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ORIGINAL REPORT

Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma

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ABSTRACT

Purpose

The FOLL05 trial compared R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and R-FM (rituximab plus fludarabine and mitoxantrone) regimens without rituximab maintenance as initial therapy for patients with advanced-stage follicular lymphoma (FL). A previous analysis with a median follow-up of 34 months showed a superior 3-year time to treatment failure, the primary study end point, with R-CHOP and R-FM versus R-CVP and showed R-CHOP to have a better risk-benefit ratio in terms of toxicity than R-FM. We report a post hoc analysis of this trial after a median follow-up of 7 years.

Patients and Methods

Of the 534 enrolled patients, 504 were evaluable. At the time of analysis, the median follow-up was 84 months (range, 1 to 119 months).

Results

The 8-year time to treatment failure and progression-free survival rates were 44% (95% CI, 39% to 49%) and 48% (95% CI, 43% to 53%), respectively. The hazard ratio for progression-free survival adjusted by FL International Prognostic Index 2 versus R-CVP was 0.73 for R-CHOP (95% CI, 0.54 to 0.98; $P = .037$) and 0.67 for R-FM (95% CI, 0.50 to 0.91; $P = .009$). The 8-year overall survival (OS) rate was 83% (95% CI, 79% to 87%), with no significant differences among study arms. Overall, we observed a higher risk of dying as a result of causes unrelated to lymphoma progression with R-FM versus R-CVP.

Conclusion

With an 83% 8-year OS rate, long-term follow-up of the FOLL05 trial confirms the favorable outcome of patients with advanced-stage FL treated with immunochemotherapy. The three study arms had similar OS but different activity and toxicity profiles. Patients initially treated with R-CVP had a higher risk of lymphoma progression compared with those receiving R-CHOP, as well as a higher risk of requiring additional therapy.

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INTRODUCTION

Follicular lymphoma (FL) is the most common of the indolent non-Hodgkin lymphomas (NHLs) and constitutes approximately 10% to 20% of all newly diagnosed NHLs in Western countries.[1] The natural history of FL is that of a low-grade lymphoma, with the typical pattern of relapses after initial therapy followed by remissions of increasingly shorter duration after each event and by the risk of transformation into aggressive lymphoma.[2] With the availability of anti-CD20 monoclonal antibody, the outcome for patients with FL has greatly improved, and sequential treatment with active immunochemotherapy (ICT) regimens is associated with high response rates and prolonged survival.[3] Patients with FL now

ASSOCIATED CONTENT

Appendix
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show remission rates of nearly 90%, a median progression-free survival (PFS) of 6 to 7 years, and 5-year overall survival (OS) rates approaching 90%.[4-6]

Although the use of anti-CD20 monoclonal antibody is confirmed by strong evidence, choice of chemotherapy backbone has been a matter of debate for many years and is still made based on limited evidence. In 2005, the Fondazione Italiana Linfomi initiated the randomized FOLL05 trial to identify the best ICT regimen for first-line treatment of advanced-stage FL among R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone), R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), and R-FM (rituximab plus fludarabine and mitoxantrone). In 2013, we published the primary analysis of the study, with a median follow-up of 34 months, showing the superiority of R-CHOP and R-FM over R-CVP in terms of time to treatment failure (TTF) and PFS, but our results also revealed a better toxicity profile for R-CHOP compared with R-FM.[7] Overall, these data were interpreted to suggest R-CHOP as the standard ICT for the treatment of patients with advanced-stage FL.

The use of early end points as surrogates of OS is accepted by the scientific community and enables clinical trials of indolent disease. However, the long natural history of FL warrants a long-term update of clinical trials to better evaluate the risk-benefit ratio of treatment. Here, we present an analysis of the mature results of the FOLL05 trial after a median follow-up of 7 years.

PATIENTS AND METHODS

Patients

FOLL05 was a prospective, randomized, open-label, multicenter phase III trial that included previously untreated patients with advanced-stage symptomatic FL. Eligible patients had a histologically confirmed diagnosis of grade 1, 2, or 3a FL according to the 2008 WHO classification,[8] had Ann Arbor stage II to IV disease, were age 18 to 75 years with Eastern Cooperative Oncology Group performance status of 0 to 2, and had active disease according to Italian Society of Hematology guidelines.[9] Exclusion criteria included a diagnosis of grade 3b FL, evidence of histologic transformation into an aggressive lymphoma at the time of diagnosis, CNS involvement, or history of previous malignancy.

