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ORIGINAL REPORT

^{90}Yttrium-Ibritumomab Tiuxetan Consolidation of First Remission in Advanced-Stage Follicular Non-Hodgkin Lymphoma: Updated Results After a Median Follow-Up of 7.3 Years From the International, Randomized, Phase III First-Line Indolent Trial

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ABSTRACT

Purpose
Updated results are presented after a median follow-up of 7.3 years from the phase III First-Line Indolent Trial of yttrium-90 (^{90}Y) –ibritumomab tiuxetan in advanced-stage follicular lymphoma (FL) in first remission.

Patients and Methods
Patients with CD20^{+} stage III or IV FL with complete response (CR), unconfirmed CR (CRu), or partial response (PR) after first-line induction treatment were randomly assigned to ^{90}Y-ibritumomab consolidation therapy (rituximab 250 mg/m^2 days −7 and 0, then ^{90}Y-ibritumomab 14.8 MBq/kg day 0; maximum 1,184 MBq) or no further treatment (control). Primary end point was progression-free survival (PFS) from date of random assignment.

Results
For 409 patients available for analysis (^{90}Y-ibritumomab, n = 207; control, n = 202), estimated 8-year overall PFS was 41% with ^{90}Y-ibritumomab versus 22% for control (hazard ratio [HR], 0.47; $P < .001$). For patients in CR/CRu after induction, 8-year PFS with ^{90}Y-ibritumomab was 48% versus 32% for control (HR, 0.61; $P = .008$), and for PR patients, it was 33% versus 10% (HR, 0.38; $P < .001$). For ^{90}Y-ibritumomab consolidation, median PFS was 4.1 years (*v* 1.1 years for control; $P < .001$). Median time to next treatment (TTNT) was 8.1 years for ^{90}Y-ibritumomab versus 3.0 years for control ($P < .001$) with approximately 80% response rates to second-line therapy in either arm, including autologous stem-cell transplantation. No unexpected toxicities emerged during long-term follow-up. Estimated between-group 8-year overall survival rates were similar. Annualized incidence rate of myelodysplastic syndrome/acute myeloblastic leukemia was 0.50% versus 0.07% in ^{90}Y-ibritumomab and control groups, respectively ($P = .042$).

Conclusion
^{90}Y-ibritumomab consolidation after achieving PR or CR/CRu to induction confers 3-year benefit in median PFS with durable 19% PFS advantage at 8 years and improves TTNT by 5.1 years for patients with advanced FL.

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INTRODUCTION

As the second most common subtype of non-Hodgkin lymphoma,[1,2] follicular lymphoma (FL) is generally thought of as an indolent disease, although it is typically of an advanced stage at initial diagnosis and is considered incurable with currently available treatment options.[3] The recent addition of rituximab to current therapies has significantly improved survival outcomes[4-6]; however, standard treatment approaches remain unsatisfactory because of multiple episodes of relapse and eventual death as a result of the disease or its complications.[4]

Multiple studies have demonstrated a clinical benefit in treating patients with FL with the radioimmunotherapy regimen yttrium-90 (^{90}Y) -ibritumomab tiuxetan (Zevalin),[7-10] including the First-Line Indolent Trial (FIT). FIT was a prospective, randomized, open-label, phase III international trial that compared no further treatment versus consolidation therapy with ^{90}Y-ibritumomab in patients with previously untreated advanced FL who

achieved a partial response (PR) or complete response (CR) to first-line induction therapy.[11] After ^{90}Y-ibritumomab consolidation, patients showed a 77% PR to CR/unconfirmed CR (CRu) conversion rate, with a final CR rate of 87% for the ^{90}Y-ibritumomab arm compared with 53% in the control arm. At a median 3.5 years of observation, the median progression-free survival (PFS) was significantly prolonged with ^{90}Y-ibritumomab compared with no further treatment (36.5 *v* 13.3 months, respectively; $P < .001$), regardless of whether patients achieved a PR, CR, or CRu after induction treatment. The most common acute (early) toxicity associated with ^{90}Y-ibritumomab was hematologic, and grade 3 or 4 infections occurred in 8% of patients receiving ^{90}Y-ibritumomab compared with 2% for patients in the control group. Following the report of these first FIT results, both the US Food and Drug Administration and European Medicines Agency approved ^{90}Y-ibritumomab for use as consolidation therapy in patients with previously untreated FL achieving a PR or CR to first-line induction therapy.

