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Treatment of Older Patients With Mantle Cell Lymphoma (MCL): Long-Term Follow-Up of the Randomized European MCL Elderly Trial

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abstract

PURPOSE In an update of the randomized, open-label, phase III European Mantle Cell Lymphoma (MCL) Elderly trial (ClinicalTrials.gov identifier: NCT00209209), published in 2012, we aimed to confirm results on long-term outcome focusing on efficacy and safety of long-term use of rituximab maintenance.

PATIENTS AND METHODS Five hundred sixty patients with newly diagnosed MCL underwent a first random assignment between rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab, fludarabine, and cyclophosphamide (R-FC) induction, followed by a second random assignment in 316 responders between rituximab and interferon alfa maintenance, to be continued until progression. We compared progression-free survival from the second randomization and overall survival (OS) from the first or second randomizations.

RESULTS After a median follow-up time of 7.6 years, the previously described difference in OS between the induction arms persisted (median, 6.4 years after R-CHOP [n = 280] *v* 3.9 years after R-FC [n = 280]; $P = .0054$). Patients responding to R-CHOP had median progression-free survival and OS times of 5.4 and 9.8 years, respectively, when randomly assigned to rituximab (n = 87), compared with 1.9 years ($P < .001$) and 7.1 years ($P = .0026$), respectively, when randomly assigned to interferon alfa (n = 97). In 58% and 32% of patients treated with R-CHOP, rituximab maintenance was still ongoing 2 and 5 years from start of maintenance, respectively. After R-FC, rituximab maintenance was associated with an unexpectedly high cumulative incidence of death in remission (22% at 5 years). Toxicity of rituximab maintenance was low after R-CHOP (grade 3-4 leukopenia or infection < 5%) but more prominent in patients on rituximab maintenance after R-FC, in whom grade 3-4 leukopenia (up to 40%) and infections were frequent (up to 15%).

CONCLUSION The excellent results of R-CHOP followed by rituximab maintenance until progression for older patients with MCL persisted in a mature follow-up. Prolongation of rituximab maintenance beyond 2 years is effective and safe.

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INTRODUCTION

The outcome of patients with mantle cell lymphoma (MCL) has largely improved over the past decades.[1-3] The introduction of rituximab and the use of high-dose cytarabine followed by stem-cell rescue have contributed to this improvement. However, with a median age of 65 years, most patients are not considered candidates for high-dose therapy. For them, separate trials have been designed, not only aimed at better induction regimens, but also at improvement of postinduction maintenance therapy.

In 2012, we described the superior outcome of older patients with MCL who had responded to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy and had received rituximab maintenance in the randomized MCL Elderly trial (ClinicalTrials.gov identifier: NCT00209209) of the European MCL Network.[4] With a median follow-up time of 3.5 years, these patients had an overall survival (OS) probability of 87% at 4 years. An unexpected finding was the poor outcome of the experimental induction arm consisting of rituximab, fludarabine, and cyclophosphamide (R-FC). Although complete remission (CR) rates after induction were not significantly different, more patients in the R-FC arm experienced progressive disease, and survival was substantially shorter, suggesting that salvage therapy was not feasible after R-FC induction. However, a group of responsive patients who survived the toxic R-FC scheme seemed to have an excellent outcome. Remarkably, they seemed to benefit less from rituximab maintenance, which was then not well understood.

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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When this trial was planned, there was much discussion about the duration of rituximab maintenance. We decided to not just give maintenance rituximab for a restricted period of 2 years, but to continue maintenance until progression. From a previous study in younger patients, we knew that the median time to progression after induction therapy and interferon alfa (IFN) maintenance was only 17 months and that, at 3 years, only 25% of patients were free from progression.[5] We expected that the majority of these elderly patients would have to stop rituximab maintenance after 1-2 years. However, we observed that most patients tolerated rituximab well for longer periods and that it was strongly effective. With so many new questions arising after the publication of our study and much longer follow-up, we aimed to confirm the initial results and to study the long-term safety and efficacy of rituximab maintenance.

METHODS

Patients

Eligibility criteria have been described previously.[4] Patients with newly diagnosed stage II-IV MCL, who were ≥ 65 years old (or 60-65 years old if ineligible for high-dose treatment), with an Eastern Cooperative Oncology Group performance status ≤ 2, were included. Patients with so-called leukemic non-nodal (indolent) MCL[6] were excluded.

