VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Consolidation Therapy With Yttrium-90–Ibritumomab Tiuxetan Compared With No Additional Therapy After First Remission in Advanced Follicular Lymphoma

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Submitted March 17, 2008; accepted July 16, 2008; published online ahead of print at www.jco.org on October 13, 2008.

Supported by Bayer Schering Pharma AG, Berlin, Germany.

Presented in part at the 49th Annual Meeting of the American Society of Hematology, December 8-11, 2007, Atlanta, GA.

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

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0732-183X/08/2632-5156/$20.00

DOI: 10.1200/JCO.2008.17.2015

ABSTRACT

Purpose
We conducted an international, randomized, phase III trial to evaluate the efficacy and safety of consolidation with yttrium-90 (^{90}Y)–ibritumomab tiuxetan in patients with advanced-stage follicular lymphoma in first remission.

Patients and Methods
Patients with CD20$^+$ stage III or IV follicular lymphoma, who achieved a complete response (CR)/unconfirmed CR (CRu) or partial response (PR) after first-line induction treatment, were randomly assigned to receive ^{90}Y-ibritumomab tiuxetan (rituximab 250 mg/m^2 on day −7 and day 0 followed on day 0 by ^{90}Y-ibritumomab tiuxetan 14.8 MBq/kg; maximum of 1,184 MBq) or no further treatment (control). The primary end point was progression-free survival (PFS), which was calculated from the time of random assignment.

Results
A total of 414 patients (consolidation, n = 208; control, n = 206) were enrolled at 77 centers. ^{90}Y-ibritumomab tiuxetan consolidation significantly prolonged median PFS (after a median observation time of 3.5 years) in all patients (36.5 *v* 13.3 months in control arm; hazard ratio [HR] = 0.465; $P < .0001$) and regardless of whether patients achieved PR (29.3 *v* 6.2 months in control arm; HR = 0.304; $P < .0001$) or CR/CRu (53.9 *v* 29.5 months in control arm; HR = 0.613; $P = .0154$) after induction treatment. Median PFS with consolidation was prolonged in all Follicular Lymphoma International Prognostic Index risk subgroups. After ^{90}Y-ibritumomab tiuxetan consolidation, 77% of patients in PR after induction converted to CR/CRu, resulting in a final CR rate of 87%. The most common toxicity with ^{90}Y-ibritumomab tiuxetan was hematologic, and grade 3 or 4 infections occurred in 8% of patients.

Conclusion
Consolidation of first remission with ^{90}Y-ibritumomab tiuxetan in advanced-stage follicular lymphoma is highly effective with no unexpected toxicities, prolonging PFS by 2 years and resulting in high PR-to-CR conversion rates regardless of type of first-line induction treatment.

J Clin Oncol 26:5156-5164. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Follicular lymphoma is the most common form of indolent non-Hodgkin's lymphoma (NHL) in Western countries, and its disease course is typically characterized by multiple relapses and progressively shorter response durations with subsequent therapies. Conventional chemotherapy is not curative, with a median survival time of 8 to 10 years in advanced-stage follicular lymphoma.[1,2] To improve outcomes, different therapeutic approaches have been tested as part of first-line therapy in randomized phase III trials, including immunotherapy with interferon[3] and/or rituximab[4-8] and consolidation with myeloablative therapy followed by autologous stem-cell transplantation (ASCT).[9-11] These approaches induce variable complete response (CR)/unconfirmed CR (CRu) rates ranging from 20% to 75%, but additional treatment strategies are needed to further improve CR rates, thereby potentially improving response duration and outcome.

Follicular lymphoma is a radiosensitive malignancy, and earlier stages of the disease are treated with radiotherapy with curative intent. A more targeted strategy using radiotherapy involves the use of radiolabeled monoclonal antibodies such as iodine-131 (^{131}I)–labeled or yttrium-90 (^{90}Y)–labeled anti-CD20 antibodies. Radioimmunotherapy is the most effective single-agent treatment for follicular lymphoma.[12] ^{90}Y-ibritumomab tiuxetan (Zevalin; Bayer Schering Pharma AG, Berlin, Germany) is an immunoconjugate comprising the murine immunoglobulin $G_1\kappa$, anti-CD20 monoclonal antibody ibritumomab covalently bound to the chelator tiuxetan, which provides stable linkage to the radioisotope ^{90}Y. Because ^{90}Y is a pure β emitter with 90% of its energy absorbed within a radius of 5.3 mm (corresponding to approximately 100- to 200-cell diameters),[13] ^{90}Y-ibritumomab tiuxetan can be administered safely in the outpatient setting. In previous studies in patients with relapsed and/or refractory low-grade NHL, a single dose of ^{90}Y-ibritumomab tiuxetan induced overall response rates of 73% to 83% and CR/CRu in 15% to 51% of patients.[14-17] This agent is particularly effective when used earlier in the disease course[18] and in less bulky ($<$ 5 cm in diameter) disease.[19] In addition, a recent meta-analysis demonstrated that the response rates, response duration, and safety profile of ^{90}Y-ibritumomab tiuxetan in elderly patients ($\geq$ 70 years) were similar to those of younger patients.[20] Therefore, consolidation with ^{90}Y-ibritumomab tiuxetan after first-line induction therapy may allow more patients with disseminated disease at diagnosis to benefit from radioimmunotherapy and may present an attractive treatment option, particularly in older patients (age $\geq$ 60 years) who represent roughly 50% of patients with newly diagnosed indolent NHL.[21,22] We conducted this international, randomized, open-label, controlled, phase III First-Line Indolent Trial (FIT) to evaluate the safety and efficacy of consolidation therapy with a single dose of ^{90}Y-ibritumomab tiuxetan in patients who achieved a partial response (PR) or better with first-line induction treatment.