Long-term evaluations of the efficacy and safety of this first-line consolidation strategy with ^{90}Y-ibritumomab, including the management of relapse, are needed to best integrate this option into current FL treatment algorithms. The objective of this report is to provide updated results from the FIT study after a median follow-up of 7.3 years. Data have been collected for PFS, time to next treatment (TTNT), response to second-line treatment, overall survival (OS), and safety, specifically regarding the incidence of second malignancies.

PATIENTS AND METHODS

Patients

The criteria for patient eligibility were previously reported.[11] Briefly, eligible patients were ≥ 18 years of age, had stage III or IV histologically confirmed CD20$^+$ FL (grade 1 or 2), had a WHO performance status of 0 to 2, and were in CR/CRu or PR after first-line therapy, with the last dose of therapy administered 6 to 12 weeks before the start of study treatment. Patients were required to have an absolute neutrophil count ≥ 1.5×10^9/L, hemoglobin levels ≥ 9 g/dL, platelet counts ≥ 150×10^9/L, and less than 25% bone marrow lymphoma involvement as measured by biopsy. All patients gave informed consent.

Study Design

Patients in remission (PR or CR/CRu) after first-line therapy were randomly assigned to receive no treatment (control) or consolidation with ^{90}Y-ibritumomab (Appendix Fig A1, online only). First-line therapy consisted of chlorambucil; cyclophosphamide, vincristine, prednisone (CVP); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); CHOP-like regimen; fludarabine combination; or rituximab combination. Patients in the ^{90}Y-ibritumomab group received rituximab 250 mg/m^2 intravenously on days −7 and 0, followed on day 0 by a single infusion of ^{90}Y-ibritumomab 14.8 MBq/kg (0.4 mCi/kg), not exceeding a total dose of 1,184 MBq (32 mCi).

The primary end point was PFS of all randomly assigned patients and PFS stratified by response to first-line induction therapy (ie, PR or CR/CRu). Secondary end points included PFS by type of first-line induction regimen, improvement in CR rate, OS, and safety. PFS was also analyzed according to Follicular Lymphoma International Prognostic Index (FLIPI) scores,[12] which were retrospectively determined. The FIT study was conducted in accordance with the Declaration of Helsinki and approved by each center's institutional review board.

Assessments

PFS was calculated from the date of random assignment to the date of documented recurrence, disease progression (PD), or death. OS was calculated from the date of random assignment to the date of death. TTNT was calculated from the date of random assignment to the date of first administration of second-line therapy. Tumor assessments on all target lesions identified at baseline were performed by computed tomography scans of the neck, thorax, abdomen, and pelvis at week 14, month 6, and every 6 months thereafter. The determination of tumor response was based on International Workshop Criteria per Cheson et al[13] (with no positron emission tomography scanning), and in accordance with an independent central review board. Adverse events were assessed throughout the study, with toxicity grading based on National Cancer Institute Common Toxicity Criteria Version 2.0.

Statistical Analyses

Efficacy and safety evaluations were performed for all randomly assigned patients with the exception of five patients (four control and one ^{90}Y-ibritumomab) who were withdrawn immediately after random assignment and for whom no data beyond the date of random assignment were available. These patients were included formally in the original publication,[11] but were censored in all analyses at day 1. PFS and OS were analyzed by the Kaplan-Meier method, and curves were compared by using a log-rank test with a significance level of $\alpha = .05$. Cox regression analysis was applied for multivariate analysis and for testing the interaction between disease characteristics and treatment effect. Hazard ratios (HRs) reported in the Results section are from Cox regression analyses for treatment arms adjusted for response to first-line treatment (CR/CRu *v* PR).

RESULTS

Patient Characteristics

A total of 414 patients (^{90}Y-ibritumomab, n = 208; control, n = 206) with newly diagnosed FL were enrolled at 77 international centers. Of the 409 patients in the analysis, 39 declined participation in the long-term follow-up; patients were censored in the analysis at date

Table 1. Baseline Characteristics

Characteristic	Control (n = 202) No.	Control (n = 202) %	^{90}Y-Ibritumomab Tiuxetan (n = 207) No.	^{90}Y-Ibritumomab Tiuxetan (n = 207) %
Male sex	101	50	99	48
Age at random assignment, years				
Median	53		55	
Range	27-74		29-78	
> 60	48	24	58	28
Ann Arbor classification, stage				
I	0		1	0.5
II	6	3	1	0.5
III	62	31	73	35
IV	134	66	132	64
FLIPI score				
≤ 1	124	61	117	57
2	60	30	66	32
> 2	18	9	24	12
Response to first-line treatment				
CR/CRu	108	53	107	52
PR	88	44	100	48
SD	4	2	0	
PD	1	0.5	0	
Not assessed	1	0.5	0	

