

Yttrium 90-Ibritumomab Tiuxetan Plus Rituximab Maintenance as Initial Therapy for Patients With High-Tumor-Burden Follicular Lymphoma: A Wisconsin Oncology Network Study

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Abstract: *Introduction:* Yttrium 90-ibritumomab tiuxetan (⁹⁰Y-IT) radioimmunotherapy has proved to be effective in relapsed follicular lymphoma (FL). We conducted a clinical trial in which ⁹⁰Y-IT followed by maintenance rituximab (MR) was evaluated as initial therapy for high-tumor-burden FL. *Methods:* Eligible patients had histologically confirmed FL and met the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria for high tumor burden. All patients received a single dose of ⁹⁰Y-IT. Patients with platelet counts of 150,000/mm³ or higher received 0.4 mCi/kg, and patients with platelet counts between 100,000/mm³ and 149,000/mm³ received 0.3 mCi/kg. At 6 months, patients without progressive disease (PD) received rituximab weekly for 4 weeks at a dose of 375 mg/m² (consolidation therapy), followed by MR consisting of the same dose every 3 months for a planned 5 years. *Results:* From January 2005 through November 2007, a total of 16 patients were enrolled. The median age was 52 years (range, 37-75). The major toxicity from ⁹⁰Y-IT was myelosuppression, with 88% and 31% of the patients experiencing grade 3 and grade 4 hematologic toxicity, respectively. The responses to ⁹⁰Y-IT induction therapy were as follows: 7 patients with complete response/unconfirmed complete response (CR/Cru), 4 with partial response (PR), 3 with stable disease (SD), and 2 with progressive disease (PD). We identified 6 patients with early PD (range, 4-16 months) and 10 patients with prolonged remission (range, 37-101+ months). Compared with the patients who had prolonged remission, the patients who had early PD tended to have larger baseline nodal masses. The median progression-free survival (PFS) has not been reached after a median follow-up period of 48 months. The 3-year PFS and overall survival (OS) rates were 56% (95% CI, 37%-87%) and 93% (95% CI, 80%-100%), respectively. *Conclusion:* The overall response rate (ORR) to ⁹⁰Y-IT was 69% in patients who had previously untreated, high-tumor-burden FL, which is lower than what

is observed with contemporary rituximab/chemotherapy combinations. MR after ^{90}Y -IT did convert all PRs to CRs. Alternative therapies should be considered for patients who have FL with large nodal masses (≥ 9 cm), whereas very durable responses are possible in patients who have intermediate-size masses (< 9 cm).

Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL), accounting for approximately 22% of new cases of NHL, and is typically characterized by a slowly progressive course with inevitable relapses.¹ There is no consensus frontline therapy for FL. Multiple regimens are considered appropriate, ranging from involved-field radiotherapy or single-agent rituximab (Rituxan, Genentech/Biogen Idec) for patients with a low tumor burden to combination chemotherapy plus rituximab for those with a high tumor burden.² Patients meeting any one of the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria are defined as having high-tumor-burden disease, which is associated with lower rates of progression-free survival (PFS) and overall survival (OS).³⁻⁵

In high-tumor-burden FL, rituximab plus cytotoxic chemotherapy has been shown to improve both PFS and OS in comparison with chemotherapy alone.⁶⁻⁸ According to the National LymphoCare Study database, between 2004 and 2007, the most commonly used induction regimens were rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; 55%), rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP; 23%), and R-fludarabine-based regimens (16%).⁹ However, a significant percentage of patients with FL are elderly with multiple comorbidities, so that it is often difficult for them to tolerate multiple-agent chemotherapy and its numerous side effects. This problem has led to interest in developing more tolerable induction strategies.