PATIENTS AND METHODS

Patients

Eligible patients were age $\geq$ 18 years, had CD20$^+$ histologically confirmed grade 1 or 2 follicular lymphoma (Revised European-American Lymphoma/WHO classification[23,24]), stage III or IV disease at diagnosis, and WHO performance status of 0 to 2. Patients were required to have achieved a CR/CRu or PR (International Workshop Criteria[25]) after first-line therapy, with the last dose of therapy administered 6 to 12 weeks before start of study treatment; less than 25% bone marrow involvement by lymphoma on biopsy; an absolute neutrophil count $\geq 1.5 \times 10^9$/L; hemoglobin levels $\geq$ 9 g/dL; and a platelet count $\geq 150 \times 10^9$/L. Patients were excluded if they had received prior radiation therapy or myeloablative therapy, had symptomatic CNS lymphoma or known HIV positivity, total bilirubin more than 1.5$\times$ the upper limit of normal, or ALT levels more than 2.5$\times$ the upper limit of normal. All patients gave informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review boards at all study sites. The study has been registered at ClinicalTrials.gov under NCT00185393.

Study Design and Treatment

Patients in remission after first-line therapy were randomly assigned to receive no treatment (control) or consolidation with ^{90}Y-ibritumomab

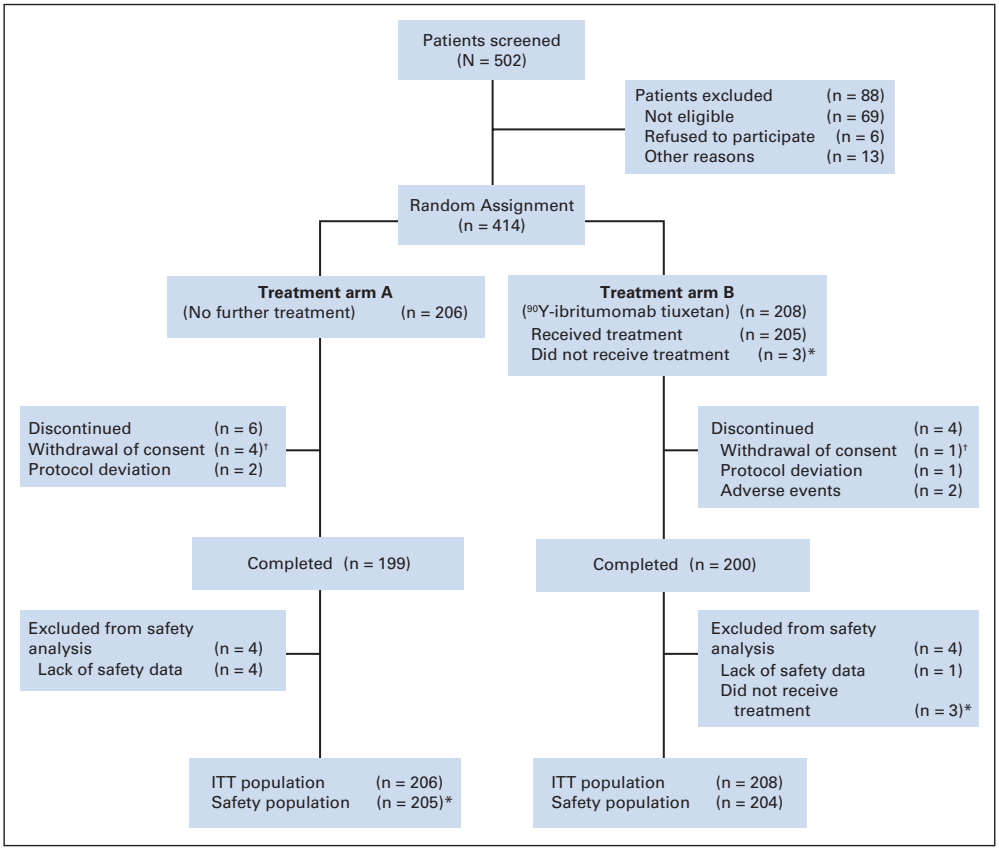

Fig 1. Patient enrollment and disposition (CONSORT diagram). (*) Three patients who did not receive yttrium-90 (^{90}Y)–ibritumomab tiuxetan were allocated to the control arm for safety analysis. (†) No postbaseline data were available for the five patients who withdrew consent. ITT = intent to treat.