Abbreviations: ^{90}Y, yttrium-90; CR, complete response; CRu, unconfirmed CR; FLIPI, Follicular Lymphoma International Prognostic Index; PD, progressive disease; PR, partial response; SD, stable disease.

of last contact (between 2003 and 2007). Of the remaining patients still alive, 116 had last follow-up in 2012, 173 in 2011, and 19 between 2008 and 2010, of whom 12 were marked as lost to follow-up. The median follow-up of the 349 patients still alive was 7.3 years, although 25% of these patients had a follow-up longer than 8.1 years. Patient baseline characteristics (Table 1) and distribution of first-line induction treatments were well balanced between treatment groups.

Efficacy

The median PFS was 4.1 years in the ^{90}Y-ibritumomab group and 1.1 years in the control group (HR, 0.47; 95% CI, 0.37 to 0.60; $P < .001$; Fig 1A). The estimated 8-year overall PFS was 41% in the ^{90}Y-ibritumomab group compared with 22% in the control group.

Although the FIT study was not powered to detect significant differences in PFS outcomes between ^{90}Y-ibritumomab and control within subgroups, PFS was higher for the patients treated with ^{90}Y-ibritumomab in all subgroups categorized by response to first-line treatment, FLIPI score, and type of first-line treatment (Table 2). The beneficial effect of ^{90}Y-ibritumomab was more pronounced (test for interaction $P = .052$) for patients with PR after first-line treatment (HR, 0.38; 95% CI, 0.27 to 0.52; Fig 1C) compared with patients in CR/CRu (HR, 0.61; 95% CI, 0.43 to 0.88; Fig 1B). The impact of ^{90}Y-ibritumomab on PFS was not significantly different among the three FLIPI subgroups (test for interaction $P = .78$) and among subgroups with different types of first-line treatment (test for interaction $P = .82$).

The median TTNT for all randomly assigned patients differed significantly between treatment groups. For patients in the ^{90}Y-ibritumomab group, median TTNT was 8.1 years (8-year TTNT-free, 51%) versus 3.0 years (8-year TTNT-free, 31%) in the control group (HR, 0.47; 95% CI, 0.36 to 0.61; $P < .001$; Fig 1D). A total of 45 patients (22 ^{90}Y-ibritumomab and 23 control) showed transformation to diffuse large B-cell lymphoma. There were 115 patients (56%) in the ^{90}Y-ibritumomab group and 148 patients (73%) in the control group with PD and follow-up data after progression. Second-line treatment is detailed in Table 3. The majority of patients in both groups received rituximab as part of their second-line therapy (^{90}Y-ibritumomab, n = 73 [63%] and control, n = 107 [72%]),

