Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

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Summary

Background Patients with follicular lymphoma can have long survival times, but disease progression typically occurs 3–5 years after initial treatment. We assessed the potential benefit of 2 years of rituximab maintenance after first-line treatment in patients with follicular lymphoma receiving a rituximab plus chemotherapy regimen.

Methods The randomised, open-label PRIMA study was undertaken in 223 centres in 25 countries. 1217 patients with previously untreated follicular lymphoma needing systemic therapy received one of three non-randomised immunochemotherapy induction regimens used in routine practice. 1019 patients achieving a complete or partial response were then randomly assigned to receive 2 years of rituximab maintenance therapy (375 mg/m^2 every 8 weeks) or observation. Treatment was assigned equally by centralised block randomisation, stratified by induction regimen, response, region, and centre. Neither the participants nor those giving the interventions, assessing outcomes, and analysing data were masked to group assignments. The primary endpoint was progression-free survival (PFS). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00140582.

Findings 505 patients were assigned to rituximab maintenance and 513 to observation (one patient died during randomisation). With a median follow-up of 36 months (IQR 30–42), PFS was 74·9% (95% CI 70·9–78·9) in the rituximab maintenance group (130 patients progressed) and 57·6% (53·2–62·0) in the observation group (218 progressed; hazard ratio [HR] 0·55, 95% CI 0·44–0·68, p<0·0001). 2 years after randomisation, 361 patients (71·5%) in the rituximab maintenance group were in complete or unconfirmed complete response versus 268 (52·2%) in the observation group (p=0·0001). Overall survival did not differ significantly between groups (HR 0·87, 95% CI 0·51–1·47). Grade 3 and 4 adverse events were recorded in 121 patients (24%) in the rituximab maintenance group and 84 (17%) in the observation group (risk ratio 1·46, 95% CI 1·14–1·87; p=0·0026). Infections (grades 2–4) were the most common adverse event, occurring in 197 (39%) and 123 (24%) patients, respectively (risk ratio 1·62, 95% CI 1·35–1·96; p<0·0001).

Interpretation 2 years of rituximab maintenance therapy after immunochemotherapy as first-line treatment for follicular lymphoma significantly improves PFS.

Funding Groupe d'Etude des Lymphomes de l'Adulte (GELA) and F Hoffmann-La Roche.

Introduction

Follicular lymphoma is the second most common lymphoma subtype and, despite substantial improvements in survival, disseminated disease is usually incurable.[1,2] The disease characteristically responds well to first-line therapy but typically manifests repeated relapses with the need for recurrent therapeutic interventions, with disease-free intervals becoming progressively shorter.[3,4] Although some patients can initially be managed with watchful waiting because they are asymptomatic with no adverse prognostic features, most need systemic cytotoxic-based treatment. In the past decade, several randomised studies[5–8] have established that the combination of the anti-CD20 monoclonal antibody rituximab with various chemotherapy regimens can improve patients' overall survival, and this combination is now regarded as the standard of care in first-line follicular lymphoma.

Rituximab, in view of its efficacy, pharmacokinetic characteristics, and safety profile, has already been investigated as maintenance treatment in patients with follicular lymphoma.[9–13] Previous studies have shown a significant clinical benefit of rituximab maintenance in patients with relapsed disease after chemotherapy with or without rituximab.[11,12] The use of rituximab maintenance has also been studied after initial treatment with single-agent rituximab[9,10] or chemotherapy alone;[13] however, neither of these induction

regimens is considered optimum as initial treatment for patients in need of therapy. Hence, the PRIMA (Primary RItuximab and MAintenance) study was designed to assess the potential benefit of 2 years of rituximab maintenance after first-line treatment in patients with follicular lymphoma receiving a rituximab plus chemotherapy regimen.

Methods

Study design and patients

This open-label, international, multicentre randomised study was undertaken between December, 2004, and April 2007, in 223 centres in 25 countries. The trial consisted of two phases, induction and maintenance.

Patients were eligible for induction if they were older than 18 years and presented with untreated follicular lymphoma (grade 1, 2, or 3a) diagnosed by a lymph-node biopsy (done within 4 months of study registration). Eligibility required at least one criterion of high tumour burden—namely, bulky disease (one lymphoma lesion greater than 7 cm); three separate nodes of 3 cm or more; symptomatic splenic enlargement; organ compression by tumour, pleural, or peritoneal effusion; raised serum concentrations of either lactate dehydrogenase or β_2-microglobulin; or the presence of B symptoms. Patients had to have a performance status of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale and adequate haematological function (unless due to lymphoma). Non-eligibility criteria were a diagnosis of follicular lymphoma grade 3b or transformed into diffuse large B-cell lymphoma, CNS involvement, or a life expectancy of less than 6 months. Patients with a previous history of cancer (apart from adequately treated non-melanoma skin cancer or in-situ cervical cancer), with poor renal or hepatic function (unless due to lymphoma), or a previous history of allergy to murine products were not eligible. Patients with a known HIV infection or an active hepatitis B or hepatitis C virus infection were also excluded, but pretreatment testing was not initially mandated. We excluded patients if they had had any major surgical procedure or used corticosteroids at doses greater than 20 mg per day within 1 month before study entry.

