1)	1 (<1)
INFLUENZA LIKE ILLNESS	-	1 (<1)	1 (<1)
Total Number of AEs	1	3	4
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	3 (<1)
CARPAL TUNNEL SYNDROME	-	1 (<1)	1 (<1)
PERIPHERAL MOTOR NEUROPATHY	1 (<1)	-	1 (<1)
SUBARACHNOID HAEMORRHAGE	-	1 (<1)	1 (<1)
Total Number of AEs	1	2	3

REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Total Pts With at Least one AE	1 (<1)	2 (<1)	3 (<1)
MENSTRUATION IRREGULAR	1 (<1)	1 (<1)	2 (<1)
MENOPAUSAL SYMPTOMS	-	1 (<1)	1 (<1)
Total Number of AEs	1	2	3
IMMUNE SYSTEM DISORDERS			
Total Pts With at Least one AE	1 (<1)	1 (<1)	2 (<1)
HYPERSENSITIVITY	-	1 (<1)	1 (<1)
HYPOGAMMAGLOBULINAEMIA	1 (<1)	-	1 (<1)
Total Number of AEs	1	1	2
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	2 (<1)	2 (<1)
DEEP VEIN THROMBOSIS	-	1 (<1)	1 (<1)
VENA CAVA THROMBOSIS	-	1 (<1)	1 (<1)
Total Number of AEs	-	2	2
HEPATOBILIARY DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
HEPATITIS FULMINANT	-	1 (<1)	1 (<1)
Total Number of AEs	-	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total Pts With at Least one AE	1 (<1)	-	1 (<1)
RADIUS FRACTURE	1 (<1)	-	1 (<1)
Total Number of AEs	1	-	1
METABOLISM AND NUTRITION DISORDERS			
Total Pts With at Least one AE	-	1 (<1)	1 (<1)
DIABETES MELLITUS	-	1 (<1)	1 (<1)
Total Number of AEs	-	1	1
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS			
Total Pts With at Least one AE	1 (<1)	-	1 (<1)
ABORTION MISSED	1 (<1)	-	1 (<1)
Total Number of AEs	1	-	1
PSYCHIATRIC DISORDERS			
Total Pts With at Least one AE	1 (<1)	-	1 (<1)
DEPRESSION	1 (<1)	-	1 (<1)
Total Number of AEs	1	-	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.

- **Discussion on clinical safety**

Based on the results from the pivotal study, the most common AE in the rituximab arm during the maintenance/observational phase, was infection and infestations (especially bronchitis and upper respiratory tract infection), which was reported for 37% of patients in the rituximab arms vs. 22 % of patients in the observation arm. Also AE belonging to the blood and lymphatic system class were more frequently observed in the rituximab maintenance arm. The difference was mainly caused by higher number of neutropenia cases (14 in the rituximab arm vs. 5 in the observation arm).
Overall, the most common class of SAE was neoplasm, occurring in both trial arms (17 patients in the observation arm and 20 in the rituximab arm).
The most common class of SAE in the rituximab arm was infections and infestations (25 patients in the rituximab arm vs. 6 patients in the observational arm).
The number of deaths was higher in the observation arm than in the rituximab arm (18 vs. 13 patients). Also the incidence of non-lymphoma deaths was higher in the observation arm than in the rituximab arm.

The results from the supportive study concerning the reported AEs and the difference between maintenance rituximab and observation were comparable with the AEs reported in the pivotal study. More AEs in the blood and lymphatic system and infections were observed in the rituximab maintenance arm in comparison with the observational arm.
The potential risk of PML and the risk of second malignancies require additional risk minimization activities and the proposed monitoring is adequate. As a consequence, section 4.4 of the SmPC has been updated to include information on the PML risk. Finally, since PML occurs predominantly in patients that are immunosuppressed, section 4.3 of the SmPC has been updated to include contraindication for patients in a severely immunocompromised state.

Due to postmarketing cases of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Posterior Leukoencephalopathy Syndrome (RPLS), the SmPC has been updated to reflect the risk factors for PRES/RPLS.
Overall, rituximab maintenance therapy was well tolerated and no unexpected safety findings were observed.

Pharmacovigilance

Risk Management plan
The MAH has provided an updated Risk Management Plan (RMP) version 5.1.