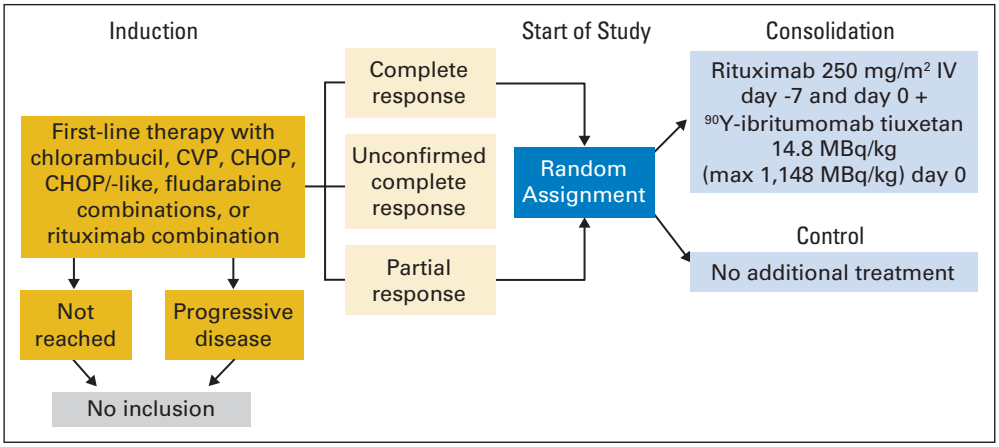

Fig 2. Study schema. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; CR, complete response; CRu, unconfirmed complete response; NR, no response; PD, progressive disease; PR, partial response; ^{90}Y, yttrium-90.

tiuxetan (Fig 1). After induction therapy, patients randomly assigned to the consolidation arm received two infusions of rituximab 250 mg/m^2 1 week apart, with the first infusion administered alone and the second infusion followed immediately by ^{90}Y-ibritumomab tiuxetan 14.8 MBq/kg (not to exceed a total dose of 1,184 MBq) administered as a slow intravenous push over 10 minutes. In a portion of patients who underwent dosimetry evaluations, the first infusion of rituximab was followed immediately by indium-111–ibritumomab tiuxetan 185 MBq for imaging studies.

The primary end point of the study was overall progression-free survival (PFS) and PFS stratified by response to first-line induction therapy (ie, PR or CR/CRu). The secondary end point was PFS based on type of first-line induction regimen. PFS was also analyzed according to Follicular Lymphoma International Prognostic Index (FLIPI) scores,[26] which were retrospectively determined. Additional secondary study end points included improvement in CR rate, conversion rate to *bcl-2* polymerase chain reaction (PCR)–negative status in the blood, overall survival (OS), and safety.

Assessments

PFS was calculated from the date of random assignment to the date of documented relapse, disease progression, or death from any cause. OS was calculated from the date of random assignment to the date of death from any cause. Tumor assessments were performed on all target lesions identified at baseline by computed tomography scans (neck, thorax, abdomen, and pelvis) at week 14, month 6, and every 6 months thereafter. Tumor response was based on International Workshop Criteria[25] evaluated by an independent central data review board. Real-time quantitative PCR (RQ-PCR) evaluation of peripheral-blood samples for the *bcl-2* t(14;18) translocation was performed at baseline, week 14, months 6 and 12, and yearly thereafter. Safety was assessed by adverse events (AEs), with toxicity grading based on the National Cancer Institute Common Toxicity Criteria (version 2), clinical laboratory evaluations, and physical examinations.

Statistical Analysis

At the inception of the study, the planned sample size was 350 patients to detect a prolongation of PFS by 50% with ^{90}Y-ibritumomab tiuxetan (increase in expected 4-year PFS rate from 30% with first-line chemotherapy to 45%) and to obtain 80% power with a two-sided significance level of $\alpha = .05$. The sample size was re-evaluated when the protocol was amended to allow for inclusion of patients treated with rituximab-containing first-line regimens, which was expected to extend the time to progression. To maintain the required statistical power, the sample size was adjusted to 364 patients.

Efficacy evaluations were based on the intent-to-treat population (ie, all patients who were randomly assigned), and safety evaluations were based on the safety population (ie, all patients who were randomly assigned and had postbaseline data). PFS and OS were analyzed by the Kaplan-Meier method, and a comparison of curves was performed using a two-sided stratified log-rank test (significance level of $\alpha = .05$). Patients without postbaseline data because of withdrawal of consent were censored for PFS and OS at time 0. Differences between treatment arms for change of response status (PR to CR) were assessed using two-sided Fisher's exact test. Patients with PR who had no postbaseline data were counted as having no change in response status. Evaluations for change in *bcl-2* RQ-PCR status (positive to negative) and safety were performed using descriptive statistics.

RESULTS

Patient Characteristics

From August 2001 to January 2005, 414 patients were enrolled from 77 study centers in 12 European countries and Canada. Of these patients, 208 were randomly assigned to receive ^{90}Y-ibritumomab tiuxetan consolidation, and 206 were assigned to the control arm (Fig 2). Baseline patient and disease characteristics were well balanced between treatment arms (Table 1).

Efficacy

After a median observation period of 3.5 years, median PFS time was 36.5 months in the ^{90}Y-ibritumomab tiuxetan consolidation arm and 13.3 months in the control arm (hazard ratio [HR] = 0.465; $P < .0001$; Fig 3A). For the subgroup of patients in PR after first-line induction treatment, median PFS time was 29.3 months in the consolidation arm and 6.2 months in the control arm (HR = 0.304; $P < .0001$; Fig 3B). Similarly, for the subgroup of patients in CR/CRu after induction, the median PFS time was 53.9 months in the consolidation arm and 29.5 months in the control arm (HR = 0.613; $P = .0154$; Fig 3C). Data on median PFS based on first-line therapy and on retrospective assignment of FLIPI scores are listed in Table 2. At current follow-up, there is no difference in OS between study arms (Appendix Fig A1, online only).

In the ^{90}Y-ibritumomab tiuxetan consolidation arm, 78 (77%) of 101 patients with a PR after induction therapy converted to a CR/CRu after consolidation, whereas in the control arm, 17 (17.5%) of 97 patients with a PR after induction therapy converted to CR/CRu after random assignment ($P < .001$). The proportion of patients converting from PR to CR/CRu was significantly higher in the ^{90}Y-ibritumomab tiuxetan consolidation arm than in the control arm

Table 1. Baseline Characteristics

Characteristic	Control Arm (n = 205)		^{90}Y-Ibritumomab Tiuxetan Arm (n = 204)		*P*
	No. of Patients	%	No. of Patients	%	
Male	103	50.2	97	47.5	.59
Age, years					.14
Median	53		55		
Range	27-74		29-78		
Body weight, kg					.16
Median	75		74		
Range	44-124		43-124		
Ann Arbor stage classification					.15
I	0	0	1	0.5	
II	6	2.9	1	0.5	
III	63	30.7	72	35.3	
IV	136	66.3	130	63.7	
"B" symptoms					.59
No	162	79.0	156	76.5	
Yes	42	20.5	46	22.5	
Response after first-line treatment*					.76
CR/CRu	109	53	107	51	
PR	97	47	101	49	
First-line induction regimen					.98
Chlorambucil	19	9.3	20	9.8	
CVP/COP	54	26.3	52	25.5	
CHOP	58	28.3	64	31.4	
CHOP-like	31	15.1	30	14.7	
Fludarabine combination	11	5.4	11	5.4	
Rituximab combination	32	15.6	27	13.2	
bcl-2 RQ-PCR positive at time of random assignment†	59	39	68	46	.04
FLIPI risk score‡					.62
Low (0-1 factor)	62	42.5	56	37.3	
Intermediate (2 factors)	54	37.0	58	38.7	
High (3-5 factors)	30	20.5	36	24.0	

Abbreviations: ^{90}Y, yttrium-90; CR, complete response; CRu, unconfirmed complete response; PR, partial response; CVP/COP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RQ-PCR, real-time quantitative polymerase chain reaction; FLIPI, Follicular Lymphoma International Prognostic Index.

*Percentage based on intent-to-treat population (control, n = 206; ^{90}Y-ibritumomab tiuxetan, n = 208).

†Percentage based on 186 patients for whom clinical data, a peripheral-blood sample at the time of random assignment, and at least one follow-up sample were available.

‡FLIPI data could be collected retrospectively in 71% of the intent-to-treat population (control, n = 146; ^{90}Y-ibritumomab tiuxetan, n = 150).

in nearly all subgroups categorized by type of first-line induction treatment (Table 3). The final CR/CRu rate was 87.4% after consolidation with ^{90}Y-ibritumomab tiuxetan compared with 53.3% in the control arm. For assessment of peripheral-blood *bcl-2* RQ-PCR status, only patients who had clinical data, a peripheral-blood sample at the time of random assignment, and at least one follow-up blood sample were included in the analysis. Among 186 patients assessable for *bcl-2* RQ-PCR status, 127 were RQ-PCR positive at the time of random assignment. In the ^{90}Y-ibritumomab tiuxetan consolidation arm, 61 (90%) of 68 patients who were RQ-PCR positive after induction converted to RQ-PCR–negative status after consolidation treatment. In the control arm, 21 (36%) of 59 patients converted from RQ-PCR–positive status to RQ-PCR–negative status at follow-up evaluation.

Safety

The most common grade 3 or 4 AEs in the ^{90}Y-ibritumomab tiuxetan consolidation arm were hematologic toxicities (Table 4). Among the patients with grade 3 or 4 neutropenia, median time to neutrophil nadir from start of ^{90}Y-ibritumomab tiuxetan therapy was 44.5 days (range, 14 to 775 days) and 46 days (range, 11 to 70 days), respectively, and the median time to neutrophil recovery was 20 days (range, 4 to 388 days) and 28 days (range, 6 to 385 days), respectively. Among the patients with grade 3 or 4 thrombocytopenia, median time to platelet nadir was 35 days (range, 14 to 64 days) and 39.5 days (range, 36 to 55 days), respectively, and the median time to recovery was 20 days (range, 4 to 654 days) and 35 days (range, 24 to 847 days), respectively. In the consolidation arm, a total of 36 patients (17.6%) received growth factor support for neutropenia, and 42 patients (20.6%) received platelet transfusions. Grade 3 or 4 anemia was reported in only seven patients, four of whom required RBC transfusions. The most frequent nonhematologic AEs affecting more than 10% of patients in the ^{90}Y-ibritumomab tiuxetan consolidation arm were primarily grade 1 or 2 and included fatigue (32.8%), nasopharyngitis (19.1%), nausea (18.1%), asthenia (14.2%), arthralgia (11.8%), cough (11.3%), headache (11.3%), diarrhea (10.8%), and pyrexia (10.3%). Grade 3 or 4 nonhematologic AEs affecting more than five patients in the ^{90}Y-ibritumomab tiuxetan consolidation arm were infections (7.9%; grade 4 in 1%), pyrexia (3%; grade 4 in 0.5%), and hypertension (2.9%; no grade 4). Grade 4 toxicities were uncommon and occurred in 5.4% of patients in the consolidation arm and