Radioimmunotherapy (RIT), consisting of a radioisotope conjugated to an anti-CD20 antibody, is an attractive strategy if one desires to minimize short-term treatment-related side effects. The treatment can be completed in 1 week. Myelosuppression is the major treatment-related toxicity, and patients are generally spared significant extramedullary toxicities, such as nausea/vomiting, asthenia, and peripheral neuropathy. The 2 agents approved in the United States are iodine 131-tositumomab (^{131}I -tositumomab; Bexxar, Glaxo-SmithKline; discontinued) and yttrium 90-ibritumomab tiuxetan (^{90}Y -IT; Zevalin, Spectrum Pharmaceuticals). Both agents are approved in the United States for use in relapsed/refractory FL based upon trials showing overall response rates (ORRs) of 65% to 83% and durations of response ranging from 8.7 months to more than 24 months.¹⁰⁻¹⁴

Although response rates to RIT are high, the responses are not always durable. Maintenance strategies may improve the response duration after RIT. Maintenance rituximab (MR) has been shown in several studies to improve PFS, with an acceptable toxicity profile, in FL.¹⁵⁻¹⁸ Most trials have arbitrarily selected an MR duration of 2 years. Whether MR for a longer period is safe or improves the duration of remission is unknown.

Given the tolerability and effectiveness of ^{90}Y -IT in the setting of relapsed/refractory disease, as well as the lack of data for MR beyond 2 years, investigators within the Wisconsin Oncology Network (a collaboration between the University of Wisconsin Carbone Cancer Center and several community-based practices) sought to conduct a trial of "chemotherapy-free" treatment for patients with high-tumor-burden FL. Herein, we report the results of a prospective study of ^{90}Y -IT plus MR for 5 years in such patients.

Patients and Methods

Eligibility Criteria

Eligible patients had biopsy-proven grade 1, 2, or 3 FL and met the GELF criteria for high tumor burden, which consisted of any one of the following: nodal or extranodal mass 7 cm or larger, 3 (or more) nodal masses larger than 3 cm in diameter, any systemic B symptoms, splenomegaly larger than 16 cm on computed tomography (CT) scan, and risk of compression of a vital organ. Other eligibility criteria included the following: no prior chemotherapy, radiotherapy, or immunotherapy; age 18 years or older; measurable disease (mass/lesion ≥ 1.5 cm in diameter); no history of HIV infection or hepatitis B; no prior history of malignancy; white blood cell (WBC) count $3000/\text{mm}^3$ or higher; absolute neutrophil count (ANC) $1500/\text{mm}^3$ or higher; hemoglobin concentration 10 g/dL or higher; platelet count $100,000/\text{mm}^3$ or higher; serum creatinine level 2 times the upper limit of normal (ULN) or lower; total bilirubin level 2 times the ULN or lower; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) level 5 times the ULN or lower; Eastern Cooperative Oncology Group (ECOG) performance status 0 through 2; no active or uncontrolled infections; less than 25% bone marrow involvement with lymphoma and more than 15% overall bone marrow cellularity within 42 days of registration; absence of cytogenetic abnormalities compatible with myelodysplastic syndrome or dysplastic bone marrow by morphology; no granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) within 2 weeks before IT administration and no pegylated G-CSF within 4 weeks before administration; and no documented central nervous system lymphoma. Eligible women could not be pregnant or breast-feeding.

Treatment Schedule: Ibritumomab Tiuxetan

All patients initially received rituximab at 250 mg/m² followed immediately by 1.6 mg of indium 111–ibritumomab tiuxetan (¹¹¹In-IT) for the purpose of biodistribution imaging. Any patients with altered biodistribution were not eligible to receive ⁹⁰Y-IT. For those patients with appropriate biodistribution, a second rituximab infusion at 250 mg/m² was administered 1 week later, followed immediately by ⁹⁰Y-IT. If the baseline platelet count was 150,000/mm³ or higher, ⁹⁰Y-IT was administered at 0.4 mCi/kg. If the baseline platelet count was 100,000/mm³ to 149,000/mm³, ⁹⁰Y-IT was administered at 0.3 mCi/kg. The maximum allowable dose was 32 mCi.

