VOLUME 31 · NUMBER 27 · SEPTEMBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Rituximab Maintenance Compared With Observation After Brief First-Line R-FND Chemoimmunotherapy With Rituximab Consolidation in Patients Age Older Than 60 Years With Advanced Follicular Lymphoma: A Phase III Randomized Study by the Fondazione Italiana Linfomi

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See accompanying editorial on page 3307

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Published online ahead of print at www.jco.org on August 19, 2013.

Supported by Roche SpA, Monza, Italy.

Presented in part at the American Society of Hematology Annual Meeting, December 10-13, 2011, San Diego, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT01144364.

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0732-183X/13/3127w-3351w/$20.00

DOI: 10.1200/JCO.2012.44.8290

ABSTRACT

Purpose
To evaluate the efficacy of rituximab maintenance in 60- to 75-year-old patients with advanced follicular lymphoma responding to brief first-line chemoimmunotherapy followed by rituximab consolidation.

Patients and Methods
A total of 234 treatment-naive 60- to 75-year-old patients began chemoimmunotherapy with four monthly courses of rituximab, fludarabine, mitoxantrone, and dexamethasone (R-FND) followed by four weekly cycles of rituximab consolidation. Of these, 210 patients completed the planned treatment, and 202 responders were randomly assigned to rituximab maintenance (arm A) for 8 months, once every 2 months for a total of four doses, or to observation (arm B).

Results
Median ages in arms A and B were 66 and 65 years, respectively. After induction and consolidation therapy, the overall response rate was 86%, with 69% complete remissions (CR). After a 42-month median follow-up from diagnosis, 3-year progression-free survival (PFS; the primary end point) and overall survival (OS) were 66% (95% CI, 59% to 72%) and 89% (95% CI, 85% to 93%), respectively. After randomization, 2-year PFS was 81% for rituximab maintenance versus 69% for observation, with a hazard ratio of 0.74 (95% CI, 0.45 to 1.21; $P = .226$), although this was not statistically significant. No differences between the two arms were detected for OS. Overall, the regimen was well-tolerated. The most frequent grade 3 to 4 toxicity was neutropenia (25% of treatment courses), with 13 infections. Two toxic deaths (0.8%) occurred during induction treatment.

Conclusion
A brief R-FND induction plus rituximab consolidation achieved excellent results with high CR and PFS rates, supporting the feasibility of this regimen in patients older than 60 years. A short rituximab maintenance did not achieve a statistically significant PFS improvement over observation.

J Clin Oncol 31:3351-3359. © 2013 by American Society of Clinical Oncology

INTRODUCTION

The advent of chemoimmunotherapy has greatly enhanced clinical outcomes in follicular lymphoma (FL).[1-7] At least half of patients with FL are older than 60 years of age.[8] Advanced age alongside age-related comorbidities precludes the use of aggressive therapies such as those aiming to achieve prolonged progression-free survival (PFS) in this patient subgroup.[9] According to the Follicular Lymphoma International Prognostic Index (FLIPI),[10,11] advanced age (> 60 years) is considered a negative prognostic feature. Thus the goal of treatment in elderly patients with FL is to maintain clinical efficacy while minimizing toxicity and preserving the patient's quality of life. To this end, the combination

of rituximab and fludarabine-based chemotherapy (fludarabine, mitoxantrone, dexamethasone; R-FND) has been shown to be well-tolerated and effective also in elderly patients.[12,13]

Despite improved first-line therapies, many patients with FL experience disease progression and relapse, necessitating the use of maintenance therapy to extend the duration of remission. Rituximab has been increasingly used in maintenance therapy regimens and, regardless of induction therapy, has been shown to prolong the duration of response in treatment-naive patients as well as in those with relapsed/refractory disease.[14-17] However, none of these trials were designed specifically for patients older than 60 years, and there are little data on maintenance therapy in this setting.

The aim of this study was to evaluate the efficacy and safety of a short rituximab maintenance regimen compared with observation in patients aged 60 to 75 years with advanced FL who had responded to a brief first-line treatment regimen consisting of four courses of R-FND chemoimmunotherapy followed by four weekly doses of rituximab consolidation.

PATIENTS AND METHODS

Study Design and Treatment

This was a randomized, multicenter, open-label phase III study conducted by the Fondazione Italiana Linfomi in 33 Italian centers. Written informed consent was obtained from all patients, and study procedures were conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the ethics committees of all participating institutions.

During the induction phase (months 1 through 8), patients received four monthly courses of R-FND regimen consisting of 375 mg/m^2 of rituximab (day 1), 25 mg/m^2 of fludarabine (days 2 through 4), 10 mg/m^2 of mitoxantrone (day 2), and 10 mg of dexamethasone (days 2 through 4). One month after the fourth course of R-FND, patients underwent tumor response evaluation. Those who had complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), and stable disease (SD) received four weekly infusions of 375 mg/m^2 rituximab consolidation treatment.

Responders (defined as those showing at least PR) were stratified into two groups: stratum 1 clinical complete responders who achieved polymerase chain reaction (PCR) negativity in bone marrow for *BCL2*/immunoglobulin H (*IgH*) rearrangement and stratum 2 clinical complete responders who were bone marrow PCR positive, partial responders independent of PCR status, or complete responders who had no PCR-amplifiable *BCL2/IgH* rearrangement at baseline.

