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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

RITUXIMAB FOR THE FIRST LINE MAINTENANCE TREATMENT OF FOLLICULAR NON-HODGKIN'S LYMPHOMA

Roche Submission to the
National Institute for Health and Clinical Excellence
10th August 2010

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.126' rather than 'One trial126').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see 'Related procedures for evidence submission', appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

Brand name: MabThera®
Approved name: Rituximab

Principal mechanism of action

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.
Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on > 95 % of all B cell non-Hodgkin's lymphomas.
Rituximab causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all thought to be involved.

Marketing status

Rituximab does not currently have a UK marketing authorisation for the indication detailed in this submission (maintenance therapy in previously untreated follicular lymphoma patients responding to induction with chemotherapy plus rituximab).

Marketing authorisation (centralised process) has been applied for and a type II variation (90 day procedure) was started with the European Medicines Agency (EMA) on 19th March 2010. It is anticipated that opinion from the Committee on Medicinal Products for Human Use (CHMP) will follow on 23rd September 2010, with full European Union marketing authorisation following 44 days after this. Thus an estimated date for final authorisation is 7th November 2010

Pharmaceutical formulation

Two vials are currently available, and the same ones will be available for the new indication:
1: Single-use vial containing rituximab 100 mg/10 ml (2 x vials per pack).
2: Single-use vial containing rituximab 500 mg/50 ml (1 x vial per pack).
Each ml of solution contains 10 mg of rituximab.

Dose and dosing frequency

375mg/m^2 every 8 weeks for 2 years, or until disease progression.

Acquisition cost

The NHS cost of a 10 ml vial of rituximab (excluding VAT) is £174.63.
The NHS cost of a 50 ml vial of rituximab (excluding VAT) is £873.15.

Average cost of a course of treatment: £14,669 (excl VAT) for a 2 year course of treatment based on an average BSA of 1.8m^2.

Indication

It is expected that the new licence will allow the use of rituximab maintenance therapy in any follicular lymphoma patient responding to induction therapy. The following wording is anticipated in the summary of product characteristics (SmPC) (currently being evaluated by the regulatory authorities):
"Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy."

Thus the current wording in the SmPC limiting the use of rituximab maintenance to relapsed/refractory follicular lymphoma patients responding to induction therapy will be broadened to reflect the anticipated licence extension for rituximab maintenance in previously untreated patients.

Recommended course of treatment

The recommended dose of rituximab used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment with chemotherapy, with or without MabThera, is: 375 mg/m^2 body surface area once every 2 months until disease progression or for a maximum period of two years.

Comparators

The most appropriate comparator for first-line maintenance therapy in FL patients is "watch and wait" or observation, which is current standard clinical practice in the UK in patients responding to rituximab plus chemotherapy. The pivotal PRIMA trial, which forms the core of this submission, evaluated the benefit of maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in comparison with observation in previously untreated FL patients.

In the final scope, NICE have also recommended the inclusion of Zevalin consolidation as a comparator, however, for of the following reasons we have not considered it as a valid comparator:

- Zevalin's efficacy on patients pretreated with r-chemotherapy induction therapy has not been proven. PFS in progression-free survival (PFS) with Zevalin compared to observation (HR=0.722; p=0.4583)
- Usage of Zevalin consolidation after first-line rituximab plus chemotherapy in advanced FL in the UK is minimal. IMS hospital usage data for Zevalin reported £34,836 worth of Zevalin was dispensed in 2009. This equates to a total of **5 patients** being treated with Zevalin (across all indications)

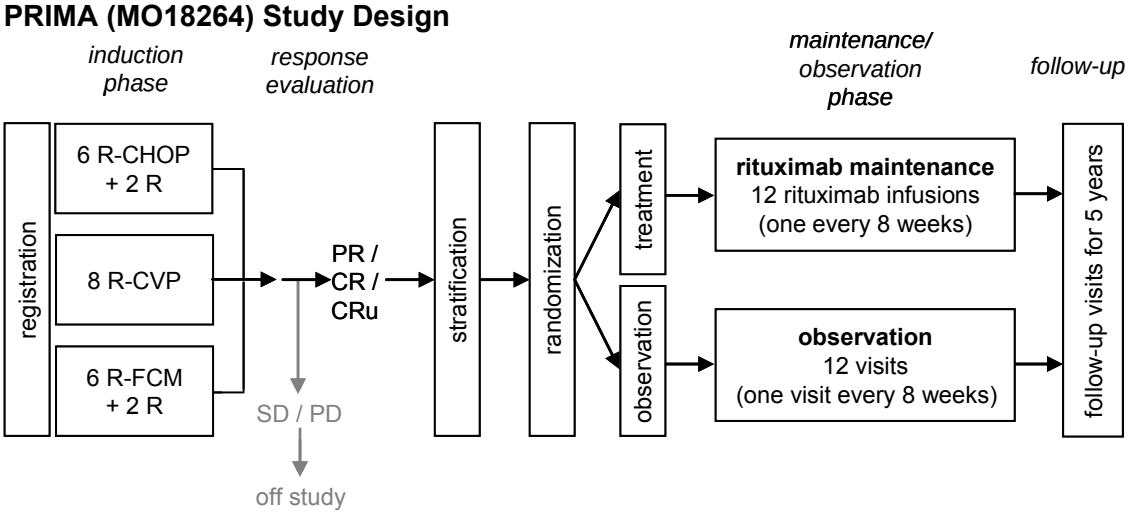
Key clinical evidence

The key clinical evidence in this submission comes from a single multi-centre randomised phase III study, PRIMA (see study design below). The primary objective of the PRIMA study was to evaluate the benefit of maintenance therapy with rituximab on progression-free survival as compared to no maintenance therapy (observation), after induction of response with chemotherapy plus rituximab in previously untreated patients with high-tumor-burden follicular lymphoma.

Secondary objectives included comparison of the following parameters between the maintenance and observation arms:

- event-free survival
- overall survival
- time to next anti-lymphoma treatment
- time to next chemotherapy treatment
- response rates at the end of maintenance/observation
- transformation rate at first relapse
- quality of life
- safety profile

PRIMA (MO18264) Study 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).

PRIMA Results

At the end of the induction phase, [redacted] of 1193 patients ([redacted]) achieved a response (CR: [redacted] patients, [redacted]; CRu: [redacted] patients, [redacted]; PR: [redacted] patients, [redacted]), and 1019 patients were randomized in the maintenance/observation phase.

Maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in patients with high-tumor-burden follicular lymphoma resulted in a clinically relevant and statistically significant improvement in the primary endpoint of progression-free survival as compared to no maintenance therapy (observation). This result was supported by improvements in all of the secondary efficacy endpoints. Under a nominal significance level of $\alpha = 0.05$ (two-sided), significant improvements were observed for all of the secondary endpoints except overall survival and transformation rate. Both of these parameters require longer follow-up and/or more events to draw meaningful conclusions, although in both cases the results obtained so far tend towards favouring the rituximab maintenance arm.

Overview of efficacy parameters (MITT)

Efficacy Parameter	Observation N = 513	Rituximab N = 505	HR / OR	p-value*
Primary Endpoint: PFS				
Investigator-Assessed PFS (Section 5.5.2.1.1)				
Median time to event	NE	NE		
25th percentile	507 days (16.7 months)	1096 days (36.0 months)	HR = 0.50 [0.39;0.64]	p < 0.0001
One-year PFS rate [95% CI]	0.82 [0.79;0.85]	0.89 [0.87;0.92]		
IRC-Assessed PFS (Section 5.5.2.1.2)				
Median time to event	939 days (30.9 months)	1130 days (37.1 months)		
25th percentile	458 days (15.0 months)	804 days (26.4 months)	HR = 0.54 [0.42;0.70]	p < 0.0001
One-year PFS rate [95% CI]	0.81 [0.78;0.85]	0.87 [0.84;0.90]		
Secondary Endpoints				
Event-free Survival (Section 5.5.2.2.1)				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted]	[redacted]		
Overall Survival (Section 5.5.2.2.2)				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted]	[redacted]		
Time to Next Anti-Lymphoma Treatment (Section 5.5.2.2.3)				
Median time to event	NE	NE		
25th percentile	746 days (24.5 months)	1135 days (37.3 months)	HR = 0.61 [0.46;0.80]	p = 0.0003
One-year event-free rate [95% CI]	0.89 [0.87;0.92]	0.92 [0.89;0.94]		
Time to Next Chemotherapy Treatment (Section 5.5.2.2.4)				
Median time to event	NE	NE		
25th percentile	884 days (29.0 months)	1135 days (37.3 months)	HR = 0.60 [0.44;0.82]	p = 0.0011
One-year event-free rate [95% CI]	0.91 [0.89;0.94]	0.92 [0.90;0.95]		
Overall Response Rate at End of Maintenance/Observation (Section 5.5.2.2.6)				

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 5.5.2.2.7)				
Patients with progression	[redacted]	[redacted]		
Transformation	[redacted]	[redacted]	[redacted]	[redacted]
No transformation (no progression or missing)	[redacted]	[redacted]	[redacted]	

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).

Quality of life

Quality of life analyses based on both the FACT-G and QLQ-C30 questionnaires showed that active therapy with rituximab maintenance did not adversely affect patient-reported quality of life.

Safety results

During the maintenance/observation phase, 97% of patients in the rituximab arm and 90% of patients in the observation arm experienced at least one toxicity as recorded on a customized toxicity checklist. Adverse events (Grade 3–5 toxicities, Grade 2–5 infections, and serious adverse events) were more common in the rituximab arm than in the observation arm (52% vs 35%), and the incidence of Grade 2–5 infections was also higher in the rituximab arm than in the observation arm (37% vs 22%). However, most infections were mild to moderate in severity: the incidence of Grade 3–5 infections was only 4% in the rituximab arm compared with less than 1% in the observation arm. At the time of clinical cut-off, a total of 31 patients (MSAP) had died (18 observation, 13 rituximab). Disease progression accounted for the deaths of 22 patients, and there were five fatal adverse events. Two additional deaths from progressive multifocal leukoencephalopathy were reported after the clinical cut-off in patients who had received subsequent therapy for progressive lymphoma. Overall, there were no unexpected safety findings in this study.

Overview of safety during the maintenance/observation phase (MSAP)

Safety Parameter	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
Toxicities[a]	459 (90)	485 (97)

Adverse Events[b]	179 (35)	263 (52)
Grade 3/4 AEs	81 (16)	114 (23)
Serious Adverse Events	63 (12)	95 (19)
Withdrawal from treatment due to toxicity	1 (<1)	10 (10)
AEs leading to treatment discontinuation	8 (2)	19 (4)
AEs leading to dose modification	–	30 (6)
AEs leading to death	2 (<1)	3 (<1)
Infection AEs (Grade ≥ 2)	114 (22)	184 (37)
Grade 3/4 infections	5 (<1)	22 (4)
AEs occurring within one day after treatment/observation visit	46 (9)	61 (12)
Total Deaths	18 (4)	13 (3)
Death due to cause other than lymphoma	6 (1)	3 (<1)

a Toxicities are based on the checklist CRF page (regardless of grade).
b Includes Grade 3–5 toxicities, Grade 2–5 infections, and SAEs regardless of grade, as recorded on the AE CRF pages.

Clincial Effectiveness Conclusions

The results of the primary analysis of the PRIMA trial in patients with previously untreated follicular lymphoma responding to induction with rituximab plus chemotherapy show:

A highly statistically significant and clinically meaningful benefit of rituximab maintenance therapy compared with observation in terms of progression-free survival ($p < 0.0001$, stratified log-rank test). The risk of disease progression or death was significantly reduced by 50% in patients receiving rituximab maintenance therapy compared with those in the observation arm (investigator assessment: stratified HR 0.50, 95% CI [0.39;0.64]). An updated analysis of investigator-assessed PFS performed on data from randomization up to January 15, 2010 with an additional 12 months of follow-up confirmed the results of the primary PFS analysis (stratified HR [redacted], 95% CI [redacted]).

Analysis of PFS based on an independent review of cases gave consistent results and confirmed the significant risk reduction with rituximab maintenance therapy compared with observation (IRC assessment: stratified HR 0.54, 95% CI [0.42;0.70], $p < 0.0001$, stratified log-rank test).

All prespecified sensitivity analyses showed that the PFS results were robust, and the benefit of rituximab maintenance was confirmed across key patient subgroups.

Analysis of the secondary endpoints event-free survival, time to next anti-lymphoma treatment, time to next chemotherapy, and overall response also support the benefit of rituximab maintenance treatment, with statistically and clinically significant improvements for patients in the rituximab arm.

There were too few deaths to make definitive conclusions on overall survival at the time of the primary or updated analysis (clinical cut-off January 15, 2010)—a longer follow-up is required to evaluate the effects of rituximab maintenance on overall survival in this study.

The safety profile observed in the PRIMA study was consistent with the known safety profile of rituximab. There were no new or unexpected safety signals during or after maintenance treatment with rituximab.

Quality of life analyses based on the outcomes of both FACT-G and EORTC QLQ-C30 questionnaires confirmed that maintenance therapy with rituximab did not have a detrimental effect on patient-reported quality of life.

In summary, the PRIMA study provides strong evidence that maintenance therapy with rituximab, after response to induction with rituximab plus chemotherapy, is effective in prolonging PFS in patients with previously untreated follicular lymphoma. Furthermore, maintenance therapy with rituximab is well tolerated and confers little additional toxicity compared with observation.

Demonstrating the Cost Effectiveness of Rituximab in 1st line maintenance

Introduction

The economic evaluation utilises the key outcomes of the PRIMA clinical trial and is designed for the purposes of estimating life-time NHS costs and QALYs for rituximab (intervention) and observation (comparator) in 1st line maintenance. The model conforms with the reference case as described in NICE's Guidance to the Methods of Technology Appraisal. The economic model developed was a four-state Markov model, where patients are assumed to be within one of four possible discrete health states at any given time; "progression-free survival in 1st line maintenance" (PF1), "progression-free survival in 2nd line" (PF2), "progressed disease" (PD) or "death".

Methods

The model was developed over a 25 year life-time time horizon to capture the lifetime of an average FL patient. This required extrapolation of the primary endpoint, PFS 1st line (PF1), beyond the PRIMA follow-up period (median 38.37 months) using the most appropriate parametric fit. A number of parametric models were fitted on the trial data and the Gompertz model was found to provide the best fit. Gompertz was used to extrapolate PF1 beyond the trial follow-up for both the intervention and comparator arms. Cumulative hazard plots over time demonstrate that the treatment effect of rituximab maintenance is maintained long after patients stop receiving treatment. Similar trends in terms of rituximab's treatment effect have been observed in other R-maintenance trials, such as the EORTC 20981. Taking a conservative approach and consistent with other trials and NICE submissions the treatment effect of R-maintenance was applied for the first 72 months (mean follow-up from Van Oers study demonstrating sustained treatment effect of rituximab maintanence) rather than for the entire duration patients remain in PF1.

Due to extensive censoring of overall survival in PRIMA (95% and 84% in the rituximab and observation arms, respectively), the probability of progressing and the probability of dying in second-line or third line were obtained from the EORTC 20981 trial which provides a robust data source for examining 2nd line outcomes (6 years median follow-up) (van Oers et al., 2010). According to NICE guidance (TA 137) patients in 2nd line should be treated with R-CHOP induction followed by rituximab

maintenance. Data from PRIMA showed that 11.9% of patients in the treatment group relapsed within one year of receiving their last rituximab dose (year 3 post-randomisation), while 19.3% of patients in the observation arm of the study relapsed within 1 year of receiving rituximab treatment (year 1 post randomisation). It has been assumed in the model that these patients will not receive further treatment with rituximab in 2nd line but will be treated with chemotherapy induction.

There have been no studies or trials investigating patient outcomes with prolonged exposure to rituximab in multiple lines of therapy. However the Appraisal Committee in the consideration of rituximab as a 2nd line therapy heard from clinical experts that "the evidence indicated that follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy. Although it noted this as an area of uncertainty, the Committee accepted that this was biologically plausible given its [rituximab's] mechanism of action" (FAD TA 137). This evaluation minimised the impact of these uncertainties by extracting the latest data from the follow-up from the EORTC study and applying the transition probabilities in both arms of this evaluation.

Predicted time in each health state was weighted using published and previously NICE utilised follicular lymphoma utility scores, derived from UK FL patients using the EQ-5D uinstrument (Pettengell et al. 2008). Thisaccounted for patient quality of life and estimate the Quality Adjusted Life Years (QALYs).

Remaining model inputs were taken from the published literature where possible and supplemented with UK expert medical opinion where necessary.

Cost Effectiveness Results

Rituximab 1st line maintenance treatment cost an additional £14,699 per patient (12 cycles in accordance to the expected licensed dosing, although patients in PRIMA received 10.5 cycles on average). Over an expected lifetime, R-maintenance is estimated to generate an additional £ 14,702 of total costs per patient compared to observation. R-maintenance is predicted to extend progression free survival (PF1) by 1.554 years and discounted overall survival by 1.27 years compared to observation.

The cost per QALY has been demonstrated to be robust when subject to structural, deterministic and probabilistic sensitivity analysis. Rituximab treatment can be regarded as a highly cost effective treatment for the 1st line maintenance treatment of FL with a high degree of certainty.

The base case incremental cost effectiveness ration for R-maintenance in 1st line compared to observation is estimated to be **£15,978 per QALY**. This is comfortably below the lower NICE threshold of £20,000 per QALY gained. The detailed results are shown in the table below.

Table 1: Base-case cost-effectiveness results

	Intervention – Observation (in 1st line maintenance)	Intervention – Rituximab 1st line maintenance
Technology acquisition cost	£0	£12,222 per cycle
Administration cost	£0	£251 per infusion
Total life-time costs	£66,721	£85,402

Incremental total costs	18,681	
LYG	9.02	10.29
Incremental LYG	1.271	
QALYs	7.21	8.38
QALY difference	1.17	
ICER	**15,977**	
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: MabThera®

Approved name: Rituximab

Therapeutic class: Antineoplastic chimeric monoclonal antibody

1.2 What is the principal mechanism of action of the technology?

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on > 95 % of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce direct cell death via apoptosis.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Rituximab does not currently have a UK marketing authorisation for the indication detailed in this submission.

Marketing authorisation (centralised process) has been applied for and a type II variation (90 day procedure) was started with the European Medicines Agency (EMA) on 19th March 2010. It is anticipated that opinion from the Committee on Medicinal Products for Human Use (CHMP) will follow on 23rd September 2010, with full European Union marketing authorisation following 44 days after this. Thus an estimated date for final authorisation is 7th November 2010.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

N/A. Marketing authorisation is not anticipated until November 2010.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

It is expected that the licence will allow the use of Rituximab maintenance therapy in any follicular lymphoma patient responding to induction therapy. The following wording is anticipated in the summary of product characteristics (SmPC) (currently being evaluated by the regulatory authorities):

"Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy."

Thus the current wording in the SmPC limiting the use of rituximab maintenance to relapsed/refractory follicular lymphoma patients responding to induction therapy will be broadened to reflect the anticipated licence extension for rituximab maintenance in previously untreated patients.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The interim analysis from the pivotal PRIMA study will be published in full in a peer-reviewed journal (anticipated early 2011) and will include additional follow-up data. Key clinical outcomes following an additional clinical cut-off made on 15th Jan 2010 (providing an additional 12 months of follow-up data) are also included in sections 5.5.3 and 5.9.2.13 of this submission. The PRIMA interim data were presented at the ASCO[1] and EHA[2] annual meetings in 2010.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

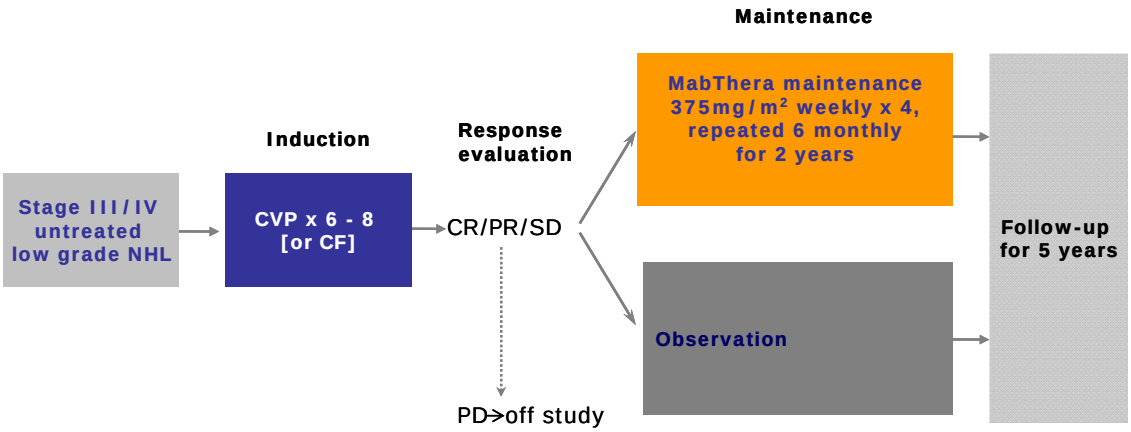
The technology will be available for use as maintenance therapy for previously untreated follicular lymphoma once marketing authorization is granted by the European Medicines Agency (EMA) in November 2010.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Rituximab is currently licensed in the USA as maintenance therapy in first-line low grade non-Hodgkin lymphoma patients following CVP combination chemotherapy based on data from the randomised phase III ECOG 1496 study[3]. The study design is outlined in

Figure 1 below. Using 4 weekly doses of rituximab every 6 months for up to 2 years, this study demonstrated significantly prolonged median PFS with CVP followed by maintenance vs CVP alone (4.3 years vs 1.3 years $p<10^{-9}$).

Figure 1: ECOG 1496 study design



1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The indication in this submission will also be evaluated by the Scottish Medicines Consortium in October 2010. Full guidance to NHS Scotland is expected by January 2011.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	Two vials are currently available, and the same ones will be available for the new indication: 1: Single-use vial containing rituximab 100 mg/10 ml. 2: Single-use vial containing rituximab

	500 mg/50 ml. Each ml of solution contains 10 mg of rituximab.
Acquisition cost (excluding VAT)	The NHS cost of a 10 ml vial of rituximab (excluding VAT) is £174.63. The NHS cost of a 50 ml vial of rituximab (excluding VAT) is £873.15.
Method of administration	Rituximab is administered by intravenous infusion typically in a hospital chemotherapy day-case unit or outpatient clinic.
Doses	375mg/m^2
Dosing frequency	Every 8 weeks for 2 years, or until disease progression.
Average length of a course of treatment	2 years
Average cost of a course of treatment	£14,669 (excl VAT) for a 2 year course of treatment based on an average BSA of 1.8m^2.
Anticipated average interval between courses of treatments	Treatment is for a maximum period of 2 years (or until disease progression).
Anticipated number of repeat courses of treatments	Patients will receive one (2 year) course of treatment in the first-line setting.
Dose adjustments	No dose adjustments of Rituximab are recommended.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are required to select previously untreated follicular lymphoma patients for treatment with rituximab maintenance. All patients identified as having a partial response or complete response to first-line induction therapy will be eligible for rituximab maintenance. Intravenous administration of rituximab does utilise healthcare resources.

Rituximab is administered during hospital day-case visits. Whenever rituximab is administered, patients require routine nursing observation for the duration of rituximab infusion, in case of toxicity that may require intervention (usually in the form of interruption or slowing of the rituximab infusion). It has been reported that a patient's first rituximab infusion (a dose of 375mg/m^2) takes a mean of 5.2 hours, with subsequent infusions typically taking about 3.5 hours when the licensed infusion schedule is followed [4]. Maintenance infusions are treated as a subsequent infusion and take closer to this shorter time of 3.5 hours.

Roche is also aware that an accelerated infusion schedule has been increasingly adopted by UK treatment centres. This unlicensed schedule allows most patients to receive second and subsequent infusions of rituximab over much shorter times, with a total dose of 375mg/m^2 being given over 90 minutes[5].

Since rituximab is already widely used for the treatment of diffuse large B-cell lymphoma and follicular lymphoma within the NHS, and as maintenance therapy in relapsed/refractory follicular lymphoma, staff will be very familiar with the infusion procedure and monitoring required during drug infusion and it is not anticipated that any additional training will be required.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

In order to receive maintenance rituximab, which is given as an intravenous (IV) infusion, an additional 12 outpatient treatments will be required. It is likely that these

will, generally, be incorporated into routine follow-up appointments, which are generally scheduled in 2-3 monthly intervals, so that they will not require patients to make extra hospital visits.

Whenever rituximab is administered, patients require routine nursing observation for the duration of rituximab infusion, in case of toxicity that may require intervention (usually in the form of interruption or slowing of the rituximab infusion).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Maintenance rituximab is given alone. The only additional medications mandated in the SmPC for use in conjunction with rituximab are premedication with paracetamol and an antihistamine immediately prior to each infusion. These are given to reduce the incidence and severity of infusion reactions.

Occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids are required for symptomatic treatment of severe infusion related reactions.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

What is follicular lymphoma?

Follicular lymphoma is one of a group of diseases known collectively as non-Hodgkin lymphomas (NHLs) - cancers arising from the lymphoid cells of the immune system. These cells normally have a key role in protecting the body from pathogenic microorganisms.

Presentation of follicular lymphoma

Malignant transformation of lymphocytes results in their uncontrolled replication. This usually starts within the lymph nodes, mainly those of the neck, armpits and groin. Swelling of these structures often provides the first clinical manifestation of illness, though other symptoms including fever, drenching night sweats, weight loss (so-called "B-symptoms") and tiredness may also be present at diagnosis or develop later.

Epidemiology of follicular lymphoma

In 2007 there were 10,917 new cases of NHL recorded in England and Wales[6]. It can be assumed that 22% (2,024) of these were follicular lymphomas (Non-Hodgkin's Lymphoma Classification Project, 1997)[7] and that 85% (1,720) of these would have been diagnosed as Stage III/IV cancers requiring systemic therapy[8].

For NHL as a whole, The age-standardised incidence rate for NHL increased by more than a third (35%) in the twenty-year period between 1988-2007. mirroring the increases in many other countries[6]. Although unexplained, it is considered that this increase in incidence is genuine rather than a result of improved diagnosis and that it is the consequence of an increase in the incidence of several lymphoma subtypes, including follicular lymphoma[6]. In the late 1990's and early 2000's incidence showed signs of levelling off suggesting that the recent rapid growth in new cases of NHL is slowing.

The incidence of NHL is similar in men and women (M/F ratio 1.1/1.0) and increases with age – rates increase sharply in people over 50 and around two-thirds of all cases are diagnosed in people over 60 years of age[6].

Most cases of NHL, including follicular lymphoma, have no identifiable cause though a number of risk factors are known. These include chronic immunodeficiency caused by disease (e.g. rheumatoid arthritis and acquired immunodeficiency syndrome) or drugs (e.g. long-term antirejection therapy following organ transplantation), and certain infectious agents (e.g. Helicobacter pylori infection, which is associated with MALT lymphomas). Environmental factors such as occupational exposure to tetrachloroethylene and agricultural biocides have also been suggested as possible causes of lymphoma[6].

Prognosis in follicular lymphoma

Survival for patients with follicular lymphoma is prolonged. Different figures for median survival have been reported, but 8-10 years from diagnosis is typical[9,10]. However, these are likely to be underestimates since there is good evidence from recent large population-based[11] and single institution studies[12,13,14] that survival is improving, probably as a consequence of improved treatment. Even at 8-10 years, survival is about double that reported in the years before the advent of cytotoxic chemotherapy indicating that appropriate treatment does alter the long-term course of the disease [15].

Despite this, most patients with follicular lymphoma ultimately die of their disease. For example, amongst a group of 147 patients followed for over 15 years from diagnosis by Lister, 94 died during the observation period, with 76 deaths attributed to progressive lymphoma [10].

Prognosis is partly determined by the extent of disease at diagnosis, which is usually described using the Ann-Arbor staging system, as shown in Table 3:

Table 3: Ann-Arbor staging system of non-Hodgkin's lymphoma[16]

Stage I	Involvement of a single lymph node region (I), or localised involvement of a single extralymphatic organ or site (IE).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localised involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), that may also be accompanied by localised involvement of an extralymphatic

	organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Other factors besides disease stage have been identified as having prognostic significance. Five of these were incorporated into the International Prognostic Index (IPI) which allows a composite IPI score to be calculated[17]. This has been shown to be highly predictive of long-term survival. Although the IPI was formulated for aggressive lymphomas it was also applied to more indolent forms of the disease, like follicular lymphoma. More recently, the Follicular Lymphoma Prognostic Index (FLIPI) has been devised specifically for this type of lymphoma[18].

Although the FLIPI is well accepted as having prognostic significance, it is not routinely used to guide treatment, which is generally determined by disease stage plus clinician and patient preference for a particular chemotherapy regimen.

2.2 How many patients are assumed to be eligible? How is this figure derived?

All stage III/IV previously untreated follicular lymphoma patients responding to induction therapy will be eligible for treatment with rituximab maintenance. This is anticipated to equate to 1656 patients per year in the UK, as outlined in the model below[19].

Table 4: Number of UK patients eligible for first-line rituximab maintenance therapy

	Assumptions	References
UK Population	**61,205,249**	Mid-2007 ONS UK population estimates: http://www.statistics.gov.uk Isle of Man: http://www.iomguide.com/peoplelivingfactfile.php Guernsey: http://www.gov.gg/ccm/policy-and-hr/facts-and-figures/2008-facts-and-figures-booklet.en Alderney:http://www.alderney.gov.gg/index.php/pid/51/view/109 Jersey: http://www.gov.je/ChiefMinister/Statistics/News/Population2007.htm
Incidence of NHL	0.017%	Cancer Research UK 2005 (http://info.cancerresearchuk.org/cancerstats/types/nhl/incidence/)
Number of NHL patients	*10466*	
% follicular lymphoma (FL)	22%	The non-Hodgkin's lymphoma classification project (1997). A clinical evaluation of the international lymphoma study group classification of non-Hodgkin's lymphoma. Blood 89(11): 3909-3918
Number of FL patients	*2303*	
% watch and wait	6%	Synovate Market Research 2006
Number of FL patients requiring treatment	*2164*	
% stage III/IV	85%	Shipp MA, Mauch PM, Harris NL. (1997) Non-Hodgkins Lymphomas. In: DeVita, Jr. VT Hellman S, Rosenberg SA, eds. Cancer. Principles and Practice of Oncology. Volume 2 (ed. 5). Philadelphia: Lippencott-Raven: 2165-2220
Number of stage III/IV patients	*1840*	
% eligible for rituximab	100%	
No. eligible patients for 1st line therapy	*1840*	
1st line therapy (rituximab + chemotherapy) response rate (%)	90%	Clinical Study Report – MO18264 (PRIMA) – Report No. 1034795 – March 2010
Number eligible for 1st line maintenance therapy	*1656*	

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Current NICE guidelines on the use of rituximab in previously untreated follicular lymphoma (TA110) only specify the use of R-CVP in this setting, as was consistent with the marketing authorization for rituximab at the time of review in 2006. The licence for rituximab has since been broadened in January 2008 to accommodate its use in combination with any chemotherapy, based on more recent evidence and is reflected in the European ESMO guidelines[21] and SMC guidance[20].

NICE technology appraisal 137 provides guidance on the use of rituximab with any suitable chemotherapy for induction in patients with relapsed/refractory follicular non-Hodgkin lymphoma, followed by rituximab maintenance every three months for two years, or until disease progression.

The current technology appraisal considers the use of rituximab maintenance treatment in patients with previously untreated follicular lymphoma requiring treatment who respond to first line immunochemotherapy based on the phase III, PRIMA trial. The PRIMA study was not powered to show significant differences between subgroups. Consequently, any subgroup analyses are exploratory in nature. Furthermore, the licensed indication for rituximab is not anticipated to be restrictive in terms of the population and hence the intention to treat (ITT) population within the PRIMA trial was considered the most appropriate population upon which to base the economic evaluation. It was also considered that this population is representative of the likely patient group that will receive rituximab maintenance in the UK.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Diagnosis

Recent European Society of Medical Oncology guidelines set out the accepted procedure for diagnosis and staging of follicular lymphoma [21]. Treatment of patients once diagnosed will depend on the staging of their disease after thorough assessment including; computed tomography (CT) scan of the next, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy. Patients would also receive a full blood count and routine blood chemistry.

Staging

Staging is made according to the Ann Arbor system (Table 3 above) with mentioning of bulky disease[16]. The Follicular Lymphoma-specific International Prognostic Index should be determined for prognostic purposes. As set out in the guidelines, it is imperative that staging is completed thoroughly, as it will determine patients' treatment.

First Line Treatment

Stage I/II Disease

Approximately 15% of patients present with early-stage disease[8]. Patients considered to have limited, stage I-II, disease may be candidates for localized radiotherapy treatment, which can have a curative potential[21]. Around half of patients so treated are free of relapse after 5 years. Patients who reach this point have a very low risk of future relapse. In one large series, relapse-free survival rates were 55%, 44%, 40% and 37% at 5, 10, 15 and 20 years, respectively, suggesting that only a subpopulation of patients will have a prolonged disease-free interval after radiotherapy, but that for this group, relapse more than 10 years after treatment is rare.[22]

Stage III/IV Disease

Systemic therapy is only recommended in patients with stage III and IV disease with evidence of systemic symptoms, high tumour burden, rapid disease progression, or other key features. To date, no curative therapy had been established for patients with advanced follicular lymphoma[21], so the natural course of the disease once treatment is required follows a cycle of treatment induced remission followed by eventual relapse – with each remission duration becoming shorter and less patients responding to each cycle of therapy[23,24].

European guidelines currently specify that if complete remission and long progression free survival is to be achieved, rituximab in combination with chemotherapy (CHOP, CVP or FC(M) or bendamustine) should be used in advanced stage FL patients requiring treatment.[21] Current NICE guidelines on the use of rituximab in previously untreated follicular lymphoma (TA110) only specify the use of R-CVP in this setting, as was consistent with the marketing authorization for rituximab at the time of review in 2006[25]. The licence for rituximab has since been

broadened to accommodate it's use in combination with any chemotherapy, based on more recent evidence and is reflected in the European guidelines[21] and SMC guidance[26].

Antibody monotherapy or single agent alkylating agents (e.g. chlorambucil) can be considered an alternative in previously untreated follicular lymphoma patients with particularly low risk disease, or those unsuitable for more intensive treatments[21].

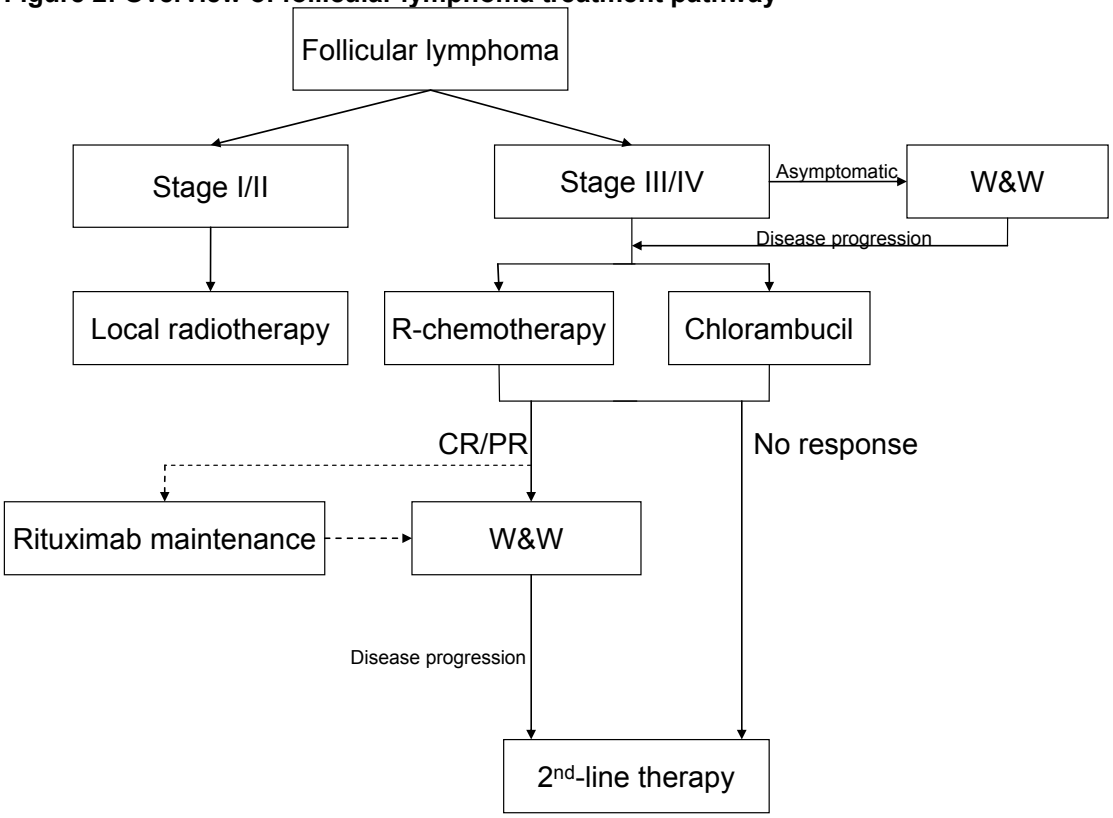
Until recently, the benefit of maintenance and consolidation treatment options after response to first line chemotherapy was not clear. The current standard approach in the UK is observation, with retreatment at relapse. The 2010 ESMO guidelines state that "rituximab maintenance is currently [being] tested in first line therapy" – referring to the ongoing PRIMA trial, and go on to state "Radioimmunotherapy consolidation prolongs progression free survival after chemotherapy [alone], but its benefit following rituximab combinations has not been established"[21]. To date, no NICE guidance has endorsed the use of a radioimmunotherapy consolidation approach in this setting.

Maintenance therapy is not currently widely used after patient's first response to immunochemotherapy, and standard practice in the UK is to closely observe patients until evidence of disease progression, at which point second-line therapy is initiated.

Impact of first line maintenance

The aim of using rituximab maintenance therapy in previously untreated follicular lymphoma patients responding to induction therapy is to extend and deepen the first and often most durable remission[23,24]. It would be expected, as in the relapsed/refractory follicular lymphoma setting, that extended progression free survival yielded by rituximab maintenance would delay time to relapse and therefore the burden of further chemotherapy treatment.[27,*28*] As demonstrated in the relapsed setting this approach may also ultimately extend patient overall survival but will require a significantly longer period of follow-up to become apparent.

Figure 2: Overview of follicular lymphoma treatment pathway



As regards how the introduction of first-line rituximab maintenance will impact on subsequent lines of treatment, it is likely that patients who have had a "durable" period of remission after finishing maintenance therapy will qualify for re-treatment with R-chemotherapy induction. Patients subsequently responding to second-line rituximab plus chemoptherapy are also likely to qualify for re-treatment with rituximab maintenance. This approach is supported by current ESMO guidelines, which state that, in terms of the treatment of relapsed disease "…Rituximab should be added if the previous antibody containing scheme achieved a >6-month duration of remission" and "Rituximab maintenance for up to 2 years has a favourable side-effect profile and based on a systematic meta-analysis, substantially prolongs PFS and overall survival in relapsed disease even after antibody-containing induction"[21]. Several clinical trials also support the concept of re-treatment with rituximab at relapse (Table 5), suggesting that re-treatment with either rituximab monotherapy or in combination with chemotherapy can induce equally long or even longer response durations that those obtained following the intial use of rituximab. Finally, NICE have also considered the concept of rituximab re-treatment in TA137. The appraisal committee in it's consideration of the evidence heard from clinical experts that "the evidence indicated

that follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy. Although it noted this as an area of uncertainty, the Committee accepted that this was biologically plausible given its [rituximab's] mechanism of action"[29].

Table 5: Clinical trials using rituximab as re-treatment in follicular lymphoma

Study[Ref] (year)	No. (evaluable)	Disease	Re-treatment regimen	RR (%)	CR (%)	[1]PFS or [2]TTP/RD months (after first R course)
Johnston et al (2010)[30]	178	B-NHL	Rx4 R-chemotherapy	66	37	13.2 (12.5) / NA
Igrashi et al (2001)[31]	13	IL	Rx4	38	0	15.1 (8.2) / NA
Davis et al (2000)[32]	58 (57)	FL=95% SLL=5%	Rx4	40	11	[2]17.8# (12.4) / 16.3* (9.8)
Coiffier et al (2002)[33]	59	B-NHL	Rx4 R-chemotherapy	93	42	[2]20 (12) / NA

RR: response rate: CR: complete remission; PFS: progression-free survival; TTP: time to progression; RD: response duration; IL: indolent lymphoma; FL: follicular lymphoma; SLL: small lymphocytic lymphoma; NHL: Non-Hodgkin lymphoma; R: rituximab (375mg/m2); NA: not available; * Kaplan-Meier estimates.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Approximately 93% of all eligible previously untreated stage III-IV follicular lymphoma patients in the UK currently receive rituximab in combination with chemotherapy as standard treatment[34]. Of these patients, and according to current NICE guidance (TA110), approx 67% are treated with rituximab plus CVP, 16% are treated with R-CHOP, with the remainder receiving rituximab combined with other chemotherapies34. The lack of consensus in terms of the preferred combination partner for rituximab in this setting is likely driven by several factors, including (i) a breadth of data from several randomised trials and a meta-analysis[51,52,53,35,36,37, 38] demonstrating that the clinical benefit associated with the addition of rituximab to chemotherapy is independent of the chemotherapy backbone. It should be noted that it was these data that formed the core of a filing package submitted to the EMA by

Roche that lead to a broadened R-chemotherapy licence for rituximab in January 2008 for patients with previously untreated follicular lymphoma; (ii) robust health outcomes data demonstrating the cost-effectiveness of R-chemotherapy[39] (NB this will be the subject of a NICE re-review, scheduled for October 2010); (iii) no directly comparative, randomised trial data exists to show that the addition of doxorubicin to rituximab-based upfront immunochemotherapy improves clinical outcomes (ie no head-to-head data directly comparing R-CHOP vs R-CVP); and (iii) individual preference amongst haematologists as to whether to spare patients from anthracycline-related toxicities up front and reserve R-CHOP for when a patient's disease relapses or transforms, or treat more aggressively upfront so as decrease the risk of disease transformation.

2.6 Please identify the main comparator(s) and justify their selection.

The most appropriate comparator for first-line maintenance therapy in FL patients is "watch and wait" or observation, which is current standard clinical practice in the UK in patients responding to rituximab plus chemotherapy. In the final scope, NICE have also recommended the inclusion of Zevalin consolidation as a comparator, however, for of the following reasons we strongly believe that this is not appropriate:

- The patients addressed in the decision problem in this submission i.e. adults with advanced follicular lymphoma that have responded to first line rituximab plus chemotherapy is a sub-population of the wider group of patients defined in the final scope by NICE i.e. adults with advanced follicular lymphoma that have responded to first line chemotherapy. This population was refined on the advice of a panel of UK clinical experts who stipulated that the decision problem should address first-line patients responding to standard UK treatment ie R-chemotherapy. With this in mind, there is no clinical evidence to support the clinical benefit of Zevalin in previously untreated advanced FL patients induced with rituximab plus chemotherapy. The trial population in the FIT study (phase III study which supports the Zevalin consolidation licence) only included 14% of patients who received standard of care rituximab as part

of their induction therapy[40]. In addition, within this small subgroup of patients (n=59 out of a total of 414 randomised patients) there was shown to be no significant improvement in progression-free survival (PFS) with Zevalin compared to observation (HR=0.722; p=0.4583).

- Further to the lack of clinical evidence supporting the use of Zevalin consolidation after first-line rituximab plus chemotherapy in advanced FL, usage of this technology in the UK is minimal. This is demonstrated by IMS hospital usage data for Zevalin (below), which reported £34,836 worth of Zevalin dispensed in 2009. This equates to a total of 5 patients being treated with Zevalin (across all indications) over this period, assuming that one dose of Zevalin in administered per patient[41]. Of note, usage in 2009 is actually reduced compared to the previous year, with no recorded sales year-to-date in 2010.

Table 6: IMS hospital usage for Zevalin in the UK

	2006	2007	2008	2009	YTD May 2010
ZEVALIN	£7,250	£29,000	£43,500	£34,836	£0

In a recent JNCI article, potential reasons for the low use of Zevalin and other radioimmunotherapies were suggested to include clinicians discomfort with giving radioactive drugs, the fact that the drugs cannot be given to patients with cancer that has spread extensively to the bone marrow, concerns about causing secondary malignancies, and worries that using the drugs will preclude later treatments by destroying the marrow[42]. It should also be noted that current ESMO treatment guidelines and SMC guidance do not recommend usage of Zevalin in newly diagnosed follicular lymphoma patients[21,43.]

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The only additional medications mandated in the SmPC for use in conjunction with rituximab are premedication with paracetamol and an antihistamine immediately prior

to each infusion. These are given to reduce the incidence and severity of infusion reactions.

Occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids are required for symptomatic treatment of severe infusion related reactions.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Rituximab is administered by intravenous infusion typically in a hospital chemotherapy day-case unit or outpatient clinic. It is anticipated that the cost involved in administering rituximab maintenance will be £251 per infusion (daycase, delivery of subsequent elements of chemotherapy cycle; SB15Z)[44]. Patients are assumed to be monitored at the time of administration, therefore no additional cost is associated with monitoring.

2.9 Does the technology require additional infrastructure to be put in place?

No. Since rituximab is already widely used for the treatment of non-Hodgkin's lymphoma (NHL) within the NHS, staff treating follicular lymphoma patients will be familiar with the monitoring required during drug infusion and it is not anticipated that any additional infrastructure and/or training will be required.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Not applicable.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with advanced follicular lymphoma that have responded to first line chemotherapy	Adults with advanced follicular lymphoma that has responded to first line rituximab plus chemotherapy	R-chemo induction therapy is the current gold standard for previously untreated follicular lymphoma patients in the UK, with approx 93% of eligible patients receiving this treatment option. The vast majority of patients who are not treated with R-chemo, receive chlorambucil monotherapy (approx 5% of all eligible first-line FL patients[34]). These patients tend to be older, frailer, and with comorbidities that make them ineligible for treatment with either R-chemo or rituximab maintenance therapy.
Intervention	Rituximab maintenance therapy	As final scope.	
Comparator(s)	• Standard management without rituximab	• Standard management without rituximab	• No evidence to support clinical benefit of Zevalin in previously

	maintenance therapy • Ibritumomab tiuxetan (Zevalin)	maintenance therapy (ie watch and wait)	untreated advanced FL patients induced with rituximab plus chemotherapy. • Minimal Zevalin usage in UK.
Outcomes	• Progression free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	As final scope	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope	A Markov model with four health states: Progression Free Survival (PFS) first line; PFS second line; Progressed or Death was developed over a lifetime time horizon. This required extrapolation of the primary endpoint, PFS (first line), beyond the PRIMA trial follow-up period (median 38.37 months) using the best parametric fit. The monthly probability of dying in PFS was derived based on observed PFS deaths in PRIMA. The proportion of patients transitioning from PFS first line was based on distribution of patients in PRIMA receiving rituximab versus other treatments after progression. Due to extensive censoring of overall survival in PRIMA (95% and 84%

			in the rituximab and observation arms, respectively), the probability of progressing or the probability of dying in second line or third line were obtained from the EORTC 20981 trial (6 years median follow-up). Drug administration, patient monitoring and pharmacy costs, AEs and post progression treatments are considered from an NHS and PSS perspective and were taken from the NHS schedule of reference costs and the published literature. Both costs and outcomes were discounted by 3.5%.
Subgroups to be considered	• whether rituximab was received in combination with first line chemotherapy • type of first line chemo-immunotherapy regimen received • type of response (that is, complete versus partial response) achieved after first line treatment	See rationale	• Given the revised patient population in the decision problem (ie patients responding to first-line chemotherapy plus rituximab), the "subgroup" addressed in the first bullet is no longer relevant. Please note, the PRIMA trial, which forms the core of this submission, did not include a sub-population of patients induced with chemotherapy alone. Instead, all patients received standard first-line therapy for

			previously untreated follicular lymphoma; rituximab plus chemotherapy. The potential impact of baseline demographics and prognostic factors on the treatment effect in the PRIMA study was assessed by analysing the following subgroups (non-randomised) and will be addressed in the submission: age (≥ 60 years, < 60 years), gender (male, female), pre-induction FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR).
Special considerations, including issues related to equity or equality	N/A		

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A systematic review was conducted on behalf of Roche by Abacus International (Oxfordshire). Studies of interest were identified by searching the following electronic databases with no restrictions on date or language of publication. Searches were conducted on 5th February 2010.

- The Cochrane Library
  - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - The Database of Abstracts of Reviews of Effects (DARE)
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Health Technology Assessment Database (HTA)
- OVID Medline 1950 to present day
- OVID EMBASE, 1980 to present day

- Clinical trials in haematological malignancies (www.hematology-studies.org)[i]

A search strategy was developed to identify studies indexed in the Cochrane library and then modified for searches of MEDLINE and EMBASE to account for differences in syntax and thesaurus headings. Searches included terms for free text and MESH terms. The search strategy is detailed in Appendix 1 of this report.

Additional studies were identified by hand searching the following resources (conducted Feb 2010)

- Reference lists of previous trials and systematic reviews
  - The reference lists of relevant studies retrieved for full review were manually checked for any additional references that had not been identified by the search strategies
  - The reference lists of systematic reviews and relevant qualitative reviews were also checked for additional references that had not been identified by the search strategies
- Conference proceedings (2005–2010):
  - European Haematology Association (EHA)
  - American Society of Haematology (ASH)
  - American Society of Clinical Oncology (ASCO).
  - ISPOR

Further to this, in recognition of the fact that the Abacus international systematic review searches were conducted in February 2010 (6 months before submission) – Roche have conducted further searches for the months spanning January to July 2010 to ensure no relevant data published in the intervening period were missed.

The search was conducted similar to the above, with the exception of the timeframe. The following resources were used:

- The Cochrane Library

[i] This database is not one that Abacus have used before but is mentioned in the Vidal et al systematic review in follicular lymphoma and appears to be a freely accessible resource on haematological malignancies

- The Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Medline – search limited Jan 2010 to present day
- Medline in process
- EMBASE – search limited Jan 2010 to present day
- EMBASE in process

Additional studies were identified by hand searching the following resources

- Reference lists of any further discovered trials and systematic reviews
  - The reference lists of relevant studies retrieved for full review were manually checked for any additional references that had not been identified by the search strategies
  - The reference lists of systematic reviews and relevant qualitative reviews were also checked for additional references that had not been identified by the search strategies
- Conference proceedings (both June 2010):
  - European Haematology Association (EHA)
  - American Society of Clinical Oncology (ASCO).

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table 7: Eligibility criteria used in search strategy

Inclusion criteria	**Population** Patients with stage III/IV follicular non-Hodkin lymphoma responding (CR or PR) to first-line rituximab plus chemotherapy induction treatment, thus eligible for maintenance. **Interventions** Rituximab maintenance vs. observation following response (CR or PR) to first-line rituximab plus chemotherapy. Other agents used as maintenance or consolidation following

	response (CR or PR) to first-line rituximab plus chemotherapy. The other maintenance or consolidation treatments searched for in this setting are: • Oral alkylating agents: ▪ Chlorambucil ▪ Cyclophosphamide • Chemotherapeutic agents ▪ Fludarabine ▪ Bendamustine ▪ Oblimersen • Other monoclonal antibodies ▪ Alemtuzumab ▪ Ofatumumab • Radioactive monoclonal antibodies ▪ 90Y-ibritumomab tiuxetan ▪ Tositumomab • Vaccines ▪ BioVaxID ▪ Oncoquest-L • Other agents ▪ Interferon 2-alpha • Any combination regimen containing at least one of the treatments identified above **Outcomes** Clinical outcomes reported at the end of maintenance therapy • Response to treatment

	▪ overall response (OR) ▪ complete response (CR) ▪ partial response (PR) • Overall survival (OS) • Event-free survival (EFS) • Progression-free survival (PFS) • Time to first progression (TFP) • Time to re-treatment ▪ Time to next chemotherapy ▪ Time to next anti-lymphoma treatment • Transformation rate • Therapy-related morbidity and mortality • FLIPI index Incidence of specific adverse events: Any Grade 3-4 adverse event • Neutropenia • Thrombocytopenia • Infection • Any other grade 3-4 adverse event reported Serious adverse events • Serious adverse events • Specific adverse events (any reported) Withdrawals due to: any reason, lack of efficacy and adverse events **Study design** Only randomised, controlled, phase III clinical trials discussing the above, or meta-analyses and systematic reviews of such trials, were included. . **Language restrictions**

	No language restrictions were used.
Exclusion criteria	**Population** Patients: • that do not demonstrate stage III/IV follicular non-Hodgkin lymphoma • not receiving rituximab maintenance after responding (CR or PR) to first-line rituximab plus chemotherapy induction treatment. **Interventions** • Studies not including rituximab maintenance vs. observation after response (CR/PR) to first-line rituximab plus chemotherapy induction therapy • Studies without rituximab plus chemotherapy as first line induction therapy **Outcomes** None excluded **Study design** Studies that were not randomised, controlled, phase III clinical trials, or reviews or meta-analyses of such trials were excluded. **Language restrictions** None used

5.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.**

Figure 3: Quorum statement for systematic review conducted by Abacus international – February 2010

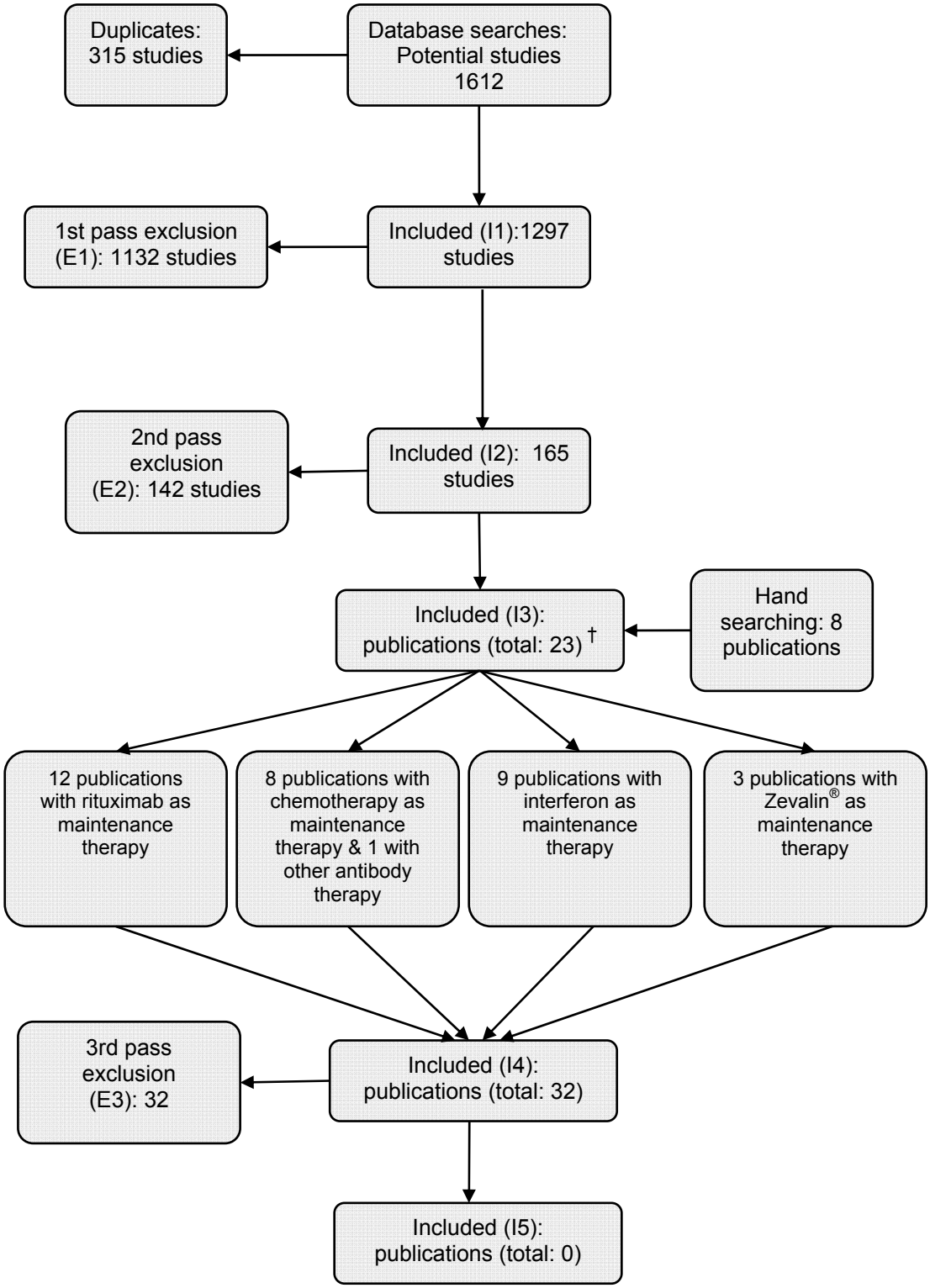
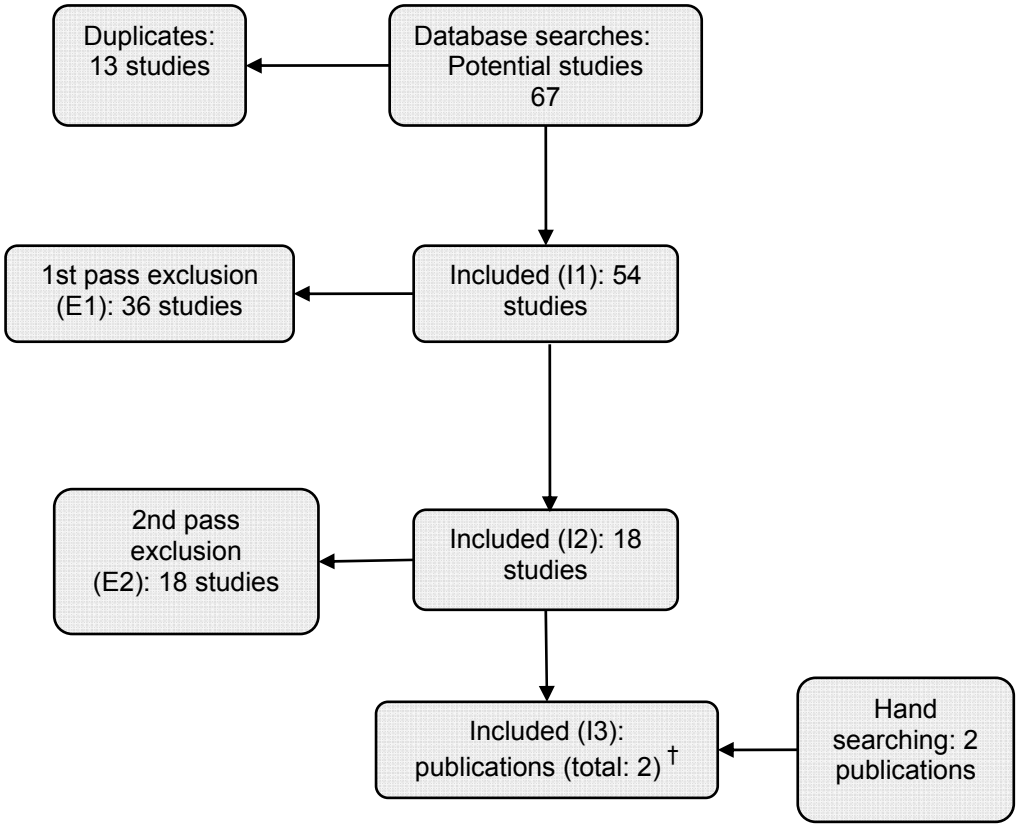


Figure 4: Quorum statement for systematic review conducted by Roche Jan 2010-July 2010



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The PRIMA study has been published as two abstracts this year (ASCO and EHA, both June 2010). Also, unpublished data from the PRIMA study are provided in the form of the Roche internal clinical study report (Study MO18264, Research report No. 1034795).

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient

group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 8: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Trial 1 (PRIMA)	Rituximab maintenance following response (CR/PR) to first-line rituximab plus chemotherapy induction treatment	Observation following response (CR/PR) to first-line rituximab plus chemotherapy induction treatment	Patients with stage III/IV follicular lymphoma responding (CR/PR) to first-line rituximab plus chemotherapy induction treatment	Salles et al. America Society of Clinical Oncology Meeting, Chigaco 2010. Abstract no.? Salles et al. European Haematology Association meeting, Barcelona 2010. Abstract no.?

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The PRIMA study highlighted above compares rituximab maintenance vs observation following response (CR or PR) to first-line rituximab plus chemotherapy, in patients with stage III/IV high-tumour-burden follicular lymphoma.