The protocol was approved by local or national ethics committees according to the laws of each country, and the study was undertaken in accordance with the Declaration of Helsinki. Patients were required to provide written informed consent before registration.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to observation or rituximab maintenance (12 infusions of 375 mg/m² given intravenously, one every 8 weeks) starting 8 weeks after the last induction treatment. The duration and schedule of rituximab maintenance in this study was derived from previous studies using either eight infusions[11] or 16 infusions[13] over 2 years and from pharmacokinetic studies suggesting that 2-month intervals might be more suitable than 3 months to reach a trough in serum rituximab concentration of 25 μg/mL.[14,15] Randomisation was stratified for induction regimen, response to induction treatment, geographical region, and centre, with a block size of four. Investigators enrolled the participants, and assignment to trial groups was done with a computer-assisted randomisation allocation sequence (generated by a statistician) that took place centrally at Groupe d'Etude des Lymphomes de l'Adulte (GELA) central offices with a fax process, without the intervention of investigators. Neither the participants nor those giving the interventions, assessing outcomes, and analysing data were masked to group assignment.

Procedures

Initial staging included physical examination; standard laboratory assessments; CT scans of the chest, abdomen, and pelvis; and bone marrow biopsy. Pathological specimens were centrally reviewed by a panel of expert pathologists in each country or in the GELA pathology centre.

During the induction phase, patients were treated with one of three standard immunochemotherapy regimens, with each centre selecting the preferred regimen for all patients enrolled in that centre. The three chemotherapy regimens combined with rituximab were: CVP (cyclophosphamide 750 mg/m² given intravenously on day 1, vincristine 1·4 mg/m² [capped at 2 mg] given intravenously on day 1, and prednisone 40 mg/m² given orally on days 1–5, with each cycle repeated every 3 weeks for eight cycles), CHOP (cyclophosphamide 750 mg/m² given intravenously on day 1, vincristine 1·4 mg/m² [capped at 2 mg] given intravenously on day 1, doxorubicin 50 mg/m² given intravenously on day 1, and prednisone 100 mg given orally on days 1–5, with each cycle repeated every 3 weeks for six cycles), or FCM (fludarabine 25 mg/m² given intravenously on days 1–3, cyclophosphamide 200 mg/m² given orally on days 1–3, and mitoxantrone 6 mg/m² given intravenously on day 1, with each cycle repeated every 4 weeks for six cycles). Rituximab (375 mg/m² for each infusion) was administered at day 1 of each chemotherapy course, with two additional infusions administered in patients given CHOP (every 3 weeks after the last cycle) and FCM (2 weeks after the first and the fourth cycles) to provide an equivalent exposure to the antibody during induction.

Response to induction[16] was assessed 2–4 weeks after the last induction treatment course. Patients who obtained a complete response, an unconfirmed complete response, or a partial response were eligible for randomisation to the maintenance phase of the study. Additionally, patients were required to have received at least six cycles of rituximab plus CVP (R-CVP), four cycles of rituximab plus CHOP (R-CHOP), or four cycles of rituximab plus FCM (R-FCM) (each with at least six infusions of rituximab) without a delay of more than 2 weeks between each cycle. Any severe underlying

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For the **protocol for the PRIMA study** see http://prima.gela.org

medical disorder that could impair participation or any major induction treatment-related toxic effect precluded eligibility.

Patients were assessed by clinical examination every 8 weeks and CT scans every 6 months during the 2-year maintenance phase of the study. An end-of-