This study was conducted in compliance with the Declaration of Helsinki and in accordance with Good Clinical Practice rules and was approved by a research ethics committee. All enrolled patients provided written informed consent. Patients were randomly assigned to receive eight doses of rituximab combined with eight courses of CVP (arm A [R-CVP]), six cycles of CHOP (arm B [R-CHOP]), or six cycles of FM (arm C [R-FM]). Because its cost was not reimbursed in 2005, maintenance was not admitted and was considered to be failure for the primary study end point if administered.

Response was assessed with clinical examination, contrast-enhanced computed tomography, and bone marrow biopsy if required. [^{18}F]fluorodeoxyglucose positron emission tomography was not mandatory for response assessment but was performed in a significant proportion of patient cases.[10] When available, [^{18}F]fluorodeoxyglucose positron emission tomography was not considered for staging or definition of response. Clinical examination of patients who completed treatment was planned every 3 months for the first 6 months, every 6 months for 3 years, and then annually. Computed tomography scans were performed every 6 months for 2 years, then annually or when clinically indicated. Follow-up updates were actively conducted among participating institutions. Relapses or progressions were determined based on clinical or radiologic assessment.

Statistical Methods

In addition to TTF, the primary study end point, this long-term analysis was conducted to evaluate PFS, OS, cause-specific mortality (CSM), cumulative incidence of second malignancies (SMs), and frequency of late adverse events. For this analysis, the initial definition of sample size was not applicable; the analysis was conducted as a post hoc long-term observational study of patients enrolled in the FOLL05 trial. Molecular response was also included as a secondary end point and results published in a separate report.[11]

TTF was defined as the time from random assignment to discontinuation of treatment of any reason, including disease progression, treatment toxicity, start of maintenance therapy, or death. PFS was defined as the time from random assignment to progressive disease or death resulting from any cause. OS was calculated as the time from patient random assignment to death resulting from any cause. Adverse events were registered in accordance with the standard Common Toxicity Criteria for Adverse Events (version 3).

For the analysis of CSM, cause of death was described as reported by the local investigator and classified as lymphoma related in the case of documented uncontrolled progression of lymphoma or non–lymphoma related (NLR) in patients who died as a result of causes not directly related to lymphoma progression. NLR events were additionally classified as resulting from SMs or other causes. Death resulting from SM was considered in the case of death directly associated with the presence of an uncontrolled and/or progressive SM or occurring during treatment for SM; death resulting from causes other than lymphoma progression or SM was classified as resulting from other causes.

Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Effect sizes were reported as hazard ratios (HRs) with 95% CIs and estimated using the Cox proportional hazards regression method, adjusted by relevant confounding factors when needed. Risk of SM was reported as a cumulative incidence function, with death as a competing risk, using the method of Gooley et al[12]; comparisons between curves were performed using the Gray test[13] and Fine-Gray regression.[14] The cumulative risk of histologic transformation and CSM was reported according to the Nelson-Aalen estimator. For the purposes of this study, only biopsy-proven histologic transformations were considered.

All reported tests were two sided, and $P < .05$ was considered to indicate moderate strength of evidence against the null hypothesis. P values were not adjusted for multiple comparisons. The analysis was performed according to the intention-to-treat (ITT) approach, except for studies involving SMs and late adverse events, which were analyzed according to actual therapy received.

RESULTS

From March 2006 to September 2010, 534 patients were enrolled in the FOLL05 trial by 58 Italian institutions; of these patients, 504 were eligible for ITT analysis (Fig 1). The main characteristics of eligible patients, whose median age was 55 years (range, 30 to 75 years), were described in the original report.[7]

The median follow-up was 84 months (range, 1 to 119 months). Overall, 43 patients were lost to follow-up (8.5%) after a median time of 64 months (range, 1 to 101 months). Minimum follow-up for surviving patients not lost to follow-up was 4.5 years. With prolonged follow-up, the 8-year TTF was 44% (95% CI, 39% to 49%). R-CHOP and R-FM had better TTF rates than R-CVP: 45% (HR, 0.73; 95% CI, 0.55 to 0.98; $P = .033$) and 49% (HR, 0.70; 95% CI, 0.52 to 0.93; $P = .016$) versus 38% at 8 years, respectively (Fig 2A).

