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A Randomized Phase III Study in Low Grade Lymphoma Comparing Maintenance Anti-CD20 Antibody versus Observation following Induction Therapy: A trial of the ECOG- ACRIN Cancer Research Group (E1496)

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Abstract

Background—In the ECOG-ACRIN Cancer Research Group study, E1496, we reported that maintenance rituximab prolonged progression-free survival when compared to observation alone in patients with indolent lymphoma after induction chemotherapy. Here we present the long-term follow-up of the same patient cohort.

Methods—Patients with indolent lymphoma received induction chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP). Patients with stable disease or better were then randomized to weekly rituximab (375mg/m²) ×4 every 6 months for 2 years (MR) or observation (OBS). The primary endpoint was progression-free survival (PFS); secondary endpoints were overall survival (OS), response rate and toxicities.

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Results—Of 387 patients who initially received CVP induction, 158 were randomized to MR and 153 to OBS. After a median follow-up of 11.5 years, patients on MR had a longer median PFS (4.8 years) than patients on OBS (1.3 years; hazard ratio (HR) 0.49; $p < 0.0001$). However, there was no difference in OS between MR and OBS (10-year OS 67% vs. 59%; median OS: 13.5 years vs. not reached; HR 0.91; $p = 0.69$). Only minimal residual disease after induction therapy was significantly associated with PFS on multivariate analysis (HR 0.71; $p = 0.02$). Low initial tumor burden, minimal residual disease, follicular histology, high FLIPI score, and male gender, were associated with OS. There was no difference in the rate of second primary malignancies between MR and OBS.

Conclusions—With long term follow up, MR did not influence the OS. The PFS benefit was maintained. MR should be considered optional in patients with indolent B-cell lymphoma.

Keywords

rituximab; rituximab maintenance; indolent lymphoma; follicular lymphoma; Non-Hodgkin lymphoma

Introduction

The CD20-directed monoclonal antibody rituximab was initially approved by the US FDA as a single agent for patients with indolent B-cell and follicular non-Hodgkin lymphoma (NHL) in 1997. When administered as a single agent on a weekly schedule of $375\text{mg}/\text{m}^2 \times 4$ doses, the activity was relatively modest (progression-free survival [PFS] of 9.0 months). The complete response (CR) rate was 6% and the partial response (PR) rate was 42%, but the toxicity profile was very favorable (4% of 3 grade adverse events).¹ Since then, studies have demonstrated that rituximab administered concurrently with a backbone of conventional chemotherapy, immunochemotherapy, not only leads to higher response rates and improved PFS compared to chemotherapy alone in the treatment of patients with follicular lymphoma both in the upfront and relapsed setting, but also prolongs overall survival (OS).^{2–4}

Retrospective analyses of large cohort studies provide further evidence for the significant impact of rituximab on outcomes in indolent NHL. The median survival for patients with follicular lymphoma (FL), the most common indolent NHL, has improved over the last decade from 5–7 years to currently well over 10 years.^{5–9} This led to a paradigm shift in the approach to the treatment of indolent lymphomas, which are invariably characterized by their relapsing course. The previous dogma that choice of initial therapy had no impact on overall survival (OS) was revised. However, while the significant impact of rituximab in general is undisputed with combined immunochemotherapy the standard of care, the role of rituximab maintenance therapy after induction is less well defined.¹⁰

E1496 was one of the first randomized phase III studies to explore the role of rituximab as a maintenance strategy following induction chemotherapy in indolent lymphomas, albeit after induction with a chemotherapy only regimen. When first reported, median follow up was 3.7 years. Patients assigned to rituximab maintenance (MR) following cyclophosphamide, vincristine, and prednisone (CVP) induction therapy, had a 60% reduction in the risk of

progression or death compared to observation (OBS) ($p=0.44\times 10^{-10}$), and there was a trend for improved overall survival (relative risk [RR] of death 0.4; one-sided log-rank test $p=0.05$). Here we present the long-term results of E1496 with a median follow up of 11.5 years.