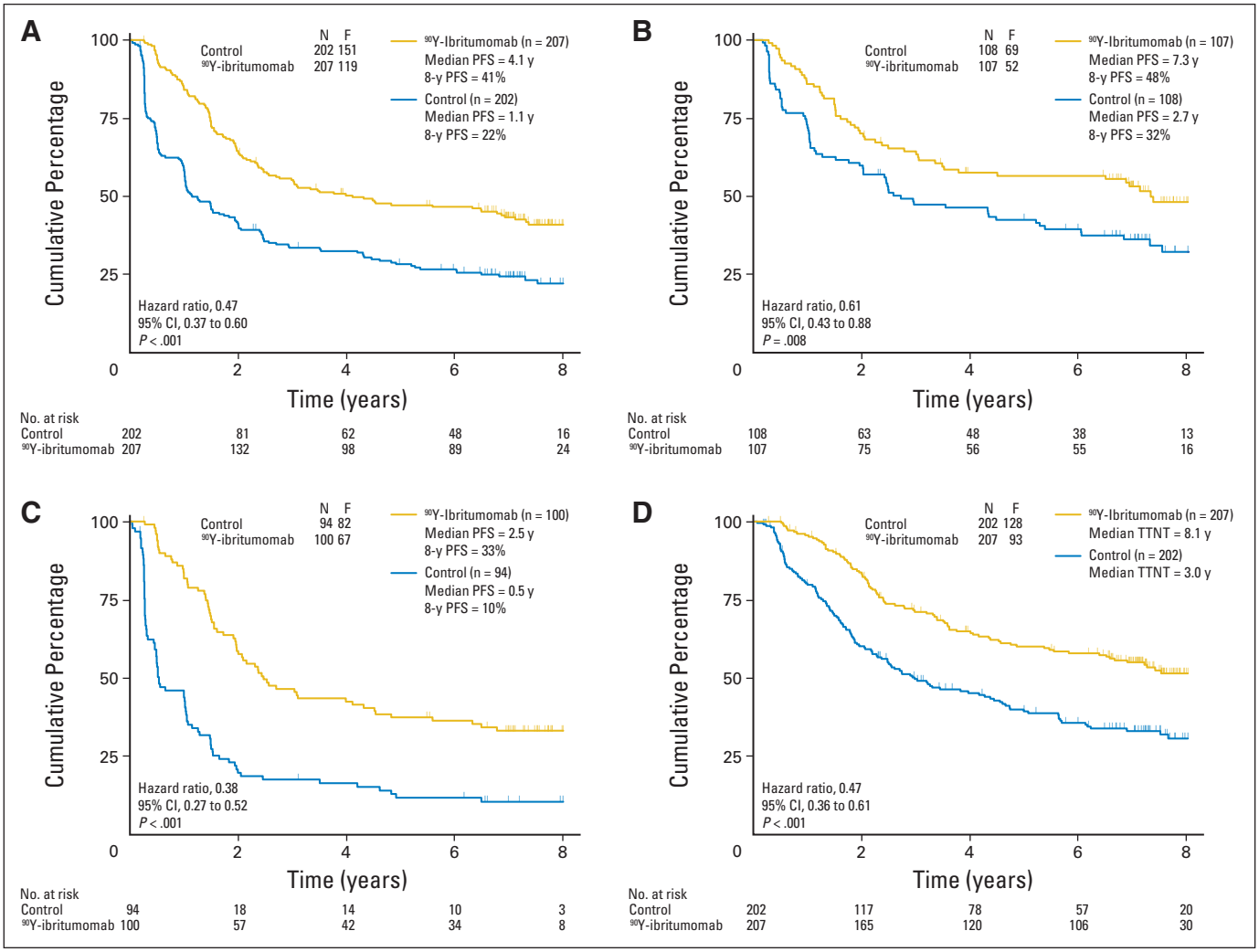

Fig 1. Progression-free survival (PFS). (A) Overall PFS for treatment groups. (B) PFS for patients achieving a complete response or unconfirmed complete response to first-line induction treatment. (C) PFS for patients achieving a partial response to first-line induction treatment. (D) Time to next treatment (TTNT). ^{90}Y, yttrium-90; N, number of patients at risk; F, failure (defined as number of patients who relapsed or died [PFS] and number of patients who started a new treatment [TTNT]).

Table 2. Median PFS According to Response to Induction Therapy, First-Line Regimen, and FLIPI Score

Parameter	Control			^{90}Y-Ibritumomab Tiuxetan			HR	95% CI	P*
	No. of Patients	Median PFS (years)	Estimated 8-Year PFS (%)	No. of Patients	Median PFS (years)	Estimated 8-Year PFS (%)			
Response to first-line regimen									.052†
CR/CRu	108	2.7	32	107	7.3	48	0.61	0.43 to 0.88	.008
PR	94	0.5	10	100	2.5	33	0.38	0.27 to 0.52	< .001
First-line regimen									.82†
Chlorambucil	19	1.0	20	20	4.5	50	0.33	0.15 to 0.75	.008
CVP	53	0.7	17	53	2.5	31	0.48	0.31 to 0.75	.001
CHOP	57	1.0	13	65	3.0	37	0.46	0.30 to 0.70	< .001
CHOP-like	31	2.4	29	30	6.9	46	0.57	0.30 to 1.09	.090
Fludarabine combination	11	2.4	27	11	3.0	45	0.62	0.21 to 1.86	.40
Rituximab combination	31	4.9	45	28	> 7.9	56	0.70	0.33 to 1.49	.36
FLIPI score									.78†
≤ 1	124	1.0	21	117	3.3	40	0.51	0.37 to 0.69	< .001
2	60	1.1	22	66	4.8	43	0.51	0.33 to 0.90	.003
> 2	18	2.6	31	24	6.9	41	0.68	0.31 to 1.51	.35

Abbreviations: ^{90}Y, yttrium-90; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CRu, unconfirmed CR; CVP, cyclophosphamide, vincristine, prednisone; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; PFS, progression-free survival; PR, partial response.
*First-Line Indolent Trial was not powered to detect significant differences in outcomes according to individual types of induction therapy.
†*P* value for the test of interaction between the factor and treatment group. All tests performed for interactions between treatment groups showed no significance.

mainly combined with chemotherapy regimens including fludarabine combinations; ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, cytarabine, and cisplatin (DHA[P]) or oxaliplatin (DHA[Oxa]); etoposide, methylprednisolone, cytarabine, and cisplatin (ESHA[P]); or bendamustine. Autologous stem-cell transplantation was given as consolidation therapy in 19 patients (17%) in the ^{90}Y-ibritumomab group and 34 patients (23%) in the control group. The overall response rate to second-line therapy was 81% in the ^{90}Y-ibritumomab group (59% CR/CRu and 22% PR) and 79% in the control group (61% CR/CRu and 18% PR; Table 3).