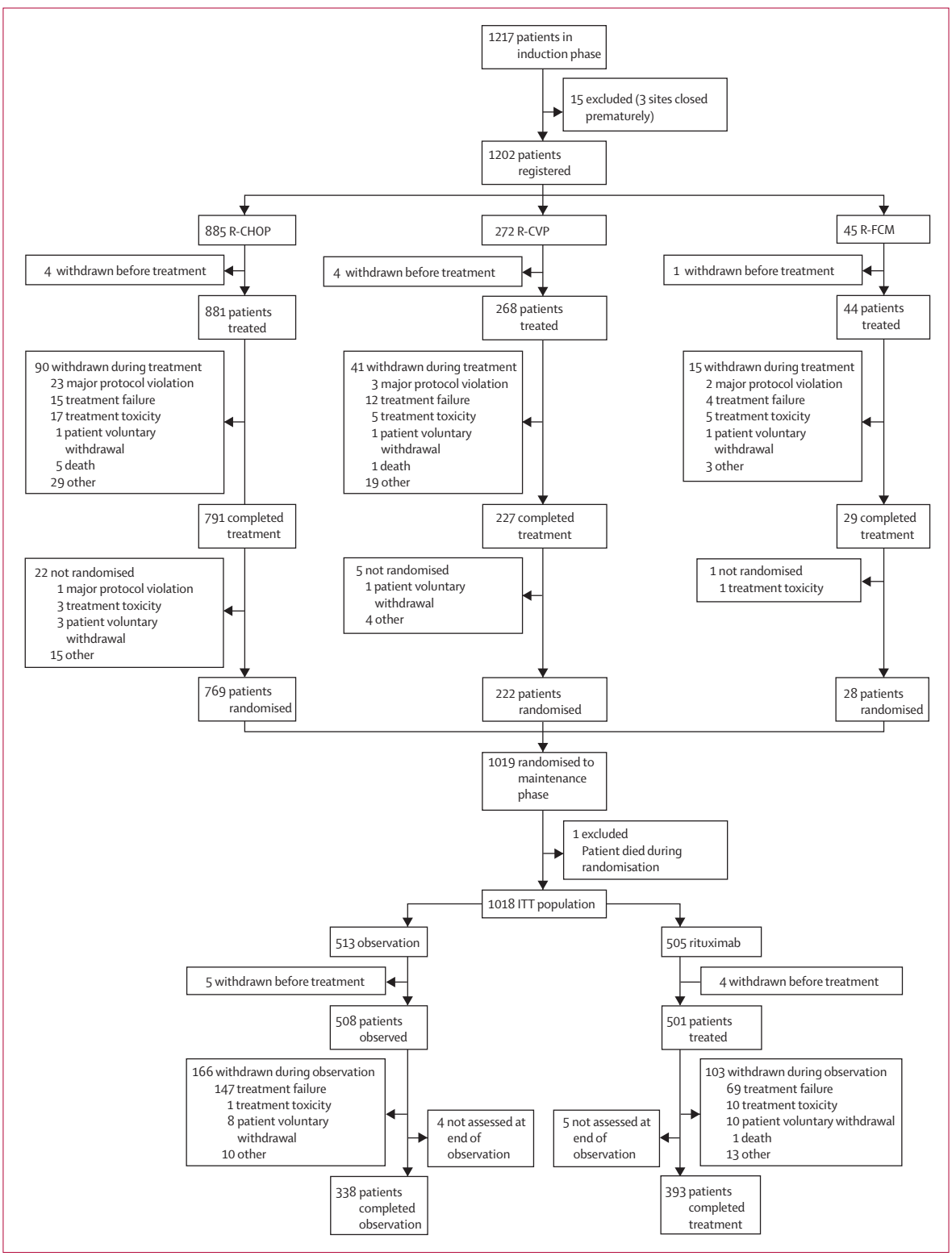

Figure 1: **Trial profile**
When the reasons for withdrawal categorised as other were investigated and centrally reviewed, of the 184 patients withdrawing from registration until randomisation, the main reasons leading to withdrawal were: major protocol violation (including eligibility criteria or inadequate induction treatment, n=61); complete or partial response not achieved after induction therapy (n=46); toxic effects or delays during induction treatment administration (n=44); underlying medical disease or death (n=18); patient decision (n=8); and investigator decision (n=7). R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CVP=rituximab, cyclophosphamide, vincristine, and prednisone. R-FCM=rituximab, fludarabine, cyclophosphamide, and mitoxantrone. ITT=intention to treat.

treatment assessment also required a bone marrow biopsy if initially involved. Follow-up assessments included clinical evaluation every 3 months and CT scans every 6 months for an additional 3 years. Quality-of-life questionnaires for functional assessment of cancer therapy—general (FACT-G) score and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 scale were planned to be completed by patients at registration, at the end of induction, and then every 12 months.

Statistical analysis

The study was designed to show a 45% increase in median progression-free survival (PFS) from the time of randomisation (6 months after the start of induction therapy) with a power of 80% and an overall two-sided type I error of 5%, with use of a two-sided log-rank test. The trial was intended in 2004 to register 640 patients and randomly assign 480 (assuming that 75% of the patients would be randomly assigned on the basis of response rate and eligibility criteria). Mature information then became available from earlier trials,[11,17,18] indicating a 6-month delay before seeing a benefit of maintenance after immunochemotherapy, and patient accrual was more rapid than was expected. Therefore, two protocol amendments were implemented before the first data analysis, increasing the final sample size to 1200 patients registered and 900 randomly assigned, and allowing a more meaningful examination of the primary endpoint in subgroups. Two interim analyses were originally scheduled to be done after 50% (n=172) and 75% (n=258) of the total number of anticipated events (n=344). The protocol was subsequently amended to remove the first interim analysis because the results would have been regarded as clinically immature with short follow-up. The α-spending function with the O'Brien–Fleming boundary was applied for the interim analysis to maintain the overall two-sided type I error of 0·05. Subgroup analyses for PFS were planned according to age, sex, categories defined by the initial follicular lymphoma international prognostic index (FLIPI),[19] induction regimen, and response to induction (complete or unconfirmed complete response, or partial response).

The primary study endpoint was PFS from the time of randomisation to rituximab maintenance or no further treatment (observation). Secondary endpoints were event-free survival, time to next chemotherapy treatment, time to next antilymphoma treatment, overall survival, response rate at the end of maintenance, safety, toxic effects, and quality of life.

Response and progression were defined with international standard criteria.[16] Survival functions were estimated by the Kaplan-Meier method and compared by log-rank test stratified by induction regimen and induction treatment response. Cox regression analysis was done to adjust for the effect of known prognostic factors (age, sex, FLIPI category, induction treatment, and response to induction) in the assessment of maintenance effect. Response rates and frequency of adverse events were compared with the χ^2 test. To establish whether the study treatment groups differed in quality of life assessed at the end of treatment, independent of any differences in quality of life assessed at the end of induction, we used ANCOVA. FACT-G total