Table 28. Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
NHL/CLL – Identified Risks		
Acute infusion related reactions	Routine	Routine: Infusion-related reactions cannot be reliably predicted or prevented. However, the incidence and severity may be reduced by premedication and appropriate monitoring and treatment. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure.
Infections	Routine	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
Neutropenia	Routine + planned analysis of prolonged neutropenia in ML17102/CLL-8 study	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure An Analysis of prioloned neutropenia in ML17107 and BO17102 is being prepared and will be made available I January 2011 to fully assess this risk.
HBV reactivation	Routine	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
Tumour lysis syndrome	Routine	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
PML	Routine + continued expedited reporting of new cases/questionnaire used to better characterise all such reports (all indications).	Routine: There are no treatments available to prevent, retard, stop, or reverse the disease once established in patients. Enhanced pharmacovigilance practices including the use of a guided questionnaire and regular assessment reports of all PML cases are performed to monitor cases of PML. The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk with extended information in the label.
Serious viral infection	Routine	Routine: See Infections
GI perforation	Routine	Routine: There are no known ways of preventing GI perforation in patients receiving rituximab for haematological malignancies. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
Posterior Reversible Encephalopathy Syndrome (PRES)	Routine plus guided questionnaire	Routine: an update to the SmPC has been proposed with this based on the result of an issue workup on the subject DSR# 1036264. The MAD commits to the implementation of a guided questionnaire for PRES in the oncology indications. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
Impaired immunization response	Routine	Routine: an update to the SmPC has been proposed [based on results of a study in patients with NHL. All cases/reports will be evaluated and reported in the PSUR per routine PV procedure
NHL/CLL – Potential Risks		

Prolonged B-cell depletion	Routine + Further analysis of PRIMA (MO18264) study (expected 2011)	Routine: B-Cell depletion is the expected therapeutic outcome with rituximab. but detailed information on B-cell and immunoglobulin changes is provided in the SmPC. The effect of prolonged B-cell depletion in the rituximab maintenance population will be analysed using long-term follow-up from PRIMA. Additionally, the MAH considers the wording in the SmPC sufficient to inform prescribers of this risk.
Grade 3/4 and serious blood and lymphatic AEs in patients > 70 years with CLL	Routine	Routine. The SmPC already includes information on blood and bone marrow system disorders (without reference to age categories). The new text is also proposed for the SmPC.
Opportunistic infections	Routine	Routine: See Infections
AML/MDS	Routine	Routine: Cases of AML/MDS will be evaluated and reported in the PSUR per routine PV procedure
NHL/CLL – Missing Information		
Prolonged neutropenia	See neutropenia above	See neutropenia above
Pregnancy and Lactation	Routine	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of pregnancies that occur and their outcomes is carried out. The BSRBR, ARTIS and RABBIT register the occurrence of pregnancies in enrolled patients and follows outcome of the pregnancy by asking the patients.
Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
RA – Identified Risks		

Infections (including serious infections)	Routine Pharmacovigilance Activities	Routine: The labelling for the RA indication cautions prescribers regarding the use of rituximab in patients with an active infection or other predispositions to serious infection, and regarding the prompt evaluation and treatment of infections that occur following rituximab therapy. Company representatives will be informed as part of their training to draw prescribers' attention to this information. Additional: In ongoing and planned clinical trials, prospective monitoring of laboratory markers of humoral immune status (eg, B cell counts, Ig counts/titres, complete blood counts) is performed. The clinical trials allow placebo comparisons of humoral immunity markers during the double blind period, as well as long term follow up for patients who continue with rituximab in open label extensions. In ongoing and planned clinical trials, prospective data collection and focused evaluation of all infections/symptoms of infection is conducted. Spontaneous reports of hepatitis B infection will be assessed using a standardized questionnaire to determine if the infection is de novo or a reactivation of a previous infection. All reports of Hepatitis B or reactivation of Hepatitis B are expedited for reporting to the agency, with regular data reviews. All reports of tuberculosis or reactivation of tuberculosis will be carefully analysed and reported to the agency. As part of its rituximab-specific protocol, the BSRBR, ARTIS and RABBIT will collect data regarding the incidence of serious infections and the administration of IV immunoglobulins.
Acute Infusion-Related Reactions	Routine Pharmacovigilance Activities	Routine: The decision for all patients to receive IV corticosteroid pre-medication was based on the reduced incidence and severity of acute infusion reactions in patients in study WA17043, who were pre-treated with IV corticosteroid. In study WA17043, medically-reviewed acute infusion reactions following the first infusion of the first course occurred in 18/65 (28%) patients who received rituximab (1 g dose) without IV corticosteroid pre-medication compared to 24/127 (19%) patients who received rituximab with IV corticosteroid premedication. The addition of oral corticosteroid between rituximab infusions did not appear to provide any additional benefit over use of IV corticosteroid alone for the prevention of acute infusion reactions. Therefore the sponsor considers the use of IV corticosteroid as pre-medication to be advisable prior to all rituximab infusions. This advice is reflected in the SmPC. Additional: Spontaneous reports of possible infusion reactions will be assessed and evaluated using good pharmacovigilance practices. In ongoing and planned clinical trials, prospective data collection and evaluation of serious/severe infusion reactions will continue to be carried out in long term follow-up for patients in open-label extensions. As part of the proposed rituximab-specific protocols, the British Society of Rheumatology Biologics Register (BSRBR), the Swedish registry (ARTIS) and the German registry (RABBIT) will report serious infusion reactions.

Impaired immunization Response	Routine Pharmacovigilance Activities	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk.
RA – Potential Risks		
De Novo HBV, HBV reactivation and Opportunistic Infections	Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT	Routine: See recommendations for infections (including serious infections) above. Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any infection is carried out. Comparisons of incidence and rates between rituximab and placebo are made using pooled analyses from long term follow up of patients who continue with rituximab in open label studies is conducted. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding infections and outcomes. The MAH plans to update the SmPC section 4.4. informing that reactivation of hepatitis B infection can occur in Rheumatoid Arthritis patients receiving MabThera.
PML	The occurrence of PML is being monitored through the sponsor's enhanced pharmacovigilance system. For events reported to the sponsor's pharmacovigilance system as spontaneous reports, additional data will be collected by means of a Guided Questionnaire.	Additional: Patient alert card was implemented. Continued collection of reports from spontaneous reporting and clinical trial sources. The MAH aggressively pursues additional information from reporters for a number of pre defined terms that could potentially be representative of PML, in the form of a guided questionnaire [7296].
Malignant events	Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT and clinical trial observation	Routine: There are no options above and beyond standard cancer screening methods for malignant neoplasms. Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any neoplasm is carried out. Comparisons of incidence and rates between rituximab and placebo are made using pooled analyses from long-term follow-up of patients who continue with rituximab in open-label studies is conducted. Standardised Incidence Ratios (SIRs) compared to the US general population are made using the SEER database, together with comparison of SIRs to those from other RA cohorts. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding malignant events and outcomes.

Use in Pregnancy/lactation	Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of pregnancies that occur and their outcomes is carried out. The BSRBR, ARTIS and RABBIT register the occurrence of pregnancies in enrolled patients and follows outcome of the pregnancy by asking the patients.
Impact on cardiovascular disease	Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT	Routine: The MAH considers the wording in the SmPC sufficient to inform prescribers of this risk. Additional: Good pharmacovigilance practices will be utilized to identify any signals of impact on cardiovascular disease. Cardiac events will be monitored as part of the RMP in the PSURs. As part of the respective core protocols, the BSRBR, ARTIS and RABBIT collect data regarding the incidence of any serious co-morbidity leading to hospitalization, including serious cardiac events.
Gastrointestinal perforation	Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT	Routine: GI perforations in patients treated in autoimmune indications will continue to be monitored by the MAH. Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of gastrointestinal perforation is carried out. Data regarding gastrointestinal perforation will be monitored in the PSURs. BSRBR, ARTIS and RABBIT collect data regarding the incidence of any serious co-morbidity leading to hospitalization, including gastrointestinal perforation. This information will be included in 6-monthly reports to be provided by the registries to the MAH.
RA – Missing Information		
Immunogenicity and autoimmune disease	Routine and clinical trial observation, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT	Routine: N/A Additional: In ongoing and planned clinical trials, evaluation of serology data for HACA is carried out prospectively under open-label conditions. Focused evaluation of symptoms of immune complex disorder (eg, serum sickness) is also carried out. As part of their rituximab-specific protocols, the BSRBR, ARTIS and RABBIT will document the occurrence of serious immunological reactions. Data accrued from all clinical trials, spontaneous reports, and planned observational studies will be evaluated regularly for overall trends, new signals, and consistencies and/or inconsistencies across the various data sources. Spontaneous reports will continue to be analysed using event report frequencies. Data from ongoing and planned trials will be reported in Annual Safety Reports and from spontaneous reports and literature sources within Periodic Safety Update Reports.

4 Benefit risk assessment

Benefits

Beneficial effects

The data presented from the pivotal PRIMA trial and the supporting ECOG 1496 trial showed that rituximab maintenance therapy every two months for two years gives a significant improvement of PFS in patients with advanced follicular lymphoma who have responded to standard induction chemotherapies. PFS has been recognized by the CHMP as a relevant primary endpoint in this clinical situation, and as such, an improvement in PFS may be of clinical relevance.

The results of the PRIMA study showed that the 25th percentile PFS for patients on observation was 16.7 months and for patient on rituximab maintenance was 36 months, with a HR 0.50 [(CI 0.39; 0.64), investigator based] or 0.54 (IRC-based). However, it is difficult to evaluate the absolute PFS gain with nearly 75% of the patients still classified as responders at the end of the maintenance phase. The median has not been reached in the investigator-assessed dataset. For the IRC-assessed dataset the median PFS gain is 6.2 months (from 30.9 to 37.1 months). In the context of a very long natural history (median OS about 10 years) of the targeted disease, the long-term benefit of this gain is still uncertain.
Furthermore, there is no difference in OS for the two treatment strategies (observation vs. maintenance).
On the positive side, rituximab maintenance significantly delays time to next anti-lymphoma therapy by a year (a secondary endpoint) and may decrease the transformation rate (non statistically significant result). More patients are classified as responders (CR/CRu/PR) at the end of maintenance therapy (74% versus 55%).

The results of the supportive ECOG1496 were comparable to the results of the PRIMA study: a statistically significant increase of the PFS was observed (HR of 0.37 with a CI of 0.25; 0.56) after rituximab maintenance therapy in comparison with observation only. The PFS improvement in this study seems to be even better than in the PRIMA study. However the benefit might be overestimated as the patients included in the observational arm didn't receive rituximab at any moment of the trial.

Uncertainty in the knowledge about the beneficial effects

A median follow-up of about 2 years is relatively short for the assessment of long-term benefit of rituximab maintenance although the cut-off date allows a final analysis of the primary endpoint PFS. Taking into account that all patients will have a continuous pattern of relapse and retreatments, it is not realistic to evaluate the influence of rituximab maintenance on OS. However, patients must be followed up for PFS and OS for at least five years, final OS data should be submitted in time (FUM).

There certainly are data to support that a long remission after first-line therapy predicts a better response to subsequent therapies and a longer survival. However, as maintenance therapy after first-line treatment has yet to show an OS benefit, the biology may be different in patients who relapse on the background of rituximab maintenance therapy than in patients who have only been observed. The rituximab resistance rate after rituximab maintenance therapy at first remission has not been studied. More data about the rituximab resistance rate as the result of post-first line maintenance therapy are needed to estimate this effect on the success (response, PFS, OS) of eventual rituximab retreatment.

Both the pivotal study and the supportive study showed a clear trend towards a lower HR for PFS events in younger patients (0.45 in patients < 60 yrs. vs. 0.59 in patients > 60 yrs in the PRIMA trial). One might suspect that the benefit is further diluted in even older patients, e.g. patients > 70 year, who make up a considerable fraction of follicular lymphoma patients (25-30 %), according to a Dutch population-based registry study (Maartense et al. (2002), Ann Oncol 13(8): 1275-1284.) and approximately 20% in the ECOG 1496 study. Further subgroup analyses of the PRIMA trial (for which the trial is not powered) indicate that patients older than 70 or 75 years may have lesser benefit from rituximab maintenance therapy (HRs between 0.80 and 1.15, with very wide confidence intervals). A further subgroup analysis of the elderly patients is needed when more mature data become available, with more events making the subgroup statistics more meaningful.

The PRIMA study included only patients with a high-tumour burden according to the GELF criteria and it is not entirely clear whether the data can be extrapolated to all patients with follicular lymphoma.

However, the supportive ECOG study included patients with stage III-IV according to the Ann Arbor staging system making the claimed indication reasonable.

Risks

Unfavourable effects

Safety data from the pivotal PRIMA trial are in line with the SmPC and previous post-marketing experience for this monoclonal antibody that has been marketed in the EU since 1998. The important difference in safety is a clear increase in the incidence of infections and leuko-/neutropenia in patients treated with rituximab as maintenance. There is an increased incidence of SAEs related to infections, cardiac disorders and gastrointestinal disorders in the rituximab arm. The numbers are still rather low (maybe even if compared to an age-matched background population).

There is a clearly increased incidence of infectious AEs and SAEs in the rituximab arm. While the difference is clear regarding SAEs, the numbers are quite low (25 infectious SAEs in the rituximab arm and 6 SAEs in the observation arm).

The data do not raise concerns about a high risk of HBV reactivation during rituximab maintenance therapy. As in other studies, it is uncertain whether the observed sporadic occurrence of PML is secondary to rituximab or to previous chemotherapy/compromised immune system function. Unconfounded cases of PML have been reported in patients with RA treated with rituximab.

Furthermore, significant laboratory value differences between the rituximab and the observation arms are the suppressed level of B-cells and the (usually within normal ranges) reduced immunoglobulin counts in the rituximab arm.

It is reassuring that the numbers of deaths are lower in the rituximab maintenance arm with regards to both lymphoma-related and non-lymphoma-related deaths.

Uncertainty in the knowledge about the unfavourable effects

Relatively few elderly patients (>75 yrs) were included in the pivotal study. AEs and SAEs do not seem to increase with age. However, the elderly patients selected for a randomised trial do not necessarily reflect an age-matched background population for which we are concerned when considering the risk/benefit balance.

Balance

Importance of favourable and unfavourable effects

It is a dogma in cancer therapy that achievement of durable remission is of clinical benefit because eradication of all neoplastic cells is a prerequisite for long-term cure. A lesser reduction in the tumour burden for a period of time may also be of clinical benefit. Therefore, PFS represents an accepted intermediate efficacy endpoint. PFS should generally be supported by a prolongation in OS. However, considering the very long natural history for patients with newly diagnosed follicular lymphoma with a median survival of about 10 years, PFS remains the only realistic efficacy endpoint. In evaluating the importance of a clear PFS gain as shown in this application, one has to take into account the natural course of disease of patients with follicular lymphoma. The disease usually follows an indolent course with a continuous pattern of relapses after each therapy, the remissions having decreasing duration with increasing number of retreatments. In younger and middle-aged patients the cause of death is most commonly the lymphoma or the therapy related with secondary malignancies. At the time of death many patients will have had transformation to a more malignant aggressive lymphoma.

On that clinical background a PFS gain in a rather narrow time window cannot stand alone as measure of clinical benefit. Significant PFS gain has been adequately demonstrated by the pivotal and supportive study. The primary endpoint is supported by a higher response rate at the end of maintenance therapy (75%) compared to a rate of 55% in patients also reflected in a delay of 12 months in time to next therapy. Since such therapy most probably will comprise cytostatics, this delay is considered to be of clinical benefit. There are also data to support that a long remission after first-line therapy predicts a better response to subsequent therapies and a longer survival. However, these data are mainly derived from clinical series without maintenance and it is uncertain whether the findings can be extrapolated to the population in question. A high response rate will most probably also mean less constitutional symptoms but this effect has not been specifically addressed in this application. Finally, there are no indications that rituximab maintenance enhances the risk of histological transformation. Although insignificant so far, the incidence of transformation may be lower in patients receiving maintenance therapy.

On the negative side, the burden of additional maintenance therapy in terms of toxicity should be taken in account. The known safety profile of rituximab remains unchanged when the antibody is used as maintenance every two months for two years. The mortality is numerically lower in the maintenance group both in relation to lymphoma deaths and non lymphoma deaths.
Therefore, no serious unfavourable effects have been detected.

Benefit-risk balance

Discussion on the benefit-risk assessment

The application has demonstrated a very clear gain in PFS supported by a higher remission rate at the end of maintenance, a delay in the time to next antilymphoma therapy and a potential lower rate of histological transformation.
No serious safety concerns have been identified.

Therefore, the CHMP considered that the Benefit-Risk ratio of rituximab for the treatment of follicular lymphoma patients responding to induction therapy is positive.

All the proposed consequential changes to sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9 and 5.1 of the SmPC and to the Package Leaflet were agreed.

Further, the MAH has updated annex IIB to reflect the latest version of the Risk Management Plan (version 5.1) agreed with the CHMP, which is acceptable. Minor editorial changes have also been implemented.