Long-Term Safety

The number of second malignancies that occurred after treatment in the ^{90}Y-ibritumomab and control groups was not statistically different (^{90}Y-ibritumomab, n = 26; control, n = 14; $P = .086$; Table 4). The median time from diagnosis to a second malignancy was 71 months (range, 10 to 125 months), and the median time from registration/random assignment to second malignancy was 58 months (range, 4 to 92 months). Myelodysplastic syndrome (MDS) or acute myeloblastic leukemia (AML) was reported in seven patients (actuarial 8-year incidence of MDS/AML, 4.2%) in the ^{90}Y-ibritumomab group at median 4.8 years (range, 1.8 to 7.0 years) after random assignment compared with MDS in one (actuarial 8-year incidence of MDS/AML, 0.6%) patient in the control group ($P = .042$). The patient in the control group had been treated with ^{90}Y-ibritumomab after PD 2.9 years before the diagnosis of MDS. The annualized rate of MDS/AML was 0.50% (95% CI, 0.24% to 1.06%) in the ^{90}Y-ibritumomab group compared with 0.07% (95% CI, 0.01% to 0.53%) in the control group. No additional late toxicities or congenital malformations were detected.

Cytogenetics testing revealed a commonality among the eight patients with MDS/AML who received various treatments after relapse. The −7 and/or deletion of 5q cytogenetics was observed in six of the eight patients with MDS/AML (Table 5). This chromosomal abnormality is typical for therapy-induced MDS/AML.[14] The median time from diagnosis to MDS or AML was 65 months (range, 29 to 102 months), and from registration/random assignment, it was 57 months (range, 22 to 84 months).

OS

There was no significant difference in OS between treatment groups (HR, 0.82; 95% CI, 0.50 to 1.37; $P = .45$ (Appendix Fig A2, online only). A total of 60 patients have died since the start of the trial, 28 in the ^{90}Y-ibritumomab group (8-year OS, 84%) and 32 in the control group (8-year OS, 81%). Causes of death were predominantly progressive lymphoma disease (13 ^{90}Y-ibritumomab and 22 control), second malignancies (eight ^{90}Y-ibritumomab and four control), and other (seven ^{90}Y-ibritumomab and six control). Specific causes of death resulting from second malignancies in the ^{90}Y-ibritumomab group included MDS/AML (four patients, including one death as a result of sepsis after AML treatment and one after subdural hematoma due to thrombocytopenia), infection (due to basal cell skin carcinoma), and pancreatic cancer/carcinoma (two patients). Specific causes of death as a result of second malignancies in the control group included stomach adenocarcinoma, metastasis (from breast cancer), progressive endometrial carcinoma, and metastatic squamous cell lung cancer in the lower lobe.

DISCUSSION

The goals of consolidation therapy in advanced FL are to improve response to first-line induction therapy, prolong time before the patient experiences PD requiring further therapy, and ultimately, increase OS. In this report, after a median follow-up of 7.3 years from FIT, ^{90}Y-ibritumomab consolidation conferred a median PFS benefit of 3 years for patients with advanced FL, with an HR of 0.47 ($P < .001$) and a 19% reduction in the risk of relapse at 8 years compared with no

Table 3. Treatments Administered After PD and Responses After Second-Line Therapy

Treatment After PD	Control (n = 148*) No.	Control (n = 148*) %	^{90}Y-Ibritumomab Tiuxetan (n = 115*) No.	^{90}Y-Ibritumomab Tiuxetan (n = 115*) %
No treatment given after PD	20	14	22	19
Treatment given after PD	128	86	93	81
Rituximab (single-agent or combination)	107	72	73	63
Autologous transplantation	34	23	19	17
Fludarabine, FC(M), FM	16	11	10	9
DHA(P)/DHA(Oxa)/ESHA(P)	13	9	10	9
^{90}Y-ibritumomab tiuxetan	12	8	1	1
Allogeneic transplantation	5	3	1	1
ICE	2	1	3	3
Bendamustine	2	1	3	3
Other†	12	8	15	13
	(n = 128)‡		(n = 93)‡	
Response to second-line therapy after PD				
ORR	101	79	75	81
CR/Cru	78	61	55	59
PR	23	18	20	22
SD	5	4	1	1
PD	2	2	2	2