	Patients who received induction treatment (n=1193)	Randomised patients	
		Observation (n=513)	Rituximab maintenance (n=505)
Age >60 years	423 (35%)	180 (35%)	176 (35%)
Age (years)	56 (22–87)	55 (22–84)	57 (26–79)
Male sex	622 (52%)	263 (51%)	270 (53%)
Ann Arbor stage III/IV	1075 (90%)	459 (89%)	459 (91%)
ECOG performance status ≥1	434 (36%)	172 (34%)	181 (36%)
B symptoms present	388 (33%)	156 (30%)	160 (32%)
Bone marrow lymphoma involvement	654 (55%)	285 (56%)	275 (54%)
Lactate dehydrogenase >ULN*	403 (34%)	164 (32%)	173 (34%)
Haemoglobin <120 g/L	239 (20%)	96 (19%)	100 (20%)
β_2 microglobulin ≥3 mg/L*	348 (32%)	132 (28%)	148 (32%)
FLIPI score†			
Low (0–1 risk factors)	254 (21%)	110 (21%)	106 (21%)
Intermediate (2 risk factors)	423 (36%)	187 (36%)	183 (36%)
High (3–5 risk factors)	514 (43%)	216 (42%)	215 (43%)
Initial local diagnosis of FL (other than grade 3B)	1188 (100%)	512 (100%)	504 (100%)
Central pathological review done	1115 (93%)	487 (95%)	467 (92%)
Confirmed FL (other than grade 3B)	994 (84%)	433 (84%)	425 (84%)
Diagnosis of other lymphoma subtype‡	56 (5%)	28 (5%)	16 (3%)
Unclassifiable or not assessable for technical reasons	65 (6%)	26 (5%)	26 (5%)
Induction immunochemotherapy regimen			
R-CHOP	885 (74%)	386 (75%)	382 (76%)
R-CVP	272 (23 %)	113 (22%)	109 (22%)
R-FCM	45 (4%)	14 (3%)	14 (3%)
Response to induction			
Complete response	..	195 (38%)	205 (41%)
Unconfirmed complete response	..	165 (32%)	155 (31%)
Partial response	..	152 (30%)	139 (28%)
Other§	..	1 (≤1%)	6 (1%)

Data are number (%) or median (range). ECOG=Eastern Cooperative Oncology Group. ULN=upper limit of normal. FLIPI=follicular lymphoma international prognostic index. FL=follicular lymphoma. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CVP=rituximab, cyclophosphamide, vincristine, and prednisone. R-FCM=rituximab, fludarabine, cyclophosphamide, and mitoxantrone. *Lactate dehydrogenase and β_2-microglobulin serum concentrations available for only 1188 and 1101 patients, respectively. †FLIPI scores were collected at registration. The risk score includes five factors: age (>60 years), Ann Arbor stage (III or IV), haemoglobin (≤120 g/L), serum lactate dehydrogenase (>ULN), and number of nodal areas involved (five or more).[17] Data are available for 1191 patients. ‡Other lymphoma subtypes enrolled included FL grade 3B (n=12), combined diffuse large B-cell lymphoma and FL (n=24), diffuse large B-cell lymphoma (n=10), mantle cell lymphoma (n=6), small lymphocytic lymphoma (n=2), Hodgkin's lymphoma (n=1), and angioimmunoblastic T-cell lymphoma (n=1). §After data cleaning, one patient in the observation group and four in the rituximab maintenance group were assessed as having stable disease at randomisation, and two other patients in the rituximab maintenance group missed standard assessment procedures.

Table 1: **Baseline demographics and clinical characteristics of patients at enrolment (before immunochemotherapy induction treatment), and at randomisation, according to study group**

scores and EORTC QLQ-C30 global health scores were collected during rituximab maintenance or observation, with repeated measurements over time (censored at the date of disease progression to avoid potential biases related to toxic effects of second-line treatment), and analysed with an unstructured covariance model. All efficacy analyses were done in the intention-to-treat randomised population.

On Jan 14, 2009, 267 events were recorded, leading to the protocol-specified interim analysis undertaken by the data safety monitoring committee that declared the primary endpoint of PFS had been met and that the study should be fully analysed. The study was then terminated; at that time the median follow-up after randomisation was 25 months (IQR 19–30) with 231 patients still to complete the maintenance or observation period. This report describes the analysis done after an additional year of follow-up, with a cutoff date of Jan 15, 2010, when all randomised patients had reached the time for end-of-treatment evaluation or were withdrawn.

The study is registered with ClinicalTrials.gov, number NCT00140582.

Role of the funding source

The GELA acted as the sponsor of the study and developed and undertook the study protocol in collaboration with several other lymphoma study groups, F Hoffmann-La Roche, and Biogen IDEC. All case report forms were sent to the GELA central operation office (GELA-RC), and double data entry was undertaken for verification purposes. Queries and on-site monitoring data were used for final validation, and GELA-RC had full control of the database. An independent data safety monitoring committee examined the safety data every year, advised on protocol amendments, and undertook the prescheduled interim analysis of the efficacy results. Final statistical analyses were done independently by GELA-RC and F Hoffmann-La Roche. The corresponding author was responsible for data analysis, data interpretation, and writing of the report; had full access to all the data in the study; and had the final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. On-site monitoring showed that three centres did not adhere to good clinical practice and were closed (excluding 15 patients); nine other registered patients withdrew before receiving any treatment. Therefore, 1193 patients had complete data at study enrolment (table 1). Of those, 1115 (93%) had central pathology review done, and follicular lymphoma (except grade 3B) was confirmed in 994 cases (89%). We noted no differences in demographics or disease characteristics at enrolment between patients who