Overall, 252 events were recorded for PFS, including 68 additional episodes compared with the initial report (five progressions,

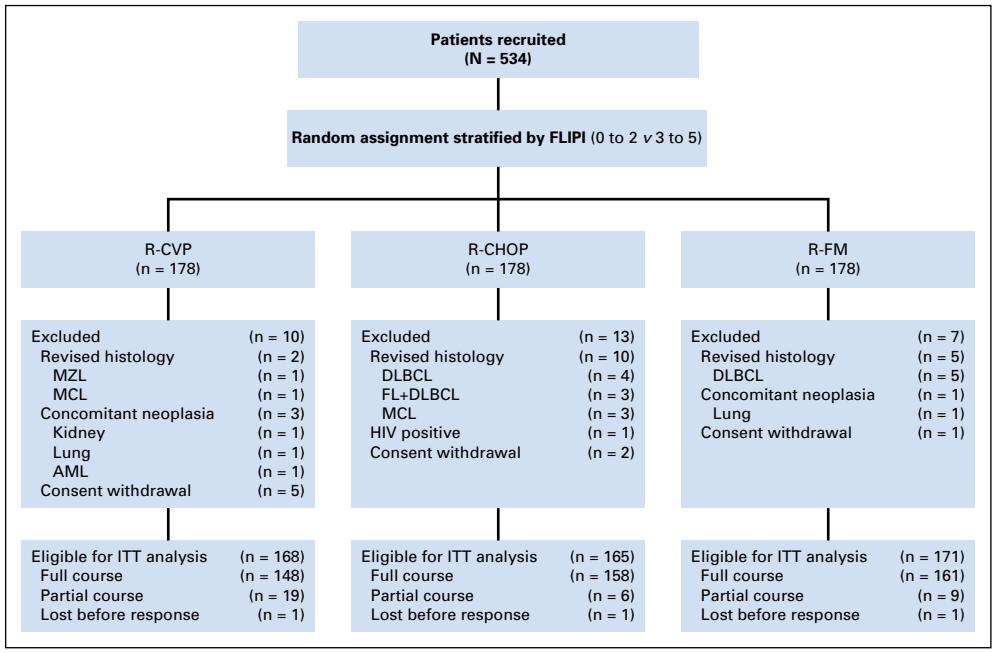

Fig 1. Treatment allocation and No. of patients included in the analysis. AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intention to treat; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone.

58 relapses, and five deaths not related to lymphoma progression; Table 1). The 8-year PFS rate was 48% (95% CI, 43% to 52%); for patients randomized to the R-CVP, R-CHOP, and R-FM arms, it was 42% (95% CI, 35% to 50%), 49% (95% CI, 40% to 57%), and 52% (95% CI, 45% to 60%), respectively (Fig 2B). Considering PFS adjusted by the FL *International Prognostic Index 2*, the HRs between R-CHOP versus R-CVP and R-FM versus R-CVP were 0.73 (95% CI, 0.54 to 0.98; $P = .037$) and 0.67 (95% CI, 0.50 to 0.91; $P = .009$).

Salvage Therapy

Overall, 208 of 248 patients who had primary refractory or experienced progressive or relapsed disease required salvage treatment: 90 received conventional ICT, 75 underwent autologous stem-cell transplantation (ASCT), 33 were treated with immunotherapy alone, and 10 were treated with radiotherapy alone (Table 2).

Among the 75 patients who underwent ASCT, a similar distribution by study arm was observed (n = 27, 27, and 21 for