Abbreviations: ^{90}Y, yttrium-90; CR, complete response; CRu, unconfirmed CR; DHA(Oxa), dexamethasone, cytarabine, oxaliplatin; DHA(P), dexamethasone, cytarabine, cisplatin; ESHA(P), etoposide, methylprednisolone, cytarabine, cisplatin; FC, fludarabine and cyclophosphamide; FM, fludarabine, mitoxantrone; ICE, ifosfamide, carboplatin, etoposide; M, mitoxantrone; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

*Number of patients with PD and follow-up data; patients may have received one or more treatments.

†Patients received another treatment and none of the above.

‡Number of patients who received treatment after PD.

Table 4. Second Malignancies That Emerged During Extended Follow-Up

Second Malignancy	Control (n = 202) No.	Control (n = 202) %	^{90}Y-Ibritumomab Tiuxetan (n = 207) No.	^{90}Y-Ibritumomab Tiuxetan (n = 207) %	Total (n = 409) No.	Total (n = 409) %
AML/MDS	1	0.5	7	3	8	2
Pancreas	—		3	1	3	1
Prostate	—		3	1	3	1
Other	13*	6	13†	6	26	6
Overall total (P = .086)	14	7	26	13	40	10

Abbreviations: ^{90}Y, yttrium-90; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

*Other for control includes adenocarcinoma of the stomach, basocellular carcinoma of the skin, basocellular epithelioma, Bowen's disease (squamous cell carcinoma), breast cancer, cancer coli, endometrial carcinoma, epidermoid carcinoma of the lower lip, intermediate differentiated adenocarcinoma, melanoma, papillary thyroid cancer, pulmonary adenocarcinoma, and squamous cell carcinoma of the lung.

†Other for ^{90}Y-ibritumomab includes adenocarcinoma of p-T1N0M0, basocellular carcinoma of the skin (two patients), basocellular epithelioma, breast cancer (two patients), colon cancer, invasive dural carcinoma left breast, lung cancer, spinocellular carcinoma left hilar (c-T4N0M0), spinocellular carcinoma of the facial skin, squamous cell carcinoma of the skin, and vesical transitional cell carcinoma TgGA-2.

further treatment (Fig 1). This significant PFS advantage persisted in patients who received ^{90}Y-ibritumomab while in CR/CRu after induction, with an estimated 8-year PFS of 48% (ie, 16% higher than in the control group) and also in patients with a PR after induction with an estimated 8-year PFS of 33% (ie, 23% higher than in the control group; Table 2).

Several studies have also demonstrated PFS improvements with rituximab maintenance therapy[4,15]; however, because of differences in study design, it is difficult to compare the data with the current FIT results. Perhaps the most appropriate comparator to FIT, in which only 14% of patients received rituximab as part of induction, may be the Eastern Cooperative Oncology Group (ECOG) 1496 study, in which 228 patients with previously untreated FL were induced with CVP without rituximab and were randomly assigned to either 16 infusions of rituximab maintenance (four cycles of rituximab every 6 months during a maximum of 2 years) or no further treatment. Strikingly, in such a comparison, both a consolidation with the ^{90}Y-ibritumomab tiuxetan regimen—which includes two rituximab infusions in addition to ^{90}Y-ibritumomab tiuxetan—and a maintenance strategy with 16 infusions of rituximab appear equally effective in terms of prolonging PFS (45 months with ^{90}Y-ibritumomab consolidation v 13.3 months in the control group; 51.6 months with rituximab maintenance v 15.6 months in the control group).[15]

Although the FIT study was not powered to demonstrate a significant difference in the relatively small rituximab chemotherapy subgroup, it is important to note that this long-term follow-up of the FIT study shows that the median PFS has not yet been reached (> 7.9 years) for patients receiving ^{90}Y-ibritumomab consolidation after a rituximab combination induction regimen, whereas it is 4.9 years in the control group (Table 2). The median PFS of 4.9 years (from random assignment) of rituximab chemotherapy–induced patients in the control arm in our study is similar to the median PFS of 5.5 years (from registration) achieved in the control arm of the GELA-GOELAMS FL2000 study with rituximab plus cyclophosphamide, doxorubicin, teniposide, and prednisone plus interferon (R-CHVP-IFN),[16] reinforcing confidence in our data. Although remaining statistically nonsignificant (8-year PFS, 56% v 45%; P = .36), this increased PFS after ^{90}Y-ibritumomab consolidation, which was not evident in the previous report,[11] suggests that ^{90}Y-ibritumomab may indeed improve PFS in patients after first-line rituximab chemotherapy induction.[16,17]