Material and Methods

Study Population

Patients aged 18 years or older with stage III or IV (Ann Arbor classification) small lymphocytic, follicular-small cleaved, or follicular mixed small cleaved and large cell lymphoma histology as per the Working Formulation (WF) classification were eligible for E1496. Patients with lymphoma that had both diffuse and follicular architectural elements were eligible as long as 50% of the cross-sectional areas were follicular. Additionally, as the WF lymphoma classification was revised during the study period, patients with marginal zone and lymphoplasmacytoid lymphoma became eligible. All cases underwent central pathology review by a hematopathologist (RDG). Patients were required to have measurable disease (lesions ≥ 2 cm or splenomegaly on imaging), an ECOG performance status ≤ 2 , and not have received prior lymphoma-directed (including radiation) therapy. The National Cancer Institute, ECOG, and the local IRB of each participating institution approved the protocol; informed consent was obtained according to institutional guidelines.

Study Design and Treatment

Study design and treatment were previously described in detail elsewhere.¹¹ Briefly, patients were initially randomized to receive either intravenous (IV) cyclophosphamide $1000\text{mg}/\text{m}^2$ and vincristine $1.4\text{mg}/\text{m}^2$ (capped at 2.0mg) on day 1 as well as oral prednisone ($100\text{mg}/\text{m}^2$) on days 1–5 of a 3-week cycle (CVP) to maximum response for at least 6 and at most 8 cycles; or IV cyclophosphamide $1000\text{mg}/\text{m}^2$ on day 1 and fludarabine $20\text{mg}/\text{m}^2$ on days 1–5 every 4 weeks (CF) for 4–6 cycles to best response. For this analysis, only patients enrolled on the CVP arm will be reported as the CF arm was closed early after an increased number of induction deaths had been observed (8 out of 115). Patients underwent CT imaging 4 weeks after completion of CVP or CF therapy to assess response. Patients with progressive disease (PD) as defined by a $\geq 25\%$ increase in the sum of the products of the diameters of the pre-treatment lesions or new disease were taken off study. All other patients were randomized to either observation (OBS) or to receive maintenance rituximab (MR) with weekly IV rituximab ($375\text{mg}/\text{m}^2$) $\times 4$ every 6 months for a total of 2 years starting 4 weeks after completion of CVP or CF therapy. Randomization was stratified based on initial tumor burden (low tumor burden vs. high tumor burden defined as either ≥ 3 lymph nodes $>3\text{cm}$; one lesion $>7\text{cm}$; “B” symptoms; spleen size $>16\text{cm}$ by CT scan; leukemic phase [$>5000/\text{mm}^3$ atypical lymphocytes]; cytopenias; or risk of extrinsic compression of a vital organ), extent of residual disease after induction therapy (minimal residual disease vs. gross residual disease defined as either $\geq 10\%$ bone marrow involvement or any lesion $\geq 2\text{cm}$ or with $<75\%$ size reduction), and histological subtype (follicular vs. other). CT imaging was repeated every 6 months for 2 years, then annually for 5 years; bone marrow biopsies were repeated annually for 5 years. This analysis is restricted to patients who were randomized to either MR or OBS after CVP induction.

Statistical Analysis

The primary end-point for the maintenance portion of the study was progression free survival (PFS) defined as time from maintenance randomization to death or lymphoma progression. OS was measured from random assignment to death as a result of any cause. After modifications following the early closure of the CF arm, the study required 172 failures and accrual estimate of 300 patients randomized to either MR or OBS for 83% power and a 5% one-sided type I error to detect a 50% increase in median PFS (2.5 years with OBS versus 3.75 years with MR). After 50% of events occurred, the study passed the O'Brien-Fleming boundary for positive results. Although accrual had been completed and all enrolled patients had been randomized by that time, investigators were given the option to treat OBS patients with MR. Comparisons between treatment groups were conducted according to the intent-to-treat principle among eligible patients with a stratified log-rank test. Three stratification factors were employed, including histology (follicular vs. other), residual disease after CVP (minimal or gross), and initial tumor burden (low or high). The Kaplan-Meier method and Cox proportional regression model were used to estimate failure rates, hazard ratios (HRs), and 95% confidence intervals (CIs). Toxicity was evaluated in all patients regardless of eligibility. Time-varying covariate was used in Cox proportional regression to test the proportional hazard assumption in OS evaluation.