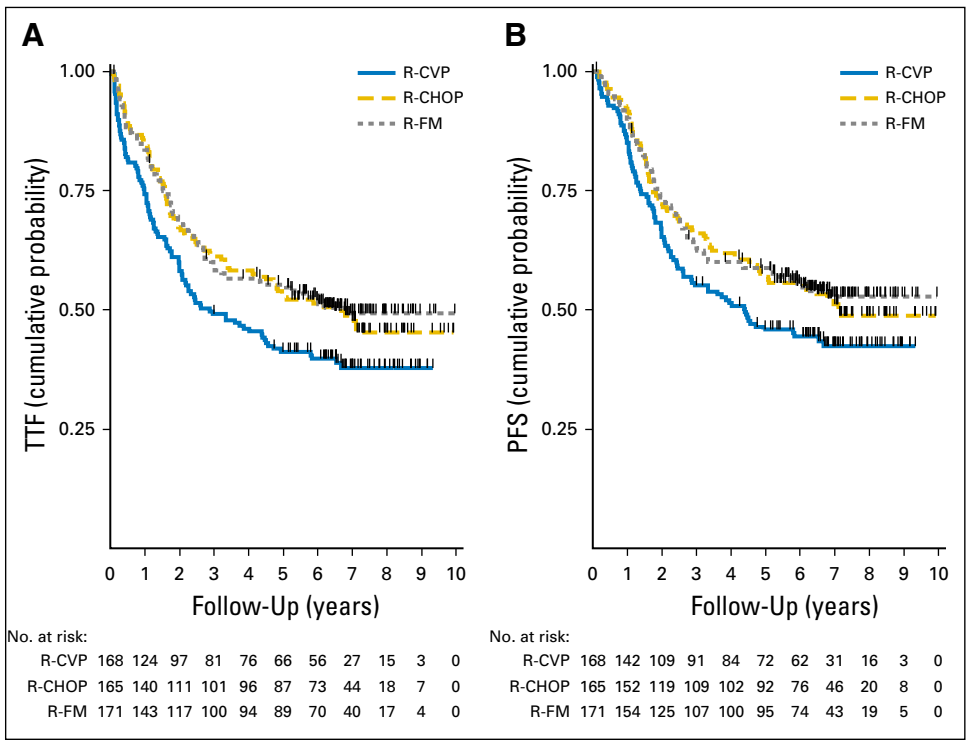

Fig 2. (A) Time to treatment failure (TTF; R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone] *v* R-CVP [rituximab plus cyclophosphamide, vincristine, and prednisone]: $P = .033$; R-FM [rituximab plus fludarabine and mitoxantrone] *v* R-CVP: $P = .016$) and (B) progression-free survival (PFS) by treatment arm (R-CHOP *v* R-CVP adjusted by Follicular Lymphoma International Prognostic Index 2 [FLIPI-2]: $P = .037$; R-FM *v* R-CVP adjusted by FLIPI-2: $P = .009$).

Table 1. PFS-Defining Events and Causes of Death by Treatment Arm

Event	ITT									
	R-CVP (n = 168)			R-CHOP (n = 165)			R-FM (n = 171)			
	Early	Update	Total	Early	Update	Total	Early	Update	Total	Total
PFS										
Progression	3	—	3	4	—	4	6	—	6	13
Progression after SD	7	2	9	2	1	3	2	2	4	16
Relapse from CR/PR	64	16	80	44	25	69	44	17	61	210
Death resulting from any cause	—	2	2	2	2	4	6	1	7	13
Total	74	20	94	52	28	80	58	20	78	252
Cause of death										
FL progression	4	13	17	6	8	14	8	7	15	46
SM	—	1	1	1	3	4	4	3	7	12
Cardiopathy	—	1	1	1	1	2	2	—	2	5
Sepsis	—	—	—	—	1	1	2	1	3	4
GVHD liver	—	—	—	—	—	—	—	1	1	1
Cachexia	—	—	—	1	—	1	—	—	—	1
Car accident	—	—	—	1	—	1	—	—	—	1
Hemorrhage	—	—	—	—	—	—	1	—	1	1
Intestinal infarction	—	—	—	—	—	—	—	1	1	1
Unknown	—	2	2	—	—	—	—	1	1	1
Total	4	17	21	10	13	23	17	14	31	75

Abbreviations: CR, complete remission; FL, follicular lymphoma; GVHD, graft-versus-host disease; ITT, intention to treat; PFS, progression-free survival; PR, partial remission; SD, stable disease; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone; SM, second malignancy.

R-CVP, R-CHOP, and R-FM, respectively). Overall, patients initially randomly assigned to R-CVP were at higher risk for requiring a second-line therapy (91 patients [55%]), compared with those receiving R-CHOP (n = 63 [38%]) or R-FM (n = 54 [32%]; $P < .001$). Patients treated with R-CVP had 43% higher probability of requiring salvage therapy versus those receiving R-CHOP.