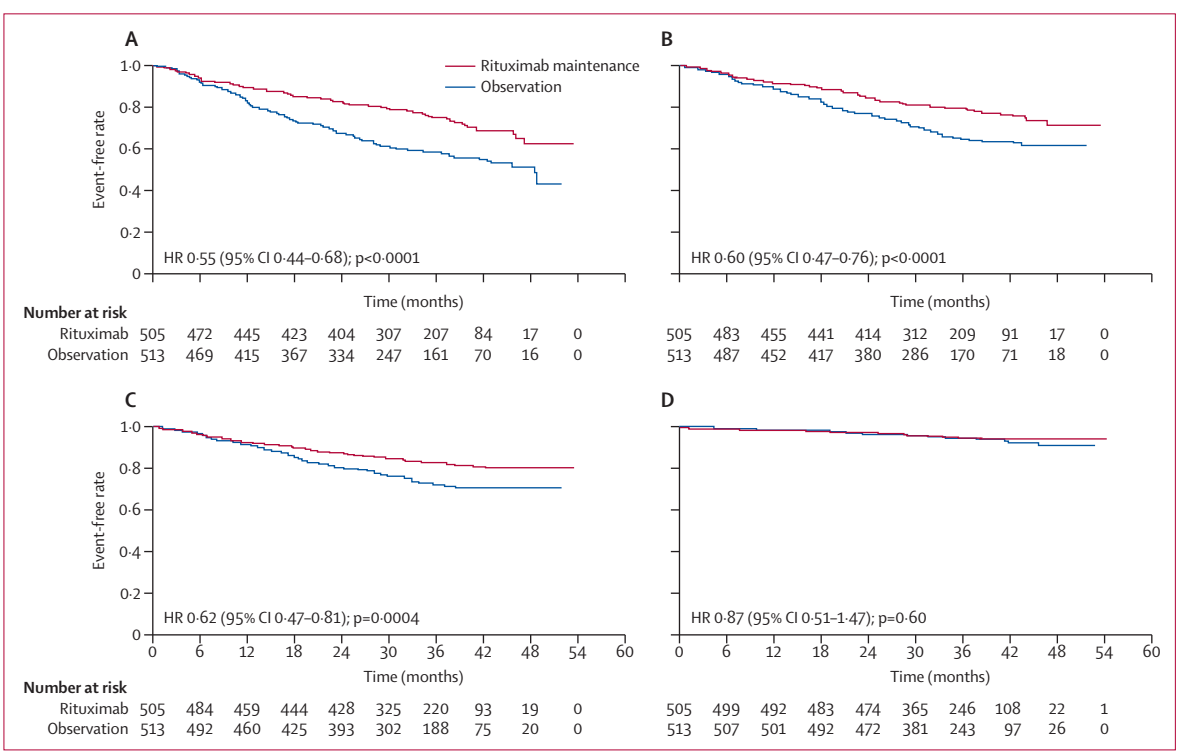

Figure 2: **Kaplan-Meier estimates of progression-free survival (A), time to next antilymphoma treatment (B), time to next chemotherapy (C), and overall survival (D) from randomisation with rituximab maintenance versus observation**
HR=hazard ratio.

received R-CHOP (n=885), R-CVP (n=272), or R-FCM (n=45) induction (data not shown). 146 patients withdrew during induction treatment, a further 28 completed induction but were not randomly assigned (figure 1), and one patient died before notification of the randomisation. Therefore, from randomisation, the intention-to-treat population consisted of 1018 patients (505 in the rituximab maintenance group and 513 in the observation group; table 1).

With a median follow-up of 36 months in both groups (IQR 30–42), 130 of 505 patients in the rituximab maintenance group and 218 of 513 in the observation group had documented disease progression, and five and three patients, respectively, had died before disease progression. 3-year PFS was 74·9% (95% CI 70·9–78·9) in the rituximab maintenance group and 57·6% (53·2–62·0) in the observation group (stratified log rank, p<0·0001; figure 2A). The risk of progression was significantly reduced for the rituximab maintenance group (hazard ratio [HR] 0·55, 95% CI 0·44–0·68). The median time to progression was not reached in the rituximab maintenance group and was estimated to be 48·3 months (95% CI 38·0 to not reached) in the observation group.

Pre-planned analyses of patient subgroups categorised by age, sex, FLIPI score category, induction chemotherapy, and response to induction showed that the effect of rituximab maintenance was consistent across these different subgroups, although with borderline results for patients having received R-CVP (number for those having received R-FCM are too small to conclude) (figure 3). In a Cox regression multivariate analysis adjusted by prognostic factors, a longer PFS was significantly associated with randomisation to the rituximab maintenance group (HR 0·55, 95% CI 0·44–0·68; p<0·0001), an age of 60 years or older (0·68, 0·54–0·86; p=0·0013), female sex (0·76, 0·62–0·94; p=0·013), lower FLIPI score categories (overall p<0·0001), and R-CHOP or R-FCM as induction treatment (0·39, 0·17–0·89; p=0·0029).

Overall, 102 of 505 patients in the rituximab maintenance group and 167 of 513 patients in the observation group had begun a new antilymphoma treatment, which was a chemotherapy regimen in 80 patients in the rituximab maintenance group and 129 in the observation group. We recorded significant reductions in the risk of starting a new antilymphoma treatment or death (figure 2B) or starting a new chemotherapy or death (figure 2C) in the rituximab maintenance group. Event-free survival was also significantly improved in the rituximab maintenance group (stratified HR 0·59, 95% CI 0·48–0·72). With only 26 deaths recorded in the rituximab maintenance group and 30 in the observation group with present follow-up, we noted no significant difference in overall survival (figure 2D).