Treatment Schedule: Rituximab

Patients with documented complete response/unconfirmed complete response (CR/CRu), partial response (PR), or stable disease (SD) 24 weeks after ⁹⁰Y-IT administration went on to receive rituximab consolidation at a dose of 375 mg/m² weekly for 4 weeks, followed by a course of MR. This consisted of a single dose of rituximab at 375 mg/m² administered every 3 months for a total of 5 years (20 doses in total). MR was to be discontinued for treatment-related adverse effects or PD.

Patient Evaluation and Response Criteria

Disease was re-staged with CT of the neck, chest, abdomen, and pelvis at weeks 6, 12, and 24. Patients underwent a second bone marrow biopsy at 24 weeks. During rituximab maintenance, the patients underwent CT before odd-numbered cycles (every 6 months). Response criteria were according to the 1999 report of an international workshop to standardize response criteria for non-Hodgkin’s lymphomas.¹⁹

Statistical Methods

The primary endpoint of this prospective study was to determine the median PFS. Secondary endpoints included an estimation of the best CR rate and ORR, estimation of the CR and CRu rates at 6 months (assessing IT), and recording the toxicities associated with this regimen. The calculated sample size (N=36) was based on a z test comparing the logarithm of the hazard ratio with an anticipated increase in the median PFS from 24 months (null hypothesis) to 45 months, an accrual period of 24 months with a follow-up period of 12 months, and a 1-sided significance level of 0.10. PFS was analyzed with the Kaplan-Meier method.²⁰ The Kaplan-Meier curve was generated along with the corresponding 95% CI band. The CR rate and ORR were reported in tabular format along with the corresponding 95% CIs, which were calculated with the Agresti-Coull method. Statistical analysis was conducted with SAS software version 9.3 (SAS Institute, Cary, North Carolina).

Table 1. Baseline Characteristics (N=16)

	Median	Range
Age, y	52	37-75
Hemoglobin, g/dL	13.7	11.9-17.5
	No.	Percentage
Stage of disease		
III	7	44
IV	9	56
FLIPI		
1	3	19
2	7	44
3	4	25
4	2	12
Performance status		
0	4	25
1	12	75
Bone marrow		
Negative	7	44
Positive	9	56
Elevated LDH	6	38
Nodal mass ≥5 cm	8	50
Nodal mass ≥9 cm	5	31

FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase.

Results

Clinical Characteristics

Between January 2005 and November 2007, a total of 16 eligible patients were enrolled. The protocol was closed May 2008 because of slow accrual (planned N=36). The baseline characteristics are shown in Table 1. The median age was 52 years, 9 patients were male, 7 patients had stage III disease, and 9 patients had stage IV disease. The Follicular Lymphoma International Prognostic Index (FLIPI) score distribution was 19% low, 44% intermediate, and 37% high. Figure 1 shows the treatment schema and therapies delivered for all 16 eligible patients.

Toxicity

The major grade 3 and 4 toxicities from ⁹⁰Y-IT are shown in Table 2. The major toxicities from ⁹⁰Y-IT were expected myelosuppression, with 88% and 31% of the patients experiencing grades 3 and 4 hematologic toxicity, respectively. The median nadir was 752/mm³ for the ANC, 46,000/mm³ for the platelet count, and 11.5 g/dL for the hemoglobin level. The median durations of grade 3 and grade 4 toxicities were 2.5 weeks (range, 1-7) and 1 week (range, 1-2), respectively. Transfusions were required for 4 of the patients, and 4 patients received growth factors. One patient developed myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). This patient achieved a best response

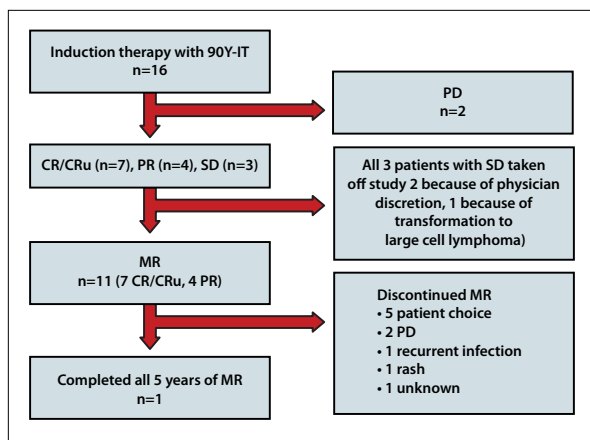


Figure 1. Treatment schema.