Stratified responder patients were randomly assigned 1:1 to receive either maintenance (375 mg/m^2 of rituximab once every 2 months, for a total of four doses; arm A), or observation (arm B; Appendix Fig A1, online only). A random sequence was produced using various sized blocks in random order. The web-based randomization procedure was kept concealed from all participants until treatment assignment.

Pneumocystis jiroveci prophylaxis with cotrimoxazole since the beginning of chemoimmunotherapy and levofloxacin ± itraconazole only in case of neutropenia were planned. Granulocyte colony-stimulating factor was allowed according to institutional guidelines.

Patients

Between January 2004 and December 2007, this study enrolled 242 treatment-naive patients aged 60 to 75 years with diagnosis of CD20-positive follicular non-Hodgkin lymphoma (NHL) grade 1, 2, and 3a (according to the Revised European-American Lymphoma classification[18] and to WHO criteria). Patients had to have stage II, III, or IV disease, including at least one of the following: bulky disease (> 7 cm), active disease with rapid progression, lactate dehydrogenase more than normal, systemic symptoms, β-2 microglobulin more than 3 mg/L, and extranodal involvement. The presence of comorbidities was assessed by the local investigator based on the patient's medical history. Exclusion criteria included autoimmune cytopenia, CNS involvement by the lymphoma, severe renal or pulmonary disease, and HIV-, hepatitis B virus (HBV)–, or hepatitis C virus–positive status. After an amendment in June 2007, occult HBV carrier (anti-HBc-positive) patients were also eligible. Careful monitoring was performed according to the Italian Association for the Study of the Liver guidelines.[19]

Patients were screened for *BCL2/IgH* rearrangement at study entry. If found, patient bone marrows were tested at eight fixed time points (months 5, 8, 12, 18, 24, 30, 36, and 42) or until relapse. Minimal residual disease was assessed by both nested PCR and real-time quantitative PCR as described elsewhere.[20] The results of this extensive analysis are ongoing and will be the subject of a separate report.

Evaluation and Response Criteria

During induction and maintenance, clinical tumor assessments were performed at screening, before each course of treatment, by physical examination and hematology and blood chemistry. Patients underwent tumor response assessment after cycle 4 of R-FND, 1 to 2 months after completion of rituximab consolidation, at month 18, and during the follow-up period (months 30 and 42).

Response evaluation included physical examination, hematology, blood chemistry, and chest-abdominal computer tomography. Criteria for tumor evaluation were based on those previously published.[21]

Statistical Methods

The primary efficacy parameter was PFS in arm A (rituximab maintenance) and arm B (observation), measured from randomization to the date of disease progression, relapse, or death from any cause. Secondary efficacy parameters were overall survival (OS) and response rates. Safety was evaluated according to CTCAE (Common Terminology Criteria of Adverse Events) version 3.0.

An absolute difference in PFS of 20% at 3 years in favor of the maintenance arm was expected. Assuming a 3-year PFS of 50% for patients randomly assigned to observation, 186 patients were required to show an absolute 20% improvement in favor of the maintenance arm with a two-tailed α error of 0.05 and a β error of 0.20 using a two-sample log-rank test. Assuming a loss of ~10% of patients during induction, 207 enrolled patients were needed to randomly assign 186 patients during three years of enrollment. Because of a slower accrual and a higher proportion of dropouts during the induction phase (~15%), a protocol amendment in June 2007 prolonged enrollment until the end of 2007 and increased the number of enrolled patients to 234. To ensure sufficient power of the analysis for the primary end point, a maximum follow-up of 42 months from enrollment (or 34 months from randomization) was necessary, with at least 72 events (progression or death) occurring after randomization.

The protocol entitled an interim analysis on the first 80 patients for safety; the steering committee did not find unexpected adverse event rates or reasons to prematurely stop the trial.

Results from the following analysis populations are given: (1) induction phase population, including all enrolled patients who started the induction phase; and (2) intent-to-treat (ITT) population, including all patients randomly assigned to arm A or B. The occurrence of efficacy and safety end points was reported for the induction phase population. Kaplan-Meier survival curves were calculated for all time-to-event end points. The Cox proportional hazards model was used to compare PFS according to FLIPI (1 to 2, ≥ 3), age (as continuous), and comorbidities (none, one, two, or more).

Efficacy comparisons were performed on an ITT basis. Differences between the two randomized arms were estimated using a Cox proportional hazards model (with hazard ratios [HR] and 95% CIs), stratified for the stratification groups. As exploratory analysis, the comparison between the two arms was also performed using a Cox proportional hazards model, adjusting for stratification group and known prognostic factors or potential confounders (age, sex, Eastern Cooperative Oncology Group performance status [ECOG PS], and FLIPI score).