At the end of the maintenance phase of the study, 361 of 505 patients (71·5%; 95% CI 67·3–75·4) in the rituximab maintenance group were in complete or unconfirmed complete response compared with 268 of 513 patients (52·2%, 47·8–56·6) in the observation group (estimated difference 18·0%, 12·3–23·6; p=0·0001). More patients who were in partial response at the time of randomisation converted to complete or unconfirmed complete response after 2 years in the rituximab maintenance group (72/139 [52%]) than did those in the observation group (45/152 [30%]; estimated difference 22·2%, 95% CI 11·2–33·3, p=0·0001).

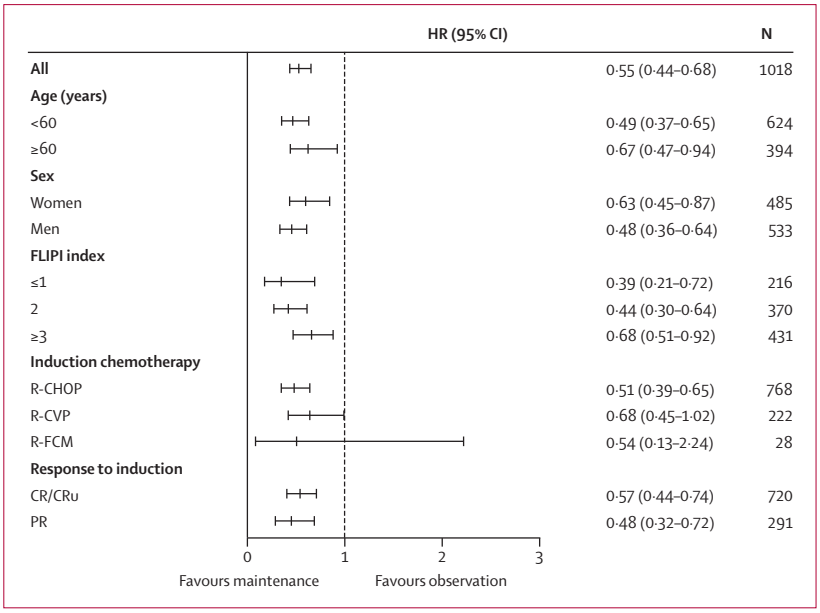

Figure 3: **Risk of progression with rituximab maintenance versus observation, according to prespecified subgroups**

HR=hazard ratio. FLIPI=follicular lymphoma international prognostic index. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CVP=rituximab, cyclophosphamide, vincristine, and prednisone. R-FCM=rituximab, fludarabine, cyclophosphamide, and mitoxantrone. CR=complete response. CRu=unconfirmed complete response. PR=partial response.

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

Data are number (%). NA=not applicable. *Safety during maintenance was assessed for patients who undertook at least one visit (rituximab treatment or observation) after randomisation. All adverse events, defined as any adverse change from the patient's baseline condition, whether considered related to treatment or not, were collected and graded according to the Common Terminology Criteria for Adverse Events 3.0 grading system.[18] All grade 3 and 4 events plus grade 2 infections were recorded in detail during maintenance or observation and 6 months thereafter. †Other events leading to treatment discontinuation were pyrexia, fulminant hepatitis, hypersensitivity, post-procedural fistula, and lung disorder (one case each).

Table 2: **Grade 3 and 4 adverse events* experienced by 2% or more of patients and adverse events leading to treatment discontinuation, after randomisation to rituximab maintenance or observation**

	Baseline (randomisation)		After 1 year		End of maintenance phase	
	Maintenance	Observation	Maintenance	Observation	Maintenance	Observation
IgA						
n	131	125	118	89	111	61
g/L	1·33 (0·63)	1·57 (3·55)	1·26 (0·58)	1·40 (0·88)	1·25 (0·50)	1·55 (0·91)
IgG						
n	131	125	118	89	100	60
g/L	7·87 (2·26)	7·76 (2·13)	7·73 (2·12)	8·22 (2·22)	7·48 (2·13)	8·31 (2·32)
IgM						
n	127	121	113	89	110	61
g/L	0·64 (0·52)	0·59 (0·55)	0·55 (0·39)	0·55 (0·31)	0·51 (0·39)	0·58 (0·25)

Immunoglobulin concentrations are given as mean (SD). Serum concentrations of immunoglobulins were assessed only in a subset of patients in one participating country.

Table 3: **Serum concentrations of immunoglobulins at randomisation, after 1 year of maintenance, and at the end of the maintenance phase**