Potential prognostic factors initial tumor burden, histology, residual disease status post CVP, FLIPI score, and gender were evaluated for associations with PFS and OS by univariate analyses using a log-rank test. Variables with a p-value ≤ 0.20 were then included in the multivariate model together with treatment arm with Cox proportional hazard model.

Results

Patient characteristics

Three hundred eighty seven patients were enrolled into the CVP induction. The overall response rate was 73% (60% PR, 13% CR). Following response assessment after CVP, 311 patients were randomized to the maintenance phase (Figure 1). Table 1 outlines the patient characteristics and demonstrates that patients on MR and OBS did not differ significantly in prognostic features with the exception of a higher prevalence of B-symptoms at baseline in patients assigned to MR (17% vs. 31%; $p=0.005$). Most patients had follicular histology (73%), high initial tumor burden (65%), high FLIPI scores (40%) and entered the maintenance phase with minimal residual disease (56%).

During the 2-year maintenance phase, 22% ($n=35$) of MR patients improved their response from PR to CR ($n=33$) or from SD to PR or CR ($n=1$ each). In comparison, significantly fewer OBS patients (7%), ($n=10$; $p=0.00006$) demonstrated improvement in their response (PR to CR, ($n=9$); SD to PR, ($n=1$)). As previously reported, grade 3 and 4 toxicities during the maintenance phase were generally rare and not significantly different between MR and OBS except for grade 4 neutropenia (2% vs. 0%).¹¹

Maintenance: survival results

After a median follow-up of 11.5 years, the median PFS for the MR arm among all evaluable patients was 4.8 years compared to 1.3 years for patients on the OBS arm ($p<0.0001$). The stratified hazard ratio (HR) was 0.49 (95% confidence interval (CI), 0.37–0.64). The results amongst patients with FL histology were similar, with a median PFS of 4.6 and 1.3 years respectively for the MR and OBS arm (stratified HR 0.46; 95% CI, 0.34–0.63; $p<0.0001$). Figure 2 shows the PFS for all evaluable patients and patients with FL histology. The improvement in PFS was maintained throughout the entire follow-up period, with 5 and 10 year PFS rates of 47% and 26% for MR vs. 26% and 9% for OBS, respectively (Table 2). The results were similar in the subset of patients with follicular lymphoma (supplemental Table 1S).

The OS curves crossed at approximately 12 years, however the interaction between the treatment groups and time was not statistically significant ($p=0.1$) which suggests that the proportional hazard assumption was not violated. Therefore, no statistical significant difference in OS was observed by stratified log-rank test ($p=0.41$). The median OS was 13.5 years for the MR arm, and has not been reached for the OBS arm. The stratified hazard ratio (HR) was 0.86 (95% CI, 0.61–1.23). Extended Cox regression with time-varying covariates revealed a stratified HR for MR over OBS of 0.80 (95% CI, 0.56–1.15) before 12 years and 5.61 (95% CI, 0.58–46.3) after 12 years. Neither time interval difference was significant ($p=0.23$ and $p=0.16$, respectively), which further confirms that there is no significantly difference in OS between MR and OBS. The results among patients with FL histology were similar, with a median OS of 13.5 years for patients receiving MR and not reached for patients on the OBS arm (stratified HR=0.91; 95% CI, 0.59–1.42; $p=0.69$). The interaction between the treatment groups and time was statistically significant ($p=0.05$) in the Cox model. However, extended Cox regression with time-varying covariates revealed a stratified HR for MR over OBS of 0.81 (95% CI, 0.51–1.28) before 12 years and 6.65 (95% CI, 0.70–63.0) after 12 years. Neither time interval difference was significant ($p=0.38$ and $p=0.10$, respectively). Figure 2a and 2b demonstrate the OS for all evaluable patients and the FL subset, respectively. The Kaplan-Meier estimates of survival rate at different time points are shown in Table 2 (Supplemental Table 2S for the follicular subset).

Patients experienced an approximately 50% improvement in PFS with MR versus OBS irrespective of initial tumor burden, residual disease after CVP induction or lymphoma histology (Table 3). There was no difference in OS between the subgroups. (Kaplan-Meier curves for the subgroups can be found in the supplemental material). When the analysis was restricted to only female patients, there was no difference in OS between MR and OBS. There was no significant interaction between the variables maintenance assignment and gender.