Trial Design

This open-label, randomized, European investigator–initiated, phase III trial was registered at ClinicalTrials.gov (identifier: NCT00209209). The treatment assignment consisted of an initial 1:1 randomization between 2 induction regimens, and after induction, a second 1:1 randomization was performed for all responding patients between 2 maintenance regimens. For both randomizations, patients were stratified according to national study group, age, and International Prognostic Index (IPI) risk profile.[7] The second randomization was also stratified by induction regimen and response quality.

Induction and Maintenance Treatment

Induction therapy consisted of either 6 cycles of R-FC every 4 weeks or 8 cycles of R-CHOP every 3 weeks as described.[4] If insufficient recovery had occurred after a 1-week delay, fludarabine, cyclophosphamide, or doxorubicin had to be adapted. The use of hematopoietic growth factors was optional.

The second randomization between maintenance with IFN or rituximab was offered to all responding patients (CR, unconfirmed CR, or partial remission) with leukocytes $> 3 \times 10^9$/L and platelets $> 100 \times 10^9$/L ($> 75 \times 10^9$/L from 2009). Maintenance therapy was set to be started within 1 month after the date of the second randomization and to continue until progression. Rituximab (375 mg/m^2) was given every 2 months, regular IFN (3 million units subcutaneously) was administered 3 times a week, and pegylated IFN was given at a dose of 1 μg/kg/wk.

Staging Procedures and Response Monitoring

Staging and response monitoring according to the 1999 Cheson criteria[8] were performed as described previously.[4] Response after induction was determined 4 weeks after the last chemotherapy cycle. During follow-up, response evaluations were performed twice yearly until progression.

Statistical Methods

Primary trial outcomes were the CR rate for the comparison of induction treatments and progression-free survival (PFS) from end of induction in responding patients for the comparison of maintenance treatments; both outcomes were evaluated using modified intent-to-treat populations, as previously reported.[4] For efficacy evaluation, we report here an overrunning analysis of the primary maintenance question and secondary strict intent-to-treat evaluations for the following time-to-event end points. In line with the factorial trial design, we performed stratified and interaction analyses according to induction treatment of questions related to the different maintenance strategies.

Failure-free survival (FFS) was calculated from start of treatment to stable or progressive disease (failure) or death from any cause. OS was calculated from first randomization to death from any cause. For the comparison of maintenance groups, PFS was calculated from the start of the second randomization to progression or death from any cause; OS was calculated from the start of the second randomization to death from any cause. OS was censored at the latest follow-up date for patients alive at last contact. PFS and FFS were censored at the latest lymphoma assessment for patients without documented lymphoma progression with their lymphoma assessment more than 3 months before the last contact. For patients with stable or progressive disease during follow-up, OS from first treatment failure was calculated, censoring patients still alive at latest follow-up date.

Time-to-event variables were described using Kaplan-Meier estimates and compared with the log-rank test. Follow-up was calculated using reverse Kaplan-Meier estimates.[9] Cox regression was used for estimating hazard ratios (HRs) and for formal interaction tests. For composite time-to-event end points and duration of maintenance, competing risk analyses for estimation and comparison of the cumulative incidence rates using subdistribution hazards were performed according to Gray.[10] To estimate FFS and OS according to the intent-to-treat principle with a specific induction followed by a specific maintenance without restriction to responding patients randomly assigned to maintenance, multiple imputation was used to account for missing second randomization. Statistical analysis was performed using SAS, Version 9.3 (SAS Institute, Cary, NC) and R version 3.5.1 (www.r-project.org).

RESULTS

Between 2004 and 2010, 560 patients (median age, 70 years; 82% stage IV, 41% intermediate MIPI risk, and 50% high MIPI risk[11,12]; Table 1) were included in the first induction randomization between R-FC and R-CHOP. Next, 316 responders were randomized for maintenance between IFN and rituximab. The clinical cutoff date was September 11, 2018. The median follow-up estimate for survival of all patients was 7.6 years.

Outcome of Induction Therapy

After the end of induction, the CR rates, including unconfirmed CRs, were not significantly different between both treatment groups. Overall response rates were slightly but not significantly higher after R-CHOP than after R-FC (84% *v* 78%, respectively) as a result of more partial remissions and more patients in the R-FC arm with refractory disease (Table 1).

Updated analyses still showed overlapping FFS (median, 2.2 and 2.4 years with R-FC and R-CHOP, respectively; $P = .90$; Fig 1A). The significant difference in OS, described in 2012, persisted during longer follow-up (median, 6.4 years after R-CHOP *v* 3.9 years after R-FC; $P = .0054$; Fig 1B). A competing risk analysis for the composite end point of FFS showed that the cumulative incidence of death without treatment failure was significantly higher after R-FC at 5 years (19% after R-FC *v* 9% after R-CHOP; $P = .0043$; Fig 1C), whereas more relapses were observed after R-CHOP compared with R-FC ($P = .054$). Finally, the OS after first treatment failure was poor, with a strong difference between both arms (OS after treatment failure, 2.3 years for R-CHOP *v* 1 year after R-FC; $P = .0012$; Fig 1D).