SMs

During follow-up, 41 SMs were reported: 14 were hematologic and 27 were solid cancers. Twenty-one SMs were diagnosed in patients who never experience relapse and never received salvage therapy (n = 1, 10, and 10 for R-CVP, R-CHOP, and R-FM, respectively; Table 3). The cumulative incidence of SMs at 8 years was 9.4% (95% CI, 6.8% to 13.0%), and the median time to SM development was 33 months (range, 8 to 96 months). The cumulative incidence by actual treatment at 8 years was 6.2% (95% CI, 2.5% to 14.8%), 12% (95% CI, 7.7% to 18.7%), and 9.6% (95% CI, 6.0% to 15.2%) for R-CVP, R-CHOP, and R-FM, respectively (Gray test $P = .077$). The HRs for SMs between R-CHOP and R-CVP and between R-FM and R-CVP were 2.59 (95% CI, 1.09 to 6.20; $P = .032$) and 2.29 (95% CI, 0.94 to 5.56; $P = .067$),

Table 2. Details of Salvage Therapies Prescribed After First Relapse or Progression of FL

Second Line	No. (%)			
	ITT			
	R-CVP (n = 165)	R-CHOP (n = 166)	R-FM (n = 171)	Total (n = 504)
Stable CR/PR	67 (41)	84 (51)	88 (51)	239 (47)
Death in CR/PR or lost to follow-up	3 (2)	4 (2)	10 (6)	17 (3)
Second-line treatment	91 (55)	63 (38)	54 (32)	208 (41)
Immunochemotherapy	44 (27)	19 (11)	27 (16)	90 (18)
R-CHOP ± RT	26 (16)	—	15 (9)	41 (8)
Rituximab + fludarabine	9 (6)	5 (3)	1 (1)	15 (3)
Rituximab + bendamustine	5 (3)	13 (8)	5 (3)	23 (5)
Rituximab + other	4 (2)	1 (1)	6 (4)	11 (2)
HDT	27 (16)	27 (16)	21 (12)	75 (15)
Immunotherapy	16 (10)	13 (8)	4 (2)	33 (7)
Radiotherapy	4 (2)	4 (2)	2 (1)	10 (2)
None/watch and wait	3 (2)	5 (3)	10 (6)	18 (4)
Not available	4 (2)	9 (5)	9 (5)	22 (4)

NOTE. Percentages refer to all patients, not only to those with relapsed disease.
Abbreviations: CR, complete remission; FL, follicular lymphoma; ITT, intention to treat; PR, partial remission; HDT, high-dose therapy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone; RT, radiotherapy.

Table 3. SMs by Treatment Arm for All Patients in FOLL05 Trial and for Those Without Relapsed Disease or Salvage Therapy

SM	Actual Treatment							
	No Relapse or Salvage Therapy				All Patients in Study			
	R-CVP (n = 69)	R-CHOP (n = 87)	R-FM (n = 98)	Total (n = 254)	R-CVP (n = 165)	R-CHOP (n = 166)	R-FM (n = 171)	Total (n = 502)
Breast cancer (female)	—	1	—	1	1	2	1	4
Uterine cancer	—	1	2 (1*)	3 (1*)	—	1	2 (1*)	3 (1*)
Prostate cancer	—	1	1	2	2	1	1	4
Lung cancer	—	2 (1*)	1*	3 (2*)	—	2 (1*)	1*	3 (2*)
Kaposi sarcoma/skin cancer	—	—	1	1	1	1	2	4
GI tract	—	1	—	1	1	1	1*	3 (1*)
Urothelial cancer	—	2	—	2	—	2	—	2
Pancreatic cancer	—	—	—	—	—	—	1*	1*
Melanoma	1	—	1	2	1	—	1	2
Glioblastoma	—	1*	—	1*	—	1*	—	1*
AML/MDS	—	1	3 (2*)	5 (2*)	1*	3 (2*)	5 (3*)	9 (6*)
Hodgkin lymphoma	—	—	1	1	—	1	1	2
Multiple myeloma	—	—	—	—	—	1	—	1
CLL	—	—	—	—	—	1	—	1
SMZL	—	—	—	—	—	1	—	1
Total	1	10 (2*)	10 (4*)	21 (6*)	7 (1*)	18 (4*)	16 (7*)	41 (12*)
Histologic transformation	—	—	—	—	5 (2*)	4 (3*)	2	11 (5*)

Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic lymphoma; MDS, myelodysplastic syndrome; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone; SM, second malignancy; SMZL, spleen marginal zone lymphoma.
*Indicates patients who have died (Nos. in brackets indicate deaths).

respectively. At time of relapse, 81 of 210 patients had undergone biopsy; histologic transformation was documented and biopsy confirmed in 11 patients, with a 2.9% (95% CI, 1.5% to 5.5%) cumulative incidence at 8 years (Table 3).