CR, complete response; CRu, unconfirmed complete response; IT, ibritumomab tiuxetan; MR, maintenance rituximab; PD, progressive disease; PR, partial response; SD, stable disease.

of SD after induction with ⁹⁰Y-IT and was subsequently treated with R-CHOP; rituximab, ifosfamide, carboplatin, and etoposide (R-ICE); and bendamustine (Treanda, Teva). MDS/AML was detected at 29 months after ⁹⁰Y-IT treatment. The major grade 3 and 4 toxicities from MR were expected lymphopenia, with common grade 1 and 2 toxicities including fatigue and infection.

Response

All 16 patients were evaluable for response. After induction therapy with ⁹⁰Y-IT, 7 patients achieved a CR/CRu, 4 patients achieved a PR, 3 patients had SD, and 2 patients had PD, for an ORR of 69% (Table 3). A total of 11 patients (7 CR/CRu, 4 PR) went on to receive consolidation and MR (median number of cycles, 10; range, 3-20). None of the 3 patients with SD received MR (2 patients were taken off study because of physician discretion and 1 patient because of transformation to large cell lymphoma). All 4 patients with PR achieved a CR/CRu during maintenance treatment, with 3 of those 4 patients experiencing durable responses of 39 to 101+ months. The median PFS has not yet been reached after a median follow-up of 48 months. Given our low accrual rate, we were unable to demonstrate a statistically significant increase in the median PFS, as stated in the original null hypothesis. The 3-year PFS and OS rates were 56% (95% CI, 37%-87%) and 93% (95% CI, 80%-100%) respectively (Figures 2 and 3). Durable responses (range, 37-101+ months) were obtained in 10 patients, while 6 patients had early PD (range, 4-16 months). The baseline nodal masses of the patients who had early PD tended to be larger than those of the patients who had durable responses, with a median longest diameter of the largest involved node (LoDLIN) of 10.3 cm (6.8-11.4 cm) vs

Table 2. Grade 3 and 4 Toxicities After Radioimmunotherapy

Toxicity	Grade 3	Grade 4
White blood cell count	9	1
Absolute neutrophil count	6	2
Platelet count	6	1
Leukopenia	3	–
Neutropenia	1	–
Anemia	1	–
Thrombocytopenia	1	1
Infection	1	–

Table 3. Summary of Responses

Response	No.	Percentage	95% CI
CR/CRu	7	44%	23%-67%
PR	4	25%	10%-50%
SD	3	19%	6%-44%
PD	2	13%	3%-36%
Overall response	11	69%	44%-86%

CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; PD, progressive disease; PR, partial response; SD, stable disease.

median LoDLIN of 5.7 cm (3.0-8.2 cm). All 5 patients with baseline masses 9 cm or larger experienced early PD, whereas 10 of 11 patients with masses smaller than 9 cm experienced prolonged remissions (≥36 months). There were no instances of altered biodistribution of ¹¹¹In-IT.

Rituximab Levels

Rituximab levels were measured 3 months after consolidation rituximab (just before the first MR dose) and again 9 months after consolidation rituximab (just before the fourth MR dose). The mean levels (with ranges) were 67.4 µg/mL (12-303 µg/mL) and 9 µg/mL (3.1-25.7 µg/mL), respectively. Large interpatient variability was observed (Table 4). Because of the small numbers, the levels could not be correlated with tumor burden or response.

