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Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study

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PURPOSE We compared 2 years of rituximab maintenance (RM) with a response-adapted postinduction approach in patients with follicular lymphoma who responded to induction immunochemotherapy.

METHODS We randomly assigned treatment-naïve, advanced-stage, high-tumor burden follicular lymphoma patients to receive standard RM or a response-adapted postinduction approach on the basis of metabolic response and molecular assessment of minimal residual disease (MRD). The experimental arm used three types of postinduction therapies: for complete metabolic response (CMR) and MRD-negative patients, observation; for CMR and MRD-positive (end of induction or follow-up) patients, four doses of rituximab (one per week, maximum three courses) until MRD-negative; and for non-CMR patients, one dose of ibritumomab tiuxetan followed by standard RM. The study was designed as noninferiority trial with progression-free survival (PFS) as the primary end point.

RESULTS Overall, 807 patients were randomly assigned. After a median follow-up of 53 months (range, 1-92 months), patients in the standard arm had a significantly better PFS than those in the experimental arm (3-year PFS 86% v 72%; $P < .001$). The better PFS of the standard versus experimental arm was confirmed in all the study subgroups except non-CMR patients ($n = 65$; $P = .274$). The 3-year overall survival was 98% (95% CI, 96 to 99) and 97% (95% CI, 95 to 99) in the reference and experimental arms, respectively ($P = .238$).

CONCLUSION A metabolic and molecular response-adapted therapy as assessed in the FOLL12 study was associated with significantly inferior PFS compared with 2-year RM. The better efficacy of standard RM was confirmed in the subgroup analysis and particularly for patients achieving both CMR and MRD-negative.

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INTRODUCTION

The use of the monoclonal anti-CD20 antibody rituximab (R) has improved the outcome of patients with newly diagnosed follicular lymphoma (FL).¹⁻³ R is currently used in combination with chemotherapy for the induction treatment of patients with high-tumor burden FL and is recommended for 2-year maintenance treatment in patients responding to induction immunochemotherapy (ICT).^{4,5} The use of R for maintenance treatment is based on a formal demonstration of its ability to reduce the risk of FL progression compared with observation only.⁵⁻⁸ However, lacking a similar effect on the overall survival (OS) efforts to better predict the individual risk of failure in patients with FL early in the course of

disease has become a key research priority in the field.

Among the several prognostic factors and indices that have been correlated with patients' outcomes, recent data have demonstrated the prognostic role of metabolic or molecular response evaluated by using ¹⁸F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) or by applying minimal residual disease (MRD), respectively. FDG-PET is now the recommended technique to define end-induction response on the basis of international criteria.⁹⁻¹² MRD evaluation by polymerase chain reaction (PCR) targeting the BCL2-immunoglobulin heavy chain (IGH) rearrangement is the most widely used and standardized molecular approach in FL on the basis of the

ASSOCIATED CONTENT

See accompanying editorial on page 698

Appendix

Data Sharing Statement

Data Supplement Protocol

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

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CONTEXT

Key Objective

The FOLL12 study has been conducted with the hypothesis that a fluorodeoxyglucose-positron emission tomography and minimal residual disease response–adapted postinduction management of patients with high-tumor burden follicular lymphoma (FL) responding to standard immunochemotherapy was noninferior in terms of progression-free survival compared with standard rituximab maintenance (RM).

Knowledge Generated

We demonstrated that (1) RM was better than the response-adapted management in terms of progression-free survival, (2) Standard RM reduced the risk of disease progression also for patients with the best quality of response, and (3) the lack of any overall survival difference between study arms.

Relevance (J.W. Friedberg)

The results of the FOLL12 trial do not support a response-adapted treatment paradigm in FL. Minimal residual disease needs further validation before being incorporated as an integral biomarker in future trials of FL.*

*Relevance section written by JCO Editor-in-Chief Jonathan W. Friedberg, MD.

documentation of the independent predictive value of MRD detection in FL.¹³ MRD negativity in the bone marrow and peripheral blood has been strongly associated with a reduced risk of recurrence, and MRD reappearance during follow-up may anticipate clinical progression.¹⁴⁻¹⁷

Although the results of randomized trials have confirmed that rituximab maintenance (RM) improves patient outcomes, the question is whether there is an alternative to standard RM to manage postinduction treatment. To this end, there are convincing arguments to support the use of available methods to define the quality of response and to adapt the intensity of the intervention to an accurate assessment of FL response. The FOLL12 trial aimed to show the noninferiority of a response-adapted postinduction strategy on the basis of FDG-PET and MRD response assessment after ICT, with 2-year maintenance with rituximab in patients with previously untreated advanced FL. Here, we present the mature results of the study performed after a median follow-up of 50 months.¹⁸

METHODS

FOLL12 was a prospective randomized open-label multicenter phase III trial designed for patients with previously untreated FL. The study was conducted in compliance with the Declaration of Helsinki, was approved by the appropriate Research Ethics Committee, and required that each patient gives written informed consent before registration and random assignment (ClinicalTrials.gov identifier: [NCT02063685](https://clinicaltrials.gov/ct2/show/study/NCT02063685)).