TABLE 1. Baseline Characteristics and Response Rates

Characteristic and Response	R-CHOP (n = 280)	R-FC (n = 280)
Median age, years (range)	70 (61-87)	70 (60-85)
Stage, %		
II	5	6
III	11	12
IV	84	81
Male, %	68	72
Bone marrow involvement, %	76	75
MIPI score, %		
Low	7	9
Median	43	39
High	50	52
Response after induction		
Response evaluable, No.	267	265
CR, %	32	38
CR + CRu, %*	46	51
PR, %	37	28
Overall response, %†	84	78
Stable disease, %	6	5
Progressive disease, %	6	14
Early death, %	4	3

Abbreviations: CR, complete remission; CRu, unconfirmed complete remission; MIPI, Mantle Cell Lymphoma International Prognostic Index; PR, partial remission; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-FC, rituximab, fludarabine, and cyclophosphamide.

*$P = .30$ by Fisher's exact test.

†$P = .15$ by Fisher's exact test.

Causes of Death

Causes of death were equally distributed among the randomly assigned treatment groups, except for more cardiac causes after R-CHOP (8% *v* 2% for R-FC) and more secondary acute myeloid leukemia or myelodysplastic syndrome after R-FC (5% *v* 0% for R-CHOP; Table 2). There were, however, marked differences in the time points of death between R-CHOP and R-FC. In the R-FC group, compared with R-CHOP, death occurred more frequently after progression during induction therapy (22% *v* 12%, respectively) and in first remission (28% *v* 14%, respectively). In contrast, in the R-CHOP group, compared with R-FC, death occurred more frequently after progression following first remission (60% *v* 34%, respectively).

Outcome of Maintenance Therapy

At a median follow-up time of 8 years for the 316 responding patients, the significant PFS difference documented in 2012[4] between rituximab and IFN persisted (median PFS, 5.2 years for rituximab and 2.0 years for IFN; $P = .0109$). In addition, we now also observed an OS difference (median OS, 9.8 years for rituximab and 6.4 years for IFN; $P = .009$). Patients responsive to R-CHOP benefitted most from rituximab, in terms of both PFS (median, 5.4 years after rituximab *v* 1.9 years after IFN; $P < .001$; Fig 2A) and OS (median, 9.8 years after rituximab *v* 7.1 years after IFN; $P = .0026$; Fig 2 B).

To mimic real life (outside trial) and accounting for the fact that nonresponders to induction were not randomly assigned for maintenance, we estimated the outcome with R-CHOP followed by maintenance based on the intent-to-treat principle at first randomization and included patients not randomly assigned for maintenance (as a result of the various reasons reported previously[4]). This yielded a median FFS from start of induction of 3.8 years with R-CHOP plus rituximab versus 1.9 years with R-CHOP plus IFN and a median OS from trial registration of 7.9 years with R-CHOP plus rituximab versus 5.0 years with R-CHOP plus IFN (Data Supplement).

With more mature follow-up, we observed that patients responsive to R-FC also showed a significantly better PFS after rituximab (median, 5.0 years after rituximab *v* 2.6 years after IFN; $P = .0315$), although this did not translate into an OS difference ($P = .53$; Figs 2A and 2B). A

