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ORIGINAL REPORT

Watchful Waiting in Low–Tumor Burden Follicular Lymphoma in the Rituximab Era: Results of an F2-Study Database

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ABSTRACT

Purpose
Patients with follicular lymphoma (FL) registered in the F2-study and initially managed without treatment were analyzed to describe the presentation and outcome of a watch and wait (W&W) strategy in the rituximab era, to identify parameters for initiating treatment, and to evaluate whether initial W&W could have deleterious effects on treatment efficacy after progression or relapse.

Patients and Methods
Between 2003 and 2005, 120 patients selected from the 1,093 treatment-naive patients with FL in the F2-study cohort were initially managed expectantly (W&W), and 107 patients were assessed. Most of these patients (80%) had disseminated disease with a low tumor burden according to Groupe d'Etudes des Lymphomes Folliculaires criteria.

Results
After a median follow-up of 64 months, treatment was initiated in 54 patients (50%), with a median delay of 55 months for the entire cohort. In a univariate analysis, involvement of more than four nodal areas (hazard ratio [HR], 2.26) and serum albumin less than 3.5 g/dL (HR, 3.51) were predictive of a shorter time to lymphoma treatment initiation. In a multivariate analysis, only involvement of more than four nodal areas remained significant (HR, 2.32). The 4-year freedom from treatment failure (FFTF) rate of W&W patients (79%; 95% CI, 69% to 85%) was not inferior to that of a subgroup of 242 patients from the F2-study cohort with good prognosis characteristics who were initially treated with a rituximab-based regimen (69%; 95% CI, 61% to 76%; $P = .103$).

Conclusion
In the rituximab era, patients with FL in a selected prognostically favorable group can still be managed with W&W. W&W does not seem to have detrimental effects on FFTF and overall survival rates after treatment.

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INTRODUCTION

The management of patients with clinically nonaggressive follicular lymphoma (FL) is still a matter of debate. Several retrospective analyses have suggested that an initial watch and wait (W&W) period is feasible in selected patients, because it does not seem to have deleterious effects on prognosis. In 43 patients with localized disease (Ann Arbor stages I and II), 27 patients were not treated at a median follow-up of 86 months, and 16 patients required treatment after a median delay of 22 months.[1] In 83 patients with advanced disease who were initially managed by the Stanford group without therapy, 51 patients required therapy after a median delay of 3 years.[2] The Stanford group extended their experiments with an initial no treatment policy to a group of 314 patients with similar results.[3]

Three randomized trials have prospectively compared W&W until clinically significant progression versus immediate chemotherapy with an intensive regimen,[4] with chlorambucil,[5] or with either prednimustine or interferon alfa[6] in patients with indolent lymphoma (mostly FL). No significant difference in overall survival (OS) between W&W until progression and immediate chemotherapy was observed in any of these trials. Moreover, some patients

could remain free of treatment for a long time (10 years for 19% of patients in one of these trials).[5]

In the era of anti-CD20 monoclonal antibodies, some investigators advocate the immediate treatment of all patients with FL because reaching a complete remission results in improved OS[7]; some active treatments, such as rituximab given alone, are well tolerated and may improve long-term progression-free survival (PFS)[8]; and rituximab-based treatments have largely improved the prognosis of FL,[9] whereas chemotherapy only, such as in the previously mentioned randomized trials, did not clearly modify the natural course of the disease.[3] Recently, preliminary results of a randomized trial comparing W&W versus rituximab (in a population of patients similar to those reported herein) with or without maintenance have shown that treatment with rituximab, especially if followed by rituximab maintenance, delayed time to next lymphoma treatment.[10]

In 2003, the International Follicular Lymphoma Prognostic Factor Project launched the F2-study, a prospective collection of clinical, pathologic, biologic, and therapeutic parameters of patients with FL to prospectively validate the Follicular Lymphoma International Prognostic Index (FLIPI)[11] and to propose an accurate and up-to-date index for PFS. More than 1,000 patients were included. A new prognostic index for PFS, the FLIPI2, has been proposed for initially treated patients based on the F2-study.[12] We report herein on the clinical characteristics, evolution, and prognostic parameters influencing treatment initiation and response to this treatment in the subgroup of patients who were initially monitored without treatment and were therefore excluded from the initial FLIPI2 analysis.

PATIENTS AND METHODS

The inclusion criteria for registration in the prospective F2-study have been previously detailed.[12] Briefly, all patients with pathologically confirmed FL of grade 1 to 3a according to the WHO 2001 classification[13] were included irrespective of age, Ann Arbor stage, comorbidities, and planned therapeutic approach. The decision on whether to treat patients immediately or not and the choice of treatment modalities were made by the responsible physician at each participating center. The Executive Committee proposed an initial W&W approach in patients with advanced disease and low tumor burden according to Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria,[6] modified with respect to bulky disease definition[12]; specific criteria for these patients were as follows: asymptomatic disease; involvement of less than three nodal sites with a diameter of more than 3 cm; no substantial splenic enlargement; no serous effusion; absence of local risk of compression (epidural, ureteral, and so on); no leukemia or blood cytopenia; and absence of a bulky tumor mass (longest diameter $>$ 10 cm for nodal tumors and $>$ 6 cm for mediastinum).

Patients were considered to be initially untreated if no treatment other than diagnostic excisional biopsy was given during the first 3 months after diagnosis. Initial staging was performed using conventional methods that did not include positron emission tomography scan. All patients were observed according to the institutional guidelines of each center. There was no standardization of computed tomography scan evaluation.