The trial included previously untreated patients age 18-75 years with a histologically confirmed diagnosis of FL grade 1, 2, or 3a according to the WHO classification,¹⁹ Ann Arbor stage II-IV, Eastern Cooperative Oncology Group performance status of 0-2, and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) of > 0. The complete list of eligibility criteria is listed in the Data Supplement (online only).

Random Assignment and Treatment Protocol

Eligible patients were centrally randomly assigned before treatment start and were stratified by FLIPI2 score (1-2 v 3-5).²⁰

All patients received induction therapy with six cycles of R in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or bendamustine (choice made by the local investigator) followed by two additional doses of R.

At the end of induction (EOI) ICT, response was determined by the local investigator by computed tomography (CT) scan according to the 2007 revised international criteria.²¹ For the purpose of this study, EOI response was also assessed using FDG-PET and using BCL2/IGH MRD analysis by nested PCR on peripheral blood and bone marrow samples in patients with available molecular marker (MM). Both EOI FDG-PET and MRD analyses were conducted in a centralized laboratory (refer to the Data Supplement for details).

For all patients showing partial remission or complete remission at EOI CT scan, postinduction management was delivered according to random assignment. Patients randomly assigned to the reference arm were prescribed standard maintenance, which consisted of 12 doses of R administered at 375 mg/m² (one dose every 8 weeks).

For patients randomly assigned to the experimental arm, postinduction treatment was managed on the basis of metabolic response (MR) as defined by FDG-PET and MRD analysis (Data Supplement).

Patients with a complete metabolic response (CMR, Deauville score 1-3) who were MRD-negative by nested PCR were only observed and were followed up with MRD monitoring and CT scan at 6-month intervals for 2 years and then annually. Patients with CMR who were MRD-positive at EOI assessment or who turned MRD-positive during follow-up received four weekly rituximab doses before an