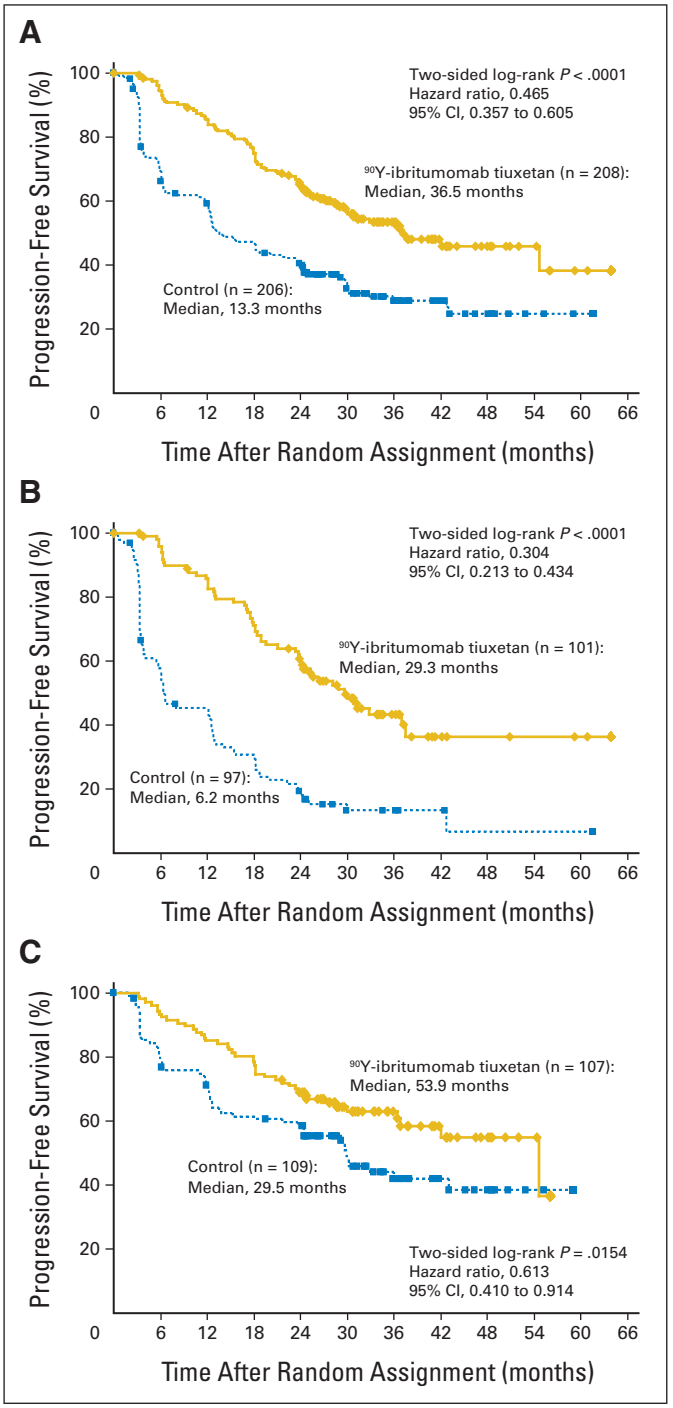

Fig 3. Kaplan-Meier plots for progression-free survival (PFS) in all patients and PFS stratified by response to first-line induction treatment. (A) PFS plot for all randomly assigned patients. (B) PFS plot for patients achieving a partial response to first-line induction treatment. (C) PFS plot for patients achieving a complete response/unconfirmed complete response to first-line induction treatment. ^{90}Y, yttrium-90.

5.9% of patients in the control arm (Table 4). In the ^{90}Y-ibritumomab tiuxetan consolidation arm, 7.4% of patients required hospitalization because of infections. Among 69 patients who underwent dosimetry evaluations, radiation exposure was within the protocol-defined upper limit to normal organs (20 Gy) and red marrow (3 Gy).

After a median observation period of 3.5 years, 11 patients have died; six patients in the consolidation arm died as a result of neutropenic sepsis after subsequent chemotherapy (n = 1), pancreatic carcinoma (n = 1), acute myeloblastic leukemia (AML) approximately 2 years after the start of study treatment (n = 1), and progressive disease (n = 3). The patient who developed AML had received eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as first-line induction therapy. In the control arm, five patients died as a result of sepsis (n = 1) and progressive disease (n = 4).

DISCUSSION

Consolidation therapy aims to rapidly improve the quality of response achieved with initial remission induction treatment, thereby extending the duration of disease control. In our study of patients responding to first-line therapy, consolidation with ^{90}Y-ibritumomab tiuxetan resulted in significant prolongation of median PFS, by approximately 2 years, compared with no further treatment. The 2-year PFS advantage achieved with ^{90}Y-ibritumomab tiuxetan consolidation was observed in patients with a PR and also those with a CR/CRu to initial induction therapy. This PFS advantage after ^{90}Y-ibritumomab tiuxetan consolidation in patients with a CR/CRu is in keeping with the finding that 90% of patients who were *bcl-2* PCR positive in the blood after induction converted to PCR negativity and suggests that ^{90}Y-ibritumomab tiuxetan may have a role in eliminating minimal residual disease. Moreover, consolidation with ^{90}Y-ibritumomab tiuxetan prolonged PFS across FLIPI subgroups. In patients with high-risk FLIPI, the median PFS with consolidation was numerically superior compared with the control arm (23.8 *v* 6.5 months, respectively), but this difference was not statistically significant. Median PFS in patients with intermediate-risk or high-risk FLIPI treated with ^{90}Y-ibritumomab tiuxetan consolidation seemed similar to previous reports of time to progression in these FLIPI subgroups receiving rituximab plus CHOP (R-CHOP) or rituximab plus cyclophosphamide, vincristine, and prednisone (CVP; median time to progression, 39 to 52 months in intermediate-risk FLIPI; 26 to 30 months in high-risk FLIPI).[6,27] To date, no direct comparative data on the efficacy of rituximab-based chemotherapy versus chemotherapy followed by radioimmunotherapy are available. Data from the ongoing phase III Intergroup trial (NCT00006721; ClinicalTrials.gov) are awaited to shed light on this question.