Subgroup analyses on PFS was performed to explore potential heterogeneity of treatment by patient's characteristics. For each subgroup, a Cox

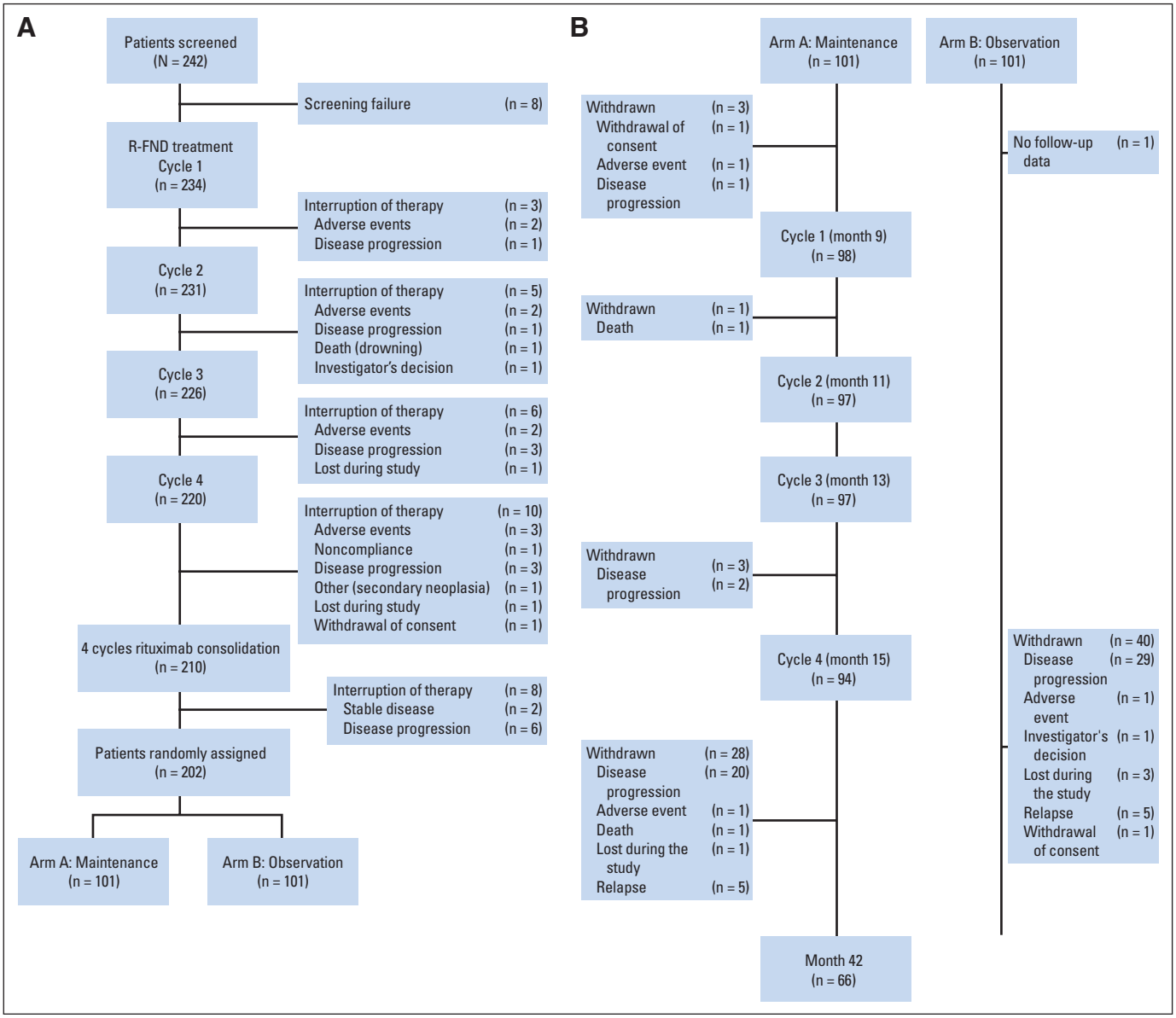

Fig 1. CONSORT diagram. (A) During induction and consolidation phase; (B) during maintenance/observation phase. R-FND, rituximab, fludarabine, mitoxantrone, and dexamethasone.

proportional hazards model was estimated adjusting for the stratification variable, age, sex, ECOG PS, and FLIPI score. Interaction was tested by inserting an interaction term between the treatment group and the subgroup covariate of interest. The treatment effect (HR) and its 95% CI were presented along with the *P* value for the interaction terms evaluated with the Wald test.

For all statistical tests, two-tailed *P* values and 95% CIs were calculated. Randomization and all statistical procedures were performed by an independent academic center.

RESULTS

Patients

A total of 234 treatment-naive patients with diagnosis of FL began treatment with R-FND; 220 completed four courses of R-FND. Of these, 210 patients received four weekly doses of rituximab consolidation, and 202 were randomly assigned to 8 months of rituximab maintenance (arm A) or observation (arm B) (Fig 1).

Baseline clinical characteristics of the study population as a whole and by study arm are listed in Table 1. Median age was 66 years (range, 60 to 75 years), more than half of the patients had high-risk (FLIPI score $\geq$ 3) disease, and 118 patients had *BCL2/IgH* rearrangement at baseline. Patients in both arms were well-balanced with respect to baseline disease status.