An important consideration in treating patients with indolent disease is the amount of time before second-line therapy is required and the patient's ability to respond to subsequent therapies. In FIT, ^{90}Y-ibritumomab significantly prolonged median TTNT by approximately 5.1 years compared with control, with a consistent 20% TTNT difference observed after 5 years from random assignment between the ^{90}Y-ibritumomab group and the control group (Fig 1D). The majority of patients in both groups received rituximab when treated after PD, and consolidation therapy with ^{90}Y-ibritumomab did not appear to rule out any second-line treatment approach, including harvesting an autologous stem-cell graft and subsequent autologous stem-cell transplantation (Table 3). Response rates to second-line therapy were 81% in the ^{90}Y-ibritumomab group (59% CR/CRu and 22% PR) and 79% in the

Table 5. Cytogenetics and Treatments Given After Relapse for Patients Who Developed MDS or AML

Patient	Induction	Relapse	Treatment After Relapse	MDS or AML Diagnosis	Cytogenetics
^{90}Y-ibritumomab tiuxetan					
1	FND	1st relapse	3 × R-ESHA(P), BEAM + ASCT	MDS → AML	−7
		2nd relapse	R-bortezomib		
2	Chlorambucil	At relapse	8 × R-CHOP/ESHA(P), BEAM + ASCT	MDS	−7
3	CVP	No relapse		MDS → AML	−7, del 5q
4	CVP	1st relapse	2 × 2.0 Gy	MDS → AML	−7, t(2;11), t(12;15), dic (16;17)
		2nd relapse	2 × 2.0 Gy		
		3rd relapse	DLBCL → 8 × R-CHOP		
5	Chlorambucil	No relapse		AML	No cytogenetic abnormalities
6	CF	At relapse	40 Gy involved-field radiotherapy	MDS	−7, del 5q, der (3;5), der (5;7), der (13;14)
7	CHOP	No relapse		MDS	−7; del 5q, 11q23, 17p
Control					
1	CHOP	1st relapse	5 × R-FC	MDS	t (1;4)
		2nd relapse	6 × R-CVP/^{90}Y-ibritumomab		
		3rd relapse	R-mono + 2 × R-bendamustine		

Abbreviations: ^{90}Y, yttrium-90; AML, acute myelogenous leukemia; ASCT, autologous stem-cell transplantation; BEAM, carmustine, etoposide, cytarabine, melphalan; CF, chlorambucil, fludarabine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; ESHA(P), etoposide, methylprednisolone, cytarabine, cisplatin; FC, fludarabine, cyclophosphamide; FND, fludarabine, mitoxantrone, dexamethasone; MDS, myelodysplastic syndrome; mono, monotherapy; R, rituximab.

control group (61% CR/CRu and 18% PR). Of note, 19% of patients who relapsed after ^{90}Y-ibritumomab did not receive any subsequent therapy compared with 14% in the control group. By restricting the analysis to patients with PD, the median time from PD until initiation of next treatment was 0.7 years for the control group versus 0.8 years for the ^{90}Y-ibritumomab group ($P = .263$). This does not suggest a more indolent relapse following ^{90}Y-ibritumomab.

Consistent with a recent report by Burnette et al,[18] the similar number of patients in each group shown here (22 ^{90}Y-ibritumomab, and 23 control) that transformed to higher-grade lymphoma suggests that ^{90}Y-ibritumomab does not have an impact on the risk of high-grade transformation.

The actuarial 8-year incidence of treatment-induced MDS or AML in FIT was 4.2% in the ^{90}Y-ibritumomab group, a rate similar to that reported in the Southwest Oncology Group (SWOG) S0016 study (3%) with iodine-131(^{131}I) -tositumomab consolidation after CHOP, with a shorter follow-up of 4.9 years,[19] but was also similar to the 3.3% incidence of MDS reported at a median follow-up of 9.5 years in the SAKK 35/98 trial which did not investigate radioimmunotherapy but rather reflects what can be expected in most patients with FL pre-treated with chemotherapy.[20] The annualized rate of MDS or AML in the ^{90}Y-ibritumomab arm of our study was 0.50% (95% CI, 0.24% to 1.06%) compared with 1.0% (95% CI, 0.4% to 1.7%) reported by Czuczman et al.[21] Still, the fact that all eight patients with secondary MDS/AML had received ^{90}Y-ibritumomab, either as first-line consolidation (seven patients) or subsequent treatment for PD (one patient in the control arm), suggests that this agent is associated with a risk of secondary MDS/AML.