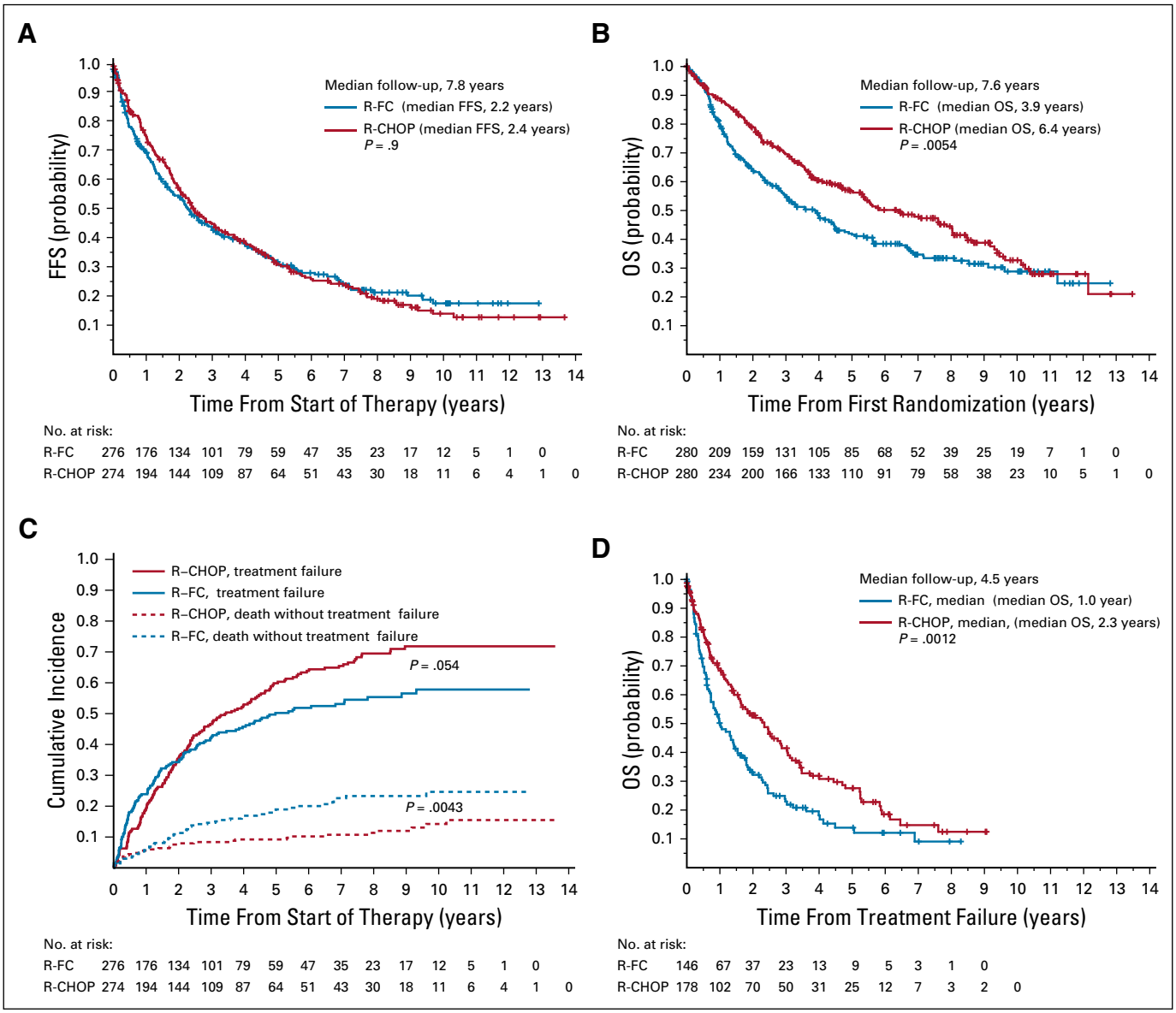

FIG 1. (A) Failure-free survival (FFS) from start of therapy according to treatment groups (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] and rituximab, fludarabine, and cyclophosphamide [R-FC]) in intent-to-treat analysis. Of the original 560 patients, in 10 patients, FFS was not assessable, including 4 patients in R-FC group (B-cell chronic lymphocytic leukemia, n = 1; no restaging documentation, n = 1; administrational reason, n = 1; patient withdrawal, n = 1) and 6 patients in R-CHOP group (patient withdrawal, n = 3; diffuse large B-cell lymphoma, n = 1; follicular lymphoma, n = 1; administrational reason, n = 1). Five-year FFS probability estimates were 31% (95% CI, 26% to 37%) for R-CHOP and 31% (95% CI, 25% to 37%) for R-FC. (B) Overall survival (OS) according to induction treatment groups (R-CHOP and R-FC). Five-year OS probability estimates were 57% (95% CI, 51% to 63%) for R-CHOP and 42% (95% CI, 36% to 49%) after R-FC. (C) Cumulative incidence of failure and death without failure for both induction groups. (D) OS after first treatment failure in both groups.

competing risk analysis in this R-FC group showed that rituximab maintenance had a strong effect in delaying progression. However, the cumulative incidence of death in remission (22% at 5 years, mainly as a result of infections or secondary tumors) remained high (Data Supplement).