Clinical Response: Induction Phase

In the 234 patients, the overall response rate (ORR) was 86%. After the four cycles of R-FND, there were 55% CR/CRu, 37% PR, 4% PD/SD, and 4% adverse events (AEs)/other. Rituximab consolidation resulted in an improvement in response rates, with 69% CR/CRu, 17% PR, 7% PD/SD, and 7% AEs/other at the end of induction. Of the

Table 1. Clinical Characteristics of the Study Population

Characteristic	Induction Population (N = 234)		Randomly Assigned Patients (n = 202)		Arm A, Maintenance (n = 101)		Arm B, Observation (n = 101)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	66		66		66		65	
Range	60-75		60-75		60-75		60-75	
Male sex	99	42	82	41	37	37	45	45
FLIPI score								
1	25	11	21	10	9	9	12	12
2	80	34	74	37	36	36	38	38
> 2	129	55	107	53	56	56	51	51
Ann Arbor stage III/IV	202	86	174	86	89	88	85	84
Hemoglobin < 120 g/L	30	13	20	10	14	14	6	6
Lactate dehydrogenase ULN	42	18	31	15	18	18	13	13
> 4 Nodal sites	113	48	96	48	49	49	47	47
Bone marrow								
Abnormal	129	55	110	54	50	50	60	59
Normal	104	44	91	45	50	50	41	41
Missing	1	< 1	1	1	1	1	0	0
ECOG performance status								
0	178	76	160	79	81	80	79	78
1	40	17	29	14	12	12	17	17
2	16	7	13	6	8	8	5	5
"B" symptoms	42	18	31	15	16	16	15	15
Comorbidities								
None	94	40	81	40	41	41	40	40
1	85	36	76	38	35	35	41	41
> 1	55	24	45	22	25	25	20	20
BCL2/IgH rearrangement								
Negative	111	48	82*	80	47*	81	35*	80
Positive	118	50	14*	14	7*	12	7*	16
Not evaluable	5	2	6*	6	4*	7	2*	5
Response to induction + consolidation†								
Complete remission (CR/CRu)	160	69	160	79	80	79	80	79
Partial remission	40	17	40	20	20	20	20	20
Stable disease	3	1	1	< 1	1	< 1	0	0
Disease progression	14	6	0	0	0	0	0	0
Missing	1	< 1	1	< 1	0	0	1	< 1
Other/AE	16	7	0	0	0	0	0	0

Abbreviations: AE, adverse event; CRu, unconfirmed complete remission; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; ULN, upper limit of normal.

*Results are referred to patients with *BCL2/IgH* rearrangement at baseline and randomized after induction phase (n = 102).

†Induction + consolidation: rituximab, fludarabine, mitoxantrone, and dexamethasone for four cycles + four weekly cycles of rituximab.

87 patients who had PR after R-FND treatment, 36 (41%) were converted to CR after rituximab consolidation.

Overall Outcome

After a median follow-up of 42 months, an estimated 3-year OS of 89% (95% CI, 85% to 93%; 27 deaths) and PFS of 66% (95% CI, 59% to 72%; 88 events) were achieved for the induction population (Fig 2A). Three-year PFS for the subgroup with FLIPI scores 1 and 2 was 80% (95% CI, 71% to 87%), and 54% (95% CI, 45% to 62%) for those with FLIPI scores ≥ 3 (HR = 2.66; 95% CI, 1.66 to 4.25; $P < .001$; Fig 2B). Age did not seem to have a significant effect on 3-year PFS (HR per 5-year increase = 1.04; 95% CI, 0.81 to 1.32; $P = .776$). Three-year PFS was 67% (95% CI, 59% to 73%) for the subgroup of patients younger than 70 years and 63% (95% CI, 48% to 75%) for those ≥ 70 years of age. There were no differences in 3-year PFS for patients with none, one, or two or more comorbidities.

Efficacy: Maintenance Phase

Overall, 202 eligible patients who had completed four cycles of R-FND induction plus rituximab consolidation were randomly assigned to rituximab maintenance (arm A; n = 101) or observation (arm B; n = 101). One patient (patient 11009; arm B) did not have postrandomization follow-up data and was excluded from the analysis. The median follow-up time was 34 months from randomization. Two-year PFS was 81% (30 events) for arm A and 69% (35 events) for arm B with a stratified HR of 0.74 (95% CI, 0.45 to 1.21; $P = .226$; Fig 3). Adjusted HR was 0.71 (95% CI, 0.43 to 1.17; $P = .174$; Table 2).