Discussion

The Wisconsin Oncology Network undertook a prospective study of ⁹⁰Y-IT plus MR in the frontline setting in patients with high-tumor-burden FL. A total of 16 patients were enrolled and evaluable for response. After induction therapy with ⁹⁰Y-IT, we observed an ORR of 69% (44% CR/CRu, 25% PR).

Since the completion of this study, it has been shown that the earlier use of RIT (ie, in the second-line setting) results in higher response rates and longer response durations than does its use later in the disease course.²¹ Subsequently,

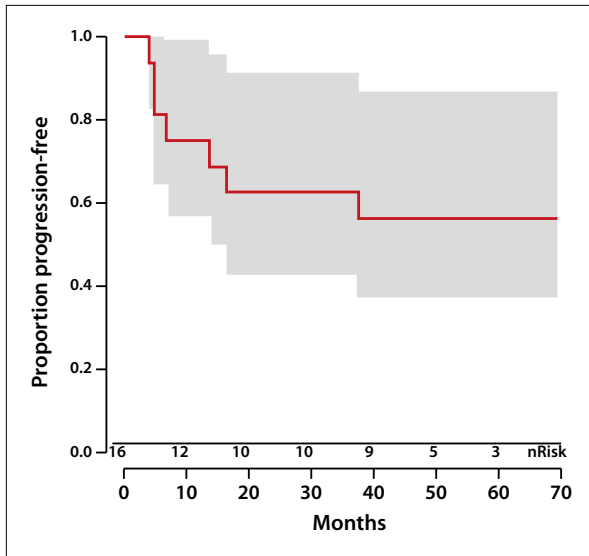


Figure 2. Kaplan-Meier curve for progression-free survival with 95% confidence interval band.

nRisk, number of patients at risk for progression/event.

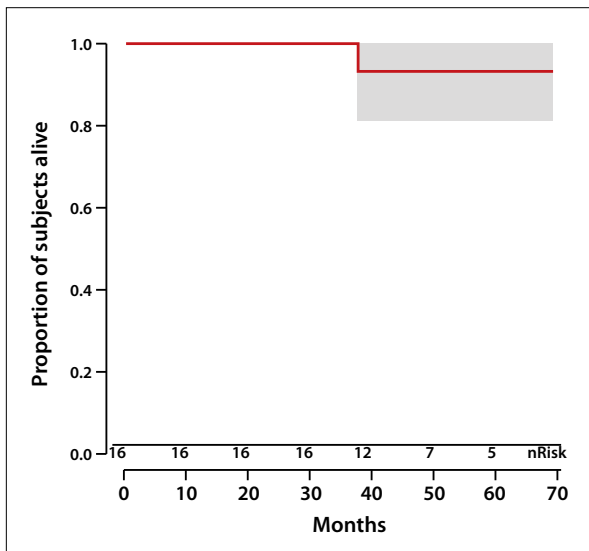


Figure 3. Kaplan-Meier curve for overall survival with 95% confidence interval band.

nRisk, number of patients at risk for progression/event.

several studies have been published looking at RIT in the frontline setting in FL. Kaminski and colleagues first reported on RIT (¹³¹I-tositumomab) in the frontline setting for FL and found an ORR of 95% (75% CR, 20% PR); however, only 43% of the patients had masses 5 cm or larger, and it is unclear how many patients had masses larger than 9 cm.²² Scholz and colleagues subsequently performed a study of ⁹⁰Y-IT as first-line therapy in FL and had an ORR of 87% (56% CR/CRu and 31% PR); however, again only 31% of the patients had tumors larger than 5 cm.²³ Our ORR of 69% is clearly much lower than the rates achieved in these studies.

Table 4. Rituximab Levels

Patient No.	Level Before MR Dose 1, µg/mL	Level Before MR Dose 4, µg/mL
1	48.7	9.2
2	22.7	Missing
4	26.6	5.4
6	12.0	Missing
7	47.1	12.7
8	61.3	14.0
9	38.3	9.0
12	303.0	25.7
13	Missing	3.1
14	17.8	5.7
16	96.6	Missing
Mean	67.4	9.0

MR, maintenance rituximab.