Maintenance Duration and Toxicity of Rituximab

According to the protocol, maintenance should stop if serious toxicity developed or if relapse or progression of lymphoma occurred. However, because of local policy, rituximab was stopped in 9% and 1% of all patients after 2 and 3 years, respectively, despite the fact that the patients were still in remission and did not report adverse effects. IFN was stopped most often and largely within the first year (median duration, 10 months after R-CHOP and 4 months after R-FC; Data Supplement), mainly because of toxicity. Rituximab maintenance was ongoing 2 years after end of R-CHOP in 58% of patients and 5 years after R-CHOP in

TABLE 2. Causes of Death and Time Points of Death Among Deceased Patients

	Overall		R-CHOP		R-FC	
Cause and Time Point of Death	**No.**	**%**	**No.**	**%**	**No.**	**%**
Cause						
Lymphoma progression	183	59	87	60	96	58
Infection	36	12	17	12	19	11
Secondary tumor	17	5	7	5	10	6
Cardiac	16	5	12	8	4	2
Secondary AML/MDS	8	3	0	0	8	5
Leukoencephalopathy	3	1	1	1	2	1
Pulmonal (no infection)	5	2	2	1	3	2
Traumatic cerebral bleeding	2	1	0	0	2	1
Cerebrovascular ischemia	2	1	2	1	0	0
GI bleeding	1	0	1	1	0	0
Cerebral bleeding	1	0	0	0	1	1
Unclear	37	12	16	11	21	13
No. of patients who died	311	100	145	100	166	100
Time points of death						
During induction therapy	20	6	12	8	8	5
After premature stop of induction therapy	13	4	4	3	9	5
After progression during induction therapy	48	15	12	8	36	22
After SD during induction therapy	19	6	9	6	10	6
In first remission	66	21	20	14	46	28
After progression following first remission	144	46	87	60	57	34
Insufficient documentation	1	0	1	1	0	0

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-FC, rituximab, fludarabine, and cyclophosphamide; SD, stable disease.

32% of patients (median duration, 2.2 years). After response to R-FC, rituximab maintenance was ongoing in 40% and 20% of patients after 2 and 5 years, respectively (median duration, 1.9 years). Rituximab maintenance was more frequently stopped as a result of causes other than treatment failure (toxicity, secondary malignancies, or physician or patient decisions) after R-FC (33% at 2 years and 48% at 5 years) than after R-CHOP (20% at 2 years and 34% at 5 years; Data Supplement).

To determine whether continuation of rituximab after R-CHOP induction for $>$ 2 or 3 years was effective, we performed exploratory landmark analyses for PFS analyzing only the patients in remission 2 and 3 years from end of R-CHOP, respectively, stratifying by whether rituximab had been stopped before the respective landmark time point. At 2 and 3 years, 11 of 61 and 18 of 53 patients had stopped rituximab, respectively, mainly because of physician decision to stop at 2 or 3 years (5 and 9 patients, respectively) but not because of adverse effects; other reasons included patient wish (2 and 2 patients, respectively), secondary malignancy (1 and 2 patients, respectively), and reason unknown (3 and 5 patients, respectively). It seemed that PFS remained significantly better for patients who continued rituximab after 2 years (median 9.2 *v* 4.4 years from end of induction for patients who stopped rituximab; P = .0146; MIPI-adjusted HR, 0.37) or 3 years (9.8 *v* 4.9 years; P = .0038 for patients who stopped rituximab; MIPI-adjusted HR, 0.29; Fig 3).

In the rituximab group, early and late toxicity during the first 5 years after induction was more prominent after pretreatment with R-FC than after R-CHOP (Data Supplement). In particular, grade 3-4 cytopenias were more frequent (for WBCs: up to 40% after R-FC *v* $<$ 5% after R-CHOP). Infections of all grades occurred in 30%-40% of patients, again with more grade 3 infections after R-FC (10%-15%) compared with after R-CHOP ($<$ 5%). The majority of adverse events occurred during the first 2 years, but granulocytopenia after R-FC persisted in 30%-40% of patients at up to 5 years of maintenance (Data Supplement).

Outcome and Salvage Therapy

During follow-up, 324 patients have experienced treatment failure, and 311 patients have died. Causes of death are listed in Table 2. Despite the fact that more patients experienced failure after R-CHOP (n = 178) than after R-FC (n = 146), their OS after failure was better (Fig 1D), suggesting that salvage therapy after R-CHOP was more successful than after R-FC. The Data Supplement provides a summary of the various salvage regimens offered. After R-FC, the most frequent regimen was R-CHOP-like, whereas after R-CHOP, most patients received fludarabine or bendamustine-based immunochemotherapy. Only 2 patients were offered ibrutinib. After R-FC, patients treated with rituximab plus chemotherapy had the longest survival. However, if only the rituximab plus chemotherapy regimens are considered, all regimens still had a poor outcome with completely overlapping curves (1.4-1.9 years). Similarly, after R-CHOP, any combination with rituximab (rituximab plus chemotherapy) showed a trend to perform better than without rituximab. In addition, R-FC still performed worse as a salvage regimen after R-CHOP compared with other rituximab plus chemotherapy regimens (Data Supplement).

Because new regimens containing rituximab did better than chemotherapy alone, despite prior rituximab, we analyzed the outcome after first treatment failure to R-CHOP with respect to rituximab resistance. Data are shown in the Data Supplement. In both groups, rituximab-resistant patients (n = 50) and non–rituximab-resistant patients (n = 61), patients treated with rituximab plus chemotherapy tended to have a longer OS from first treatment failure, suggesting that the addition of rituximab to chemotherapy after R-CHOP failure is equally effective in rituximab-resistant and nonresistant patients.

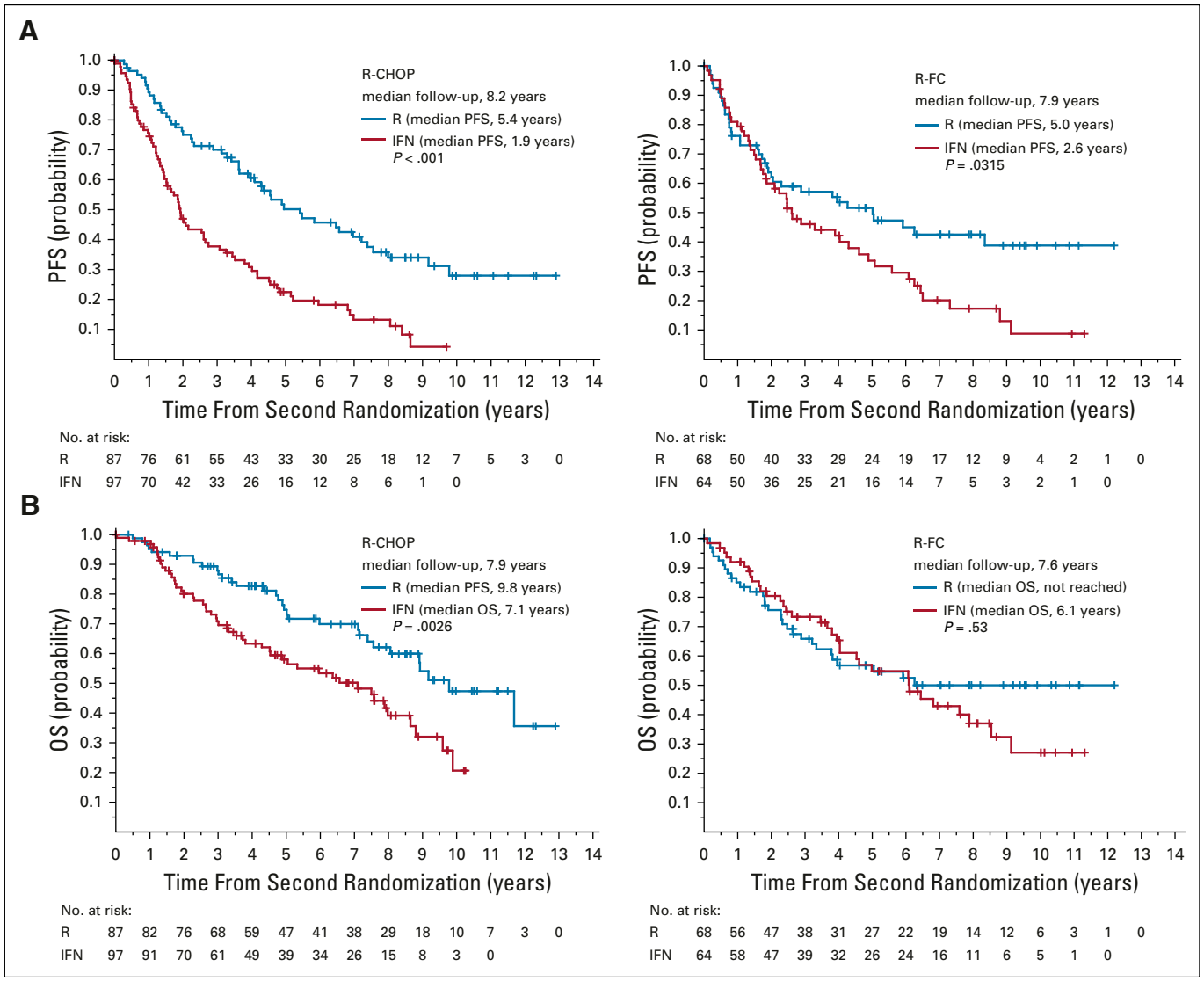

FIG 2. (A) Intent-to-treat analysis of progression-free survival (PFS) from second randomization according to maintenance groups (rituximab [R] and interferon alfa [IFN]) after (left) rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) induction and (right) rituximab, fludarabine, and cyclophosphamide (R-FC) induction. For patients treated with R-CHOP, 5-year PFS estimates were 50% (95% CI, 40% to 63%) with R and 22% (95% CI, 15% to 33%) with IFN. For patients treated with R-FC, 5-year PFS estimates were 52% (95% CI, 41% to 66%) with R and 34% (95% CI, 23% to 49%) with IFN. Hazard ratios with adjustment for Mantle Cell Lymphoma International Prognostic Index (MIPI) score for R versus IFN were 0.42 (95% CI, 0.29 to 0.60) among patients treated with R-CHOP and 0.56 (95% CI, 0.37 to 0.87) among patients treated with R-FC ($P = .29$ for testing the null hypothesis of identical hazard ratios). (B) Intent-to-treat analysis of overall survival (OS) from