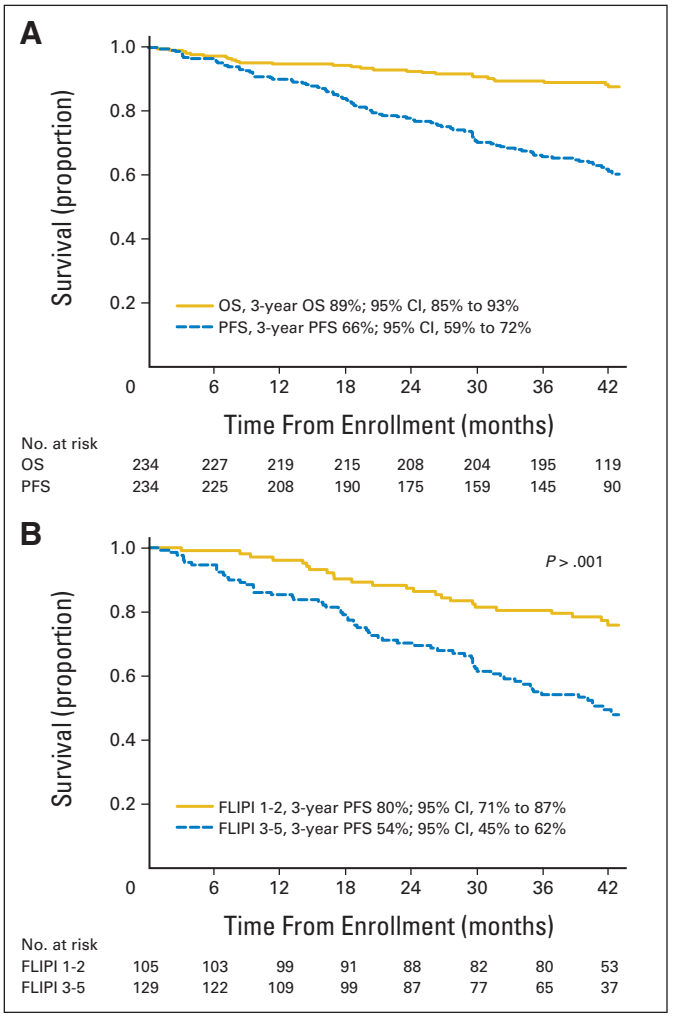

Fig 2. (A) Overall survival (OS) and progression-free survival (PFS) of the whole enrolled population. Kaplan-Meier plot of OS and PFS from study enrollment (N = 234). (B) PFS subgroup analysis according to Follicular Lymphoma International Prognostic Index (FLIPI).

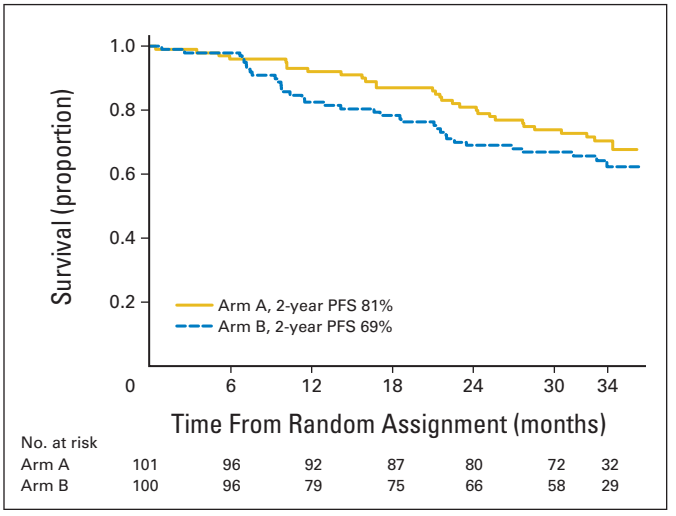

Fig 3. Effect of rituximab maintenance treatment on progression-free survival (PFS). Kaplan-Meier plot of PFS after rituximab maintenance (arm A; n = 101) or observation (arm B; n = 101). Median follow-up period: 34 months from randomization. Stratified hazard ratio of 0.74 (95% CI, 0.45 to 1.21; $P = .226$).

Among the other factors included in the Cox model, adverse significant associations were found for FLIPI score ≥ 3 (HR = 2.86; 95% CI, 1.64 to 5.01; $P < .001$), randomization stratum 2 (HR = 2.11; 95% CI, 1.16 to 3.83; $P = .015$) and male sex (HR = 1.95; 95% CI, 1.18 to 3.21; $P = .009$; Table 2).

The maintenance versus observation comparison was further analyzed within preplanned subgroups according to randomization stratum, FLIPI score, symptoms, age, comorbidities, sex, bone marrow involvement, and ECOG PS. In none of these subgroups the results showed statistically significant difference with respect to the overall effect (Fig 4).

At month 18 (3 months after the end of the maintenance phase), 88 (87%) of 101 patients in the maintenance group were in CR/CRu compared with 72 (71%) of 101 patients in the observation group ($P = .006$). More patients who were in PR at the time of randomization converted to CR/CRu at month 18 in the maintenance group (12 [60%] of 20) than in the observation group (three [15%] of 20; Fisher's exact $P = .008$).

No differences could be detected between study arms for OS. Overall, 27 patients died (18 in the nonrandomized group) because of lymphoma (n = 18), toxicity during treatment (n = 2), cardiovascular disease (n = 4), acute myelogenous leukemia (n = 1), other malignant disease (n = 1), and drowning (n = 1).

Safety

The most frequently occurring grade 3 to 4 toxicity during the induction and consolidation phase was neutropenia (in 25% of the courses), but with only 13 serious infections (Table 3). Thirty-five patients (15%) received granulocyte colony-stimulating factor support. Two patients (0.8%) died during treatment: one as a result of HBV reactivation in an occult carrier in the absence of viral prophylaxis and the other to Stevens-Johnson syndrome. Overall, the treatment was well-tolerated, and there were no differences in the frequency of AEs according to age or presence of comorbidities (Table 3).

Treatment was well-tolerated in the maintenance/observation phase, with comparable numbers of AEs in both arms (Table 4). Grade 3 to 4 neutropenia occurred with a higher frequency in arm A (14 compared with one patient in arm B). Of these 15 patients, all but one

Table 2. Estimation of Treatment and Other Prognostic Factor Effects on Progression-Free Survival by Cox Proportional Hazards Model in the Randomly Assigned Population

Variable	HR	95% CI	*P*
Maintenance *v* observation	0.71	0.43 to 1.17	.174
Age, per 5-year increase	1.10	0.82 to 1.47	.533
Male *v* female	1.95	1.18 to 3.21	.009
FLIPI ≥ 3 *v* FLIPI ≤ 2	2.86	1.64 to 5.01	< .001
Stratum 2 *v* stratum 1	2.11	1.16 to 3.83	.015
ECOG PS ≥ 1 *v* ECOG PS 0	1.69	0.97 to 2.95	.062

Abbreviations: CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; PCR, polymerase chain reaction; PS, performance status; stratum 1, CR PCR negative; stratum 2, CR PCR positive/partial response/no PCR amplifiable *BCL2/IgH* rearrangement at baseline.