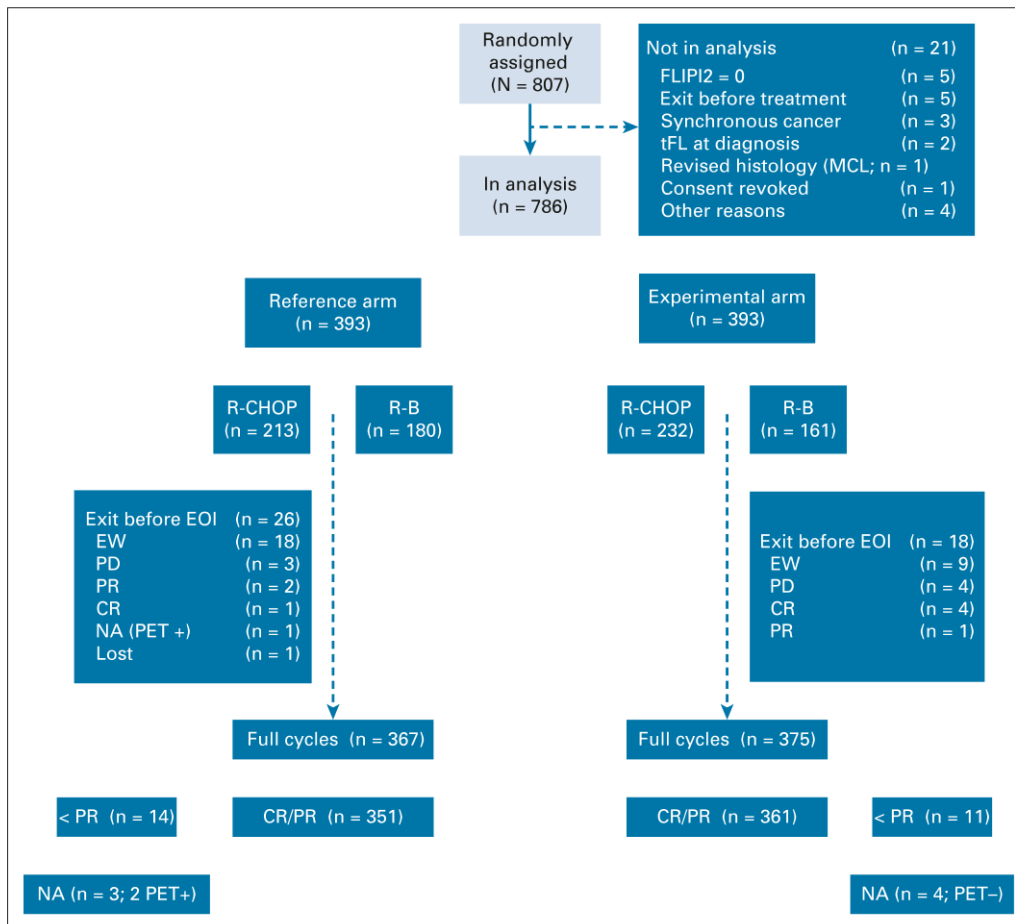


FIG 1. Treatment allocation and number of patients included in analysis, according to the CONSORT statement. Other reasons: 1 LFEV < 50%, 1 stage Ia, 1 PET-, and 1 HBV+. CR, complete remission; EOI, end of induction; EW, early withdrawal; FLIPI2, Follicular Lymphoma International Prognostic Index 2; tFL, transformed follicular lymphoma; HBV, hepatitis B virus; LFEV, left ventricular ejection fraction; MCL, mantle cell lymphoma; NA, not assessed; PD, progressive disease; PET, positron emission tomography; PR, partial remission; R-B, rituximab plus bendamustine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

additional MRD assessment as suggested by a previous experience.²² The weekly dose of R was repeated until MRD negativity was achieved (one dose per week, maximum 12 R doses overall) or up to three times. Patients with CMR for whom a MM at baseline was not available remained under observation with regular follow-up.

Patients without CMR, regardless of their MRD status, received intensified treatment with radioimmunotherapy (RIT) with (90)Y-ibritumomab tiuxetan followed by RM every 2 months, for a total of 11 infusions.

Statistics and Assessment of Efficacy

The primary end point was progression-free survival (PFS), defined as the time from the date of study entry to the last follow-up or to one of the following events: disease progression or relapse confirmed at CT scan or to the date of death from any cause.

Additional study end points were OS, response, and toxicity.

The study was initially designed as a superiority trial. However, as the first interim monitoring showed a higher-than-expected rate of CMR, the study was amended to a noninferiority design (see the Data Supplement for details) that was based on the hypothesis that the primary end point was not inferior in the experimental versus the reference arm in terms of PFS. A total accrual of 770 patients with 387 expected failures was planned under H1 to give 83% power to demonstrate noninferiority between the two arms, with an increased risk of < 1.309 in the PFS failure rate (see the Data Supplement for statistical details).

RESULTS

Between December 2012 and March 2018, 807 patients were randomly assigned by 50 Italian institutions. Twenty-one (2.6%) patients were subsequently excluded, leaving 786 patients who were fully eligible, 393 in the reference arm and 393 in the experimental arm (Fig 1). The two arms

were balanced in terms of patient characteristics and response to induction treatment (Data Supplement).

Of the 786 patients, 744 (368 in the reference arm and 376 in the experimental arm, respectively) completed induction therapy and were assessed for response (Table 1).

Of these 744 patients, 712 achieved a response, defining an overall response rate of 96% (95% CI, 94 to 97).

After a median follow-up of 53 months (range, 1-92 months), 197 PFS events were recorded, including 186 disease progressions and 11 deaths for causes unrelated to

lymphoma progression. Overall, the 3-year PFS was 79% (95% CI, 76 to 82): 86% (95% CI, 82 to 89) for the reference arm and 72% (95% CI, 67 to 76) for the experimental arm (Fig 2A). The experimental arm was worse than the reference arm, even given the noninferiority margin. The risk of progression was significantly higher for the experimental arm (hazard ratio, 1.92; 95% CI, 1.43 to 2.56, also when adjusted by FLIPI2 and induction treatment, $P < .001$).

Details on MR at EOI were available for 691 of 712 patients: CMR was confirmed in 628 (90%), whereas 65 patients had positive EOI FDG-PET (9%) and two patients had indefinite result. Overall, the 3-year PFS was 81% (95% CI, 77 to 84) and 60% (95% CI, 47 to 71) for patients with and without CMR, respectively ($P < .001$). Among patients with CMR, the 3-year PFS was 90% (95% CI, 86 to 93) and 72% (95% CI, 67 to 77) in the reference and experimental arms, respectively ($P < .001$; Fig 3A).

According to the intention-to-treat analysis, of the 65 patients who did not achieve CMR, the 3-year PFS for the 31 cases in the reference arm was 50% (95% CI, 32 to 66) and for the 34 cases in the experimental arm, it was 70% (95% CI, 51 to 82; $P = .274$; Fig 3B).

Overall MM was lacking in 334 of the 786 randomly assigned eligible patients. In the subgroup of 712 patients who responded to induction therapy, 300 were identified as no marker, and no further MRD analysis was conducted in this group. The absence of the baseline MM was not associated with a different PFS compared with patients with MM (data not shown).

Of the 345 patients with MM of the 628 who achieved a CMR, 299 were MRD-negative (87%) at EOI and 46 (13%) were MRD-positive. The 3-year PFS for MRD-negative patients was 92% (95% CI, 78 to 91) in the reference arm ($n = 143$) and 78% (95% CI, 61 to 77) in the experimental arm ($n = 156$; $P < .001$; Fig 3C).

During follow-up, 81 of the 299 (27%) MRD-negative patients became MRD-positive, at a median time from EOI of 14 months (range, 5-36 months): 26 patients in the reference arm and 55 in the experimental arm. Overall, 51 patients were MRD-positive in the reference arm and 76 in the experimental arm, of whom 46 received weekly rituximab according to protocol. After receiving weekly R, 26 of these 46 patients achieved a molecular response at the subsequent MRD time points. Of the 51 MRD-positive patients in the reference arm, 32 achieved negative MRD status at subsequent time points (Data Supplement).

Overall, the use of weekly R in MRD-positive patients in the experimental arm was associated with inferior 3-year PFS compared with that of MRD-positive patients in the reference arm (Fig 3D; $P < .001$).

The better performance of the reference arm over the experimental was consistent across all different subgroups in a post hoc exploratory analysis of patient subgroups

TABLE 1. Characteristics of Patients at Baseline and Response With Full Induction Treatment ($n = 744$)

Variable	Reference Arm No. (%)	Experimental Arm No. (%)	Total No. (%)
Age, years			
> 60	176 (48)	192 (51)	368 (49)
Sex			
Female	191 (52)	195 (52)	386 (52)
B2M			
> UNL	199 (54)	200 (53)	399 (54)
BM			
+	202 (55)	213 (57)	415 (56)
LoDLIN, cm			
> 6	203 (55)	212 (56)	415 (56)
Hemoglobin, g/ dL			
< 12	61 (17)	49 (13)	110 (15)
Nodal sites			
> 4	157 (43)	146 (39)	303 (41)
Ann Arbor stage			
III-IV	324 (88)	335 (89)	659 (89)
LDH			
> UNL	79 (22)	81 (22)	160 (22)
FLIPI2			
1-2	221 (60)	227 (60)	448 (60)
3-5	147 (40)	149 (40)	296 (40)
FLIPI			
0-1	90 (25)	89 (24)	179 (25)
2	142 (40)	152 (42)	294 (41)
3-5	122 (34)	123 (34)	245 (34)
Response at EOI			
CR	601 (82)	300 (80)	301 (81)
PR	50 (14)	61 (16)	111 (15)
ORR	351 (96)	361 (96)	712 (96)

Abbreviations: B2M, beta-2-microglobulin; BM, bone marrow; CR, complete remission; EOI, end of induction; FLIPI2, Follicular Lymphoma International Prognostic Index 2; LDH, lactate dehydrogenase; LoDLIN, longest diameter of the largest involved node; ORR, overall response rate; PR, partial remission; UNL, upper normal level.

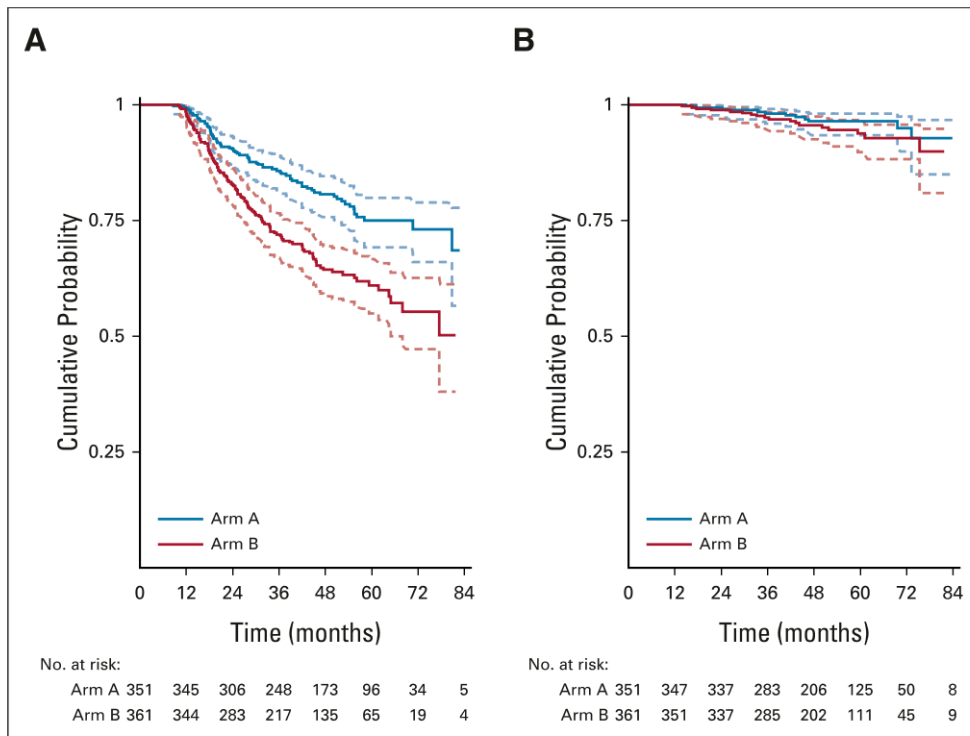


FIG 2. (A) PFS and (B) OS in the reference and experimental arms ($n = 712$). Arm A, reference arm; Arm B, experimental arm; OS, overall survival; PFS, progression-free survival.

categorized by age, sex, induction treatment, FLIPI and FLIPI2 scores, stage III-IV, and nodal areas (Fig 4).

At the time of current update, 30 deaths were recorded, of which 15 were associated with disease progression or recurrence. Other causes of death were secondary malignancies ($n = 3$, 10% [gastric cancer, lung cancer, and mesenchymal abdominal cancer]), sepsis ($n = 5$, 17%), heart failure ($n = 1$, 3%), central nervous system disease ($n = 2$, 6%), pulmonary edema ($n = 1$, 3%), and three with cause not reported (10%). The 3-year OS was 98% (95% CI, 96 to 99) in the reference arm and 97% (95% CI, 95 to 99) in the experimental arm ($P = .238$; Fig 2B).

Safety

The safety analysis was available for 786 patients in the induction phase and for 712 in the postinduction phase.

During the induction phase, no difference in toxicity was observed between the two study arms (Data Supplement).

During the postinduction phase, 254 events with any grade were reported. In patients with CMR after induction ICT, the most common grade 3-4 adverse event was neutropenia (13.0% ν 3.6%, in reference and experimental arms, $P < .001$). In patients without CMR after induction ICT ($n = 30$ in the reference arm and $n = 32$ in the experimental arm), the most frequent grade 3-4 events were neutropenia (10.0% ν 43.8%; $P = .004$) and thrombocytopenia (0% ν 37.5%; $P < .001$; Table 2).

In the group of 712 patients analyzed for the principal end point of the study, 39 second malignancies (SM) were registered. Considering deaths as a competing risk, the overall 5-year cumulative incidence (CI) of SM was 6.4% (95% CI, 4.6 to 8.9; Data Supplement).

DISCUSSION

The FOLL12 prospective, randomized, open-label multicenter phase III trial was conducted to assess the efficacy of a response-adapted postinduction treatment in patients with FL who responded to ICT. The study demonstrated that our response-adapted postinduction therapy resulted in significant inferiority compared with standard maintenance in terms of 3-year PFS (86% ν 72%), with a hazard ratio of 1.92. Inferiority of the response-adapted experimental arm was found in most subgroups and, in particular, in patients with the highest quality of response defined by both CMR and MRD negativity. On the basis of these results, we conclude that patients with FL responding to induction ICT should be offered 2-year R maintenance to guarantee the lowest risk of lymphoma progression.

The FOLL12 findings require careful reflection to try to understand these negative results. The rationale of the FOLL12 was based on the confirmed correlation between either metabolic or molecular response and the risk of disease progression and of death^{10,12,14,16,23} and on the suggested combined role of both parameters in improving the ability to predict patient outcomes.²⁴ The hypothesized

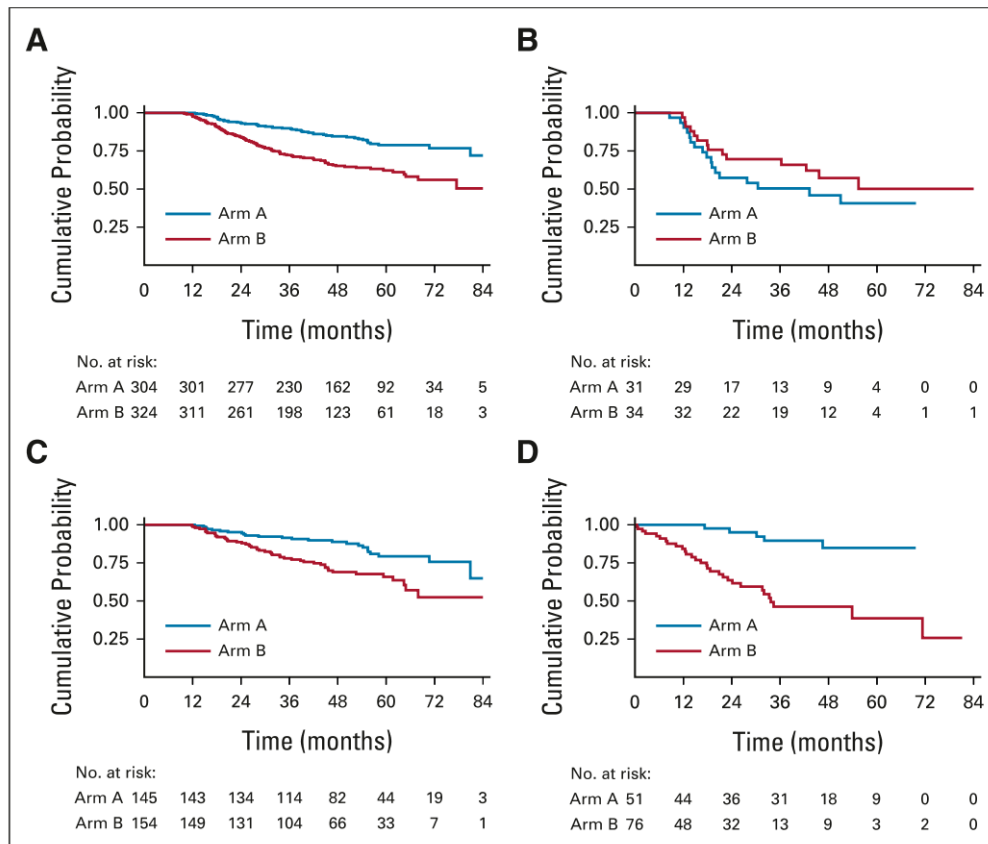


FIG 3. PFS for patients in CR/PR after EOI with reviewed PET and MRD: (A) EOT PET⁻, (B) EOT PET⁺, (C) EOT PET/MRD^{-/-}, and (D) EOT PET⁻ and MRD-positive at EOT or repositivized during follow-up. Arm A, reference arm; Arm B, experimental arm; CR, complete remission; EOI, end of induction; EOT, end of treatment; MRD, minimal residual disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial remission.

success of our response-adapted approach was based on the combined efficacy of therapeutic intervention for non-CMR patients and for MRD-positive patients, as suggested by the promising results achieved in a previous experience of our group,^{22,25} and of no intervention for patients with the best response defined by both CMR and MRD negativity, assuming that the risk of progression in the latter group could not be modified by maintenance therapy. In this context, the significant reduction in the risk of progression observed for the group of patients with both CMR and MRD negativity who received standard maintenance had the greatest impact on the trial results. Thus, even if we were able to confirm the role of MR in predicting the risk of FL progression, we nevertheless conclude that the better response as defined by FDG-PET was not enough to keep the risk of progression low without RM. In the setting of CMR, molecular assessment of response was not able to further contribute to our response-adapted approach. Indeed, most of the patients with CMR also achieved MRD negativity (87%), although those in the experimental arm still experienced a higher risk of progression, heralded by subsequent MRD reappearance. Interestingly, for the smaller subgroup of CMR/MRD-positive patients for whom

weekly rituximab was administered in the experimental arm, treatment was still associated with inferior efficacy compared with RM. Further analyses are thus required to improve the favorable predictive value of a good response to ICT in FL and to implement novel algorithms able to capture the concept of MRD as a kinetic approach during the different phases of treatment rather than as a static analysis.

We expected that the intensification of treatment—the administration of one dose of ibrutinomab tiuxetan before RM—would contribute significantly to the efficacy of our response-adapted approach for non-CMR patients. The choice of using RIT in this group of patients was based on the combined findings of two randomized trials that showed the efficacy of consolidation of RIT after induction ICT²⁶ and also suggested the need for RM in this group of high-risk patients treated with RIT.²⁷ Unfortunately, we were not able to reach any conclusion on the efficacy of the planned intervention mainly because of the low number of treated patients. Indeed, one important result of the FOLL12 is the 90% CMR rate in our series, which was much higher than what was initially expected but in line with what other recent trials have reported.^{2,28} Moreover, the observed poorer

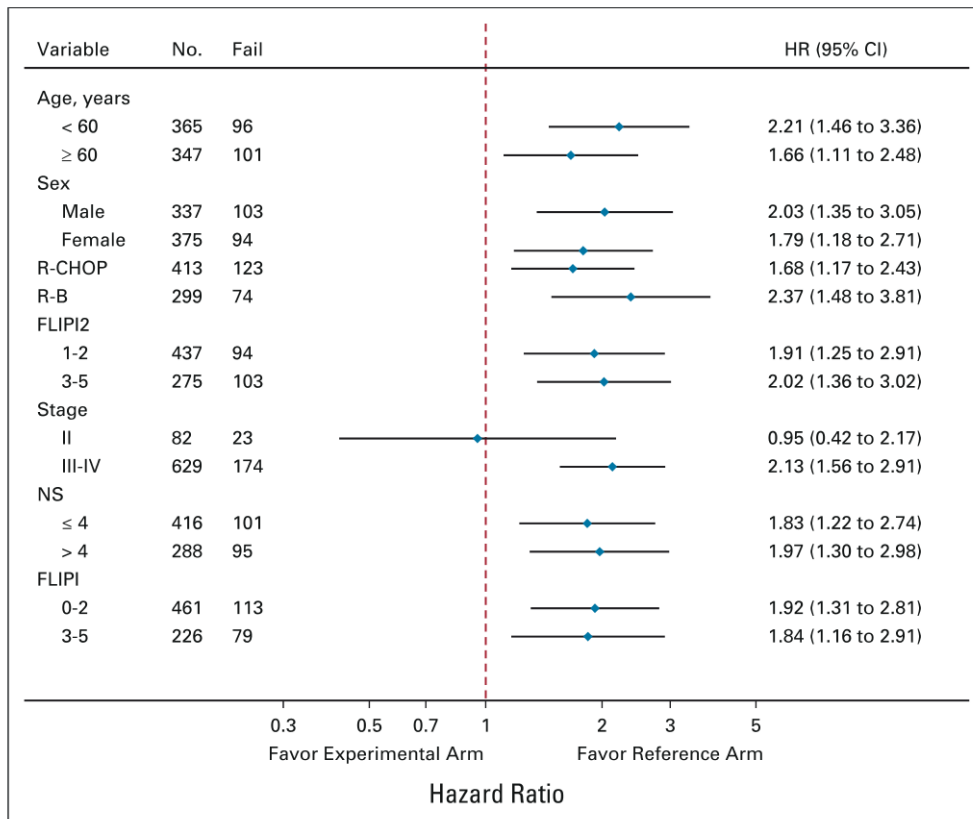


FIG 4. PFS with interaction terms (forest plot; $n = 712$). FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; NS, nodal sites; PFS, progression-free survival; R-B, rituximab plus bendamustine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

survival of non-CMR versus CMR patients confirmed that non-CMR patients are a high-risk group for whom more effective active therapeutic options are warranted.

On the basis of the above observations, the FOLL12 trial suggests that postinduction maintenance is appropriate for all responding patients. Our study, however, also confirms that even if treated with standard therapy, FL shows heterogeneous outcomes. Treatment adaptation is thus a relevant clinical question to optimize treatment exposure, safety, and costs, but caution should be used, as putative benefits may not compensate for an acceptable loss of efficacy, as shown in the present study.

For the small group of nonresponding high-risk patients, there is room to explore the activity of some of the new agents that are currently in clinical development. Among these, lenalidomide is currently being investigated in addition to maintenance rituximab therapy in PET+ FL patients in the PETREA trial by colleagues in the United Kingdom and Australia. More interestingly, novel bispecific agents and CART represent promising new options to overcoming the poor outcome of non-CMR high-risk patients in a response-adapted approach to patients with FL.

Conversely, for the larger group of patients with a low-risk profile, we believe that there is still room for treatment adaptation. As our results show, not administering RM in this group of patients increases their risk of lymphoma progression. Thus, we believe that a more promising strategy for patients with low-risk FL could be to act on the cytotoxic component of ICT, reducing it when not necessary.

In this scenario, the main aspect of treatment personalization is related to the choice of accurate predictors and to the combination of available prognostic factors to define accurate predictive models.

The FOLL12 study has some limitations. The first is related to the choice of the molecular technique used to conduct MRD analysis: BCL-2/IGH PCR, although standardized by the EuroMRD group,²⁹ is still characterized by a 40% rate of patients who cannot be assessed because of the unavailability of a MM. To overcome this issue, we managed patients without MMs only on the basis of PET results, although this practical choice might have affected the efficacy of the experimental strategy. This important issue of no marker cases might be managed in future trials by increasing the number of translocation cluster regions³⁰ or

TABLE 2. Hematologic and Extra-Hematologic Adverse Events With CTCAE > 2 During Maintenance or Follow-Up in Patients With PET– and Patients With PET+ by Arm