second randomization according to maintenance groups (R and IFN) after (left) R-CHOP induction and (right) R-FC induction. For patients treated with R-CHOP, 5-year OS estimates were 75% (95% CI, 66% to 86%) with R and 58% (95% CI, 48% to 70%) with IFN. For patients treated with R-FC, 5-year OS estimates were 57% (95% CI, 46% to 71%) with R and 55% (95% CI, 43% to 70%) with IFN. Hazard ratios with adjustment for MIPI score for R versus IFN were 0.50 (95% CI, 0.32 to 0.79) among patients treated with R-CHOP and 0.76 (95% CI, 0.46 to 1.24) among patients treated with R-FC ($P = .23$ for testing the null hypothesis of identical hazard ratios).

DISCUSSION

In this mature update of the European MCL Network trial for older patients, we confirm the initial results as far as PFS and OS are concerned after R-CHOP induction followed by long-term rituximab maintenance. These patients, with a median age of 70 years at start, had a median survival of 9.8 years if responsive to induction and treated with rituximab maintenance. When we recalculated OS for all patients who started R-CHOP with the intention to receive rituximab maintenance and included all patients, even the patients who were not randomly assigned to maintenance treatment, the OS was still good, with a median OS time of 7.9 years. This is in contrast with reviews on MCL that describe a median survival of 4 to 5 years.[6,13] More recent studies confirm improvement of OS for elderly patients. For example, a phase III study of R-CHOP versus bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) described a median OS of 7.6 years in the