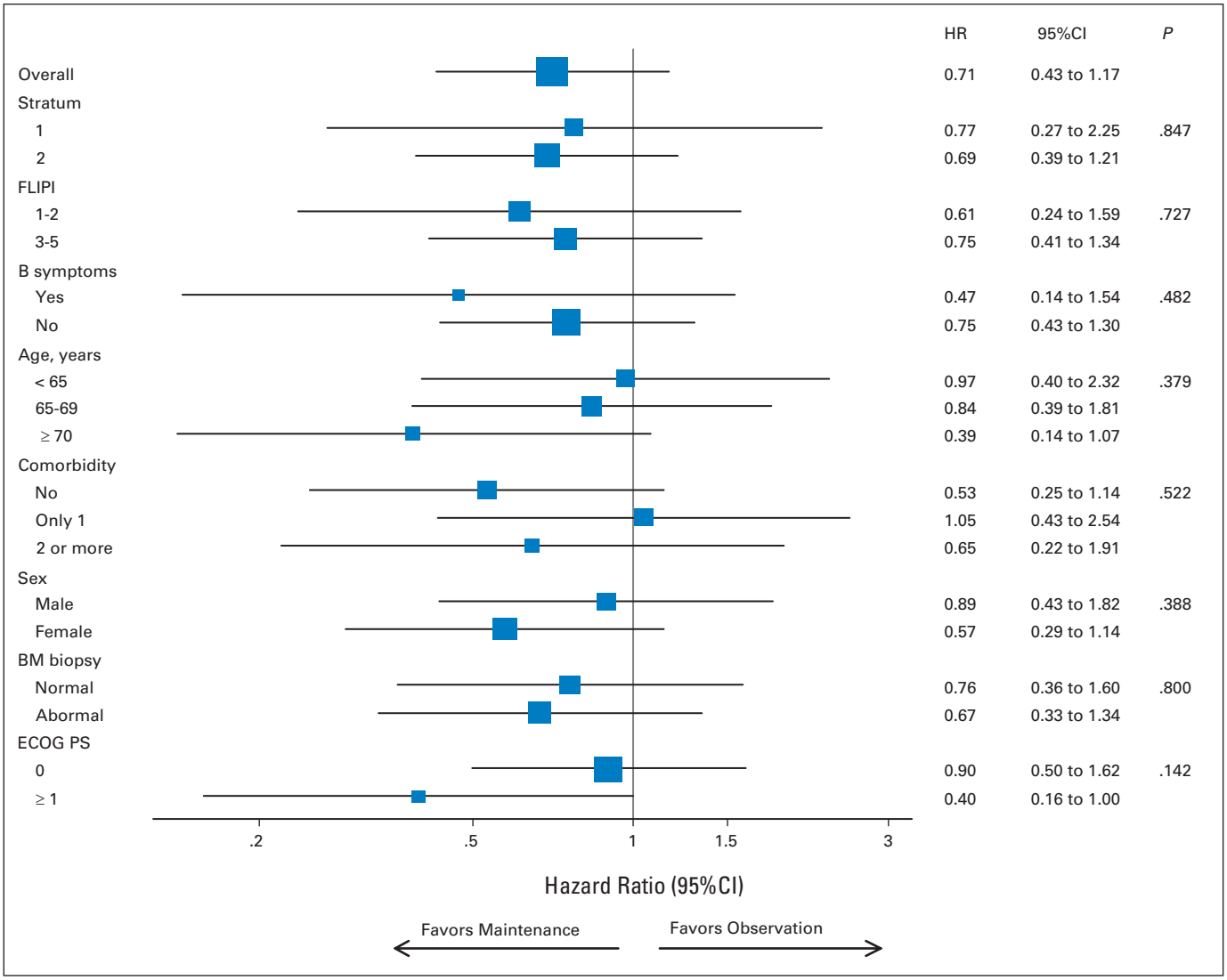

Fig 4. Maintenance versus observation: subgroup analysis for progression-free survival. Stratum 1: complete remission (CR) polymerase chain reaction (PCR) negative; stratum 2: CR PCR positive/partial response/no PCR-amplifiable *BCL2/IgH* rearrangement at baseline. BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio.

recovered, and no grade 3 to 4 infections occurred during the neutropenia periods. Grade 3 to 4 infections occurred in one patient in arm A and in three patients in arm B.

DISCUSSION

The results from this study show several key findings. First, in treatment-naive patients aged 60 to 75 years with high-risk FL, brief outpatient R-FND induction therapy plus rituximab consolidation resulted in 3-year OS of 89% and PFS of 66%. Second, of the patients who completed four cycles of R-FND, 55% had CR/CRu; four cycles of rituximab consolidation therapy further improved response parameters, increasing CR/CRu to 69%. Third, an 8-month rituximab maintenance treatment showed a PFS of 81% versus 69% in patients on observation, with an HR of 0.74, although these results did not achieve statistical significance. This difference was roughly confirmed across all subgroups, regardless of age, sex, or disease status.

The lack of statistical significance in our findings may have several causes. First, it is possible that rituximab maintenance may have a small clinical benefit that could not be statistically demonstrated with the sample size of this study (powered to detect an absolute difference of at least 20%). More importantly, the maintenance regimen used here was relatively short compared with those previously published (one infusion of rituximab every 2 months, for a total of four doses), and this may have reduced the efficacy. During the design of our study, however, this was the only available data on rituximab maintenance.[22] The follow-up period reported here is also much shorter compared with previously published findings (up to 6 years[17]). Moreover the results of the observation arm were better than expected, and this may have resulted in a smaller absolute difference in favor of the maintenance. Nevertheless, our results echo the findings of a recent meta-analysis of randomized trials on rituximab maintenance in patients with FL.[23] All studies showed statistically significant improvements in PFS.[23] In the same meta-analysis, rituximab maintenance resulted in

Table 3. Overall Treatment-Related Toxicity According to Age and Comorbidities Reported During Induction and Consolidation Phase As Events on a Total of 1,119 Treatment Courses Administered to 234 Patients: Grade 3 to 4 Toxicity Evaluated on Total Administered Treatment Courses

	Induction Population (n = 234)		Age				Comorbidities					
			< 70 Years (n = 180)		≥ 70 Years (n = 54)		None (n = 94)		1 (n = 85)		≥ 2 (n = 55)	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Neutropenia	280	25	202	23	78	31	115	26	99	24	66	26
Anemia	4	< 1	0		4	2	2	< 1	2	< 1	0	
Infections*	13	1	10	1	3	1	9	2	1	< 1	3	1
Rituximab infusion reactions	7	< 1	5	< 1	2	< 1	4	< 1	3	< 1	0	
Cardiac	3	< 1	1	< 1	2	< 1	0		1	< 1	2	< 1
Pulmonary	4	< 1	4	< 1	0		3	< 1	1	< 1	0	
No. of courses administered	1,119		864		255		448		415		256	

*Infections: sepsis (n = 2), neutropenic fevers (n = 5), tonsillitis (n = 1), viral reactivation (n = 5; herpes zoster virus = 3, cytomegalovirus = 1, hepatitis B virus = 1).

improved OS, particularly evident in patients with relapsed/refractory disease (pooled HR for death = 0.76; 95% CI, 0.62 to 0.92). Interestingly, treatment-naive patients derived no survival benefit (pooled HR for death = 0.86; 95% CI, 0.60 to 1.25).

Since the initiation of this study in 2004, additional clinical data on the efficacy and safety of rituximab maintenance have been published. Preliminary phase II studies explored the use of rituximab maintenance with different schedules and promising results.[3,22,24] These results prompted phase III randomized trials. The European Organisation for Research and Treatment of Cancer phase III trial showed statistically significant benefits in PFS and OS on rituximab maintenance treatment (every 3 months for 2 years) after chemotherapy or chemoimmunotherapy in patients with relapsed/resistant FL.[17] Results of the PRIMA trial in patients responding to first-line chemoimmunotherapy at 36 months after randomization indicate significant PFS benefits with 2 years of rituximab maintenance (74.9% *v* 57.6%); however, no effects on OS were seen.[25]

The question regarding the optimal dosing and duration of rituximab maintenance is still open. Thus far, all dosing schedules have been effective,[14] but the greatest variation is seen in the duration of rituximab maintenance. The optimal duration of rituximab maintenance is currently being investigated in the SAKK 35/03 trial, which will compare short (8 months) or prolonged (up to 5 years) rituximab maintenance.[26]

The treatment of FL in older patients poses special challenges owing to multiple factors that hamper treatment decisions and outcomes. Many elderly patients have poor performance status and comorbidities.[27] The use of some chemotherapy regimens, particularly if administered for the full course (ie, six or eight cycles), are associated with hematologic and infectious toxicities and therefore may not be suitable for the elderly.[8] The FND combination has been shown to be effective and well tolerated in indolent lymphomas.[12,28] Overall, the results of our induction treatment with only four cycles of R-FND followed by rituximab consolidation yielded 69% CR/CRu, an estimated 3-year OS of 89%, and PFS of 66%. These results are comparable to those of previously published reports on fludarabine plus rituximab[29]; rituximab plus cyclophosphamide, vincristine, and prednisone[30,31]; and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone,[5] although these regimens were administered for more prolonged periods. Although these trials included a proportion of patients older than 60 years, none were designed specifically for the elderly (Appendix Table A1, online only).

The treatment regimen used in this study was well-tolerated, both during the induction and maintenance phases. There was a relatively low level of hematologic toxicity overall. There were no differences in the occurrence of grade 3 to 4 toxicities in patients older than or younger than 70 years or in those with comorbidities. In the maintenance arm, 14 patients had neutropenia; however, this was not accompanied by a significant increase in infectious events. The low rate of discontinuations owing to AEs or withdrawal of consent supports the feasibility of this treatment regimen in patients with FL aged 60 to 75 years. The reduction to only four R-FND courses may have

Table 4. Grade 3 to 4 Toxicity During Maintenance/Observation Phase

	All Patients (n = 202)		Arm A, Maintenance (n = 101)		Arm B, Observation (n = 101)	
Toxicity	No.	%	No.	%	No.	%
Neutropenia	15	7	14	14	1	1
Anemia	0		0		0	
Infections	4	2	1*	1	3†	3
Rituximab infusion reactions	1	< 1	1	1	0	
Cardiac	9	4	4	4	5	5
Pulmonary	3	1	2	2	1	1

*Pneumonia and sepsis (n = 1).
†Pneumonia (n = 2) and hepatitis (n = 1).

contributed to the low rate of toxicity. These results underscore the importance of developing tailored therapies for the elderly, exploring the use of brief chemoimmunotherapy regimens beyond the age of 75 years. However, the follow-up of our study is relatively short, and these patients need to be monitored for a more prolonged period to rule out the occurrence of secondary malignancies.