Prognostic factors

Table 4 lists the results of the univariate and multivariate analyses of prognostic factors in all evaluable patients ($n=311$). Low initial tumor burden (HR 0.68; $p=0.005$), minimal residual disease (HR 0.35; $p=0.0005$) and complete response to CVP induction (HR 0.58; $p=0.005$) were associated on univariate analysis with improved PFS, but histology, FLIPI, or sex were

not. On multivariate analysis, only minimal residual disease on imaging remained statistically significantly associated with PFS (HR 0.71; 95%CI 0.54–0.94; $p=0.02$), while low tumor burden and response to CVP showed a trend towards longer PFS (HR 0.79, $p=0.11$; and HR=0.67, $p=0.06$, respectively). MR significantly improved PFS compared to OBS (HR=0.47, $p<0.0001$) after adjusting for other prognostic factors in the multivariate model. For OS, low tumor burden (HR 0.52; $p=0.0009$), minimal residual disease (HR 0.51; $p=0.0001$), follicular histology (HR 0.56; $p=0.001$), response to CVP (HR 0.57, $p=0.04$) and female gender (HR 0.65, $p=0.02$) were associated on prolonged OS, while high FLIPI scores (HR 1.77; $p=0.001$) predicted for worse OS on univariate analysis. In the multivariate model, all factors except response to CVP remained significantly associated with OS, while treatment arm (MR vs. OBS) remained non-significant.

Second primary malignancies

A total of 63 second primary cancers developed in 55 patients; 6 patients had multiple second malignancies (Supplemental Table 3S). Based on the Fisher's exact test, significantly less patients developed secondary primary cancer in the MR arm compared to the OBS arm ($p=0.03$), with 25 cancers occurring in 20 patients on MR versus 38 cancers in 35 patients on OBS. The 2 most common second malignancy were lung cancer ($n=15$) and non-melanomatous skin cancer ($n=10$). Hematological malignancies occurred in 1 patient on the MR arm (Hodgkin lymphoma (HL)) and 5 patients on the OBS arm ($n=1$ each for FL, reticulosarcoma, HL, chronic myelogenous leukemia (CML), and myelodysplastic syndrome (MDS).

Discussion

The long-term follow-up results for E1496 after a median follow up of 11.5 years demonstrate a substantial improvement in PFS with rituximab maintenance (MR) after induction therapy with CVP in patients with indolent B-cell lymphomas. With more than one decade after the completion of induction chemotherapy, an approximately 50% reduction in the composite outcome of lymphoma PFS was observed in the MR group, although no improvement in OS.

The classical prognostic factors for OS, such as the FLIPI score, initial tumor burden, and response to induction treatment,^{12–14} were significant in E1496 study. The PFS benefit of MR was similar in all subgroups, irrespective of initial tumor burden, response to induction chemotherapy, or histological subtype. There was no increase in secondary primary malignancies in patients treated with MR, and toxicities were generally manageable as previously described.¹¹ After 50% of the events had occurred, investigators had the option to treat patients randomized to OBS with MR. Cross-over therefore could have attenuated the difference on PFS and OS. Unfortunately information on second-line treatment was not available, which furthermore might have confounded our findings.

Our findings are consistent with the published literature. Rituximab maintenance following upfront systemic therapy was first formally assessed by Hainsworth and colleagues in a multi-center phase 2 trial. Sixty patients with indolent NHL (follicular and small lymphocytic lymphoma) received induction with 4 weekly doses of rituximab. Patients with

SD or better then proceeded to maintenance with 4 further courses of weekly rituximab x4 every 6 months, similar to E1496. The observed actuarial median PFS of 34 months constituted a significant improvement compared to historical data for rituximab induction alone.¹⁵ Ghielmini and colleagues on behalf of the Swiss Group for Clinical Cancer Research (SAKK) confirmed in SAKK35/98 that rituximab maintenance following rituximab induction with 4 weekly doses improved the PFS when administered as a single dose every 2 months x4 versus observation alone in untreated patients with FL (19 vs. 36 months; $p=0.009$).¹⁶ An unspecified number of patients in these studies had low tumor burden disease when based on accepted criteria, such as the GELF criteria,¹⁴ and might not be considered candidates for induction chemotherapy. Our study also involved low and high tumor burden patients, and the PFS benefit of MR was seen in both groups. Not surprisingly, we also report a longer OS in patients with low tumor burden compared to high tumor burden patients.