In conclusion, long-term efficacy and safety evaluations from the FIT study suggest that first-line consolidation therapy with ^{90}Y-ibritumomab remains a highly valuable treatment option for patients with advanced FL. Treatment with ^{90}Y-ibritumomab conferred a durable PFS benefit and significantly prolonged TTNT, with no unexpected toxicities or second malignancies, providing patients with a longer time before experiencing PD or receiving second-line treatment. At the time of the follow-up analysis, there was no significant difference in OS between treatment groups, and the median OS had not yet been reached in either treatment group. Given the causes of death in each arm, our explanation for this lack of difference in OS is presumably that salvage treatment, with mostly rituximab-containing regimens, was effective in both arms.

Ongoing studies, such as the Spanish PETHEMA Cooperative Group study, which compares the benefits of administering ^{90}Y-ibritumomab or rituximab maintenance after rituximab-containing first-line induction regimens in patients with previously untreated FL,[22] will provide more insight into the safety and efficacy of both strategies after rituximab-containing first-line induction regimens and help better assess the importance of treatment options achieving higher CR/CRu rates, such as with ^{90}Y-ibritumomab in this setting.

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.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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Appendix

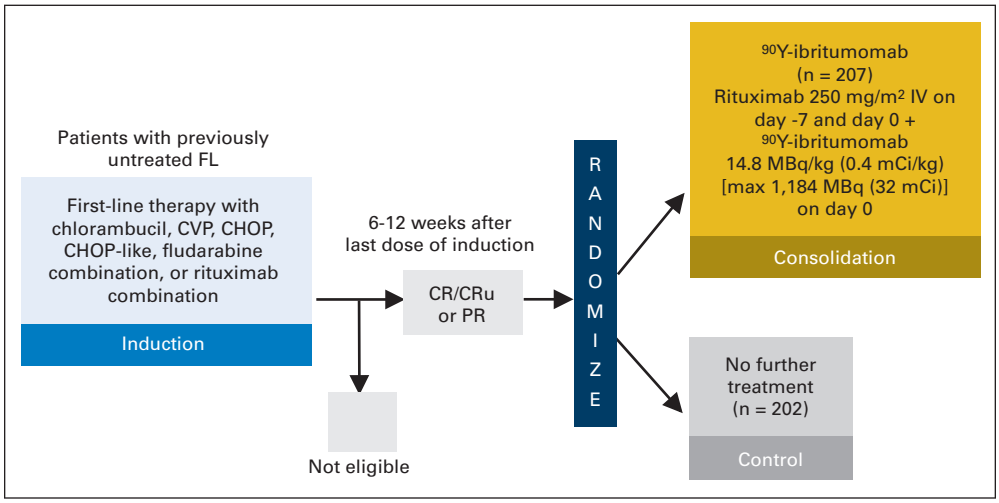

Fig A1. First-Line Indolent Trial study schema. ^{90}Y, yttrium-90; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CRu, unconfirmed CR; CVP, cyclophosphamide, vincristine, prednisone; FL, follicular lymphoma; IV, intravenously; PR, partial response.

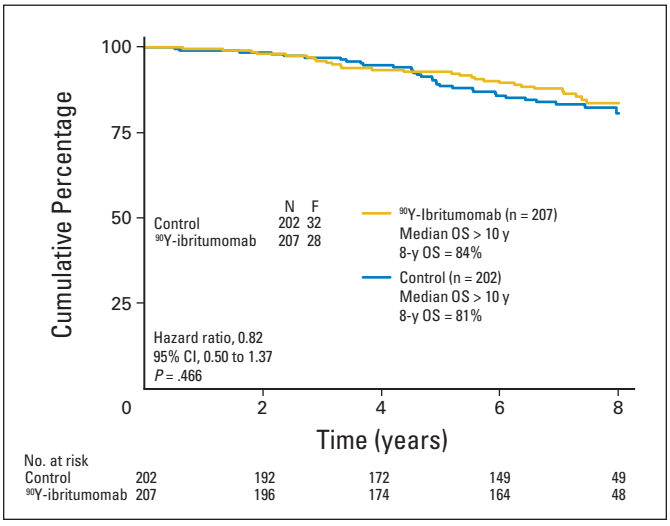

Fig A2. Overall survival (OS). ^{90}Y, yttrium-90; N, number of patients at risk; F, failure (defined as number of patients who relapsed or died [progression-free survival] and number of patients who started a new treatment [time to next treatment]).