OS

Overall, 75 deaths were reported: 21, 23, and 31 in the R-CVP, R-CHOP, and R-FM arms, respectively. The 8-year OS rate was 83% (95% CI, 78% to 86%); by ITT analysis, it was 85% (95% CI, 77% to 91%), 83% (95% CI, 75% to 89%), and 79% (95% CI, 71% to 85%) for R-CVP, R-CHOP, and R-FM, respectively (P = .243; Fig 3).

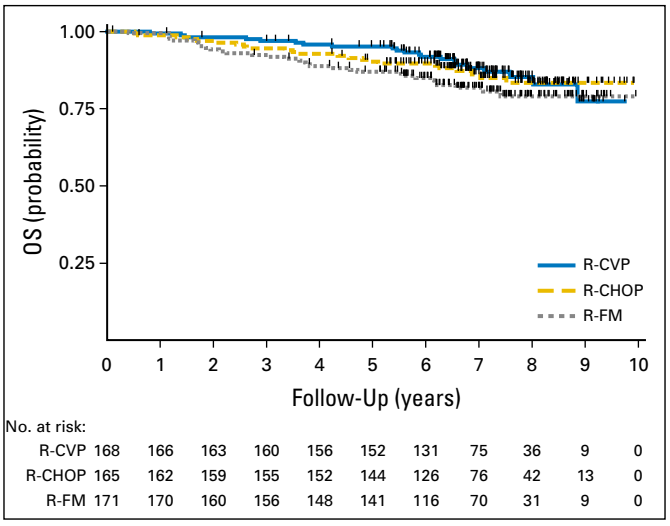

Fig 3. Overall survival (OS) by treatment arm according to intention-to-treat analysis (R-CVP [rituximab plus cyclophosphamide, vincristine, and prednisone] *v* R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone] *v* R-FM [rituximab plus fludarabine and mitoxantrone]: log-rank P = .243).

Forty-six deaths (61%) resulted from lymphoma progression, and 29 (39%) resulted from other causes (Table 1). None of the fatal infectious events occurred during induction therapy or in patients who never experienced relapse. The risk of death resulting from lymphoma was comparable among study arms (P = .900), whereas the risk of death resulting from NLR causes was higher with R-FM (11.2% at 8 years) than with R-CVP (1.8%; P = .005); the NLR CSM difference between R-CVP and R-CHOP (6.4% for R-CHOP) was not statistically significant (P = .157; Figs 4A and 4B). Of the 12 deaths resulting from SMs, seven were reported in the R-FM arm, four in the R-CHOP arm, and one in the R-CVP arm (Table 3); in the only patient treated with R-CVP and in one patient treated with R-CHOP, an SM was diagnosed after salvage ASCT. The CSM curves by SMs and by other causes are provided in Figures 4C and 4D.

DISCUSSION

With our long-term analysis of the FOLL05 trial, we provide new and more detailed data on the randomized comparison among R-CVP, R-CHOP, and R-FM. Overall, the observed 8-year OS rate of 84% clearly shows that the natural history of patients with FL has improved compared with the past. In addition, a significant proportion of patients (48% in this study) were still free from lymphoma progression 8 years after initial diagnosis, and at least in some patients, this result may translate into a possible cure of lymphoma. Although the study was not originally powered for OS analysis, no differences were observed for OS among the three study arms; however, this result was achieved with the need for second-line therapy in one of four patients treated with R-CVP versus those randomly assigned to R-CHOP and at the cost of higher mortality

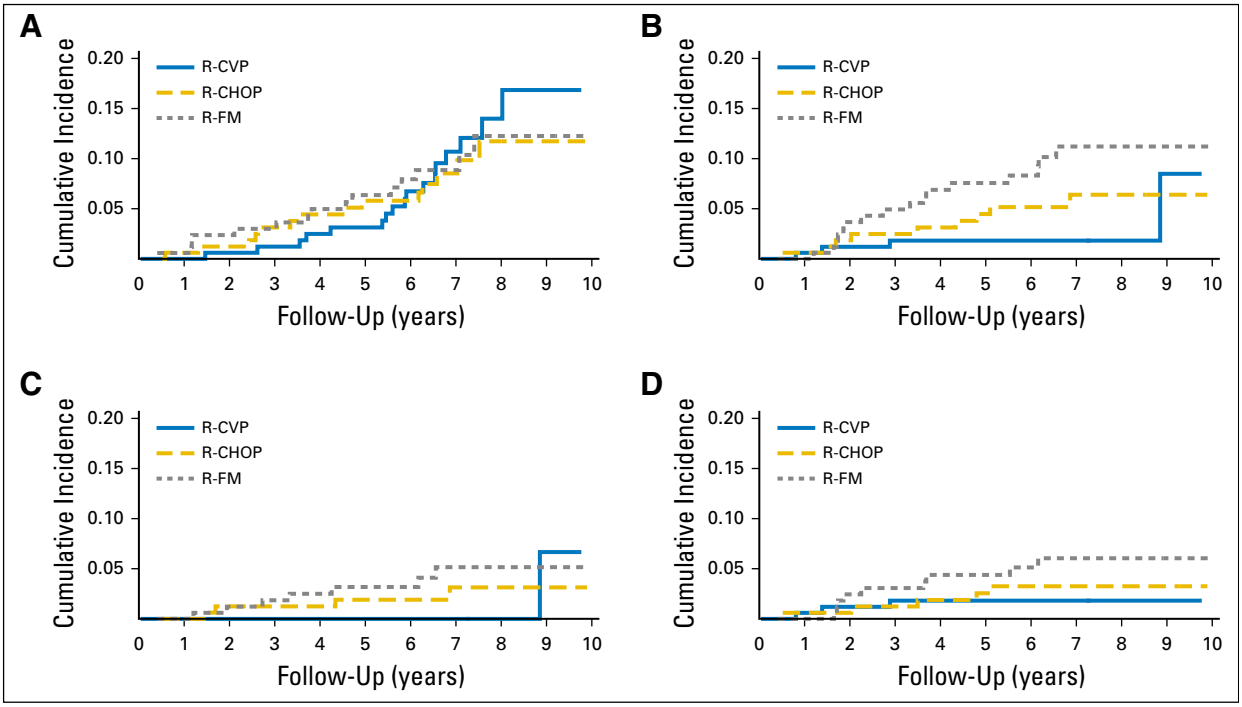

Fig 4. Cumulative incidence of cause-specific mortality stratified by arm. (A) All lymphoma-related causes of death (overall $P = .900$); (B) all non–lymphoma-related (NLR) causes of death (overall $P = .019$); (C) second-cancer NLR causes of death only ($P = .090$); and (D) all other NLR causes of death, excluding second malignancies ($P = .179$). R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone.

for causes unrelated to lymphoma observed among patients treated with R-FM compared with R-CVP.

Our results compare favorably with those of similar studies. In the 83-month observation of the FL2000 study,[15] the 8-year event-free survival and OS rates were 44.1% and 78.6% for patients randomly assigned to R-CHVP (cyclophosphamide, adriamycin, vincristine, and prednisone) and interferon. In the OSHO#39 (East German Study Group of Hematology and Oncology) study,[16] after a median follow-up of 102 months, the 8-year OS rate was 76.1%, and the median event-free survival was 89.6 months for surviving patients treated with R-MCP (rituximab plus mitoxantrone, chlorambucil, and prednisolone). Finally, the 6-year update from the PRIMA (Primary Rituximab and Maintenance) trial described a 6-year PFS rate of 42.7% and a favorable 6-year OS rate of 88.7% for patients randomly assigned to the observation arm.[17]

With this update of the FOLL05 study, we contribute to the definition of standard ICT in the initial treatment of patients with advanced-stage FL. Our CSM data provide a better description of the consequences of late events for patient survival, focusing on life-threatening events and reducing the impact of curable conditions that are also subject to under-reporting. Patients treated with R-FM had high rates of SMs and a higher risk of dying as a result of causes unrelated to lymphoma progression compared with those receiving R-CVP.