In addition to E1496, the only other large randomized phase III trial assessing MR after chemotherapy-based induction is the PRIMA trial, which reported at a median follow-up of 36 months a 45% improvement in PFS (HR 0.55; 95%CI 0.44–0.68) without an OS benefit for patients on MR.¹⁷ In this study by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), 1217 patients with previously untreated high-tumor burden FL received induction therapy with either R-CVP, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-FCM, following which patients with CR or PR were randomized to MR (12 infusions, one every 2 months; $n=505$) or observation ($n=513$). As in E1496, the PFS benefit was observed in all patient subgroups independent of FLIPI score, age, sex, or response to induction therapy. In the PRIMA study, only 28 patients received R-FCM for induction, and there were no conclusions about the benefit in this subgroup. Following R-CHOP induction, patients experienced a borderline increased PFS benefit compared to R-CVP induction (HR 0.51 (95%CI 0.39–0.65) vs. HR 0.69 (95%CI 0.41–1.02)). The PFS benefit of MR in E1496 is similar to the PRIMA study, where all patients also received rituximab in the induction treatment.

Considering the median survival for patients with indolent lymphomas, and specifically FL, which currently exceeds 10 years, long-term follow-up for interventional therapeutic studies in this setting is of utmost importance to determine whether improvement in surrogate markers for OS, such as response rates or PFS, eventually translate into an OS benefit.^{7,18} In the SAKK 35/98 trial at a median follow-up 9.5 years, there was a persistent event-free survival (EFS) benefit in untreated patients (HR 0.59; 95%CI 0.39–0.88), which is comparable to E1496. When comparing both studies it needs to be noted that in SAKK 35/98 the primary outcomes was EFS, defined as time from first induction to either progression, relapse, second tumor, or death from any cause, as opposed to PFS, defined in E1496 as time to death or lymphoma progression. While 45% of patient in the MR arm were still alive at 8 years without events, there was no OS benefit.¹⁹ However, given the low death rate, the significant impact of salvage therapy on survival, and the fact that patients might have received MR later, influencing OS might be an unachievable objective with a therapeutic intervention early in the disease course when the therapeutic intervention eventually will become available to all patients. This might be different in a later setting. A meta-analysis examining the benefit of MR found improved OS in the relapsed setting (HR

for death 0.58; 95%CI 0.42–0.79), while no OS benefit was apparent for MR in the upfront setting.²⁰

Considerations that have to be taken into account when evaluating the PFS gain with MR are safety, quality of life, and cost-effectiveness. In the PRIMA trial that incorporated initial immunochemotherapy, toxicities in patients on MR were mainly grade 2–4 infections (39% vs. 24%; HR 1.62; $p < 0.0001$), although no differences between MR and OBS in immunoglobulin levels were seen. The most common infections affected the upper airways and urinary tract.¹⁷ A meta-analysis described an infection-related adverse event rate that was double in MR patients (HR 1.99; 1.21–3.27; $p = 0.007$).²⁰ Other immediate and late toxicities are cytopenias, specifically neutropenia (5–10%),^{15–17,21} and reactivation of hepatitis B or C, which can occur late, but has not yet been systematically quantified.²² Most of these toxicities are considered mild to moderate and manageable. We and others did not find an increase in second cancers.¹⁹ The influence of MR on the rate of histological transformation remains unclear, as information on histological transformation was not routinely collected during follow up for E1496. While there is controversy about improvement in quality of life with rituximab maintenance,^{17,23,24} some studies suggest an economic benefit.^{25–27}