A potential reason for this result may be that most of our patients had large (>5 cm) baseline nodal masses; we did find that all patients with tumor masses 9 cm or larger had early progression, whereas almost all patients with tumor masses smaller than 9 cm experienced durable responses.

Despite our low ORR, we did find that 10 of the 16 patients (36%) achieved highly durable responses (37-101+ months). It has been reported that a response to ⁹⁰Y-IT lasting at least 12 months might be a sign of durability; however, this hypothesis was not tested here, given that all patients who responded received consolidation and MR.²⁴ The median PFS of 25.9 months reported by Scholz and colleagues is lower than the median PFS in our study. This may be explained by the use of rituximab following induction therapy in our study, which has been shown to improve PFS after standard chemotherapy.¹⁵⁻¹⁸ This study was powered to detect an increase in PFS from 24 months to 45 months; however, because the original accrual goal of 36 patients was not met, we did not observe a statistically significant increase in PFS.

A concern with RIT, given the high rates of myelosuppression, is that patients receiving RIT are not able to receive subsequent therapies at the time of progression because of persistent cytopenias; however, it has been shown that patients can receive future therapies, including stem cell transplant.^{25,26} Of the 16 patients in our current study, 6 patients required subsequent treatment for PD. These therapies included R-CHOP and R-bendamustine. Of these 6 patients, 5 were able to receive 4 to 6 cycles of therapy. The 1 patient who had subsequent treatments complicated by significant cytopenias went on to develop therapy-related MDS/AML, which is a known, albeit uncommon, consequence of RIT.^{27,28} This patient also had received R-CHOP, R-ICE, and bendamustine before the development of MDS/AML.

At the time this study was developed, it was known that MR after standard chemotherapy improved PFS, but it was unclear if this still held true after induction with rituximab plus chemotherapy. This was answered in the PRIMA (Primary Rituximab and Maintenance) trial, in which patients with untreated advanced FL who responded to initial treatment with rituximab chemotherapy were randomly assigned to 2 years of MR or observation. The 2-year PFS was 75% in the MR arm vs 58% in the observation arm ($P < .0001$).²⁹ The question of whether extending MR beyond 2 years provides additional benefit was addressed in the SAKK (Swiss Group for Clinical Cancer Research) 35/03 trial. Patients with untreated, relapsed, or stable FL were treated with an initial 4-week induction course of rituximab. This was followed by randomization to a short maintenance arm (4 administrations every 2 months, maximum of 8 months) or a prolonged maintenance arm (maximum of 5 years or until PD). The study did not reveal any undue toxicity in the prolonged arm. The primary endpoint of event-free survival (EFS) was not met because of an early separation in the EFS curves at a time when the treatment was the same in both arms (ie, during the first 8 months of MR). However, when a retrospective analysis was done looking at EFS after 8 months, it was significantly longer in the prolonged arm.³⁰ Given the inconclusive results of the SAKK study and the inability of most of our patients to complete the 5-year MR plan, prolonged MR cannot be recommended at this time. Of note, only 1 of our patients on MR maintained a rituximab trough level above 25 $\mu\text{g}/\text{mL}$, which has correlated with improved patient response in comparison with lower levels.³¹ This observation suggests that a dosing interval of every 2 months may be preferable in high-tumor-burden FL.

We speculated that a “chemotherapy-free” regimen would be attractive to patients and treating physicians. However, this trial suffered from slow accrual, presumably due to the lack of enthusiasm for RIT, and it was closed early. Recently, 2 large randomized trials using ¹³¹I-tositumomab failed to show benefit for RIT in comparison with rituximab plus chemotherapy.^{32,33} Given sluggish sales and a continued struggle to find a well-defined place for ¹³¹I-tositumomab in the management of lymphoma, it was pulled from the US market in early 2014, although ⁹⁰Y-IT still remains an available treatment option in both the frontline and relapsed/refractory setting for patients with FL.