The association between fludarabine-based regimens and SMs has been already reported for NHLs.[18-22] Sacchi et al[23] described a 12-year cumulative incidence rate of 10.5% for 563 patients with indolent NHL enrolled in Gruppo Italiano Studio Linfomi trials from 1988 to 2003. More recently, in a GELCAB (Grup d'Estudi dels Linfomes de Catalunya i Balears) study, the 10-year risk of SM was 8%, similar to what was found in our study,[24] and the 10-year rate was high (27%) in FND (fludarabine, mitoxantrone, and dexamethasone) –treated patients, as reported by Nastoupil et al.[25] Although the risk of SM is known with fludarabine combinations, we should acknowledge that FCR (fludarabine, cyclophosphamide, and rituximab) is well regarded as a highly effective and appropriate regimen for patients with chronic lymphocytic lymphoma and is the current standard against which other regimens are compared. With increasing treatment efficacy, the problem of SM is suggested as a relevant issue in FL and has been observed in other lymphoma subtypes similarly treated with rituximab-containing regimens.[26-28]

In our initial report, we suggested that R-CHOP was a better option than R-CVP. Considering the updated results, we conclude with high confidence that patients treated with R-CHOP had a lower risk of progressive disease than those treated with R-CVP. In addition, our analysis of OS suggests that survival is similar between R-CHOP and R-CVP. Regarding the OS data, however, it should be emphasized that because of the small number of events, these results are not sufficiently powered to draw definitive conclusions. In addition, the choice of salvage therapy in patients with progressive disease was not defined in the protocol, and actually, high heterogeneity among second-line therapies was seen (Table 2). Our data suggest that patients initially treated with R-CVP maintained high chances of achieving second remission but also had a 43% higher risk of requiring second-line treatment compared with those receiving R-CHOP. In particular, when salvage treatment was needed after R-CVP, this included R-CHOP in 26 patient cases (27% of relapsed disease cases) or high-dose therapy in 27 patient cases (28%). Moreover, if durable remission may translate into a so-called cure of FL in a proportion of patients, we can also conclude that

considering R-CHOP as initial therapy, patients have a higher chance of being cured with the first course of therapy.

To put our results in perspective, we should acknowledge some possible concerns. First, no maintenance therapy was allowed in the FOLL05 trial, and we were unable to estimate the effect of prolonged use of rituximab in the comparison among study arms. Even if it has been shown that the risk of progressive disease is significantly reduced by maintenance rituximab, no data are available to suggest a different activity of maintenance between R-CHOP and R-CVP. Moreover, considering that in the 6-year update of the PRIMA trial, maintenance therapy did not result in any difference in OS,[17] we assume that our results might also be reproduced under the conditions of maintenance therapy. Second, because the analysis of late events is time dependent, and several events were reported after salvage therapies, longer follow-up would be required.

Third, in recent years, the combination of BR (bendamustine and rituximab) has been rapidly imposed as first-choice therapy for patients with advanced-stage FL in need of treatment and is now widely adopted.[29,30] BR has been compared with R-CHOP or R-CVP in two different trials, showing discordant results in favor of higher antilymphoma activity of the new combination but also showing strong evidence in favor of a better toxicity profile of BR.[27,31] Recently, long-term follow-up data from these studies have been presented, confirming activity and safety data of the BR combination; however, similarly to our study, differences in terms of PFS did not translate into OS differences.[32,33] Thus, given the similar efficacy of BR versus R-CHOP, we believe they both represent the best available options to achieve long-lasting remissions in patients with previously untreated FL. Further improvement is expected with the adoption of maintenance therapy and with the substitution of rituximab with the novel anti-CD20 agent obinotuzumab, which was recently shown to further reduce the risk of progression.[34]

Finally, as ancillary results, we were also able to complete our study with details on the histologically documented transformation of FL into aggressive lymphoma. The observed transformation rate was low compared with those in previous reports from retrospective studies[35-37] and similarly low compared with the 4.1% rate at 6 years recently reported from the analysis of the PRIMA trial.[38] Although a formal and appropriate methodologic demonstration is lacking, a protective effect of rituximab on the rate of transformation can be suggested, as also recently reported by a large retrospective international study.[39]

In conclusion, this long-term update of the FOLL05 trial confirms the high efficacy of ICT for the initial treatment of patients with advanced-stage FL in need of therapy. In addition, with the longer follow-up, we can conclude that if the aim of initial therapy is to maximize treatment activity and increase the chance of durable disease control, R-CHOP should be the preferred option among the three regimens. Conversely, R-CVP might be seen as a good option in patients for whom the goal of therapy is treatment tolerability; in this case, however, patients should be informed about the higher probability of requiring second-line treatment.

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Disclosures provided by the authors are available with this article at jco.org.

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