In conclusion, first-line MR for indolent lymphomas following chemotherapy with CVP results in a substantial and sustained PFS improvement with an acceptable safety profile irrespective of initial tumor burden or response to induction therapy. Progression free survival was nearly 3 times longer with maintenance rituximab (4.8 vs 1.3 years) and at 3 years nearly twice as many patients had not progressed (66% vs 35% progression free). Nonetheless, even after median follow up of 11.5 years, there is no benefit in overall survival as the curves come back together after 10 years. This suggests a prolonged effect on remission, but eventual salvage with subsequent therapy. Furthermore, scientific questions that remain unanswered are the optimal schedule and length of rituximab maintenance, the benefit of MR following induction therapy compared to a rituximab retreatment “as-needed” approach as pioneered by the RESORT trial.²⁸ The long-term follow up data from E1496 demonstrate that MR has a long-lasting impact on PFS without long-term toxicity, making it an attractive option for patients. Given the lack of impact on OS, MR should be considered an optional intervention in the management of indolent lymphoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Consort diagram for E1496

Figure 2. Progression-free survival for a) all evaluable patients (n=311) and b) patients with follicular lymphoma (n=228)

Figure 3. Overall survival for a) all evaluable patients (n=311) and b) patients with follicular histology (n=228)

Table 1

Characteristics of evaluable patients who entered the maintenance phase

Characteristics	All (%)	All patients (n=311)		Follicular lymphoma (n=228)	
		MR n (%)	OBS n (%)	MR n (%)	OBS n (%)
Age (median; range)	57 (26–86)	58 (26–84)	56 (32–86)	58 (30–84)	54 (32–80)
Male sex	171 (55)	86 (54)	85 (56)	59 (51)	62 (55)
ECOG PS 0	204 (66)	112 (71)	92 (60)	80 (70)	72 (64)
Histology: Follicular	228 (73)	115 (37)	113 (36)	115 (37)	113 (36)
Histology: non Follicular	83 (27)	43 (14)	40 (13)		
SLL/CLL	47 (15)	29 (9)	18 (6)		
LPL	2 (<1)	1 (<1)	1 (<1)		
Unclassifiable	7 (2)	3 (1)	4 (1)		
Other	15 (5)	6 (2)	9 (3)		
Missing	12 (4)	4 (1)	8 (3)		
FLIPI score					
Low	57 (24)	28 (24)	29 (225)	23 (26)	24 (27)
Intermediate	82 (35)	43 (36)	39 (34)	32 (36)	32 (36)
High	95 (41)	48 (40)	47 (41)	33 (38)	33 (37)
Stages IV	217 (70)	109 (69)	108 (71)	73 (64)	72 (64)
Elevated LDH ^a	53 (23)	29 (25)	24 (21)	24 (27)	19 (22)
High tumor burden	200 (64)	96 (61)	104 (68)	69 (60)	75 (66)
Minimal residual disease	175 (56)	89 (56)	86 (56)	67 (58)	65 (58)
Response to CVP					
Complete response	49 (16)	25 (16)	24 (16)	18 (16)	15 (13)
Partial response	210 (68)	110 (69)	100 (65)	81 (70)	77 (68)
Stable disease	40 (13)	17 (11)	23 (15)	12 (10)	17 (15)
Not evaluable	12 (4)	6 (4)	6 (4)	4 (4)	4 (4)
Response on maintenance ^b					
Complete response	92 (30)	59 (37)	33 (22)	43 (37)	24 (21)

Characteristics	All (%)	All patients (n=311)		Follicular lymphoma (n=228)	
		MR n (%)	OBS n (%)	MR n (%)	OBS n (%)
Partial response	170 (55)	78 (49)	92 (60)	60 (52)	68 (60)
Stable disease	37 (12)	15 (9)	22 (14)	8 (7)	17 (15)
Not evaluable	12 (4)	6 (4)	6 (4)	4 (3)	4 (4)

Abbreviations: MR, maintenance rituximab; OBS, observation; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma.

^aNot available for all patients.