Adverse Events in Patients With PET– at EOI (A = 284 and B = 280)					
Hematologic Adverse Event	Reference Arm, No. (%)		Experimental Arm, No. (%)		P ^a
	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
Anemia	13 (4.6)	2 (0.7)	3 (1.1)	1 (0.4)	1.00
Leukopenia	19 (6.7)	2 (0.7)	6 (2.1)	2 (0.7)	1.00
Neutropenia	15 (5.3)	37 (13.0)	2 (0.7)	10 (3.6)	< .001
Thrombocytopenia	6 (2.1)	1 (0.3)	5 (1.8)	0	1.00
Febrile neutropenia	0	0	0	0	—
Adverse Events in Patients With PET+ at EOI (A = 30 and B = 32)					
Extra-Hematologic Adverse Event	Reference Arm, No. (%)		Experimental Arm, No. (%)		P ^a
	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
Cardiac disorders	4 (1.4)	4 (1.4)	5 (1.8)	5 (1.8)	.750
Congenital and/or familial and/or genetic disorders	0	0	0	0	—
Ear and labyrinth disorders	6 (2.1)	0	2 (0.7)	0	—
Endocrine disorders	0	0	0	2 (0.7)	—
Eye disorders	0	0	2 (0.7)	0	—
GI disorders	6 (2.1)	0	10 (3.6)	1 (0.4)	.496
General disorders	7 (2.5)	0	18 (6.4)	0	—
Hepatobiliary disorders	1 (0.3)	0	1 (0.4)	0	—
Immune system disorders	0	0	0	1 (0.4)	.496
Infections and infestations	10 (3.5)	1 (0.3)	9 (3.2)	4 (1.4)	.214
Injury and/or poisoning and/or procedural complications	0	0	0	0	—
Investigations	0	0	1 (1.4)	1 (0.4)	.496
Metabolism and nutrition disorders	2 (0.7)	0	1 (0.4)	0	—
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.3)	10 (3.6)	0	1.00
Neoplasms benign and/or malignant and/or unspecified	3 (1.1)	1 (0.3)	2 (0.7)	4 (1.4)	.214
Nervous system disorders	6 (2.1)	0	8 (2.9)	2 (0.7)	.246
Pregnancy and/or puerperium and perinatal conditions	0	0	0	0	—
Psychiatric disorders	1 (0.3)	0	1 (0.4)	1 (0.4)	.496
Renal and urinary disorders	3 (1.1)	1 (0.3)	4 (1.4)	1 (0.4)	1.00
Reproductive system and breast disorders	1 (0.3)	0	1 (0.4)	1 (0.4)	.496
Respiratory or thoracic and mediastinal disorders	13 (4.6)	0	21 (7.5)	1 (0.4)	.496
Skin and subcutaneous tissue disorders	3 (1.1)	0	10 (3.6)	1 (0.4)	.496
Surgical and medical procedures	0	0	1 (0.4)	0	—
Vascular disorders	2 (0.7)	0	5 (1.8)	0	—
Others (specify)	9 (3.2)	1 (0.3)	11 (3.9)	2 (0.7)	.622

(continued on following page)

TABLE 2. Hematologic and Extra-Hematologic Adverse Events With CTCAE > 2 During Maintenance or Follow-Up in Patients With PET– and Patients With PET+ by Arm (continued)

Adverse Events in Patients With PET+ at EOI (A = 30 and B = 32)					
Hematologic	Reference Arm, No. (%)		Experimental Arm, No. (%)		P ^a
	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
Thrombocytopenia	0	0	4 (12.5)	12 (37.5)	< .001
Febrile neutropenia	1 (3.3)	0	0	0	—
Extra-Hematologic	Reference Arm, No. (%)		Experimental Arm, No. (%)		P ^a
	Grade 1-2	Grade > 2	Grade 1-2	Grade > 2	
GI disorders	2 (6.7)	3 (10.0)	1 (3)	0	.107
General disorders	1 (3.3)	0	3 (9.4)	0	—
Infections and infestations	0	0	2 (6.2)	0	—
Injury and/or poisoning and/or procedural complications	0	0	0	0	—
Musculoskeletal and connective tissue disorders	0	0	1 (3.1)	0	—
Neoplasms benign and/or malignant and/or unspecified	0	0	0	1 (3.1)	1.00
Nervous system disorders	0	1 (3.3)	0	0	.484
Respiratory or thoracic and mediastinal disorders	3 (10.0)	0	2 (6.2)	0	—
Skin and subcutaneous tissue disorders	1 (3.3)	0	3 (3.1)	0	—
Others (specify)	0	0	2 (6.2)	0	—

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EOI, end of induction; PET, positron emission tomography.

^aFisher's exact test of frequency CTCAE grade > 2 between reference and experimental arms.

by moving to high throughput technology, which, however, have only offered very preliminary data in FL so far.³¹⁻³⁵

As a second limitation, we acknowledge that a better assessment of a nonlifefaving therapy such as RM should integrate the evaluation of efficacy, safety, and patient-reported outcomes including quality of life that was lacking in our trial. Moreover, we also acknowledge that, as frequently observed in pure academic trials, there is a

tendency to under-report safety events. However, this limitation does not affect the main study results, thanks also to the randomized design.

In conclusion, the FOLL12 study clearly shows that, although MR and MRD negativization are prognostic for PFS, the 2-year maintenance approach with R is clearly superior in different subgroups, especially in those defined at low risk of recurrence on the basis of PET and MRD response.

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A complete list of the investigators who participated in the FOLL12 clinical trial is provided in Appendix [Table A1](#) (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Response-Adapted Postinduction Strategy in Patients With Advanced-Stage Follicular Lymphoma: The FOLL12 Study**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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APPENDIX

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