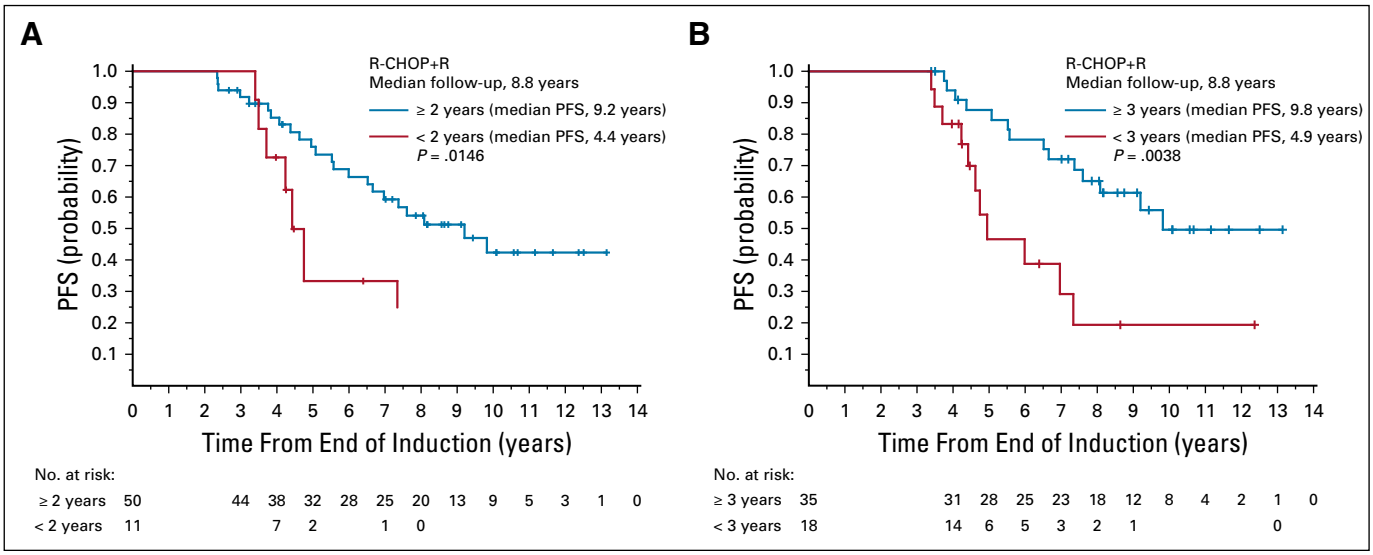

FIG 3. Landmark analysis to study progression-free survival (PFS) from end of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) induction in patients in remission after (A) 2 years or (B) 3 years, according to status of maintenance rituximab (R; ongoing *v* stopped). The hazard ratios for patients who continued rituximab after 2 or 3 years, adjusted for Mantle Cell Lymphoma International Prognostic Index score, were 0.37 (95% CI, 0.15 to 0.91) and 0.29 (95% CI, 0.13 to 0.66), respectively.

VR-CAP arm.[14] In addition, a phase II study of rituximab plus lenalidomide both at induction and maintenance showed a 5-year OS of 77%.[15] Finally, in the StiL NHL7-2008 MAINTAIN study (ClinicalTrials.gov identifier: NCT00877214), studying bendamustine plus rituximab with or without maintenance rituximab, the OS seemed to be in the 6- to 7-year range.[16] In contrast to our first report, with a longer follow-up time, our results demonstrate that patients pretreated by R-FC benefitted from rituximab maintenance as far as PFS was concerned, although this still did not translate to a better OS as a result of increased toxicity-related deaths.

Although R-FC, which in the past was considered so promising,[17-19] performed badly in our trial as far as efficacy and toxicity were concerned, the scheme seemed extremely effective in a small subgroup of patients who tolerated the toxicity. After R-FC induction, far more patients became minimal residual disease negative than after R-CHOP (data not shown). The OS curves in the R-FC group followed by rituximab maintenance even showed a tendency to plateau around 50% after 6-7 years (Fig 2B), although numbers at risk evidently were low.

The duration of rituximab maintenance was a matter of debate before we started our study. Rituximab maintenance for 2 years is standard for first-line treatment of follicular lymphoma[20,21] and after relapse.[22] Prolongation of rituximab maintenance up to 4 years, as is being studied in the phase III StiL NHL7-2008 MAINTAIN study, seems to result in a longer PFS.[23] For younger patients with MCL after autologous stem-cell transplantation, 3 years of maintenance were effective.[24] Our protocol prescribed that rituximab should be continued until progression or until serious toxicity occurred. Despite this, in a considerable number of patients still in remission, rituximab was stopped after 2 years as a result of local policy. This offered us the opportunity to compare PFS between patients in remission who continued the drug versus patients who stopped. We showed that for patients who continued rituximab beyond 2 and 3 years, compared with those who stopped, subsequent PFS remained significantly longer, with an almost 5-year difference in favor of those who continued rituximab (approximately 9.5 years *v* 4.5 years, respectively). Because the reason for stopping rituximab maintenance was administrational in approximately half of the patients and none reported adverse effects as reason, we think this effect cannot be explained by selection bias.

The long duration of rituximab was well tolerated, with only minor serious toxicity after R-CHOP induction. In contrast, R-FC induction followed by rituximab maintenance was complicated by far more hematologic toxicity and infections, up to the 5 years that we analyzed. Because rituximab plus bendamustine is now frequently offered as first-line treatment to older patients with MCL,[25,26] it is important to realize that long-term hematologic toxicity and immune deficiency, also in relation to persistent low CD4 counts,[27] might interfere with maintenance rituximab therapy.[23]

With so many new options for relapsed MCL, such as rituximab plus bendamustine and ibrutinib,[28] we attempted to analyze the outcome after first-line treatment failure. The protocol did not prescribe any second-line regimen, and a large variety of regimens were seen, thus preventing any meaningful analysis. After R-FC, all regimens performed badly, explaining the poor outcome after induction failure.

In contrast, after R-CHOP, new regimens (still containing rituximab) had median survival curves beyond 2 years, except when R-FC was offered, which resulted in only a 1.6-year median OS.

In conclusion, the excellent results of R-CHOP followed by rituximab maintenance for older patients with MCL persisted in a mature follow-up. Prolongation of rituximab maintenance beyond 2 or 3 years is effective and safe.

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Treatment of Older Patients With Mantle Cell Lymphoma (MCL): Long-Term Follow-Up of the Randomized European MCL Elderly Trial

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