In this study, we show that 77% of patients with advanced follicular lymphoma who had achieved only a PR with induction therapy converted to CR/CRu with a single dose of ^{90}Y-ibritumomab tiuxetan. This constitutes one of the highest PR-to-CR conversion rates reported in published phase III randomized studies in first-line follicular lymphoma, including studies that evaluated consolidation with ASCT,[9-11] which resulted in PR-to-CR conversion rates ranging from 38% to 69% (A. Hagenbeek, personal communication, December 2007). Interestingly, data from our study largely confirm the results from phase II studies of consolidation with the radioimmunotherapy agent ^{131}I-tositumomab, which reported conversions to CR in 49%, 60%, and 84% of patients who achieved stable disease or PR to first-line induction with CHOP, CVP, or fludarabine, respectively.[28-30] In the phase II study of first-line CHOP followed by ^{131}I-tositumomab, the estimated 5-year PFS rate was 67% after a median

Table 2. Median PFS According to First-Line Regimen and FLIPI Score

Regimen and FLIPI Score	Control		^{90}Y-Ibritumomab Tiuxetan		HR	95% CI	*P**
	No. of Patients	PFS (months)	No. of Patients	PFS (months)			
First-line regimen							
Chlorambucil	19	11.9	20	NR	0.344	0.150 to 0.793	.0088
CVP/COP	53	7.9	53	28.5	0.383	0.235 to 0.625	.0001
CHOP	61	12.5	66	35.9	0.391	0.246 to 0.622	< .0001
CHOP-like	31	29.2	30	NR	0.474	0.219 to 1.029	.0533
Fludarabine combination	11	24.3	11	41.4	0.884	0.283 to 2.769	.8332
Rituximab combination	31	NR	28	NR	0.722	0.304 to 1.714	.4583
FLIPI risk score							
Low	62	24.1	56	NR	0.599	0.357 to 1.006	.0502
Intermediate	54	11.3	58	53.9	0.227	0.134 to 0.385	< .0001
High	30	6.5	36	23.8	0.587	0.322 to 1.070	.0789

Abbreviations: PFS, progression-free survival; FLIPI, Follicular Lymphoma International Prognostic Index; ^{90}Y, yttrium-90; HR, hazard ratio; NR, not reached; CVP/COP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Two-sided log-rank test.

follow-up time of 5.1 years.[28-30] Although this PFS outcome is impressive relative to data from our phase III FIT study, direct comparisons are not possible between the studies because of differences in study design and follow-up period and potential heterogeneity in the patient and/or disease characteristics.

In the subgroup of patients in the FIT study who received rituximab as part of induction, we observed a higher PR-to-CR conversion rate after ^{90}Y-ibritumomab tiuxetan consolidation compared with that of the control arm, but the difference was not statistically significant. Of note, data from recent phase II studies of ^{90}Y-ibritumomab tiuxetan consolidation after first remission with short-duration R-CHOP demonstrate PR-to-CR conversion rates of 54% to 81%,[31,32] lending additional support to the ability of ^{90}Y-ibritumomab tiuxetan to improve responses in patients who are pretreated with rituximab-based combination therapy. Because these phase II studies used short courses of R-CHOP rather than the standard six to eight courses of therapy, it remains to be seen whether consolidation with ^{90}Y-ibritumomab tiuxetan provides similar benefit after a full course of R-CHOP. In the subgroup of patients who received rituximab-based induction in our study, PFS was not significantly different between treatment arms, and median PFS times have not yet been reached in either arm; further follow-up is needed to evaluate whether the addition of ^{90}Y-ibritumomab tiuxetan confers PFS benefit in this subgroup. However, it is important to note that the FIT study was neither designed nor statistically powered to detect differences in PFS outcomes based on first-line induction treatments.

As would be expected from previous experience, the most common AEs with ^{90}Y-ibritumomab tiuxetan consolidation were hematologic toxicities, which were predictable and manageable; the majority of patients with grade 3 or 4 hematologic toxicities did not require transfusion or growth factor support. Dosimetric analysis demonstrated that radiation exposure with ^{90}Y-ibritumomab tiuxetan consolidation was within safe limits both to normal organs and to red marrow. Although infectious events were more common in the ^{90}Y-ibritumomab tiuxetan consolidation arm, grade 4 infections were rare, despite the high incidence of grade 3 or 4 neutropenia. The percentage of patients requiring hospitalization for infections in this study (7.4%) was similar to that reported in previous studies (7%) with ^{90}Y-ibritumomab tiuxetan.[17,33] No conclusion can be drawn from the single case of AML diagnosed 2 years after ^{90}Y-ibritumomab tiuxetan. Additional follow-up is required to determine potential long-term AEs with ^{90}Y-ibritumomab tiuxetan consolidation.

The efficacy and favorable safety profile demonstrated in our study suggest that consolidation with a single dose of ^{90}Y-ibritumomab

Table 3. Improvement in Response Quality (conversion from PR to CR/CRu) According to First-Line Induction Treatment

First-Line Treatment	Control Arm			^{90}Y-Ibritumomab Tiuxetan			*P*
	Total No. of Patients	No. of Patients Who Converted*	%	Total No. of Patients	No. of Patients Who Converted*	%	
All patients	97	17	17.5	101	78	77.2	< .001
Chlorambucil	13	1	7.7	13	11	84.6	< .001
CVP/COP	29	3	10.3	22	16	72.7	< .001
CHOP	32	8	25.0	41	31	75.6	< .001
CHOP-like	8	0	0	13	10	76.9	< .005
Fludarabine combination	3	0	0	5	5	100.0	< .05
Rituximab combination	12	5	41.7	7	5	71.4	.34

Abbreviations: PR, partial response; CR, complete response; CRu, unconfirmed complete response; ^{90}Y, yttrium-90; CVP/COP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*No. of patients with PR after first-line therapy who converted to CR/CRu at post–random assignment follow-up.

Table 4. Summary of Grade 3 or 4 Adverse Events

	Control Arm (n = 205)				^{90}Y-Ibritumomab Tiuxetan Arm (n = 204)			
	Grade 3		Grade 4		Grade 3		Grade 4	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic*								
Lymphopenia	22	10.8	0	0	123	60.3	0	0
Neutropenia	4	2.0	1	0.5	82	40.2	54	26.5
Thrombocytopenia	0	0	0	0	120	58.8	4	2.0
Anemia	0	0	0	0	6	2.9	1	0.5
Nonhematologic								
Any grade 3 or 4	27	13.2	12	5.9	48	23.5	11	5.4
Infections	5	2.4	0	0	14	6.9	2	1.0
Pyrexia	0	0	0	0	5	2.5	1	0.5
Hypertension	1	0.5	0	0	6	2.9	0	0

NOTE. Adverse events affecting at least five patients.
Abbreviation: ^{90}Y, yttrium-90.
*In the control group, two patients did not have data recorded for laboratory evaluations of hematologic toxicities; hence, hematologic toxicity data in the control group were available for 203 patients.

tiuxetan may be considered as part of the current treatment algorithms of follicular lymphoma.[34,35] It is noteworthy that, for patients who received non–rituximab-containing induction, a significantly higher conversion rate from PR to CR (> 71%) was observed with ^{90}Y-ibritumomab tiuxetan consolidation regardless of the type of first-line induction chemotherapy administered, including less potent regimens such as CVP or even single-agent chlorambucil. Therefore, consolidation with ^{90}Y-ibritumomab tiuxetan has the potential to maximize tumor response without using aggressive induction regimens and may reduce the need for aggressive chemotherapy. This may be particularly relevant for elderly patients or those with comorbidities who are not eligible to undergo aggressive combination chemotherapies or ASCT. Maintenance therapy with rituximab administered every 2 to 3 months for 2 years after chemotherapy is another emerging treatment approach in first-line follicular lymphoma.[36] The optimal maintenance regimen has yet to be defined, however, and the potential benefit of adding rituximab maintenance after first-line rituximab-based combination therapy is currently being investigated in a large phase III trial.

In conclusion, consolidation therapy with ^{90}Y-ibritumomab tiuxetan in patients achieving an initial response to first-line induction treatment is well tolerated with no unexpected toxicities and significantly prolongs PFS by 2 years compared with no further treatment. Notably, consolidation with ^{90}Y-ibritumomab tiuxetan led to high conversion rates from PR to CR regardless of the first-line treatment regimen administered. Results from our study suggest that first-line consolidation with ^{90}Y-ibritumomab tiuxetan is a highly efficacious treatment option in patients with follicular lymphoma responsive to first-line therapy. Further randomized studies incorporating ^{90}Y-ibritumomab tiuxetan consolidation in patients responsive to rituximab-based combination regimens are warranted to determine the best first-line therapy in advanced follicular lymphoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

Employment or Leadership Position: Jens Kuhlmann, Bayer Schering Pharma (C) **Consultant or Advisory Role:** John Radford, Bayer Schering Pharma (C); Pierre Soubeyran, Bayer Schering Pharma (C); Herve Tilly, Bayer Schering Pharma (C); Francesco d'Amore, Bayer Schering Pharma (U); Angelika Bischof-Delaloye, Bayer Schering Pharma (C); Anton Hagenbeek, Bayer Schering Pharma (C), Roche International (C) **Stock Ownership:** None **Honoraria:** Franck Morschhauser, Bayer Schering Pharma; Achiel Van Hoof, Bayer Schering Pharma; Pierre Soubeyran, Bayer Schering Pharma; Herve Tilly, Bayer Schering Pharma; Arne Kolstad, Bayer Schering Pharma, Roche; Francesco d'Amore, Bayer Schering Pharma; Angelika Bischof-Delaloye, Bayer Schering Pharma; Gilles Salles, Bayer Schering Pharma, Roche; Anton Hagenbeek, Bayer Schering Pharma, Roche International **Research Funding:** Arne Kolstad, Bayer Schering Pharma; Ama Rohatiner, Bayer Schering Pharma **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).