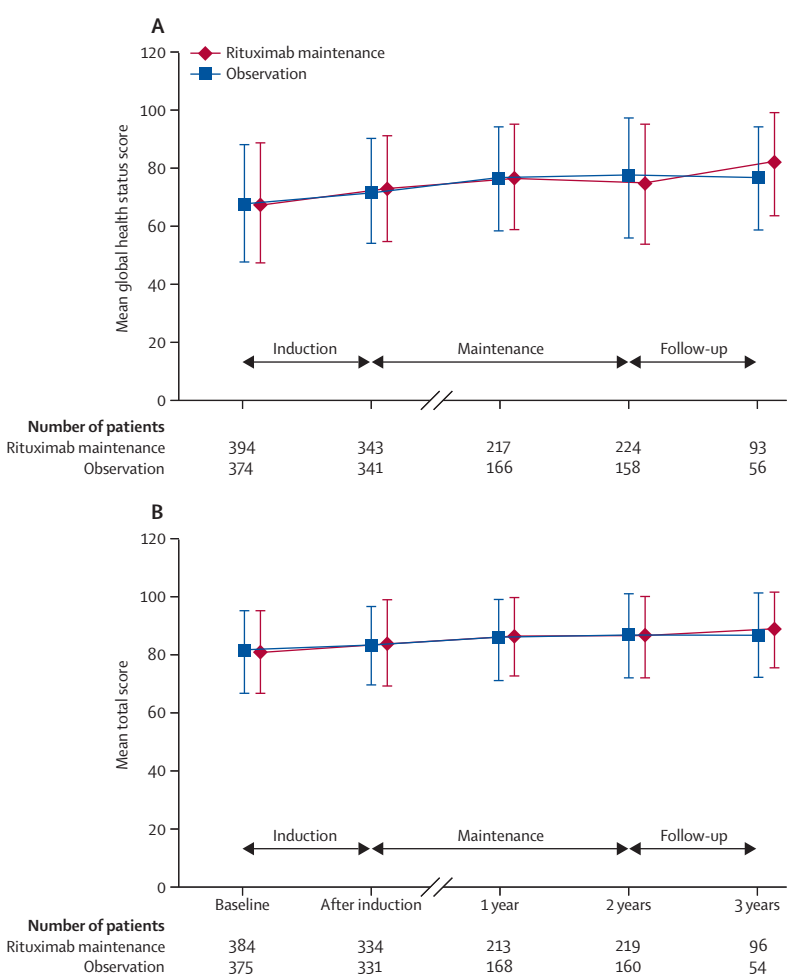

Figure 4: **Quality of life during 2 years of treatment with rituximab maintenance versus observation alone**
(A) European Organisation for Research and Treatment of Cancer quality-of-life questionnaire C30 scale. (B) Functional assessment of cancer therapy—general scale. Quality-of-life assessments were censored at time of progression.

Of the 1009 patients assessed for safety, adverse events were reported in 281 of 501 (56%) patients in the rituximab maintenance group and 189 of 508 (37%) in the observation group (risk ratio 1·51, 95% CI 1·32–1·73; p<0·0001). The most common adverse events reported were grade 2–4 infections in 197 of 501 (39%) patients and 123 of 508 (24%) patients, respectively (risk ratio 1·62, 1·35–1·96; p<0·0001). The five most common infections reported in the rituximab and observation groups were bronchitis (54 and 28 cases, respectively), upper respiratory tract infections (28 and 11 cases), sinusitis (21 and eight cases), urinary tract infections (14 and nine cases), nasopharyngitis (11 and 14 cases), and urinary tract infections (14 and nine cases), whereas the cumulative number of herpes viruses-related infections were 19 and 12, respectively. Grade 3 or 4 adverse events[20] (table 2) occurred in 121 of 501 (24%) patients in the rituximab group and 84 of 508 (17%) patients in the observation group (risk ratio 1·46, 1·14–1·87; p=0·0026). 19 (4%) and eight (2%) events, respectively, resulted in treatment discontinuation (risk ratio 2·41, 1·06–5·45; p=0·029).

Only one death (fulminant hepatitis B in the absence of viral suppressive therapy in the rituximab maintenance group) was reported to be possibly related to treatment toxic effects; other causes of deaths before lymphoma recurrence were attributed to other malignant diseases (four cases; one in rituximab maintenance group and three in observation group), or pulmonary haemorrhage, accident, or unknown (sudden death) (one case each in rituximab maintenance group). Two other patients (one from each group) developed progressive multifocal leukoencephalopathy after lymphoma relapse and subsequent treatments, which included investigational agents for both patients. At the end of 2 years of rituximab maintenance or observation, median serum concentrations of immunoglobulin isotypes did not differ significantly between the rituximab maintenance and observation groups (table 3).

The mean adjusted FACT-G total scores at the end of treatment were 86·6 (95% CI 85·0–88·3) in the rituximab maintenance group and 87·2 (85·3–89·1) in the observation group, suggesting no association of these scores with treatment group (ANCOVA adjusted for scores at the end of induction, p=0·68). Consistently, the EORTC QLQ-C30 global health status mean scores were 75·5 (72·8–78·2) and 75·2 (72·0–78·4), respectively (p=0·89; figure 4). The analysis of repeated measures was consistent with ANCOVA, and did not show any statistical difference on either scale (data not shown).

Discussion

Results of the PRIMA study show that 2 years of rituximab maintenance therapy significantly prolongs PFS, delays the time to next antilymphoma treatment and next chemotherapy, and improves the quality of response in patients with previously untreated follicular

lymphoma that is responsive to first-line rituximab plus chemotherapy. Rituximab maintenance was well tolerated, with a limited number of adverse events resulting in treatment discontinuation, and there were no unexpected safety findings. In line with other studies,[21] we recorded a significantly increased incidence of infectious events, mostly of mild to moderate severity, despite no significant decrease in serum immunoglobulin concentrations. Physicians and patients should be aware of this risk to optimise the management of these patients. Further follow-up of immunoglobulin concentrations will also be done in the trial. Nevertheless, despite the higher frequency of adverse events in the rituximab maintenance group than in the observation group, few patients withdrew from the study because of toxic effects. Furthermore, the burden associated with repeated infusions over 2 years did not seem to impair patient quality of life, which was similar in both study groups. However, since only a subset of patients completed the quality-of-life questionnaires, these data should be interpreted cautiously, because we cannot exclude a reporting bias favouring patients who did not have treatment-related adverse events.