^bResponse on maintenance was defined as best response during the maintenance phase

Table 2

Survival probabilities all evaluable patients (n=311)

	MR (n=158)	OBS (n=153)
PFS (95% CI)		
3 years	0.66 (0.58–0.73)	0.35 (0.28–0.43)
5 years	0.47 (0.39–0.55)	0.26 (0.19–0.34)
10 years	0.26 (0.17–0.36)	0.09 (0.04–0.15)
Median PFS	4.8 years	1.3 years
OS (95% CI)		
3 years	0.92 (0.87–0.96)	0.86 (0.80–0.91)
5 years	0.85 (0.78–0.89)	0.78 (0.71–0.84)
10 years	0.67 (0.58–0.73)	0.59 (0.51–0.67)
Median OS	13.5 years	Not reached

Abbreviations: MR, maintenance rituximab; OBS, observation; PFS, progression-free survival; 95% CI, 95% confidence interval, OS, overall survival.

Table 3

Progression-free and overall survival for MR vs. OBS by subgroups

	PFS			OS		
	10-yr PFS MR vs OBS	Hazard Ratio (95% CI)	P	10-yr OS MR vs OBS	Hazard Ratio (95% CI)	P
All Patients (n=311)	0.26 vs 0.09	0.49 (0.37–0.64)	<0.0001	0.67 vs 0.59	0.86 (0.61–1.23)	0.41
Tumor burden						
Low (n=111)	0.38 vs 0.11	0.46 (0.29–0.74)	0.006	0.79 vs 0.74	1.01 (0.50–2.04)	0.98
High (n=200)	0.20 vs 0.08	0.50 (0.36–0.69)	<0.0001	0.59 vs 0.52	0.82 (0.54–1.23)	0.33
Histology						
Follicular (n=228)	0.28 vs 0.08	0.46 (0.34–0.63)	<0.0001	0.72 vs 0.65	0.91 (0.59–1.42)	0.69
Other (n=83)	0.20 vs 0.12	0.57 (0.35–0.94)	0.03	0.53 vs 0.43	0.83 (0.47–1.47)	0.51
Residual disease						
Minimal (n=175)	0.27 vs 0.12	0.51 (0.35–0.74)	0.0004	0.74 vs 0.66	0.81 (0.48–1.37)	0.43
Gross (n=136)	0.23 vs 0.05	0.47 (0.33–0.68)	<0.0001	0.57 vs 0.50	0.91 (0.56–1.46)	0.68

Abbreviations: MR, maintenance rituximab; OBS, observation; PFS, progression-free survival; 95% CI, 95% confidence interval, OS, overall survival.

* Hazard ratios were based on Cox proportional hazards models stratified by all the stratification factors used in randomization (tumor burden, histology, and residual disease) except the one being analyzed. P-value was based on stratified log rank-test.

Univariate and multivariate analysis of prognostic factors in all evaluable patients (n=311)

Table 4

	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Treatment Arm								
MR (n=158) vs OBS (n=153)	0.49 (0.37–0.63)	<0001	0.47 (0.36–0.61)	<0001	0.90 (0.64–1.27)	0.56	0.88 (0.63–1.25)	0.49
Tumor burden								
Low (n=111) vs. High (n=200)	0.68 (0.51–0.89)	0.005	0.79 (0.59–1.06)	0.11	0.52 (0.35–0.77)	0.0009	0.64 (0.43–0.96)	0.03
Histology								
Follicular (n=228) vs. Other (n=83)	0.99 (0.74–1.31)	0.92			0.56 (0.39–0.80)	0.001	0.56 (0.39–0.81)	0.002
Residual disease								
Minimal (n=175) vs. Gross (n=136)	0.63 (0.49–0.82)	0.0005	0.71 (0.54–0.94)	0.02	0.51 (0.36–0.73)	0.0001	0.62 (0.42–0.90)	0.01
Response to CVP								
CR (n=49) vs. Other (n=262)	0.58 (0.39–0.85)	0.005	0.67 (0.44–1.02)	0.06	0.57 (0.33–0.98)	0.04	0.78 (0.44–1.41)	0.41
FLIPI								
High risk (n=95) vs. Other (n=216)	1.05 (0.79–1.38)	0.75			1.77 (1.24–2.52)	0.001	1.75 (1.21–2.53)	0.003
Gender								
Female (n=140) vs. Male (n=171)	0.85 (0.66–1.11)	0.23			0.65 (0.46–0.93)	0.02	0.58 (0.40–0.83)	0.003

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval