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Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG1496 Study

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ABSTRACT

Purpose
To determine if maintenance rituximab (MR) after standard chemotherapy improves progression-free survival (PFS) in advanced-stage indolent lymphoma.

Patients and Methods
Patients with stage III-IV indolent lymphoma with responding or stable disease after cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy were stratified by initial tumor burden, residual disease after CVP (minimal or gross), and histology, and randomly assigned to observation (OBS) or MR 375 mg/m^2 once per week for 4 weeks every 6 months for 2 years. PFS was the primary end point.

Results
Three hundred eleven (282 with follicular lymphoma) evaluable patients who received CVP were randomly assigned to OBS (n = 158) or MR (n = 153). Best response improved in 22% MR versus 7% OBS patients (P = .00006). Toxicity was minimal in both study arms. Three-year PFS after random assignment was 68% MR versus 33% OBS (hazard ratio [HR] = 0.4; $P = 4.4 \times 10^{-10}$ [all patients]) and 64% MR *v* 33% OBS (HR = 0.4; $P = 9.2 \times 10^{-8}$ [patients with follicular lymphoma]). There was an advantage for MR regardless of Follicular Lymphoma International Prognostic Index score, tumor burden, residual disease, or histology. In multivariate analysis of MR patients, minimal disease after CVP was a favorable prognostic factor. OS at 3 years was 92% MR versus 86% OBS (HR = 0.6; log-rank one-sided P = .05) and, among patients with follicular lymphoma, OS was 91% MR versus 86% (HR = 0.6; log-rank one-sided P = .08). A trend favoring MR was observed among patients with high tumor burden (log-rank one-sided P = .03).

Conclusion
The E1496 study provides the first phase III data in untreated indolent lymphoma that MR after chemotherapy significantly prolongs PFS.

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INTRODUCTION

Although highly responsive to single-agent and combination chemotherapy, indolent lymphomas follow a continuous relapse pattern and, during a 30-year period of study, no single chemotherapy regimen has been considered to provide a definitive progression-free (PFS) or overall survival (OS) advantage. In the past, chemotherapy had been used to maintain the response after induction chemotherapy in studies conducted by the Eastern Cooperative Oncology Group (ECOG) and the St Bartholomew's group.[1,2] Although efficacy was demonstrated in these small trials, the ability to continue to deliver chemotherapy in full dosage was limited by myelosuppression and patient and physician acceptance. Subsequently, some prospectively randomized studies supported the role of maintenance interferon (IFN) in follicular lymphoma (FL) and indolent lymphomas, dependent on the induction regimen and dose and duration.[3-6] Although a meta-analysis demonstrated longer PFS for IFN in this setting, dependent on dose and induction, IFN was not widely adopted due to the need for continuous administration, poor tolerance, and modest benefit.[7] These experiences with continuation or

maintenance therapy suggested, however, that an active biologic agent with a favorable safety profile and high patient acceptability would improve clinical outcome in indolent lymphoma.

The anti-CD20 monoclonal antibody rituximab, which has high affinity for normal B cells and more than 90% of B-cell lymphomas, was approved for use in relapsed FL and indolent lymphoma in 1997. In this setting, the objective response rate was 48% and the agent had rare serious adverse effects, generally limited to infusional toxicity.[8] The approved dose and schedule, 375 mg/m^2 once per week for 4 weeks, resulted in B-cell depletion that persisted for up to 6 months.[9] In addition, pharmacokinetic data showed detectable serum rituximab 3 to 6 months after four infusions.[9-11] On the basis of these early efficacy, tolerance, and pharmacodynamic data the E1496 study, to our knowledge, was the first to test rituximab to maintain response to chemotherapy in indolent lymphoma. A schedule of administration once per week for 4 weeks was repeated every 6 months (four courses) during 2 years. The primary study end point was PFS after chemotherapy for maintenance rituximab (MR) versus observation (OBS). During the conduct of this study (designed in 1996), and subsequent to its termination, other groups reported on extended rituximab schedules as a single-agent maintenance approach in untreated and relapsed disease.[12-14] We now report our results with more than 4 years median follow-up.

PATIENTS AND METHODS

Study Design

The primary study end point was progression-free survival (PFS), defined as progression or death at 2 years after random assignment to MR or OBS. Secondary end points were response rate to induction regimens and OS. Initially the study randomly compared cyclophosphamide 1,000 mg/m^2 intravenously (IV) day 1, vincristine 1.4 mg/m^2 (maximum 2.0 mg) IV day 1, prednisone 100 mg/m^2 orally days 1 to 5 every 21 days (CVP) versus cyclophosphamide 1,000 mg/m^2 IV day 1, fludarabine 20 mg/m^2 IV days 1 to 5 every 28 days (CF). However, the CF arm was closed after eight (primarily infectious) induction deaths when 234 patients had been accrued; all subsequent patients received CVP.[15] As a result, the total 401 CVP patients included 119 randomly assigned patients and 282 assigned patients. The statistical design was based on an estimated 300 evaluable randomly assigned CVP patients accrued during 3.33 years with 2.33 additional years of follow-up, providing 84% power to detect a 50% improvement in PFS from 2.5 years for the OBS arm to 3.75 years for the MR arm (one-sided 5% type I error). Interim analyses were planned for 25%, 50%, and 75% of anticipated events. At the second interim review, with 49% of events available, the study passed the O'Brien-Fleming boundary for positive results and maintenance random assignment was terminated. Investigators were given the option to treat OBS patients with MR. All time-based comparisons for maintenance therapy used one-sided log-rank analysis.

Eligibility

Patients with stage III and IV Working Formulation small lymphocytic, follicular small cleaved, and follicular mixed small and large cell were eligible. Patients with diffuse architecture were eligible if more than 50% follicular and the diffuse areas were predominantly small centrocytes with only scattered centroblasts (any large B-cell lymphoma area resulted in exclusion). Given that lymphoma classification was revised during the course of E1496, the new indolent histologies marginal zone and lymphoplasmacytoid were also considered eligible. Lymph node biopsy within 12 months was required and independently reviewed by the study pathologist (R.D.G.). Eligible patients also met these criteria: measurable disease, age older than 18 years, no prior therapy, and ECOG performance status 0 or 1. All patients signed informed consent documents as approved by the National Cancer Institute, ECOG, and the local institutional review board.

Treatment, Measurement of Effect, and Follow-Up

CVP was administered every 21 days to best response plus two cycles for a minimum of six and maximum of eight cycles. Dose adjustments were made for absolute neutrophil count less than 1,500/μL (delay 1 week, with granulocyte colony-stimulating factor [G-CSF] added for any subsequent delay) and platelets less than 75,000/μL (delay 1 week). Patients with nadir absolute neutrophil count less than 500/μL for more than 5 days or complicated neutropenia were treated with G-CSF on subsequent cycles. For recurrent delays or complicated/prolonged neutropenia while receiving G-CSF, cyclophosphamide dose was decreased by 25%. Criteria for response were complete response (CR; all lymph nodes $\leq 1.0 \times 1.0$ cm or, if larger, biopsy-negative nodes or no enlargement during 3 months without therapy and no bone marrow involvement) and partial response (PR; $\geq$ 50% reduction in the sum of the products of the diameters of measurable lesions). Progressive disease was defined as a more than 25% increase in the sum of the products of pretreatment lesions or new disease. Stable disease met none of these criteria. Best response required confirmation at 4 weeks. Computed tomography (CT) scans were repeated every 2 cycles until best response and after induction chemotherapy.

Patients with responding or stable disease were randomly assigned to MR (rituximab 375 mg/m^2, once per week for 4 weeks every 6 months for four courses), to begin 4 weeks after the last CVP cycle, or to OBS. Randomization was stratified for histology (follicular *v* other), residual disease after CVP (minimal or gross), and initial tumor burden (low or high). Minimal residual disease was defined as less than 10% marrow involvement, no lymph node larger than 2 cm, and reduction of a bulky nodal mass by more than 75%. Low tumor burden was defined as none of seven features: three or more lymph nodes larger than 3 cm, tumor mass larger than 7 cm, "B" symptoms, splenomegaly larger than 16 cm by CT scan, risk of extrinsic compression of vital organ, leukemic phase, or

Table 1. Characteristics of Evaluable Patients Treated With CVP

Characteristic	All Patients (N = 387) No.	%	Patients With FL (n = 282) No.	%
Age > 60 years	164	42	109	39
Median age, years	58		56	
Range	26-86		30-84	
Male sex	214	55	150	53
ECOG PS 1	143	36	102	36
High tumor burden	251	65	185	65
Stage IV	271	70	179	64
B symptoms	99	26	73	26
Bone marrow involvement	271	70	179	64
Hemoglobin $\geq$ 12 G/dL	307	79	231	82
LDH elevated*	78	27	63	29
$\geq$ Five nodal groups	159	44	109	41
FLIPI risk*				
Low	62	21	52	24
Intermediate	92	32	73	33
High	136	47	94	43

Abbreviations: CVP, cyclophosphamide, vincristine, and prednisone; FL, follicular lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index.
*Not available for all patients.

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significant cytopenia. Patients were observed with CT scans every 6 months for 2 years, then annually for 5 years, and marrow biopsies were repeated annually for 5 years.

RESULTS

CVP Induction

Patient characteristics, including histology and the Follicular Lymphoma International Prognostic Index (FLIPI), are shown in Table 1 for all 387 evaluable patients (eligible with correct histology by central review), and for the 282 evaluable patients with follicular histology. Patients with nonfollicular histology included 57 small lymphocytic, 10 marginal zone, and six lymphoplasmacytoid histologies. No difference in any characteristic was noted between the randomly assigned and assigned CVP patients. The major toxicities observed with CVP were 10% grade 3 and 20% grade 4 neutropenia, and 6% grade 3 and 1% grade 4 infection. One patient experienced a fatal cardiac event during CVP. The response rate was 73% (95% CI, 68 to 78) including 60% partial response (62% follicular) and 13% CR (12% follicular), which required both less than 1 × 1 cm residual disease and confirmation at 4 weeks. Seventy-three patients (19%) had stable disease and only 14 patients (4%) had progressive disease. Seventeen patients (4%) were not evaluable. The median number of chemotherapy cycles was eight, with 52% patients receiving eight cycles, 31% receiving six cycles, and 17% other. Of 387 evaluable patients, 74 were not randomly assigned to maintenance because of progressive disease (n = 14), incomplete response data (n = 17), withdrawal/refusal (n = 11), complications/toxicity (n = 15), use of nonprotocol therapy (n = 11), or unknown (n = 6).

Maintenance Results

A total of 311 evaluable patients, 228 with follicular histology, were randomly assigned to MR (n = 158) or OBS (n = 153; two additional exclusions were due to disease progression). Table 2 shows no differences between study arms except fewer MR patients had B symptoms (17% *v* 31%; $P = .005$). Fifty-six percent of patients achieved minimal disease, 65% had high tumor burden, and 40% were high FLIPI risk. Confirmed response rates to CVP were similar in the treatment arms (Table 2). Among MR patients, 35 (22%) demonstrated improved disease response with rituximab, including 33 converting to CR from PR, one to CR from stable disease, and one to PR from stable disease. In comparison, 10 (7%) of the OBS group continued to improve, with nine converting to CR from PR and one converting to PR from stable disease. This difference is significant ($P = .00006$). Toxicity during MR included 1% grade 3 and 2% grade 4 neutropenia compared with 1% grade 3 neutropenia in the OBS

Table 2. Characteristics of Evaluable Randomly Assigned Patients

Characteristic	All Patients (N = 311)				Follicular Lymphoma Patients (n = 228)			
	MR (n = 158)		OBS (n = 153)		MR (n = 115)		OBS (n = 113)	
	No.	%	No.	%	No.	%	No.	%
Age > 60 years	68	43	57	37	47	41	38	34
Median age, years	58		56		58		54	
Male sex	86	54	85	56	59	51	62	55
ECOG PS 1	46	29	61	40	35	30	41	36
High tumor burden	96	61	104	68	69	60	75	66
Minimal residual disease	89	56	86	56	67	58	65	58
Stage IV	109	69	108	71	73	64	72	64
B symptoms	27	17	47	31	22	19	34	30
Marrow involvement	108	68	110	72	71	62	74	66
Hemoglobin level ≥ 12	133	84	126	82	100	87	96	86
LDH elevated*	29	25	24	21	24	27	19	22
≥ 5 nodal groups*	58	39	66	47	37	34	47	43
FLIPI*								
Low	28	24	29	25	23	26	24	27
Intermediate	43	36	39	34	32	36	32	36
High	48	40	47	41	33	38	33	37
Confirmed response to CVP								
CR	25	16	24	16	18	16	15	13
PR	110	69	100	65	81	70	77	68
SD	17	11	23	15	12	10	17	15
Not evaluable	6	4	6	4	4	4	4	4
Response after maintenance random assignment								
CR	59	37	33	22	43	37	24	21
PR	78	49	92	60	60	52	68	60
SD	15	9	22	14	8	7	17	15
Not evaluable	6	4	6	4	4	3	4	4

Abbreviations: MR, maintenance rituximab; OBS, observation; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index; CVP, cyclophosphamide, vincristine, and prednisone; CR, complete response; PR, partial response; SD, stable disease.

*Not available for all patients.

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arm. The grade 3 infection rate was 1% in both arms. Other grade 3 toxicities (all 1%) for the MR group included pulmonary, cardiac, allergy, weight gain, and neurologic, and 3% others (*v* 4% in OBS patients).

MR markedly prolonged PFS compared with OBS. The median PFS for MR patients was 4.3 years after maintenance random assignment (approximately 4.9 years from start of CVP) compared with 1.3 years (approximately 1.9 years from start of CVP) for OBS patients. This result is highly significant (hazard ratio [HR] = 0.4; 95% CI, 0.3 to 0.5; $P = 4.4 \times 10^{-10}$). Longer PFS was observed in MR patients regardless of initial tumor burden, histology, residual disease after CVP, or FLIPI index (Table 3). PFS results were similar for the 228 FL patients (HR = 0.4; 95% CI, 0.3 to 0.6; $P = 9.2 \times 10^{-8}$; Table 3) and for subsets of the follicular cohort (all $P \leq .005$; data not shown). Figure 1 demonstrates PFS for all evaluable randomly assigned patients and for the follicular patient subset. At 3 years, PFS was 68% for MR versus 33% for OBS patients; for the follicular subset the figures are 64% for MR versus 33% for OBS patients (all $P < .001$). Intent-to-treat analyses inclusive of all 322 randomly assigned patients yielded identical results (data not shown).

With a median follow-up of 3.7 years after random assignment, 51 patients (45 with lymphoma progression) have died, including 21 in the MR arm and 30 in the OBS arm. Lymphoma progression preceded death in 81% (n = 17) of MR patients and in 93% (n = 28) of OBS patients. The 3-year OS for all evaluable patients is 92% MR versus 86% OBS (HR = 0.6; 95% CI, 0.4 to 1.1; $P = .05$) and, among follicular patients, OS is 91% MR versus 86% OBS (HR = 0.6; 95% CI, 0.3 to 1.2; $P = .08$; Fig 2). Survival did not achieve statistical significance in defined subsets, although there was a trend favoring MR among patients with high tumor burden ($P = .03$ for all patients; $P = .03$ for patients with follicular histology).

Prognostic Factors

For all 387 evaluable patients treated with induction CVP, initial tumor burden was the only variable associated with PFS ($P = .002$), whereas high tumor burden ($P = .006$), high-risk FLIPI score ($P = .02$), and nonfollicular histology ($P = .02$) predicted for shorter OS (all log-rank two-sided *P* values). Tumor burden, residual disease, response to CVP, FLIPI index (high risk *v* other), and histology were evaluated in univariate and Cox proportional hazards models for the 158 evaluable MR patients (all log-rank two-sided *P* values). Median PFS after CVP was 5.1 years for patients with minimal disease MR compared with 3.1 years for those with gross disease (HR = 0.6; 95% CI, 0.5 to 0.8; $P = .0004$; Fig 3A). Similarly, residual disease after CVP predicted for PFS in

Table 3. Outcomes in Randomly Assigned Patients

Characteristic	Median PFS MR *v* OBS (years)	No. of Deaths MR *v* OBS	3-Year PFS MR *v* OBS (%)	3-Year OS MR *v* OBS (%)	Estimated RR	95% CI	One-Sided Log-Rank *P*
PFS							
All patients (N = 311)	4.3 *v* 1.3		68 *v* 33		0.4	0.3 to 0.5	4.4×10^{-10}
Tumor burden							
Low (n = 111)	NR *v* 2.9		73 *v* 50		0.4	0.2 to 0.7	.0006
High (n = 200)	4.0 *v* 1.0		65 *v* 25		0.4	0.3 to 0.6	2.1×10^{-7}
Histology							
Follicular (n = 228)	4.3 *v* 1.3		64 *v* 33		0.4	0.3 to 0.6	9.2×10^{-8}
Other (n = 83)	4.2 *v* 1.3		79 *v* 32		0.3	0.2 to 0.6	.00006
Residual disease							
Minimal (n = 175)	5.1 *v* 1.6		80 *v* 43		0.3	0.2 to 0.5	7.6×10^{-8}
Gross (n = 136)	3.1 *v* 1.0		53 *v* 21		0.5	0.3 to 0.7	.0002
FLIPI (n = 234)							
Low (n = 57)	4.2 *v* 1.4		69 *v* 32		0.3	0.2 to 0.7	.0012
Intermediate (n = 82)	3.5 *v* 1.5		56 *v* 39		0.6	0.3 to 1.1	.04
High (n = 95)	3.6 *v* 1.3		69 *v* 29		0.4	0.2 to 0.7	.0004
OS							
All patients (N = 311)		21 *v* 30		92 *v* 86	0.6	0.4 to 1.1	.05
Tumor burden							
Low (n = 111)		5 *v* 3		92 *v* 98	1.4	0.3 to 5.9	.31
High (n = 200)		16 *v* 27		92 *v* 80	0.6	0.3 to 1.0	.03
Histology							
Follicular (n = 228)		14 *v* 20		91 *v* 86	0.6	0.4 to 1.2	.08
Other (n = 83)		7 *v* 10		95 *v* 86	0.7	0.3 to 1.8	.21
Residual disease							
Minimal (n = 175)		8 *v* 12		94 *v* 90	0.6	0.3 to 1.5	.14
Gross (n = 136)		13 *v* 18		89 *v* 80	0.6	0.3 to 1.3	.09
FLIPI (n = 234)							
Low (n = 57)		3 *v* 7		92 *v* 85	0.4	0.1 to 1.4	.06
Intermediate (n = 82)		5 *v* 5		91 *v* 89	0.9	0.3 to 3.1	.43
High (n = 95)		10 *v* 12		91 *v* 79	0.7	0.3 to 1.7	.24

Abbreviations: PFS, progression-free survival; MR, maintenance rituximab; OBS, observation; OS, overall survival; FLIPI, Follicular Lymphoma International Prognostic Index; NR, not reported.

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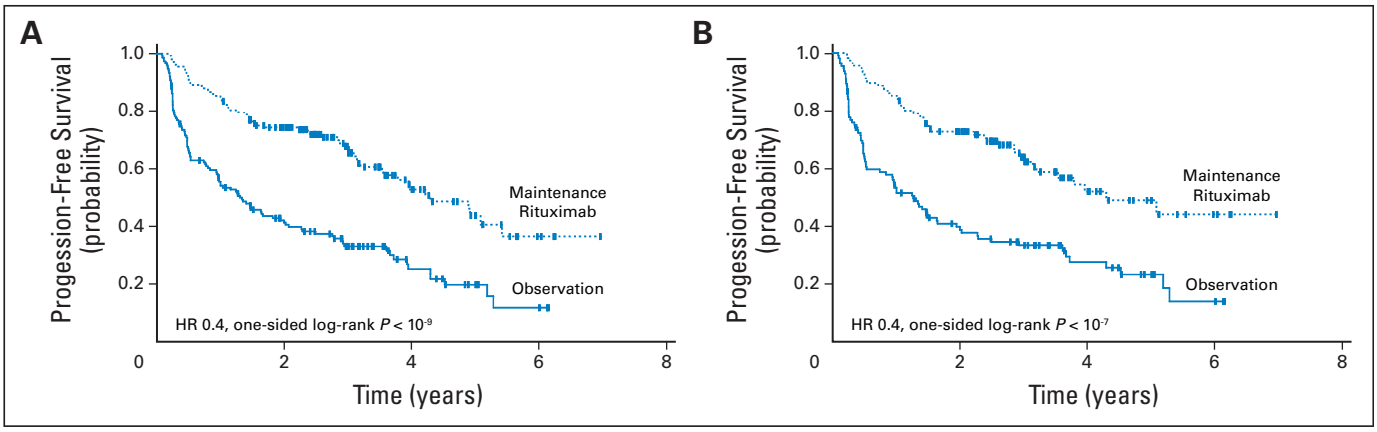

Fig 1. (A) Progression-free survival (PFS) for 311 evaluable indolent lymphoma patients randomly assigned to maintenance rituximab (MR; n = 158) or observation (OBS; n = 153). (B) PFS for 228 evaluable follicular lymphoma patients randomly assigned to MR (n = 115) or OBS (n = 113).

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follicular MR patients (HR = 0.5; 95% CI, 0.3 to 0.9; $P = .015$; Fig 3B). In addition to minimal disease, CR ($P = .04$) also predicted for longer PFS (96% *v* 71% at 2 years). In multivariate analysis for PFS, only minimal residual disease after CVP was significant (HR = 0.5; $P = .009$). For OS, minimal residual disease ($P = .04$) was the only favorable prognostic factor, but this did not achieve statistical significance in the Cox model ($P = .11$).

Crossover

Among the 153 CVP plus OBS patients, 14 were recorded to have crossed over to rituximab without experiencing disease progression after the interim analysis results showed superiority of MR. Censoring these patients at the time of rituximab addition did not change the PFS (HR = 0.4; $P = 4.3 \times 10^{-11}$) or OS (HR = 0.6; $P = .04$). An alternative analysis, censoring all data at November 2003 likewise did not alter the outcomes or their significance.

DISCUSSION

Our study confirmed the hypothesis that rituximab would be an effective and safe maintenance after CVP chemotherapy. The results demonstrate prolongation of PFS for MR-treated patients with a median more than three times longer (4.3 *v* 1.3 years) and a 60% reduction in progression risk (HR = 0.4; $P < 10^{-9}$). Improved PFS was seen in all patient subsets receiving MR. When our results are compared with data from others, these median PFS values should be adjusted to account for the length of CVP induction.

Three-year survival data do not achieve statistical significance (HR = 0.6; 95% CI, 0.4 to 1.1; $P = .05$) but show a positive trend. Lack of a significant survival benefit may relate to immaturity of the data with a small number of events, inclusion of patients with low tumor burden, sample size, mixed indolent histologies, and the efficacy of secondary treatment with rituximab in the OBS arm. Notably, patients with low tumor burden randomly assigned to OBS had a 98% 3-year survival despite the fact that half had experienced relapse at that time. Among patients with high tumor burden, OS at 3 years showed a strong trend favoring MR (HR = 0.6; 95% CI, 0.3 to 1.0; $P = .03$).

Subsequent to the design and conduct of our study, four European trials comparing rituximab plus chemotherapy versus chemotherapy alone were reported in FL patients requiring treatment.[16-19] Each study demonstrated a significant prolongation of PFS with rituximab plus chemotherapy. Differences in eligibility and design, particularly the use of IFN or transplantation, make it difficult to compare these studies with one another or our study. Nonetheless, all four

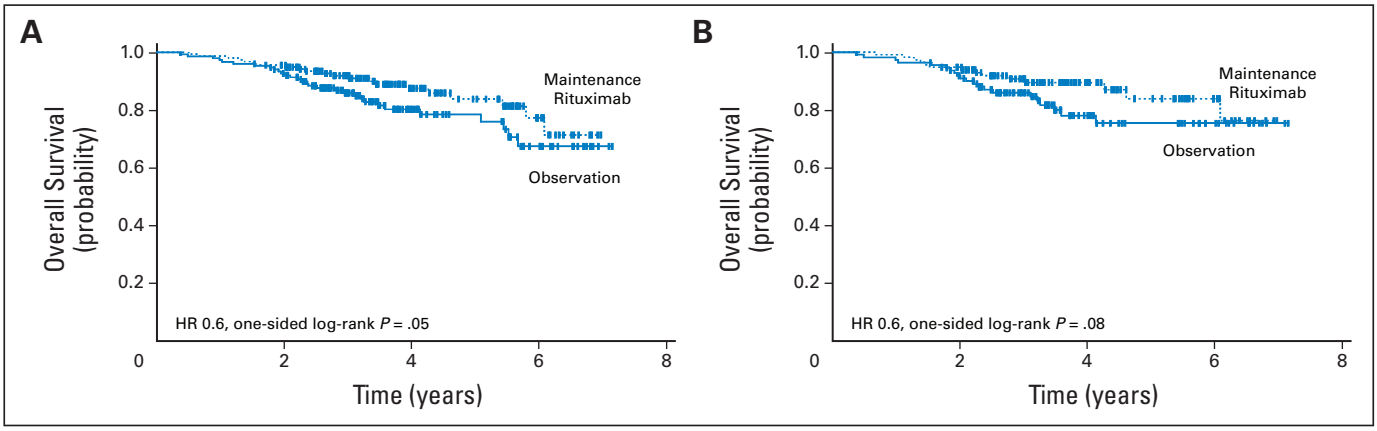

Fig 2. (A) Overall survival (OS) for 311 evaluable indolent lymphoma patients randomly assigned to maintenance rituximab (MR; n = 158) or observation (OBS; n = 153). (B) OS for 288 evaluable follicular lymphoma patients randomly assigned to MR (n = 115) or OBS (n = 113).

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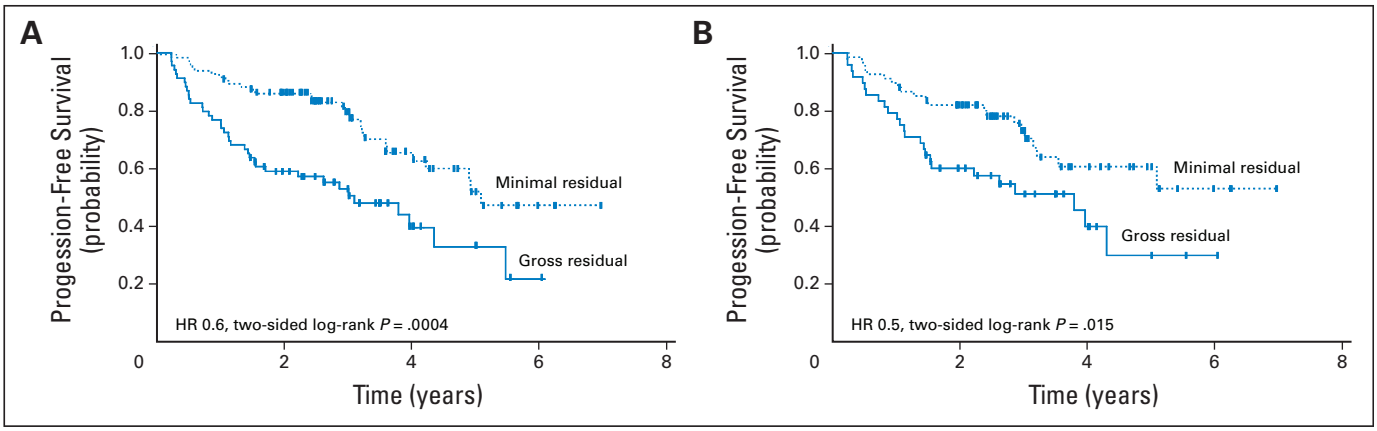

Fig 3. (A) Progression-free survival (PFS) for 158 evaluable maintenance rituximab (MR) patients according to minimal (n = 89) or gross (n = 69) residual disease after cyclophosphamide, vincristine, and prednisone (CVP) therapy. (B) PFS for 115 evaluable MR follicular lymphoma patients according to minimal (n = 67) or gross (n = 48) residual disease after CVP.

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studies have strikingly concordant PFS results despite differences in chemotherapy regimen and consolidative treatment. Notably, the PFS hazard rates (0.4) for the rituximab plus CVP and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) studies are identical to that observed in our study. To date, three of the four trials demonstrate a survival advantage for rituximab plus chemotherapy versus chemotherapy alone. Because the statistical significance of survival data are driven by event rates, the performance of the control arms, with attention to the availability and use of rituximab as second-line treatment, will be of interest as the data continue to mature. For example, the impact of second-line treatment was emphasized in a study of high-dose sequential treatment (including rituximab) plus transplantation versus R-CHOP in unfavorable FL.[20] In that study, which featured a cross-over design for those who experienced treatment failure after R-CHOP therapy, a highly significant PFS was observed in favor of the transplantation arm but OS was essentially overlapping. Description of additional therapy in the context of the reported chemoimmunotherapy randomized trials discussed would considerably enlighten the issue.

MR use has been reported after CHOP ± rituximab in the European Organisation for the Research and Treatment of Cancer 20981 study of patients with rituximab-naïve FL who had experienced treatment failure after one or more prior regimens.[14] In this 2 × 2 factorial design, patients receiving either R-CHOP induction ($P < .001$) or MR ($P < .001$) had significantly longer PFS. MR after CHOP ± rituximab induction ($P = .01$) prolonged OS. Whereas patients receiving R-CHOP had longer PFS with MR (HR = 0.54; $P = .004$), a survival benefit has not been observed in this subgroup to date. MR after rituximab plus fludarabine, cyclophosphamide, and mitoxantrone also significantly extended response duration in a small German Low-Grade Lymphoma Study Group study of patients with recurrent FL.[21]

The maintenance schedule devised for E1496 was based on the observed time to B-cell recovery with rituximab monotherapy, whereas selection of 2 years duration was subjective. To date, a variety of MR schedules in monotherapy and chemotherapy settings have prolonged PFS.[12,14,21,22] Hainsworth et al[12] independently devised the same schedule and duration of MR, whereas Ghielmini et al[13] studied a schedule of a single dose once every 2 months after rituximab monotherapy. Pharmacokinetic data from the pivotal trial, single doses, and the ongoing ECOG 4402 study indicate marked individual variability.[11,23,24] Questions remain about how to optimize the therapeutic potential of MR. We observed that achievement of minimal disease after CVP significantly predicted longer PFS in MR patients. One interpretation of these data suggests a strategy to achieve more complete cytoreduction going forward, whereas the alternate interpretation is that chemotherapy response also predicts MR benefit. Furthermore, the relapse pattern supports a longer period of MR, as is being studied by our group and others.

The use of murine anti-CD20 antibody conjugated to a radioisotope, either iodine-131 or yttrium-90 represents an alternative mode of consolidation therapy. The Southwest Oncology Group reported prolonged PFS, 67% at 5 years, with CHOP plus iodine-131 tositumomab, and results of a phase III trial comparing this approach versus R-CHOP are awaited.[25] Early data from an international trial of patients with untreated FL, 20% to 25% of whom had high-risk disease, show significantly longer PFS in patients in remission after varied chemotherapy plus yttrium-90–labeled ibritumomab tiuxetan compared with chemotherapy alone; the median PFS was 37 months.[26] Ongoing studies are evaluating the use of radioimmunotherapy after rituximab plus chemotherapy and with or without MR. Of potential importance, preclinical data suggest the possible complication of competition for the CD20 antigen with these approaches.[27]

In extrapolating our study results to current practice, several points should be considered. First, indolent lymphoma has a variable clinical course and patients with favorable status and low tumor burden were under-represented in our study. Although such patients had longer PFS with MR, the OS in the OBS arm was 99% at 2 years, a figure that will be difficult to improve on. In fact, none of the published rituximab plus chemotherapy studies included asymptomatic patients with favorable status, for whom watchful waiting remains an option as well as ongoing investigational trials. Second, although our results establish definitive benefit for MR after CVP in untreated patients, they do not address the benefit of MR after combined rituximab plus chemotherapy. A fully accrued study of rituximab plus chemotherapy ± MR will answer this question in untreated patients who require therapy.

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Finally, all trials of MR require ongoing surveillance for long-term safety.

In summary, the E1496 study provides the first phase III data (to our knowledge) in untreated indolent lymphoma that MR after chemotherapy significantly prolongs PFS, to a far greater extent than achieved by any prior strategy and with minimal toxicity. Observations from this study inform the design of future studies and add to a substantial body of evidence that the combination of rituximab with chemotherapy is a new standard for patients with indolent lymphoma who require treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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