The significant reduction in rate of lymphoma progression in the rituximab maintenance group was consistent between patients with different demographics, disease characteristics, and prognostic factors, within the limitations of the study eligibility criteria. Together with the results of the multivariate Cox regression analysis, these data suggest that all analysed categories of patients eligible for first-line immunochemotherapy benefited from rituximab maintenance. Notably, we recorded a reduction in the risk of lymphoma recurrence irrespective of the intensity of the first-line induction therapy and the response achieved. Although we noted no gain in overall survival, the reduction in the risk of disease progression after responding to induction is likely to be preferred by patients with follicular lymphoma. This preference should be balanced with the constraints and costs associated with 2-year rituximab maintenance. However, in view of the substantial improvement in patient survival during the past decade[2] and the indication that rituximab maintenance might also result in overall survival benefits in relapsed follicular lymphoma,[11,21,22] we should not exclude such a possible benefit of this intervention in the long term.

Different mechanisms of action have been proposed for the therapeutic activity of rituximab.[23] When used as a single agent in a prolonged maintenance scheme, the immune-mediated activity of the antibody could possibly be more potent than other mechanisms. Data suggest that anti-CD20 antibodies might induce a T-cell-specific response against lymphoma cells.[24,25] Other studies investigating the mechanisms of follicular lymphoma development have suggested that lymphoma precursor cells are able to survive for years both in healthy individuals[26] and in patients,[27,28] where they can lead to disease recurrence. Rituximab maintenance might eventually exert a long-term control on these cells.

Follicular lymphoma is an indolent disease, with prolonged survival even in cases that are ultimately fatal. The efficacy of salvage therapies used after initial treatment failure could also preclude the demonstration of an overall survival benefit associated with first-line therapy.[22,29–31] With the present 3-year follow-up, less than 5% of patients in either group had died, with no significant difference between the two groups, and salvage therapy results are still immature. However, a higher proportion of patients achieved a complete response at the end of rituximab maintenance treatment than in the observation group. Attainment of a complete response is associated with improved long-term survival in patients with follicular lymphoma.[32] Since longer follow-up will be needed to show any possible effect of rituximab maintenance on overall survival, we will continue to follow up these patients. The results of other studies assessing radioimmunotherapy consolidation with iodine-131 labelled tositumomab (regis-tered with ClinicalTrials.gov, numbers NCT00006721 and NCT00770224) or rituximab maintenance for 4 or 5 years (NCT00877214 and NCT00227695) might also provide some insights about how to improve the outcome of patients with follicular lymphoma.

In summary, the data from this study suggest that rituximab maintenance in patients with high tumour burden follicular lymphoma, who respond to rituximab plus chemotherapy induction, improves PFS and should now be considered as first-line treatment for these patients (panel).

***Panel:* Research in context**

Systematic review

We searched Medline from January, 1995, to November, 2010, for full papers reporting randomised clinical trials and meta-analyses with the terms "rituximab maintenance" and "lymphoma". We identified five randomised clinical trials in patients with follicular lymphoma,[9-13] with two updates[22,33] and one meta-analysis.[21]

Interpretation

Together, these studies provide substantial evidence that rituximab maintenance improves the outcome of patients with follicular lymphoma in term of progression-free and overall survival. The use of rituximab maintenance is associated with an increased risk of infections. Our results are consistent with findings from other studies, but provide evidence that this intervention improves progression-free survival and response rate in patients with follicular lymphoma responding to a combination of chemotherapy plus rituximab administered as first-line treatment.

Contributors

GS, JFS, FO, AL-G, LX, PF, PB, CH, AH, AL, AS, MM, BC, and HT designed the study. GS, JFS, FO, AL-G, DB, LX, LMP, SL, TI, MGdS, AH, AL, and MM were responsible for the conduct of the study centrally or at the country-specific level. GS, JFS, FO, AL-G, LX, PF, PB, CH, LMP, SL, TI, MGdS, RB, JVC, DC, AD, DS, PS, OC, CF, CS, JAE, GM, AH, AL, AS, MM, BC, and HT contributed research data to the study. GS, JFS, FO, AL-G, LX, PF, PB, CH, AH, AL, AS, BC, and HT contributed to data analysis and interpretation. GS drafted the report, which all co-authors critically revised for significant scientific content.

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Conflicts of interest

GS, JFS, ALG, DB, PF, PS, CH, SL, AH, OC, AL, BC, AD, and HT declared consultancy, honoraria, and/or advisory board membership from Roche and/or Genentech. PF, CH, AD, SL, PS, OC, AL, and BC received grant support from Roche. GS, JFS, DB, CH, AD, SL, PS, MGdS, and BC received travel support from Roche. GS, JFS, ALG, SL, and AL have received support for preparation of educational materials and/or lectures from Roche. PF has received payment for participation in data review meetings and has stock options with Roche. MM is a paid employee of Roche and has stock options with Roche. GS is also an advisory board member for Celgene, Janssen-Cilag, Genzyme, and Calistoga; and has received travel support from Pfizer and support for educational materials from Janssen-Cilag and Celgene. ALG has received support for educational materials from Celgene. HT is an advisory board member for Celgene and Seattle Genetics; has received grant support from Celgene and Amgen; and has received support for preparation of educational materials from Celgene, Amgen, Janssen-Cilag, and Pfizer. SL declared consultancy and honoraria for Bayer and has received travel support from GlaxoSmithKline. FO, LX, JVC, RB, PB, DC, LMP, DS, TI, CF, CS, JE, GM, and AS declare that they have no conflicts of interest.

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