5.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

N/A

List of relevant non-RCTs

5.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.**

N/A

5.3 Summary of methodology of relevant RCTs

5.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

5.3.1.1 PRIMA (MO18264): Introduction

5.3.1.1.1 Background and rationale

Follicular lymphoma is a slow-growing malignancy of the lymphatic system, involving mature B-cells. In the World Health Organization's classification, the disease is further classified histologically into grade 1, 2, or 3 follicular lymphoma, depending on the percentage of centroblasts seen per high-power field[45]. Biologically, follicular lymphoma is characterized in most cases by a t(14;18) translocation affecting the bcl 2 gene of B-lymphocytes. This causes overexpression of the bcl-2 protein, which inhibits apoptosis of lymphoid cancer cells[46].

The clinical course of indolent non-Hodgkin's lymphoma (NHL) is characterized by repeated cycles of response to therapy followed by inevitable relapse. The disease is generally incurable with currently available treatment options, and the majority of patients die after multiple remissions and subsequent relapses. Historically, the median survival in these patients was about 8–10 years from diagnosis[47]. Initial treatment with (immuno)chemotherapy, such as alkylating agents, prednisone, anthracycline, vinca alkaloids, or purine analogues combined with monoclonal antibodies such as rituximab (MabThera®, Rituxan®) or occasionally with interferon, is associated with a high rate of clinical response followed invariably by relapse. However, the duration of response decreases with subsequent regimens[23, 48]. In approximately 30% of cases, follicular lymphoma eventually transforms to a high-grade lymphoma[49, 50] that responds only to aggressive combination treatment regimens containing anthracyclines or cytosine arabinoside or to high-dose chemotherapy with autologous stem-cell transplantation. Given the limitations of currently available treatment options, there is a need to improve the clinical outcome for patients with follicular lymphoma.

At the time the present study, Primary Rituximab and Maintenance (PRIMA), was planned, a number of Phase II and Phase III studies in follicular lymphoma had demonstrated the efficacy and safety of adding rituximab to a range of chemotherapy regimens, including CVP (cyclophosphamide, vincristine, and prednisone)[51, 52], CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)[53], and FCM (fludarabine, cyclophosphamide, and mitoxantrone)[54, 55]. These

immunochemotherapy combinations induced high response rates in patients with follicular lymphoma, but the pattern of continuous relapse in responding patients remained a problematic clinical situation. Since it was known that patients who achieve a complete response that is maintained for a prolonged period of time survive longer than other patients, methods of maintaining response were of considerable interest[, 23,56, 57]. Prolonging remission would also have the beneficial effect of delaying the need for repeat chemotherapy. In this regard, rituximab was an attractive agent to use for maintenance therapy, given its lack of cumulative myelotoxicity and evidence that patients previously responding to rituximab may respond to a second course of therapy[58].

Phase II and Phase III trials in patients with follicular lymphoma have also shown that prolonged exposure to rituximab (maintenance treatment) may improve event-free survival, response duration, and the proportion of patients still in response at one year[59]. In these studies, prolonged treatment was shown to be effective after induction treatment with rituximab monotherapy or combination chemotherapy (without rituximab). However, data from clinical trials demonstrated that induction treatment with a combination of rituximab and chemotherapy provided superior outcomes compared to chemotherapy alone in the first-line treatment of patients with follicular lymphoma[52], raising the question whether rituximab maintenance would still provide improved outcomes even after receiving induction with the most effective known regimens, rituximab plus chemotherapy. The PRIMA study was designed to answer that question by comparing the outcomes of rituximab maintenance (one infusion every eight weeks for two years, for a total of 12 doses) compared with observation, in previously untreated patients with high-tumor-burden follicular lymphoma who responded to a standard induction regimen of rituximab plus chemotherapy (R-CVP, R-CHOP, or R-FCM).

5.3.1.1.2 Objectives

The primary objective of the PRIMA study was to evaluate the benefit of maintenance therapy with rituximab on progression-free survival (PFS), as assessed by the study investigator, as compared to no maintenance therapy (observation), after induction of

response with chemotherapy plus rituximab in previously untreated patients with high tumor-burden follicular lymphoma. PFS was also analyzed based on assessments by an Independent Review Committee (IRC). PFS as assessed by the IRC was used to support the analysis based on the investigator assessments and will be considered the primary endpoint of the study for US regulatory labeling purposes.

Secondary objectives of the study included comparison of the following parameters between the maintenance and observation arms:

• event-free survival
• overall survival
• time to next anti-lymphoma treatment
• time to next chemotherapy treatment
• response rates at the end of maintenance/observation
• transformation rate at first relapse
• quality of life
• safety profile (including incidence of toxicities).

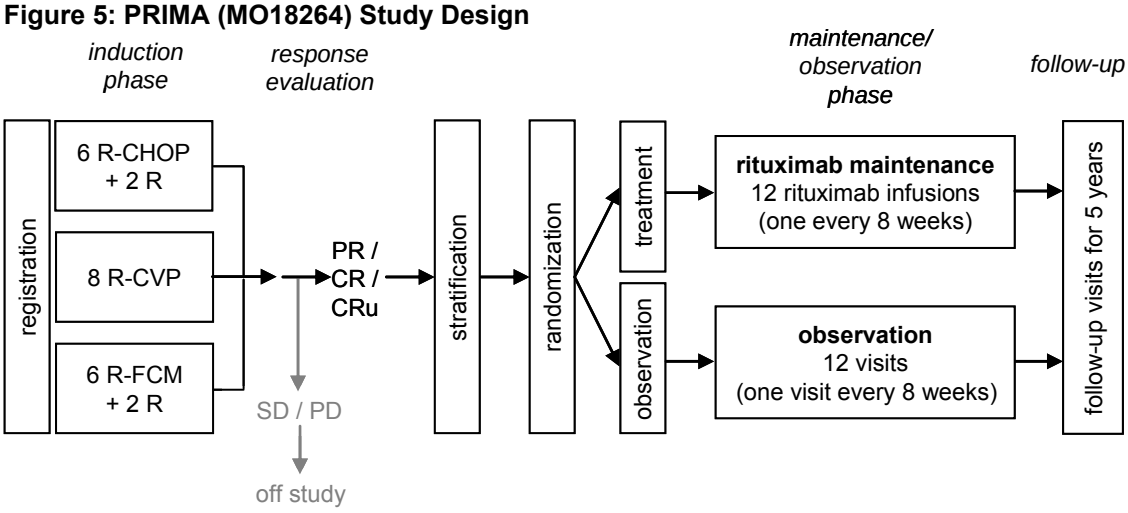
5.3.1.2 Methods

5.3.1.2.1 Trial design

The PRIMA study was an open-label, international, multicenter, randomized trial with two treatment phases. During the first phase ('induction phase'), patients with advanced follicular lymphoma were evaluated for response to one of three different rituximab plus chemotherapy induction regimens (R-CVP, R-CHOP, R-FCM). The choice of a single induction regimen was established on a per center basis, according to the standard regimen in use at a given center for patients with previously untreated follicular lymphoma requiring treatment and suitable for the trial. Patients who responded to induction treatment (ie, achieved a confirmed or unconfirmed complete response [CR/CRu] or partial response [PR])[60] were randomized to receive either rituximab maintenance therapy (one dose every eight weeks for two years, for a total of 12 doses) or no further treatment (observation) in the second phase of the study ('maintenance/observation phase'). Randomization in the maintenance/observation phase was stratified according to induction regimen, center, region, and response to induction treatment (CR/CRu or PR). All randomized

patients were treated or observed for two years or until disease progression, whichever occurred first. All patients who completed the maintenance/observation phase were then followed up for a further five years according to the same visit schedule for both study arms. The study design is outlined in figure 5 below.

Figure 5: PRIMA (MO18264) Study 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).

An interim efficacy analysis was scheduled after 75% (n = 258) of the total number of planned events (n = 344) had been observed. This number of events was reached in January 2009 (data cut-off: January 14, 2009) after a median follow-up of 25 months. Results of the interim analysis based on the investigators' and IRC's assessments were reviewed by an independent Data and Safety Monitoring Committee (DSMC) in September 2009. On the basis of these data, the DSMC considered that the study had met its Primary objective and recommended that the study be fully analyzed and results disclosed publicly. The clinical data were cleaned further, and the final database used in this submission is based on the same clinical data cut-off (January 14, 2009). In addition, a supplementary (snapshot) analysis of both safety and efficacy is provided in Sections 5.5.3 and 5.9.2.13, based on a later clinical cutoff date of January 15, 2010. The supplementary analysis provides data after an additional 12 months of follow-up.

Study follow-up is still ongoing. Additional annual follow-up analyses of key survival and safety parameters are planned and will be reported at a later date.

5.3.1.2.2 Participants

The study population comprised adults with previously untreated, high-tumor-burden follicular lymphoma. It was planned that a total of 1200 patients would be enrolled in the first (induction) phase of the study. With an estimated overall response rate of 75%, it was expected that approximately 900 patients with either partial, complete, or unconfirmed complete response after induction treatment would be randomized in the second (maintenance/observation) phase of the study.

Eligibility Criteria (Induction Phase)

Inclusion Criteria

To be eligible for study entry, patients had to meet the following criteria:
• 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 (see Section 2.1.1.4).
• 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-tumor-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 ECOG scale.
• Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to registration, including

hemoglobin ≥ 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 thereafter.

• Signed informed consent.

Exclusion Criteria

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 central nervous system (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 × 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).

Eligibility Criteria (Maintenance/Observation Phase)

Inclusion Criteria

To enter the maintenance/observation phase, patients had to meet the following criteria:

• Patients must have achieved a partial or complete response (CR/CRu or PR) at the end of induction treatment.
• All indicator lesions reported on the on-study form must have been re-evaluated.

Exclusion Criteria

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.

5.3.1.2.3 Study settings

The PRIMA study is an international and intergroup study sponsored by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), France, in collaboration with

F. Hoffmann–La Roche Ltd (Roche) and Biogen Idec. The study was coordinated internationally by the GELA Clinical Research Center (GELARC) under the lead of the Principal Investigator, Prof. Gilles Salles.

The study was conducted in collaboration with the following major study groups:
• Haematology Trials Group (HTG), UK (formerly the Lymphoma Trials Office)
• Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON)
• Czech Lymphoma Study Group (CLSG)
• Australasian Leukemia and Lymphoma Group (ALLG).
Selected single centers from South America, Eastern Europe, Asia, and the Middle East also participated in the study.

In total, 220 centers in 24 countries participated in the PRIMA study: Argentina, Australia, Belgium, Brazil, China, Colombia, Croatia, Czech Republic, Denmark, Finland, France, India, Israel, Netherlands, New Zealand, Peru, Portugal, Serbia, Spain, Thailand, Turkey, UK, Uruguay, Venezuela.

5.3.1.2.4 Interventions

Induction Treatment

Induction therapy had to start within seven days of registration (table 9). All regimens included eight cycles of rituximab.

Table 9: Rituximab plus Chemotherapy Induction Regimens

R-CHOP (1 cycle=21 days)			**Cycles 1–6**				
Drug	**Dose**	**Route**	**day 1**	**day 2**	**day 3**	**day 4**	**day 5**
rituximab[a]	375 mg/m^2	i.v.	×				
cyclophosphamide	750 mg/m^2	i.v.	×				
doxorubicin	50 mg/m^2	i.v. push	×				
vincristine[b]	1.4 mg/m^2	i.v. push	×				
prednisone[c]	100 mg/day	p.o.	×	×	×	×	×
additional rituximab[a]	375 mg/m^2	i.v.	Cycle 7, day 1			cycle 8, day 1	
R-CVP (1 cycle=21 days)			**Cycles 1–8**				
Drug	**Dose**	**Route**	**day 1**	**day 2**	**day 3**	**day 4**	**day 5**
rituximab[a]	375 mg/m^2	i.v.	×				
cyclophosphamide	750 mg/m^2	i.v. push	×				
vincristine[b]	1.4 mg/m^2	i.v. bolus	×				
prednisone[c]	40 mg/m^2	p.o.	×	×	×	×	×
R-FCM (1 cycle=28 days)			**Cycles 1–6**				
Drug	**Dose**	**Route**	**day 1**		**day 2**		**day 3**
rituximab[a]	375 mg/m^2	i.v.	×				
cyclophosphamide	200 mg/m^2	i.v.	×		×		×
fludarabine	25 mg/m^2	i.v.	×		×		×
mitoxantrone	6 mg/m^2	i.v.	×				
additional rituximab[a]	375 mg/m^2	i.v.	cycle 1, day 15			cycle 4, day 15	

a Premedication comprising an analgesic/antipyretic (eg, acetaminophen) and an antihistaminic agent (eg, diphenhydramine) was administered 30 min before each infusion of rituximab.
b Maximum dose per cycle: 2 mg (for patients aged ≥ 70 years, the dose could be capped at 1.5 mg).
c Prednisone was administered prior to rituximab infusion.

Rituximab Maintenance

For the maintenance/observation phase, patients randomized to the treatment arm received 375 mg/m2 rituximab administered by i.v. infusion every eight weeks starting eight weeks (± 7 days) after the last induction treatment (ie, immunochemotherapy or rituximab, whichever was later). A total of 12 doses of rituximab were given in the maintenance phase. Premedication comprising an analgesic/antipyretic (eg, acetaminophen) and an antihistaminic agent (eg, diphenhydramine) was to be administered prior to each infusion of rituximab.

Dose Modification

Chemotherapy dosages could be adjusted in case a patient's body weight changed by ≥ 10% compared to baseline, leading to a change in the body surface area. The same dose of rituximab was infused throughout the study regardless of any fluctuations in a patient's body weight.

In case a rituximab-induced infusion reaction occurred, all symptoms should have resolved prior to the administration of chemotherapy.

If administration of chemotherapy was delayed for any cycle, administration of the corresponding dose of rituximab was also delayed so that CHOP/CVP/FCM and rituximab were given on the same day. Patients who experienced a delay of more than 14 days in the initiation of the next planned cycle of induction therapy were withdrawn from the study. Recommended dose modifications for chemotherapy drugs and actions to be taken in case of hematological, non-hematological, cardiac, neuro-, and gastrointestinal toxicity are described in detail in the protocol.

Rituximab dose modifications were not allowed. Management of rituximab infusion-related reactions was as follows:

• Life-Threatening or Severe Reactions: In the event of a life-threatening reaction, including anaphylaxis, hypersensitivity reaction, renal failure, severe cardiopulmonary events, and severe mucocutaneous reactions, rituximab was to be discontinued and no further rituximab administered. Patients who experienced any such reaction were discontinued from study treatment.
• Tumor Lysis Syndrome (TLS): For patients with evidence of TLS, rituximab was to be discontinued and the patient treated as clinically indicated. Following complete resolution of TLS complications, rituximab could be re-administered at the full dose during the next cycle in conjunction with prophylactic therapy.
• Hypersensitivity Reactions: For hypersensitivity (presumed non-IgE-mediated) or infusion-related reactions, the infusion was to be temporarily slowed or interrupted and the patient observed and treated as clinically indicated. Treatment with diphenhydramine and acetaminophen was recommended; additional treatment with bronchodilators or i.v. saline could be indicated. Medications for the treatment of

hypersensitivity reactions (eg, epinephrine, antihistamines, and corticosteroids) should have been available for immediate use in the event of a reaction during administration. Upon complete resolution of the patient's symptoms, infusion could resume at 50% of the infusion rate prior to the reaction.
• Cardiac or Pulmonary Events: Patients who had pre-existing cardiac or pulmonary conditions or who had a prior clinically significant cardiopulmonary adverse event were to be monitored throughout the infusion and the post-infusion period.

5.3.1.2.5 Outcomes

Primary Efficacy Endpoint

Progression-free survival (PFS) during the maintenance/observation phase was measured from the day of randomization to the maintenance/observation phase to the date of first documented disease progression, relapse, or death from any cause. Assessment of progression and relapse was based on the criteria for evaluation of response in NHL[60].

For investigator-assessed PFS, patients who did not experience documented disease progression/relapse by the investigator or death were censored at the date of the last clinical examination or imaging performed by the investigator. Start of a new anti-lymphoma treatment after the randomized study treatment was not counted as an event or as a reason for censoring. For IRC-assessed PFS, patients who did not experience documented disease progression/relapse by the IRC or death at the time of the analysis were censored at the date of the last paired radiologist/oncologist tumor response assessed by the IRC. Initiation of a new anti-lymphoma treatment after the randomized study treatment was not counted as an event nor as a reason for censoring. However, as images were not collected after the start of a new treatment, patients who started a new anti-lymphoma treatment without IRC-assessed disease progression were censored for the IRC analysis of PFS.

Secondary Efficacy Endpoints

Event-free survival (EFS) was measured from the date of randomization to the maintenance/observation phase to the date of first documented progression, relapse, initiation of a new anti-lymphoma treatment (chemotherapy, radiotherapy,

radioimmunotherapy, immunotherapy) or death from any cause. Patients who did not experience an event at the time of the analysis were censored at the date of the last clinical examination or imaging performed by the investigator.

Overall survival (OS) was measured from the date of randomization to the maintenance/observation phase to the date of death, regardless of cause. Patients who had not died at the time of the analysis were censored at the date the patients were last known to be alive.

Time to next anti-lymphoma treatment (TTNLT) was measured from the date of randomization to the maintenance/observation phase to the date of first documented administration of any new anti-lymphoma treatment (chemotherapy, radiotherapy,

radioimmunotherapy, immunotherapy). Patients who did not experience an event at the time of the analysis were censored at the date of the last clinical examination or imaging performed by the investigator.

Time to next chemotherapy treatment (TTNCT) was measured from the date of randomization to the maintenance/observation phase to the date of first documented administration of new chemotherapy or new cytotoxic agent. For any given patient, the TTNCT may be the same as the TTNLT. Patients who did not experience an event at the time of the analysis were censored at the date of the last clinical examination or imaging performed by the investigator.

Overall response rate at the end of maintenance/observation was assessed at the end of the two-year maintenance/observation phase by the investigator. Assessment of response was based on the 1999 International Workshop criteria for evaluation of response in non-Hodgkin's lymphomas[60].

Transformation rate at first progression was restricted to patients with a biopsy at first progression. This parameter was defined by the appearance of diffuse areas of large lymphoma cells within a tumor site. For this purpose, a biopsy or a cytological examination was obtained at progression, where possible, and made available for central pathological review.

Quality of life (QoL) measurements were made using the FACT-G and QLQ-C30 questionnaires collected over time, and were compared for patients receiving rituximab maintenance and for those in the observation arm (see Section 5.5.2.9).

5.3.1.2.6 Changes to outcomes

The first version of the PRIMA study protocol implemented was Version 3.0 (dated July 28, 2004). The PRIMA trial was initially designed to compare event-free survival (EFS) between the maintenance and observation arms as the primary endpoint. It was planned for 640 patients to be enrolled in the induction phase in order to have 480 patients randomized in the maintenance/observation phase, and two interim analyses were planned upon reaching 100 and 150 events.

Five amendments were made to the PRIMA study protocol in total. Features of three key amendments affecting outcomes are described below:

• Amendment 2 (Protocol Version 3.2), dated February 14, 2006: This amendment increased the target enrollment from 640 patients (with 480 to be randomized in the maintenance/observation phase) to 900 patients (with 675 to be randomized in the maintenance/observation phase) to allow for more informative subgroup analyses within each induction immunochemotherapy group.
• Amendment 3 (Protocol Version 4.0), dated August 16, 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 in rituximab treatment benefit following randomization. In line with these changes, the number of PFS events that would trigger interim efficacy analyses 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 randomization, 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 February 22, 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 had occurred.

5.3.1.2.7 Sample size

A two-sided stratified log-rank test was planned to test the difference in progression-free survival between the rituximab maintenance and observation arms. The overall significance level for the final analysis was 5% (two-sided). The null hypothesis (H0) was that there is no difference between the two arms with respect to investigator-assessed PFS. The alternative hypothesis (H1) stated that there is a difference between the two arms. The formal hypothesis was as follows (PFS denotes the survival distribution of the parameter time to progression-free survival):

H0: PFS (maintenance) = PFS (observation)
versus H1: PFS (maintenance) ≠ PFS (observation)

The primary analysis of PFS was a stratified analysis using the stratification factors induction therapy received (R-CHOP, R-CVP, or R-FCM) and response to induction therapy (CR/CRu or PR).

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 randomization (six months after the start of induction therapy), for example, from 37.2 months to 54 months, 900 patients were required to be randomized in the maintenance /observation period.

The sample size calculation was based on the following assumptions:

• overall alpha = 5%
• power = 80%
• 1:1 randomization 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 randomization (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 randomized 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.

Based on these assumptions, 344 events were required to detect an increase in median PFS from 37.2 months in the observation arm to 54 months in the maintenance arm. 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.

5.3.1.2.8 Interim analyses and stopping guidelines

One interim efficacy analysis was scheduled after reaching 75% of the total number of planned PFS events (ie, 258 of 344 events). The required number of events was reached in January 2009 (clinical cut-off date January 14, 2009) after a median follow-up of 25 months. The interim analysis followed a group sequential design

according to O'Brien and Fleming as implemented by Lan and DeMets using an α-spending function. The interim analysis was performed, as planned, under the lead of the independent statistician of the DSMC as defined in the DSMC charter. On the basis of these results, the DSMC recommended that the study be fully analyzed and the results disclosed publicly. This submission discusses the results of this full analysis, which is based on the same clinical data cut-off (January 14, 2009) and is considered the final (primary) analysis of the study. In addition, a supplementary (snapshot) analysis of both efficacy and safety is provided in Sections 5.5.3 and 5.9.2.13, based on a later clinical cut-off date of January 15th, 2010. This supplementary analysis provides data after an additional 12 months of follow-up and is intended to ensure that the most up-to-date data are presented.

5.3.1.2.9 Randomisation sequence generation

Patients who achieved a complete (confirmed or unconfirmed) or partial response (CR/CRu or PR) after induction treatment and also fulfilled all other eligibility criteria were randomized in the maintenance/observation phase of the study. Randomization of eligible patients was performed centrally by fax from the GELA randomization center (GELARC) at Hôpital Saint Louis–Centre Hayem. The random allocation sequence was generated by an SAS programmer according to the specifications of a biostatistician.

5.3.1.2.10 Randomisation type

A stratified block randomization procedure (block size: four) was used. Randomization 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 center (in countries other than France and Belgium, the country was considered as a single center). Patients were allocated in a ratio of 1:1 to receive rituximab maintenance or no treatment (observation).

5.3.1.2.11 Randomisation allocation concealment mechanism

The SAS database that was imported in the GELARC randomization tool was not readable. Thus, neither the physicians nor the randomization assistants had access to the random allocation sequence, which was kept by the biostatistics department.

5.3.1.2.12 Randomisation implementation

The randomization was performed centrally by fax in the GELA randomization centre (GELARC) - Hôpital Saint Louis - Centre Hayem.

5.3.1.2.13 Blinding

The PRIMA trial was an open-label study and no placebo infusions were given during the maintenance/observation phase. In order to assess potential bias in the primary endpoint (investigator-assessed PFS), CT scans and relevant clinical efficacy data were also assessed by an Independent Review Committee (IRC), blinded as to treatment allocation and investigator assessment of response/progression.

5.3.1.2.14 Similarity of interventions

Not applicable.

5.3.1.2.15 Statistical methods

The statistical tests for the primary and secondary endpoints are summarized in

Table 10 below.

Table 10: Statistical Analysis of Efficacy Endpoints

Endpoint[a]	Test	Stratification[b]/Adjustment[c]
primary		
PFS (investigator and IRC assessments)	two-sided log-rank	induction therapy, response to induction therapy[b]; non-stratified (sensitivity)
	Cox regression	adjusted for treatment effect and prognostic factors[c]
Secondary		
EFS, OS, TTNLT, TTNCT	two-sided log-rank	induction therapy, response to induction therapy[b] non-stratified (sensitivity)
	Cox regression (OS only)	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 (Data Reporting and Analysis Manual) (available on request).
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.

5.3.1.2.16 Additional analyses

Main and Subgroup Analysis Populations

Induction analysis population (IAP): all patients who received at least one component of the planned induction treatment regimen (R-CVP, R-CHOP, R-FCM). Patients were analyzed according to the induction therapy that they received in the first treatment cycle.

Maintenance intent-to-treat population (MITT): all randomized patients regardless of whether they received study treatment or not were included in this analysis population according to the maintenance therapy that they were randomized to receive. The primary efficacy analysis of progression-free survival was based on this population.

Maintenance per protocol population (PPP): all randomized 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 (the minimum number of treatment courses/observation visits was reduced from eight as stated in the protocol to six prior to database closure). Patients who fulfilled any of the criteria listed below were considered not to have adhered to the protocol and were excluded from the per protocol population:

• received less than six courses of maintenance treatment or completed less than six observation visits (except for early progression or death),
• unconfirmed diagnosis of follicular lymphoma (according to the independent histological review),
• received chemotherapy for NHL prior to induction,
• inadequate tumor assessment at baseline,
• violation of major registration and/or randomization criteria,
• major violation of treatments administered.

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 safety parameters are presented according to the trial treatment that the patient received in the maintenance/observation phase (ie, patients who received at least one dose of rituximab maintenance or attended one observation visit, and had at least one safety follow-up, were included in the rituximab maintenance arm and observation arm, respectively).

For subgroup analyses of efficacy and safety, the populations defined above were split by subgroup category as described in Table 11 below.

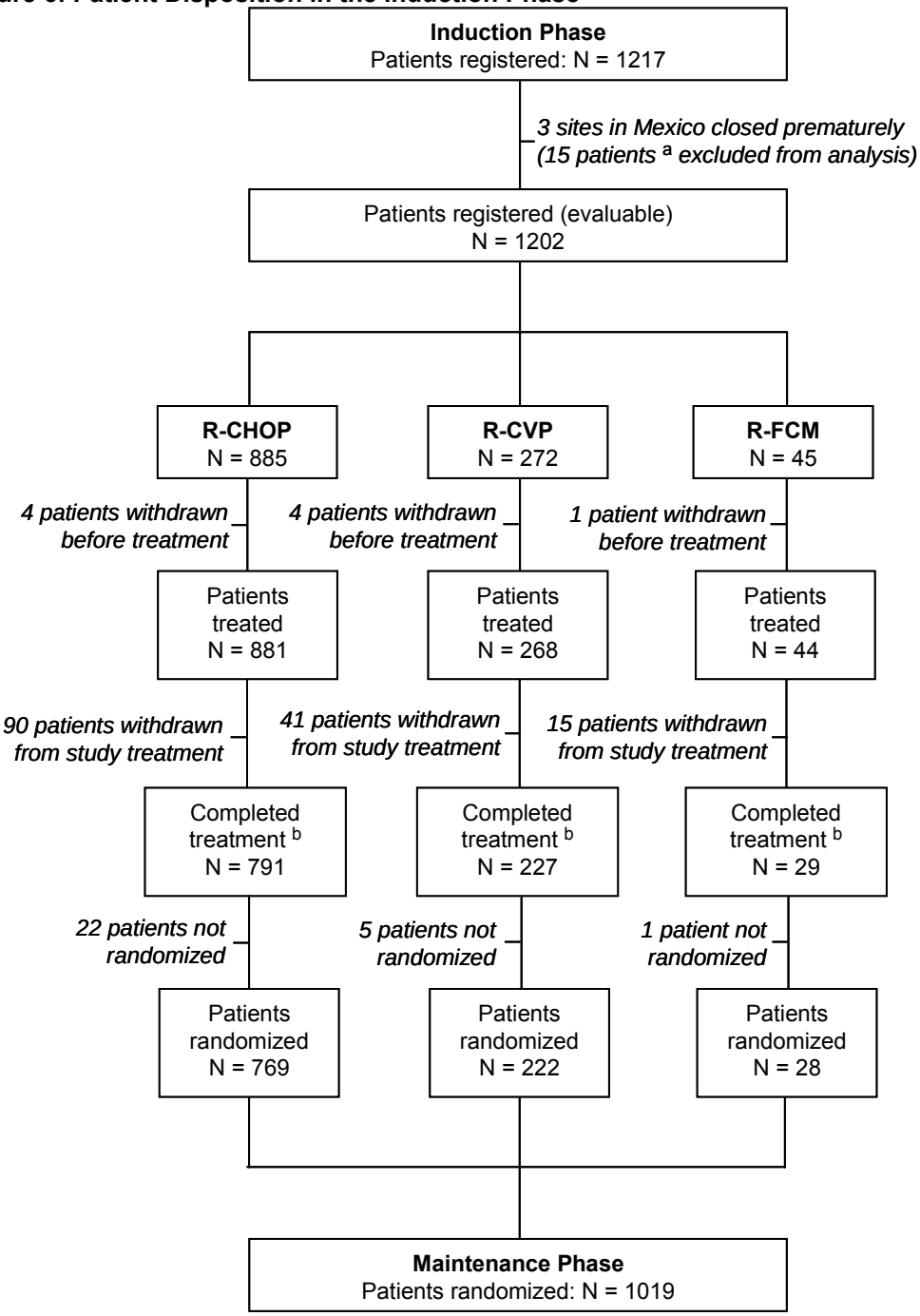
Table 11: Prespecified Subgroup Categories

Subgroup	Category	Subgroup Analysis	
		efficacy	safety
Age	< 60 years, ≥ 60 years	×	×
	<65 years, 65-74 years, ≥ 75 years (US)		×
Gender	male, female	×	×
Induction treatment	R-CHOP, R-CVP, R-FCM	×	×
FLIPI score	low risk (FLIPI ≤ 1), intermediate risk (FLIPI = 2), high risk (FLIPI ≥ 3)	×	
Response to induction therapy	CR/CRu, PR	×	
Completion of maintenance/ observation	patients who received 12 doses or completed 12 observation visits		×
Site-specific	for certain laboratory parameters, only French sites are considered		×

Subgroups with a very high percentage of missing values were excluded. The minimum size of a subgroup was set to 20 patients

5.3.1.2.17 Participant flow

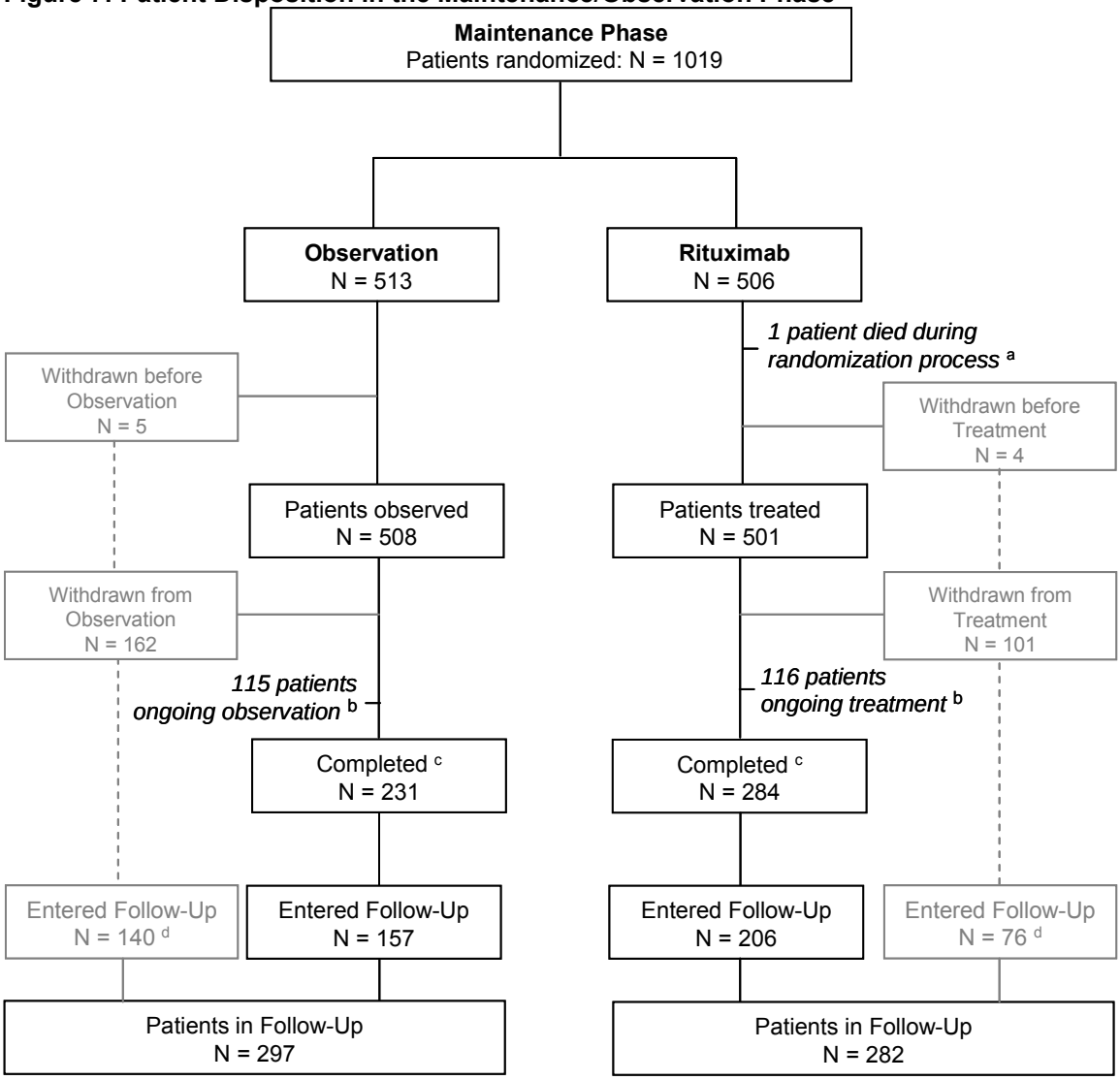
Figure 6: Patient Disposition in the Induction Phase



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.

Figure 7: Patient Disposition in the Maintenance/Observation 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.

5.3.1.2.18 Losses and exclusions after randomisation

The maintenance intent-to-treat (MITT) population comprised 1018 evaluable patients: 513 patients in the observation arm, and 505 patients in the rituximab arm. In addition to a single patient who died during the randomization process, nine patients withdrew from the maintenance/observation phase prior to the first treatment cycle or observation visit (five from the observation arm, four from the rituximab arm). In the rituximab arm, three patients withdrew owing to treatment failure (ie, disease progression) and one patient withdrew owing to an underlying medical condition

(other cancer). The five withdrawals in the observation arm were a result of treatment failure, an underlying medical condition (tongue cancer), violation of the randomization time frame, refusal of the assigned arm, and voluntary withdrawal, respectively.

Of the 1009 patients who received a first course of maintenance treatment or attended their first observation visit (ie, the maintenance safety analysis population [MSAP]), 263 patients (26%) discontinued during the maintenance/observation phase (

Table 12). More patients in the observation arm than in the rituximab arm withdrew from the study (162 patients vs 101 patients; 32% vs 20%). Most withdrawals (80% of all withdrawals) were due to treatment failure (ie, disease progression). Withdrawals as a result of treatment failure were more than twice as frequent in the observation arm as in the rituximab arm (28% vs 13%). Withdrawals due to toxicity were low in both arms but, as expected, more frequent in the rituximab arm than in the observation arm (10 patients vs 1 patient; 2% vs <1%). The underlying medical condition for the eight patients who withdrew from the observation arm were prostate cancer (patient 10137/1003), myeloma (patient 10218/1013), gastric cancer (patient 20129/1010), adrenal cancer (patient 21011/1013), anal cancer (patient 60111/1011), pregnancy (patients 21331/1019 and 60135/1008), and corticosteroid therapy for suspected dermatomyositis (patient 20129/1004). The underlying medical conditions for the nine patients who withdrew from the rituximab maintenance arm were colon cancer (patients 10105/1041 and 10119/1004), adenocarcinoma (patient 70701/1054), carcinoma of the skin (Merkel cancer) (patient 10187/1004), post-procedural fistula following an intestinal obstruction (patient 10114/1009), pregnancy (patients 10133/1006, 10534/1015, and 40121/1004), and hepatitis B (patient 60511/1009).

Table 12: Summary of Withdrawals during the Maintenance/Observation Phase (MSAP)

	OBSERVATION N = 508	RITUXIMAB N = 501	TOTAL N = 1009
Reasons For Withdrawal (CRF Pre-Specified)			
n	162	101	263
TREATMENT FAILURE	144 (89%)	67 (66%)	211 (80%)
TREATMENT TOXICITY	1 (<1%)	10 (10%)	11 (4%)
DEATH	-	1 (<1%)	1 (<1%)
PATIENT VOLUNTARY WITHDRAWAL	6 (4%)	6 (6%)	12 (5%)
OTHER	11 (7%)	17 (17%)	28 (11%)
OTHER Reason For Withdrawal (Roche Coding)			
n	11	17	28
INVESTIGATOR'S DECISION BASED ON RESIDUAL DISEASE	-	1 (6%)	1 (4%)
INVESTIGATOR'S DECISION BY MISTAKE	-	1 (6%)	1 (4%)
LOST TO FOLLOW-UP	2 (18%)	-	2 (7%)
PATIENT VOLUNTARY WITHDRAWN	-	3 (18%)	3 (11%)
PATIENT REFUSED OBSERVATION ARM	1 (9%)	-	1 (4%)
PATIENT REFUSED RANDOMIZATION	-	1 (6%)	1 (4%)
PATIENT'S NON COMPLIANCE	-	2 (12%)	2 (7%)
UNDERLYING MEDICAL CONDITION	8 (73%)	9 (53%)	17 (61%)

5.3.1.2.19 Recruitment

A total of 1217 patients were enrolled in the PRIMA trial over a period of 29 months: the first patient was registered on December 24, 2004, and the last patient was registered on April 11, 2007.

5.3.1.2.20 Reason for stopped trial

An interim efficacy analysis was scheduled after 75% (n = 258) of the total number of planned events (n = 344) had been observed. This number of events was reached in January 2009 (data cut-off: January 14, 2009) after a median follow-up of 25 months. Results of the interim analysis based on the investigators' and IRC's assessments were reviewed by an independent Data and Safety Monitoring Committee (DSMC) in September 2009. On the basis of these data, the DSMC considered that the study had met its primary objective and recommended that the study be fully analyzed and results disclosed publicly.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 13: Comparative summary of methodology of the RCTs

Trial no. (acronym)	MO18264 (PRIMA)
Location	220 centers in 24 countries (see section 5.3.1.2.3)
Design	A Multicenter, Phase III, Open-Label, Randomized Study
Duration of study	First patient registered: December 24, 2005 Data cut-off (primary analysis): January 14, 2009
Method of randomisation	A stratified block randomization procedure (block size: four) was used (see section 5.3.1.2.10)
Method of blinding (care provider, patient and outcome assessor)	PRIMA was an open label study (see section 5.3.1.2.13)
Intervention(s) (n =) and comparator(s) (n =)	Rituximab maintenance (n=505) versus observation (n=513)
primary outcomes (including scoring methods and timings of assessments)	Progression-free survival as assessed by the investigators (see section 5.3.1.2.5)
Secondary outcomes (including scoring methods and timings of assessments)	Event-free survival, overall survival, time to next anti-lymphoma treatment, time to next chemotherapy treatment, response rates at the end of maintenance/observation, transformation rate at relapse, quality of life (see section 5.3.1.2.5)
Duration of follow-up	The required number of events to trigger a planned interim analysis was reached in January 2009 (data cut-off: January 14, 2009) after a median follow-up of 25 months.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

See section 5.3.1.2.2

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Induction phase

Overall, the three induction treatment groups were balanced with respect to sex, age, height, weight, and body surface area at induction baseline (Table 14) and had similar baseline disease characteristics (

Table 15). The treatment groups were also balanced with respect to follicular lymphoma international prognostic index (FLIPI) scores (Table 16).

Table 14: Induction phase: summary of demographic and characteristic data by induction trial treatment (IAP)

Treatment (IAP)
Protocol(s): MO18264 (A18264M)
Analysis: IAP Center: ALL CENTERS
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009

	R-CHOP N = 881	R-CVP N = 268	R-FCM N = 44
Sex			
MALE	463 (53%)	137 (51%)	22 (50%)
FEMALE	418 (47%)	131 (49%)	22 (50%)
n	881	268	44
Age (years) At Registration			
Mean	55.4	57.0	51.3
SD	11.47	12.66	10.87
SEM	0.39	0.77	1.64
Median	56.0	57.5	50.0
Min-Max	22 - 80	22 - 87	29 - 74
n	881	268	44
Age Category 1 At REG			
<=40	96 (11%)	34 (13%)	7 (16%)
]40, 50]	194 (22%)	42 (16%)	16 (36%)
]50, 60]	286 (32%)	83 (31%)	12 (27%)
]60, 70]	221 (25%)	68 (25%)	6 (14%)
>70	84 (10%)	41 (15%)	3 (7%)
n	881	268	44
Age Category 2 At REG			
<=40	96 (11%)	34 (13%)	7 (16%)
>40	785 (89%)	234 (87%)	37 (84%)
n	881	268	44
Age Category 3 At REG			
<=60	576 (65%)	159 (59%)	35 (80%)
>60	305 (35%)	109 (41%)	9 (20%)
n	881	268	44
Height in cm			
Mean	168.46	169.00	164.70
SD	9.555	10.073	9.544
SEM	0.322	0.615	1.439
Median	168.00	169.00	165.00
Min-Max	141.0 - 197.0	140.0 - 191.0	147.0 - 185.0
n	881	268	44
Weight in kg			
Mean	73.271	76.003	73.500
SD	15.0210	15.7267	18.9175
SEM	0.5061	0.9607	2.8519
Median	72.000	74.000	69.500
Min-Max	35.00 - 143.00	43.00 - 146.00	34.00 - 130.00
n	881	268	44
Body Surface Area in sqm			
Mean	1.824	1.861	1.801
SD	0.2078	0.2140	0.2522
SEM	0.0070	0.0131	0.0380
Median	1.810	1.850	1.745
Min-Max	1.26 - 2.67	1.34 - 2.61	1.19 - 2.45
n	881	268	44

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
PM16 29OCT2009:09:01:45 (1 of 2)

Table 15: Induction phase: summary of disease staging by induction trial treatment (IAP)

idm16ds_f Induction Phase, Summary Of Disease Staging By Induction Trial Treatment (IAP)
Protocol(s): MO18264 (A18264M)
Analysis: IAP Center: ALL CENTERS
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009

	R-CHOP N = 881	R-CVP N = 268	R-FCM N = 44
Bone Marrow Involvement			
INVOLVED	474 (54%)	156 (58%)	24 (55%)
NOT DONE	21 (2%)	-	-
NOT INVOLVED	374 (42%)	109 (41%)	20 (45%)
UNSPECIFIED	12 (1%)	3 (1%)	-
n	881	268	44
B Symptoms			
NO	601 (68%)	175 (65%)	29 (66%)
YES	280 (32%)	93 (35%)	15 (34%)
n	881	268	44
Extra-Nodal Involvement			
<2 Extra-Nodal Sites	491 (56%)	145 (54%)	21 (48%)
>=2 Extra-Nodal Sites	390 (44%)	123 (46%)	23 (52%)
n	881	268	44
ECOG			
0	574 (65%)	161 (60%)	24 (55%)
1	272 (31%)	94 (35%)	16 (36%)
2	35 (4%)	13 (5%)	4 (9%)
n	881	268	44
Ann Arbor Stage			
I	19 (2%)	4 (1%)	-
II	68 (8%)	22 (8%)	5 (11%)
III	167 (19%)	53 (20%)	7 (16%)
IV	627 (71%)	189 (71%)	32 (73%)
n	881	268	44

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics.
DM16 29OCT2009:09:00:40 (1 of 2)

Table 16: Induction phase: summary of FLIPI data by induction trial treatment (IAP)

idm16fi_f Induction Phase, Summary Of FLIPI Data By Induction Trial Treatment (IAP)
Protocol(s): MO18264 (A18264M)
Analysis: IAP Center: ALL CENTERS
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009

	R-CHOP N = 881	R-CVP N = 268	R-FCM N = 44
FLIPI Age Factor			
<=60	576 (65%)	159 (59%)	35 (80%)
>60	305 (35%)	109 (41%)	9 (20%)
n	881	268	44
FLIPI Ann Arbor Stage Factor			
I-II	87 (10%)	26 (10%)	5 (11%)
III-IV	794 (90%)	242 (90%)	39 (89%)
n	881	268	44
FLIPI Hemoglobin Factor			
<12	179 (20%)	52 (19%)	8 (18%)
>=12	702 (80%)	216 (81%)	36 (82%)
n	881	268	44
FLIPI LDH Factor			
<=NR	583 (66%)	174 (65%)	28 (64%)
>NR	295 (34%)	92 (35%)	16 (36%)
n	878	266	44
FLIPI No. Of Nodal Areas Factor			
<5	317 (36%)	100 (37%)	11 (25%)
>=5	564 (64%)	168 (63%)	33 (75%)
n	881	268	44
FLIPI as reported on the CRF			
0	33 (4%)	15 (6%)	4 (9%)
1	160 (18%)	39 (15%)	3 (7%)
2	312 (35%)	91 (34%)	20 (45%)
3	242 (28%)	76 (28%)	12 (27%)
4	115 (13%)	38 (14%)	4 (9%)
5	18 (2%)	8 (3%)	1 (2%)
n	880	267	44
Baseline Prognosis			
LOW RISK DISEASE (FLIPI<=1)	193 (22%)	54 (20%)	7 (16%)
INTERMEDIATE RISK DISEASE (FLIPI=2)	312 (35%)	91 (34%)	20 (45%)
HIGH RISK DISEASE (FLIPI>=3)	375 (43%)	122 (46%)	17 (39%)
n	880	267	44

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
n represents number of patients contributing to summary statistics
DM16 29OCT2009:09:00:39 (1 of 2)

Maintenance phase

The demographic characteristics of patients in the MITT population at induction baseline were well balanced across the two arms (Table 17). Overall, a similar number of male and female patients were randomized (52% vs 48%). The median age of patients at randomization was 57.0 years (range 23–85 years).

Table 17: Summary of demographic data at baseline* (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
Age (years) At Randomization			
Mean	55.5	56.5	56.0
SD	12.06	11.12	11.61
SEM	0.53	0.49	0.36
Median	56.0	58.0	57.0
Min-Max	23 - 85	26 - 79	23 - 85
n	513	505	1018
Height in cm			
Mean	168.32	168.77	168.54
SD	10.051	9.495	9.777
SEM	0.444	0.423	0.306
Median	168.00	169.00	168.00
Min-Max	141.0 - 193.0	140.0 - 197.0	140.0 - 197.0
n	513	505	1018
Weight in kg			
Mean	73.266	74.819	74.036
SD	14.6532	15.4356	15.0590
SEM	0.6470	0.6869	0.4720
Median	72.000	73.000	73.000
Min-Max	34.00 - 130.00	37.00 - 143.00	34.00 - 143.00
n	513	505	1018
Body surface area in sqm			
Mean	1.825	1.844	1.835
SD	0.2123	0.2063	0.2094
SEM	0.0094	0.0092	0.0066
Median	1.810	1.830	1.820
Min-Max	1.19 - 2.44	1.27 - 2.67	1.19 - 2.67
n	513	505	1018

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM16 29OCT2009:08:58:37
* Induction baseline (registration), unless otherwise specified.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Primary efficacy parameter - Progression-Free Survival

The efficacy parameter, PFS, is a well accepted and clinically relevant trial endpoint according to the "Guideline on the evaluation of anticancer medicinal products in man" published by the CHMP[61]. This is especially true for studies in a disease with a long time course (like follicular lymphoma) and a disease in which several further lines of treatment (probably including rituximab-containing regimens) are likely to be given. The effect of subsequent therapy likely to occur in this setting may hamper the detection of a relevant treatment effect on OS.

In clinical practice, prolongation of PFS is a key treatment goal as it provides a meaningful clinical benefit to patients by extending the time without disease progression and its associated symptoms, and by delaying the need for further therapy, in particular chemotherapy. Subsequent chemotherapies are associated with toxicity and with a progressively reduced likelihood of achieving a durable response. It is therefore important to patients to prolong the period of time without treatment.

Response and progression were assessed in the PRIMA study according to the 1999 National Cancer Institute-Working Group (NCI-WG) recommendations for NHL[60]. Since then, updated guidelines have become available[62] but these do not differ greatly from the 1999 guidelines in the fundamentals of assessing response and progression in patients with follicular lymphoma.

For details on measures used to assess PFS in the PRIMA trial see section 5.3.1.2.5.

Secondary efficacy parameters

See section 5.3.1.2.5.

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

For details on statistical analysis see sections 5.3.1.2.7 and 5.3.1.2.15.

The primary population for the efficacy analyses was the intent-to-treat population (MITT), comprising all patients who completed the randomization process (Table 18). The MITT population comprised 1018 patients: 513 patients in the observation arm and 505 patients in the rituximab arm.

Based on all patients randomized, five patients in each arm were excluded from the maintenance safety analysis population (MSAP) as they did not receive study drug or did not attend an observation visit, respectively, after randomization.

A total of 844 patients were included in the maintenance per protocol population (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). The most common reason for exclusion from the PPP was inadequate diagnosis of follicular lymphoma (81 patients: 47 patients in the observation arm and 34 patients in the rituximab arm). Some patients were excluded from the PPP for more than one reason. Seven patients who were randomized despite having an inadequate response at the end of the induction phase were also excluded from the PPP.

Table 18: Overview of Maintenance Analysis Populations and Reasons for Exclusion (All Patients Randomized, 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.

For definitions of analysis populations see section 5.3.1.2.16.

Censoring

For investigator-assessed PFS, patients who did not experience documented disease progression/relapse by the investigator or death were censored at the date of the last clinical examination or imaging performed by the investigator. Start of a new anti-lymphoma treatment after the randomized study treatment was not counted as an event or as a reason for censoring. For IRC-assessed PFS, patients who did not experience documented disease progression/relapse by the IRC or death at the time of the analysis were censored at the date of the last paired radiologist/oncologist tumor response assessed by the IRC. Initiation of a new anti-lymphoma treatment after the randomized study treatment was not counted as an event nor as a reason for censoring. However, as images were not collected after the start of a new treatment, patients who started a new anti-lymphoma treatment without IRC-assessed disease progression were censored for the IRC analysis of PFS.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Investigator-Assessed PFS Subgroup Analysis

The potential impact of baseline demographics and prognostic factors on the treatment effect was assessed by analyzing the following subgroups: age (≥ 60 years, < 60 years), gender (male, female), pre-induction FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR). This was a pre-planned analysis. As outlined in section 5.3.1.2.6, a protocol amendment in February 2006 increased the target enrollment from 640 patients (with 480 to be randomized in the maintenance/observation phase) to 900 patients (with 675 to be randomized in the maintenance/observation phase) to allow for more informative subgroup analyses within each induction immunochemotherapy group.

Participant flow

5.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

See section 5.3.1.2.17.

5.4 Critical appraisal of relevant RCTs

5.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.**

- Was the method used to generate random allocations adequate?

Yes. See sections 5.3.1.2.9 and 5.3.1.2.10.

- Was the allocation adequately concealed?

Yes. See section 5.3.1.2.11.

- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

Yes. The treatment groups were well balanced with respect to follicular lymphoma international prognostic index (FLIPI) scores (see section 5.3.4,Table 16).

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

PRIMA was an open-label study, therefore, it is likely that the aforementioned parties were aware of treatment allocation. However, the assessment of follicular lymphoma post-treatment is very objective and it is therefore unlikely that this will have biased results.

In addition, an IRC comprising three hemato-oncologists and seven radiologists (including two adjudicators) assessed all patients randomized in the maintenance/observation phase in a blinded manner for response and progression based on computed tomography (CT) scans and reports of pertinent clinical findings (including physical examination and laboratory results) according to the IRC Charter.

- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

See section 5.3.1.2.18.

- Is there any evidence to suggest that the authors measured more outcomes than they reported?

No. All pre-defined primary and secondary outcomes have been reported.

- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Yes, as detailed in section 5.3.1.2.16. Efficacy and economic analyses are subsequently presented for the intention-to-treat population. This was an appropriate approach in order to preserve the randomisation scheme and avoid selection bias. A

sensitivity analysis of investigator-assessed PFS was performed to account for missing data.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See section 9.3, appendix 3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Not applicable. There is only one relevant RCT - PRIMA.

5.5 Results of the relevant RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

The results presented for the PRIMA study in this section are based on the primary data cut-off date of January 14, 2009. As induction treatment was not assigned through a randomized process but according to clinical practice at the individual investigational sites, the statistical analysis of parameters measured during this phase should be considered as exploratory only. The efficacy analyses for the

maintenance/observation phase of the study were based on patients randomized after induction of response with rituximab plus chemotherapy.

5.5.2 Induction phase

Response rates at the end of the induction phase based on the investigators' assessments are summarized in the table below. At the end of the induction phase, [redacted]/1193 patients ([redacted]) had achieved a response: complete response ([redacted] patients, [redacted]), unconfirmed complete response ([redacted] patients, [redacted]), and partial response ([redacted] patients, [redacted]). This response rate was considerably higher than the 75% response rate expected when the study was designed.

Table 19: Summary of Investigator-Assessed Tumor Response after Induction Treatment (IAP)

	R-CHOP (N=881)	R-CVP (N=268)	R-FCM (N=44)
Responders$	[redacted]	[redacted]	[redacted]
Non-Responders	[redacted]	[redacted]	[redacted]
95% CI for Response Rates*	[redacted]	[redacted]	[redacted]
Difference in Response Rates		[redacted]	[redacted]
95% CI for Difference in Response Rates#		[redacted]	[redacted]
Complete Response (CR and CRu)	[redacted]	[redacted]	[redacted]
95% CI for CR and CRu Rates*	[redacted]	[redacted]	[redacted]
Difference in CR and CRu Rates		[redacted]	[redacted]
95% CI for Difference in CR and CRu Rates#		[redacted]	[redacted]
Partial Response (PR)	[redacted]	[redacted]	[redacted]
95% CI for PR Rates*	[redacted]	[redacted]	[redacted]
Difference in PR Rates		[redacted]	[redacted]
95% CI for Difference in PR Rates#		[redacted]	[redacted]
Stable Disease (SD)	[redacted]	[redacted]	[redacted]
95% CI for SD Rates*	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]
95% CI for PD Rates*	[redacted]	[redacted]	[redacted]
Not Evaluated (NE)	[redacted]	[redacted]	[redacted]
95% CI for NE Rates*	[redacted]	[redacted]	[redacted]
Missing (No Response Assessment)	[redacted]	[redacted]	[redacted]

Response To Ind., Cat. (CR incl. uCR) (A_IRSPC)
$ Patients with a response of CR, CRu or PR at the end of the induction treatment
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

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Exploratory Analyses—Overall Study

Exploratory analyses of time-to-event endpoints (investigator-assessed PFS, EFS, OS, TTNLT, and TTNCT) were performed, measured from the date of registration to the induction phase (data available on request). Note that these data should be interpreted with care in view of the fact that induction treatment was selected by center and not allocated by randomization. Additionally, a comparison between patients later randomized in the maintenance/observation phase with patients who were not randomized should also be interpreted with care.

5.5.2 Maintenance phase

An overview of the efficacy results for the MITT population is provided in the table below. The median follow-up duration at the clinical cut-off date (January 14, 2009) was 25 months. Maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in patients with high-tumor-burden follicular lymphoma resulted in a clinically relevant and statistically significant improvement in the primary endpoint of progression-free survival as compared to no maintenance therapy (observation). This result is supported by improvements in all of the secondary efficacy endpoints. Under a nominal significance level of $\alpha = 0.05$ (two-sided), significant improvements were observed for all of the secondary endpoints except overall survival and transformation rate. Both of these parameters require longer follow-up and/or more events to draw meaningful conclusions, although in both cases the results obtained so far tend towards favoring the rituximab maintenance arm.

Table 20: Overview of Efficacy Parameters (MITT)

Efficacy Parameter	Observation N = 513	Rituximab N = 505	HR / OR	p-value*
***Primary Endpoint**: PFS*				
Investigator-Assessed PFS (Section 5.5.2.1.1)				
Median time to event	NE	NE		
25th percentile	507 days (16.7 months)	1096 days (36.0 months)	HR = 0.50 [0.39;0.64]	p < 0.0001
One-year PFS rate [95% CI]	0.82 [0.79;0.85]	0.89 [0.87;0.92]		
IRC-Assessed PFS (Section 5.5.2.1.2)				
Median time to event	939 days (30.9 months)	1130 days (37.1 months)		
25th percentile	458 days (15.0 months)	804 days (26.4 months)	HR = 0.54 [0.42;0.70]	p < 0.0001
One-year PFS rate [95% CI]	0.81 [0.78;0.85]	0.87 [0.84;0.90]		
Secondary Endpoints				
Event-free Survival (Section 5.5.2.2.1)				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted]	[redacted]		
Overall Survival (Section 5.5.2.2.2)				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
One-year event-free rate [95% CI]	[redacted]	[redacted]		
Time to Next Anti-Lymphoma Treatment (Section 5.5.2.2.3)				
Median time to event	NE	NE		
25th percentile	746 days (24.5 months)	1135 days (37.3 months)	HR = 0.61 [0.46;0.80]	p = 0.0003
One-year event-free rate [95% CI]	0.89 [0.87;0.92]	0.92 [0.89;0.94]		
Time to Next Chemotherapy Treatment (Section 5.5.2.2.4)				
Median time to event	NE	NE		
25th percentile	884 days (29.0 months)	1135 days (37.3 months)	HR = 0.60 [0.44;0.82]	p = 0.0011
One-year event-free rate [95% CI]	0.91 [0.89;0.94]	0.92 [0.90;0.95]		

Table 20: Overview of Efficacy Parameters (MITT) (cont.)

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 5.5.2.2.6)				
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 5.5.2.2.7)				
Patients with progression				
Transformation				
No transformation (no progression or missing)				

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).

5.5.2.1 Primary Efficacy Parameter: Progression-Free Survival

Patients were assessed for progression-free survival (PFS) from the day of randomization until the first documented day of disease progression or death from any cause, whichever occurred first. Patients who did not experience documented disease progression or death were censored at the last tumor assessment prior to the clinical cut-off date. PFS was compared using a two-sided log-rank test stratified by induction regimen (R-CHOP, R-CVP, R-FCM) and response to induction therapy (CR/CRu, PR) as described in Section 5.3.1.2.5. A non-stratified log-rank test was performed to confirm the primary analysis. PFS was analyzed for both the MITT and the PPP populations based on assessments by the investigators as well as by the

Independent Review Committee (IRC); both investigator- and IRC-assessed PFS endpoints were analyzed in the same manner.

5.5.2.1.1 Investigator-Assessed PFS

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 (ie, disease progression/relapse or death) since randomization (Table 21). The vast majority of patients had disease progression/relapse as PFS event (173 patients on observation, and 91 patients in the rituximab arm). Three patients died without documented disease progression/relapse: one patient in the observation arm (patient 21011/1013), and two patients in the rituximab arm (patients 20111/1016 and 20731/1008). For more information on these deaths, see Section 5.9.2.5.

Table 21: Summary of Composition of PFS Events (Investigators' Assessment, MITT)

	Observation N=513 No. (%)	Rituximab N=505 No. (%)
Progression/Relapse	173 (99.4%)	91 (97.8%)
Death	1 (0.6%)	2 (2.2%)
n	174	93

Percentages are based on n (total number of events)

Maintenance therapy with rituximab in patients responding to induction therapy significantly reduced the risk of experiencing a progression event by 50% compared with no further treatment (stratified HR 0.50, 95% CI [0.39;0.64], $p < 0.0001$, stratified log-rank test) (Table 22). The Kaplan–Meier estimated median PFS times could not be calculated for either arm as a longer follow-up is required. However, the 25th percentile times were calculated as 507 days (16.7 months) for patients in the observation arm and 1096 days (36.0 months) for patients in the rituximab maintenance arm.

On the basis of Kaplan–Meier estimates, 82% of patients in the observation arm and 89% of patients in the rituximab arm were progression-free at one year. The PFS rates at the end of the maintenance/observation phase (ie, at two years) were 66%

(95% CI [0.62;0.71]) in the observation arm and 82% (95% CI [0.79;0.86]) in the rituximab maintenance arm.

Table 22: Summary of Investigator-Assessed PFS (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

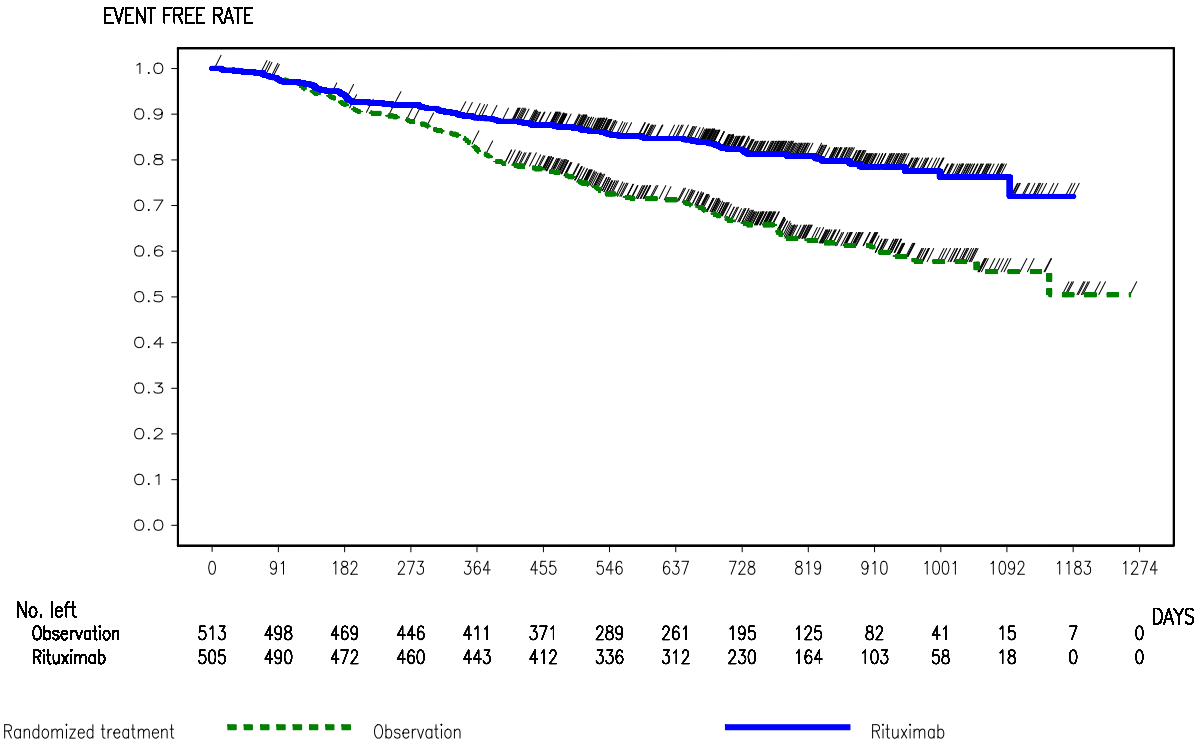
PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment.
One year duration is defined as 364 days.

A Kaplan–Meier plot of PFS rates is shown in Figure 8. The two curves begin to diverge around six months after randomization, as expected based on the washout period for rituximab given during induction and supporting the lag in treatment efficacy assumed in the statistical hypothesis.

Figure 8: Kaplan–Meier Plot of Investigator-Assessed PFS (MITT)

mg_pfskm_I Maintenance Phase, Summary Of Investigator-Assessed Progression-Free Survival, Kaplan-Meier Plots (MITT)

Protocol(s): MO18264 (A18264M)
Analysis Population: MITT (N=1018)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment.
One year duration is defined as 364 days.

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The results of Cox regression analyses without stratification by induction treatment or response to induction treatment were similar to the primary analysis (non-stratified HR 0.49, 95% CI [0.38;0.64], p < 0.0001, non-stratified log-rank test) (Table 23).

Table 23: Summary of Investigator-Assessed PFS: Stratified and Non-stratified Kaplan–Meier and Cox Models (MITT)

		Cox Regression		
Rituximab vs. Observation	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	<.0001	0.49	[0.38;0.64]	<.0001
With Stratification*	<.0001	0.50	[0.39;0.64]	<.0001

Days To Event Or Censoring (PFS) (PFSTT) - Censoring: Event (PFS) (PFSCS)
* stratified by Induction Treatment and Derived Response To Induction (patients without CR, CRu or PR are included in the PR stratum)

PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment.

Investigator-Assessed PFS in the Per Protocol Population

Investigator-assessed PFS was analyzed in the per protocol population to further quantify the potential benefit of rituximab maintenance in patients with high-tumor-burden follicular lymphoma. The analysis of PFS based on the PPP (410 patients in the observation arm, and 434 patients in the rituximab arm) was consistent with the analysis based on the MITT population. In the PPP, 152 patients on observation and 80 patients on rituximab maintenance treatment (37.1% vs 18.4%) experienced a PFS event. The per protocol analysis confirmed the results from the primary ITT analysis that rituximab maintenance treatment significantly reduced the risk of experiencing a PFS event. In the per protocol analysis, the risk of experiencing a PFS event was reduced by 55% compared with observation (stratified HR 0.45, 95% CI [0.34;0.59], p < 0.0001, stratified log-rank test). The estimated 25th percentile times to progression were 482 days (15.8 months) for patients on observation and 1096 days (36.0 months) for patients on rituximab maintenance in the per protocol population. Results of the unstratified sensitivity analysis of PFS in the per protocol population were similar to results of the stratified analysis. The corresponding Kaplan–Meier curve and summary of event-free rates over time are available on request.

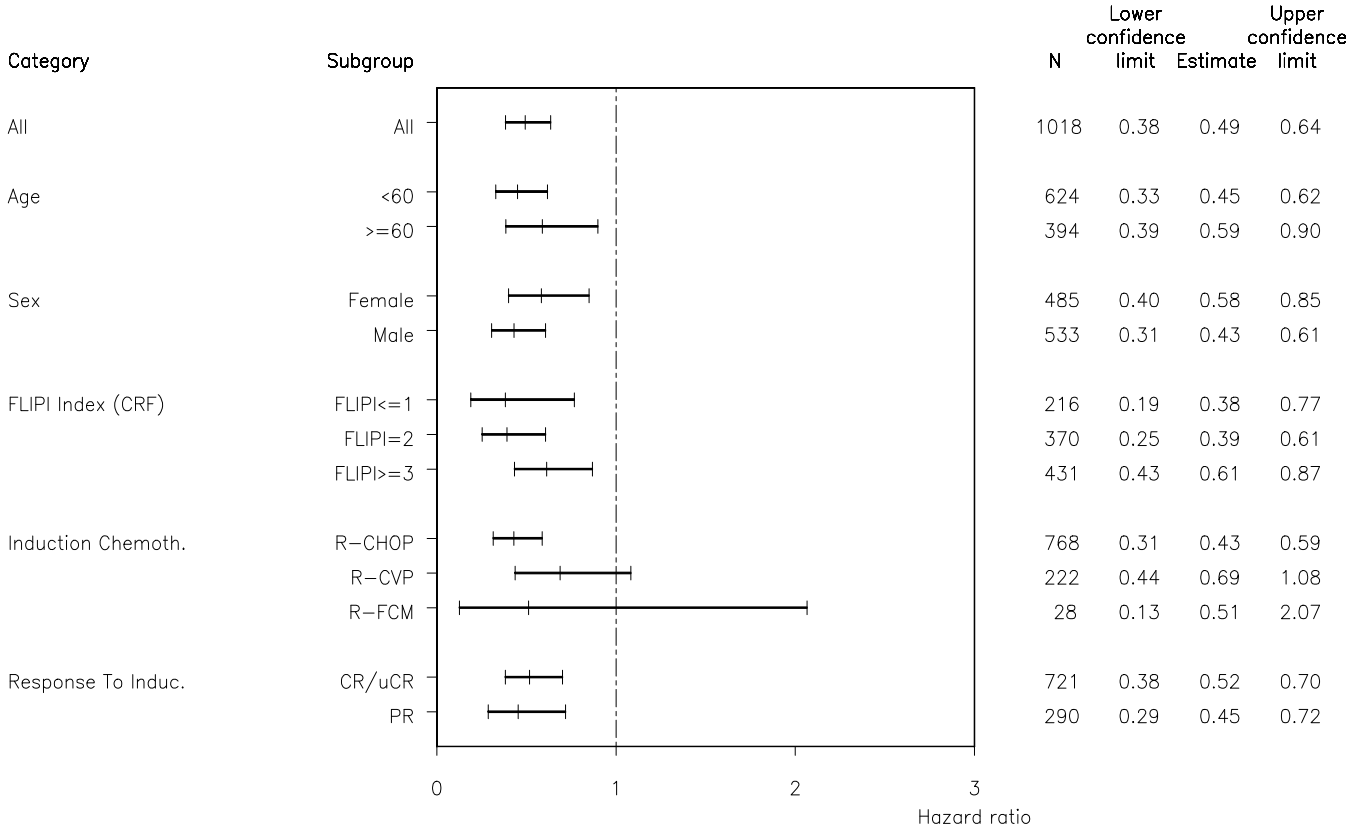
Investigator-Assessed PFS Subgroup Analysis

The potential impact of baseline demographics and prognostic factors on the treatment effect was assessed by analyzing the following subgroups: age (≥ 60 years, < 60 years), gender (male, female), pre-induction FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR).

Hazard ratios for PFS with 95% confidence intervals (observation vs rituximab) for prespecified patient subgroups are shown on the Forrest plot in Figure 9. The risk of disease progression or death was reduced in the rituximab arm compared to the observation arm in all of the subgroups tested (HR 0.38–0.69). In the R-CVP and R-FCM subgroups (the latter being a small subgroup of only 28 patients), the corresponding upper 95% confidence interval limit crossed 1.0 but the hazard ratio was clearly in favor of rituximab maintenance in both cases. Overall, the results of the PFS subgroup analyses are consistent with the primary analysis of PFS in the MITT population.

Figure 9: Subgroup Analysis of Investigator-Assessed PFS (MITT)

Protocol(s): MO18264 (A18264M)
Analysis Population: MITT (N=1018)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment.

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Applying Cox regression analyses, the consistency and heterogeneity of the observed effect of study treatment was examined across the covariates age (≥ 60 years,< 60 years), gender (male, female), FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR) by testing study treatment-by-covariate interaction. The effect of the study treatment was similar across all levels of each covariate (ie, no interaction between the study treatment and covariate was statistically significant at a significance level of 0.05). All patients benefit from rituximab maintenance therapy regardless of the examined patient characteristics.

A multiple Cox regression model with all covariates in addition to treatment (ie, all factors were added into one multivariate model including treatment) was also conducted. The hazard ratio for rituximab maintenance versus observation adjusted for all the covariates and its 95% confidence interval (multivariate adjusted HR 0.50, 95% CI [0.39;0.64]) were identical to the results obtained from the unadjusted analysis (unadjusted HR 0.50, 95% CI [0.39;0.64]).

An additional Cox analysis applying a stepwise backward selection procedure by which all factors (apart from treatment) that showed a p-value above the 5% level were eliminated from the model in subsequent steps. The final model from this stepwise elimination included (apart from treatment) as covariates gender, induction treatment (R-CHOP vs R-CVP, R-FCM), and response to induction treatment (CR/CRu vs PR). The hazard ratio adjusted for these covariates and its 95% confidence interval (stepwise backward selection model, multivariate adjusted HR 0.50, 95% CI [0.39;0.64]) were identical to the result obtained from the unadjusted analysis.

Univariate Cox regression analyses for which each model included one covariate (age, gender, FLIPI score, induction treatment, response to induction treatment) in addition to treatment were performed. Each univariate analysis was conducted by comparing the models, with and without treatment. The results of these exploratory Cox analyses confirmed that the treatment difference adjusted for each covariate favored maintenance therapy with rituximab (HR 0.49–0.50) and was consistent with the unadjusted Cox regression (unadjusted HR 0.50 95% CI [0.39;0.64]).

5.5.2.1.2 IRC-Assessed PFS

Patients were eligible for assessment for disease progression by the IRC if they had at least one valid (CR, CRu, PR, SD, PD) paired radiologist/oncologist assessment available. All scans that were collected up to the clinical cut-off date (January 14, 2009) and received by the IRC by May 20, 2009 were included in the initial review. An additional 21 scans performed prior to the January 14, 2009 clinical cut-off date were received by the IRC after May 20, 2009 and were reviewed by the IRC in February 2010 using the same blinded review process. These data are included in the analysis of IRC-assessed PFS presented in this section.

Of 1018 patients in the MITT population, [redacted] patients were assessed for disease progression by the IRC. An IRC review was missing for [redacted] patients ([redacted] patients in the observation arm, and [redacted] patients in the rituximab arm). The reasons why patients were missing from the IRC analysis included: additional informed consent for CT scan collection not obtained ([redacted] patients: [redacted] patients in the observation arm and [redacted] patients in the rituximab arm); no radiological evidence of disease at baseline and subsequent scans not evaluable ([redacted] patients: [redacted] observation and [redacted] rituximab); missing baseline scans ([redacted] patients: [redacted] observation and [redacted] rituximab); baseline scan not readable ([redacted] patients: [redacted] observation and [redacted] rituximab); and no post-baseline scan available ([redacted] patient in the rituximab arm). The baseline characteristics for those patients with no IRC assessment were similar between the two arms and similar to those of the MITT population. For the primary analysis of IRC-assessed PFS, patients without an independent assessment were censored at day 1.

At the time of the analysis, [redacted]/1018 patients ([redacted]) had experienced disease progression according to the IRC's assessments or death (Table 24). More patients in the observation arm experienced a PFS event than in the rituximab arm ([redacted] vs [redacted] patients, [redacted] vs [redacted]). Disease progression/relapse was recorded for [redacted] patients in the observation arm and [redacted] patients in the rituximab arm ([redacted] vs [redacted]). There were [redacted] deaths in the observation arm and [redacted] deaths in the rituximab arm before IRC-assessed progression/relapse.

Table 24: Summary of Composition of PFS Events (IRC Assessment, MITT)

	Observation N=513 No. (%)	Rituximab N=505 No. (%)
Progression/Relapse	[redacted]	[redacted]
Death	[redacted]	[redacted]
n		

Percentages are based on n (total number of events)

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01MAR2010 18:29 Source: mt_ipfscom_I

The risk of experiencing IRC-confirmed disease progression/relapse or death was reduced by 46% for patients receiving rituximab maintenance compared to those on observation (stratified HR 0.54, 95% CI [0.42;0.70]). Maintenance therapy with rituximab significantly prolonged IRC-assessed PFS as compared to observation ($p < 0.0001$, stratified log-rank test) (

Table 25). The Kaplan–Meier estimated median PFS was [redacted] days ([redacted] months) for the observation arm and [redacted] days ([redacted] months) for the rituximab arm. It is worth mentioning that the median is not a good measure for the treatment benefit if it is only reached at the tail end of the Kaplan–Meier curve, as is the case for the IRC-assessed PFS presented here (see Figure 10). The median is then always highly dependent on the very few patients still at risk at the time the median is reached (in this case, less than [redacted] patients were at risk in the rituximab arm). The more robust measure is the hazard ratio as it takes into consideration the entire observation period when estimating the treatment difference. This also explains why there was a comparable treatment benefit in terms of the hazard ratio between the investigators' and IRC's assessments of PFS, although in the investigator-based PFS analysis [redacted].

On the basis of Kaplan–Meier estimates, [redacted] of patients in the rituximab arm and [redacted] of patients in the observation arm were alive and progression-free at one year. At two years, [redacted] (95% CI [redacted]) of patients in the rituximab arm and [redacted] (95% CI [redacted]) of patients in the observation arm were progression-free.

Table 25: Summary of IRC-Assessed PFS (MITT)

	Observation (N=513)		Rituximab (N=505)
Patients with event	[redacted] ([redacted] %)		[redacted] ([redacted] %)
Patients without events*	[redacted] ([redacted] %)		[redacted] (XXXX %)
Time to event (days)			
Median#	[redacted]		[redacted]
95% CI for Median#	[redacted] ;.]		[redacted] ;.]
25% and 75%-ile#	[redacted] ;.		[redacted] ;.
Range##	[redacted] to [redacted]		[redacted] to [redacted]
p-Value (Log-Rank Test, stratified**)		[redacted]	
Hazard Ratio (stratified**)		0.54	
95% CI		[0.42;0.70]	
p-Value (Wald Test)		<.0001	
1 year duration			
Number left	[redacted]		[redacted]
Event Free Rate#	[redacted]		[redacted]
95% CI for Rate#	[redacted] ; [redacted]]		[redacted] ; [redacted]]

Time-To-Event (PFS Analysis 1) (PFSTT3_I) - Censoring: Event (PFS Analysis 1) (PFSCS3_I)
* censored
** stratified by Induction Treatment and Derived Response To Induction (patients without CR, CRu or PR are included in the PR stratum)
# Kaplan-Meier estimate
including censored observations

PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - independent assessment.
Censoring occurs at last response assessment.
One year duration is defined as 364 days.

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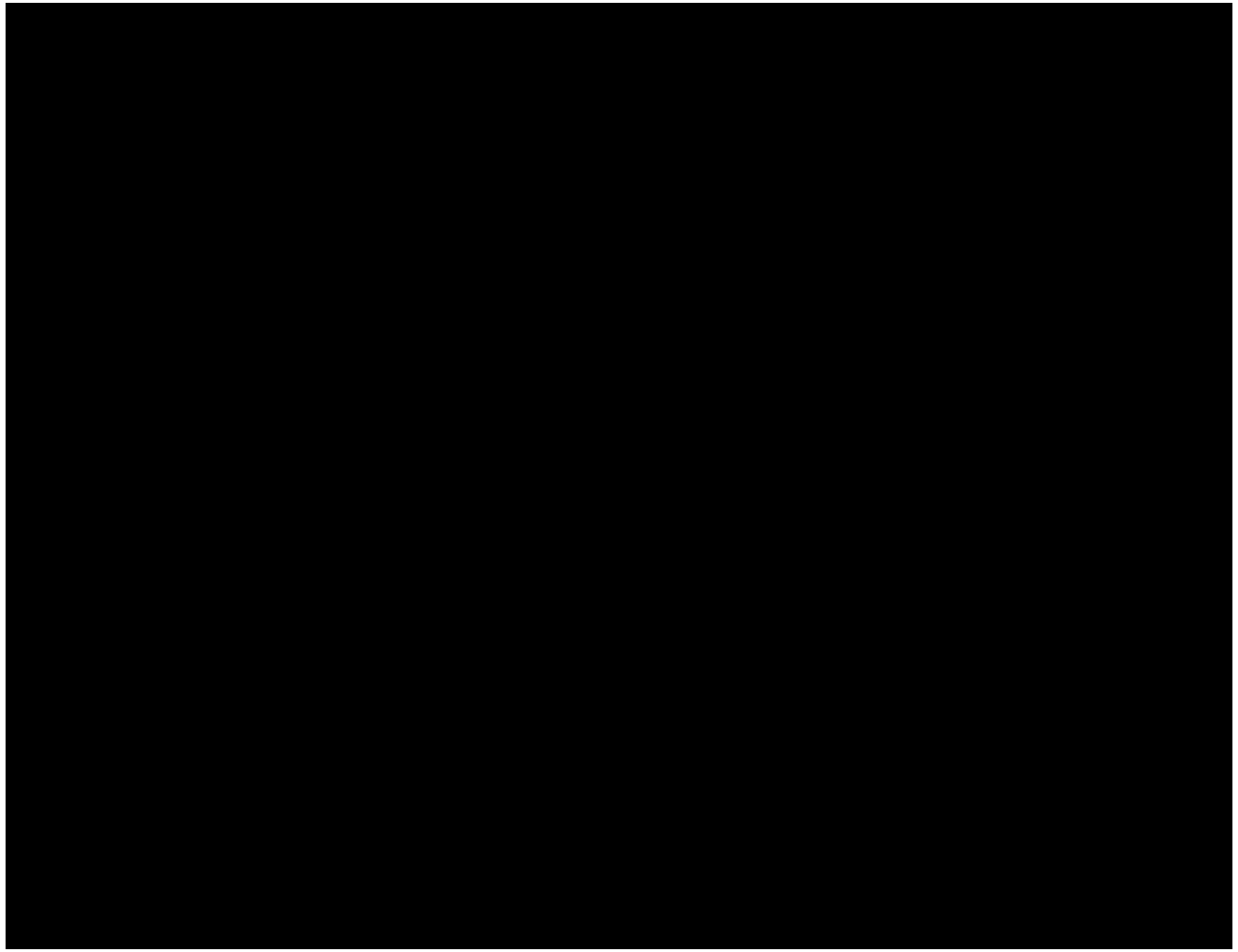
The Kaplan–Meier plot of IRC-assessed PFS shows a clear separation of the curves [redacted] (Figure 10).

Figure 10: Kaplan–Meier Plot of IRC-Assessed PFS



Results of the analysis of IRC-assessed PFS without stratification by induction treatment or response to induction treatment were similar to those of the stratified analysis (non-stratified HR [redacted], 95% CI [redacted], non-stratified log-rank test) (Table 26).

Table 26: Summary of IRC-Assessed PFS: Stratified and Non-stratified Kaplan–Meier and Cox Models (MITT)

		Cox Regression		
Rituximab vs. Observation	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	[redacted]	[redacted]	[redacted;redacted]	[redacted]
With Stratification*	<.0001	0.54	[0.42;0.70]	<.0001

Time-To-Event (PFS Analysis 1) (PFSTT3_I) - Censoring: Event (PFS Analysis 1) (PFSCS3_I)
* stratified by Induction Treatment and Derived Response To Induction (patients without CR, CRu or PR are included in the PR stratum)

PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - independent assessment.
Censoring occurs at last response assessment.

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IRC-Assessed PFS in the Per Protocol Population

IRC-assessed PFS was also analyzed in the per protocol population ([redacted] patients in the observation arm, and [redacted] patients in the rituximab arm), and the results were consistent with the MITT analysis of IRC-assessed PFS. In the PPP, [redacted] patients in the observation arm and [redacted] patients in the rituximab maintenance arm ([redacted] vs [redacted]) experienced a PFS event. The risk of experiencing a PFS event was reduced by [redacted] for patients receiving rituximab maintenance treatment compared with those on observation (stratified HR [redacted], 95% CI [redacted]). The per protocol analysis confirmed the results from the MITT IRC-assessed PFS analysis that rituximab maintenance therapy significantly prolonged PFS as compared to observation ([redacted], stratified log-rank test). The Kaplan–Meier estimated median PFS was [redacted] days ([redacted] months) in the observation arm and [redacted] days ([redacted] months) in the rituximab arm. Note again that only very few patients were at risk at the time the median was reached in the rituximab arm (less than [redacted] patients in the rituximab arm were at risk) and therefore the median in this case is not a robust measure of the observed treatment difference. Results of a per protocol

sensitivity analysis without stratification were similar to the results of the stratified analysis.

IRC-Assessed PFS Subgroup Analysis

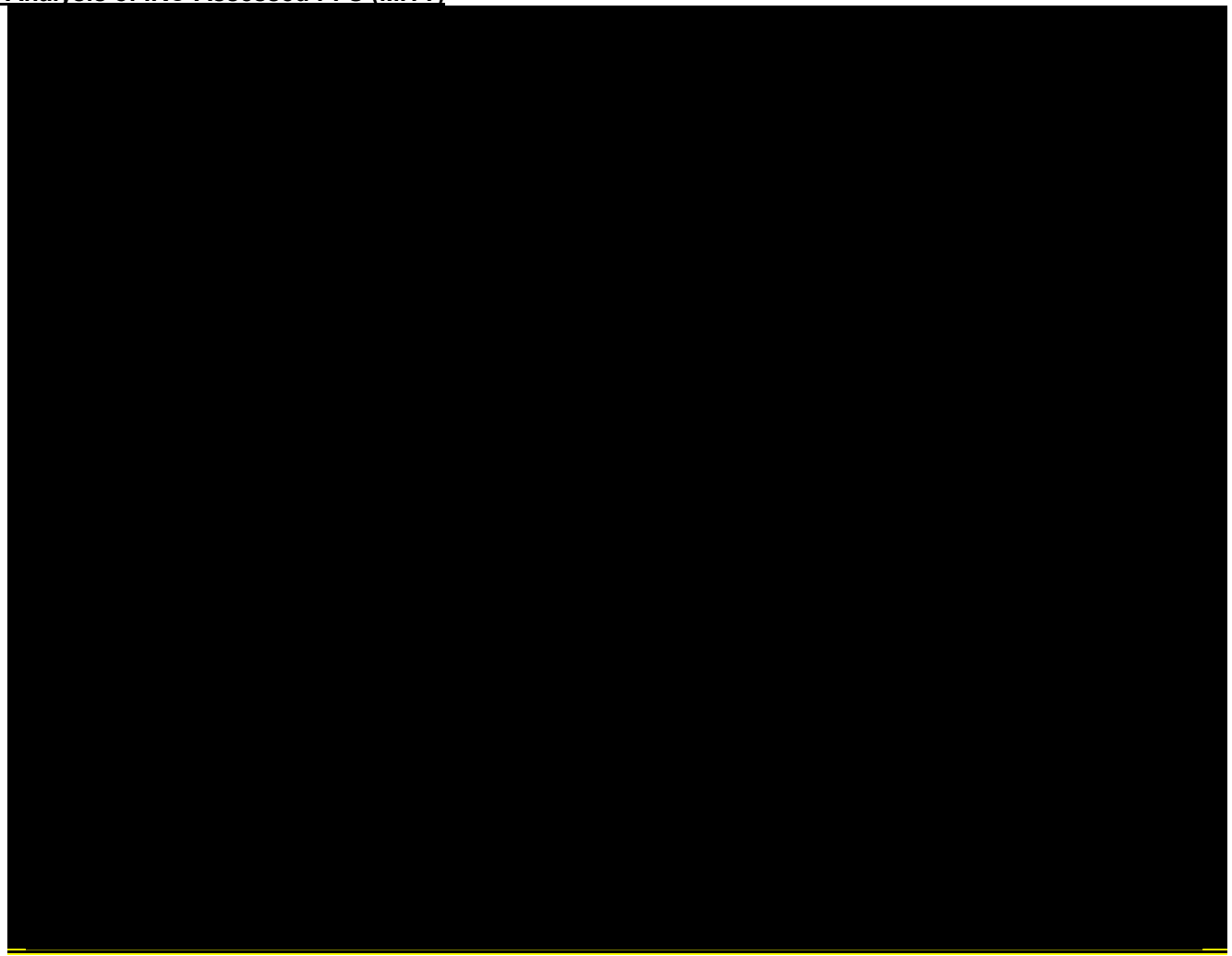
As for investigator-assessed PFS, the potential impact of baseline demographics and prognostic factors on the treatment effect as assessed by the IRC was analyzed for the following subgroups: age (≥ 60 years, < 60 years), gender (male, female), FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR). Hazard ratios for PFS with 95% confidence intervals (observation vs rituximab) for the prespecified patient subgroups are shown on the Forrest plot in Figure 11. The risk of disease progression or death was [redacted] in the rituximab arm compared to the observation arm in all of the subgroups tested (HR [redacted]). Overall, the results of the IRC-assessed PFS subgroup analyses are consistent with the primary analysis of IRC-assessed PFS in the MITT population, and with the investigator-assessed PFS analyses (Section 5.5.2.1.1).

A multiple Cox regression was performed with the covariates age (≥ 60 years,< 60 years), gender (male, female), FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR). The hazard ratio for rituximab maintenance versus observation adjusted for all the covariates and its 95% confidence interval (multivariate adjusted HR [redacted], 95% CI [redacted]) was similar to the result obtained from the unadjusted analysis (unadjusted HR 0.54, 95% CI [0.42;0.70]).

An additional Cox analysis applying a stepwise backward selection procedure was performed. The hazard ratio adjusted for the covariates and its 95% confidence interval (stepwise backward selection model, multivariate adjusted HR [redacted], 95% CI [redacted]) was similar to the result obtained from the unadjusted analysis.

The results of univariate Cox regression analyses confirmed that the treatment difference adjusted for each covariate favored maintenance therapy with rituximab (HR [redacted]) and was consistent with the unadjusted Cox regression (unadjusted HR 0.54, 95% CI [0.42;0.70]).

Figure 11: Subgroup Analysis of IRC-Assessed PFS (MITT)



Comparison of Investigator and IRC Assessments

Data for 887 patients from the MITT population were reviewed for disease response and progression by the IRC as well as by the investigators: 447 patients in the observation arm and 440 patients in the rituximab arm (87% vs 87%). An independent assessment was missing for 131 patients (13% overall; see Section 5.5.2.1.2). In the dataset of 887 patients for whom both reviews were available, there were [redacted] PFS events according to the investigators' assessments and [redacted] PFS events according to the IRC's assessments (Table 27).

Concordance between the investigators' and IRC's assessments of disease progression was analyzed in terms of whether or not disease progression occurred and the time at which disease progression occurred.

The concordance/discordance between the investigators' and IRC's assessments of disease progression is summarized in Table 27. Of the [redacted] patients in the observation arm with both reviews, the investigator and IRC agreed that an event (progression or death) occurred in [redacted] patients and did not occur in [redacted] patients, resulting in a concordance rate of [redacted] for the observation arm. Similar results were observed in the rituximab arm: the investigators and the IRC agreed that an event (progression or death) occurred in [redacted] patients and did not occur in [redacted] patients, resulting in a concordance rate of [redacted] for the rituximab maintenance arm.

Table 27: Summary of Investigator- and IRC-Assessed Progression Events (MITT, IRC-Assessed, N = 887)

	Observation N=447		Rituximab N=440		Total N=887	
	Independent Assessment		Independent Assessment		Independent Assessment	
	Event n (%)	No Event n (%)	Event n (%)	No Event n (%)	Event n (%)	No Event n (%)
Investigator Assessment:						
Event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]		[redacted]		[redacted]	
Investigator And Independent Assessment Agreement:						
Agreement	[redacted]		[redacted]		[redacted]	
No Agreement	[redacted]		[redacted]		[redacted]	
n	[redacted]		[redacted]		[redacted]	

- Event is defined as progression or death
- Percentages are based on the corresponding n

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Concordance/discordance for the investigators' and IRC's assessments was also analyzed in terms of the timing of disease progression. This analysis was based on patients who were considered to have progressed according to the investigator, the IRC, or both (Table 28). Concordant timing was defined as disease progression within 30 days according to the IRC and the investigator. Among the [redacted] patients with disease progression in the observation arm according to both the IRC and investigator, [redacted] events ([redacted]) had concordant timing, [redacted] events ([redacted]) occurred earlier according to the IRC, and [redacted] events ([redacted]) occurred later according to the IRC ([redacted]). Among the [redacted] patients with disease progression in the rituximab arm according to both the IRC and investigator, [redacted] events ([redacted]) had concordant timing, [redacted] events ([redacted]) occurred earlier according to the IRC, and [redacted] events ([redacted]) occurred later according to the IRC ([redacted]). For both arms, discordance in the timing of disease progression was mostly due to progression events that occurred earlier based on IRC assessments compared with the investigators' assessments ([redacted] in the observation arm and [redacted] in the rituximab arm; [redacted]).

Table 28: Summary of Time between Investigator- and IRC-Assessed Disease Progression (MITT, IRC-Assessed, N = 887)

	Observation N=447 No. (%)	Rituximab N=440 No. (%)
Agreement:		
Disease progression assessed at the same time point (1)	[redacted]	[redacted]
Discordance:		
Disease progression assessed only by investigator	[redacted]	[redacted]
Disease progression assessed only by independent	[redacted]	[redacted]
Disease progression assessed by independent earlier than investigator (2)	[redacted]	[redacted]
Disease progression assessed by investigator earlier than independent (3)	[redacted]	[redacted]
n (4)	[redacted]	[redacted]
Absolute difference in days between disease progression assessments (5):		
Mean	[redacted]	[redacted]
Std	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
n	[redacted]	[redacted]

(1) -30 days <= time from date of investigator disease progression to date of independent disease progression <= 30 days
(2) Time from date of investigator disease progression to date of independent disease progression < -30 days
(3) Time from date of investigator disease progression to date of independent disease progression > 30 days
(4) Number of patients who progressed (investigator, independent or both)
(5) Only for patient with absolute time from date of investigator disease progression to date of independent disease progression > 30 days

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5.5.2.1.4 Additional Robustness Analyses of PFS

The robustness of the PFS result was assessed by performing sensitivity analyses. These analyses confirmed the significant results of the primary analyses of PFS based on the investigators' assessments and the IRC's assessments and indicated that maintenance therapy with rituximab significantly prolonged PFS and reduced the risk of a PFS event. The stratified hazard ratios with 95% confidence intervals and the p-values from the stratified log-rank tests for the primary analyses of PFS based on the investigators' and IRC's assessments are summarized together with the results from the sensitivity analyses in Table 29.

Table 29: Summary of PFS: primary and Robustness Analyses (MITT)

Analysis	Stratified HR [95% CI]	
	Investigator-Assessed PFS	IRC-Assessed PFS
primary analysis	0.50 [0.39;0.64] (Table 22)	0.54 [0.42;0.70] (Table 25)
Sensitivity analysis based on the primary analysis: Ties handled using the TIES=DISCRETE option in the MODEL statement of the SAS procedure	[redacted]	[redacted]
Sensitivity analysis based on the primary analysis: Excluding non-responders after induction	[redacted]	[redacted]
Sensitivity analysis based on the primary analysis: Third stratum including non-responders after induction	[redacted]	[redacted]
Sensitivity analysis based on the primary analysis: including Mexican sites*	[redacted]	[redacted]
Sensitivity analysis based on the primary analysis: including only patients with IRC assessment(s)	[redacted]	[redacted]
Sensitivity analysis based on combining investigator and IRC data: Date of event or censoring whichever is earlier from the independent- and investigator-assessed PFS	[redacted]	
Sensitivity analysis based on the	[redacted]	[redacted]

primary analysis: Stratification information (induction treatment and response at end of induction) from the randomization list is considered (instead of the information from the case report form)		

Table 29: Summary of PFS: primary and Robustness Analyses (MITT) (Cont.)

Analysis (Cont.)	Stratified HR [95% CI]	
	Investigator-Assessed PFS	IRC-Assessed PFS
'Worst-case' sensitivity analysis: If patient was lost to follow-up, the patient was considered to have experienced disease progression. Date of disease progression was assigned to be the last assessment date + 1 day. This was applied to patients in both arms	[redacted]	[redacted]
'Worst-case' sensitivity analysis: If a visit took place later than scheduled in the protocol (regardless whether at this visit PD was reported or not), the date of PFS event (or censoring) was back-dated to the most recent previous assessment date + 1 day. This was applied to patients in the treatment arm only	[redacted]	[redacted]
'Worst-case' sensitivity analysis: If patient was prematurely withdrawn (due to toxicity or any other reason), the patient was considered to have experienced disease progression. Date of disease progression was assigned to be the last assessment date + 1 day. This was applied to patients in the treatment arm only	[redacted]	[redacted]

*[redacted].

The DSMC was informed of the closure of the three centers in Mexico on December 5, 2008. GELA and Roche proposed to exclude the data from these three centers (ie, 15 patients registered to the induction phase, 11 of whom were randomized in the maintenance/observation phase) from the analyses. The DSMC

considered this a legitimate option as long as there was full transparency about the exclusion in any report of the study. The DSMC suggested that a sensitivity analysis be performed for the final report/publication of the study. Among the 11 patients randomized at the Mexican centers, three patients had disease progression assessed by the investigator: patients 1004/60331 and 1007/60331 randomized to the observation arm, and patient 1013/60331 randomized to the rituximab arm (this patient later died). Data for the patients from the excluded Mexican sites were not reviewed by the IRC. The impact of these data on investigator-assessed progression-free survival was evaluated by a sensitivity analysis performed on the maintenance intent-to-treat population including the patients from the Mexican sites. Safety data received from the Mexican sites were not included in the safety analyses.

Secondary Efficacy Parameters

5.5.2.2.1 Event-Free Survival

Event-free survival (EFS) was measured from the date of randomization to the date of first documented disease progression (investigator-assessed), relapse, initiation of new anti-lymphoma treatment, or death from any cause, whichever occurred earlier. At the time of the analysis (clinical cut-off January 14, 2009), [redacted] patients ([redacted]) had experienced an EFS event: 34.9% in the observation arm compared with [redacted] in the rituximab arm (table below

Table 30). The majority of events were disease progression/relapse events ([redacted] events in the observation arm versus [redacted] events in the rituximab arm). A total of [redacted] patients ([redacted]) started a new anti-lymphoma treatment prior to documented disease progression (eight patients in the observation arm, and [redacted] patients in the rituximab arm).

Table 30: Summary of Composition of EFS Events (Investigators' Assessments, MITT)

	Observation N=513 No. (%)	Rituximab N=505 No. (%)
Progression/Relapse	[redacted]	[redacted]
New Anti-Lymphoma Treatment	[redacted]	[redacted]
Death	[redacted]	[redacted]
n	[redacted]	[redacted]

Percentages are based on n (total number of events)

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The risk of experiencing an event was reduced by [redacted] for patients on rituximab as compared to those on observation (stratified HR [redacted], 95% CI [redacted], [redacted], stratified log-rank test). The median time to event was [redacted] in the rituximab arm ([redacted] days [redacted] months] in the observation arm). However, there was [redacted]: [redacted] days ([redacted] months) in the observation arm and [redacted] days ([redacted] months) in the rituximab arm. The Kaplan–Meier estimate of event-free survival at one year was [redacted] in the observation arm and [redacted] in the rituximab arm (table 30

Table 31). At two years, the event-free survival rates were [redacted] in the observation arm and [redacted] in the rituximab arm (the EFS rates were [redacted] (Section 5.5.2.1.1) due to [redacted]).

Results of the analysis performed without stratification were similar to the stratified analysis of EFS (non-stratified HR [redacted], 95% CI [redacted], log-rank test) (Table 32).

The Kaplan–Meier plot of EFS is presented in Figure 12.

Table 31: Summary of EFS (Investigators' Assessments, MITT)

	Observation (N=513)	Rituximab (N=505)
Patients with event	[redacted] ([redacted] %)	[redacted] ([redacted] %)
Patients without events*	[redacted] ([redacted] %)	[redacted] ([redacted] %)
Time to event (days)		
Median#	[redacted]	.
95% CI for Median#	[redacted]	[.;.]
25% and 75%-ile#	[redacted]	[redacted]
Range##	[redacted] to [redacted]	[redacted] to [redacted]
p-Value (Log-Rank Test, stratified**)	[redacted]	
Hazard Ratio (stratified**)	[redacted]	
95% CI	[redacted]	
p-Value (Wald Test)	[redacted]	
1 year duration		
Number left	[redacted]	[redacted]
Event Free Rate#	[redacted]	[redacted]
95% CI for Rate#	[redacted]	[redacted]

Days To Event Or Censoring (EFS) (EFSTT) - Censoring: Event (EFS) (EFSCS)
* 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

EFS - day of randomization until 1st documented disease progression, relapse after response, initiation of a new anti-lymphoma treatment or death from any cause.
Censoring occurs at date of last response assessment.
One year duration is defined as 364 days.

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Output : $PROD/cd10752c/a18264m/reports/mt_efssum_I.out
29OCT2009 9:15

Table 32: Summary of EFS—Stratified and Non-stratified Kaplan–Meier and Cox Models (Investigators' Assessments, MITT)

		Cox Regression		
Rituximab vs. Observation	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	[redacted]	[redacted]	[redacted]	[redacted]
With Stratification*	[redacted]	[redacted]	[redacted]	[redacted]

Days To Event Or Censoring (EFS) (EFSTT) - Censoring: Event (EFS) (EFSCS)
* stratified by Induction Treatment and Derived Response To Induction (patients without CR, CRu or PR are included in the PR stratum)

EFS - day of randomization until 1st documented disease progression, relapse after response, initiation of a new anti-lymphoma treatment or death from any cause.
Censoring occurs at date of last response assessment.

Program : $PROD/cd10752c/a18264a/mt_efslrt.sas
Output : $PROD/cd10752c/a18264m/reports/mt_efslrt_I.out
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Figure 12: Kaplan–Meier Plot of EFS (Investigators' Assessments, MITT)

5.5.2.2.2 Overall Survival

Overall survival was measured from the date of randomization to maintenance treatment/observation to the date of death, regardless of cause. At the time of the analysis, 34 patients had died: 18 patients in the observation arm (3.5%), and 16 patients in the rituximab arm (3.2%), including three patients who withdrew prior to receiving any study treatment. Deaths are discussed in more detail in Sections 5.9.1.7 and 5.9.2.5.

At the time of the clinical cut-off (January 14, 2009), less than [redacted] of patients had died in either arm (Table 33). As the precision of the hazard ratio is impacted by [redacted], [redacted] (stratified HR [redacted], 95% CI [redacted]), [redacted]. Similar statements are true for the non-stratified analysis (non-stratified HR [redacted], 95% CI [redacted]).

Table 33: Summary of Overall Survival (MITT)

	Observation (N=513)	Rituximab (N=505)
Patients with event	[redacted] ([redacted] %)	[redacted] ([redacted] %)
Patients without events*	[redacted] ([redacted] %)	[redacted] ([redacted] %)
Time to event (days)		
Median#	.	.
95% CI for Median#	[.;.]	[.;.]
25% and 75%-ile#	.;.	.;.
Range##	[redacted] to [redacted]	[redacted] to [redacted]
p-Value (Log-Rank Test, stratified**)	[redacted]	
Hazard Ratio (stratified**)	[redacted]	
95% CI	[redacted;redacted]	
p-Value (Wald Test)	[redacted]	
1 year duration		
Number left	[redacted]	[redacted]
Event Free Rate#	[redacted]	[redacted]
95% CI for Rate#	[redacted;redacted]	[redacted;redacted]

Days To Event Or Censoring (OS) (OSTT) - Censoring: Event (OS) (OSCS)
* 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

OS - day of randomization until death from any cause.
Censoring occurs at date of last contact.
One year duration is defined as 364 days.

Program : $PROD/cd10752c/a18264a/mt_ossum.sas
Output : $PROD/cd10752c/a18264m/reports/mt_ossum_I.out
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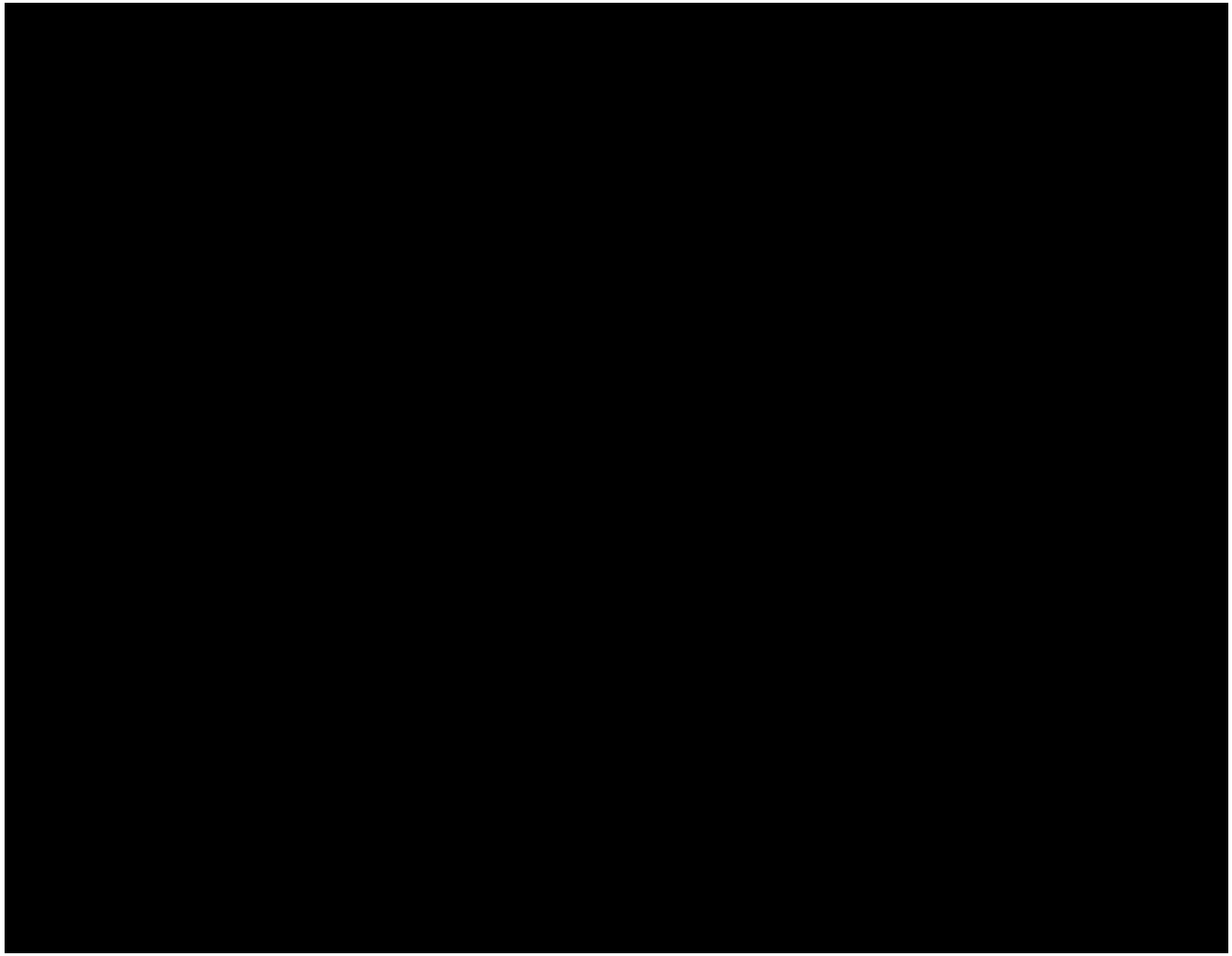
The Kaplan–Meier plot of overall survival is provided in Figure 13.

Figure 13: Kaplan–Meier Plot of Overall Survival (MITT)



Overall survival was also analyzed in the per protocol population (stratified HR [redacted], 95% CI [redacted]), but again too few deaths were observed at the time of the clinical cut-off to draw any meaningful conclusions.

A non-stratified analysis as well as sensitivity, subgroup, and Cox regression analyses were performed and yielded no unexpected findings.

An additional snapshot analysis with a cut-off date of January 15, 2010, which provides an additional 12 months of follow-up data, is presented in Section 5.5.3.

5.5.2.2.3 Time to Next Anti-Lymphoma Treatment

At the time of the data cut-off, 212 patients (20.8%) had started a new treatment for lymphoma or had died before receiving a new anti-lymphoma treatment: 130 patients in the observation arm and 82 patients in the rituximab maintenance arm (25.3% vs 16.2%). Most of these patients (206/212 patients) had started a new anti-lymphoma treatment (chemotherapy, radiotherapy, radioimmunotherapy, or immunotherapy). Six patients had died (two patients in the observation arm and four patients in the rituximab maintenance arm). The risk of new anti-lymphoma treatment or death was reduced by 39% for patients in the rituximab maintenance arm compared with those on observation (stratified HR 0.61, 95% CI [0.46;0.80], p = 0.0003, stratified log-rank test) (Table 34). The median time from randomization to initiation of new anti-lymphoma treatment or death was not reached at the time of the analysis. The 25th percentile time was 746 days (24.5 months) in the observation arm and 1135 days (37.3 months) in the rituximab arm.

Table 34: Summary of Time to Next Anti-Lymphoma Treatment (MITT)

	Observation (N=513)		Rituximab (N=505)
Patients with event	130 (25.3 %)		82 (16.2 %)
Patients without events*	383 (74.7 %)		423 (83.8 %)
Time to event (days)			
Median#	.		.
95% CI for Median#	[1163;.]		[1135;.]
25% and 75%-ile#	746;.		1135;.
Range##	1 to 1261		1 to 1199
p-Value (Log-Rank Test, stratified**)		0.0003	
Hazard Ratio (stratified**)		0.61	
95% CI		[0.46;0.80]	
p-Value (Wald Test)		0.0004	
1 year duration			
Number left	447		453
Event Free Rate#	0.89		0.92
95% CI for Rate#	[0.87;0.92]		[0.89;0.94]

Days To Event Or Censoring (TTNT) (TTNTTT) - Censoring: Event (TTNT) (TTNTCS)
* 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

TTNLT - day of randomization until initiation of a new anti-lymphoma treatment or death from any cause.
Censoring occurs at date of last visit.
One year duration is defined as 364 days.

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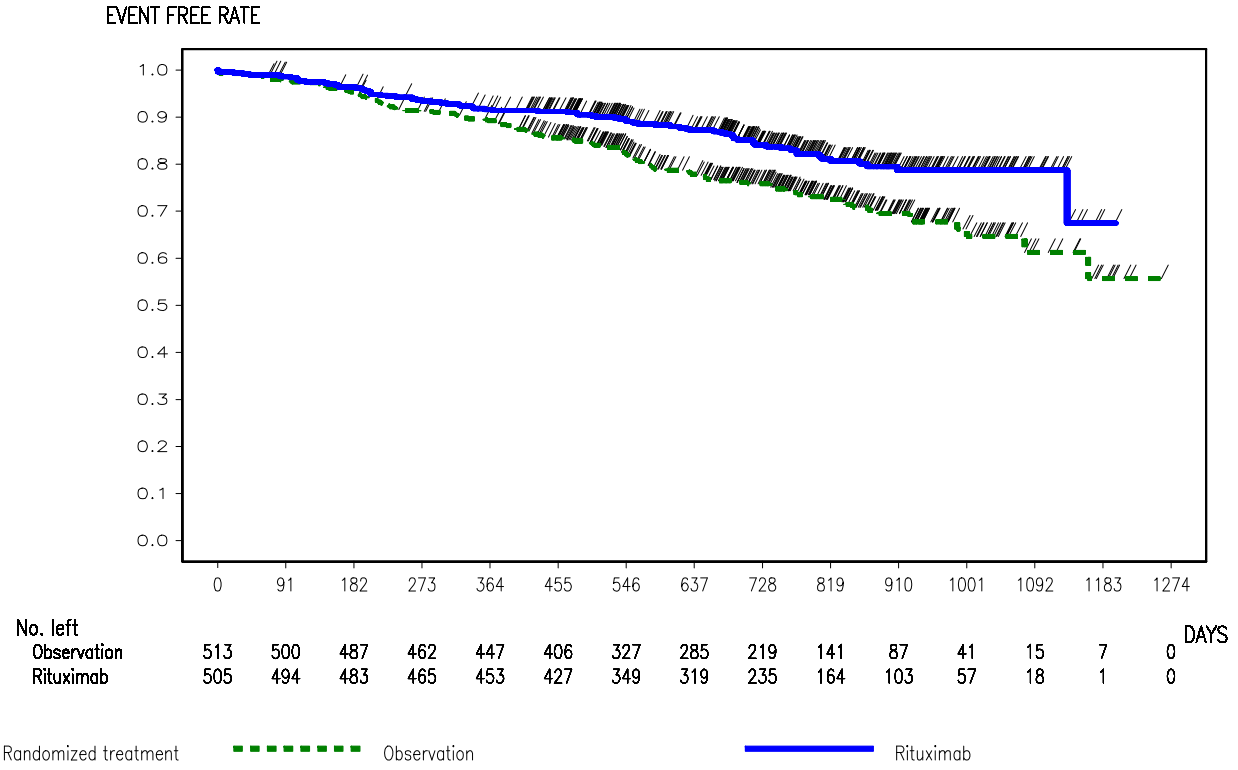
Output : $PROD/cd10752c/a18264m/reports/mt_tnasum_I.out
29OCT2009 9:16

The results of the analysis performed without stratification were similar to those of the stratified analysis (non-stratified HR 0.60, 95% CI [0.46;0.80], p = 0.0003, non-stratified log-rank test. The Kaplan–Meier plot of time to next (new) anti-lymphoma treatment or death is provided in Figure 14. The curves start to separate at six months but remain close at one year, at which time 11% of patients on observation and 8% of patients on rituximab had started a new treatment for lymphoma or died. At two years, the event-free rates were 76% in the observation arm and 84% in the rituximab arm.

Figure 14: Kaplan–Meier Plot of Time to Next Anti-Lymphoma Treatment (MITT)

Protocol(s): MO18264 (A18264M)
Analysis Population: MITT (N=1018)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



TTNLT - day of randomization until initiation of a new anti-lymphoma treatment or death from any cause.
Censoring occurs at date of last visit.
One year duration is defined as 364 days.

Program : $PROD/cd10752c/a18264a/mg_tnakm.sas / Output : $PROD/cd10752c/a18264m/reports/mg_tnakm_l.cgm
29OCT2009 9:16

5.5.2.2.4 Time to Next Chemotherapy Treatment

A total of 171 patients (16.8%) had started a new chemotherapy treatment or died before having received a new chemotherapy treatment (164 new treatments and seven deaths). More patients in the observation arm started a new chemotherapy treatment or died than those in the rituximab arm (106 patients vs 65 patients, 20.7% vs 12.9%). The risk of starting a new chemotherapy treatment or death was reduced by 40% for patients in the rituximab arm compared with those in the observation arm (stratified HR 0.60, 95% CI [0.44;0.82], p = 0.0011, stratified log-rank test) (Table 35). The median time from randomization to initiation of new chemotherapy or death was not reached at the time of the analysis. The 25th percentile time was 884 days (29.0 months) in the observation arm and 1135 days (37.3 months) in the rituximab arm.

Table 35: Summary of Time to Next Chemotherapy Treatment (MITT

	Observation (N=513)		Rituximab (N=505)
Patients with event	106 (20.7 %)		65 (12.9 %)
Patients without events*	407 (79.3 %)		440 (87.1 %)
Time to event (days)			
Median#	.		.
95% CI for Median#	[1163;.]		[.;.]
25% and 75%-ile#	884;.		1135;.
Range##	1 to 1261		1 to 1199
p-Value (Log-Rank Test, stratified**)		0.0011	
Hazard Ratio (stratified**)		0.60	
95% CI		[0.44;0.82]	
p-Value (Wald Test)		0.0013	
1 year duration			
Number left	454		457
Event Free Rate#	0.91		0.92
95% CI for Rate#	[0.89;0.94]		[0.90;0.95]

Days To Event Or Censoring (TTNCT) (TTNCTTT) - Censoring: Event (TTNCT) (TTNCTCS)
* 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

TTNCT - day of randomization until initiation of a new chemotherapy treatment or death from any cause.
Censoring occurs at date of last visit.
One year duration is defined as 364 days.

Program : $PROD/cd10752c/a18264a/mt_tncsum.sas
Output : $PROD/cd10752c/a18264m/reports/mt_tncsum_I.out
29OCT2009 9:17

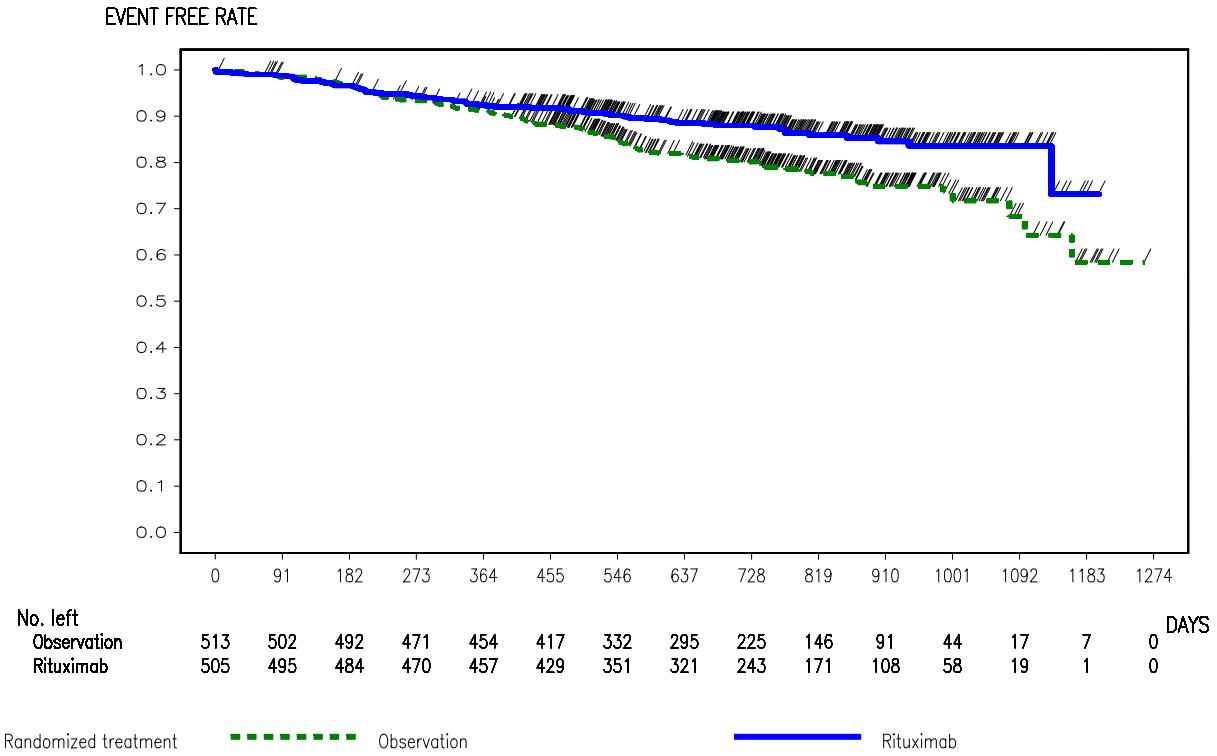
The results of the analysis performed without stratification were similar to those of the stratified analysis (non-stratified HR 0.60, 95% CI [0.44;0.81], p = 0.0011, non-stratified log-rank test). The Kaplan–Meier plot of time to next (new) chemotherapy or death (Figure 15) shows separation of the curves around one year after

randomization. The event-free rates at one year were 91% and 92% for the observation and rituximab arms, respectively, and at two years the event-free rates were 80% and 88%, respectively.

Figure 15: Kaplan–Meier Plot of Time to Next Chemotherapy Treatment (MITT)

mg_tnckm_I Maintenance Phase, Summary Of Time To Next Chemotherapy Treatment, Kaplan-Meier Plots (MITT)

Protocol(s): MO18264 (A18264M)
Analysis Population: MITT (N=1018)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



TTNCT - day of randomization until initiation of a new chemotherapy treatment or death from any cause.
Censoring occurs at date of last visit.
One year duration is defined as 364 days.

Program : $PROD/cd10752c/a18264a/mg_tnckm.sas / Output : $PROD/cd10752c/a18264m/reports/mg_tnckm_I.cgm
29OCT2009 9:17

5.5.2.2.5 Treatments after Progression

[redacted] started a new anti-lymphoma treatment after progression ([redacted] vs [redacted] patients, [redacted] vs [redacted] of patients overall, but the proportion of patients with disease progression who started a new treatment [redacted] ([redacted] of patients in the observation arm vs [redacted] of patients in the rituximab arm). The most common treatment after progression was [redacted] ([redacted] patients treated). [redacted] patients ([redacted] of the total, and [redacted] of the patients who progressed) in the observation arm and [redacted] patients ([redacted] of the total, and [redacted] of those who progressed) in the rituximab maintenance arm received [redacted] as part of their first treatment after progression. Around a quarter of patients who received subsequent treatment ([redacted] patients) received an [redacted] ([redacted] patients in the observation arm vs [redacted] patients in the rituximab arm; [redacted] vs [redacted] of the patients overall).

[redacted] patients were documented to have received further treatment subsequent to the first treatment for progression: [redacted] patients from the observation arm and [redacted] patients from the rituximab arm. Among those [redacted] patients, [redacted] patients received [redacted] as part of the second subsequent treatment ([redacted] patients from the observation arm vs [redacted] patients from the rituximab arm; [redacted]).

5.5.2.2.6 Overall Response Rate at the End of Maintenance/Observation

The overall response rate at the end of the maintenance/observation phase was analyzed on the basis of the investigators' assessments of tumor response at the end of maintenance treatment/observation (ie, excluding 231 patients still undergoing maintenance treatment/observation at the time of analysis (

Figure 7), but including patients who had disease progression or died during the maintenance/observation phase). A total of 787 patients were included in this analysis: 398 patients in the observation arm, and 389 patients in the rituximab arm. A total of 507 patients achieved a complete (CR and CRu) or partial response at the end of maintenance treatment/observation: 219 patients in the observation arm and 288 patients in the rituximab arm (55.0% vs 74.0%, $p < 0.0001$, χ^2 test) (Table below). Twenty-six patients were not evaluated (12 patients in the observation arm, and 14 patients in the rituximab arm), and 12 patients had a missing response (four vs eight patients).

The proportion of patients with a complete response (CR and CRu) was substantially higher in the rituximab arm than in the observation arm (260 patients, 66.8%, 95% CI [61.9;71.5]; vs 190 patients, 47.7%, 95% CI [42.7;52.8]). The rates of partial response were similar in both arms: 29 patients (7.3%, 95% CI [4.9; 10.3]) in the observation arm vs 28 patients (7.2%, 95% CI [4.8;10.2]) in the rituximab arm. More patients on observation had progressive disease than in the rituximab arm: 162 patients (40.7%, 95% CI [35.8;45.7]) in the observation arm vs 79 patients (20.3%, 95% CI [16.4;24.7]) in the rituximab arm.

Table 36: Summary of Investigator-Assessed Tumor Response at the End of Maintenance Treatment/Observation (MITT, Without Patients Ongoing Maintenance, N = 787)

	Observation (N=398)		Rituximab (N=389)
Responders$	219 (55.0 %)		288 (74.0 %)
Non-Responders	179 (45.0 %)		101 (26.0 %)
95% CI for Response Rates*	[50.0; 60.0]		[69.4; 78.3]
Difference in Response Rates		19.01	
95% CI for Difference in Response Rates#		[12.3; 25.7]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		2.33	
95% CI for Odds Ratio		[1.73;3.15]	
Complete Response (CR and CRu)	190 (47.7 %)		260 (66.8 %)
95% CI for CR and CRu Rates*	[42.7; 52.8]		[61.9; 71.5]
Difference in CR and CRu Rates		19.10	
95% CI for Difference in CR and CRu Rates#		[12.2; 26.0]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		2.21	
95% CI for Odds Ratio		[1.65;2.94]	
Partial Response (PR)	29 (7.3 %)		28 (7.2 %)
95% CI for PR Rates*	[4.9; 10.3]		[4.8; 10.2]
Difference in PR Rates		-0.09	
95% CI for Difference in PR Rates#		[-3.8; 3.7]	
p-Value (Chi-squared Test)		0.9618	
Odds Ratio		0.99	
95% CI for Odds Ratio		[0.58;1.69]	
Stable Disease (SD)	1 (0.3 %)		0 (0.0 %)
95% CI for SD Rates*	[0.0; 1.4]		[0.0; 0.9]
Progressive Disease (PD)	162 (40.7 %)		79 (20.3 %)
95% CI for PD Rates*	[35.8; 45.7]		[16.4; 24.7]
Not Evaluated (NE)	12 (3.0 %)		14 (3.6 %)
95% CI for NE Rates*	[1.6; 5.2]		[2.0; 6.0]
Missing (No Response Assessment)	4 (1.0 %)		8 (2.1 %)

Response (EOT, CR includes uCR) (EOTVALC)
$ Patients with end of treatment response of CR, CRu or PR
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

Program : $PROD/cd10752c/a18264a/mt_rspsum.sas
Output : $PROD/cd10752c/a18264m/reports/mt_rspsum_I_001.out
29OCT2009 9:18

The tumor responses at the end of the induction and maintenance/observation phases are summarized in Table 37 (excluding the 231 patients still in the maintenance/observation phase at the time of analysis, but not excluding patients who had disease progression or died during the maintenance/observation phase). The proportion of patients whose response improved (from CRu to CR; or from PR to CRu/CR; or from SD to PR/CR/CRu) was higher in the rituximab arm (104/389 patients, 27%) than in the observation arm (77/398 patients, 19%).

Table 37: Summary of Shift in Tumor Response from End of Induction to End of Maintenance/Observation (MITT, Without Patients Ongoing Maintenance/Observation, N = 787)

	Response at end of treatment						
Response after induction	CR	uCR	PR	SD	PD	Missing*	Total
Observation (N = 398)							
CR	91 (58.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	59 (38.1%)	5 (3.2%)	155
uCR	40 (33.9%)	22 (18.6%)	0 (0.0%)	0 (0.0%)	50 (42.4%)	6 (5.1%)	118
PR	26 (21.0%)	11 (8.9%)	29 (23.4%)	0 (0.0%)	53 (42.7%)	5 (4.0%)	124
SD	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1
Missing*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
Total	157	33	29	1	162	16	398
Rituximab (N = 389)							
CR	125 (78.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	27 (17.0%)	7 (4.4%)	159
uCR	55 (46.2%)	29 (24.4%)	0 (0.0%)	0 (0.0%)	27 (22.7%)	8 (6.7%)	119
PR	32 (30.2%)	15 (14.2%)	28 (26.4%)	0 (0.0%)	24 (22.6%)	7 (6.6%)	106
SD	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	3
Missing*	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2
Total	215	45	28	0	79	22	389

* Missing includes all missing values, non valid values or response not evaluated.

Program : $PROD/cd10752c/a18264a/mt_rspsh.sas / Output : $PROD/cd10752c/a18264m/reports/mt_rspsh_I_001.out
02NOV2009 9:33

5.5.2.2.7 Transformation Rate at First Progression

Of the [redacted] patients ([redacted]) who had documented progression ([redacted] patients in the observation arm, and [redacted] patients in the rituximab arm), transformation data were available for [redacted] patients ([redacted] vs [redacted] patients) and were missing for [redacted] patients ([redacted] vs [redacted] patients). Disease transformation was reported for [redacted] ([redacted] patients in the observation arm and [redacted] patients in the rituximab arm), and no transformation was reported for [redacted] patients ([redacted] vs [redacted] patients).

Overall, [redacted] ([redacted] patients, [redacted]) progressed with disease transformation compared with the observation arm ([redacted] patients, [redacted]) (Table 38), with a difference in transformation rates of [redacted] (95% CI [redacted], p = [redacted], χ^2 test).

Table 38: Summary of Transformation Rate at First Investigator-Assessed Progression (MITT)

	Observation (N=513)	Rituximab (N=505)
Transformation	19 (3.7 %)	11 (2.2 %)
No Transformation$	494 (96.3 %)	494 (97.8 %)
95% CI for Transformation Rates*	[2.2; 5.7]	[1.1; 3.9]
Difference in Transformation Rates	-1.53	
95% CI for Diff. in Transformation Rates#	[-3.7; 0.6]	
p-Value (Chi-squared Test)	0.1502	
Odds Ratio	0.58	
95% CI for Odds Ratio	[0.27;1.23]	

Transformation at Progression (PDTRAN)
$ Patients without PD, who died before the onset of PD, or have a missing transformation value are classified as having no transformation.
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

Program : $PROD/cd10752c/a18264a/t_ahr007_b.sas
Output : $PROD/cd10752c/a18264m/reports/t_ahr007_b_I.out
17DEC2009 14:57

5.5.2.2.8 Quality of Life

Quality of life was assessed using both the FACT-G and EORTC QLQ-C30 questionnaires, which were to be completed by patients at screening (induction baseline), at the end of the induction phase, at one year into the maintenance/observation phase, at the end of the maintenance/observation phase, and then every year for the five-year follow-up period (nine sets of questionnaires in

total). Note that questionnaires were not distributed/completed once a patient developed progressive disease. Thus, fewer questionnaires were completed for patients in the observation arm over time compared with the rituximab arm, and the effects of disease progression and any subsequent therapy for lymphoma on quality of life were not assessed. The results of the questionnaires completed up to the time of the clinical cut-off (January 14, 2009) are summarized below.

Fact-G

The FACT-G questionnaire assesses physical well-being, social and family well-being, emotional well-being, and functional well-being. The maximum score on FACT-G is 112. A higher score for the FACT-G scales and subscales indicates better quality of life.

In the PRIMA study, the initial scores at baseline (screening) were [redacted] (mean [redacted] and [redacted] in the observation and rituximab arms, respectively) and these scores did not [redacted] (Table 39). The differences between the two study arms were [redacted], and there was considerable [redacted] (Figure 16).

Table 39: Summary of FACT-G Total Scores over Time (MITT)

Scheduled Visit		FACT-G Total Score	
		Observation N = 513	Rituximab N = 505
Baseline (screening)	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
After Induction	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
After 1 Year of Maintenance/Observation	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
End of Maintenance/Observation Phase	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
1 Year after End of Maintenance/Observation	n	[redacted]	[redacted]

	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]
2 Years after End of Maintenance/Observation	n	[redacted]	[redacted]
	Mean	[redacted]	[redacted]
	SD	[redacted]	[redacted]

Analysis of the change in FACT-G score from baseline over time or from the end of the induction phase over time showed no meaningful differences in the quality of life between the two study arms.

'Treatment' refers to the maintenance/observation phase. The whiskers correspond to the minimum and maximum of the data; the lower and upper edges of the box are the 25th and 75th percentiles, respectively; the solid line near the middle of the box corresponds to the median; and the cross represents the mean.

EORTC QLQ-C30

The EORTC quality of life questionnaire (QLQ-C30) is a cancer-specific questionnaire that measures 30 single items sorted into three categories/scales: global health status/QoL scale, functional scale, and symptom scale. After linear transformation according to the EORTC manual, all scales with their sum scores have numeric values between 0 and 100. A higher score for global health status and functional scale implies a better quality of life, whereas a higher score for the symptom scale refers to worse quality of life. Again, questionnaires were not distributed/completed once a patient developed PD.

The mean scores for the QLQ-C30 survey in the PRIMA study are listed in Table 40. The mean scores at baseline for the two arms were similar, and these scores did not change substantially over the study period. The differences between the two study arms were small at every time point. The scores for global health status/QoL scale are plotted in Figure 17. There is considerable overlap between the two arms.

Table 40: Summary of EORTC QLQ-C30: Mean QoL Scores over Time (MITT)

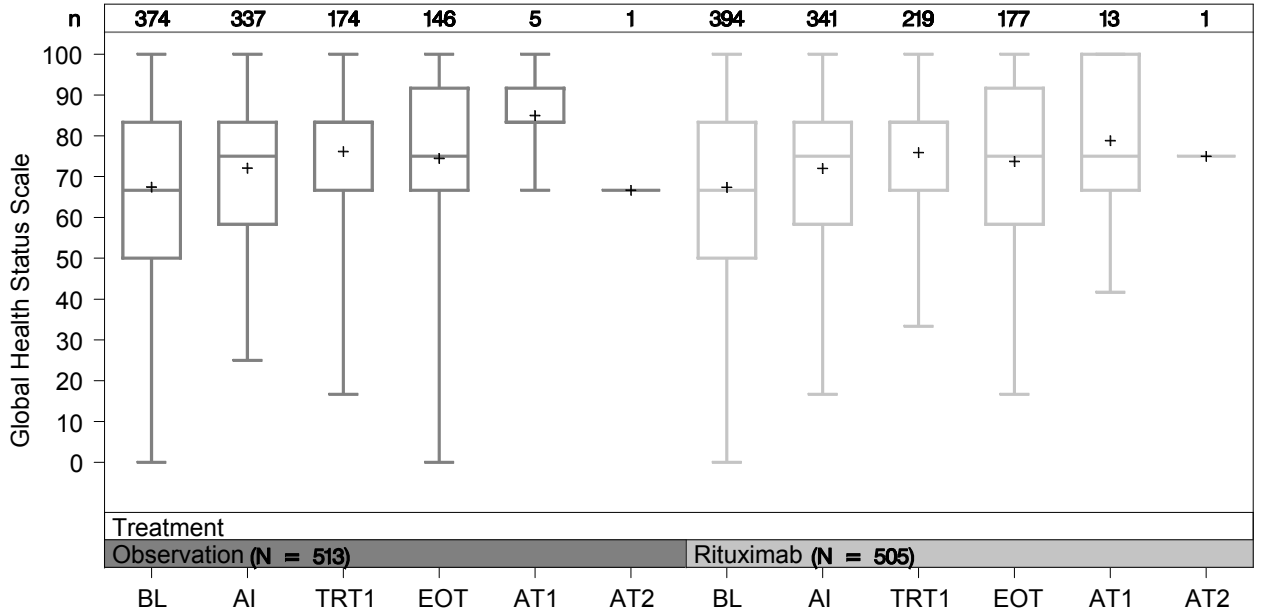
Scale	Observation, N = 513 Scheduled Visit											
	Baseline (Screening)		After Induction		After 1 Year of Maintenance/ Observation		End of Maintenance/ Observation		1 Year after End of Maintenance/ Observation		2 Years after End of Maintenance/ Observation	
	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score
Global Health Status/QoL	374	67.45 (20.59)	337	72.13 (18.13)	174	76.15 (18.00)	146	74.49 (20.84)	5	85.00 (12.36)	1	66.67
Functional Scales												
physical	386	86.48 (16.63)	345	84.22 (16.18)	178	87.84 (14.68)	150	87.69 (15.67)	6	94.44 (5.02)	1	100.00
role	384	78.99 (26.33)	345	79.52 (24.36)	178	88.48 (18.67)	150	90.11 (18.12)	6	97.22 (6.80)	1	100.00
emotional	379	71.23 (22.10)	340	77.29 (20.80)	176	81.30 (19.60)	148	83.09 (20.25)	6	84.72 (12.27)	1	100.00
social	371	81.22 (25.25)	340	78.68 (24.93)	175	90.29 (17.07)	148	90.88 (18.06)	6	94.44 (13.61)	1	100.00
cognitive	379	85.27 (20.45)	340	83.33 (21.11)	176	86.84 (17.78)	148	86.94 (17.12)	6	88.89 (13.61)	1	100.00
Symptom Scales/Items												
fatigue	385	29.44 (23.99)	345	30.31 (23.76)	178	23.44 (20.29)	150	21.52 (21.99)	6	16.67 (15.32)	1	33.33
nausea & vomiting	386	4.19 (10.70)	345	4.73 (11.72)	178	3.75 (10.70)	149	2.35 (8.23)	6	0.00	1	0.00
pain	385	19.52 (25.18)	345	16.57 (24.25)	177	12.99 (20.35)	150	15.56 (23.70)	6	2.78 (6.80)	1	0.00
dyspnoea	385	16.54 (25.47)	343	16.62 (25.22)	178	12.36 (19.33)	150	11.11 (21.04)	6	11.11 (17.21)	1	33.33
insomnia	383	32.20 (31.38)	342	26.90 (29.62)	178	23.60 (26.61)	148	21.40 (25.79)	6	22.22 (17.21)	1	0.00
appetite loss	385	13.42 (24.45)	345	9.86 (21.40)	176	5.87 (15.84)	149	6.94 (17.01)	6	0.00	1	0.00
constipation	379	14.95 (25.65)	340	12.06 (21.76)	176	9.85 (19.62)	147	10.20 (20.50)	6	5.56 (13.61)	1	0.00
diarrhoea	376	9.22 (19.26)	337	8.61 (18.05)	176	6.25 (14.87)	146	4.57 (11.50)	6	0.00	1	0.00
financial difficulties	369	13.55 (26.41)	338	17.06 (28.16)	174	13.22 (24.26)	147	11.79 (23.67)	6	16.67 (18.26)	1	0.00

Table 41: Summary of EORTC QLQ-C30: Mean QoL Scores over Time (MITT) (Contd.)

Scale	Rituximab, N = 505 Scheduled Visit											
	Baseline (Screening)		After Induction		After 1 Year of Maintenance/ Observation		End of Maintenance/ Observation		1 Year after End of Maintenance/ Observation		2 Years after End of Maintenance/ Observation	
	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Score
Global Health Status/QoL	394	67.39 (21.27)	341	71.99 (18.55)	219	75.91 (18.41)	177	73.73 (20.77)	13	78.85 (18.20)	1	75.00
Functional Scales												
physical	399	86.20 (17.29)	339	83.33 (17.25)	223	88.86 (13.66)	180	87.06 (15.76)	13	89.74 (11.74)	1	80.00
role	396	78.87 (27.68)	340	78.43 (25.65)	223	87.59 (18.46)	179	85.47 (20.91)	13	84.62 (23.04)	1	66.67
emotional	399	70.23 (23.74)	339	76.79 (22.78)	219	80.05 (21.00)	178	79.37 (20.35)	13	86.54 (21.39)	1	91.67
social	391	81.59 (24.76)	340	80.34 (23.15)	219	88.89 (17.94)	178	85.49 (20.51)	13	92.31 (18.78)	1	100.00
cognitive	399	85.09 (20.39)	340	83.68 (18.88)	220	85.76 (19.62)	178	85.49 (18.92)	13	89.74 (12.80)	1	83.33
Symptom Scales/Items												
fatigue	399	30.81 (25.60)	339	32.61 (25.51)	223	23.97 (21.90)	180	24.41 (22.47)	13	23.08 (18.96)	1	22.22
nausea & vomiting	400	4.88 (12.06)	340	3.97 (11.44)	223	2.47 (8.23)	180	2.78 (7.16)	13	1.28 (4.62)	1	0.00
pain	401	18.91 (24.59)	341	14.61 (21.56)	222	11.71 (19.75)	180	13.52 (19.92)	13	10.26 (28.50)	1	33.33
dyspnoea	397	18.30 (26.39)	339	18.98 (25.97)	222	13.66 (22.83)	179	16.39 (25.57)	13	17.95 (22.01)	1	0.00
insomnia	399	34.75 (33.09)	340	27.06 (30.18)	221	25.04 (29.59)	178	22.66 (28.65)	13	12.82 (21.68)	1	66.67
appetite loss	401	15.63 (25.71)	340	9.31 (19.37)	222	5.71 (15.78)	180	4.44 (12.90)	13	2.56 (9.25)	1	66.67
constipation	398	12.48 (23.73)	340	12.35 (22.12)	220	9.85 (20.86)	178	13.30 (24.89)	13	10.26 (16.01)	1	33.33
diarrhoea	397	8.65 (18.52)	339	7.57 (17.72)	219	6.70 (15.50)	178	6.93 (16.49)	13	10.26 (16.01)	1	0.00
financial difficulties	386	14.42 (26.14)	339	16.62 (27.42)	220	10.76 (21.85)	178	12.55 (22.93)	13	7.69 (14.62)	1	0.00

Figure 17: Box Plot of EORTC QLQ-C30 Global Health Status Scale over Time (MITT)

Protocol(s): MO18264 (A18264M)
Analysis Population: MITT (N=1018)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



Program : $PROD/cd10752c/a18264a/mg_qolbox_ql2.sas
Output : $PROD/cd10752c/a18264m/reports/mg_qolbox_ql2_l.cgm
13NOV2009 18:32

'Treatment' refers to the maintenance/observation phase. The whiskers correspond to the minimum and maximum of the data; the lower and upper edges of the box are the 25th and 75th percentiles, respectively; the solid line near the middle of the box corresponds to the median; and the cross represents the mean.

Overall, despite additional active treatment and infusions for patients in the rituximab maintenance arm, patient-reported quality of life remained unchanged with no apparent difference in quality of life compared with patients in the observation arm. The EORTC QLQ-C30 findings are therefore consistent with the findings from the FACT-G questionnaire, indicating no major differences between the rituximab maintenance and observation arms.

5.5.3 Updated efficacy results from January 15 2010 snapshot

To present the most up-to-date efficacy and safety (Section 5.9.2.13) data for the PRIMA study, an additional clinical cut-off was made on 15th Jan 2010 and a supplementary analysis was performed on cleaned data from randomization up to and including this date, providing an additional 12 months of follow-up data (median 36 months).

5.5.3.1 Overview of Efficacy

An overview of the key efficacy results (progression-free survival based on the investigators' assessments, and overall survival) up to the additional clinical cut-off date (Jan 15th, 2010) is provided inTable 42. In terms of progression-free survival, the updated analysis confirms the results of the primary analysis (clinical cut-off January 14th, 2009) that there is a significant benefit of rituximab maintenance therapy over observation. As an independent review of progression/relapse was not conducted for scans collected after the first clinical cut-off date, there is no update on IRC-assessed PFS results. Finally, too few additional events had occurred to draw further conclusions about overall survival.

Table 42: Overview of Efficacy Analysis (MITT, Clinical Cut Off Jan 15, 2010)

5.5.3.2 Primary Efficacy Parameter: Progression-Free Survival

Investigator-Assessed PFS

At the time of the updated analysis, [redacted] patients in the observation arm and [redacted] patients in the rituximab arm ([redacted] vs [redacted]) had experienced a progression event (ie, disease progression, relapse, or death) since randomization (Table 43). There were [redacted] new cases of disease progression/relapse in the observation arm and [redacted] new cases in the rituximab arm ([redacted] patients vs [redacted] patients) since the January 14, 2009 clinical cut-off date. There were also [redacted] additional deaths in the observation arm and [redacted] in the rituximab arm ([redacted] patients vs [redacted] patients) prior to documented progression since the earlier cut-off date.

Table 43: Summary of Composition of PFS Events (MITT, Clinical Cut-Off Jan15, 2010)

	Observation N=513	Rituximab N=505

	No. (%)	No. (%)
Progression/Relapse	[redacted]	[redacted]
Death	[redacted]	[redacted]
N (patients with events)	[redacted]	[redacted]

Percentages are based on n (total number of events)

Results based on this longer follow-up confirmed the primary PFS analyses that maintenance therapy with rituximab significantly reduced the risk of experiencing a PFS event. In this updated analysis, the risk of experiencing a PFS event was reduced by [redacted] compared with no further treatment (stratified HR [redacted], 95% CI [redacted], [redacted], stratified log-rank test) (Table 42), compared to the results of the primary PFS analysis based on the earlier clinical cut-off date (stratified HR 0.50, 95% CI [0.39;0.64], p < 0.0001, stratified log-rank test) (Table 22). The Kaplan–Meier estimated median PFS time was [redacted], but in the [redacted].

Subgroup analysis

Hazard ratios for PFS with 95% confidence intervals (observation vs rituximab) for the prespecified patient subgroups are shown in Table 43. As per the earlier cut-off date, the risk of disease progression or death [redacted] compared to [redacted] in all of the subgroups tested (HR [redacted]). Overall, the results of the PFS subgroup analyses are consistent with the primary analysis of PFS in the MITT population.

Table 44: Subgroup Analysis of Investigator-Assessed PFS (MITT, Clinical Cut-Off Jan15, 2010)

Category	Subgroup	N	Hazard Ratio[1] [95%CI]
All		[redacted]	[redacted]
Age	<60	[redacted]	[redacted]
	≥60	[redacted]	[redacted]
Sex	Female	[redacted]	[redacted]
	Male	[redacted]	[redacted]
FLIPI	FLIPI (≤ 1)	[redacted]	[redacted]
	FLIPI (2)	[redacted]	[redacted]

	FLIPI (≥3)	[redacted]	[redacted]
Induction chemotherapy	R-CHOP	[redacted]	[redacted]
	R-CVP	[redacted]	[redacted]
	R-FCM	[redacted]	[redacted]
Response to induction	CR/uCR	[redacted]	[redacted]
	PR	[redacted]	[redacted]

1. Hazard ratio (HR) and its 95% confidence interval (CI) calculated from a non-stratified Cox regression model including only treatment as covariate.

5.5.3.3 Secondary Efficacy Parameter: Overall Survival

From the January 14, 2009 clinical cut-off date to the time of the updated analysis (January 15 2010), a further [redacted] patients in the observation arm and [redacted] patients in the rituximab arm had died ([redacted] patients vs [redacted] patients; Table 45). The results for overall survival were comparable with those from the earlier cut-off, but still too few deaths were observed ([redacted] in the observation arm and [redacted] in the rituximab arm) at the time of the updated analysis to draw meaningful conclusions (stratified HR [redacted], 95% CI [redacted], [redacted], stratified log-rank test).

Table 45: Summary of Composition of OS Events (MITT, Clinical Cut-Off Jan15, 2010)

	Observation N=513 No. (%)	Rituximab N=505 No. (%)
Patients with event	[redacted]	[redacted]
Patients without events (censored)	[redacted]	[redacted]

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

5.6.3 **If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

Not applicable.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.**

Not applicable.

5.7.2 **Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in**

section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable.

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable.

5.7.6 Please present the results of the analysis.

Not applicable.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable.

5.7.8 **If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

Not applicable.

5.7.9 **Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.**

Not applicable.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 **If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.**

Not applicable.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

The primary safety results for the PRIMA study are based on randomized patients who received at least one dose of rituximab (rituximab maintenance arm) or attended at least one observation visit (observation arm) during the maintenance/observation phase; these patients form the maintenance safety analysis population (MSAP, N = 1009).

Safety data were also collected during the induction phase and are summarized below according to induction treatment group for the induction analysis population (IAP, N = 1193; patients who received no induction treatment are excluded from these analyses).

5.9.1 Induction Phase Safety Results

In this section, safety parameters recorded during the induction phase of the study are summarized for the induction analysis population according to the induction regimen patients received. Note that only serious adverse events and toxicities were required to be recorded during the induction phase. However, some additional non-serious AEs were also reported.

5.9.1.1 Extent of Exposure to Induction Trial Medication

Of 1193 patients treated in the induction phase, [redacted] patients ([redacted]) completed all eight cycles of induction treatment. The median number of cycles received was [redacted] across all three treatment groups.

5.9.1.2 Overview of Safety during the Induction Phase

An overview of toxicities and serious adverse events recorded during the induction phase of the study is provided in Table 46. The majority of patients (99% overall) in the induction analysis population had at least one toxicity recorded during the induction phase, and 25% of all patients recorded at least one serious adverse event. Overall, the safety profile of rituximab in combination with CHOP, CVP, and FCM was consistent with the known safety profile of these induction regimens with no new or unexpected safety findings.

Table 46: Overview of Safety during the Induction Phase (IAP)

Safety Parameter	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)
Toxicities[a]	[redacted]	[redacted]	[redacted]
Adverse Events[b]	[redacted]	[redacted]	[redacted]
Serious Adverse Events	[redacted]	[redacted]	[redacted]
Grade 3/4 AEs	[redacted]	[redacted]	[redacted]
Grade 5 (fatal) AEs	[redacted]	[redacted]	[redacted]
Related AEs	[redacted]	[redacted]	[redacted]

a Toxicities are based on the checklist CRF page (Grades 1–5, regardless of causality).
b Although it was required that only serious AEs be recorded on the AE CRF page during the induction phase, some additional AEs (presumed to be non-serious) were also reported.

5.9.1.3 Toxicities during the Induction Phase

Almost all patients in the induction analysis population experienced [redacted] during the induction phase (Table 47). The most frequently recorded toxicities overall were decreases in [redacted], [redacted], or [redacted], [redacted], and [redacted]. The majority (> 75%) of these toxicities were [redacted] (ie, Grade 1/2 events). Toxicities listed under the 'other' category accounted for [redacted] ([redacted]) of all toxicities reported (note that these are not presented in Table 47). The most common 'other' categories were [redacted], [redacted], and [redacted] and [redacted].

Table 47: Summary of Toxicities by CRF Prespecified Terms* (IAP)

Body System/ Adverse Event	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	[redacted]	[redacted]	[redacted]
Total Number of AEs	[redacted]	[redacted]	[redacted]
PRE-SPECIFIED IN CRF			
Total Pts With at Least one AE	[redacted]	[redacted]	[redacted]
LEUKOCYTES	[redacted]	[redacted]	[redacted]
NEUTROPHILS	[redacted]	[redacted]	[redacted]
HEMOGLOBIN	[redacted]	[redacted]	[redacted]
GASTROINTESTINAL	[redacted]	[redacted]	[redacted]
CONSTITUTIONAL SYMPTOMS	[redacted]	[redacted]	[redacted]
NEUROLOGY	[redacted]	[redacted]	[redacted]
PLATELETS	[redacted]	[redacted]	[redacted]
INFECTION WITH NORMAL NEUTROPHILS	[redacted]	[redacted]	[redacted]
DERMATOLOGY / SKIN	[redacted]	[redacted]	[redacted]
AST / ALT	[redacted]	[redacted]	[redacted]
PULMONARY	[redacted]	[redacted]	[redacted]
ALLERGY / IMMUNOLOGY	[redacted]	[redacted]	[redacted]
FEBRILE NEUTROPENIA	[redacted]	[redacted]	[redacted]
INFECTION DOC. WITH NEUTROPHILS G3/4	[redacted]	[redacted]	[redacted]
RENAL / GENITO-URINARY	[redacted]	[redacted]	[redacted]
CREATININE	[redacted]	[redacted]	[redacted]
VASCULAR	[redacted]	[redacted]	[redacted]
CARDIAC GENERAL	[redacted]	[redacted]	[redacted]
CARDIAC ARRHYTHMIA	[redacted]	[redacted]	[redacted]
COAGULATION	[redacted]	[redacted]	-
Total Number of AEs	[redacted]	[redacted]	[redacted]

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.
AE11 19JAN2010:14:57:04

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

5.9.1.4 Adverse Events during the Induction Phase

Although it was required that only serious AEs be recorded on the AE CRF page during the induction phase, some additional AEs (presumed to be non-serious) were also reported. A total of [redacted] AEs were recorded for [redacted] patients ([redacted] overall) during the induction phase, and the great majority of these were [redacted]. AEs occurring with an incidence of at least 1% across the IAP were [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), and [redacted] ([redacted] patients, [redacted] overall) (
Table 48). Other AEs were recorded by [redacted] of patients overall.

Table 48: Summary of AEs* by Body System Occurring with a Total Incidence of ≥ 1% during the Induction Phase (IAP)

Body System/ Adverse Event	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)	Total N = 1193 No. (%)
All Body Systems				
Total Patients with at Least One AE	[redacted]	[redacted]	[redacted]	[redacted]
Total Number of AEs	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Febrile Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Immune System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Drug Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]

* Although it was required that only serious AEs be recorded on the AE CRF page during the induction phase, some additional AEs (presumed to be non-serious) were also reported.

Around [redacted] of all AEs ([redacted] AEs) were reported by the investigator as having a remote, possible, or probable relationship to trial treatment. AEs which were most commonly considered to be related to trial treatment included [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), and [redacted] ([redacted] patients, [redacted] overall).

A total of [redacted] patients ([redacted]) reported [redacted] Grade 3/4 adverse events. The most frequently observed Grade 3/4 AEs were [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), and [redacted] ([redacted] patients, [redacted] overall).

5.9.1.5 Serious Adverse Events during the Induction Phase

During the induction phase, a total of [redacted] SAEs were reported for [redacted] patients ([redacted] patients [[redacted]] in the R-CHOP group, [redacted] patients [[redacted]] in the R-CVP group, and [redacted] patients [[redacted]] in the R-FCM group) (Table 49). [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), [redacted], [redacted] ([redacted]), and [redacted] ([redacted]) were the most common categories of SAEs overall. SAEs reported for at least [redacted] of patients overall were [redacted] ([redacted] patients, [redacted]), [redacted] ([redacted] patients, [redacted]), [redacted] ([redacted] patients, [redacted]), and [redacted] ([redacted] patients, [redacted]).

Table 49: Summary of SAEs by Body System Occurring with a Total Incidence of ≥ 1% during the Induction Phase (IAP)

Body System*/ Adverse Event	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)	Total N = 1193 No. (%)
All Body Systems				
Total Patients with at Least One AE	[redacted]	[redacted]	[redacted]	[redacted]
Total Number of AEs	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Febrile Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Drug Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms Benign, Malignant, Unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]

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

5.9.1.6 Adverse Events Leading to Induction Treatment Discontinuation

A total of [redacted] patients ([redacted] overall) discontinued induction treatment as a result of adverse events ([redacted] accounted for the withdrawal of [redacted] and [redacted] patients withdrew due to [redacted] The most common AEs that led to treatment discontinuation were [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), and [redacted] [redacted] patients, [redacted] overall).

Table 50). [redacted] accounted for the withdrawal of [redacted] patients, and [redacted] patients withdrew due to [redacted]. The most common AEs that led to treatment discontinuation were [redacted] ([redacted] patients, [redacted] overall), [redacted] ([redacted] patients, [redacted] overall), and [redacted] ([redacted] patients, [redacted] overall).

Table 50: Summary of Adverse Events by Body System Leading to Withdrawals (IAP)

Body System*	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)	Total N = 1193 No. (%)
All Body Systems				
Total Patients with at Least One AE	[redacted]	[redacted]	[redacted]	[redacted]
Total Number of AEs	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms Benign, Malignant, Unspecified	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Immune System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]
Skin and Subcutaneous Tissue Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Congenital, Familial and Genetic	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]

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

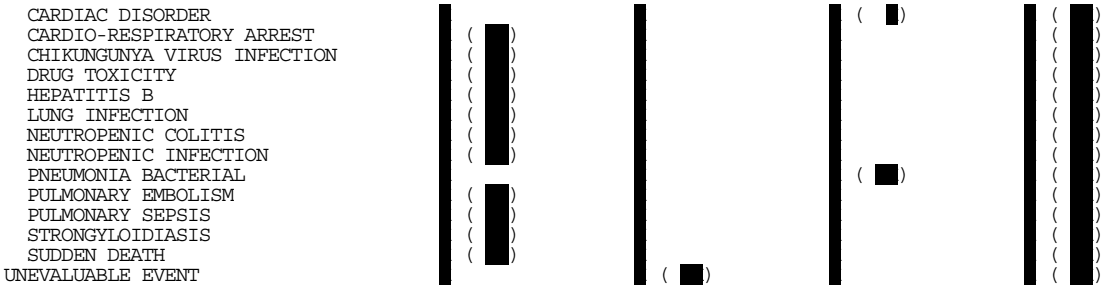
5.9.1.7 Deaths during the Induction Phase

Deaths of patients who were not treated/observed in the maintenance/observation phase are summarized in Table 51. The summary table and corresponding listing of deaths by induction treatment include also one patient who died [redacted] (patient [redacted], [redacted]) as well as three randomized patients who [redacted] (patients [redacted], [redacted], [redacted]). Deaths of patients included in the MSAP population are reported in Section 5.9.2.5.

At the clinical cut-off date (January 14, 2009), there were [redacted] deaths reported for patients who only received induction treatment in the PRIMA trial. Among these, the most common cause of death was [redacted], which accounted for [redacted] deaths. One patient died of [redacted].

Table 51: Summary of Deaths during the Induction Phase (IAP)

Cause of Death	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)	TOTAL N = 1193 No. (%)
Total No. of Deaths	[redacted]	[redacted]	[redacted]	[redacted]
LYMPHOMA	[redacted]	[redacted]	[redacted]	[redacted]
PNEUMONIA	[redacted]	[redacted]		[redacted]
SEPSIS	[redacted]	[redacted]		[redacted]
SEPTIC SHOCK	[redacted]		[redacted]	[redacted]



Investigator text for Cause of Death encoded using MedDRA version 12.0.
Percentages are based on N.
DD11 25JAN2010:13:52:47

Sixteen deaths were considered to be outcomes of adverse events (Table 52). In addition, an adverse event (hepatitis B, Grade 2) was cited as leading to the death of patient 40317/1001, although this patient was also reported to have died of lymphoma (see Section 5.9.2.9.2). The remaining four patients, who were not reported to have died of lymphoma or adverse events, died of neutropenic colitis (patient 60213/1001), sepsis (patient 71201/1096), a cardiac disorder (patient 40146/1010), and an unevaluable/unknown event (patient 10221/1009).

Table 52: Summary of Adverse Events Leading to Death (IAP)

Body System/ Adverse Event	R-CHOP N = 881 No. (%)	R-CVP N = 268 No. (%)	R-FCM N = 44 No. (%)	TOTAL N = 1193 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	14 (2)	1 (<1)	2 (5)	17 (1)
Total Number of AEs	14	1	2	17
INFECTIONS AND INFESTATIONS				
Total Pts With at Least one AE	11 (1)	1 (<1)	2 (5)	14 (1)
PNEUMONIA	2 (<1)	1 (<1)	-	3 (<1)
SEPTIC SHOCK	2 (<1)	-	1 (2)	3 (<1)
HEPATITIS B	2 (<1)	-	-	2 (<1)
CHIKUNGUNYA VIRUS INFECTION	1 (<1)	-	-	1 (<1)
LUNG INFECTION	1 (<1)	-	-	1 (<1)
NEUTROPENIC INFECTION	1 (<1)	-	-	1 (<1)
PNEUMONIA BACTERIAL	-	-	1 (2)	1 (<1)
SEPSIS	1 (<1)	-	-	1 (<1)
STRONGYLOIDIASIS	1 (<1)	-	-	1 (<1)
Total Number of AEs	11	1	2	14
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	2 (<1)	-	-	2 (<1)
DYSPNOEA	1 (<1)	-	-	1 (<1)
PULMONARY EMBOLISM	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

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.
AE11 27JAN2010:17:04:38

5.9.2 Maintenance/Observation Phase Safety Results

5.9.2.1 Extent of Exposure to Maintenance Trial Medication

A total of 1009/1019 patients received at least one dose of rituximab maintenance treatment or attended one observation visit during the maintenance/observation phase and were therefore included in the maintenance safety analysis population (MSAP): 508 patients in the observation arm, and 501 patients in the rituximab arm (see Section 5.3.1.2.16). Although six patients in the observation arm received rituximab before progression was documented, these patients are still included in the observation arm.

At the time of data cut-off, 380 patients in the safety population had completed the full course of 12 maintenance treatment or scheduled observation visits: 285 patients in the rituximab arm received 12 rituximab injections compared with 95 patients in the observation arm who attended 12 observation visits (

Table 53). A further 231 patients were still on active maintenance/observation (115 patients in the observation arm, and 116 patients in the rituximab arm), and 263 patients had withdrawn prematurely from the maintenance/observation phase (162 vs 101 patients), mostly due to disease progression (see

Figure 7). The median number of visits attended in the observation arm was nine. The median number of visits attended (cycles received) in the rituximab arm was twelve.

Table 53: Summary of Number of Maintenance Rituximab Cycles Received/Observation Visits Attended (MSAP)

Observation	Rituximab	Total
	N = 508 No. (%)	N = 501 No. (%)	N = 1009 No. (%)
Number of patients attending			
0 Visits	0 (0.0)	0 (0.0)	0 (0.0)
1 Visit	17 (3.3)	8 (1.6)	25 (2.5)
2 Visits	18 (3.5)	12 (2.4)	30 (3.0)
3 Visits	26 (5.1)	12 (2.4)	38 (3.8)
4 Visits	39 (7.7)	14 (2.8)	53 (5.3)
5 Visits	33 (6.5)	5 (1.0)	38 (3.8)
6 Visits	43 (8.5)	14 (2.8)	57 (5.6)
7 Visits	32 (6.3)	11 (2.2)	43 (4.3)
8 Visits	43 (8.5)	27 (5.4)	70 (6.9)
9 Visits	55 (10.8)	46 (9.2)	101 (10.0)
10 Visits	46 (9.1)	37 (7.4)	83 (8.2)
11 Visits	61 (12.0)	30 (6.0)	91 (9.0)
12 Visits	95 (18.7)	285 (56.9)	380 (37.7)
Number of visits attended			
Mean	8.0	10.1	9.0
SD	3.31	2.92	3.30
SEM	0.15	0.13	0.10
Median	9.0	12.0	10.0
Min	1	1	1
Max	12	12	12
n	508	501	1009

Program : $PROD/cd10752c/a18264a/mt_mt_pt_mttc.sas
Output : $PROD/cd10752c/a18264m/reports/mt_mt_pt_mttc_S.out
29JAN2010 14:35

The great majority of patients in the rituximab arm (89.8%) received over 90% of their projected rituximab dose (Table 54).

Table 54: Summary of Extent of Exposure to Maintenance Rituximab (MSAP)

	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%)

Program : $PROD/cd10752c/a18264a/mt_mt_mtdi_mtt.sas
Output : $PROD/cd10752c/a18264m/reports/mt_mt_mtdi_mtt_S.out
29JAN2010 14:35

5.9.2.2 Overview of Safety during the Maintenance/Observation Phase

An overview of safety parameters recorded during the maintenance/observation phase of the PRIMA study up to January 14, 2009, is provided in Table 55. It is important to note that Grade 1 infections and Grade 1 and 2 adverse events other

than infections were not recorded during the maintenance/observation phase except as toxicities on the checklist toxicity CRF. Furthermore, mandatory collection of serious adverse events for the observation arm was not clearly specified in the study protocol until this oversight was corrected shortly before the data cut-off. Nevertheless, the proportion of AEs that were reported as serious AEs appears to be balanced between the study arms (63/179 [35%] in the observation arm vs 95/263 [36%] in the rituximab arm) (Table 55), suggesting that there had not been systematic under-reporting of SAEs in the observation arm.

At the time of data cut-off, the majority of patients in both arms had at least one toxicity recorded during the maintenance/observation phase, based on the toxicity checklist provided in the CRF. As expected, the incidences of adverse events, Grade 3/4 AEs, and SAEs were higher in the rituximab arm than in the observation arm. However, overall, rituximab maintenance therapy was well tolerated and no unexpected safety findings were observed.

Table 55: Overview of Safety during the Maintenance/Observation Phase (MSAP)

Safety Parameter	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
Toxicities[a]	459 (90)	485 (97)
Adverse Events[b]	179 (35)	263 (52)
Grade 3/4 AEs	81 (16)	114 (23)
Serious Adverse Events	63 (12)	95 (19)
Withdrawal from treatment due to toxicity	1 (<1)	10 (10)
AEs leading to treatment discontinuation	8 (2)	19 (4)
AEs leading to dose modification	–	30 (6)
AEs leading to death	2 (<1)	3 (<1)
Infection AEs (Grade ≥ 2)	114 (22)	184 (37)
Grade 3/4 infections	5 (<1)	22 (4)
AEs occurring within one day after treatment/observation visit	46 (9)	61 (12)
Total Deaths	18 (4)	13 (3)
Death due to cause other than lymphoma	6 (1)	3 (<1)

a Toxicities are based on the checklist CRF page (regardless of grade).
b Includes Grade 3–5 toxicities, Grade 2–5 infections, and SAEs regardless of grade, as recorded on the AE CRF pages.

5.9.2.3 Toxicities during the Maintenance/Observation Phase

On the basis of the checklist of prespecified toxicities in the CRF, 97% of patients in the rituximab arm and 90% of patients in the observation arm experienced at least

one toxicity during the maintenance/observation phase (Table 56). Toxicities that were more prevalent in the rituximab arm than the observation arm included constitutional symptoms, decreases in leukocytes, neutrophils, or hemoglobin, infection with normal neutrophils, gastrointestinal disorders, increases in transaminases (AST/ALT), and pulmonary disorders. The vast majority (> 90%) of these toxicities were mild/moderate in severity (ie, Grade 1/2 events). Note that an additional 5% of patients in the observation arm and 3% of patients in the rituximab arm had toxicities recorded under the 'other' category, which is not presented in Table 56.

Table 56: Summary of Toxicities by CRF Prespecified Terms* (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	459 (90)	485 (97)	944 (94)
Total Number of AEs	1889	2680	4569
PRE-SPECIFIED IN CRF			
Total Pts With at Least one AE	434 (85)	472 (94)	906 (90)
CONSTITUTIONAL SYMPTOMS	155 (31)	203 (41)	358 (35)
LEUKOCYTES	140 (28)	201 (40)	341 (34)
INFECTION WITH NORMAL NEUTROPHILS	127 (25)	192 (38)	319 (32)
NEUROLOGY	143 (28)	145 (29)	288 (29)
GASTROINTESTINAL	114 (22)	165 (33)	279 (28)
NEUTROPHILS	93 (18)	150 (30)	243 (24)
AST / ALT	98 (19)	123 (25)	221 (22)
HEMOGLOBIN	72 (14)	136 (27)	208 (21)
PULMONARY	56 (11)	123 (25)	179 (18)
DERMATOLOGY / SKIN	75 (15)	97 (19)	172 (17)
PLATELETS	70 (14)	82 (16)	152 (15)
CREATININE	49 (10)	46 (9)	95 (9)
RENAL / GENITO-URINARY	30 (6)	40 (8)	70 (7)
CARDIAC GENERAL	28 (6)	41 (8)	69 (7)
VASCULAR	30 (6)	31 (6)	61 (6)
CARDIAC ARRHYTHMIA	14 (3)	26 (5)	40 (4)
ALLERGY / IMMUNOLOGY-OTHER	14 (3)	19 (4)	33 (3)
ALLERGY / IMMUNOLOGY-INFUSION RELATED REACTION	2 (<1)	11 (2)	13 (1)
INFECTION DOC. WITH NEUTROPHILS G3/4	2 (<1)	11 (2)	13 (1)
COAGULATION	2 (<1)	4 (<1)	6 (<1)
FEBRILE NEUTROPENIA	1 (<1)	1 (<1)	2 (<1)
Total Number of AEs	1315	1847	3162

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
* Toxicities entered as free text under the 'other' category on the toxicity CRF by the investigator were encoded and are listed separately in the source table by system organ class and preferred term.

A summary of prespecified toxicities occurring with a difference in incidence of 2% or higher in the rituximab arm compared with the observation arm is presented in Table 57.

Table 57: Summary of Toxicities by CRF Prespecified Terms Occurring with ≥ 2% Difference in Incidence in the Rituximab Arm Compared to the Observation Arm (MSAP)

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

5.9.2.4 Adverse Events during the Maintenance/Observation Phase

5.9.2.4.1 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 higher in the rituximab arm than in the observation arm (52% vs 35%). This difference was mainly due to infections and infestations (37% of patients in the rituximab arm vs 22% of patients in the observation arm). A total of 728 AEs were reported. 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 low (< 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 58.

Table 58: Summary of Adverse Events by Body System* Occurring with an Incidence of ≥ 1% in Either Arm (MSAP)

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%.

More AEs were reported in the rituximab arm compared with the observation arm (459 vs 269 events). AEs that occurred with a higher incidence (≥ 2% difference) in the rituximab arm compared with the observation arm were bronchitis (9% vs 5%), upper respiratory tract infection (5% vs 2%), sinusitis (4% vs 2%), and neutropenia (4% vs <1%) (Table 58). The incidence of all other AEs was low and comparable between the two study arms.

The majority of AEs were Grade 2 in severity (165/269 AEs [61%] in the observation arm; 291/459 AEs [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). A total of 195 patients recorded Grade 3 or 4 AEs (see Section 5.9.2.4.3). There were five Grade 5 (fatal) AEs (see Section 5.9.2.5).

Adverse Events over Time

The proportion of patients reporting AEs was slightly higher in the rituximab arm than in the observation arm at almost all visits, but there were no apparent trends for

increasing incidence with time in either arm with subsequent cycles of treatment/observation (Table 59).

Table 59: Summary of Adverse Events by Treatment Cycle/Observation Visit (MSAP)

Rituximab Cycle/ Observation Visit	Observation, N = 508		Rituximab, N = 501	
	n	Patients with at least one AE (%)	n	Patients with at least one AE (%)
1	508	40 (8)	501	49 (10)
2	491	32 (7)	493	51 (10)
3	473	31 (7)	481	40 (8)
4	447	31 (7)	469	30 (6)
5	408	26 (6)	455	36 (8)
6	375	24 (6)	450	46 (10)
7	332	28 (8)	436	42 (10)
8	300	14 (5)	425	35 (8)
9	257	10 (4)	398	38 (10)
10	202	12 (6)	352	31 (9)
11	156	12 (8)	315	18 (6)
12	95	8 (8)	285	33 (12)

Percentages are based on the corresponding n.

Adverse Events by Cumulative Rituximab Dose

A summary of the incidence of AEs based on the cumulative dose of rituximab administered during the maintenance/observation phase is provided in

Table 60. The number of Grade 2–5 infections appears to increase with cumulative rituximab dose. However, comparison with the number (percentage) of infections by treatment cycle shows that the number of infections recorded at each cycle did not increase over time (ie, the number of infections occurring in cycles 10, 11, or 12 was no greater than the number occurring in early cycles [eg, cycles 1, 2, or 3]). Therefore, the higher incidence of infections seen with increasing cumulative rituximab dose simply reflects the link between cumulative dose and longer overall observation time rather than the cumulative rituximab dose per se.

Table 60 Summary of Adverse Events in the Rituximab Arm by Cumulative Dose of Rituximab (MSAP, N = 501)

Body System	Rituximab Cumulative Dose (mg)			
	0–2000 N = 22	≥ 2000–4000 N = 36	≥ 4000–6000 N = 69	> 6000 N = 374
All Body Systems	8 (36%)	14 (39%)	32 (46%)	209 (56%)
Infections and Infestations	3 (14%)	7 (19%)	20 (29%)	154 (41%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	1 (5%)	1 (3%)	2 (3%)	18 (5%)
Blood and Lymphatic System Disorders	1 (5%)	1 (3%)	3 (4%)	21 (6%)

Percentages are based on the corresponding N.

Treatment-Related Adverse Events

AEs which were reported by the investigator as having a remote, possible, or probable relationship to trial treatment were reported for 9% of patients in the observation arm and 29% of patients in the rituximab arm. Overall, 60/269 events (22%) in the observation arm and 229/459 events (50%) in the rituximab arm were considered to be related to study treatment. AEs which were most commonly considered to be related to trial treatment included infections and infestations, and blood and lymphatic disorders (

Table 61). The occurrence of 'treatment-related' AEs in the observation arm despite no treatment (or lymphoma) being administered during the maintenance/observation phase probably reflects toxicities associated with the induction therapy being carried over into the maintenance/observation phase (a similar effect was probably also present in the rituximab arm).

Table 61: Summary of Treatment-Related Adverse Events* Occurring with an Incidence of ≥ 1% in Either Arm (MSAP)

Body System/ Adverse Event	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL N = 1009 No. (%)
INFECTIONS AND INFESTATIONS			
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)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	4 (<1)	17 (3)	21 (2)
LEUKOPENIA	1 (<1)	8 (2)	9 (<1)

Investigator text for Adverse Events encoded using MedDRA version 12.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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*Treatment-related AEs include remote, possible, or probable relationships of the AE to trial treatment.

5.9.2.4.2 Adverse Events in Special Populations

AEs occurring in patients aged under 65 years old, from 65 to 74 years old inclusive, and 75 years old and over, were analyzed for US regulatory purposes (

Table 62). Although the overall incidence of AEs appeared to increase with age in the observation arm, this was not apparent in the rituximab arm. The overall incidence of infections and infestations, blood and lymphatic system disorders, and neutropenia AEs also showed no clear increase with age in either arm, bearing in mind the low numbers of patients in the ≥ 75 years age group.

Table 62: 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)

Percentages are based on the corresponding n.

Infections were the most commonly occurring AEs in all three age categories. For patients aged under 65 years, the incidence of AEs was higher in the rituximab arm compared with the observation arm (54% vs 32%). This difference was mainly due to a higher incidence of infections (mainly bronchitis, upper respiratory tract infection, and sinusitis) and blood and lymphatic system disorders (mainly neutropenia) in the rituximab arm. For patients aged 65–74 years, the overall incidence of AEs as well as the incidence of infection AEs was balanced between the two study arms (34% in the rituximab arm vs 29% in the observation arm). In the ≥ 75 year age group, the incidence of AEs was similar between the two study arms but the incidence of infection AEs was higher in the rituximab arm than in the observation arm (35% vs 17%).

Comparing incidences of Grade 3, 4, and 5 AEs, and infection and infestation AEs in particular, across the different age groups, the overall incidence again appeared to increase with age in the observation arm but only slightly in the rituximab arm (

Table 63).

Table 63: Summary of Grade 3–5 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 Grade 3/4 AE	54 (14)	84 (22)
Total patients with at least one Grade 3/4 Infection & Infestations AE	2 (<1)	16 (4)
Total patients with a Grade 5 AE	1 (<1)	2 (<1)
Total patients with a Grade 5 Infection & Infestations AE	–	–*
65–74 inclusive	n = 97	n = 99
Total patients with at least one Grade 3/4 AE	18 (19)	24 (24)
Total patients with at least one Grade 3/4 Infection & Infestations AE	2 (2)	4 (4)
Total patients with a Grade 5 AE	1 (1)	–
Total patients with a Grade 5 Infection & Infestations AE	–	–
≥ 75	n = 24	n = 23
Total patients with at least one Grade 3/4 AE	9 (38)	6 (26)
Total patients with at least one Grade 3/4 Infection & Infestations AE	1 (4)	2 (9)
Total patients with a Grade 5 AE	–	1 (4)
Total patients with a Grade 5 Infection & Infestations AE	–	–

Percentages are based on the corresponding n.
* One patient died of fulminant hepatitis B (categorized as a hepatobiliary AE rather than an Infection & Infestation AE).

An additional analysis of AEs in patients aged < 60 years and ≥ 60 years old was also carried out and is available on request. There was no apparent difference in incidence of AEs in the different age groups. In particular, patients aged > 60 years old did not appear to experience more infection or hematological AEs than younger patients.

5.9.2.4.3 Grade 3 or 4 Adverse Events

More patients in the rituximab arm than in the observation arm experienced at least one Grade 3 or 4 adverse event (24% vs 16%). This difference was mainly due to a higher incidence of Grade 3 or 4 AEs of blood and lymphatic system disorders (mainly neutropenia) and infections in the rituximab arm than in the observation arm. Note that Grade 5 AEs (those with a fatal outcome) were analyzed separately (see Section 5.9.2.5).

Grade 3/4 AEs occurring with an incidence of 1% or higher in either arm are summarized in Table 64.

Table 64: Summary of Grade 3 or 4 Adverse Events by Body System * Occurring with an Incidence of ≥ 1% in Either Arm (MSAP)

Body System/ Adverse Event	OBSERVATION N = 508 No. (%)	RITUXIMAB N = 501 No. (%)	TOTAL N = 1009 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	5 (<1)	18 (4)	23 (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 18JAN2010:07:49:18

* 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%.

Grade 3/4 AEs that occurred with a higher incidence (≥ 2%) in the rituximab arm compared with the observation arm was neutropenia (4% vs < 1%). Grade 3/4 leukopenia was also more common in the rituximab arm than in the observation arm (2% vs <1%). The incidence of all other Grade 3/4 AEs was low (<1%) and comparable between the two study arms.

5.9.2.5 Deaths during the Maintenance/Observation Phase

At the time of clinical cut-off (January 14, 2009), a total of 31 patients in the MSAP had died during the active maintenance/observation phase or during follow-up (Table 65). (Note that the number of deaths based on the MITT population was 34 (cf Table 33), the difference being accounted for by the deaths of three patients (patients 10140/1004, 20334/1001, and 60143/1002) randomized to the rituximab arm but withdrawn from the study prior to receiving treatment.)

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 higher in the observation arm than in the rituximab arm (six patients vs three patients).

Table 65: 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)

Investigator text for Cause of Death encoded using MedDRA version 12.0.
Percentages are based on N.
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Unevaluable event corresponds to unknown cause of death.

Five of the nine non-lymphoma deaths were considered to be outcome of AEs (

Table 66). Two fatal AEs in the observation arm were a result of neoplasms: leukemia considered as possibly related to trial treatment (patient 10222/1008) and metastatic neoplasm considered to be treatment-unrelated (patient 21011/1013). The three recorded fatal AEs in the rituximab arm resulted from a treatment-unrelated disorder (unknown/unevaluable event; patient 20439/1003), hepatitis B considered to be probably treatment-related (patient 20111/1016), and pulmonary haemorrhage considered to be treatment-unrelated (patient 20731/1008).

The remaining four deaths (not due to lymphoma or to AEs) were all in the observation arm and were due to acute myeloid leukemia (patient 71501/1013), coronary artery disease (patient 10307/1013), myelodysplastic syndrome (patient 40346/1009), and sepsis (patient 60113/1004).

Table 66: 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

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.

5.9.2.6 Serious AEs during the Maintenance/Observation Phase

The guidelines for completing and reporting SAEs were modified in a protocol amendment to ensure balanced safety reporting between the rituximab maintenance and observation arms. Prior to this amendment, SAE reporting was not explicitly stated in the protocol wording for patients in the observation arm during the maintenance/observation phase. However, investigators and monitors were instructed to treat both arms equally with respect to the reporting of SAEs. Furthermore, SAEs should have been captured by the toxicity checklist which had to be completed for both arms at each visit. Subsequently, because of the requirement to enter Grade 3–5 toxicities and Grade 2–5 infections on the AE CRF page, the investigator had to indicate whether the AE was considered serious or not and therefore all SAEs of Grade 3 or higher or infection SAEs of Grade 2 or higher should have been reported for both study arms.

A total of 193 SAEs were reported for 158 patients (63 patients [12%] in the observation arm, and 95 patients [19%] in the rituximab arm) during the maintenance/observation phase (Table 67). Note that all SAEs occurred with an

incidence of less than 1% in both arms. The most common class of SAEs overall was neoplasms (39 events overall affecting 37 patients), including basal cell carcinoma (two patients in the observation arm vs four 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 six patients [1%] in the observation arm). In the rituximab arm, three patients had SAEs of pneumonia, two patients had diverticulitis, and two patients had hepatitis B (see Section 5.9.2.9.2). In the observation arm, three patients had SAEs of urinary tract infections. Other serious infections were reported by only one patient in each case.

Table 67: 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.

Serious cardiac disorders were reported for two patients in the observation arm compared with 11 patients in the rituximab arm (see Section 5.9.2.9.4).

5.9.2.7 Adverse Events Leading to Treatment Discontinuation

A total of 27 patients discontinued maintenance treatment/observation as a result of adverse events (eight 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 six patients in the observation arm and five patients in the rituximab arm (Table 68). Four patients in the rituximab arm were withdrawn as a result of infections: hepatitis B (two patients), endocarditis, and mycobacterial infection. One case of hepatitis B was considered to be unrelated to trial treatment, and the other three infections were considered as being probably

treatment-related. Five patients discontinued treatment after becoming pregnant (Section 5.9.2.10).

Table 68: Summary of Adverse Events by Body System Leading to Withdrawals (MSAP)

Body System*	Observation N = 508 No. (%)	Rituximab N = 501 No. (%)
All Body Systems		
Total Patients with at Least One AE	*8 (2)*	*19 (4)*
Total Number of AEs	*8*	*19*
Neoplasms Benign, Malignant and Unspecified	6 (1)	5 (<1)
Pregnancy, Puerperium, and Prenatal Conditions	2 (<1)	3 (<1)
Infections and Infestations	–	4 (<1)
Blood and Lymphatic System Disorders	–	1 (<1)
Cardiac Disorders	–	1 (<1)
General Disorders and Administration Site Disorders	–	1 (<1)
Hepatobiliary Disorders	–	1 (<1)
Immune System Disorders	–	1 (<1)
Injury, Poisoning and Procedural Complications	–	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	–	1 (<1)

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

5.9.2.8 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 adverse event (

Table 69). 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 (nine patients) including seven neutropenia events and five leukopenia events.

Table 69: Summary of Adverse Events by Body System Leading to Rituximab Dose Interruptions or Modifications (MSAP)

Body System	Rituximab N = 501 No. (%)
All Body Systems	
Total Patients with at Least One AE	*30 (6)*
Infections and Infestations	12 (2)
Blood and Lymphatic System Disorders	9 (2)
Cardiac Disorders	2 (<1)
Gastrointestinal Disorders	2 (<1)
General Disorders and Administration Site Disorders	2 (<1)
Neoplasms Benign, Malignant and Unspecified	2 (<1)
Psychiatric Disorders	2 (<1)
Eye Disorders	1 (<1)
Hepatobiliary Disorders	1 (<1)
Investigations	1 (<1)
Nervous System Disorders	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	1 (<1)

5.9.2.9 Adverse Events of Special Interest

5.9.2.9.1 Infusion-Related Reactions

Adverse events occurring within one day of a rituximab cycle or an observation visit were analyzed to determine the pattern of potential infusion-related reactions. More AEs were reported in the rituximab arm than in the observation arm within one day after a treatment cycle/observation visit (74 events in 61 patients [12%] vs 61 events in 46 patients [9%]). The majority of these AEs were infections (mainly upper respiratory tract infection and bronchitis). Typical rituximab infusion-related AEs, such as chills, pyrexia, nausea, and vomiting, were not reported in the rituximab arm (only one administration site disorder [mucosal inflammation] was reported), indicating that if they had occurred then they were less than Grade 3 in severity. The view that infusion-related reactions (if they occurred) were mainly Grade 1 or 2 in severity during the maintenance/observation phase is supported by the finding that the checklist toxicity 'constitutional symptoms' was reported in 155 patients in the observation arm (31%) and 203 patients (41%) in the rituximab arm throughout the maintenance/observation phase (Table 56). Most of these were Grade 1 or 2 in severity. A low incidence of severe infusion-related reactions was expected given that patients were previously exposed to rituximab during the induction phase and

were routinely premedicated with an analgesic/antipyretic and an antihistamine before each infusion of rituximab.

Tumor lysis syndrome was also not expected to occur during the maintenance/observation phase since this complication is generally associated with initial treatment of patients with bulky disease. No cases were reported during the maintenance/observation phase (although three cases were reported during the induction phase).

5.9.2.9.2 Infections and Infestations

Infections were not collected as a single category on the checklist toxicity CRF but according to neutrophil count. More patients in the rituximab arm than in the observation arm (192 patients vs 127 patients, 38% vs 25%) had an infection with normal neutrophil count. In addition, 11 patients (2%) in the rituximab arm had an infection with Grade 3/4 neutropenia (nine patients (2%) with Grade 2 infections, and two patients (<1%) with Grade 3 infections) compared with two patients (< 1%) in the observation arm (both Grade 2). One additional patient in each arm had febrile neutropenia (Grade 3).

Infections (Grade ≥ 2) were the most common class of AEs recorded, and the incidence was higher in the rituximab arm than in the observation arm (184 patients vs 114 patients, 37% vs 22%). However, most infections were Grade 2 in severity—the incidence of Grade 3 or 4 infections was only 4% in the rituximab arm and 1% in the observation arm. Similarly, infection SAEs occurred in 25 patients (5%) in the rituximab arm and in six patients (1%) in the observation arm. The proportion of patients with an infection AE that was considered to be treatment-related was 6% in the observation arm (30 patients) and 21% in the rituximab arm (107 patients). Four patients in the rituximab arm discontinued treatment and a further 12 patients had their rituximab dosing modified or interrupted as a result of infection AEs. One patient in the rituximab arm died of hepatitis B infection (patient 20111/1016—this event was coded under hepatobiliary AEs rather than infections and infestations), and one patient in the observation arm died of sepsis (patient 60113/1004). A manual search of AE preferred terms to see if any other infections were included in other categories only revealed six cases of conjunctivitis (two cases in the observation arm, and four

cases in the rituximab arm)—all cases were Grade 2 in severity and resolved without sequelae.

Most infections had no causal organism documented. Of those infection AEs with an indentified organism, the most common pathogens were viral (22 patients [4%] in the observation arm and 28 patients [6%] in the rituximab arm), bacterial (11 patients [2%] vs 23 patients [5%]), and fungal (three patients [<1%] vs nine patients [2%]).

Hepatitis B

Three patients had hepatitis B reported during the maintenance/observation phase of the study. Two of these patients had reactivation of hepatitis B infection, and one patient's past hepatitis B status was unknown. These cases are summarized in Table 70 along with patients with AEs of hepatitis B reported during the induction phase. Four additional patients had AEs reported that could potentially have been related to hepatitis B. Two of these cases were clearly due to other causes: patient 10139/1005 (cytolytic hepatitis reported during the induction phase due to infection of a biliary stent) and patient 71101/1059 (ascites reported while the patient was on observation—the patient had a known history of hepatic cirrhosis). The third patient (patient 73001/1126) developed fulminant hepatitis after seven cycles of R-CVP. The cause was uncertain, but hepatitis B serology was negative (as was other viral serology, including hepatitis A and hepatitis C). This event occurred after removal of an intravenous port for suspected (bacterial) infection, and the hepatitis resolved without sequelae. The fourth case (patient 10109/1006: Grade 4 cytolytic hepatitis reported on day 787) was not reported as an SAE and little information is available. However, the cytolytic hepatitis was reported as an unrelated adverse event 11 days after the diagnosis of progressive disease. Overall, therefore, the incidence of hepatitis B was less than 1% (six patients) in the study, but importantly three of the six patients had a fatal outcome.

Interestingly, at least three patients with a known history of hepatitis B infection entered the study and did not develop hepatitis B reactivation during treatment. Patient 20731/1025 received prophylactic lamivudine and completed R-CHOP induction treatment followed by observation without reactivation; patient 41030/31031 received prophylactic lamivudine and completed R-CHOP induction treatment and

rituximab maintenance without reactivation; and patient 10236/1002 received no prohylaxis and completed R-CHOP induction treatment without reactivation (the patient's lymphoma progressed during the observation phase).

Table 70: Summary of Patients with Hepatitis B Infection/Reactivation

Patient No./ Country	Gender/Age (years)	Day of Onset	Brief Description	Grade	Serious/ Not Serious	Outcome
Maintenance/Observation Phase						
20111/1016 Spain	M / 57	251	Reactivation of hepatitis B after four cycles of rituximab maintenance following R-FCM induction. Rituximab was stopped and patient treated with lamivudine. Fulminant hepatitis was complicated by spontaneous campylobacter peritonitis	5	Serious	Fatal
10133/1012 France	M / 65	325	Reactivation of hepatitis B after five cycles of rituximab maintenance following R-CHOP induction. Rituximab was stopped and patient treated with entecavir	2	Serious	Resolved with sequelae
60511/1009 Brazil	M / 59	226	Hepatitis B diagnosed after six cycles of rituximab maintenance following R-CHOP induction. Patient was asymptomatic. Rituximab was stopped, and the patient was treated with lamivudine. Baseline serological tests were lost, therefore it is uncertain whether this was a new infection or reactivation	2	Serious	Unresolved (but patient asymptomatic with normal liver function and virus undetectable on PCR indicating good control with lamivudine)
Induction Phase						
10218/1001 France	M / 66	148	Patient completed eight cycles of R-CHOP before hepatitis B reactivation was diagnosed. Patient was treated with lamivudine but died on day 172	5	Serious	Fatal
40317/1001 India	M / 49	123	Patient completed six cycles of R-CHOP but developed hyperbilirubinemia and hepatitis B was diagnosed (no serology provided). No further rituximab was given, and patient was treated with adefovir and, initially, hepatitis was considered unresolved (on day 174). However, patient's lymphoma progressed, no second-line treatment was given, and patient died of lymphoma on day 403. Hepatitis B was persisting at time of death	2	Serious	Fatal (patient died due to lymphoma. Hepatitis B was persisting at death)
10163/1008* Belgium	M / 61	67	Hepatitis B reactivation after three cycles of R-CHOP. Patient was HBVsAg negative, HBVeAb positive prior to therapy and presented with raised transaminases. R-CHOP was discontinued, and patient was treated with lamivudine	3	Serious	Unresolved

* Narrative not provided as this patient did not have a fatal event and was not randomized in the maintenance/observation phase.

Progressive Multifocal Leukoencephalopathy

Two cases of progressive multifocal leukoencephalopathy (PML) were reported in the course of this study and are described here for completion, although both cases were reported after the second clinical cut-off date for the updated analysis (June 30, 2009). One case was reported as an SAE after the second clinical cut-off date (patient 10109/1015). This patient was in the rituximab maintenance arm of the study and developed PML in the context of disease progression after extensive subsequent therapy, including R-ICE (rituximab, ifosfamide, cytarabine, and etoposide), high-dose chemotherapy with stem cell rescue, and investigational therapy targeting CD19 (B-cells). The patient developed neurological symptoms after the investigational therapy and subsequently died of progressive disease and PML.

With the second case (patient 73001/1117), PML was not reported as an AE within the PRIMA trial but was described as the cause of death (in August 2009). This patient, who was in the observation arm of the study, developed progressive disease while on observation and received treatment with rituximab and Apomab (an investigational antibody directed against human death receptor 5 [DR5; TRAIL-R2; TNFRSF10B]). Eleven months later, the patient died due to PML. The investigator considered the patient's death to be due to the toxicity of the subsequent therapy.

5.9.2.9.3 Blood and Lymphatic System Disorders

As expected, blood and lymphatic system AEs were reported for more patients in the rituximab arm compared with the observation arm (34 events in 26 patients [5%] vs nine events in seven patients [1%]). The majority of these events were neutropenia (19 patients in the rituximab arm and five patients in the observation arm). Grade 3 or 4 neutropenia were recorded for 18 patients in the rituximab arm compared with five patients in the observation arm. Two cases of febrile neutropenia (one patient in each study arm) and two cases of neutropenia (one patient in each study arm) were also reported as SAEs. The two patients who developed SAEs of neutropenia/febrile neutropenia in the observation arm are of note because the neutropenia appeared to occur after some delay. Patient 10105/1037 developed Grade 3 febrile neutropenia 123 days after the last dose of rituximab, and patient 20334/1008 developed Grade 4 neutropenia 148 days after the last dose of rituximab.

Seven patients in the rituximab arm had their rituximab dosing modified or interrupted as a result of neutropenia. Three of these seven patients received granulocyte-colony stimulating factor as a treatment for neutropenia. Overall, only three patients in the observation arm and 10 patients in the rituximab arm were recorded to have received colony stimulating factors for an adverse event during the maintenance/observation or follow-up phase. (See also Section 5.9.2.11.2 for laboratory assessments of neutrophil counts.)

5.9.2.9.4 Cardiac Events

Cardiac AEs were recorded for six patients in the observation arm and 16 patients in the rituximab arm. Of these, two patients in the observation arm and 11 patients in the rituximab arm experienced cardiac disorders that were considered to be SAEs (Table 71 and Table 72). In addition, one patient (patient 10634/1036) experienced a cardiac event (arrhythmia) between randomization and the first observation visit and was therefore categorized as experiencing the event during the induction phase (this patient is included in Table 72 but not in Table 71). Two of the three SAEs in the observation arm were considered to be unrelated to trial treatment, whereas in the rituximab arm three of four SAEs of cardiac failure (probable), one SAE of cardiomyopathy (possible), and one SAE of myocardial infarction (remote) were considered to be related to trial treatment (trial treatment could mean induction therapy or maintenance rituximab). Importantly, including both arms of the study, all except one patient (who developed aortic valve disease) had received R-CHOP (ie, anthracycline-containing therapy) as their induction treatment. Most of the patients also had other risk factors for cardiac disease. Despite the seriousness of the conditions, almost all the patients in the rituximab maintenance arm were able to continue with their rituximab treatment, suggesting that rituximab was not thought to be the cause or an exacerbating factor for their condition.

Table 71: Summary of Cardiac SAEs (MSAP)

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

Table 72: Summary of Serious Cardiac Events (MSAP)

Patient No.	Gender/Age* (years)	Relevant History and/or Medication at Study Entry	Day of Onset	Brief Description	Grade	Relationship to Trial Treatment**	Outcome
Rituximab Arm							
10119/1006	F / 68	Hypercholesterolemia (treated with ciprofibrate), cerebral aneurysm, thyroid nodule (treated with thyroxine), R-CHOP induction	155	Patient developed **cardiac failure** 42 days after the last infusion of rituximab maintenance and was treated with furosemide, perindopril, bisoprolol, acetylsalicylate and omeprazole. The patient went on to complete 12 cycles of rituximab maintenance	3	Probable	Resolved with sequelae
10154/1004	M / 52	No relevant history other than R-CHOP induction therapy	169	Patient developed **cardiac failure** 49 days after an infusion of rituximab maintenance, and was treated with oxygen, furosemide, dobutamine, carvedilol, perindopril, and spironolactone. Rituximab was interrupted but then resumed, and the patient completed 12 cycles	4	Probable	Resolved with sequelae
10181/1010	F / 66	Hypertension (treated with bisoprolol) hypercholesterolemia (treated with simvastatin), R-CHOP induction	3	Patient developed **cardiac failure** two days after the 9th dose of rituximab and was treated with nebivolol, spironolactone, and perindopril. Rituximab maintenance treatment was continued	1	Probable	Resolved with sequelae
10184/1011	M / 60	Angina pectoris due to coronary stenosis, myocardial infarction (treated with atenolol, pravastatin, acetylsalicylate, amlopidine, lisinopril, hydrochlorothiazide), R-CHOP induction	218	Patient (weight 143 kg) developed **cardiac failure** 45 days after the 4th dose of rituximab maintenance (the patient had previously had two episodes of Grade 2 dyspnea treated with furosemide). He was treated with furosemide, bisoprolol, pravastatin, lisinopril, amlodipine, acetylsalycilate, phenoxymethylpenicillin, valacyclovir, and cotrimoxazole, and continued on rituximab maintenance	3	Unrelated	Resolved with sequelae
10125/1015	M / 69	Hypertension and palpitations (treated with	141	Patient experienced two episodes of **atrial fibrillation** (about a year apart) eight days and 25	2	Unrelated	Resolved with

		acetylsalicylate and valsartan), R-CHOP induction		days after the doses of rituximab maintenance. Both episodes were Grade 2, but only the second episode was considered serious. He was treated with flecainide, acebutolol, tinzaparine and fluindione and continued rituximab maintenance (completing 12 cycles)			sequelae

Table 73: Summary of Serious Cardiac Events (MSAP) (Cont.)

Patient No.	Gender/Age* (years)	Relevant History and/or Medication at Study Entry	Day of Onset	Brief Description	Grade	Relationship to Trial Treatment**	Outcome
Rituximab Arm (cont.)							
72701/1044	M / 71	Hypertension (treated with trandolapril, verapamil), hyperlipdemia (treated with simvastatin), R-CHOP induction	309 321	Two episodes of **atrial fibrillation** occurred, the first starting 28 days after the last dose of rituximab maintenance, the second 40 days after the last dose. Patient was treated with verapamil, trinitrine patch, trandolapril, digoxin, simvastatin, enoxaparin, and warfarin, and rituximab maintenance was continued	2 2	Unrelated Unrelated	Resolved Resolved
10114/1002	M / 66	Hypertension (treated with amlodipine), R-CHOP induction	584	Patient experienced **angina pectoris** 54 days after the last dose of rituximab maintenance and was treated with trinitrin and atenolol. Rituximab maintenance was temporarily interrupted then resumed, and the patient completed maintenance treatment	3	Unrelated	Resolved
10126/1003	F / 53	Migraine, asthma, R-CVP induction	530	**Aortic valve disease** was diagnosed 45 days after the last dose of rituximab maintenance, and patient was treated with verapamil, clopidogrel, acetylsalicylate, celiac and mesenteric stents, and valvuloplasty. Rituximab maintenance was continued, and the patient completed planned treatment	4	Unrelated	Resolved
10124/1002	F / 60	Hypothyroidism (treated with thyroxine), mitral valve disease, auricular and ventricular premature beats, R-CHOP induction	434	Patient experienced a **cardiac arrest** 10 days after the last dose of rituximab maintenance and was treated with electroconvulsive therapy, hypothermia, midazolam, cisatracurium, amoxicillin/clavulanic acid, and implantation of an automatic defibrillator. Rituximab maintenance was continued	4	Unrelated	Resolved
10117/100	F / 72	Pleurotomy and pulmonary	617	**Cardiomyopathy** was diagnosed on the day that	3	Possible	Resolved

6		lobectomy, bilateral mastectomy, R-CHOP induction		rituximab maintenance was given (LVEF 22–25% versus 60% at screening) and treated with furosemide and ramipril and then bisoprolol. Rituximab maintenance was continued, and the patient completed planned treatment			with sequelae

Table 74: Summary of Serious Cardiac Events (MSAP)(Cont.)

Patient No.	Gender/Age* (years)	Relevant History and/or Medication at Study Entry	Day of Onset	Brief Description	Grade	Relationship to Trial Treatment**	Outcome
Rituximab Arm (cont.)							
10534/1001	M / 42	Dislipidemia, pulmonary embolism, R-CHOP induction	385	**Myocardial infarction** was diagnosed 50 days after the last (7th) dose of rituximab maintenance, and patient was treated with angioplasty and coronary stents. Rituximab maintenance was discontinued	4	Remote	Resolved with sequelae
Observation Arm							
10208/1009	F / 61	Hypertension, hypercholesterolemia myocardial infarct, hyperkalemia (treated with pravastatin, aspirin, sodium polystyrene sulfonate for hyperkalemia, and ramipril), R-CHOP induction	503	Patient experienced **arrhythmia** 681 days after the last dose of study treatment and was treated with Omacor and an unspecified medication	3	Unrelated	Resolved with sequelae
10307/1013	M / 73	Hypertension, arteritis, carotid stenosis coronaropathy, nephrectomy (unknown pathology) (treated with clopidogrel, diltiazem, isosorbide mononitrate, buflomedil), R-CHOP induction	8	Patient experienced **myocardial ischemia** 54 days after the last dose of study treatment and was treated with clopidogrel, diltiazem, isosorbide mononitrate, coronary angioplasty, and stenting. Patient developed progressive lymphoma and received subsequent therapy but finally died of 'coronaropathy'	3	Unrelated	Resolved
10634/1036 ***	M / 59	Arrhythmia (treated with flecainide and clopidogrel), R-CHOP induction	203	Patient experienced Grade 3 **arrhythmia** 54 days after the last dose of study treatment and was treated with clopidogrel, propafenone, and perindopril	3	Remote	Resolved

* Age at study entry.

** According to the investigator. Note that relationship to study treatment also includes induction treatment.

*** Patient 10634/1036 experienced SAE between randomization and the first observation visit (therefore classified as an induction phase event but included here for completion).

5.9.2.10 Pregnancies

Nine pregnancies were reported in the PRIMA trial, including two pregnancies in the wives of male patients. Two pregnancies occurred during the induction phase, and seven pregnancies occurred during the maintenance/observation phase. Of the six patients who became pregnant during the maintenance/observation phase, three patients were in the observation arm and three patients were in the rituximab arm (Table 75). With the exception of one patient (patient 20139/1006), who had a spontaneous (missed) abortion during the first trimester, and one patient (patient 10106/1003) who had a voluntary termination, the outcome of the pregnancies was generally satisfactory. No reports of post-natal complications attributable to rituximab were received.

Table 75: Summary of Pregnancies during the PRIMA Trial

Patient No.	Gender/Age (years)	Previous Gynaecologic History	Study Phase (arm)	Induction Regimen	Doses of Rituximab Maintenance Received	Pregnancy Outcome
Female Patients						
10106/1003	F / 32	2 pregnancies 2 deliveries	Induction	R-CHOP	0	Voluntary termination of pregnancy
10133/1006*	F / 35	none	Maintenance (rituximab)	R-CHOP	4	Delivery at term (41st gestational week). Normal baby
10534/1015**	F / 33	3 pregnancies 2 miscarriages 1 delivery	Maintenance (rituximab)	R-CHOP	6	Delivery at 35th gestation week. Birth weight: 2700 g
40121/1004*	F / 28	none	Maintenance (rituximab)	R-CHOP	7	Normal delivery. Healthy boy with Apgar score of 10
60135/1008*	F / 34	1 pregnancy 1 delivery	Maintenance (observation)	R-CVP	0	Normal female baby
20139/1006	F / 39	6 pregnancies 3 abortions 1 miscarriage 2 deliveries	Maintenance (observation)	R-CVP	0	Spontaneous (missed) abortion during the first trimester
21331/1019*	F / 30	1 pregnancy 1 delivery	Maintenance (observation)	R-CHOP	0	Delivery by Cesarian section because of previous pregnancy complication. Normal boy
Male Patients (Partner Pregnant)						

60144/1008	M / 33	unknown	Induction	R-CHOP	0	Healthy twins
10114/1002	M / 33	unknown	Maintenance (rituximab)	R-CHOP	10	Unknown

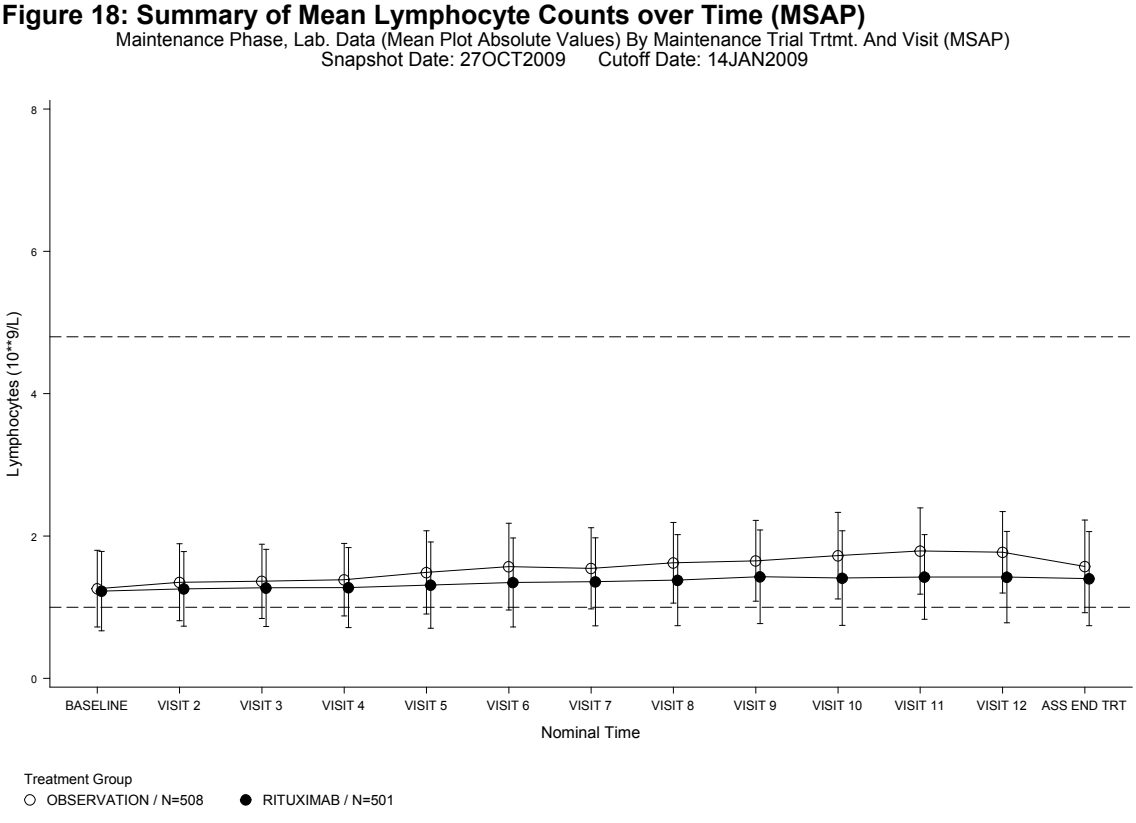
5.9.2.11 Laboratory Parameters

Hematology (including neutrophil counts) and biochemistry parameters were very similar between the two arms during the course of the maintenance/observation phase, with the exception of lymphocyte counts (Section 5.9.2.11.1).

5.9.2.11.1 Lymphocyte Counts

Lymphocyte counts increased with time in the observation arm compared with the rituximab arm (Figure 18). This difference was probably due to B-cell recovery in the observation arm compared with continued B-cell suppression in the rituximab arm (cf Figure 20).

Figure 18: Summary of Mean Lymphocyte Counts over Time (MSAP)

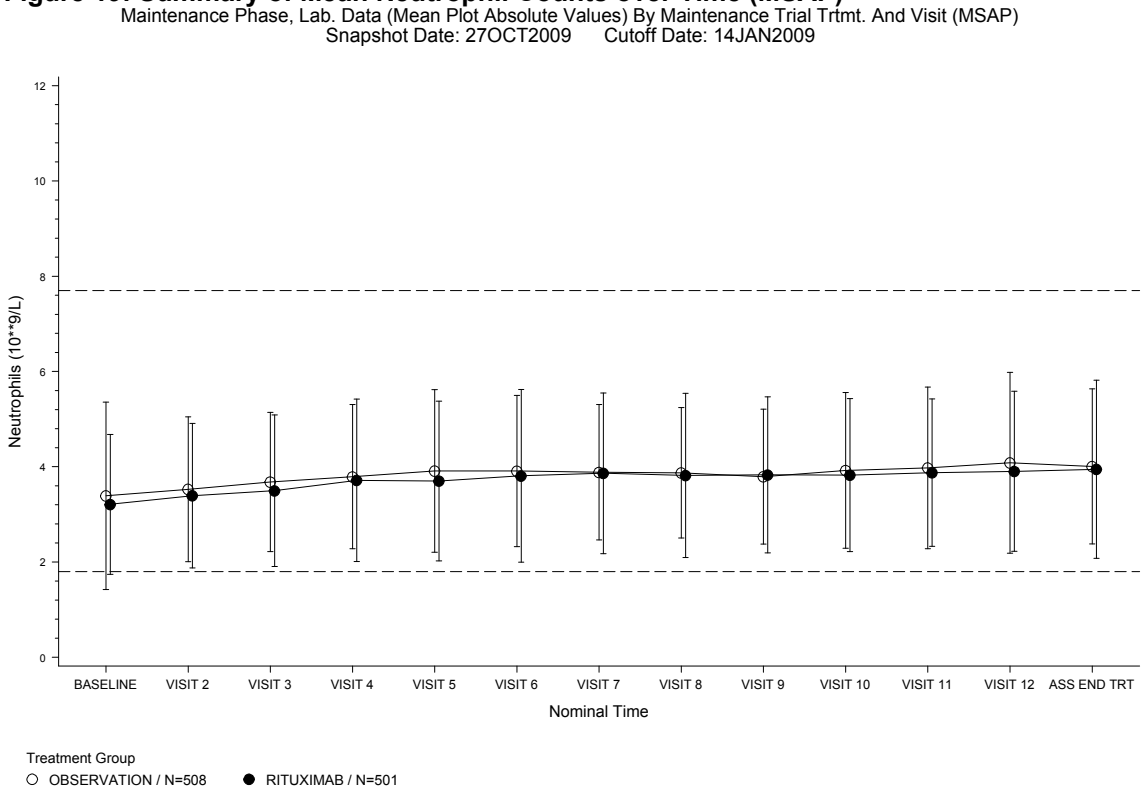


Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52a_s_lymph 30NOV2009 16:07 Project: cd10752c Protocol: a18264m

5.9.2.11.2 Neutrophil Counts

Neutrophil counts were very similar in both arms throughout the maintenance/ observation phase (Figure 19). In both arms, mean and 95% confidence intervals returned to the normal range by visit 2 and remained within this range thereafter.

Figure 19: Summary of Mean Neutrophil Counts over Time (MSAP)



Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52a_s_neutr 30NOV2009 16:07 Project: cd10752c Protocol: a18264m

5.9.2.11.3 Shifts from Baseline

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. The number of patients whose laboratory values worsened during the

maintenance/observation phase and shifted to NCI-CTC Grade 3/4 is summarized in Table 76. In the rituximab arm, a higher number of shifts to Grade 3/4 values was observed for lymphopenia as well as leukopenia 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.

Table 76: Summary of Newly Occurring Grade ≥ 3 Laboratory Values during the Maintenance/Observation Phase (MSAP)

	Observation, N = 508			Rituximab, N = 501		
	n	Grade 3 n (%)	Grade 4* n (%)	n	Grade 3 n (%)	Grade 4* n (%)
Hematology						
↓ Hemoglobin	490	–	1 (<1)	492	–	–
↓ White Blood Cells	494	4 (<1)	–	491	10 (2)	1 (<1)
↓ Neutrophils	476	8 (2)	5 (1)	480	27 (6)	10 (2)
↓ Platelets	491	–	1 (<1)	488	2 (<1)	–
↓ Lymphocytes	478	13 (3)	1 (<1)	483	45 (9)	6 (1)
Biochemistry						
↑ Lactate dehydrogenase	398	1 (<1)	2 (<1)	401	1 (<1)	–
↓ Sodium	311	3 (<1)	–	340	3 (1)	–
↓ Potassium	312	1 (<1)	–	323	5 (2)	–
↑ Potassium	320	2 (<1)	–	330	4 (1)	1 (<1)

Newly occurring Grade ≥ 3 laboratory values corresponds to shifts from baseline (randomization to maintenance/observation phase) to the end of maintenance/observation phase.
* Excluding shifts from Grade 3 to Grade 4.
↓ hypo. ↑ hyper.

5.9.2.11.4 Marked Laboratory Test Value Abnormalities

The most common Grade 3 or 4 hematological laboratory abnormalities were neutropenia and lymphopenia (Table 77). Grade 3 or 4 neutropenia and lymphopenia were more frequent in the rituximab arm (9% and 13%, respectively) than in the observation arm (4% and 6%, respectively).

Table 77: Incidence of Hematological Abnormalities by NCI–CTC Grades—Worst Value per Patient/All Cycles (MSAP)

Parameter	OBSERVATION N = 508	RITUXIMAB N = 501	TOTAL N = 1009
Hemoglobin g/dL (HYPO)			
n	493	496	989
Grade 0	414 (84%)	358 (72%)	772 (78%)
Grade 1	73 (15%)	128 (26%)	201 (20%)
Grade 2	5 (1%)	10 (2%)	15 (2%)
Grade 3	-	-	-
Grade 4	1 (<1%)	-	1 (<1%)
White blood cell (WBC) 10**9/L (HYPO)			
n	497	496	993
Grade 0	276 (56%)	224 (45%)	500 (50%)
Grade 1	195 (39%)	201 (41%)	396 (40%)
Grade 2	20 (4%)	59 (12%)	79 (8%)
Grade 3	6 (1%)	11 (2%)	17 (2%)
Grade 4	-	1 (<1%)	1 (<1%)
Platelets 10**9/L (HYPO)			
n	494	493	987
Grade 0	415 (84%)	403 (82%)	818 (83%)
Grade 1	75 (15%)	85 (17%)	160 (16%)
Grade 2	3 (<1%)	2 (<1%)	5 (<1%)
Grade 3	-	3 (<1%)	3 (<1%)
Grade 4	1 (<1%)	-	1 (<1%)
Neutrophils 10**9/L (HYPO)			
n	480	485	965
Grade 0	411 (86%)	350 (72%)	761 (79%)
Grade 1	29 (6%)	43 (9%)	72 (7%)
Grade 2	23 (5%)	49 (10%)	72 (7%)
Grade 3	10 (2%)	32 (7%)	42 (4%)
Grade 4	7 (1%)	11 (2%)	18 (2%)
Lymphocytes 10**9/L (HYPO)			
n	483	488	971
Grade 0	274 (57%)	194 (40%)	468 (48%)
Grade 1	83 (17%)	99 (20%)	182 (19%)
Grade 2	97 (20%)	131 (27%)	228 (23%)
Grade 3	27 (6%)	57 (12%)	84 (9%)
Grade 4	2 (<1%)	7 (1%)	9 (<1%)

n represents number of patients with at least one valid value within the given time window.
A patient who has only grade 0 values but one missing or non-numeric value is excluded!
Percentages are based on n. Percentages not calculated if n < 10.
LB23 29OCT2009:15:16:15
Time window: from study day 2 to 9999 and 9999 days after end of maintenance treatment.

There were fewer reports of adverse events of neutropenia or lymphopenia than Grade 3 or 4 decreases in neutrophils or lymphocytes (see Table 58 and Table 77, respectively). In the rituximab arm, 9% of patients recorded Grade 3 or 4 neutropenia based on laboratory counts, but only 4% of patients had adverse events of neutropenia reported. Similarly, 13% of patients in the rituximab arm experienced Grade 3 or 4 lymphopenia based on laboratory data, but less than 1% of patients had adverse events of lymphopenia reported. These disparities are typical in oncology studies and reflect the fact that short episodes of neutropenia and/or lymphopenia often have no adverse consequences for the patient.

5.9.2.12 Additional Laboratory Parameters

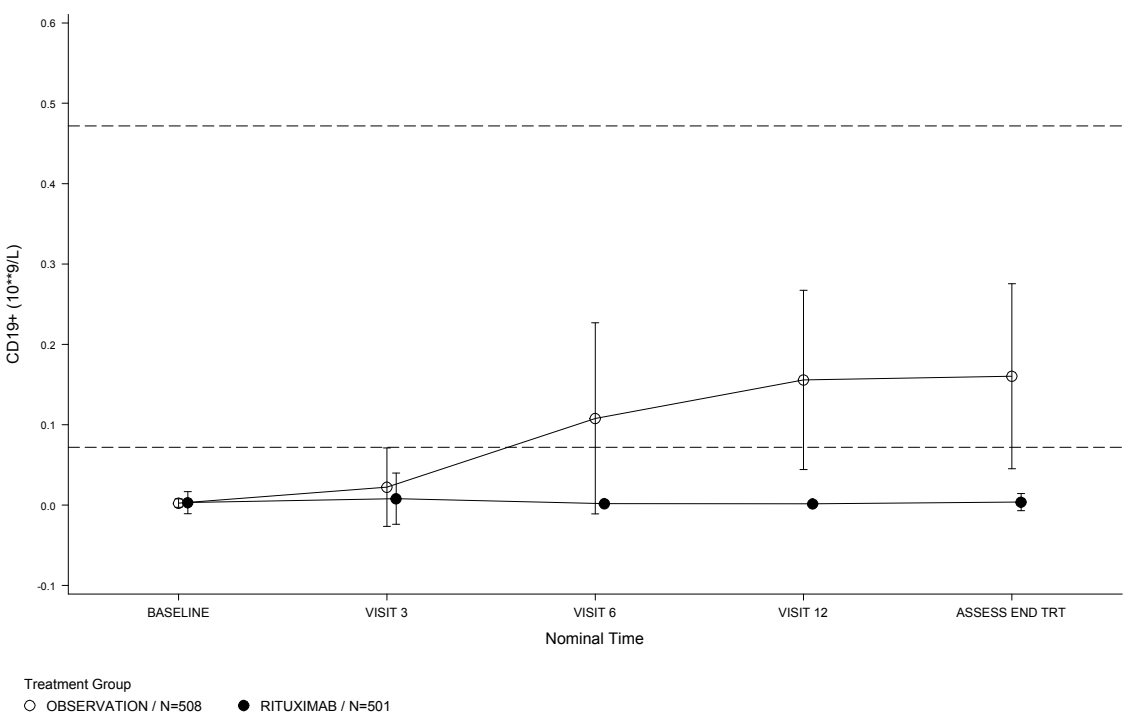
5.9.2.12.1 Differential Lymphocyte Counts

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 randomization 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 (Figure 20). 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) (Table 78). The mean B-cell count in the observation arm at the end of the maintenance/observation phase was 0.16 × 10^9/L.

Figure 20: Summary of Mean B-Cell (CD19-positive) Counts over Time (MSAP)



The dashed horizontal lines represent the upper and lower limits of the standard reference range. Between 16 and 50 patients in the observation arm and between 29 and 56 patients in the rituximab arm were assessed at each visit.

Table 78: Summary of Recovery of CD19-positive Cells (MSAP)

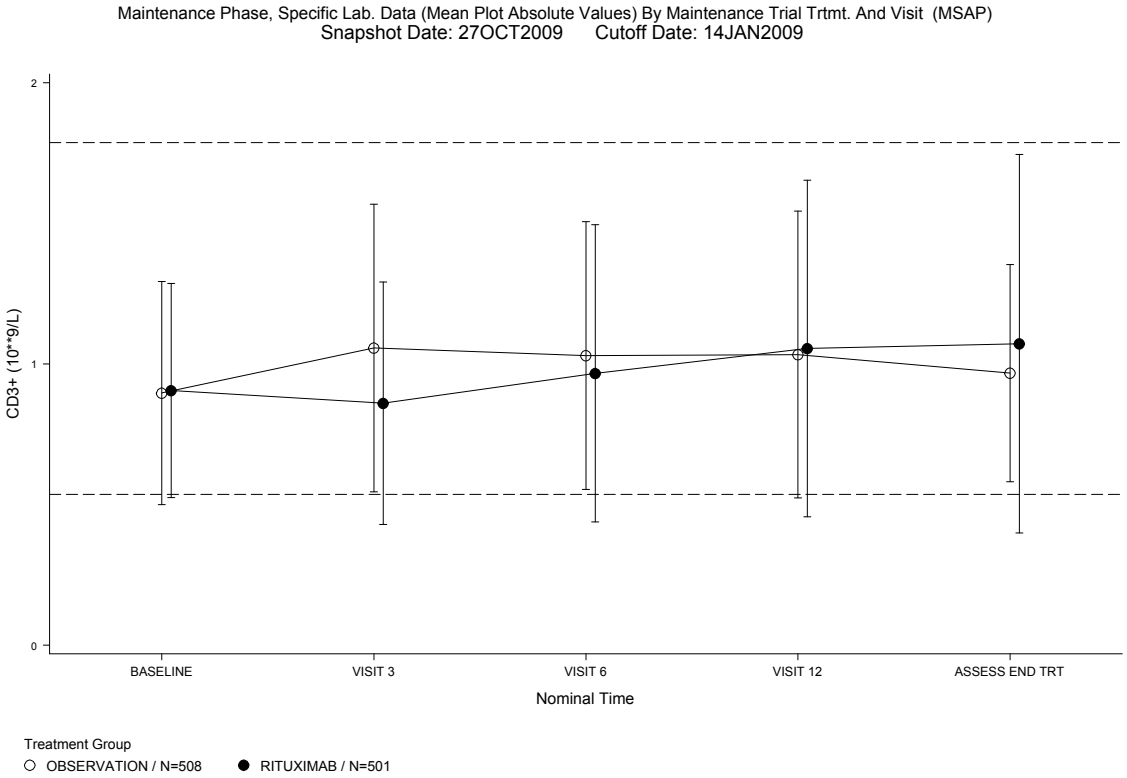
	Observation N=508	Rituximab N=501
Patients analyzed^	30	24
Patients with a recovery event*	13 (43.3%)	1 (4.2%)
Patients without a recovery	17 (56.7%)	23 (95.8%)

^ Patients with a value after complete induction < the value at screening and < LLN.
* Patients with (any) value after complete induction, either >= LLN or > value at screening.
Program : $PROD/cd10752c/a18264a/ml_itrcom_cd.sas
Output : $PROD/cd10752c/a18264m/reports/ml_itrcom_cd_S.out
12NOV2009 12:05

T-Cells

The mean T-cell counts at baseline (after completion of induction therapy) in both study arms were similar and within the standard reference range (mean 0.90 × 10^9/L in the observation arm, and mean 0.91 × 10^9/L in the rituximab arm). Although the mean values increased slightly in the observation arm and decreased slightly in the rituximab arm at visit 3 (mean 1.06 × 10^9/L in the observation arm, and mean 0.86 × 10^9/L in the rituximab arm), 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 (Figure 21).

Figure 21: Summary of Mean T-Cell (CD3-positive) Counts over Time (MSAP)



Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52aig_s_cd3 30NOV2009 15:34 Project: cd10752c Protocol: a18264m

The dashed horizontal lines represent the upper and lower limits of the standard reference range.
Between 16 and 58 patients in the observation arm and between 31 and 63 patients in the rituximab arm were assessed at each visit.

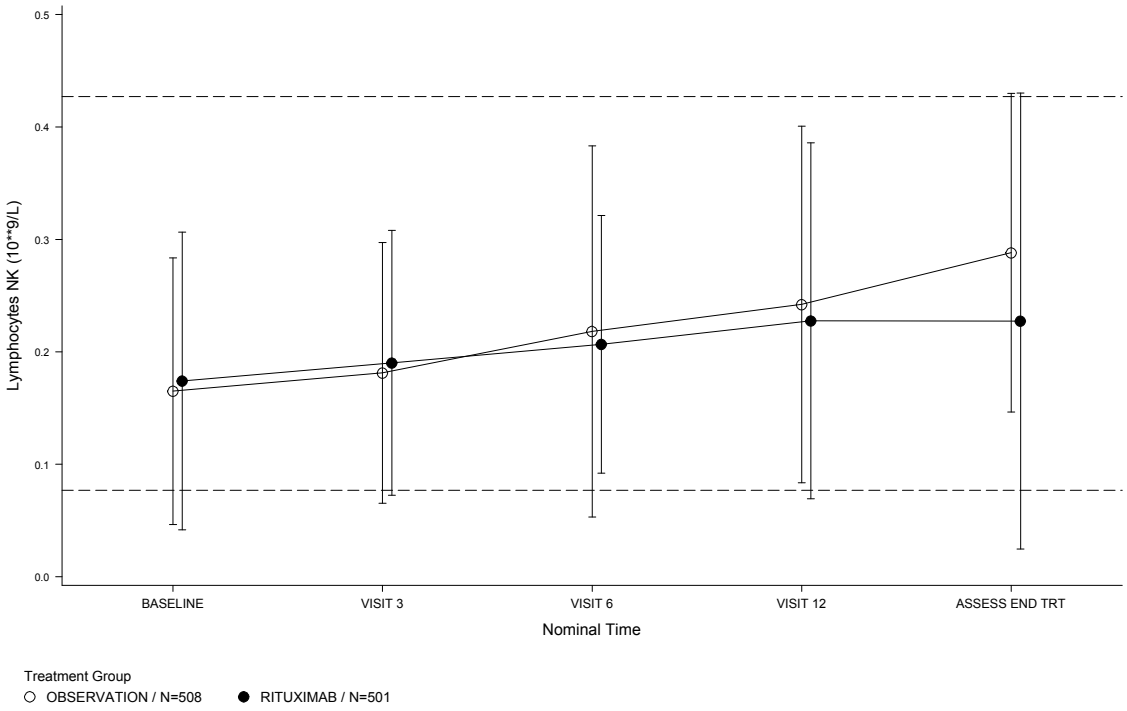
Natural Killer Cells

The mean counts of natural killer (NK) cells at baseline (after completion of induction therapy) in both study arms were similar (mean 0.17 × 10^9/L in the observation arm, and mean 0.17 × 10^9/L in the rituximab arm) and increased slightly during the course of the maintenance/observation phase (

Figure 22). At visit 12, mean NK cells counts were 0.24 × 10^9/L in the observation arm and 0.23 × 10^9/L in the rituximab arm.

Figure 22: Summary of Mean NK Cell Counts over Time (MSAP)

Maintenance Phase, Specific Lab. Data (Mean Plot Absolute Values) By Maintenance Trial Trtmt. And Visit (MSAP)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52aig_s_lymphnk 30NOV2009 15:34 Project: cd10752c Protocol: a18264m

The dashed horizontal lines represent the upper and lower limits of the standard reference range.
Between 16 and 55 patients in the observation arm and between 28 and 62 patients in the rituximab arm were assessed at each visit.

5.9.2.12.2 Serum Immunoglobulin Levels

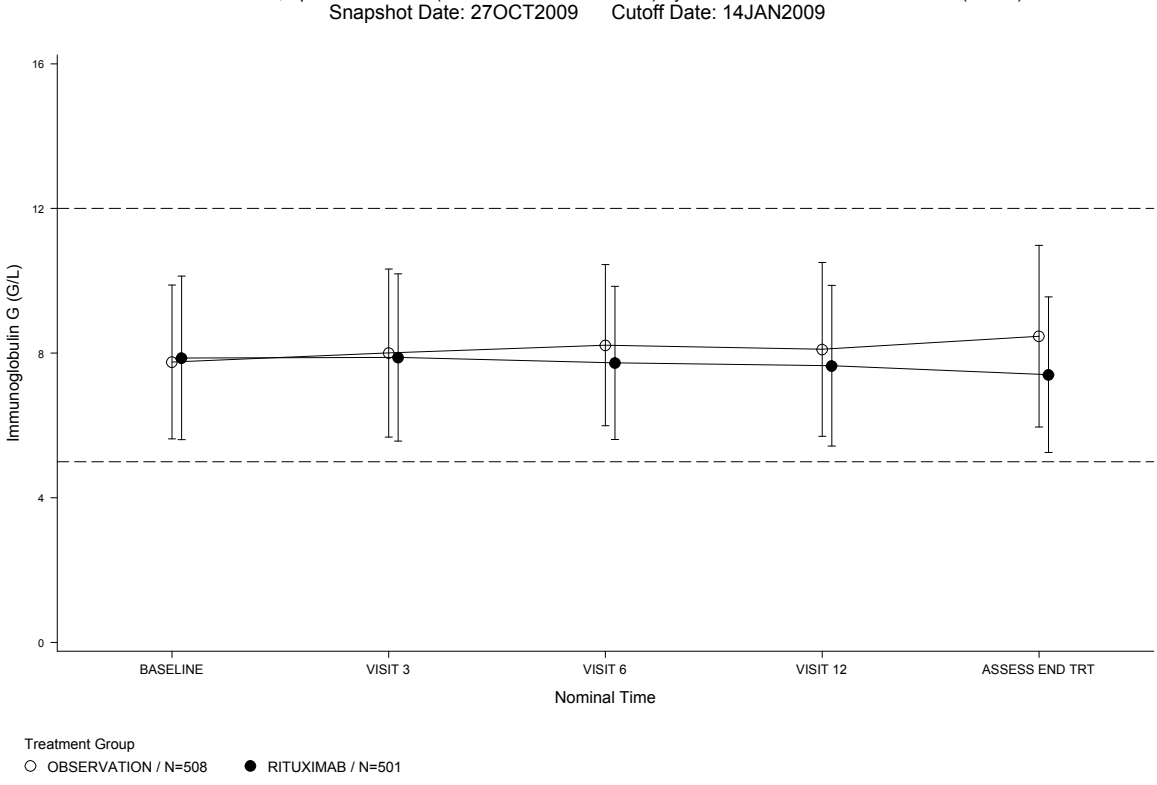
Patients at study sites in France also underwent additional sampling for immunoglobulins (IgG, IgA, and IgM). Immunoglobulin levels were assessed before induction therapy, after induction therapy (baseline), and every six months for the first three years after randomization or until recovery if not reached by this time.

Immunoglobulin G

The mean IgG levels at baseline (after completion of induction therapy) in both study arms were within the reference range of 5.00–12.00 g/L (mean 7.76 g/L in the observation arm, and mean 7.87 g/L in the rituximab arm). Over the course of the maintenance/observation phase, the mean values in both study arms remained within this reference range (Figure 23). However, there was a slight decrease in

mean IgG levels and 95% confidence intervals in the rituximab arm over time compared with the observation arm, although there was still considerable overlap.

Figure 23: Summary of Mean IgG Levels over Time (MSAP)



The dashed horizontal lines represent the upper and lower limits of the standard reference range.
Between 42 and 126 patients in the observation arm and between 77 and 131 patients in the rituximab arm were assessed at each visit.

At the end of the induction phase, IgG levels were very similar between the two arms (Table 79): 113 of 126 patients (90%) in the observation arm and 116 of 131 patients in the rituximab arm (89%) had IgG levels within the reference range (5.00–12.00 g/L). Forty-five patients (36%) in the observation arm and 46 patients (35%) in the rituximab arm had IgG levels lower than 7 g/L. Ten patients (8%) in the observation arm and 11 patients (8%) in the rituximab arm had IgG levels below the lower limit of normal (5 g/L) after induction; of these, six patients (5%) and three patients (2%), respectively, had IgG levels lower than 4 g/L.

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

Table 79: Summary of IgG Levels According to Categories (MSAP)

	End Of Induction	Maintenance Phase				
		6 Months	12 Months	18 Months	End Of Main.	Overall***
Observation (N=508)						
No. Pts with IgG Data available	126	101	89	58	42	140
IgG < LLN* g/L	10 (8%)	7 (7%)	2 (2%)	6 (10%)	3 (7%)	11 (8%)
IgG >=ULN** g/L	3 (2%)	6 (6%)	5 (6%)	2 (3%)	4 (10%)	7 (5%)
IgG < 4 g/L	6 (5%)	4 (4%)	2 (2%)	3 (5%)	1 (2%)	5 (4%)
IgG >=4 g/L	120 (95%)	97 (96%)	87 (98%)	55 (95%)	41 (98%)	136 (97%)
IgG < 7 g/L	45 (36%)	34 (34%)	30 (34%)	18 (31%)	11 (26%)	53 (38%)
IgG >=7 g/L	81 (64%)	67 (66%)	59 (66%)	40 (69%)	31 (74%)	99 (71%)
Rituximab (N=501)						
No. Pts with IgG Data available	131	113	118	93	77	172
IgG < LLN* g/L	11 (8%)	9 (8%)	9 (8%)	9 (10%)	8 (10%)	23 (13%)
IgG >=ULN** g/L	4 (3%)	8 (7%)	5 (4%)	3 (3%)	1 (1%)	11 (6%)
IgG < 4 g/L	3 (2%)	4 (4%)	2 (2%)	3 (3%)	4 (5%)	11 (6%)
IgG >=4 g/L	128 (98%)	109 (96%)	116 (98%)	90 (97%)	73 (95%)	164 (95%)
IgG < 7 g/L	46 (35%)	38 (34%)	41 (35%)	35 (38%)	36 (47%)	80 (47%)
IgG >=7 g/L	85 (65%)	75 (66%)	77 (65%)	58 (62%)	41 (53%)	120 (70%)

Percentages are based on number of patients with IgG data available.
* Lower limit of normal (LLN) = 5 g/L
** Upper limit of normal (ULN) = 12 g/L
*** Number of patients with a specified characteristic in at least one assessment during the maintenance phase.

Program : $PROD/cd10752c/a18264a/t_ahr010_a.sas / Output : $PROD/cd10752c/a18264m/reports/t_ahr010_a_S.out
18DEC2009 15:13
Between 42 and 126 patients in the observation arm and between 77 and 131 patients in the rituximab arm were assessed at each visit.

Recovery of IgG levels during the maintenance/observation phase was observed for five of the 11 patients who had IgG levels at the end of induction lower than the lower limit of normal (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) (Table 80).

Table 80: Summary of IgG Recovery (MSAP)

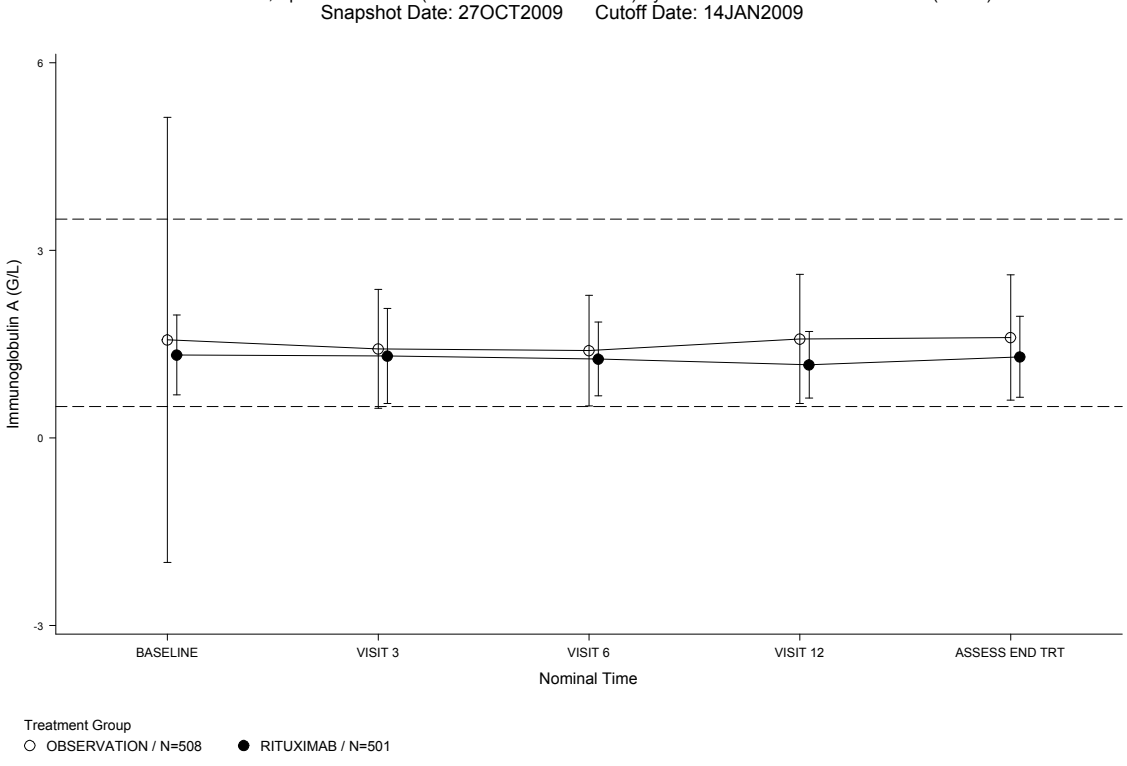
	Observation N=508	Rituximab N=501
Patients analyzed^	5	6
Patients with a recovery event*	1 (20.0%)	4 (66.7%)
Patients without a recovery	4 (80.0%)	2 (33.3%)

^ Patients with a value after complete induction < the value at screening and < LLN.
* Patients with (any) value after complete induction, either >= LLN or > value at screening.
Program : $PROD/cd10752c/a18264a/ml_itrcom.sas
Output : $PROD/cd10752c/a18264m/reports/ml_itrcom_S.out
12NOV2009 12:04

Immunoglobulin A

The mean IgA level at baseline (after completion of induction therapy) was 1.57 g/L in the observation arm and 1.33 g/L in the rituximab arm (reference range: 0.5–3.5 g/L). The mean values remained slightly higher in the observation arm over time compared with the rituximab arm. Overall, mean IgA levels and 95% confidence intervals in the rituximab arm overlapped those in the observation arm throughout the maintenance/observation phase, and no major differences were observed between the two arms (Figure 24). In both arms, mean IgA levels and 95% confidence intervals remained within the normal range throughout the maintenance/observation phase.

Figure 24: Summary of Mean IgA Levels over Time (MSAP)



Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52aig_s_iga 30NOV2009 15:34 Project: cd10752c Protocol: a18264m

The dashed horizontal lines represent the upper and lower limits of the standard reference range.
Between 42 and 126 patients in the observation arm and between 77 and 131 patients in the rituximab arm were assessed at each visit.

Seven patients (four patients in the observation arm, and three patients in the rituximab arm) had IgA levels at the end of induction that were lower than the LLN

and lower than at screening. None of these patients had a recovery in their IgA levels during the maintenance/observation phase (Table 81).

Table 81: Summary of IgA Recovery (MSAP)

	Observation N=508	Rituximab N=501
Patients analyzed^	4	3
Patients with a recovery event*	0 (0.0%)	0 (0.0%)
Patients without a recovery	4 (100.0%)	3 (100.0%)

^ Patients with a value after complete induction < the value at screening and < LLN.
* Patients with (any) value after complete induction, either >= LLN or > value at screening.
Program : $PROD/cd10752c/a18264a/ml_itrcom_a.sas
Output : $PROD/cd10752c/a18264m/reports/ml_itrcom_a_S.out
12NOV2009 12:05

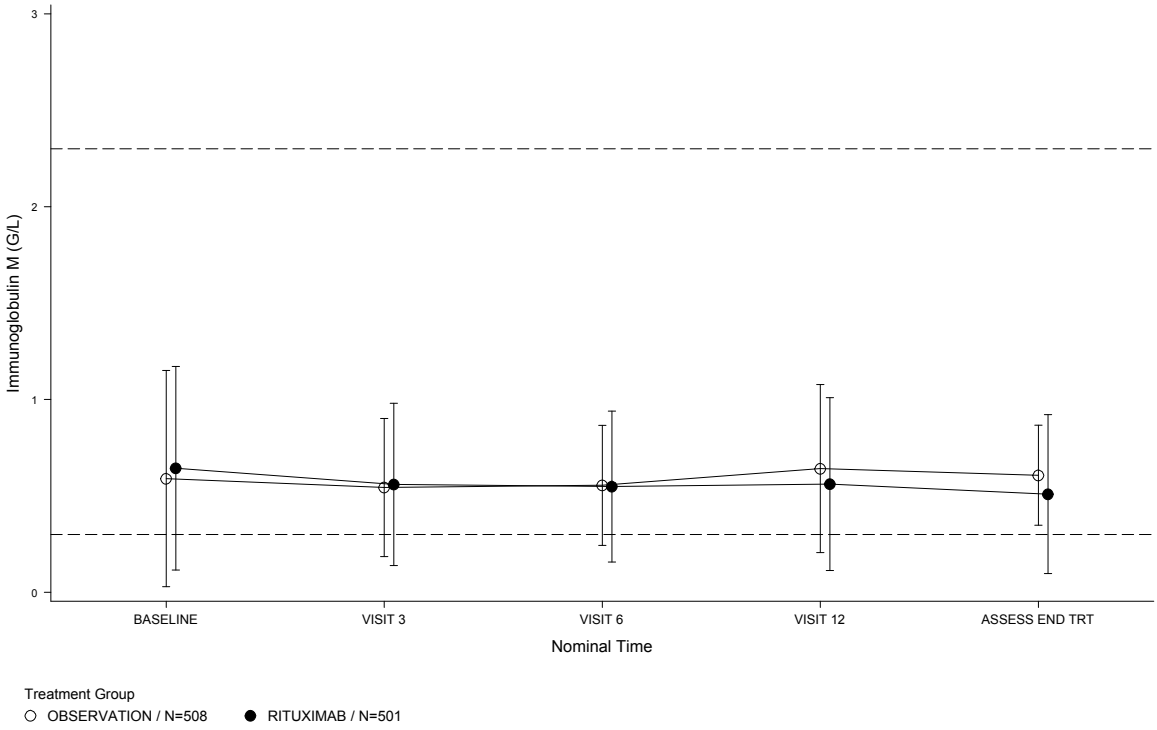
Immunoglobulin M

The mean IgM level at baseline (after completion of induction therapy) was 0.59 g/L in the observation arm and 0.64 g/L in the rituximab arm (reference range: 0.30–2.30 g/L). The mean IgM values increased slightly in the observation arm and decreased slightly in the rituximab arm during the course of the maintenance/observation phase. However, overall, mean IgM levels in the rituximab arm overlapped those in the observation arm throughout the maintenance/observation phase and no major differences were apparent between both arms (

Figure 25).

Figure 25: Summary of Mean IgM Levels over Time (MSAP)

Maintenance Phase, Specific Lab. Data (Mean Plot Absolute Values) By Maintenance Trial Trtmt. And Visit (MSAP)
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009



Dashed horizontal lines represent upper and lower limits of project-specific or standard COG3007 reference ranges.
mlb52aig_s_igm 30NOV2009 15:34 Project: cd10752c Protocol: a18264m

The dashed horizontal lines represent the upper and lower limits of the standard reference range.
Between 42 and 121 patients in the observation arm and between 76 and 127 patients in the rituximab arm were assessed at each visit.

More patients in the observation arm (9/20 patients [45%]) had recovery in IgM levels during the maintenance/observation phase compared with the rituximab arm (2/18 patients [11%]) (Table 82).

Table 82: Summary of IgM Recovery (MSAP)

	Observation N=508	Rituximab N=501
Patients analyzed^	20	18
Patients with a recovery event*	9 (45.0%)	2 (11.1%)
Patients without a recovery	11 (55.0%)	16 (88.9%)

^ Patients with a value after complete induction < the value at screening and < LLN.
* Patients with (any) value after complete induction, either >= LLN or > value at screening.
Program : $PROD/cd10752c/a18264a/ml_itrcom_m.sas
Output : $PROD/cd10752c/a18264m/reports/ml_itrcom_m_S.out
12NOV2009 12:05

5.9.2.13 Updated safety results from January 15 2010 snapshot

An overview of toxicities and adverse events recorded from randomisation up to the additional clinical cut-off (Jan 15, 2010) is provided in Table 83. There was a slight increase in the number of adverse events and SAEs recorded since the earlier cut-off (January 14, 2009) (cf Table 55). Overall, there was no change to the safety profile for the study at the time of the updated analysis.

Table 83: Overview of Safety during the Maintenance/Observation Phase (MSAP, Clinical Cut-Off Jan 15, 2010)

[redacted]

5.9.1 If any of the main trials are designed PRIMArily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Not applicable.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

See Table 58 for a summary of adverse events for each intervention group and Table 59 for a summary of adverse events over time.

Please note, the safety review for PRIMA was performed by Roche based on standard AE tables without attributable or relative risk derived.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety profile of rituximab is now well established, from over 10 years' clinical experience across all indications. Roche estimates that over 1.9 million patients have been exposed to rituximab to date.

The long-term benefits of rituximab maintenance therapy are well established in relapsed follicular lymphoma with adverse events both predictable and manageable. In the pivotal EORTC 20981 study, which supports rituximab's current maintenance licence, neutropenia was the only significant grade 3/4 adverse event associated with maintenance therapy with a median follow-up of 6 years[28]. This was associated with an increased number of grade 3/4 infections (Table 84). However, only seven of 167 patients withdrew due to infections and all recovered fully and there were no deaths from infection.

Table 84: Grade 3/4 adverse events during the maintenance phase of the EORTC 20981 study

	Observation	Maintenance	*p*-value

Grade 3/4 neutropenia	6.0	11.5	NS
Grade 3/4 infections	2.4	9.7	0.01
NS = not significant. No other grade 3/4 adverse events showed significant differences between the maintenance and observation arms.			

In a recently published meta-analysis, rituximab maintenance therapy was associated with an increased frequency of grade 3/4 infectious adverse events (risk ratio 1.99) but absolute numbers were low and discontinuations due to infection were rare[63].

In the PRIMA study, overall, there were no new or unexpected safety findings during or after maintenance therapy. Safety data from the maintenance/observation phase of the study were consistent with the established safety profile of rituximab when used as maintenance treatment for up to two years[64,65,66,67,68,69].

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The PRIMA trial is a phase III randomised study which was designed to evaluate the efficacy and safety of two years of maintenance therapy with rituximab in previously untreated patients with high-tumor-burden follicular lymphoma who responded to a rituximab-containing induction regimen. The induction regimen (R-CHOP, R-CVP, or R-FCM) was selected by center, based on the investigator's routine practice.

Study Population

A total of 1202 evaluable patients were enrolled from 24 countries. Patients had a good performance status (96% ECOG 0–1). About half the population was male (52%), and the median age was 56 years old. Ninety percent of patients had stage III/IV disease at enrollment, 98% of patients had bulky disease, and most patients had intermediate-risk (36% FLIPI = 2) or high-risk disease (43% FLIPI ≥ 3). Most patients (74%) received R-CHOP as induction therapy, and only 4% received R-FCM. Overall, the rituximab maintenance and observation arms were well

balanced for baseline demographic and disease characteristics assessed prior to induction. They were also well balanced through stratification for induction regimen received and for response to induction therapy.

General Aspects of Study Conduct

Of the 1202 evaluable patients who entered the study, 1193 received induction therapy and [redacted] of these patients responded to treatment with a complete response (CR [redacted]), unconfirmed complete response (CRu [redacted]), or partial response (PR [redacted])—an overall response rate of [redacted]. Only 46 patients (ca. 4%) withdrew from the study during or after completion of the induction phase due to stable disease or treatment failure (disease progression).

A total of 1019 patients were subsequently analyzed as randomized in the maintenance/observation phase (513 patients to the observation arm, and 506 patients to the rituximab arm), although five patients in each arm received no maintenance treatment/attended no observation visit. Of the remaining 1009 patients, 515 had completed the maintenance/observation phase (231 patients in the observation arm, and 284 patients in the rituximab arm) at the time of data cut-off for the primary analysis (January 14, 2009), and 231 patients (115 observation, 116 rituximab) were still ongoing treatment/observation in the maintenance/observation phase. In total, 297 patients in the observation arm and 282 patients in the rituximab arm were in the post-maintenance/observation follow-up phase. The median observation time from randomization was 25 months at the clinical cut-off for the primary analysis.

More patients withdrew from the observation arm (162 patients) than from the rituximab arm (101 patients) during the maintenance/observation phase. Most of these patients withdrew due to 'treatment failure' (ie, relapsed/progressive disease): 144 patients in the observation arm and 67 patients in the rituximab arm. Only 10 patients in the rituximab arm (2% of maintenance rituximab-treated patients, and 10% of treatment withdrawals in this group) withdrew from the maintenance/observation phase due to treatment toxicity.

Efficacy

Response and progression were assessed in this study according to NCI-Working Group guidelines published in 1999[60]. CT scans and relevant clinical data were also reviewed by an Independent Review Committee (IRC) who made a separate blinded assessment of response and progression.

The study showed that rituximab maintenance significantly reduced the risk of disease progression or death by 50% compared with observation (investigator assessment: stratified HR 0.50, 95% CI [0.39;0.64], p < 0.0001). The median PFS was not reached in either arm, but at the time of data cut-off 174 patients had progressed or died in the observation arm (33.9%) compared with 93 patients (18.4%) in the rituximab arm. The 25th percentile for PFS was 507 days (16.7 months) in the observation arm compared with 1096 days (36.0 months) in the rituximab arm, and the one-year PFS rate was 82% (95% CI [0.79;0.85]) and 89% (95% CI [0.87;0.92]), respectively. These significant results were confirmed when analyzing PFS based on the IRC's assessments, which showed that rituximab maintenance reduced the risk of disease progression or death by 46% (stratified HR 0.54, 95% CI [0.42;0.70]). Subgroup analyses indicated consistent PFS benefits with rituximab maintenance across all the prespecified subgroups tested. In particular, the benefits of rituximab maintenance were apparent regardless of age, FLIPI score, the induction regimen used, or the response to induction therapy. Apart from being internally consistent, both the investigator-assessed and IRC-assessed PFS benefit were shown to be robust using sensitivity analyses.

An updated analysis of investigator-assessed PFS performed on data from randomization up to January 15, 2010 with an additional 12 months of follow-up confirmed the results of the primary PFS analysis (stratified HR [redacted], 95% CI [redacted]). The median PFS was [redacted] days ([redacted] months) in the observation arm [redacted].

The significant improvement in the primary endpoint, PFS, seen with rituximab maintenance was supported by the secondary endpoints EFS (stratified HR [redacted], 95% CI [redacted]), TTNLT (stratified HR 0.61, 95% CI [0.46;0.80]), and TTNCT (stratified HR 0.60, 95% CI [0.44;0.82]). At the end of the maintenance/observation phase, the overall response rate was also substantially higher in the rituximab arm

compared with the observation arm (74% vs 55%, p < 0.0001) and this was mainly due to a higher proportion of patients in complete remission (66.8% of patients in the rituximab arm compared with 47.7% of patents in the observation arm). This difference is also reflected when evaluating the improvements in overall response achieved during the maintenance/observation phase (27% of patients in the rituximab arm improved their response status compared with 19% of patients in the observation arm).

In terms of overall survival, at the time of the clinical cut-off for the primary analysis (January 14, 2009), less than 4% of patients in either treatment arm had died (16 patients in the rituximab arm, 18 patients in the observation arm). At the time of the updated analysis (January 15, 2010), a further [redacted] patients had died (total [redacted] patients in the observation arm and [redacted] patients in the rituximab arm). Although the results for overall survival numerically favor therapy with rituximab maintenance (stratified HR [redacted], 95% CI [redacted]), the wide 95% confidence interval does not allow any definitive conclusion to be made for OS at this time. Patients continue to be followed for survival.

Safety

Overall, there were no unexpected safety findings in this study. The safety profile of rituximab-based immunochemotherapy during the (non-randomized) induction phase was as expected based on published and previously submitted data on R-CHOP[53,70,71,72], R-CVP[51,52,73,74], and R-FCM[54,55,75,76,77,78,79]. Adverse events of any grade were reported for 25% of patients during the induction phase. Infections were the most common adverse event, with Grade 2–5 infections reported in 7% of patients during the induction phase, but only 5% of these were Grade 3/4 in severity. Serious adverse events were reported in 19% of patients, but only 31 patients (2.6%) withdrew from the induction phase because of treatment toxicity. There were 16 fatal AEs.

Safety data from the maintenance/observation phase of the study were also consistent with the established safety profile of rituximab when used as maintenance treatment for up to two years[64,65,66,67,68,69]. As expected, adverse events (Grade 3–5

toxicities, Grade 2–5 infections, and serious adverse events) were more common in the rituximab arm (52% vs 35% of patients), and the incidence of Grade 2–5 infections was also higher in the rituximab arm (37% vs 22% of patients). However, most infections were mild to moderate in severity: the incidence of Grade 3–5 infections was only 4% in the rituximab arm compared with less than 1% in the observation arm. One patient died of infection during the maintenance/observation phase: a patient in the rituximab maintenance arm died of fulminant hepatitis B. Two patients were also reported to have died of PML in the study, but in both cases this occurred after disease progression and subsequent therapy for lymphoma.

An updated safety analysis performed on data from randomization up to January 15, 2010 demonstrated a slight increase in the number of adverse events and SAEs recorded since the earlier cut-off (January 14, 2009). Overall, however, there was no change to the safety profile for the study at the time of the updated analysis.

As expected, blood and lymphatic adverse events (Grade 3–5) were also more common in the rituximab arm (5% vs 1%). Serious cardiac disorders were also more common in the rituximab arm (11 vs 2 patients), however, almost all the patients in the rituximab arm could continue with their rituximab treatment.

Constitutional symptoms were reported in 155 patients in the observation arm (31%) and 203 patients (41%) in the rituximab arm, but severe (Grade 3–5) infusion-related AEs were uncommon during the maintenance/observation phase: 12% of patients in the rituximab arm had a severe AE (Grade 3–5 or Grade 2–5 infections or SAE regardless of grade) reported within one day of study treatment, but, in comparison, 9% of patients in the observation arm had an AE reported within the same time frame in relation to a study visit—a difference of only 3% between the study arms. Moreover, no Grade 3–5 chills, pyrexia, nausea, vomiting, or administration site conditions (other than mucositis) were reported within one day of administration of study treatment in the rituximab arm.

Nine pregnancies were reported during the study, including two in the partners of male patients. Apart from one patient who had a spontaneous miscarriage during the first trimester and one patient who had a therapeutic termination, no detrimental effects were reported in those patients/partners who continued their pregnancies.

Laboratory Data

The effect of rituximab on lymphocyte subsets, immunoglobulins, and anti-tetanus antibodies was also assessed during the study. Analysis of lymphocyte subsets showed continuous suppression of B-cells throughout the maintenance/observation period for patients in the rituximab arm. In comparison, patients in the observation arm showed recovery of B-cells during the maintenance/observation phase with a mean value returning to within the normal range by visit 6 (one year). These findings are consistent with the B-cell-depleting mechanism of action of rituximab and with the known pattern of B-cell recovery after rituximab treatment. Analysis of other lymphocyte subsets showed no apparent difference between patients on rituximab maintenance and patients in the observation arm and no apparent suppression of T-cells (CD3-positive) or natural killer (CD16- or CD56-positive) cells.

Analysis of immunoglobulins showed no apparent detrimental effect of rituximab maintenance on IgA or IgM levels. However, although there was considerable overlap between IgG levels in the rituximab maintenance and observation arms, there was a slight downward trend in IgG levels in the rituximab arm compared with the observation arm towards the end of the treatment period. At the end of the maintenance/observation phase, 11 patients in the observation arm (26%) and 36 patients in the rituximab maintenance arm (47%) had IgG levels lower than 7 g/L. However, only one patient in the observation arm (2%) and four patients in the rituximab maintenance arm (5%) had IgG levels lower than 4 g/L at the end of the maintenance/observation phase.

Neutrophil counts in the rituximab arm closely matched those in the observation arm during the maintenance/observation phase and most patients' counts remained within the normal range throughout the maintenance/observation phase. However, Grade 3/4 neutropenia did occur and was more frequent in the rituximab maintenance arm (9% of patients) than in the observation arm (4%).
Overall, these data are consistent with the observed safety profile of maintenance rituximab and indicate manageable B-cell suppression during maintenance treatment with a slight adverse effect on IgG levels and neutrophil counts in a minority of patients.

Quality of Life

Quality of life analyses based on both the FACT-G and QLQ-C30 questionnaires showed that active therapy with rituximab maintenance did not adversely affect patient-reported quality of life. N.B. Since no QoL questionnaires were collected after progression/relapse, these analyses did not take into account the likely detrimental effect of disease progression/relapse and its subsequent treatment, which occurred much more frequently in the observation arm

Conclusions

The results of the primary analysis of the PRIMA trial in patients with previously untreated follicular lymphoma responding to induction with rituximab plus chemotherapy show:

- A highly statistically significant and clinically meaningful benefit of rituximab maintenance therapy compared with observation in terms of progression-free survival ($p < 0.0001$, stratified log-rank test). The risk of disease progression or death was significantly reduced by 50% in patients receiving rituximab maintenance therapy compared with those in the observation arm (investigator assessment: stratified HR 0.50, 95% CI [0.39;0.64]). An updated analysis of investigator-assessed PFS performed on data from randomization up to January 15, 2010 with an additional 12 months of follow-up confirmed the results of the primary PFS analysis (stratified HR [redacted], 95% CI [redacted]).
- Analysis of PFS based on an independent review of cases gave consistent results and confirmed the significant risk reduction with rituximab maintenance therapy compared with observation (IRC assessment: stratified HR 0.54, 95% CI [0.42;0.70], $p < 0.0001$, stratified log-rank test).
- All prespecified sensitivity analyses showed that the PFS results were robust, and the benefit of rituximab maintenance was confirmed across key patient subgroups.

- Analysis of the secondary endpoints event-free survival, time to next anti-lymphoma treatment, time to next chemotherapy, and overall response also support the benefit of rituximab maintenance treatment, with statistically and clinically significant improvements for patients in the rituximab arm.

- There were too few deaths to make definitive conclusions on overall survival at the time of the primary or updated analysis (clinical cut-off January 15, 2010)—a longer follow-up is required to evaluate the effects of rituximab maintenance on overall survival in this study.

- The safety profile observed in the PRIMA study was consistent with the known safety profile of rituximab. There were no new or unexpected safety signals during or after maintenance treatment with rituximab.

- Quality of life analyses based on the outcomes of both FACT-G and EORTC QLQ-C30 questionnaires confirmed that maintenance therapy with rituximab did not have a detrimental effect on patient-reported quality of life.

In summary, the PRIMA study provides strong evidence that maintenance therapy with rituximab, after response to induction with rituximab plus chemotherapy, is effective in prolonging PFS in patients with previously untreated follicular lymphoma. Furthermore, maintenance therapy with rituximab is well tolerated and confers little additional toxicity compared with observation.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The PRIMA study was prospectively planned, adequately powered, centrally randomized, and multicenter/multinational in nature. The study is also the first randomized phase III study to investigate the benefit of rituximab maintenance therapy in previously untreated patients with follicular lymphoma who have responded to a rituximab-containing induction regimen.

The results achieved with rituximab maintenance compared with observation alone in this trial were highly statistically significant and clinically meaningful in terms of the

primary efficacy parameter, PFS, and in the secondary endpoints of EFS, time to next lymphoma treatment (TTNLT), time to next chemotherapy treatment (TTNCT) and response rate. The treatment benefits observed with rituximab maintenance were seen consistently in all of the subgroups analyzed. Results were robust, internally consistent and consistent with the PRIMA trial protocol's statistical assumptions.

Results are further supported by, and consistent with, previous rituximab maintenance studies in patients with previously untreated and relapsed/refractory follicular lymphoma (Table 85).

Table 85: Key Randomized Trials of Rituximab maintenance in Follicular Lymphoma

Study [Ref]	Induction Regimen, Response Required	Maintenance Regimen	n	Median FU (months)	Disease Control	Overall Survival
Previously untreated follicular lymphoma						
ECOG 1496 [80,3]	CVP × 6–8 ≥ SD	Rituximab: 375 mg/m^2 weekly × 4, every 6 months for 2 years vs Observation			PFS[c]	At 2 years
			R: 125[b]	27	NE	94%
			O: 123[b]		15 months	91%
					HR = 0.4 p < 0.0001	p = NS
SAKK 35/98 [66,81]	Rituximab: 375 mg/m^2 weekly × 4 ≥ SD	Rituximab 375 mg/m^2 every 2 months × 4 courses vs Observation			EFS[e]	
			R: 25[d]	35	36 months	Not
			O: 26[d]		19 months	provided
					p = 0.009	
Total			299			
Previously treated follicular lymphoma						
SAKK 35/98 [66,81]	Rituximab: 375 mg/m^2 weekly × 4 ≥ SD	Rituximab 375 mg/m^2 every 2 months × 4 courses vs Observation			EFS[e]	
			R: 48[d]	35	10 months	Not
			O: 52[d]		15 months	provided
				p=0.081		

EORTC 20981 (M39022) [27,28,82]	R-CHOP × 6 vs CHOP × 6 ≥ PR	Rituximab: 375 mg/m^2 every 3 months for up to 2 years vs Observation			PFS[f]	At 1 year
			R: 167	47.2	42.9 months	96%
			O: 167		15.7 months	93%
					HR = 0.49 p < 0.0001	HR=0.61 p=0.00243
LYM-5 [68]	Rituximab: 375 mg/m^2 weekly × 4 ≥ SD	Rituximab: 375 mg/m^2 weekly × 4, every 6 months for 2 years vs rituximab re-treatment at relapse			PFS[h]	At 3 years
			R: 44[g]	41	31.3 months	72%
			RT: 46[g]		7.4 months	68%
					p=0.007	p=NS
GLSG–FCM [54]	R-FCM vs FCM ≥ PR	Rituximab 375 mg/m^2 weekly × 4 at 3 and 9 months after end of induction vs Observation			Response Duration[j]	
			R: 41[i]	26	NR	Median
			O: 40[i]		26 months	survival
					p = 0.035	not reached
Total			505			

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CVP=cyclophosphamide, vincristine, prednisone; EFS=event-free survival; FCM =fludarabine, cyclophosphamide, mitoxantrone; FU=follow-up; HR=hazard ratio; NE = not evaluable; NR = not reached; NS=not significant; O = observation; PD=progressive disease; PFS=progression-free survival; R=rituximab; RT = retreatment; SD=stable disease.

[a] n randomized after induction

[b] Study included 322 patients; all 322 included in overall survival, N and PFS data only for the subset of 248 patients with follicular lymphoma.

[c] Progression or death measured from time of randomization to rituximab maintenance or observation.

[d] Study included 151 previously treated and previously untreated patients overall, randomized to observation vs prolonged rituximab treatment.

[e] Measured from first induction infusion to progression, relapse, second tumor or death from any cause.

[f] Calculated from second randomization (to rituximab maintenance or observation).

[g] Includes patients with both follicular (n=62) and small lymphocytic (n=28) lymphoma.

[h] Calculated from date of first rituximab treatment until PD that required other treatment.

[i] Study included patients with mantle cell lymphoma, but the table includes only those with follicular lymphoma and induction with R-FCM.

[j] Response duration defined as end of successful therapy to documentation of progressive disease.

Data from these randomized trials are supported by recently reported preliminary results from the MAXIMA trial[83]. This ongoing, non-randomized study is evaluating rituximab maintenance (375 mg/m^2 every 8 weeks for 2 years) in patients with treatment-naive and previously treated follicular lymphoma after response to induction treatment with a rituximab-containing regimen (R-CHOP in the majority of patients). After a median of 20 months follow-up, only 63 of the 545 patients enrolled have relapsed (11.6% overall). Lower relapse rates were seen in patients treated in the first-line setting (10.1% of patients) and in patients entering the maintenance phase in CR and with a low (i.e., favorable) FLIPI score. Maintenance treatment was

well tolerated with no new safety issues identified, even though approximately 20% of the rituximab maintenance doses were given by rapid infusion.

Other relevant studies include the ongoing SAKK 35/03 study[84], which is comparing a short course of rituximab maintenance (375 mg/m² every two months for a total of 4 doses) with prolonged rituximab maintenance (375 mg/m² every two months for a maximum of five years) in patients with previously treated and previously untreated follicular lymphoma after induction with rituximab alone. Only safety data have been reported to date and these indicate that prolongation of maintenance therapy beyond two years is feasible with no obvious increase in toxicity. However, at the time of reporting only 29 patients had been on maintenance therapy for 2 years or more and only 6 patients for 3 years or more.

As outlined above, there were too few deaths in the PRIMA study to make definitive conclusions on overall survival at the time of the primary or updated analysis. However, the hazard ratio was in favour of the rituximab maintenance arm (HR [redacted], 95% CI [redacted]) and it is possible that the improvements in PFS and other efficacy parameters with rituximab maintenance might translate into improved OS with the passage of time. This hypothesis is supported by a recently published study, which reported long term follow-up of newly diagnosed follicular lymphoma patients (albeit in the pre-rituximab era) and indicated that a better response to first-line treatment translates into an improved survival for patients with FL[85].

Of note, a systematic review/meta-analysis of rituximab maintenance versus observation or retreatment at relapse has recently been published including data on the studies listed in Table 85 (1143 patients, including 985 patients with follicular lymphoma)[63]. Overall, patients treated with rituximab maintenance had a statistically significantly better OS than patients in the observation arm or patients treated at relapse (HR for death 0.60, 95% CI [0.45, 0.79]). Patients with previously treated follicular lymphoma had a clear survival benefit with rituximab maintenance therapy (HR for death 0.58, 95% CI [0.42, 0.79]), but for previously untreated patients the benefit was not statistically significant (HR for death 0.68, 95% CI [0.37, 1.25]). No statistically significant heterogeneity was observed for OS, and a funnel plot of the primary outcome did not suggest any publication bias. Despite different kinds of

induction therapy and maintenance schedule, the point estimate for all pooled analyses favoured rituximab maintenance therapy.

An updated version of the aforementioned meta-analysis is currently in preparation, which includes data from new rituximab maintenance trials published since the original report (provided to Roche in advance of publication by kind permission of the authors)[86]. The updated report includes [redacted] randomised trials, [redacted] of which were included in the previous report ([redacted] with updated analyses**3**,**28**[,66]) and [redacted] trials recently reported, including [redacted],**2**[,83,87.] Similar to the original report, the updated analysis demonstrates that patients treated with rituximab maintenance had statistically significant better overall survival than patients in the observation arm or patients treated at relapse (HR for death = [redacted], 95% confidence interval (CI) = [redacted] to [redacted], [redacted] patients). Patients with refractory or relapsed (i.e., previously treated) follicular lymphoma also had a survival benefit with maintenance rituximab therapy (HR for death = [redacted], 95% CI = [redacted] to [redacted]), whereas previously untreated patients did not (HR for death = [redacted], 95% CI = [redacted] to [redacted]). Regarding the latter point, the authors speculate that this is probably due to the short periods of follow up in the included first-line trials. Unlike the original publication, in the updated report the authors also examined [redacted], which was [redacted] in each of the included trials, pooled HR [redacted] 95% CI [redacted] to [redacted] (Figure 26). This effect was consistent in patients who received [redacted] their first induction therapy (HR [redacted] 95% CI [redacted] to [redacted]), and in those who received [redacted] [redacted] after two or more inductions (HR [redacted] 95% CI [redacted] to [redacted]). The data in first-line patients is consistent with that reported in [redacted] (HR [redacted], 95% CI [redacted] to [redacted]; Jan 15th 2010 cut-off) and [redacted] [redacted] in previously untreated follicular lymphoma patients. [redacted] [redacted] in follicular lymphoma patients [redacted].

Figure 26: Pooled estimates of PFS with rituximab maintenance therapy for patients with follicular lymphoma compared with observation or rituximab at disease progression

Black squares represent the point estimate, their sizes represent their weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. IV = inverse of variance, Fixed = fixed effect model, HR = hazard ratio for disease progression or death, CI = confidence interval, MR = maintenance therapy with rituximab.

Safety data from the PRIMA study are consistent with the established safety profile of rituximab when used as maintenance treatment for up to 2 years, with no new or unexpected findings reported. In the updated meta-analysis, rituximab maintenance therapy was reported to be associated with an increased frequency of grade 3/4 infectious adverse events (Risk ratio (RR) = [redacted], 95% CI = [redacted] to [redacted]) but absolute numbers in individual trials were low and discontinuations for infections were rare[86].

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The relevance of the evidence base must be judged with reference to the therapeutic goals in stage III-IV follicular lymphoma and the principles of treatment outlined in Section 2.4.

Relevance of end-points in PRIMA to patients with relapsed Stage III-IV follicular lymphoma

As explained, stage III-IV follicular lymphoma is generally considered incurable and patients are treated when they become symptomatic with a view to inducing remission, thereby alleviating symptoms. Patients in remission are not only free of the symptoms caused by overt disease, but also from the inconvenience and toxicity of the chemotherapy that will be required when they relapse, not to mention the psychological trauma that attends relapse with a disease that is, in most cases, ultimately fatal. There is a clear understanding amongst clinicians that remissions are of immense value to patients. Therefore, treatments which can induce more frequent or longer lasting remissions represent developments which are extremely relevant to patients and their carers.

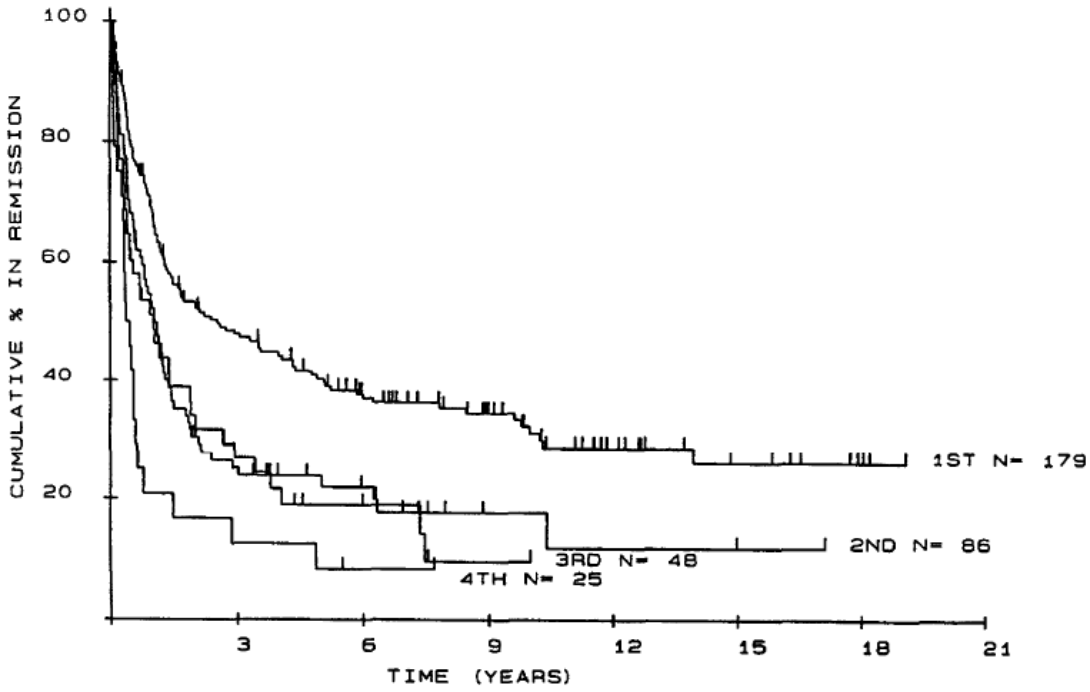
In the pivotal randomised Phase III study (PRIMA) that forms the core of this submission, the endpoints assessed (both primary and secondary) are of direct relevance to benefits that would be experienced by patients in practice. Time spent progression-free is highly relevant as discussed above and all the secondary endpoints are measured as standard in oncology trials.

Relevance of the impact of administering rituximab maintenance after successful remission induction in previously untreated follicular lymphoma

In this submission, evidence is provided demonstrating that when rituximab maintenance is administered to follicular lymphoma patients following response to first-line induction therapy with rituximab plus chemotherapy the risk of disease progression or death was significantly reduced by 50% compared with those in the observation arm (investigator assessment: stratified HR 0.50, 95% CI [0.39;0.64]). As detailed above, prolongation of PFS provides a meaningful clinical benefit to patients by extending the time without disease progression and its associated symptoms, and by delaying the need for further therapy, in particular chemotherapy. Subsequent

chemotherapies are associated with toxicity and with a progressively reduced likelihood of achieving a durable response. Indeed, several studies have shown that the duration of remission in follicular lymphoma becomes progressively shorter with multiple lines of therapy[88, 48, 23](Figure 27). It is therefore important that patients receive the best opportunity for prolonged remission as part of their upfront treatment plan.

Figure 27: Duration of remission following the first, second, third, and fourth courses of treatment[23,88,]



It is highly relevant to the population described in the decision problem that the PFS benefit associated with rituximab maintenance therapy as demonstrated in PRIMA was apparent regardless of the type of R-based immunochemotherapy induction regimen used. As described in section 2.5, approximately 93% of all eligible first-line follicular lymphoma patients in the UK receive rituximab in combination with chemotherapy as standard treatment[34]. Of these patients, and according to current NICE guidance (TA110), approx 67% are treated with rituximab plus CVP, 16% are treated with R-CHOP, with the remainder receiving rituximab combined with other chemotherapies. The lack of consensus in terms of the preferred combination partner for rituximab in this setting is supported by the pattern of induction therapy administration in UK centres participating in PRIMA, with 11 (69%) patients receiving R-CHOP and 5 (31%) receiving R-CVP (Table 86).

Table 86: Summary of registration to induction trial treatment by country

Trial Treatment (REG)
Protocol(s): MO18264 (A18264M)
Analysis: REG Center: ALL CENTERS
Snapshot Date: 27OCT2009 Cutoff Date: 14JAN2009

	R-CHOP N = 885	R-CVP N = 272	R-FCM N = 45
Country			
ARGENTINA	15 (2%)	-	-
AUSTRALIA	36 (4%)	94 (35%)	2 (4%)
BELGIUM	74 (8%)	1 (<1%)	-
BRAZIL	11 (1%)	2 (<1%)	-
CHINA	7 (<1%)	1 (<1%)	-
COLOMBIA	11 (1%)	-	-
CROATIA	7 (<1%)	-	-
CZECH REPUBLIC	33 (4%)	3 (1%)	-
DENMARK	5 (<1%)	43 (16%)	-
FINLAND	24 (3%)	-	-
FRANCE	577 (65%)	47 (17%)	-
INDIA	10 (1%)	4 (1%)	-
ISRAEL	9 (1%)	-	-
NETHERLANDS	-	18 (7%)	-
NEW ZEALAND	-	26 (10%)	-
PERU	-	10 (4%)	-
PORTUGAL	16 (2%)	-	-
SERBIA	4 (<1%)	5 (2%)	-
SPAIN	20 (2%)	-	34 (76%)
THAILAND	3 (<1%)	6 (2%)	9 (20%)
TURKEY	-	7 (3%)	-
UNITED KINGDOM	11 (1%)	5 (2%)	-
URUGUAY	3 (<1%)	-	-
VENEZUELA	9 (1%)	-	-
n	885	272	45

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM16 06NOV2009:10:21:37 (1 of 10)

This disparity is likely driven by several factors, including (i) a breadth of data from several randomised trials and a meta-analysis[35,36,37,38,51,52,53] demonstrating that the clinical benefit associated with the addition of rituximab to chemotherapy is independent of the chemotherapy backbone. It should be noted that it was these data that formed the core of a filing package submitted to the EMA by Roche that lead to a broadened R-chemotherapy for rituximab in 2008 for patients with previously untreated follicular lymphoma; (ii) robust health outcomes data demonstrating the cost-effectiveness of R-chemotherapy[39]; (iii) no directly comparative, randomised trial data exists to show that the addition of doxorubicin to rituximab-based upfront immunochemotherapy improves clinical outcomes (ie no head-to-head data directly comparing R-CHOP vs R-CVP); and (iii) individual preference as to whether to spare patients from anthracycline-related toxicities up front and reserve R-CHOP for when a patient's disease transforms or relapses or treat more aggressively upfront so as decrease the risk of disease transformation. Thus, endorsement of maintenance therapy after response to any first-line R-chemotherapy combination will allow UK clinicians the continued flexibility of using any appropriate upfront rituximab-based induction therapy, in line with current standard practice.

Burden of rituximab treatment on patients

In a disease where cure is not readily possible and treatment is intended to enhance the amount of time spent in remission and symptom-free, the tolerability of maintenance therapy is also very relevant. The toxicity data from PRIMA are highly reassuring in this regard. Apart from some largely asymptomatic changes in laboratory parameters, treatment toxicity is mostly restricted to acute reactions during drug infusion. These reactions are short-lived and have only a minor impact on patients health and quality of life. Additionally, quality of life analyses from PRIMA confirmed that active treatment with rituximab maintenance therapy did not have a detrimental effect on patient-reported quality of life. In clinical practice, delivery of maintenance will also require just 12 additional outpatient treatment appointments (each typically lasting half a day), which can usually be combined with routine follow-up visits. Overall, the burden of maintenance therapy on patients is trivial relative to the benefits.

In summary, evidence has been presented from a pivotal, well-conducted comparative Phase III study which forms the core of the application to extend the marketing authorisation for rituximab as maintenance therapy to include previously untreated follicular lymphoma patients responding to induction therapy. This study reports significant improvements in the conventional measures of treatment effectiveness in this disease above and beyond the current standard of care. Furthermore, these advances are offset by only modest increases in treatment toxicity and burden of drug administration.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical

practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Patient groups in PRIMA versus clinical practice

In routine clinical practice patients with Stage III/IV follicular lymphoma requiring treatment will undergo several courses of treatment interspersed with treatment-induced remissions. Treatment is triggered by symptoms experienced by the patient or clinical evidence that disease is compromising the function of other organs. As such patients with previously untreated follicular lymphoma requiring treatment (as defined using the GELF criteria in PRIMA) are a group that would be well recognised by UK clinicians treating follicular lymphoma in routine clinical practice.

The median age of patients presenting with follicular lymphoma is around 60-65, and with advancing age, co-morbidity and frailty treatment of any malignancy can become increasingly difficult. It is generally a feature of all oncology studies that there is an underrepresentation of older patients and this is applicable to PRIMA, where the median age of patients at registration was 56 years. Despite this, nearly 40% of all patients who qualified for randomisation to maintenance or observation in PRIMA were ≥60. Furthermore, a preplanned subgroup analysis demonstrated a consistent level of clinical benefit associated with maintenance therapy in patients ≥60 compared to those <60 (see Figure 9).

The PRIMA study also only selected patients with an ECOG performance status of 0, 1 or 2. Baseline disease characteristics at entry show that the majority of patients had a performance status of 0 (65%) or 1 (31%), which helps explain the median age of the trial group, with an expected decrease in performance status with increasing age. ECOG 0 and 1 may not reflect the true performance status of a number of frailer follicular lymphoma patients who need treatment for the first time. In reality, however, very frail patients with multiple comorbidities are unlikely to be eligible for

treatment with R-chemotherapy and subsequent treatment with rituximab maintenance (see below).

Induction therapies used

As detailed in section 2.5, approximately 93% of all eligible first-line follicular lymphoma patients in the UK receive rituximab in combination with chemotherapy as standard first-line treatment[34]. It is therefore entirely appropriate that the PRIMA trial evaluated the benefit of maintenance therapy with rituximab versus observation after the induction of response with R-chemotherapy. It is anticipated that the EU licence will allow the use of rituximab maintenance therapy in previously untreated follicular lymphoma patients responding to *any* induction therapy, based on a filing package consisting of both the PRIMA trial and the phase III ECOG 1496 trial[3]. The latter study evaluated the benefit of rituximab maintenance (using 4 weekly does of rituximab every 6 months for up to 2 years) versus observation in first-line low grade NHL patients following CVP combination therapy. This broad label is of greater relevance to other EU countries where there is still significant usage of non-rituximab containing induction therapy in previously untreated FL patients. In the UK, the vast majority of patients who are not treated with R-chemo, receive the oral alkylating agent chlorambucil as monotherapy (approximately 5% of all eligible patients)[34]. These patients tend to be older, frailer, and with comorbidities that make them ineligible for treatment with R-chemo. By virtue of their poor performance status, the likelihood of them being eligible for rituximab maintenance or indeed opting for maintenance therapy as a preferred course of treatment is extremely low.

Relevance of dosing schedules

The PRIMA study used a regimen that will become the licensed dosing schedule for rituximab maintenance therapy in previously untreated follicular lymphoma patients and as such will be documented in the SmPC.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic review of the published literature was conducted to identify cost-effectiveness studies of rituximab as a first line maintenance treatment in follicular lymphoma. The PICO method was used to develop the search strategies with reference to the decision problem and combined cost-effectiveness search terms with terms for the specific disease area. Systematic searching in standard databases was supplemented with handsearches of reference lists and relevant conference proceedings. The inclusion and exclusion criteria were chosen to identify all economic evaluations. Whilst the systematic review was not restricted to studies from specific countries, this submission presents only studies that adopt the UK perspective. The results of these searches are reported in this section.

Details of searched databases and results are presented in section 9.10, appendix 10.

The systematic review identified 397 studies in total and 14 potentially relevant cost-effectiveness studies. However, none of these studies matched requirements for inclusion in the present STA submission. Reasons for exclusion were: not relevant country/perspective in 12 studies (Berto et al., 2007[89], Brice et al., 2007[90], Deconinck et al., 2010[91], Gomez Codina et al., 2007[92], Grupo de Farmacoeconomia del Linfoma, 2008[93], Hayslip and Simpson, 2008[94], Kasteng et al., 2008[95], Maturi et al.,

2006[96], Pacull et al., 2007[97], Pompen and Huijgens, 2008[98], Thompson and van Agthoven, 2005[99], Wirt et al., 2001[100]); not relevant study population (refractory/relapsed) in two studies (Geary et al., 2007[101]) and NICE TA137 see table below.

Table 87: Reasons for exclusion of cost-effectiveness studies

Citation	Reason for exclusion[ii]
Maturi et al., 2006	not relevant country/perspective: Canada
Brice et al., 2007	not relevant country/perspective: France
Pacull et al., 2007	not relevant country/perspective: France
Deconinck et al., 2010	not relevant country/perspective: France
Berto et al., 2007	not relevant country/perspective: Italy
Pompen and Huijgens, 2008	not relevant country/perspective: the Netherlands
Thompson and van Agthoven, 2005	not relevant country/perspective: the Netherlands
Gomez Codina et al., 2007	not relevant country/perspective: Spain
Grupo de Farmacoeconomia del Linfoma, 2008	not relevant country/perspective: Spain
Kasteng et al., 2008	not relevant country/perspective: Sweden
Hayslip and Simpson, 2008	not relevant country/perspective: United States
Wirt et al., 2001	not relevant country/perspective: United States

[ii] The study population in all these citations comprised refractory/relapsed patients

Geary et al., 2007	not relevant study population: refractory/relapsed patients
NICE TA137	not relevant study population: refractory/relapsed patients

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No relevant studies were identified.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)iii or Philips et al. (2004)iv. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

[iii] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[iv] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population included in the economic evaluation is based upon the anticipated licensed population and reflects the group of patients within the licensed indication that have been treated in the 1st line setting with rituximab in combination with chemotherapy. This is aligned with the population included in the PRIMA study. The licensed indication is expected to include all patients induced with any chemotherapy regimen.

1. **Deviation from the original scope**

The deviation of the economic evaluation from the final scope and expected licensed indication is appropriate for the purposes of this appraisal as rituximab containing chemotherapy regimens are the current standard of care in the UK for 1st line patients. Furthermore current NICE guidance recommends the use of rituximab in combination with CVP for 1st line patients (TA 110). This recommendation is partly reflected in the immunochemotherapy regimens given as part of 1st line induction therapy of the PRIMA phase III registration trial. Investigators in the trial were given the option to assign patients in one of three induction regimens; R-CHOP, R-CVP, R-FCM. Responding patients were then randomised in the 2 arms of the study; R maintenance and observation. The trial was not powered to show any statistically difference between the patients with respect of their induction treatment.

2. **R-chemo induction**

NICE has not yet assessed the cost effectiveness of R in combination with any chemotherapy backbone induction for patients in 1st line. This is going to be the subject of the upcoming re-review of TA 110. TA 110 only included the assessment of R-CVP induction reflecting rituximab's license at the time of the appraisal. The license has since changed and it now includes 1st line induction in combination with any chemotherapy backbone. Despite NICE guidance recent market research data suggests that ~90% of all eligible patients are treated with R induction based chemotherapy (and of those ~16% of patients are treated with R-CHOP). The majority of UK patients in PRIMA received R-CHOP induction therapy (16 recruited; 9 patients out of 15 patients received R-CHOP (60%)). The cost effectiveness of other immunochemotherapy induction therapies in 1st line has been demonstrated in Roche's submission to the SMC (SMC guidance 8/9/2008[102]). SMC assessed the cost effectiveness of rituximab in combination with 3 chemotherapy (R-CVP, R-CHOP and R-MCP) regimens and issued positive guidance for 1st line untreated patients. The cost effectiveness results for the 3 regimens were as follows:

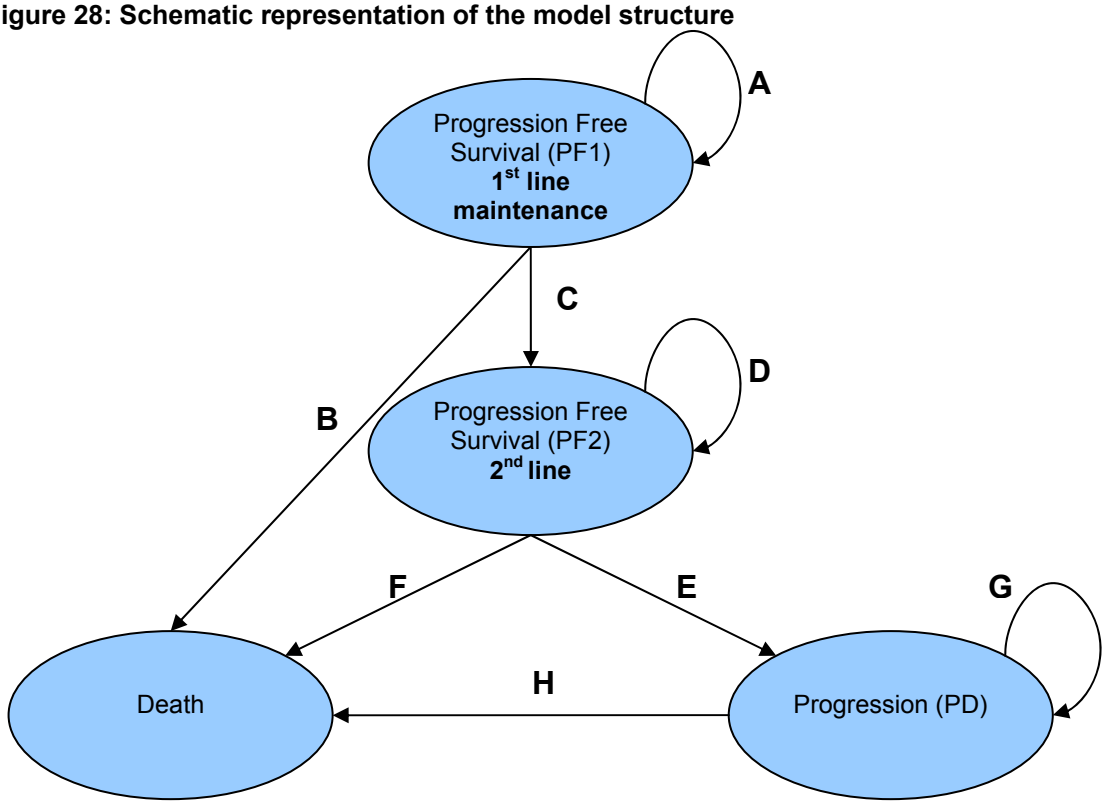
- CHOP cost an extra £8,980 per patient and yielded 0.86 QALYs at a **cost per QALY gained of £10,472**
- MCP cost an extra £9,074 per patient and yielded 1.22 QALYs at a **cost per QALY gained of £7,417**
- CHVP cost an extra £3,973 per patient and yielded 0.47 QALYs at a **cost per QALY gained of £8,549**

Based on the above analysis and the additional data that have been available since NICE's and SMC's appraisal showing that rituximab when added to chemotherapy in 1st line induction is very effective, it is expected that NICE will recommend induction with any immunochemotherapy regimen and will leave the option to clinicians to utilise the guidance and choose the appropriate background chemotherapy regimen on a patient-by-patient basis.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

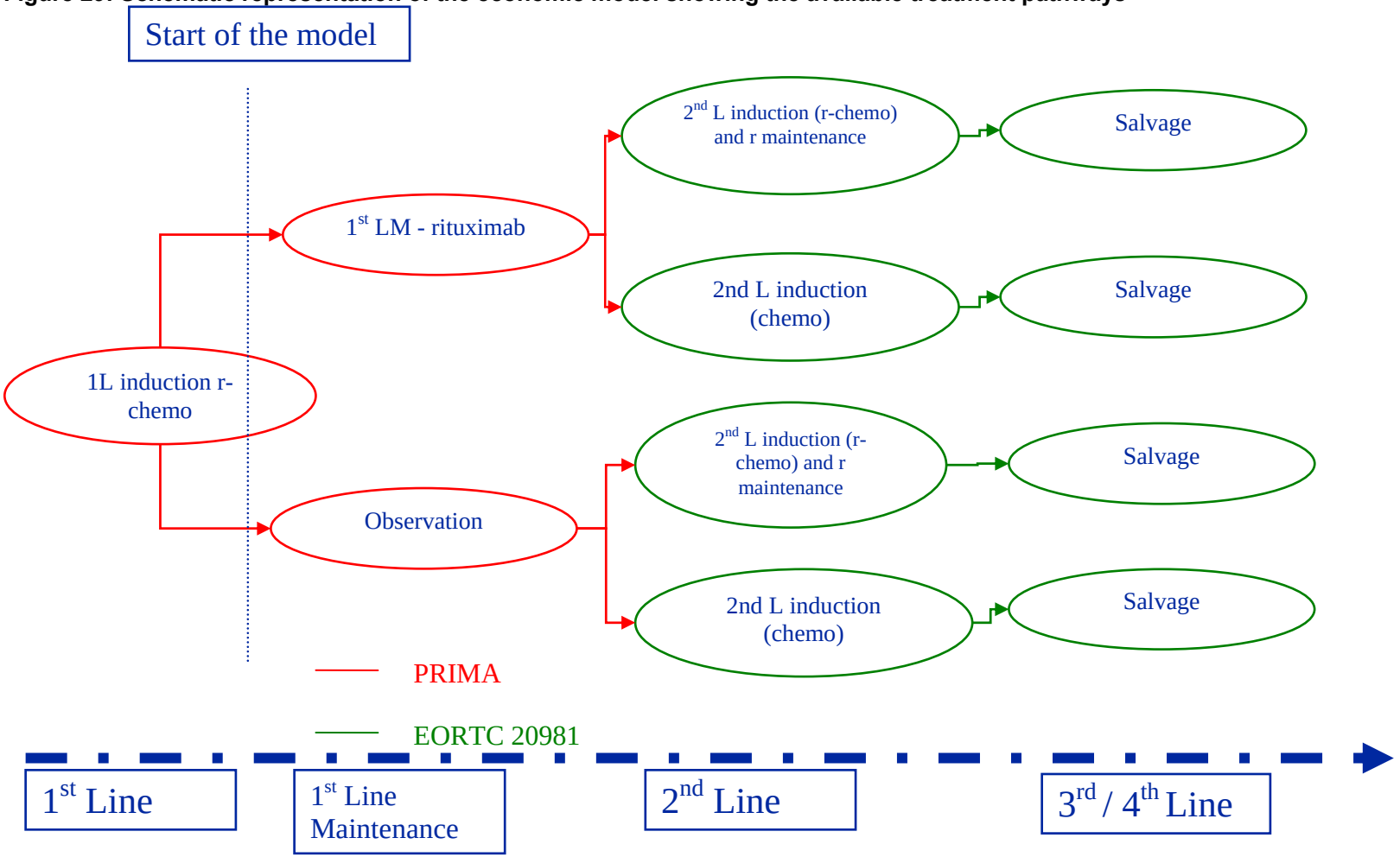
Figure 28: Schematic representation of the model structure



All patients are assumed to enter the model in the PFS (1st line maintenance; 1LM) state having successfully completed (partial/complete response as define in PRIMA) induction therapy with a rituximab-chemotherapy combination therapy. The start of the model reflects the start of the PRIMA trial (post randomisation). At the end of each cycle patients remain in progression free one (PF1) (**A**) or move to progression free two (PF2) (2L) (**C**), or die (**B**). Once a patient is within the PF2 health state, a patient may remain within the state (**D**), die at the end of each cycle (**F**) or transition to the progression (progressive disease; PD) state (**E**). Patients in the progression state can not move back to PF2 within the model. They can either remain in progression (**G**) or die at the end (**H**) of each cycle. Death is an absorbing health state within the model.

A more detailed schematic representation depicting the available pathways and treatments option in each state of the model is given in the figure below.

Figure 29: Schematic representation of the economic model showing the available treatment pathways



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The chosen model structure attempts to mirror the patient pathway and the associated second and later line treatments for a patient with follicular lymphoma. The patient pathway for a patient eligible for 1LM therapy is provided in section 2.4.

6.2.4 Please define what the health states in the model are meant to capture.

1. Progression Free Survival 1LM (PF1) – The health state represents the period that patients remain in remission. Patients either receive rituximab monotherapy maintenance therapy (for 2 years) in the intervention arm or do not receive any treatment in the comparator arm. The rates of progression in the 2 arms are defined by the observed rates in the PRIMA study (PFS).

2. Progression Free Survival 2L (PF2) – The health state follows the period that patients have progressed from PF1. Patients, however, receive additional treatment and achieve a second remission. The probability of remaining in 2nd line remission is based on the relevant intervention within the Van Oers study. Patients in this state receive treatment with rituximab chemotherapy combination 2nd line induction therapy followed by R monotherapy in accordance to NICE guidance (NICE guidance TA 137). However patients that have failed/progressed while on rituximab 1st line maintenance therapy are assumed to be ineligible/unsuitable for additional treatment with rituximab and instead receive chemotherapy induction therapy. In addition patients that relapse within 1 year of stopping rituximab treatment are also assumed to be ineligible for further R treatment (according to the British Haematology Society's and the recently published ESMO guidelines for treating FL patients). 11.9% of patients progressed within 1 year of receiving R-maintenance in PRIMA (month 36) and therefore it is assumed that they will not benefit from subsequent treatment with R. The base-case analysis assumes that 88.1% (100%-11.9%) of patients in the intervention arm receive R-chemotherapy induction followed by R monotherapy maintenance (according to the licensed indication) with the rest being treated with chemotherapy induction. For the comparator arm it was found that 19.3% relapsed within 1 year of receiving 1st line R-chemo induction (PRIMA month 12). It is

assumed that 88.1% of patients will receive R-chemo induction followed by maintenance in 2nd line with the rest receiving chemotherapy induction in 2nd line. The cost of 2nd line induction is incurred at the 1st cycle of the model (one-off) and no additional benefit is associated with 2nd line induction.

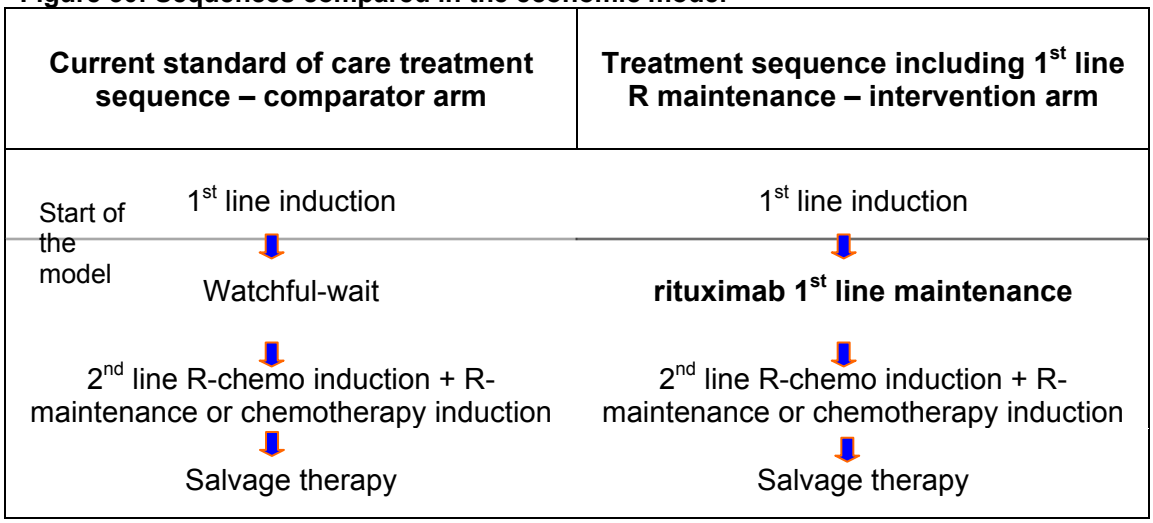
3. Progression (PD) – Patients entering the PD health state from the PF2 state and remain in this state (G) for the remainder of the model's time horizon ultimately transitioning to the death health state. During the time they spend in PD, patients are assumed to receive further salvage therapies as reflected in the post-progression therapies and outcomes of the Van Oers study.

4. Death – This is the absorbing state of the model. Patients can transition in this state from PF1, PF2 or PD. Patients remain in this state for the rest of the model. In this state no further costs or benefits are accrued.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The economic model was designed to capture all life-time costs and benefits involved in the treatment of follicular lymphoma patients following 1st line induction. According to current NICE guidance (TA 110 and TA 137) patients are not treated while in the maintenance phase of the 1st line but are monitored for signs of relapse. This submission assesses whether adding rituximab in the treatment sequence in this stage is a cost effective option for the NHS. Following the maintenance phase patients will eventually relapse and will be treated with R-chemo and R-maintenance. Following relapse in 2nd line patients are assumed to progress and receive salvage therapy. The treatment sequences explored in the cost effectiveness analysis are given below.

Figure 30: Sequences compared in the economic model



Traditionally in cancer, disease progression is modelled with a 3-state model containing a progression-free, a progressive disease and a death state. Given the wealth of evidence for follicular lymphoma patients and current NICE guidance Roche attempted to utilise the majority of evidence with respect to patient clinical outcomes, taken directly from rituximab phase III trials, and derived a 4-state model containing a progression free state (PF1) for patients in progression-free while in 1st line maintenance phase, a progression-free state patients reflecting patients in remission having been treated with 2nd line treatments (PF2), a progressive disease state (PD) and a death state. According to clinical expert opinion the structure of the model adequately describes the current clinical practice and patient pathway and how these may change after the introduction of 1st line maintenance treatment. Given that all evidence utilised to populate the model were taken from relevant rituximab phase III studies the model reflects the natural progression for the intervention of interest.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 88: Key features of analysis

Factor	Chosen values	Justification	Reference

Time horizon	25 years	This ensures that all lifetime costs and benefits of both interventions could be evaluated	In line with TA 110 appraisal of rituximab in 1st line FL
Cycle length	1 month	Common cycle length for oncology economic evaluations. Patients are monitored every 2 months during the maintenance phase. It is unlikely that clinical outcomes could change on a more frequent basis than every month	In line with most oncology economic models
Half-cycle correction	Half cycle correction was used throughout the model	In line with the NICE guide to methods	NICE guide to methods
Were health effects measured in QALYs; if not, what was used?	QALYs	In line with the NICE guide to methods	NICE guide to methods
Discount of 3.5% for utilities and costs	3.5%	In line with the NICE guide to methods	NICE guide to methods
Perspective (NHS/PSS)	NHS/PSS	In line with the NICE guide to methods	NICE guide to methods
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Rituximab maintenance treatment in the PRIMA trial consisted of a single infusion of rituximab at 375 mg/m^2 body surface area given every 2 months until disease progression, unacceptable toxicities for a maximum of two years. The expected license will reflect this dosing regimen. No drug therapy was given to the comparator arm of the study.

Planned average dose per administration of rituximab in the maintenance arm of PRIMA was used. The economic model estimates the cost of drug based on patients in PF1 receiving the full dose (planned dose) including wastage. The average planned dose (including wastage) for the cohort in PRIMA was 690.67 mg per cycle (including wastage) which is marginally to the observed average dose seen in PRIMA (686.72 mg per cycle)

On average, patients received 10.52 cycles of rituximab during the maintenance phase of the PRIMA trial, with 12 being the maximum number of cycles. The observed average number of cycles is less than the planned protocol as a small percentage of patients relapsed while receiving treatment and therefore withdrew from treatment prior to receiving the planned 12 cycles of treatment.

The base-case of the economic model assumes that 88.1% (in the intervention arm) and 80% (in the comparator arm) of patients will receive R-chemo induction followed by R-maintenance. The remaining 11.9% and 19.3% (intervention and comparator arm respectively) of patients will receive chemotherapy induction followed by watchful waiting. All patients will eventually relapse and progress to the PD state (3rd/4th line). R-chemotherapy induction, chemotherapy induction and R-maintenance in 2nd line are assumed to be given according to the licensed dosing.

Table 89: Treatments and posology

Treatment	Dose
R-CHOP (per cycle[v], x6 CHOP, 8x R)	Rituximab 375 mg/m^2 day 1 Cyclophosphamide 750 mg/m^2 day 1 Doxorubicin 50 mg/m^2 day 1 Vincristine 1.4 mg/m^2 (2 mg cap) day 1 Prednisone 100 mg/day days 1-5
R-CVP (per cycle[vi], x8):	Rituximab 375 mg/m^2 day 1 Cyclophosphamide 750 mg/m^2 day 1 Vincristine 1.4 mg/m^2 (2 mg cap) day 1 Prednisone 40 mg/m^2 days 1-5
R-maintenance (per cycle[vii], x8)	Rituximab 375 mg/m^2 day 1

[v] Cycle length 21 days
[vi] Cycle length 21 days
[vii] Cycle length 3 month

6.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Patients continue receiving treatment according to the PRIMA protocol. The base case assumes all patients in PF1 receive the recommended treatment course of 12 cycles unless disease progression occurs before this timepoint.

Monitoring at the time of infusion will ensure that patients will be treated for the duration that they remain disease free (in PF1). Currently monitoring of patients in PFS and PD occurs routinely in the NHS and therefore the addition of maintenance treatment will not add an additional burden for the patients and no additional cost for the NHS.

Patients receiving maintenance treatment in PF2 are assumed to receive the 8 cycles of rituximab monotherapy unless they progress. Again monitoring of patients in this stage of the disease occurs routinely in clinical practice. Monitoring of these patients at the time of rituximab infusion will ensure that therapy is given appropriately to patients that remain disease free.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Clinical data for a various sources were utilised in order to populate the economic model. The primary source of clinical data was the PRIMA study.

Twenty-five months median follow-up from the PRIMA trial showed rituximab, when used as maintenance, doubled the likelihood of people with follicular lymphoma living without their disease worsening compared to those who stopped treatment (based on a hazard ratio of 0.50, 95% CI, 0.39; 0.64; p=<0.0001)[103].

This economic assessment is based on the latest PRIMA dataset (38 months median follow-up, 14th June 2010 snapshot). The Kaplan-Meier estimated median PFS time was based on the median censored time for all patients not experiencing an event (table below).

Table 90: PRIMA study primary endpoint: Progress-free survival (investigator – assessed MITT

PRIMA clinical data cut off date	Observation N = 513 Median PFS	Rituximab N = 505 Median PFS	HR / OR	p-value*	Reported / incorporated into
					EMEA label
14th January 2009	■	■			Salles 2010 Salles planned manuscript

25 months median –follow-up duration			0.50 [0.39;0.64]	p <0.0001	
15th January 2010	[redacted]	[redacted]	[redacted]	[redacted]	
36 months median –follow-up duration					CSR update Salles planned manuscript
Snapshot 14th June 2010* 38 months median –follow-up duration#	[redacted]	[redacted]	[redacted]	[redacted]	Economic valuation

HR: hazard ratio; OR: odds ratio; 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 w ere calculated by using logistic regression (response rate analyses were unadjusted).
*The operational cut-off for data collection was every visit up to and including 15th Jan 2010. The monitoring staff were requested to collect and Source Data Verify every visit that took place up to this date. In turn, Data Management cleaning and Clinical Science review took place on all visits up to this date. Note: A very few visits were entered into the database unintentionally with a visit date after 15th Jan 2010 and the Study Management Team felt uncomfortable having these visits removed. As a result these few post-15th Jan 2010 results appear in the data. The clinical cut-off for the data is set as Snapshot 14th June 2010 and is the date that the data was delivered from Data Management at PPD into the Roche Biometrics environment. This is the date that appears on the tables and listings as cut-off and snapshot date.
#Based on Kaplan Meier

However, given the strong prognosis for this specific patient group and given the primary endpoint of the trial, the data were still not mature enough to show a difference in overall survival (OS). At the time of the analysis, there had been only 30 deaths in the observation arm (n=513; 483 (94.15%) patients censored) and 27 deaths in the rituximab maintenance arm (n= 505; 478 (94.65%) patients censored). As such, OS will require longer follow-up and/or more events to draw meaningful conclusions, although the results obtained so far trend towards favouring the rituximab maintenance arm. It was therefore necessary to utilise data from the 2nd line phase III EORTC 20891 trial to model long-term outcomes of patients leaving the maintenance phase (PF1) of the model.

1. **PRIMA phase III clinical data** (38 months median follow-up, 14th July 2010 snapshot)

a. The latest PFS patient data (median follow-up 38 months, un-published data) from the PRIMA trial were utilised to inform the transition probabilities for patients in PF1. The PFS trial data were extrapolated using a parametric function (further details provided below) for the 2 arms of the study deriving the 2 transition probabilities for observation and R-maintenance.

b. The rate of death observed while patients were in progression free in the PRIMA data trial was utilised in order to inform the monthly probability of dying in PF1. As very few deaths had occurred during the progression free in the PRIMA trial, life-tables for England and Wales have been utilised to inform the rate of death for this state. Background mortality is utilised when the rate of death predicted by extrapolating the PRIMA data is found to be lower than that from predicted by the life-tables.

c. Data from PRIMA demonstrating the percentage of patients that relapse within 1 year of stopping receiving rituximab for both the intervention and comparator arms were utilised to determine the appropriate 2nd line therapy assumption for each patient group.

2. EORTC 20981 phase III clinical data (van Oers et al June 2010[104], 6 year median follow-up)

a. The latest PFS Kaplan-Meier data from the phase III randomised EORTC 20981 trial were utilised to determine the probabilities of progression to PD for patients that (1) receive R-chemo induction followed by R-maintenance (R-chemo-R) or (2)receive chemotherapy induction (both groups were randomised in the trial). A limitation of the EORTC 20981 study is that, because the trial was initiated already in 1998, none of the patients had received rituximab prior to the trial. It has been assumed that the results of R-chemotherapy induction followed by maintenance and chemotherapy induction will be similar in patients who have already received prior treatment with rituximab. Published evidence as discussed below and previous NICE evaluation of rituximab in FL, supports this assumption.

Johnston et al.[105] (2010) conducted a retrospective database analysis investigating the efficacy of retreatment with rituximab with or without chemotherapy in patients with relapsed and refractory B-cell lymphomas. 178 patients that had 2 lines of rituximab therapy were included of whom 29% had diffused large cell B-cell lymphoma (DLBCL) and 28% had follicular lymphoma (FL). The authors report that that there was no statistical difference between PFS in 1st line and 2nd hence rituximab's efficacy is independent of previous rituximab treatment.

Coiffier et al[106] (2002) followed a group of NHL patients who were retreated with rituximab either alone or with chemotherapy. Results showed 93% response to the second course of rituximab. In addition 12 of the 20 patients who progressed after the second rituximab treatment received a 3rd cycle of the drug, and all responded again. It was also found that median time-to-progression (TTP) after rituximab retreatment was longer than that seen after the 1st course of rituximab (although the difference was not statistically significant). The results of the above Coiffier, Johnston studies and other studies[107] can not be utilised to indicate that rituximab retreatment has equal efficacy with rituximab treatment in untreated patients due to selection bias.

NICE has considered this area of uncertainty in the precious technology appraisal of rituximab as a 2nd line treatment in follicular lymphoma. The Appraisal Committee in its consideration of the evidence heard from clinical experts that "the evidence indicated that follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy. Although it noted this as an area of uncertainty, the Committee accepted that this was biologically plausible given its [rituximab's] mechanism of action" (FAD TA 137).

b. The transition probability with which patients die while in PF2 was derived using the rate of death while in PFS from the EORTC trial. Intervention specific transition probabilities were estimated.

c. EORTC data was also used to determine the probability of dying in the PD state although this was not directly captured in the trial. PFS and OS data were combined to estimate the post-progression survival. This was dependent on patient's 2nd line treatment (R-chemo-R or chemotherapy-observation).

d. Data from the 2006 cut-off (49 month median follow; latest data cut-off available to Roche) from the EORTC study were used to inform the post-progression treatments, adverse events and therefore associated costs.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

- Estimating long term Progression Free Survival (PF1)

To estimate future progression free survival (PFS) an extrapolation of the PFS curves from the PRIMA for both R monotherapy and observation arms was performed. A monthly, treatment- and time-dependent probability of remaining within the PF1 health state could then be calculated from these extrapolated curves to populate the Markov model.

Extrapolation of the progression free (PFS) data was carried out under the assumption that the data followed a parametric model structure. The parameters were estimated using patient level clinical data from the PRIMA data (July 14th 2010 data cut). As reported in the CSR and again seen with the 14 June 2010 snapshot, the un-stratified and stratified results were consistent and so the parametric parameters were determined using an un-stratified model [redacted]. The various models were assessed for goodness of fit. The Gompertz function was found to be the best fit to the PFS data. The table below gives the goodness of fit results for PFS for all functions evaluated. There was no indication of differences in the shapes of the treatments and no violation of the underlying assumption of proportional hazards was noted in the diagnostics (e.g. Martingales) plots.

Table 91: Summary of goodness of fit to PRIMA PFS data

Progression Free Survival 1LM Parametric Model	AIC*	BIC*
Exponential	2052.12	2061.98
Gamma	2043.96	2063.66
Gompertz	1956.30	1971.08
Log Logistic	2045.82	2060.60
Log Normal	2042.60	2057.38
Weibull	2055.64	2075.34

* Akaike Information Criteria defined as AIC = $l(\hat{b}) - 2p$ where p is the number of distributional parameters and $l(\hat{b})$ = estimated log likelihood

** Bayesian Information Criteria defined as BIC = $l(\hat{b}) - \frac{p}{2}\log(n)$ where p is the number of distributional parameters, n = number of observations and $l(\hat{b})$ is estimated log likelihood. A smaller value represents a better model fit of the data.

The decision for the Gompertz function was based on the AIC / BIC for PFS and graphical inspection of the fit. The Gompertz survival function is defined as

$$S(t) = \exp\left(\frac{\lambda}{\gamma}\exp(\gamma t - 1)\right)$$

The probability of staying in this health state is determined by the cumulative half-cycle corrected survival probabilities obtained from the Gompertz function for PFS. The table below summarises the Gompertz parameter estimates used to determine the distributions specifying the monthly probability of transitioning from PF1 to by treatment arm.

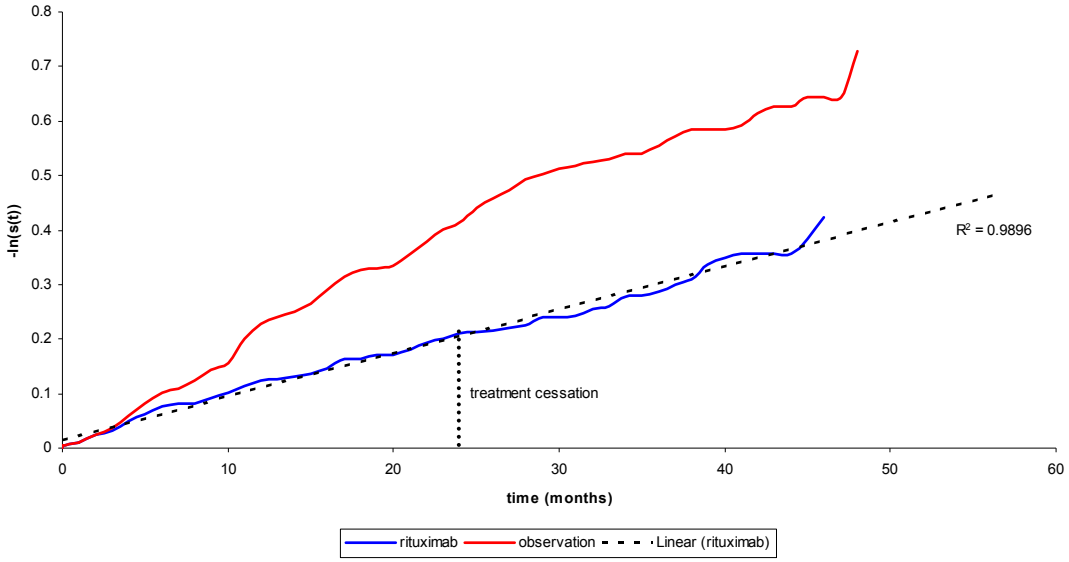
Table 92: Gompertz parameters for PFS (Rituximab vs Observation) in First-line Maintenance

Progression Free Survival (PFS 1LM)	Rituximab	Observation
Lambda (λ)	-0.008256813	-0.015186057
Gamma (γ)	0.0001	0.0001

The figure below represents the Kaplan-Meier PFS curves from PRIMA and extrapolated PFS curves for rituximab maintenance and observation using the Gompertz function (extrapolated curves using the other tested functions are given as an appendix). The impact on the ICERs of using alternative parametric curves was explored in the sensitivity analysis.

Due to the unavailability of data beyond month 48 of the trial the expected treatment effect of rituximab beyond trial follow-up was considered. Although extrapolation of the treatment effect for the duration that patients stay in PF1 was performed, it was considered as an overestimation of the rituximab benefit in 1st line maintenance since patients stop receiving treatment 24 months after initiation. However inspection of the cumulative hazard rate over time shows that the treatment effect is maintained after patients have stopped treatment (figure below; cumulative hazard over time plots of non-rounded, to the nearest month, data are given as appendix).

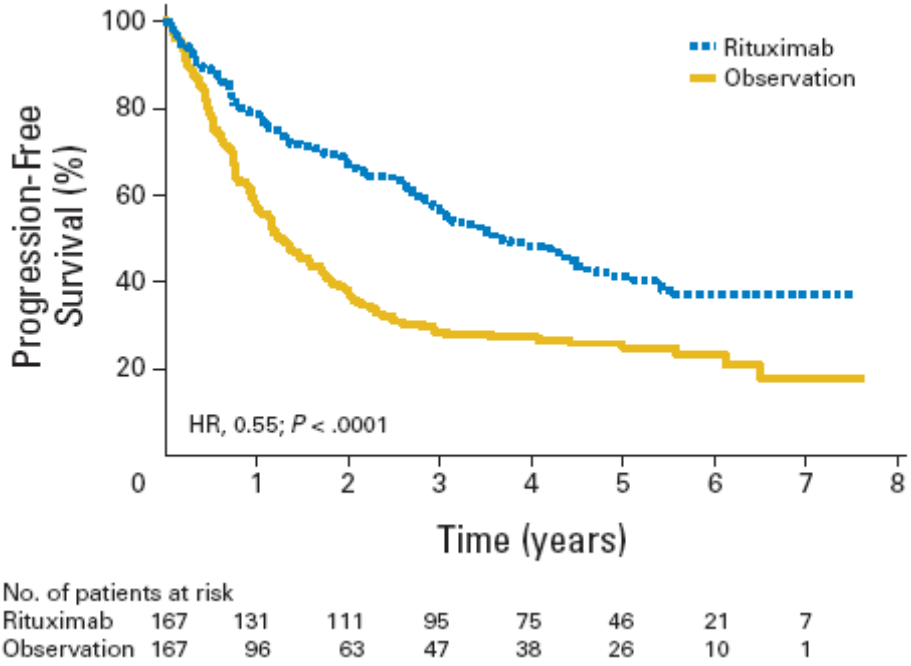
Figure 32: Cumulative hazard rate over time



Expert clinicians participating in a Roche advisory board highlighted that rituximab fundamentally changes the biology and course of the disease. In addition they noted that the treatment effect is maintained after patients have stopped treatment based on their experience in clinical practice since the introduction of rituximab in 2nd line maintenance. The assumption that patients exhibit a treatment effect long after they have stopped treatment is strengthened by the observed data from the latest van Oers study (EORTC 20981 study) and the meta-analysis performed in all rituximab maintenance studies.

The patient level data from the latest follow-up from the EORTC study was not available at the time of submission hence only visual interpretation of the results could be performed. The figures below, showing the PFS Kaplan-Meier curves of patients receiving R-maintenance or observation, suggest that the treatment effect of rituximab rate is continued long after patients have stopped treatment (72 months). Echoing the clinicians' views of the overall effect of rituximab maintenance in terms of changing the disease biology, the observed Kaplan-Meier curves may also suggest that the underlying shape of the 2 curves is different. The figure below shows the true effect of rituximab maintenance (each arm consists of 2 sub-populations; patients induced with R-chemo and patients induced with chemo; The 2 sub-populations were subject to a 2nd randomisation at the start of maintenance phase).

Figure 33: Effect of rituximab maintenance treatment on progression-free survival (PFS) in the EORTC 20981 study. Kaplan-Meier plot of PFS from second random assignment after rituximab maintenance therapy (n: 167) and observation (n: 167)



The data from PRIMA are still at an immature stage and a longer follow-up will demonstrate if rituximab will have the same effect in changing the shape (and therefore the biology of the disease) of the PFS curves in 1st line maintenance.

Taking a conservative approach in the base-case analysis, the extrapolation of the PFS curves (from PRIMA) utilises the same parametric function and the same shape. With respect to the long-term efficacy of rituximab, it is evident that the treatment effect of R-maintenance is sustained beyond treatment cessation. This has been supported by the feedback from the (1)clinical experts on the long-term effect of R-maintenance treated patients, (2)the data from the van Oers study and other studies (meta-analysis performed in studies across different lines) and (3)what is observed in the latest PRIMA data.

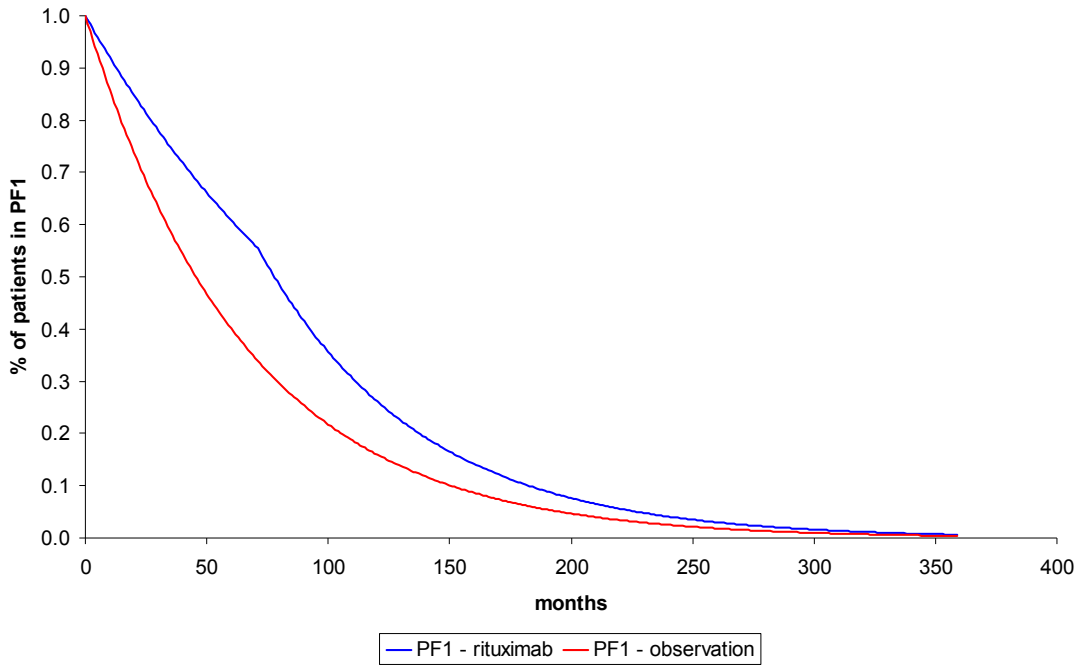
Therefore the van Oers PFS data were utilised as a proxy to determine the assumption of the duration of the rituximab treatment effect. This represents a possible conservative approach as it is assumed that the treatment effect stops at month 72 instead of being sustained for the duration patients receiving R-maintenance remain in PF1. The base-case reflects this assumption and 1st line patients exhibit the rituximab maintenance treatment effect in the first 72 months of

the model only. After this timepoint the risk of progression for patients in PF1 is assumed equal in both arms of the model.

Sensitivity analysis explores the effect on the cost effectiveness when the treatment effect is maintained for the duration the cohort of patients stay in PF1. An additional scenario examines the conservative assumption in which in the 1st line rituximab maintenance arm exhibit the treatment effect only for the duration of time for which follow-up data were reported in the PRIMA trial and a treatment effect is actually observed. In this scenario, after the maximum follow-up period (48 months), patients in the 1st line rituximab maintenance arm have the same risk of progression to PF2 as those not having received any active treatment (observation). This is implemented by applying the same transition probabilities to the rituximab arm as these of the observation arm.

The figure below depicts the modelled curves of progression for the observation and rituximab arms for patients in the PF1 state.

Figure 34: Modelled curves using the Gompertz function for patients in PF1



- Estimating the probability of death from the PF1 state

The number of patients dying is expressed as a monthly rate, rate = Nr. of PF1 patient deaths ÷ PF1 person months. For example, in the rituximab maintenance arm, five observed deaths in PFS were recorded over 16'561.02 person months. This equates to a monthly rate of 0.000301914. The rate is converted to a monthly probability of dying Pr(death| PF 1LM) = 1 – exp(-rate). Acknowledging that the monthly probability of death observed from the study may underestimate the true all cause probability of death due to the low number of observed deaths in the trial and high level of censoring, the probability of death is calculated on a monthly basis by selecting the highest probability of observed deaths in the study or background age and gender adjusted mortality (GAD life tables 2006-08[108]). For example, a patient of age 70 years has a monthly probability of dying (UK background mortality) of 0.17% whereas the observed probability of dying in PF1 is 0.03%. Therefore death while in PF1 for a patient of age 70 years will be based on background mortality.

Table 93: Monthly probability of Death; First-line Progression Free

	Rituximab	Observation
Nr of PFS Deaths	5	3
PFS Person-Months	16561.02	14658.43
Monthly Rate of PFS Deaths	0.000301914	0.00020466

Rates are converted to monthly probability by 1 - exp(-rate)

- Estimating long term Progression Free Survival (2L)

a. Treatment alternatives in 2nd line

Patients progressing from PF1 are assigned to 2 treatment alternatives in 2nd line; R-chemo induction followed by R-maintenance (current NICE guidance) and chemotherapy induction followed by observation. All patients progressing into PF2 are assumed to receive induction with R-chemotherapy apart from those that relapse whilst on or within 1 year of receiving rituximab maintenance treatment. This re-treatment assumption follows NICE guidance which recommends rituximab treatment in the 2nd line induction and maintenance and the current ESMO and BSH guidelines. As previously stated there were 11.9% of patients in the intervention arm of PRIMA that relapsed whilst on therapy or within 1 year of receiving the last dose of rituximab maintenance (cumulative relapsed patient number up to month 36 post randomisation). 80.7% of patients relapsed within 1 year of rituximab therapy in the

comparator (cumulative relapsed patient number up to month 12 post randomisation).

Patients are assumed to be treated in the 1st cycle of PF2 with either R-chemo or chemotherapy. Although all patients incur the cost (one-off) of induction in the model, **no additional benefit** is accrued. Following induction in 2nd line, the base-case analysis model assigns patients to either the rituximab maintenance arm (2L) or observation.

Table 94: Proportion of patients receiving the 2 alternative treatments in 2nd line

	R-CHOP 2nd line induction and R-maintenance	CHOP 2nd line induction followed by observation
Rituximab (1LM) – intervention arm	88.1%	11.9%
Observation (1LM) – comparator arm	80.7%	19.3%

A number of patients observed in the PRIMA study progressed within 12 months of rituximab maintenance therapy (table below) and were thus ineligible for second-line induction with the same chemotherapy, CHOP (ESMO clinical practice guidelines (Dreyling 2010)) and will receive alternative induction with CVP backbone. This only affects the costing of the 2nd line induction. It has been assumed that patient outcomes during the maintenance phase of the 2nd line is not confounded by the choice of induction chemotherapy backbone when combined with rituximab.

Table 95: Percentage of PRIMA patients not eligible for 2nd line induction with R-CHOP

Induction (1L)	Rituximab	Observation
R-CHOP	7.327%	12.671%
R-CVP	4.158%	5.848%
R-FCM	0.396%	0.780%

- Estimating long term post-PF1 survival

b. Overall survival (OS) data from PRIMA insufficient to derive long term outcomes of patients leaving the PF1 state

Due to extensive censoring in the overall survival data in PRIMA, (June 14th 2010 cut-off) [redacted] in the rituximab and observation arms respectively (figure below), the probability of post–progression and overall survival were obtained

from the EORTC 20981 trial (72 month median follow-up). The following section (c) describes how the EORTC data were utilised and implemented in the model.

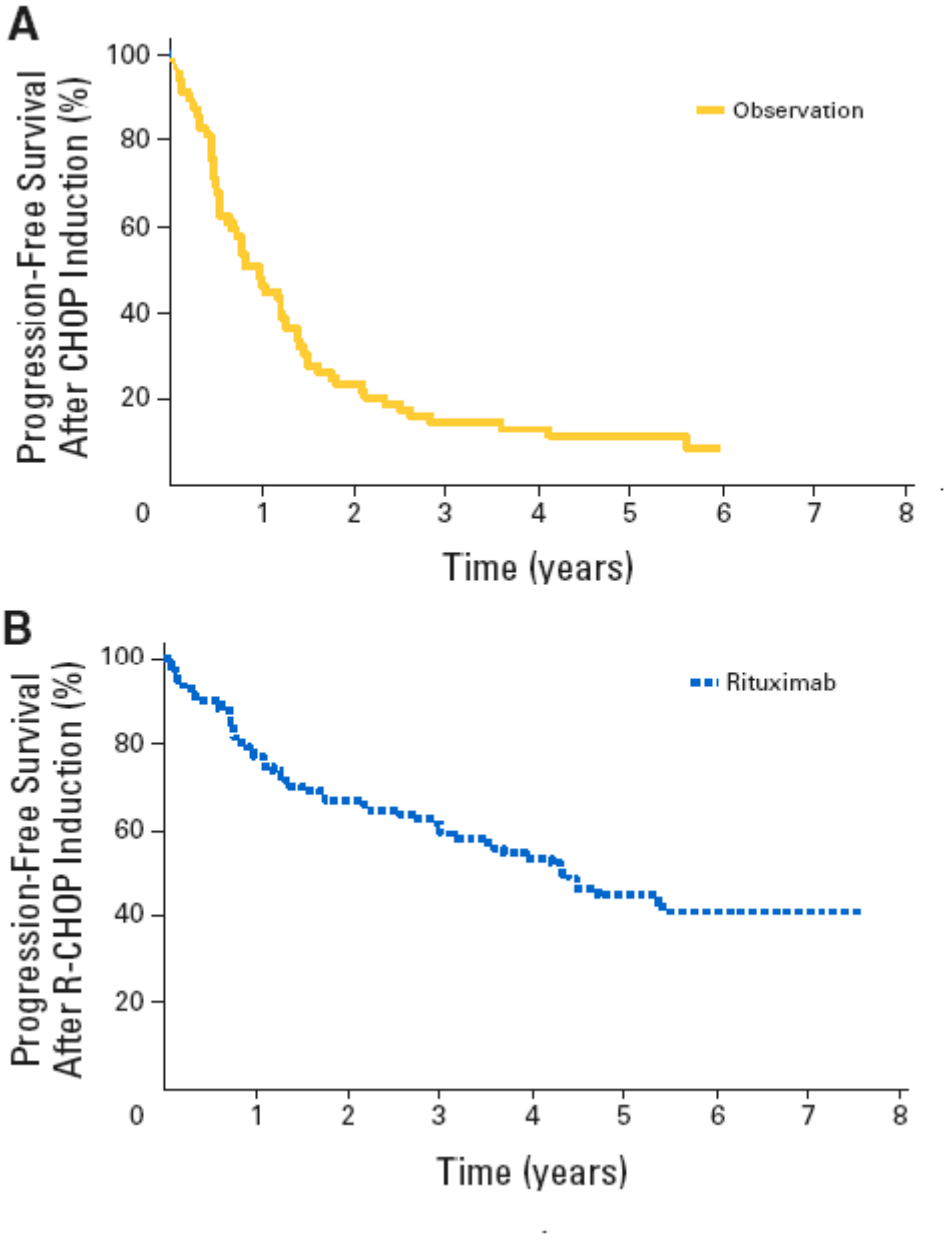
c. Estimating the transition from PF2 health state to PD health state

Data from the EORTC 20981 study were utilised to inform the long-term outcomes of patients according to the treatment they receive in 2nd line (induction and maintenance). There is no direct of linkage between the PRIMA and EORTC trials. However, there is a body of evidence to support that a long remission after 1st line therapy predicts a better response to subsequent therapies and a longer survival[109,110,111].

The rate of progression to PD (progressive disease) from 2nd line seen in the 72 month median follow-up data (van Oers June 2010) was calculated for the 2 assumed regimens. Progression free survival by second-line induction and maintenance (R-CHOP to Rituximab and CHOP to Observation) were modelled using ordinary least squares (OLS) to obtain an estimate of the probability of transitioning from PF2 to progression (third-line; salvage therapies). As the patient level data for the longest follow up of the Van Oers study was not a available to

Roche, the graphs (figures below) from the publication were digitized using TechDig software to enable analysis and extrapolation as required, digitised.

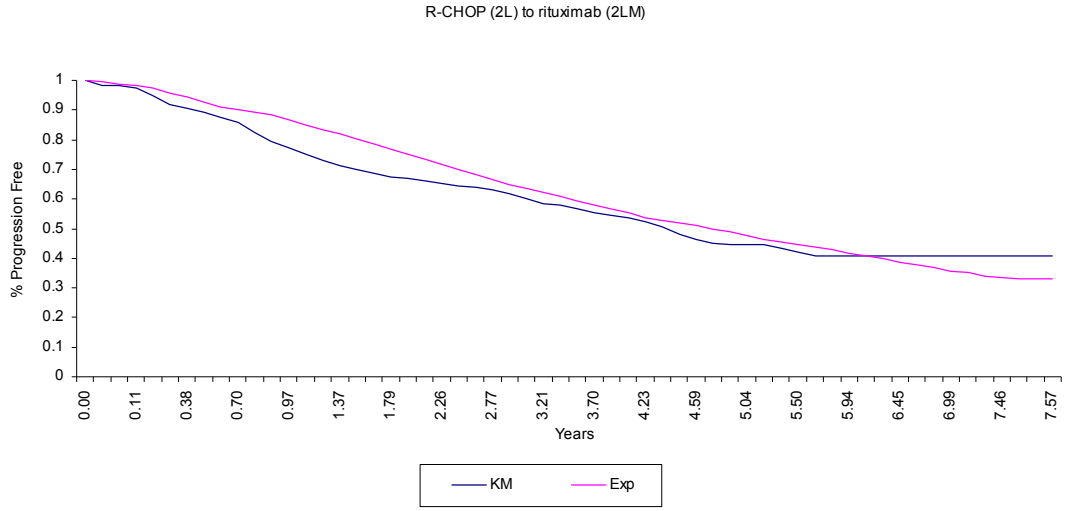
Figure 36: PFS after induction (van Oers et al. June 2010)



The monthly transition probabilities were then derived from the OLS generated overall intercepts and time estimates. The ability of these estimates to predict the outcome was assessed graphically by overlaying the parametric curve (exponential) onto the Van Oers Kaplan-Meier curves (figures below); goodness of fit could not be formally assessed due to not having the patient-level data. The fitting of exponential function on the digitised data does not provide an exact fit but this has a limited

impact on the cost effectiveness of rituximab in 1st line maintenance as the rates derived from the fitting are applied in both the comparator and intervention arms. Parameter uncertainty was included in the probabilistic sensitivity analysis. Distributions and parameter ranges are given in the sensitivity analysis section below.

Figure 37: Kaplan-Meier curve from the EORTC R-CHOP-R arm and exponential fitted curve representing the rate of progression to PD in PF2 for patients receiving the regimen



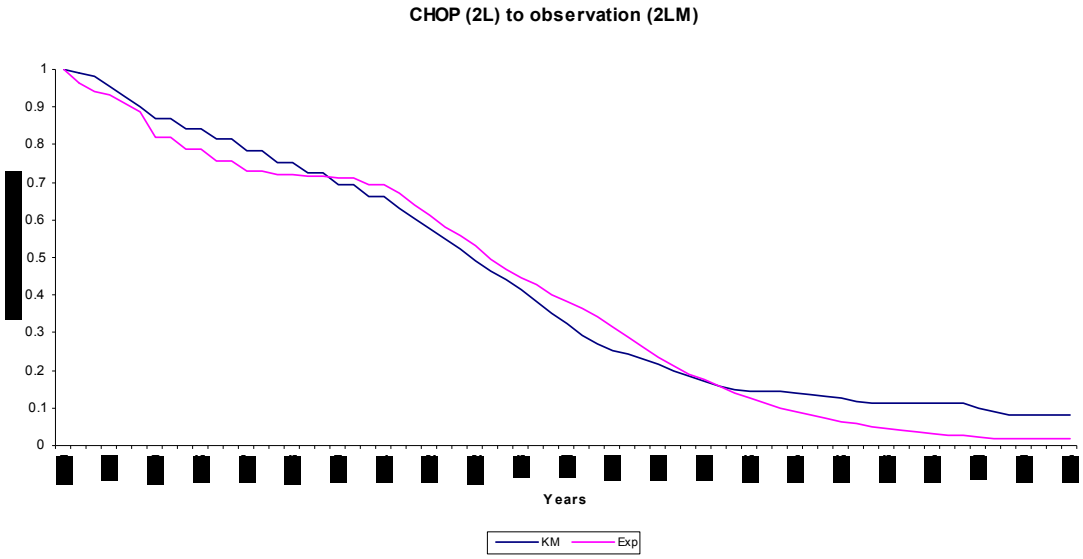
Regression Statistics

Multiple R	0.974
R Square	0.948
Adjusted R Square	0.948
Standard Error	0.070
Observations	58.000

ANOVA statistics

	Df	*SS*	*MS*	*F*	*Significance F*	
Regression	1.000	5.090	5.090	1031.135	0.000	
Residual	56.000	0.276	0.005			
Total	57.000	5.367				
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.115	0.016	7.069	0.000	0.083	0.148
X Variable 1	0.122	0.004	32.111	0.000	0.114	0.129

Figure 38: Kaplan-Meier curve from the EORTC CHOP-observation arm and exponential fitted curve representing the rate of progression to PD in PF2 for patients receiving the regimen



Regression Statistics

Multiple R	0.958044
R Square	0.917848
Adjusted R Square	0.916585
Standard Error	0.251351
Observations	67

ANOVA statistics

	Df	*SS*	*MS*	*F*	*Significance F*	
Regression	1	45.88082	45.88082	726.2204	0.000	
Residual	65	4.10654	0.063178			
Total	66	49.98736				
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	0.259469	0.046039	5.635843	4.05E-07	0.167523	0.351416
X Variable1	0.42062	0.015608	26.94848	5.46E-37	0.389448	0.451792

Based upon the above exponential functions, the transition probability of progressing from PF2 to PD for patients receiving R-CHOP (2L) and rituximab in 2nd line maintenance was calculated to be 0.0195 per month. The transition probability of progressing for patients receiving CHOP followed by observation was calculated to be 0.0551 per month. The rates were applied in the model for the two 2nd line treatment regimens independently of the treatment patients received in 1st line maintenance.

Table 96: Second line transition probabilities (per month)

	2nd line maintenance treatment	
1st line maintenance treatment	rituximab	observation
Rituximab	0.0195	0.0551
Observation	0.0195	0.0551

In order to avoid overcomplicating the model, the transition probabilities of progressing from PF2 were not varied over time. Varying the probabilities over time would require tracking patients' progression within the model and would result in an exponential increase of the size and complexity of the model with limited impact to the cost effectiveness of rituximab in 1st line maintenance. The same transition probabilities are utilised in the 2 arms (intervention and comparator) of the model and therefore the impact of simplifying the progression rates in 2nd line is minimised.

- Estimating the transition rate from **PF2 to death**

The monthly probability of dying in PF2 [Pr(Death|PF2)] (table below), was calculated in the same manner as in first-line PFS. In this case the rate of dying was based on the observed deaths in PFS in the EORTC 20981 study (49 month median follow) [patient level data was only available for this clinical cut-off]. The monthly probability of dying is given in the table below

Table 97: Monthly probability of Death; Second-line Progression Free (PF2)

	Rituximab	Observation
Nr of PFS Deaths	7	3
PFS Person-Months	5911.2	3804.7
Monthly Rate of PFS Deaths	0.0012	0.0008

Rates are converted to monthly probability by 1 - exp(-rate)

- Estimating the transition rate from **progressive disease to death**

Given that rituximab is clinically beneficial as observed in the PRIMA and EORTC 20891 studies then one can expect the risk of progressing from PF2 to PD to be less than the risk of dying in PD. Given that overall survival (OS) can be expressed as

the time spent in progression free and the time spent in progression (PD = OS - PFS) then the risk of dying in OS should be greater than or minimally equal to the risk of progressing while in PF2 given the terminal nature of this disease. In the absence of bridging studies where the risk of death in the progressive state is either known or can be calculated for previously 1st and 2nd line rituximab treated patients, the risk of dying for the progressive state was calculated as the additive risk of progressing in PF2 and OS; Risk of Death in PD (PPS) = Risk of death in OS + Risk of progressing from PF2.

The rate of progression from PD to death was estimated using the digitised PFS and OS data from the EORTC study (figures below).

Figure 39: PFS of patients in the EORTC trial (patients on rituximab 2LM or observation post 2nd randomisation)

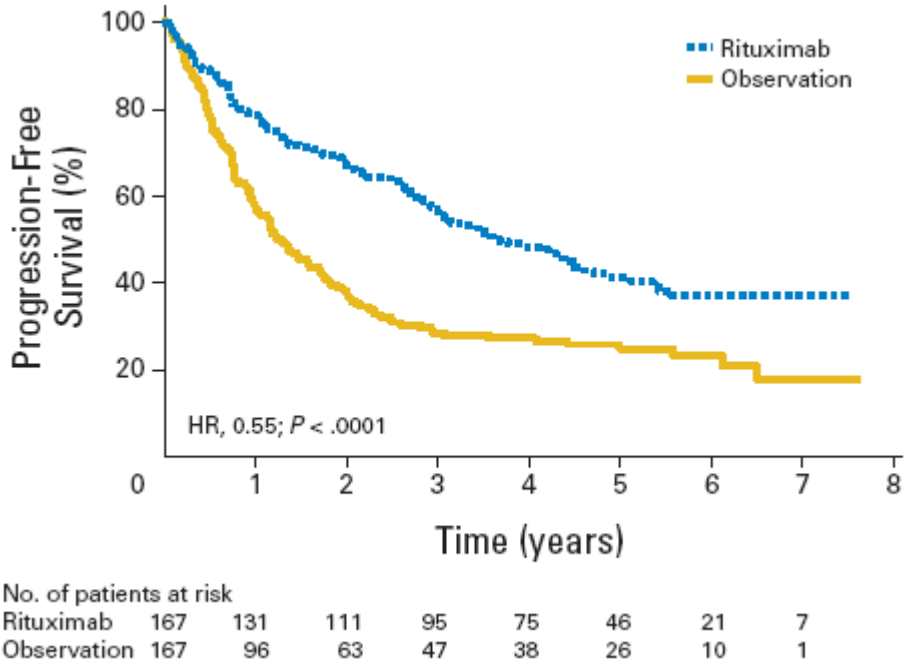
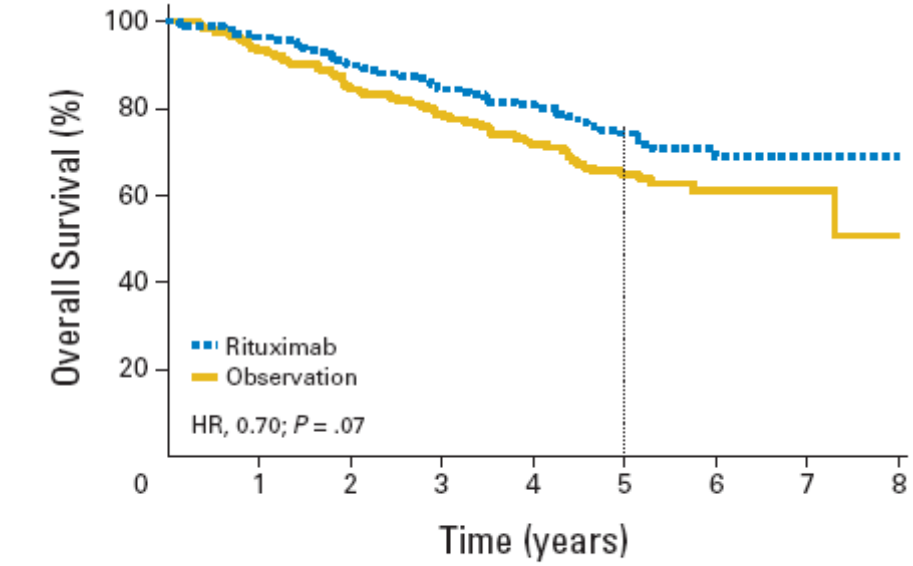


Figure 40: OS of patients in the EORTC trial (patients on rituximab 2LM or observation post 2nd randomisation)



No. of patients at risk

Rituximab	167	161	150	141	124	86	44	13
Observation	167	155	139	128	104	67	28	9

In an attempt to credibly estimate the transition from PD to death (PPS) data from the sub-analysis according to maintenance regimen from the van Oers study were utilised. PPS KM curves were not available from the publication and therefore it was assumed that the transition probability of dying while in PD is a function of the PFS and the OS rates. The above PFS and OS curves were digitised and the -log(s(t)) were fitted using OLS. The derived intercept and coefficients of the 2 curves were summed, assuming an underlying exponential model, to give an overall rate of progression to death. The derived PPS models for patients receiving R 2LM or observation are shown in the figures below.

Figure 41: Kaplan-Meier and exponentially fitted curves for PFS and OS in the observation arm of the EORTC study. Derived post-progression survival (PPS) is shown with the dotted line

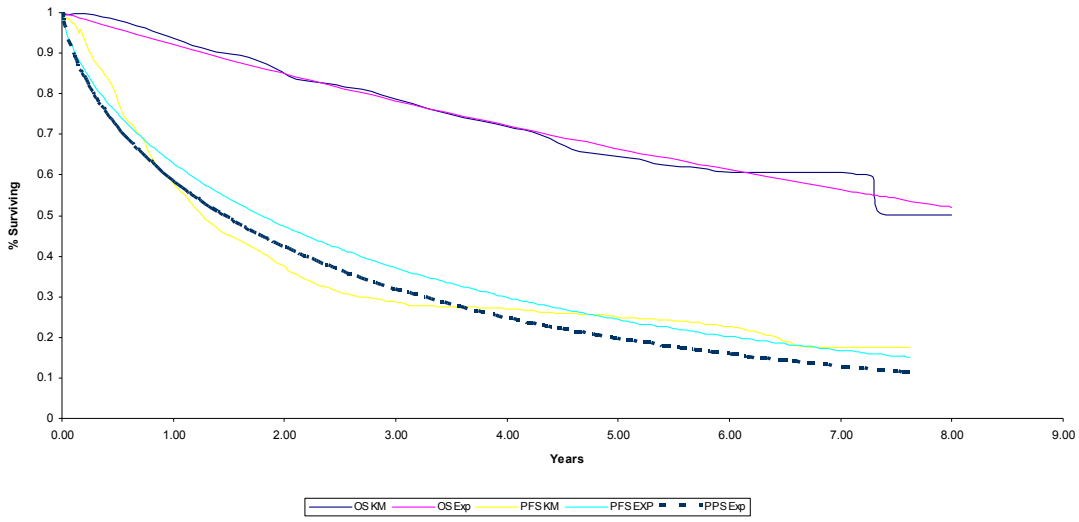
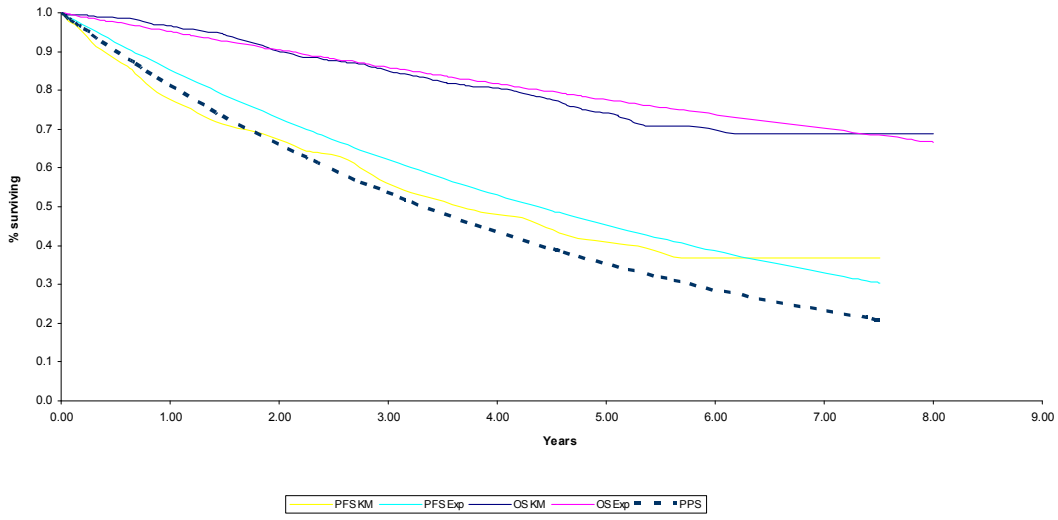


Figure 42: Kaplan-Meier and exponentially fitted curves for PFS and OS in the rituximab arm of the EORTC study. Derived post-progression survival (PPS) is shown with the dotted line



The derived PPS rate to death for patients receiving rituximab 2LM was 0.0222. The PPS transition probability not receiving any treatment in 2LM was 0.0500. These rates were equally applied in both the intervention and comparator arm of the analysis.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no evidence that transition probabilities in the 1st line maintenance phase of the model vary over time. The cumulative hazard plots explored above show a linear rate of increase for both observation and rituximab in PF1.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcomes were used. All benefit is generated from patients staying in either one of the PFS states (PF1 or PF2) and the progressed state (PD).

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[viii]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

[viii] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical expert opinion was sought to assessed the applicability of the available or estimated values.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 98: Summary of variables applied in the economic model

Variable	Value	Min and Max
Average age of cohort	55.5 years	22-84 years
Body weight	74.04 Kg	34-143 KG
Height	168.54 cm	140.0-197.0 cm
BSA (body surface area)	1.835	1.19-2.67 m^2

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In

particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Follicular lymphoma (FL) has a long term progression with survival rates long exceeding the time frame of the main clinical trials (median OS from diagnosis is about 6-10 years[112]). Therefore in order to estimate clinical outcomes and the resulting costs beyond the follow-up of the PRIMA trial modelling was required. Both clinical outcomes and costs were extrapolated beyond the latest trial follow-up.

With respect to clinical outcomes while patients remain in PF1, data were utilised from the PRIMA trial. KM plots (with data from the latest cut-off) were fitted with a range of parametric models (see section 6.3.2 above fo a full explanation of the methods involved) and the Gompertz function was chosen as the best fit of the data in PF1. Given the evidence from other rituximab maintenance studies and the results from the meta-analysis it was assumed that the treatment benefit is sustained for 72 months post treatment initiation. Beyond that point patients on the treatment arm have the same probability of progression to PF2 as patients in the observation arm.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients with active FL may present with multiple sites of lymphadenopathy and/or bone marrow disease [advanced-stage disease (III/IV)]. This may manifest itself with B symptoms such as fatigue, weight loss, fever and night sweats. Restricted movement, cosmetic disfigurement, compressive symptoms and pain may also occur due to enlarged lymph nodes. Treatment generally attempts to control rather than cure the disease and improve patient's quality of life by eliminating debilitating symptoms. In a recent publication in which 761 lymphoma survivors in the US were asked to complete a range or quality of life and health status questionnaires, being disease free was shown to significantly improve both physical and mental health[i]. With specific reference to follicular lymphoma, Pettengell and colleagues recently reported that patients who have relapsed are more likely to experience worse HRQoL and other patient-reported health outcomes than patients newly diagnosed, in partial or complete remission or when completely disease free[ii]. Of note, this paper reported no significant difference in HRQoL in newly diagnosed FL patients who were on "watch and wait" compared to those who were being actively treated. This paper concluded that it is the patient's disease status that had the greatest impact on patient-reported health outcomes and that prolonging a patient's status quo as

disease free (i.e. prolonging the time to treatment failure either by more intense induction or by maintenance treatment) is important in terms of improving HRQoL.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

The course of progressive follicular lymphoma is typified by sequential remissions and relapses, disease dissemination, and eventual resistance to current treatment approaches. There is a paucity of relevant literature and research on the quality of life of patients over the course of their disease, however, based on the paper by Pettengell and colleagues it would seem likely that each time a patients relapses they are likely to experience a worse HRQoL[90]. Issues such as uncertainty (especially in relation to relapse), perceived lack of control, feelings of dependency, anxiety and depression are also important in a recurrent cancer such as FL.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

EQ-5D was not collected as part of the trial protocol. HRQoL data was collected in the PRIMA trial in the form of the QLQ-C30 and FACT-G questionnaire. The graph below shows that no significant differences in quality of life were observed between the observation and treatment arms of the PRIMA trial (January 2010 follow-up). The data collected in the trial are inconsistent with NICE's reference case and therefore have been not been utilised in the model and the cost effectiveness analysis. Instead, published resources (see section 6.4.5) and assumptions were used to inform the health state utilities of the model. The figures below show the top-line results from the analysis of the FACT-G and EORTC QLQ-C30 data respectively. A

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was used.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic review was conducted to identify quality of life studies relevant to rituximab as a maintenance treatment in follicular lymphoma. Standard quality-of-life search filters were applied to the disease area search terms detailed previously. The inclusion and exclusion criteria were designed to identify all quality of life studies and particularly studies assessing a preference based measure of quality-of-life, either generic or valued in a separate study with appropriate methods (i.e. standard gamble or time trade off) or a non-preference quality-of-life measures (specifically, SF-12 or SF-36). Details of the search strategies are presented in section 9.12, appendix 12.

The systematic review identified 143 studies in total and eight potentially relevant studies. Only one of the identified studies met the criteria to be included in this submission (Pettengell et al., 2008[113]). The remaining seven studies were excluded for the following reasons: three studies did not address the relevant population (Cheung et al., 2009[114], Witzens-Harig et al., 2009[115], Witzens-Harig et al., 2007[116]); two studies reported no relevant outcome (Walker et al., 2009[117], Aviles et al., 2004[118]); and there was no relevant comparator in two studies (D'Amore et al., 2008[119], Vitolo et al., 2008[120]) see table below.

Additional searches were undertaken to identify mapping techniques for preference based utility indices; three studies were identified in these additional searches. One of these three studies was a duplicate (Cheung et al., 2009). The other two studies of these additional searches have been excluded on the basis of recruiting an inappropriate population (Wu et al., 2007[121], Dobrez et al., 2007[122]) see table below.

Table 100: Excluded HRQL studies

Citation	Reason for exclusion
Cheung et al., 2009	not relevant study population: refractory/relapsed patients

Witzens-Harig et al., 2009	not relevant study population: refractory/relapsed patients
Witzens-Harig et al., 2007	not relevant study population: refractory/relapsed patients
Walker et al., 2009	No relevant outcome: SF-36
Aviles et al., 2004	No relevant outcome: patient care monitor survey
D'Amore et al., 2008	No relevant comparator: 90Y-ibritumomab tiuxetan
Vitolo et al., 2008	No relevant comparator: 90Y-ibritumomab tiuxetan
Wu et al., 2007	not relevant study population: metastatic hormone-refractory prostate cancer patients
Dobrez et al., 2007	not relevant study population: not relevant type of cancer

Details of the included study are provided in the following section.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.

- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Data from the single included study were identified from two sources by the systematic review; a full paper (Pettengell et al., 2008) and an ISPOR poster citation (Wild et al., 2006[123]). Further details of the poster were available in an unpublished report provided by the manufacturer (Wild et al., 2006). The published study (Pettengell et al., 2008) reports outcomes from the same study population (i.e. from the same clinical trial) as the unpublished report. In this unpublished study, EQ-5D and FACT-LYM were used as methods to identify utilities. The study has previously been referenced by Roche in TA110 and TA137.

Details of the Pettengell, 2008/Wild, 2006 study:

The data set included 222 patients, aged ≥ 18 years with histologically confirmed follicular lymphoma and an ECOG performance status of 0 to 2. Patients were recruited from eight UK sites. The objective of the study was to calculate utilities and HRQoL and consequently, treatment plans and the occurrence of adverse events were not reported. Health states were divided into five groups:

· Active disease: newly diagnosed

· Active disease relapsed

· Partial response to therapy

· Complete response to therapy/remission

· Disease free (no detectable diseases)

These health states were considered appropriate, considering normal treatment pathways and possible disease stages for patients with follicular lymphoma.

Utilities were elicited from patients using EQ-5D questionnaire and results were presented both for utility values calculated using the York tariff and for those recorded using the EQ-5D Visual Analogue Scale (VAS). In addition to completing the EQ-5D, patients also filled in a variety of other outcome measures (Function Assessment of Chronic Illness Therapy-general, FACT-G, and a 15-item lymphoma-specific additional concerns subscale, LYM) and also supplied demographic information.

Of the 222 returned case report forms, 215 participants responded by returning completed EQ-5D questionnaires and 218 by returning complete VAS data. FACT-G data were added to LYM data to calculate FACT-LYM scores. Between-group differences were investigated using the Kruskal-Wallis H-test or Mann-Whitney (for on or off chemotherapy). Ordinary least-square regression analysis was performed to check for the impact of external confounding factors and to enhance the power of the estimation procedure (by estimating variation by disease state). The 'active disease – newly diagnosed' group acted as reference variable. Results were presented with confidence intervals. The table below presents the utility values for each disease stage. The study has been used for a cost-effectiveness analysis in the previously mentioned appraisals, approved by NICE (Wild et al., 2006, Pettengell et al., 2008).

Table 101 Utility values for each disease stage

Disease state	N	Mean (SD)/[SE]	Range	
			Minimum	Maximum
Active disease – Newly diagnosed	50	0.83 (0.22)[0.03]	-0.24	1.00
Active disease – Relapsed	33	0.62 (0.32)[0.06]	-0.08	1.00
Partial response to therapy	39	0.77 (0.21)[0.03]	0.02	1.00
Remission/Full response to therapy	66	0.79 (0.23)[0.03]	-0.08	1.00
Disease free	27	0.88 (0.15)[0.03]	0.49	1.00

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No EQ-5D data was collected in the PRIMA trial and therefore no comparison to the literature reported values could be performed.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

According to the data collected in the PRIMA trial in the form of EORTC QLQ-C30 disease specific questionnaire treatment does not affect patients' quality of life. Adverse events with rituximab are often transient and non-symptomatic.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 102: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
PF1	0.88	(0.81, 0.95)	Section 6.4.6	Published utility value (Pettengell et al 2008)
PF2	0.79	(0.72, 0.86)	Section 6.4.6	Published utility value (Pettengell et al 2008)
Progressive disease	0.62	(0.48, 0.76)	Section 6.4.6	Published utility value (Pettengell et al 2008)

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical expert opinion was sought with respect to HRQoL values

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patient experience is described in section 6.4.1 Regarding potential variation, this is addressed in section 6.4.14 below.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

All health effects identified in the literature have been taken into account. Health effects from the trial were not collected in the form of the EQ-5D utilities and therefore the results are inconsistent with the NICE reference case.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life has been assumed to be the same in both arms of the economic evaluation.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

It has been assumed that HRQoL remains constant for the duration patients stay in each health state. The point estimates of the utilties derived from the utility study represent a mid-point of the utility for that health state. No evidence has been found to suggest that HRQoL change over time within each health state.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

HRQoL data were not collected in the clinical trial. The values informing the health states have been sourced from the available literature.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

1. Cost of administering rituximab.

The cost of administering rituximab was taken from the most NHS reference cost scheedule. The most appropriate reference cost for the administration of rituximab in this setting was found to be described by the daycase tariff SB15Z[124] "Deliver subsequent elements of a Chemotherapy cycle" (Chemotherapy Delivery: Daycase and Regular Day / Night). The associated cost for tariff was £251.4 per infusion. No haematology specific tariff was identified.

The additional cost of preparing rituximab for infusion was taken from the Unit costs of health and social care (PSSRU 2009[125]). It has been assumed that it will take one hour for a qualified pharmacist to prepare the infusion. This will add an additional cost of £32 for each administration of rituximab.

No administration cost was associated with the comparator arm as this does not include any drug therapy.

2. Supportive care costs

Roche commissioned a costing study to identify the resources involved in the current clinical practice for treating follicular lymphoma patients. Tolley Health Economics

held an advisory board with UK clinical experts and follow-up semi-constructed interviews to develop further understanding in the treatment pathway and obtain details on the extent of resource use.

It was clear from the expert consultation that clinical practice is variable across treatment centres but consistency was found in core aspects.

(a) Current clinical practice involves no drug therapy for patients that have successfully responded to 1st line immunochemotherapy

(b) Clinical experts considered that resource use will not change from the introduction of 1st line maintenance

Experts agreed that resource of 1st line patients in either the R-maintenance phase or observation/watchful waiting post induction therapy will be the same and will involve the following costs. The table below provides details on the costs involved in current clinical practise.

Figure 45: Resource use and costs for surveillance during first- line R 1st line maintenance treatment and observation phase

Items	Total Resource use estimates for phase	Average monthly resource use	Estimated per month cost £**
Hospital clinic visits			
Haematologist led	12	0.5	£65.50
Tests/investigations			
CT scans	1	0.008*	£1.31
FBC, patient history, physical exam	12	0.5	£3.50
Immunoglobulin tests, LFT, U & E lactate dehydrogenase.	6	0.25	£5.00
TOTAL			£75.31

All unit costs used for items in this table are from the NHS reference costs 2008-09
* Based on an assumption that 20% of patients receive a CT scan

The table below provides details and references on the selected costs.

Table 103: Unit costs applied from NHS reference costs 2008-09

Resource	Unit cost	Definition/Source

	£	
Hospital clinic visit with haematologist	131	Code: 303 – Clinical haematology Consultant Led: Follow up Attendance Non-Admitted Face to Face.
Hospital clinic visit with junior doctor/specialist nurse	83	Code: 303 – Clinical haematology Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face.
CT Scan	157	Code: RA14Z – CT scan, more than 3 areas.
Full blood count	3	Code: DAP823 – Haematology (exc. Anticoagulant services)
Patient history/physical exam	4	Code: DAP842-Other pathology service
Liver function test	4	Code: DAP842-Other pathology service
Urea & Electrolytes	4	Code: DAP842-Other pathology service
Immunoglobulin	8	Code DAP830-Immunology.
Bone marrow biopsy	26	Code: DAP824: Histology/histopathology
Lactate dehydrogenate test	4	Code: DAP842-Other pathology service
HIV serology	3	Code: DAP823 – Haematology (exc. Anticoagulant services)
Hepatitis serology	3	Code: DAP823 – Haematology (exc. Anticoagulant services)

(i) PF1 supportive care costs

The average cost for surveillance during maintenance in PF1 was calculated 3 phases; years 1-2, years 3-4 and year 5. The tables below summarises the medical resource utilisation and costs involved during the 3 phases of PF1.

Table 104: Resource use and costs for surveillance during first- line R-maintenance treatment phase

Items	Total Resource use estimates for phase	Average monthly resource use	Estimated per month cost £*	Total cost over time period £
YEAR 1-2 (12 months)				
Hospital clinic visits				
Haematologist led	8	0.33	£43.67	£1,048
Tests/investigations				
CT scans	0	0	£0.00	£0.00
FBC, patient history, physical exam	8	0.33	£3.00	£72.00
Immunoglobulin tests, LFT, U & E lactate dehydrogenase.	4	0.17	£3.33	£80.00
TOTAL			**£49.33**	**£1,184**

YEAR 3-4 (24 months)				
Hospital clinic visits				
Haematologist led	6	0.25	£32.75	£786
Tests/investigations				£157
CT scans	1	0.04	£6.54	
FBC, patient history, physical exam	6	0.25	2.25	£54
Immunoglobulin tests, LFT, U & E lactate dehydrogenase.	3	0.13	2.50	£60
TOTAL			**£43.54**	**£1,045**
YEAR 5 (12 months)				
Hospital clinic visits				
Haematologist led	2	0.17	£21.83	£262
Tests/investigations				
CT scans	0	0	£0.00	£0.00
FBC, patient history, physical exam	2	0.17	£1.50	£18.00
Immunoglobulin tests, , LFT, U & E lactate dehydrogenase.	1	0.08	£1.67	£20.00
TOTAL			**£24.67**	**£296.00**
TOTAL over whole 5 years			**£42.08**	**£2,525.00**

The average cost of £42.08 per month was used as an input in the model in order to inform the supportive care costs involved in PF1. The average supportive care cost was assumed to be the same in both arms. One-way sensitivity analysis altering this cost by +/- 50% was assessed in DSA.

(ii) PF2 supportive care costs

The average cost for surveillance during PF2 was calculated based on assumed duration for an average duration of 6 years. (4.5 mos of 2nd line induction, 24 mos of maintenance, 30 months of remission). The tables below summarises the medical resource utilisation and costs involved during the PF1. One-way sensitivity analysis altering this cost by +/- 50% was assessed in DSA.

Table 105: Resource use and costs for progressive disease state

Resource item	Estimated per month cost £*
Clinic visits, tests and investigations during treatment	£57.82
SCT	£52.09
Surveillance: clinic visits, tests and investigations during follow-up	£27.13
TOTAL PD cost	**£137.04**

*Based on duration of 58.5 months (4.5 months R-CHOP, 24 months R-mtce, 30 months remission to relapse)

(iii) PD supportive care costs

The management of progressive disease and the associated costs could not be accurately defined hence 2 sources of information were used; (a)Literature reporting associated costs for palliative care and (b)costs associated with 3rd line treatments observed in the EORTC 20981 trial.

a. Of the studies reviewed, the estimate by Ward et al.[126] (2004) was considered the most appropriate, as it was produced to support NICE clinical guidance on cancer palliative/supportive care, and is the most recent study. This primarily covers the costs of support provided by specialist hospital/community palliative care teams, including hospice type care, day care, hospital inpatient/outpatient support, bereavement services and continuous support for dying patients. Ward et al reported a cost per cancer death of £3,236, which uprated to 2008 values using HCHS pay and prices index is £4,077. This nominal cost has been divided by average time patients spend in PD predicted by the economic model (16 months) to result in a monthly cost of £284.81.

b. Post-progression treatment patient level data from the EORTC study were used to determine the average cost of treatments in this setting. However, only patient numbers were collected and not dosage information for each therapy. Therefore those therapies representing resources used by more than 2% of the patient population were costed by utilising standard doses for each therapy of interest and applying unit costs from BNF 57. The average patient

cost for 3rd-line treatment was £3,931. In order to include a monthly figure into the cost of supportive care in the progressed state, this value was divided by the average months spent in the progression state (as predicted by the model) between the R-maintenance and comparator arms (16 months). This resulted in a monthly cost applied to the progressed state of £245.7.

Based on the above information the total average monthly cost for patients in the PD state was £500.53. Uncertainty in the cost of supportive care is assessed with one-way sensitivity analysis and PSA.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs 2008-09 provide enough granularity and can be applied to determine the cost of medical resource utilisation in the treatment of follicular lymphoma patients.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study

- costs for use in economic analysis
- technology costs.

No specific searches were undertaken. Relevant studies were identified from the systematic review of cost-effectiveness studies (see section 6.1.1).

Nine studies were identified in the systematic review. Six studies reported data from other countries than the UK (Van Agthoven et al., 2005[127], Tomas et al., 2009[128], Herold et al., 2002[129], Schmitz et al., 2006[130], Gleeson et al., 2008[131], Gruschkus et al., 2009[132]). These studies were excluded, because UK-specific data was also available. Two studies were excluded for not reporting data from the relevant population (Pettengell and Ryan, 2008[133], Hutchinson et al., 2006[134]). The remaining UK study is considered to be out-dated (published more than 10 years ago) (Tolley et al., 1998[135]) see Table 106.

Table 106: Reasons for exclusion of resource studies

Citation	Reason for exclusion
Van Agthoven et al., 2005	not relevant country/perspective: the Netherlands
Tomas et al., 2009	not relevant country/perspective: Spain
Herold et al., 2002	not relevant country/perspective: Canada, Germany and Italy
Schmitz et al., 2006	not relevant country/perspective: Germany
Gleeson et al., 2008	not relevant country/perspective: United States
Gruschkus et al., 2009	not relevant country/perspective: United States
Pettengell and Ryan, 2008	not relevant study population: refractory/relapsed patients
Hutchinson et al., 2006	not relevant study population: refractory/relapsed patients
Tolley et al., 1998	Outdated: published in 1998

Relevant recent UK-specific data are now available from a costing study that Roche conducted for the purposes of this appraisal (Tolley Health Economics, section above).

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following detailsix:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Roche did not directly seek clinical expert opinion. Clinical expert opinion via an advisory board and follow-up interviews facilitated by Tolley Health Economics provided estimates of resource utilisation. Details on the structure of the interviews can be provided upon request.

Intervention and comparators' costs

[ix] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Table 107: Unit costs associated with the technology in the economic model

Items	Rituximab 1LM arm	Ref. in submission	Observation arm	Ref. in submission
Technology cost	100mg vial: £174.63 500mg vial: £873.13	BNF 56	No associated cost	N/A
Mean cost of technology treatment	£1,222.39 per cycle (assuming BSA=1.84; including wastage)	BNF 56	No associated cost	N/A
Administration cost	£251.4 per infusion	6.5.1	No associated cost	N/A
Pharmacy cost	£32 per infusion	6.5.1 (PSSRU 2009)		N/A
Monitoring cost in PF1 (including cost of tests)	£42.08 per month	6.5.1	£42.08 per month	6.5.1
Drug costs in PF2	R-CHOP induction: R-CVP induction: R maintenance: CHOP induction: CVP induction: *All costs based on BNF 56*		£11,308 (total) £10,284 (total) £1,222.39 per cycle £1,529 (total) £504 (total)	
Supportive care cost in PF2 (including cost of tests)	£137.03	6.5.1	£137.03	6.5.1
Supportive care costs PD (includes salvage therapies cost)	£500.5	6.5.1	£500.5	6.5.1
Cost of treating AEs (one-off cost)	£272.6		£59.63	

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Table 108: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
PF1 (R maintenance)	R maintenance per cycle	£1,222,39	
	Administration per infusion	£251.4	6.5.1
	Monitoring per month	£75.31	6.5.3
PF1 (observation)	Monitoring per month	£75.31	6.5.3
PF2	R-chemo induction (one-off)	R-CHOP induction: £11,308 R-CVP induction: £11,308	6.5.6
	R maintenance:	£1,222.39 per cycle	
	Chemotherapy induction	CHOP induction: £1,529 (total) CVP induction: £504 (total)	
	R maintenance per cycle	£1,222,39	
	Administration per infusion	£251.4	6.5.1
	Monitoring per month	£137.03	6.5.1
PD	Supportive care costs (including salvage therapies)	£500.5	6.5.6

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a

rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Each adverse event observed in PRIMA (observation and R-maintenance arm) was considered in turn with regards to the resource utilisation potentially required in order to provide an associated cost. The same was performed for the EORTC study. For simplicity, it was assumed that Grade 3 and 4 events would incur the same costs. The average cost of treating treatment related AEs each arm (comprator and intervention) of the economic model was derived costing the AEs reported in the PRIMA and EORTC trials. For example the cost of treating AEs in the intervention arm was derived by combining the cost of treating AEs reported in the PRIMA R-maintenance arm together with the weighted average cost for treating patients' AEs taken from the two arms in the EORTC study (rituximab maintenance and observation arms). The cost of treating adverse events in PF1 and PF2 was combined for each arm of the analysis and included as a one-off cost at the fist cycle of the model. This is a conservative assumption as the cost is not subject to discounting or a reduced proportion of patients experiencing the treatment related adverse event if incorporated at a later timepoint in the model. The majority of AEs observed in the PRIMA and EORTC trials had a very low incidence rate (less than 2 events) and therefore these are excluded from the analysis. The table below provides a list of the included AEs and the nominal cost for treating such an event.

Table 109: List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
Neutropenia	Comparator and Intervention	£3,272 per episode	
Leukopenia		£0 no intervention	
Arthralgia		£0 no intervention	
Depression		£44 per episode	
Pneumonia		£2,494 per episode	
Dysrhythmias		£606 per episode	
Infection		£1,077 per episode	
Granulocytes		£1514 per episode	
Deep vein thrombosis		£792 per episode	

The total average cost for treating the AEs related to the intervention arm treatment strategy were estimated to be £272 were as the average cost of treating AEs related

to the comprator arm treatment strategy was £59. Uncertainty around these estimates was tested in DSA (+/-50%) and PSA.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No other miscellaneous costs have been included in the model.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

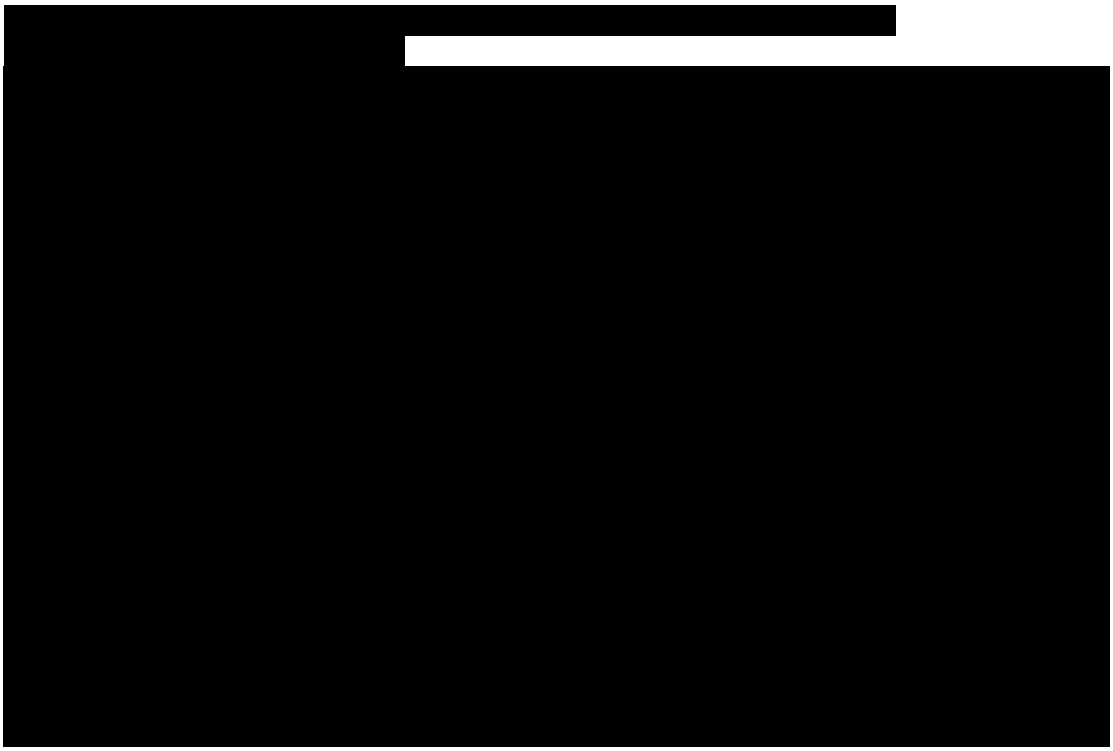
All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated,

including a description of the alternative scenarios in the analysis.

A scenario that assumes the hazard rate of progression for 1st line maintenance rtiuximab is sustained beyond the latest trial follow-up was tested as a structural scenario analysis. The figure below presents the fitted curves assuming that the treatment effect of rituximab maintenance is sustained for the life-time horizon of the model.



An alternative worst-case scenario in which the treatment effect of rituximab is only maintained for the duration of the trial follow-up (48 months) was also tested in the sensitivity analysis.

Selection of the correct parametric function to inform the survival analysis may be considered a source of structural uncertainty and therefore alternative functions were evaluated. Extrapolation of the progression free data was carried out under the assumption that the data followed a parametric model structure. The various models were assessed for goodness of fit. Alternative parametric survival functions (Exponential, Log Logistic, Log Normal, and Gamma, and Weibull) were evaluated in the sensitivity analysis. The alternatively parametric fitted curve plots are presented in Appendix III.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The following variables were subject to deterministic sensitivity analysis. Published sources were used to inform the range and distribution of the parameters.

1.) Adverse event costs

Monthly adverse event costs were both increased and decreased by 50%.

2.) Monthly supportive care costs

For the PF1, PF2 and progressed health states, costs were both increased and decreased by 50%.

3.) Drug administration costs

The upper (£267) and lower (£176) quartiles for "Deliver subsequent elements of a Chemotherapy cycle" (SB15Z) respectively (from reference costs 2008/09) were tested.

4.) Time-horizon

The sensitivity analysis of the model around the time-horizon was tested. 2 alternative time horizons were tested, 20 and 30 years.

5.) Extreme scenario in which patients that progress in PF1 transition to the death state

This extreme scenario assumes that all patients exiting the PF1 state transition to death. This is to evaluate the impact of 1st line rituximab maintenance only, to avoid any potential confounding from benefits and drivers of the ICER derived post progression. All transition probabilities post PF1 were set to 1 (100% probability of progressing to death).

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken to assess the robustness of cost effectiveness results. All variables were included in the PSA. An assumption of 1,000 samples was used in order to achieve reasonably tight distributions around the mean estimate. Lower sample numbers result in very wide and flat distributions, which were deemed to be meaningless. The table below summarizes the variables included withinthe PSA, assumptions relating to distributions and ranges of each parameter included. Parameters that were not included in the PSA are age of the cohort, weight, height. These parameters are patient characteristics and were assumed to relate to 1st order uncertainty i.e. variability not uncertainty.

Table 110: PSA variables, values and distributions

Variables	Base case	Distribution and parameters
Utilities		
PF1	0.88	Beta(0.88, 0.000105) (Min: 0.843, Max: 0.903)
PF2	0.79	Beta(0.79, 0.000166) (Min: 0.745, Max: 0.823)
PD	0.62	Beta(0.63, 0.000235) (Min: 0.579 Max: 0.673)
Costs		
Rituximab 1st line monthly supportive costs	£75.31	Gamma(11.05 , 3.8088)
Cost of rituximab administration	£251.4 (pharmacy & consultation)	Gamma(122.11, 2.06)
Observation 1st line monthly supportive costs	£75.31	Gamma(11.05 , 3.8088)
2nd monthly line supportive costs	£137.03	Gamma(8.50 , 16.1206)
Monthly cost of 3rd line and supportive care	£438.17	Gamma(7.38 , 73.1128)

Rituximab administration cost	£251.4	Gamma(122.11 , 206)
All adverse events costs	See AE cost sheet of the model	Distribution of AE costs: Gamma. Parameters for each cost were calculated separately
Monthly probabilities		
PF1 to PF2 (rituximab) **		Gompertz(-0.008256813, 0.0001)
PF1 to PF2 (observation) **		Gompertz(-0.015186057, 0.0001)
PF1 rituximab to death		1 – exp(- 0.000301914)
PF1 observation to death		1 – exp(- 0.000204639)
PF2 to PD – R-chemo-R **		1 – exp(- (0.115212+0.121682))
PF2 to PD – chemo-observation **		1 – exp(- (0.259469+0.42062))
PF2 to death – R-chemo-R		1 – exp(- 0.001184194)
PF2 to death – chemo-observation		1 – exp(- 0.000788502)
PD to death – rituximab (in 2LM) **		1 – exp[- {(0.033578457-0.00469)+(0.185066051+0.055308)}]
PD to death – observation (in 2LM) **		1 – exp[- {(0.331674-0.01381)+(0.211688+0.085513)}]

** Probabilistic values are determined assuming Normality of the parameters on the log scale. The parameters vary according to the variance-covariance matrix decomposed via Cholesky decomposition. The decomposed covariance matrix is multiplied to a random unitary Normal distribution and added to the deterministic un-transformed estimates (e.g., Intercept, treatment effect and scale parameters).

The decomposed variance matrix for the transition probabilities were created using the standard error of the parameter estimates (Intercept X- variable (Time parameter)) and the correlation between the dependent (scrapped survival probabilities (log scale)) and independent variable (time parameter) (Decision Modelling for Health Economic Evaluation, A. Briggs, M. Sculpher, K. Claxton, Oxford University Press (2006))

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As 94% of patients in the PRIMA study are still alive at the latest follow-up, a comparison of the estimated mean survival from the model with that observed in PRIMA was not possible.

The tables below summarises the main clinical results from the economic model.

Table 111: Summary of model results compared with clinical data (intervention – R-maintenance)

Outcome	Clinical trial result	Model result (mean years)
Progression-free survival PF1	N/A	6.151
Progression-free survival PF2 with R-chemo-R	N/A	2.220
Progression-free survival PF2 with chemo-obs	N/A	0.122
Progressed survival PD with R-chemo-R in 2L	N/A	1.667
Progressed survival PD with R-chemo-obs in 2L	N/A	0.127
Overall survival	N/A	10.288

(Half-cycle corrected results, not discounted)

Table 112: Summary of model results compared with clinical data (comparator – observation)

Outcome	Clinical trial result	Model result (mean years)
Progression-free survival PF1	[redacted]	4.045
Progression-free survival PF2 with R-chemo-R	N/A	1.783
Progression-free survival PF2 with chemo-obs	N/A	0.173
Progressed survival PD with R-chemo-R in 2L	N/A	1.064

Progressed survival PD with R-chemo-obs in 2L	N/A	0.141
Overall survival	NA	7.21

(Half-cycle corrected results, not discounted)

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The tables below provide the Markov trace for patients on the intervention and comparator arm of the model for years 0, 1, 2, 5, 10, 15, 20 and 25. Further granularity can be found in the accompanying economic model.

Table 113: Markov trace of survival for the intervention arm (R-maintenance)

year	PF1	PF2 – (R-chemo-R)	PD - (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)	death
0	0.996	0.004	0.000	0.000	0.000	0.000
1	0.871	0.070	0.008	0.008	0.002	0.040
2	0.762	0.112	0.000	0.010	0.006	0.110
5	0.510	0.149	0.075	0.004	0.010	0.252
10	0.184	0.148	0.114	0.007	0.009	0.538
15	0.062	0.074	0.087	0.002	0.004	0.771
20	0.020	0.029	0.045	0.001	0.001	0.904
25	0.007	0.009	0.019	0.000	0.000	0.964

**Half-cycle corrected and discounted values*

Table 114: Markov trace of survival for the comparator arm (observation)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)	death
0	0.992	0.006	0.000	0.002	0.000	0.000
1	0.799	0.115	0.013	0.024	0.007	0.042
2	0.643	0.176	0.039	0.030	0.018	0.094
5	0.000	0.206	0.109	0.022	0.026	0.637
10	0.112	0.118	0.116	0.008	0.015	0.631
15	0.038	0.050	0.069	0.003	0.004	0.836
20	0.012	0.018	0.032	0.001	0.001	0.935
25	0.004	0.006	0.013	0.000	0.000	0.977

**Half-cycle corrected and discounted values*

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are accrued by multiplying the half-cycle corrected and discounted proportion of patients with the utility value associated with each health state. Markov traces are given below for the intervention and comparator arms.

Table 115: Markov trace of accrued utility for the intervention arm (R-maintenance)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)
0	0.876	0.003	0.000	0.000	0.000
1	0.767	0.056	0.005	0.006	0.001
2	0.671	0.089	0.000	0.008	0.004
5	0.449	0.119	0.046	0.003	0.006
10	0.162	0.118	0.070	0.006	0.006
15	0.054	0.060	0.054	0.002	0.002
20	0.018	0.023	0.028	0.001	0.001
25	0.006	0.007	0.012	0.000	0.000

**Half-cycle corrected and discounted values*

Table 116: Markov trace of accrued utility for the comparator arm (observation)

year	PF1	PF2 – (R-chemo-R)	PD – (R-chemo-R in PF2)	PF2 – (R-chemo-obs)	PD (R-chemo-obs in PF2)
0	0.876	0.003	0.000	0.000	0.000
1	0.767	0.056	0.005	0.006	0.001
2	0.671	0.089	0.000	0.008	0.004
5	0.449	0.119	0.046	0.003	0.006
10	0.162	0.118	0.070	0.006	0.006
15	0.054	0.060	0.054	0.002	0.002
20	0.018	0.023	0.028	0.001	0.001
25	0.006	0.007	0.012	0.000	0.000

**Half-cycle corrected and discounted values*

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The table below provides a breakdown of the total QALYs and LYGs stratified by health state and intervention for the 1st line R maintanence intervention arm.

Table 117: Model outputs by clinical outcomes (intervention arm – R-maintenance)

Outcome	Mean LY	Mean QALYs	Mean Cost
Progression-free survival PF1	6.151	5.412	£35,780
Progression-free survival PF2 with R-chemo-R	2.220	1.754	
Progression-free survival PF2 with chemo-obs	0.122	0.097	£38,571
Total progression-free survival (PF1 & PF2)	*8.493*	*7.263*	*£74,351*
Progressed survival PD with R-chemo-R in 2L	1.667	1.034	
Progressed survival PD with chemo-obs in 2L	0.127	0.079	
Total progressed survival	*1.795*	*1.113*	£10,779
Overall survival	10.288	8.376	£85,403
LY, life years; QALY, quality-adjusted life year			

(Half-cycle corrected and discounted)

Table 118: Model outputs by clinical outcomes (comparator arm – observation)

Outcome	Mean LY	Mean QALYs	Mean Cost
Progression-free survival PF1	4.597	4.045	£16,734
Progression-free survival PF2 with R-chemo-R	2.257	1.783	
Progression-free survival PF2 with chemo-obs	0.219	0.173	£38,246
Total progression-free survival (PF1 & PF2)	*7.072*	*6.001*	*£54,980*
Progressed survival PD with R-chemo-R in 2L	1.717	1.064	
Progressed survival PD with chemo-obs in 2L	0.228	0.141	
Total progressed survival	*1.945*	*1.206*	£11,682
Overall survival	9.017	7.207	£66,721
LY, life years; QALY, quality-adjusted life year			

(Half-cycle corrected and discounted)

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 119: Summary of QALY gain by health state

Health state	QALY intervention (rituximab 1LM)	QALY comparator (observation)	Increment	Absolute increment	% absolute increment
Progression-free survival PF1	5.412	4.045	1.367	1.367	87.34%
Progression-free survival PF2 with R-chemo-R	1.754	1.783	-0.029	0.029	1.82%
Progression-free survival PF2 with chemo-obs	0.097	0.173	-0.077	0.077	4.89%
Total progression-free survival (PF1 & PF2)	*7.263*	*6.001*	1.262	1.262	80.63%
Progressed survival PD with R-chemo-R in 2L	1.034	1.064	-0.031	0.031	1.96%
Progressed survival PD with chemo-obs in 2L	0.079	0.141	-0.063	0.063	3.99%
Total progressed survival	*1.113*	*1.206*	-0.093	0.093	5.95%
Total	8.376	7.207	1.169	1.566	100.00%

QALY, quality-adjusted life year
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

(Half-cycle corrected and discounted)

Table 120: Summary of costs by health state

Health state	Cost intervention (rituximab 1LM)	Cost comparator (observation)	Increment	Absolute increment	% absolute increment
Progression-free survival PF1	£35,780	£16,734	£19,046	£19,046	93.94%
Progression-free survival PF2 with R-chemo-R	£38,571	£38,246	£325	£325	1.60%
Progression-free survival PF2 with chemo-obs					
Total progression-free survival (PF1 & PF2)	*£74,351*	*£54,980*	£19,371	£19,371	95.55%
Progressed survival PD with R-chemo-R in 2L	£10,779	£11,682	-£903	£903	4.45%
Progressed survival PD with chemo-obs in 2L					

Total progressed survival					
Total	£85,403	£66,721	£18,669	£20,274	100.00%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

(Half-cycle corrected and discounted)

Table 121: Summary of predicted resource use by category of cost

Item	Cost intervention (R-maintenance)	Cost comparator (observation)	Increment	Absolute increment	% absolute increment
Cost of rituximab (1LM)	£14,130	£0	£14,130	£14,130	67.43%
Administration for rituximab (1LM)	£3,091	£0	£3,091	£3,091	14.75%
Cost of Rituximab (2LM)	£11,802	£11,994	-£192	£192	0.92%
Administration Cost of Rituximab (2LM)	£2,582	£2,624	-£42	£42	0.20%
Mean Supportive Care Cost of PFS (1LM)	£18,559	£16,734	£1,825	£1,825	8.71%
Mean Supportive Care Cost of PFS (2L)	£24,188	£23,629	£559	£559	2.67%
Mean Supportive Care Cost of Progression	£10,779	£11,682	-£903	£903	4.31%
Cost of AE's	£273	£60	£213	£213	1.02%
Total	£85,403	£66,721	£18,681	£20,955	100.00%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

(Half-cycle corrected and discounted)

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base-case ICER is **£15,977 per QALY**. Details of the costs and QALYs for each arm in the model are given in the table below.

Table 122: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Observation in 1LM	£66,721	9.017	7.207	Baseline				
Rituximab in 1LM	£85,403	10.288	8.376	£18,681	1.271	1.169	**£15,978**	N/A
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

(Half-cycle corrected and discounted)

The base case analysis results in terms of overall survival, survival by health state in the model and total costs by treatment arm are presented in the figures below.

Figure 47: Costs by intervention and comparator arm

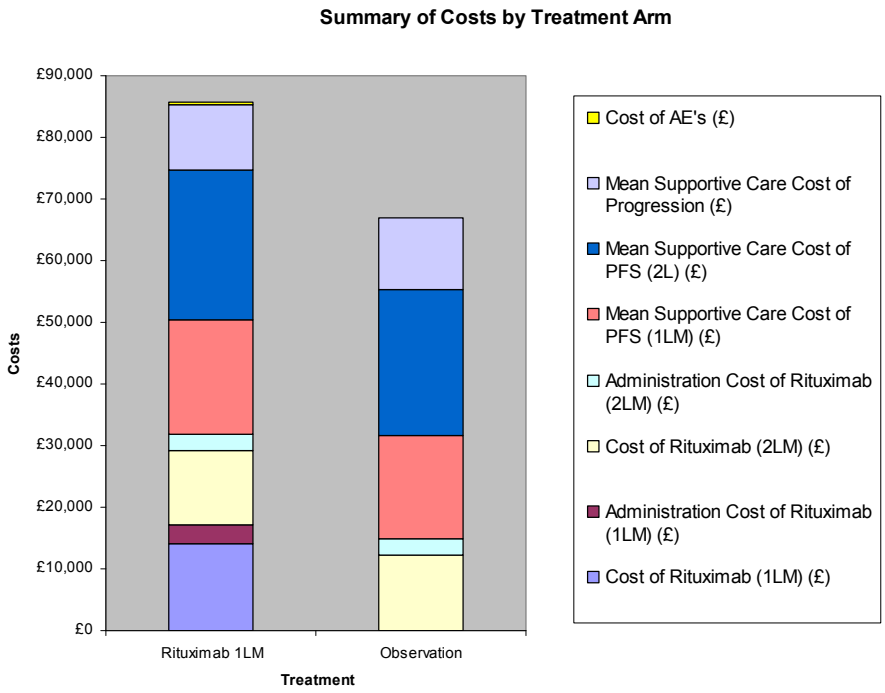


Figure 48: Modelled survival for intervention arm – R- mainteance (per health state)

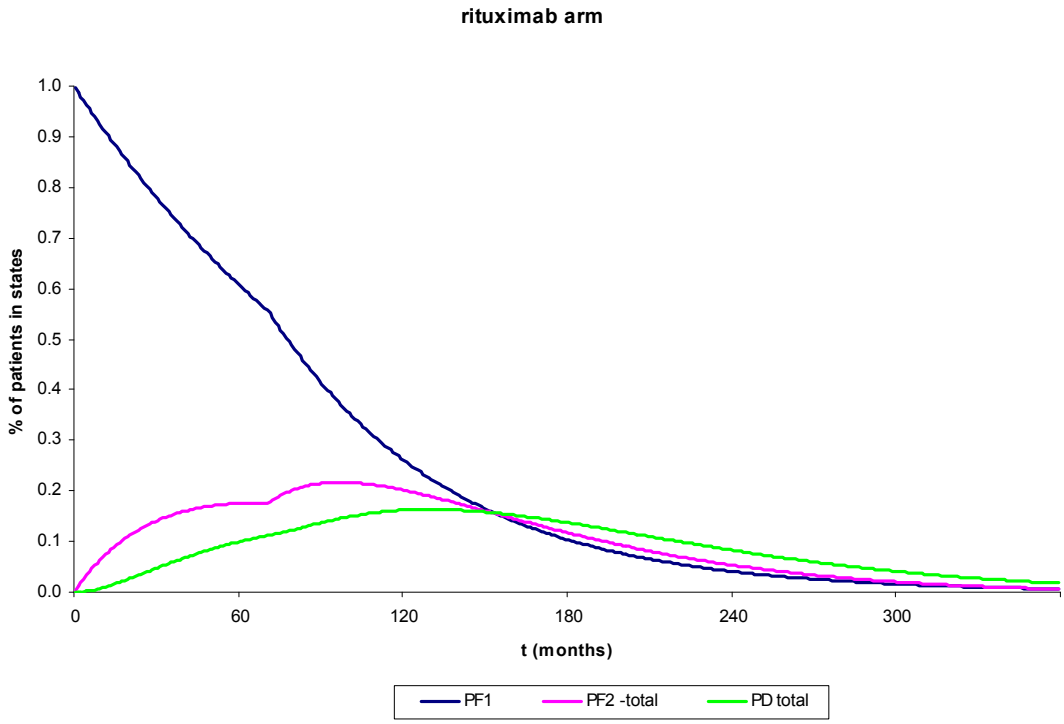


Figure 49: Modelled survival for comparator arm – observation (per health state)

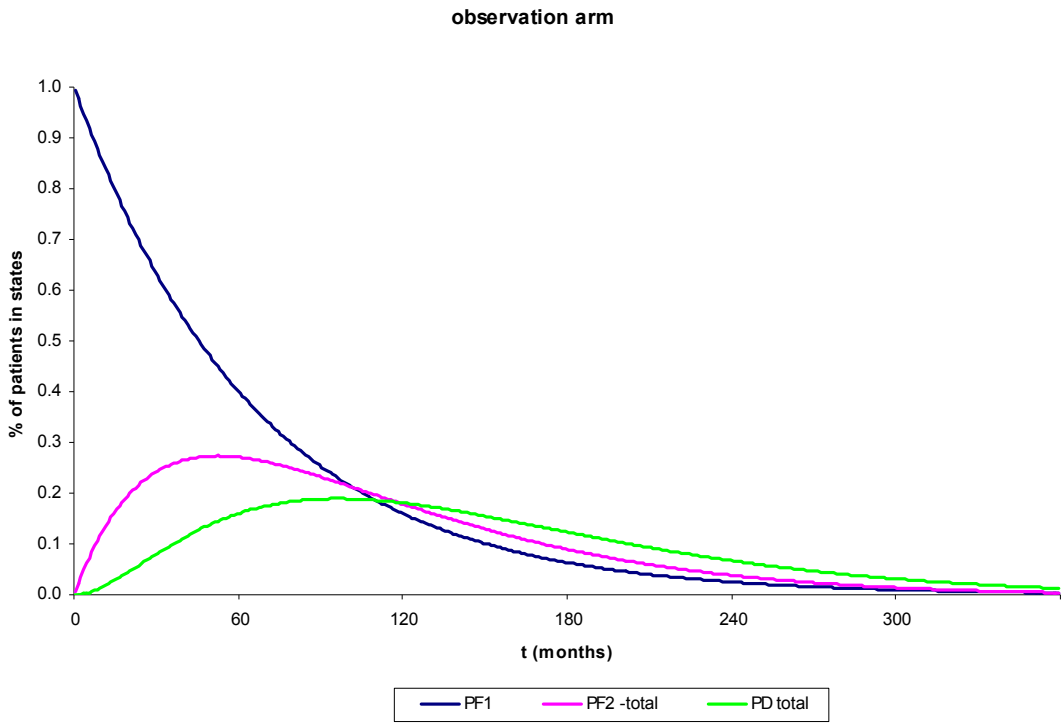
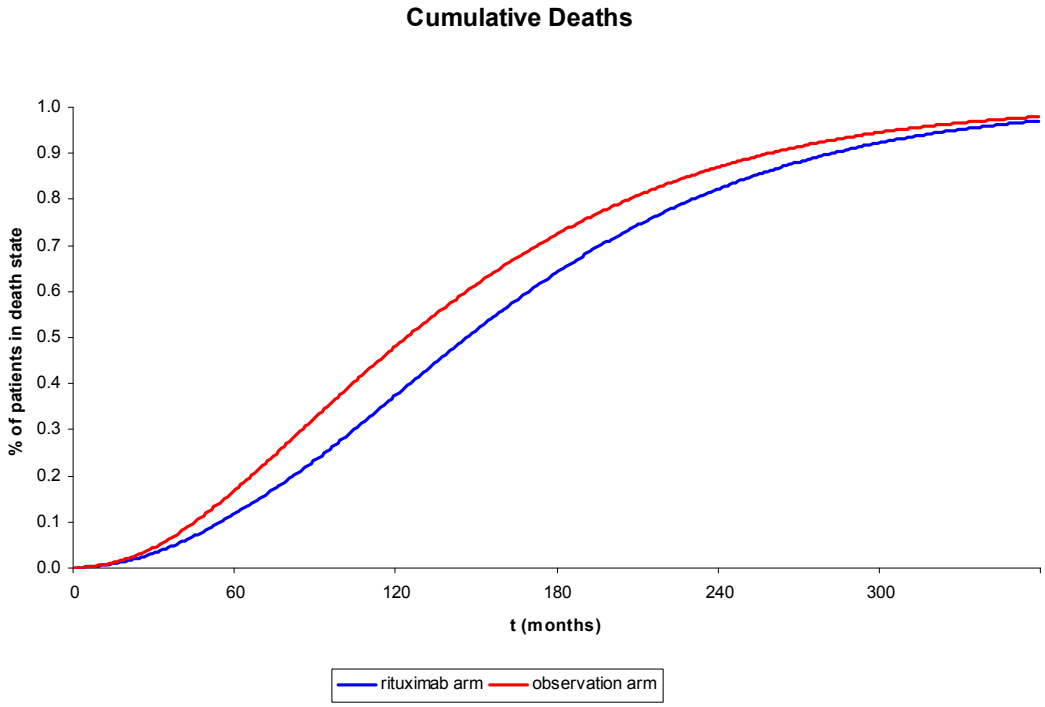


Figure 50: Estimated mortality rate for the intervention (R-maintenance) and comparator (observation) arms



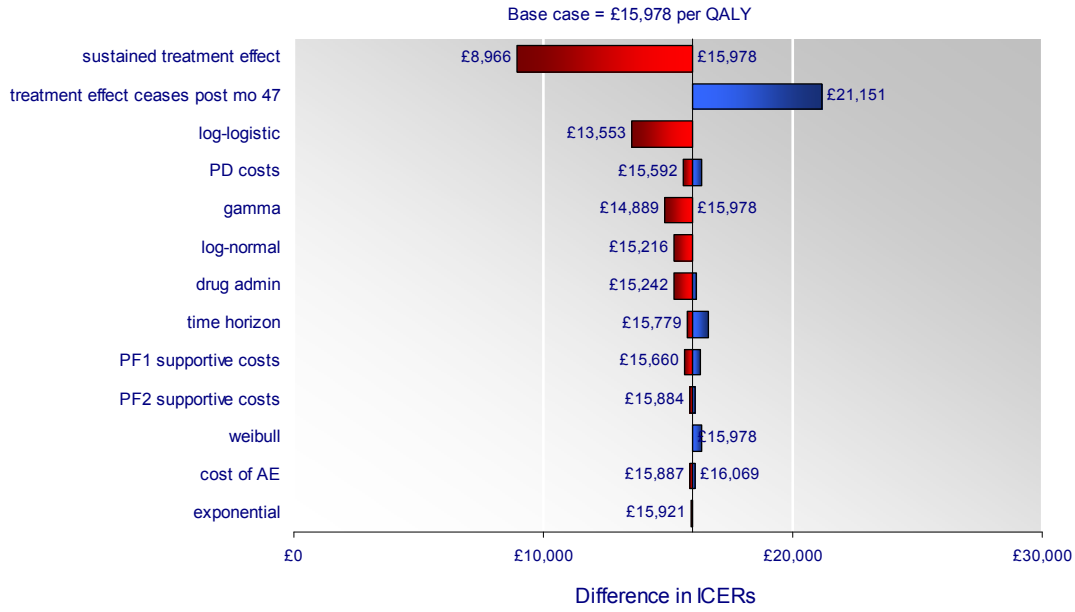
Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Structural and deterministic sensitivity analysis

Structural and deterministic sensitivity analyses were performed for all parameters according to the ranges and specifications given in the sensitivity analysis in section 6.6.2 (scenarios 1-4). The tornado diagram below shows the sensitivity of the model to these parameters.

Figure 51: Tornado diagram demonstrating the sensitivity of the model in a range of parameters



The diagram above demonstrates that rituximab in 1st line maintenance is a cost effective option for patients that have completed successfully 1st line induction with R-chemotherapy. From the analysis above it is demonstrated that the model is not sensitive to assumptions around the type of the parametric extrapolation fitted on the PRIMA trial PFS data. The model is also not sensitive to assumptions around supportive care and administration costs or the time-horizon. Wider variation in the ICERs are observed when assumptions regarding the duration of the treatment effect. However in all the scenarios explored the cost effectiveness ratio remained

well below the commonly accepted threshold of £30,000 per QALY, with only one scenario marginally exceeding £20,000.

Extreme scenario (scenario 5)

Results are presented for this extreme scenario, in which probabilities of progressing to death are set to 100%, in the table below. Even though the analysis is not representative of what could happen in a real-life scenario it presents the isolated impact of rituximab 1st line maintenance to the cost effectiveness. The cost effectiveness of this extreme scenario was determined to be **£13,901 per QALY**.

Table 123: Cost effectiveness results for extreme scenario isolating the impact of R 1st line maintenance

	Intervention arm (rituximab 1LM)	Comparator arm (observation)	Incremental
Mean life years	6.151	4.579	1.572
Mean total QALYS	5.41	4.04	1.37
Mean total cost	£35,779	£16,734	£19,045
ICER			**£13,901 per QALY**

The estimated cost per QALY determined in this scenario is lower than in the base-case as the incremental costs and benefits are not diluted by assumptions around treatments and benefits made in PF2 and PD. For example, in the base-case, although patients in the intervention arm experience an incremental benefit (QALYs) in PF1 this is offset by a QALY decrement in PF2. While this suggests that patients receiving R-maitnenace in 1LM accrue less QALYs in PF2 the modelled outcome reflects the postivie outcome of R-maintenace in PF1 where patients remain in this state for longer, transitioning to PF2 and PD with a slower rate than in the observation arm and therefore accruing less QALYs in these states.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

PSA was run using 2,000 Monte Carlo simulations. The mean resulting ICER was **£15,770 per QALY**. This finding reinforces the result of the deterministic analysis demonstrating that the ICER is robust under a wide range of variation in the

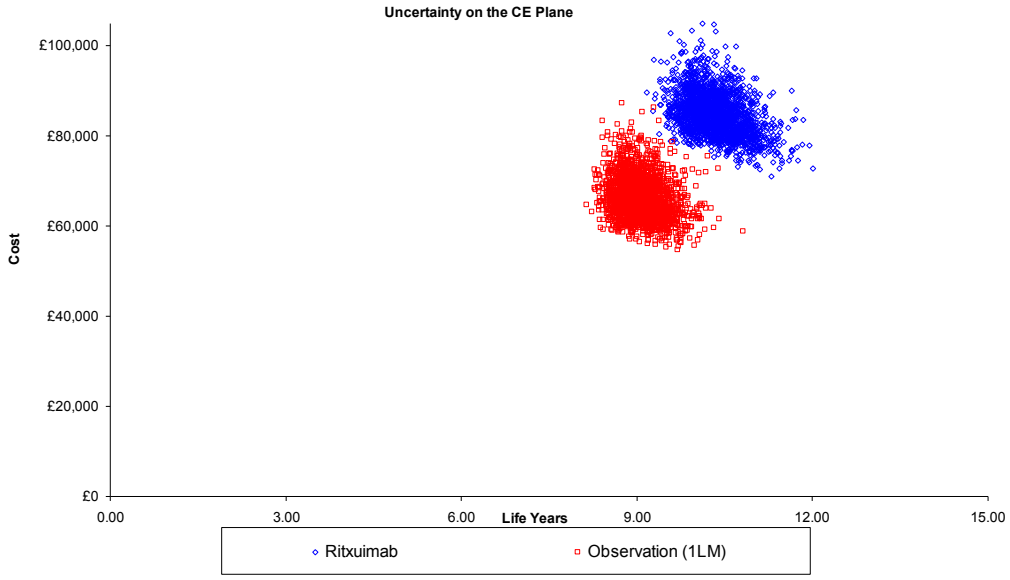
underlying parameters. The table below summarises the results of the probabilistic sensitivity analysis.

Table 124: Summary PSA results of survival and costs (2,000 simulations)

	Rituximab 1LM	Observation	Incremental
Mean life years	10.350	9.077	1.273
95% CI	(9.61, 11.28)	(8.49, 9.82)	(0.89, 1.69)
Total Mean Time in PFS (yrs)	8.591	7.158	1.433
95% CI	(7.66, 9.88)	(6.43, 8.16)	(0.95, 2.00)
Mean Time in Progression (yrs)	1.759	1.919	-0.160
95% CI	(1.35, 2.08)	(1.62, 2.19)	(-0.31, -0.06)
Mean QALYs	8.440	7.265	1.175
95% CI	(7.71, 9.38)	(6.69, 8.03)	(0.80, 1.59)
Mean QALY in PFS	7.349	6.075	1.274
95% CI	(6.50, 8.54)	(5.41, 6.99)	(0.84, 1.78)
Mean QALY in Prog	1.092	1.191	-0.099
95% CI	(0.84, 1.30)	(1.00, 1.37)	(-0.19, -0.03)
Mean Total Cost (£)	84,922.78	66,393.22	18,529.56
95% CI	(76,682.55, 95,465.37)	(58,671.85, 77,241.24)	(15,076.15, 21,316.19)
Mean Cost of PFS incl. Cost of AE's (£)	74,550.17	55,072.38	19,477.79
95% CI	(70,245.12, 79,060.12)	(51,785.35, 59,132.43)	(16,730.34, 22,069.98)
Mean Supportive Care Cost of Progression (£)	10,372.61	11,320.84	-948.24
95% CI	(3,941.49, 19,576.88)	(4,477.64, 21,213.72)	(-2,311.72, -219.57)
Cost of AE's (£)	300.02	64.27	235.75
95% CI	(246.91, 364.91)	(47.36, 89.47)	(180.57, 300.97)
Cost per Life Year Gained (£)			14,556.83
Cost per QALY Gained (£)			15,770.34

The resulting costs and benefits from the simulation are graphically represented for the intervention and comparator arm in the figure below demonstrating that rituximab maintenance will lead in an increase in costs but also in a clear increase in patient benefit.

Table 125: Total costs and QALYs for 2,000 Monte Carlo simulations for the intervention and comparator arms



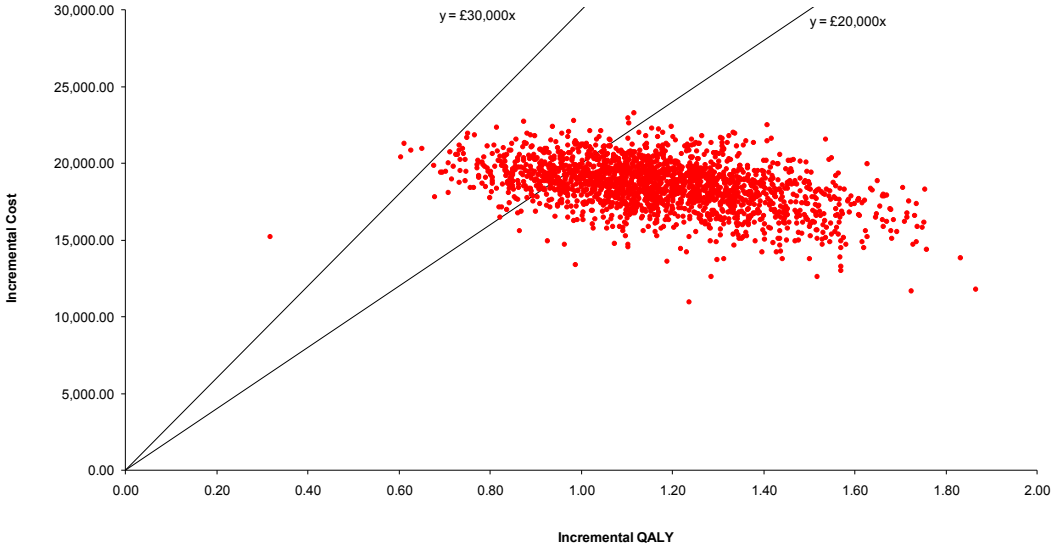
It is important to note that the majority of the simulation results lie within the £20,000 to £30,000 per QALY range. The table below shows the percentage of simulations results below £20,000 and within the 2 cut-off points.

Table 126: Percentage PSA resulting ICERs being less or equal to £20,000, £30,000 per QALY

	ICERs ≤ £20,000 per QALY	ICERs ≤ £30,000 per QALY	ICERs > £30,000 per QALY
ICERs within the range	84.2%	99.7%	0.3%

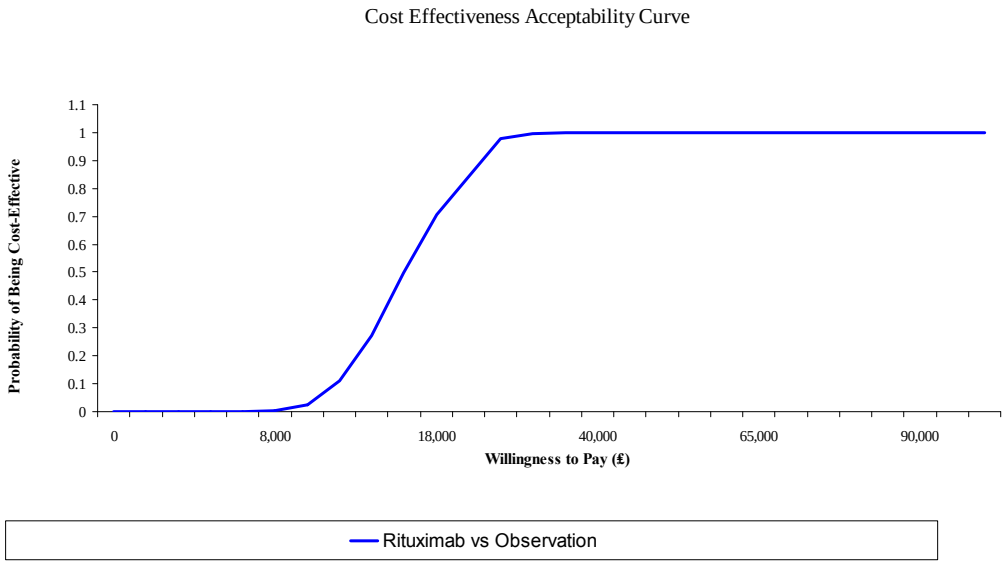
The distribution of the resulting ICERs can be best demonstrated in the figure below showing the cost effectiveness plane, the resulting ICERs and the currently used thresholds of £20,000 and £30,000 per QALY.

Figure 52: Cost effectiveness plane showing scatter plot of 2,000 Monte Carlo model simulations



The CEAC graph shows the likelihood of the R 1st line maintenance (1LM) treatment being cost-effective at different WTP per QALY thresholds. The probability of R in 1LM not surpassing the commonly used threshold of £30,000 per QALY compared to observation is 99.7%. Therefore, the PSA illustrates the robustness of the cost-effectiveness of R 1LM compared to observation.

Figure 53: Cost-effectiveness acceptability curve of R 1LM vs. observation (example: 2,000 Monte Carlo simulations)



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Please see section 6.7.7 above.

6.7.10 What were the main findings of each of the sensitivity analyses?

Three types of sensitivity analysis were undertaken in order to assess the robustness of the cost effectiveness analysis.

1. Structural sensitivity analysis

The results showed that the ICERs are stable when a different extrapolation method of the PFS trial data was used. When exploring the different methods of extrapolation the ICER was found to be overestimated in the majority of scenarios (log-logistic, gamma, log-normal, exponential). Only one method of extrapolation (Weibull) was found to result in a higher ICER, but the effect on the ICER was marginal (£420 per QALY).

The treatment effect duration was explored and it was found that the ICER is most sensitive to this parameter. When the treatment effect of Rituximab was extended for the duration that patients stay in PFS the ICER was decreased by ~£7K per QALY. When the treatment effect was assumed to stop at the last trial follow-up, the ICER was increased by ~£6K per QALY. Inspecting the cumulative hazard plots provided in a section above it is evident that the hazard rate for rituximab remains stable for the duration of the trial. Given strong evidence, from other rituximab trials, that suggests that the treatment effect of rituximab maintenance is usually maintained long after patients have stopped receiving treatment and the cumulative hazard rate data from PRIMA it would appear unrealistic to assume that the hazard rate of patients in the treatment arm in PRIMA will be equal to those patients receiving placebo immediately following the end of the follow-up.

The 2 scenarios investigating the effect on the ICER with respect to assumption on the duration of the treatment effect should be presented side-by-side to give an estimate of the variation but should be regarded as the 2 extremes. All the available

data suggest that rituximab's treatment effect is sustained for at least 72 months post treatment initiation (section 6.3.2, figure 32).

2. Deterministic sensitivity analysis

A range of parameters were tested in the deterministic one-way sensitivity analysis. None of the parameters tested had a significant impact to the base-case ICER. Utilising the actual dose observed in the trial rather than the planned dose had the biggest impact decreasing the ICERs by £1,700 per QALY. This suggests that the base-case is likely overestimating the ICERs of R 1LM compared to observation. Variation in all other parameters tested such as the cost of administration, supportive costs in PF1, PF2 and PD, costs of treating adverse events and the time-horizon used had a marginal effect on the base-case ICER.

3. Probabilistic sensitivity analysis

All major parameters in the model were tested in the probabilistic sensitivity analysis. The results demonstrated that 99.7% of the different 'scenarios' tested fall within the commonly accepted threshold of £30,000 per QALY. It is important to highlight that the majority of the resulting ICERs are lower than £20,000 per QALY demonstrating the robustness and underpinning the base-case ICER of £15,978 per QALY.

6.7.11 What are the key drivers of the cost-effectiveness results?

The cost effectiveness analysis relies on assumptions on clinical aspects of the disease and expected outcomes of patients that are eligible for 1st line maintenance therapy with rituximab. Due to the more chronic nature of follicular lymphoma and early evaluation of this indication (not yet licensed as of 10th August 2010) the model is dependent on a number of assumptions regarding the expected long-term outcomes of patients receiving rituximab in 1st line maintenance. This uncertainty is however somewhat reduced due to to the high quality and relatively long follow-up phase III trial data being available for 2nd line patients, published in the Van Oers study.

A key driver of the model is the assumed duration of the treatment effect. Consideration of all the available evidence and the PRIMA data and observed trends

in terms of the hazard rates observed suggest that the treatment effect of R-maintenance is sustained after patients stop receiving treatment. The base-case assumption applying the treatment effect for the first 72 months of the model was tested in a series of deterministic and probabilistic sensitivity analysis. The 2 extreme scenarios tested demonstrated that the cost effectiveness ratio is even lower than in the base-case or remains well below the £30,000 per QALY threshold.

Extensive deterministic and probabilistic sensitivity analysis has also demonstrated the robustness of the cost effectiveness results under a range of values for the parameters included in the model. The majority of ICERs in the scenarios tested were under £20,000 per QALY.

In the scenario in which all transition probabilities are set to 1 (100%) after patients have progressed from PF1, although extreme and unlikely, isolates the impact of 1st line rituximab maintenance. The cost effectiveness of this scenario was £13,368 per QALY and it is within the range of the base-case ICER.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

This is attached as an appendix

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Consistent with previous technology appraisals of rituximab in haematology and also current clinical practice, no sub-group of patients was identified.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

6.9.3 Please describe how the statistical analysis was undertaken.

N/A

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

N/A

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

No sub-groups were identified. No valid sub-group of patients for which the PRIMA trial was powered to identify were found.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No published economic evaluation was identified in the literature therefore no comparisons can be drawn.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

No clinically relevant sub-groups were identified in the clinical trial and therefore no cost effectiveness analysis on sub-groups was performed. Given the wealth of clinical results from PRIMA and other rituximab trials (van Oers, Marcus, Hiderman, see meta-analysis section) it is very unlikely that rituximab has a differential effect in a specific sub-group of patients.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The incremental clinical effects of rituximab in 1st line maintenance compared to observation are based upon the largest randomised head-to-head controlled trial demonstrating a significant treatment effect of adding rituximab in the current treatment pathway. Based on the PRIMA trial and other rituximab follicular lymphoma trials the certainty of the treatment effect of rituximab and the subsequent incremental clinical advantages of R-maintenance compared to observation is strong.

   Utilising this data results in ICERs comfortably below the lower NICE threshold of £20,000 per QALY gained, thus providing a strong case for the cost-effectiveness of rituximab in 1st line maintenance.

2. Considering the proximity of the submission to expected marketing authorisation, the extrapolation of the primary endpoint, PFS, from the PRIMA study is based on a relatively long and the very latest follow-up (June 14th 2010) period of over 3 years, with follow-ups for some patients extending to over 4 years.

3. Outcomes for patients receving 2nd line and later treatments within the economic evaluation have also been informed by a large phase III RCT with realtiely long mature follow up that includes the likely treatment startegies for UK FL patients. Therefore whilst the long term outcomes from the PRIMA study are still subject to uncertainty this is somewhat supplemented and compensated for by the Van Oers study.

4. All possible uncertainties have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be very stable to wide variations in model parameters.

Weaknesses

1. Assumptions have been made with respect to the treatment pathway and patient outcomes progressing from PF1 and subsequent lines of therapy. There have been no studies or trials investigating patient outcomes with prolonged exposure to rituximab in multiple lines of therapy. The Appraisal Committee in the consideration of rituximab as a 2nd line therapy heard from clinical experts that "the evidence indicated that follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy. Although it noted this as an area of uncertainty, the Committee accepted that this was biologically plausible given its [rituximab's] mechanism of action" (FAD TA 137). This evaluation attempted to address these uncertainties by extracting the latest data from the follow-up from the EORTC study and applying the transition probabilities in both arms of this evaluation in an unbiased manner.

2. Resource data utilisation was not collected as part of the PRIMA protocol. Resource utilisation and costs associated with subsequent treatments, drug administration and patient monitoring could be improved within the model via actual UK observational data.

3. NICE's preferred QoL instrument (EQ-5D) was not collected as part of the PRIMA trial protocol. This evaluation relies on published resources to inform the HRQoL for each of the health states in the economic model.

4. Clinical practice with respect to backbone chemotherapy used in induction (1st and 2nd line) varies. According to the PRIMA protocol the choice of the backbone chemotherapy was at the discretion of the investigator at each recruiting centre. It was found that 9 out of the 15 UK patients (16 patients recruited; 1 did not receive any treatment) received R-CHOP as 1st line induction therapy which is consistent to the 75% choice of R-CHOP in the trial. Even though NICE recommends CVP and CHOP as chemotherapy backbone in 1st and 2nd line induction respectively, usage of these regimens varies within the current clinical practice in the UK. For the purposes of this evaluation it has been assumed that the treatment effect of rituximab in 1st and 2nd line maintenance is not confounded by choice of the chemotherapy backbone in induction.

5. It has been assumed that there is no utility decrement for the period of progression prior to 2nd line induction. Regular monitoring of patients already in place in the NHS will minimise the time period between relapse in 1st line and remission in second line after successful induction. Patients transitioning to PF2 and induced in 2nd line are also assumed to receive no benefit during the induction phase. The above 2 assumptions combined are thought to give a balanced estimate of the immediately before and during the 2nd line induction phase.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

1. Extrapolation of PFS and OS outcomes for R-maintenance and observation based upon longer follow-up of the PRIMA study as it emerges. When further follow-up data is available, patients' progression to PD could be re-stratified according to 2nd line therapies. The OS results however may be con-founded by the choice of 2nd line treatments in PRIMA (and cross-over). These may be in contrast with UK normal clinical practice and NICE guidance.

2. A study that investigates outcomes in 2nd line on patients previously treated with rituximab in 1st line induction and maintenance will help to determine the treatment effect when rituximab is used in multiple lines.

3. Availability of the latest patient level data from the EORTC 20981 study could potentially increase the precision of the transition probabilities in 2nd line and 2nd line maintenance and improve the completeness of the current model. Implementing time-dependent transition probability in 2nd line will increase the accuracy of the estimates but also the complexity and size of the model as patients will have to be 'tracked' within the model so that information around the duration they spend in PF1 is carried forward in the later stages of the model.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Patient population projections for those eligible for the licensed indication of rituximab as maintenance are shown in the table below, for years 2011-2015. Baseline population projections were taken from Office for National Statistics[136] for England and Wales.

The NHL annual incidence rate was taken from Cancer Research[137]; follicular lymphoma incidence rate from the Non-Hodgkin's lymphoma classification project[138]; patients who could receive drug treatment was taken from Synovate[139]; and incidence of patients with stage III/IV tumours from Shipp et al. (1997)[140]. It was assumed all patients with stage III/IV tumours would be eligible for anti-CD20 and 1st line treatment. Those who responded to treatment are eligible for rituximab maintenance and the incidence for this is taken from Marcus et al. (2005) and Hiddemann et al. (2005).

An assumption that all the previous year's patients would carry on to the next to receive the full two-year licensed dosage regimen was made. (Note that annual costs incorporate the more realistic assumption that some patients will progress before receiving the full two-year dosing regimen. See section 1.5)

Table 127: Rituximab maintenance projected annual patient incidence

	Incidence	2011	2012	2013	2014	2015
England and Wales		55601320	55993805	56387650	56781482	57175519
NHL	0.017%	9477	9543	9611	9678	9745
Follicular Lymphoma	23.37%	2215	2230	2246	2262	2277
Drug Treated	94%	2082	2096	2111	2126	2141
Stage III/IV	85%	1770	1782	1795	1807	1820
Eligible for anti-CD20 and 1st line treatment	100%	1770	1782	1795	1807	1820
Responsive to 1st line	89.7%	1587	1598	1610	1621	1632
Eligible for rituximab maintenance		1587	1684	1696	1708	1720
Total receiving 1st year therapy		1587	1598	1610	1621	1720
Total receiving 2nd year therapy		0	1587	1598	1610	1621
Total Annual Eligible Patients		**1588**	**3187**	**3209**	**3232**	**3342**

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that a sizeable proportion of patients otherwise eligible for rituximab maintenance will be treated with the currently-used watchful wait intervention. The market share of rituximab for maintenance reflects this proportion of patients (see section 1.3).

7.3 What assumption(s) were made about market share (when relevant)?

The annual uptake of rituximab for the five-year time horizon was estimated using a market share adjustment. An annual uptake of 20% was assumed for year one increasing until 2015.

The market share-adjusted annual patient population is shown in the table below.

Table 128: Rituximab maintenance incidence adjusted for market share

	2011	2012	2013	2014	2015
Total receiving 1st year therapy	1587	1598	1610	1621	1720
Market share adjustment (%)	*0.2*	*0.4*	*0.6*	*0.7*	*0.65*
Adjusted total receiving 1st year therapy	317	639	966	1135	1061
Total receiving 2nd year therapy	0	317	639	966	1135
Total Annual Eligible Patients	**317**	**957**	**1605**	**2100**	**2196**

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Because the current standard of care utilises the same number and type of resources needed for rituximab maintenance the only additional cost considerations for the latter are the acquisition, pharmacy and intravenous infusion administration costs of the drug.

In this submission the cost impact to NHS of first two cost components have been estimated using the BNF and PSSRU. The latter has been estimated using Reference Costs (delivery of subsequent chemotherapy as a daycase). The decision to use this setting reflects the length of time required for infusion and nurse monitoring.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

NHS reference costs provide a sufficient level of detail for identifying appropriate unit costs. Only one reference cost is required for rituximab maintenance; for administering rituximab IV of £251 per infusion (daycase, delivery of subsequent elements of chemotherapy cycle; SB15Z) (Reference Costs 2008-2009).

Other unit costs are derived from the BNF for drug acquisition of 100mg and 500mg vials (£174.63 and £873.13, respectively) and the cost of pharmacy of £32 (PSSRU 2009).

Note that the unit costs for the estimated annual cost impact to the NHS are presented as an annual calculation taken from the cost-effectiveness model. This is because over the course of a year a number of patients are expected to progress, hence ceasing treatment. To use a 'bottom up' calculation of unit costs and incidence would be an overestimation of the cost burden to the NHS.

Therefore, incorporating the proportion of patients still in PFS (using the PRIMA study patient population) from the first two years in the Markov model the costs of the first two years of treatment were found. These are shown in the table below for the annual average unit costs for drug acquisition and administration and pharmacy (combined).

Table 129: Annual cost for rituximab maintenance per patient

	Year 1 of treatment	Y2 of treatment
Total cost/patient Drug Acquisition	£7,590.46	£6,539.47
Total cost/patient Pharmacy and Administration (combined)	£1,660.43	£1,430.52
Total/patient	**£9,250.89**	**£7,969.99**

7.6 Were there any estimates of resource savings? If so, what were they?

No estimates of resource savings were made although these are expected because of incremental health benefits for rituximab maintenance therapy over the current standard of care. See section 1.8.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The total cost impact to the NHS (inc VAT) of implementing rituximab maintenance is £3.5 million for 2011 increasing to £22.2 million for 2015. The budget impact estimates presented below represent the maximum possible cost to the NHS during the first five years following positive NICE guidance.

Table 130: Total annual cost to NHS for rituximab maintenance

	2011	2012	2013	2014	2015
Total drug acquisition cost	£2,411,136	£6,929,232	£11,512,350	£14,928,681	£15,473,123
Total pharmacy and administration cost	£527,441	£1,515,783	£2,518,349	£3,265,679	£3,384,776
Total (exc VAT)	£2,938,577	£8,445,015	£14,030,699	£18,194,360	£18,857,899
Total (inc VAT)	£3,452,828	£9,922,893	£16,486,072	£21,378,373	£22,158,031

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Results from the PRIMA trial show maintenance therapy with rituximab after induction of response with chemotherapy plus rituximab in patients with high-tumour-burden follicular lymphoma has a clinically relevant and statistically significant improvement in the primary endpoint of PFS as compared to no maintenance therapy (observation).

It is therefore reasonable to assume that cost-offsets will occur in the long-term because of the improved health outcomes for patients treated with rituximab maintenance.

Further, as rituximab is already used off-license in the NHS there will be no need for redirection of resources to deliver training for staff.

8 References

Please use a recognised referencing style, such as Harvard or Vancouver.

References can be found at the end of the document

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during

the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

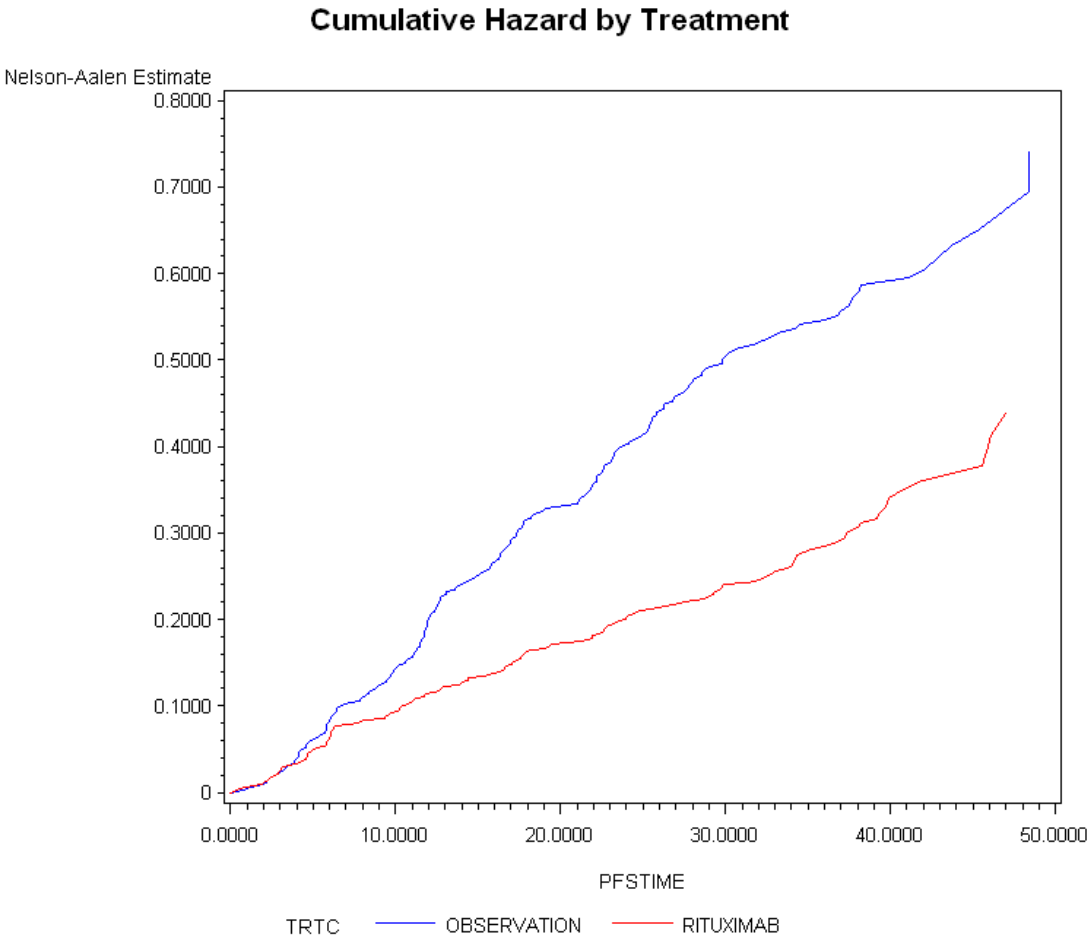
10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

Appendix I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Appendix II

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Appendix III

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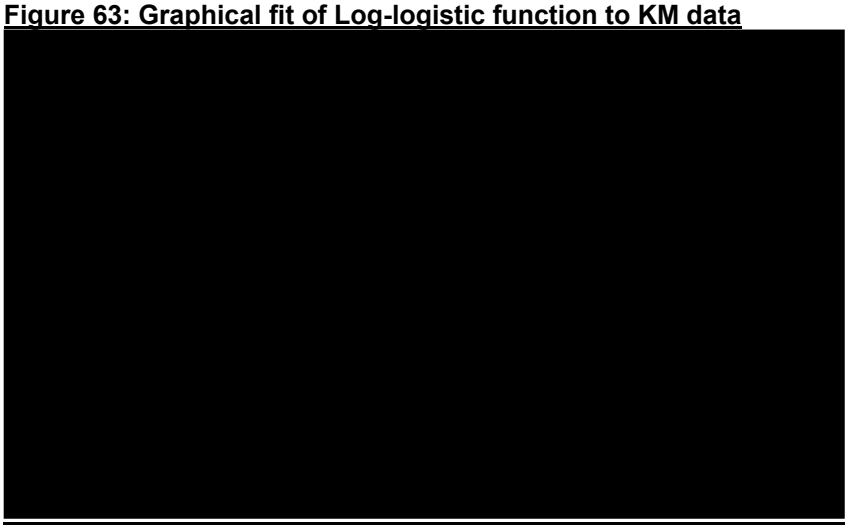
Figure 63: Graphical fit of Log-logistic function to KM data



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