In conclusion, RIT with ⁹⁰Y-IT achieved a lower response rate than standard immunochemotherapy regimens for patients with high-tumor-burden FL. ⁹⁰Y-IT treatment should not be considered for patients with large tumor masses (≥ 9 cm), whereas highly durable responses are possible in patients with small or intermediate tumor masses (< 9 cm), especially when ⁹⁰Y-IT is combined with MR.

Disclosures

Dr Kahl is a consultant for and has received research funding from Genentech and Roche. The other authors have declared no relevant conflicts of interest.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997;89(11):3909-3918.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology for Non-Hodgkin's Lymphomas. v.1.2013. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Updated January 2013. Accessed July 29, 2013.
3. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15(3):1110-1117.
4. Solal-Céligny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. *J Clin Oncol*. 1998;16(7):2332-2338.
5. Decaudin D, Lepage E, Brousse N, et al. Low-grade stage III-IV follicular lymphoma: multivariate analysis of prognostic factors in 484 patients—a study of the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1999;17(8):2499-2505.
6. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106(12):3725-3732.
7. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105(4):1417-1423.
8. Herold M, Haas A, Srock S, et al; East German Study Group Hematology and Oncology Study. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *J Clin Oncol*. 2007;25(15):1986-1992.
9. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the National LymphoCare Study. *J Clin Oncol*. 2009;27(8):1202-1208.
10. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 1999;17(12):3793-3803.
11. Wiseman GA, Gordon LI, Multani PS, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin's lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood*. 2002;99(12):4336-4342.
12. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20(15):3262-3269.
13. Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2004;22(8):1469-1479.
14. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol*. 2005;23(4):712-719.
15. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006;24(19):3121-3127.
16. Hochster HS, Weller EA, Ryan T, et al. Results of E1496: a phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL). *J Clin Oncol*. 2004;22:558.
17. Ghielmini M, Schmitz SFH, Cogliatti S, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood*. 2004;103(12):4416-4423.
18. Hainsworth JD, Litchy S, Burris HA III, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20(20):4261-4267.

19. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol.* 1999;17(4):1244.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc.* 1958;53(282):457-481.
21. Emmanouilides C, Murray JL, Vo K, et al. Earlier treatment with yttrium 90 ibritumomab tiuxetan (Zevalin) radioimmunotherapy is associated with higher response rates and longer durations of response in patients with previously treated B-cell non-Hodgkin's lymphoma (NHL): results with second-line therapy [ASH abstract 4949]. *Blood.* 2003;102:306b.
22. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med.* 2005;352(5):441-449.
23. Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. *J Clin Oncol.* 2013;31(3):308-313.
24. Wiseman GA, Witzig TE. Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) induces long-term durable responses in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Cancer Biother Radiopharm.* 2005;20(2):185-188.
25. Ansell SM, Ristow KM, Habermann TM, Wiseman GA, Witzig TE. Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol.* 2002;20(18):3885-3890.
26. Dosik AD, Coleman M, Kostakoglu L, et al. Subsequent therapy can be administered after tositumomab and iodine I-131 tositumomab for non-Hodgkin lymphoma. *Cancer.* 2006;106(3):616-622.
27. Bennett JM, Kaminski MS, Leonard JP, et al. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine I131 tositumomab. *Blood.* 2005;105(12):4576-4582.
28. Czuczman MS, Emmanouilides C, Darif M, et al. Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. *J Clin Oncol.* 2007;25(27):4285-4292.
29. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet.* 2011;377(9759):42-51.
30. Taverna MD, Martinelli G, Hitz F, et al. Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: results of the randomized phase III trial SAKK 35/03 [ASH abstract 508]. *Blood.* 2013;122(21)(suppl):508.
31. Berinstein NL, Grillo-López AJ, White CA, et al. Association of serum rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol.* 1998;9(9):995-1001.
32. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131) iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. *J Clin Oncol.* 2013;31(3):314-320.
33. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial. *J Clin Oncol.* 2013;31(13):1662-1668.