Recently, results of a phase III randomized study comparing rituximab plus bendamustine versus rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone suggested a benefit for rituximab plus bendamustine.[32] Although data for the subset of elderly patients are not yet available, bendamustine is a well-tolerated drug, and these results may prompt its use for the elderly in the future.

In conclusion, in our study, a brief R-FND induction plus rituximab consolidation provides excellent results with high CR and PFS rates in patients with FL aged 60 to 75 years, including those with high-risk disease, supporting the feasibility of this treatment regimen in this setting. A brief rituximab maintenance did not achieve a statistically significant PFS improvement over observation, but a better effect might be obtained with prolonged schedules.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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.

Employment or Leadership Position: Enrica Gamba, Roche S.p.A Italy (C) **Consultant or Advisory Role:** Umberto Vitolo, Roche (C); Francesco Zaja, Roche (C) **Stock Ownership:** None **Honoraria:** Marco Ladetto, Celgene, Janssen, Amgen, Roche, Mundipharma; Luca Baldini, Celgene, Roche, Mundipharma; Antonello Pinto, Celgene, Mundipharma, Roche; Amalia De Renzo, Roche; Francesco Zaja, Roche; Giuseppe Rossi, Roche **Research Funding:** Marco Ladetto, Celgene, Amgen, Pfizer, Italfarmaco, Mundipharma, Roche; Francesco Zaja, Roche; Giovannino Ciccone, Roche **Expert Testimony:** None **Patents:** None **Other Remuneration:** Francesco Zaja, Roche

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Acknowledgment

We thank Karen Yeow for her assistance with manuscript preparation. We are grateful to Pasqualina De Masi for her contribution to data collection, Fabio Saccona and Manuela Ceccarelli for informatics support, Sharon Supekar for study operational support, and all the nurses and physicians for their expert care of the patients enrolled onto this study.

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Table A1. Main Rituximab Chemotherapy Studies

Author	Treatment	No. of Patients	No. of Courses	Median Age (years)	Age Range (years)	Patients ≥ 60 Years (%)	ORR* (%)	CR* (%)	Median FU (months)	Outcome*
Marcus et al[30,31]	CVP *v* R-CVP	321	8	52	NS	NS	81	41	53	Median TTF: 27 months
Hiddemann et al[5]	CHOP *v* R-CHOP	428	6-8	54	29-82	37	96	20	18	Median duration of response not reached
Herold et al[4]	MCP *v* R-MCP + IFN maintenance	358	8	60	33-78	NS	92	52	49	Median PFS not reached
Salles et al[6]	CHVP *v* R-CHVP + IFN maintenance	358	6	61	25-75	51	94	63	60	5-year EFS estimates 53%
Vitolo et al, present study	R-FND + R ± R maintenance	234	4†	66	60-75	100	86	69	42	3-year PFS 66%

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHVP, cyclophosphamide, doxorubicin, etoposide, and prednisolone; CR, complete remission; CVP, cyclophosphamide, vincristine, and prednisone; EFS, event-free survival; FU, follow-up; IFN, interferon; pts, patients; MCP, mitoxantrone, chlorambucil, and prednisone; NS, not specified; ORR, overall response rate; PFS, progression-free survival; R, rituximab; TTF, time to treatment failure.

*Results refer to rituximab chemotherapy arm.

†Eight total rituximab doses.

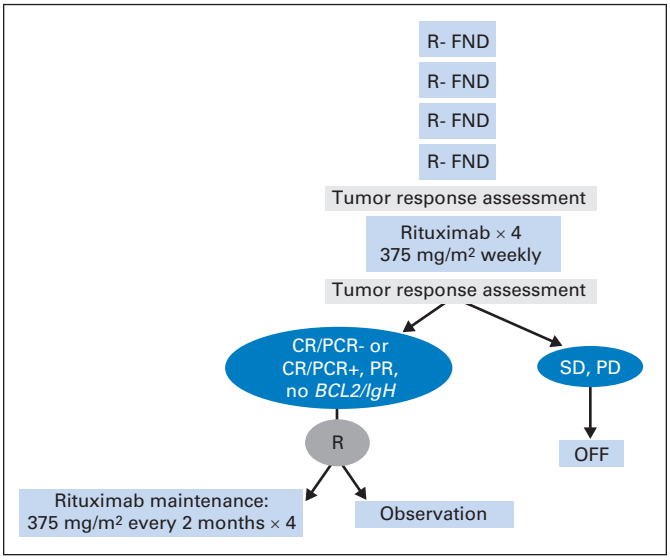

Fig A1. Treatment protocol scheme. CR PCR-, complete remission with polymerase chain reaction negativity for *BLC2/IgH* rearrangement; CR PCR+, complete remission with polymerase chain reaction positivity for *BCL2/IgH* rearrangement; no *BCL2/IgH*, no PCR-amplifiable *BCL2-IgH* rearrangement at baseline; PD, progressive disease; PR, partial remission; R, random assignment; R-FND, rituximab, fludarabine, mitoxantrone, dexamethasone; SD, stable disease.