This study was conducted in accordance with good clinical practice rules. Data were collected via a dedicated Secure Sockets Layer–protected Web site.

We examined two primary end points in this study. First, for W&W patients, we analyzed time to initiation of a lymphoma treatment (TLT). This time was defined as the period between diagnosis and initiation of immunotherapy, chemotherapy, or radiation therapy. The reasons for initiating therapy were categorized as progression (pain, "B" symptoms, or significant tumor growth as demonstrated by clinical examination or imaging techniques), histologic transformation (eg, evolution from FL to grade 3b FL or diffuse large-cell lymphoma), physician decision, or patient request.

Second, to test the hypothesis that a W&W approach could have deleterious effects on outcome, we analyzed freedom from treatment failure (FFTF) and compared the group of patients initially managed with W&W with a subgroup of 242 patients extracted from the F2-study population who had good prognostic features (ie, a low tumor burden according to the GELF criteria) and whose initial treatment included rituximab. FFTF was defined as the time from diagnosis until occurrence of one of the following: progression during treatment, salvage treatment initiation, relapse, or death from any cause.[14] In the W&W group, initiation of first treatment was not considered as an event. With this method, we could compare the whole time lag from diagnosis to a similar end point (ie, failure of treatment initiated after W&W or failure after an initial treatment in patients with FL and a good prognosis). OS was measured from the date of diagnosis until death from any cause. TLT, FFTF, and OS were estimated using the Kaplan-Meier method.[15] Categories were compared using Cox proportional hazards regression[16] both in univariate and multivariate analyses. Continuous biologic covariates were dichotomized according to usual thresholds. Variables were compared using Fisher's exact test for categorical covariates and the Mann-Whitney *U* test for continuous covariates. For this study, we did not plan any sample size, and all *P* values were two-sided. All analyses were performed using Stata Statistical Software release 10 (StataCorp, College Station, TX).

RESULTS

Between January 2003 and May 2005, 1,093 patients were included in the F2-study.[12] One hundred thirty-four patients (12%) initially monitored without treatment were not included for the purpose of compiling the FLIPI2 prognostic index for PFS.[12] Fourteen of these patients were not eligible for analysis because of a lack of data, leaving 120 patients. Of the 120 patients, five (4%) were excluded for the following reasons: unconfirmed diagnosis of FL (n = 4) and diagnosis made before the starting date of the study (n = 1). Among the remaining 115 patients, follow-up was not obtained after completion of baseline information in seven patients, and one patient was not treated because of severe comorbidities. Thus, 107 patients were included in the analysis. Their clinical and biologic characteristics are listed in Table 1 and compared with those of the 242 patients from the F2-study population who had low tumor burden according to the criteria described in Patients and Methods and who were initially treated with rituximab-containing regimens. The distribution of patients according to FLIPI and FLIPI2 is also shown.

After a median follow-up of 64 months (range, 3 to 89 months), treatment was started in 54 patients (50%). The median TLT for these patients was 14 months; for the entire cohort of 107 W&W patients, the median time of observation without therapy has been 55 months (Fig 1). The reasons for initiating treatment were known in 52 of 54 patients and included progression (n = 44, 85%), transformation (n = 2, 4%), and physician decision or patient request (n = 6, 11%). A univariate analysis of prognostic parameters present at the time of diagnosis that significantly influenced the TLT was performed. All parameters listed in Table 1 were included in this analysis. Involvement of more than four nodal sites (hazard ratio [HR], 2.26; 95% CI, 1.17 to 4.4; $P = .016$) and serum albumin level less than 3.5 g/dL (HR, 3.51; 95% CI, 1.25 to 9.87; $P = .017$) were associated with a shorter TLT. In the multivariate analysis, only the involvement of more than four nodal sites significantly correlated with TLT (HR, 2.32; 95% CI, 1.19 to 4.52; $P = .013$). Neither the FLIPI nor the FLIPI2 correlated with TLT. However, when dichotomizing between low/intermediate- and high-risk groups, the FLIPI2 significantly correlated with TLT (HR, 2.13; 95% CI, 1.02 to 4.46; $P = .044$; Fig 2).

Table 1. Initial Demographics and Clinical Characteristics of W&W Patients and of Patients With Low–Tumor Burden FL Treated Initially With Rituximab-Containing Regimens

Demographic or Clinical Characteristic	W&W Patients (n = 107) No. of Patients	W&W Patients (n = 107) %	% of Treated Patients With Low Tumor Burden (n = 242)	P*
Age, years				
Median	59		56	.196
Range	33-94		23-83	
≤ 60	57	54	61	.239
Male sex	52	49	50	.908
Histologic grade				.009
1	43	40	28	
2	52	49	48	
3	9	8	22	
Unspecified	3	3	2	
Serum LDH > UNL (n = 105)†	6	6	0	.001
Ann Arbor stage III-IV	90	84	74	.039
No. of nodal sites > 4	13	12	40	<.001
Hb level < 12 g/dL (n = 106)†	5	5	12	.048
Serum B2M > UNL (n = 90)†	28	31	36	.436
LoDLIN > 6 cm	5	5	19	<.001
Bone marrow involvement present (n = 100)†	54	50	47	.563
No. of ENS > 1	11	10	0	<.001
No systemic symptoms	107	100	100	—
ESR > 30 mm/h (n = 80)†	8	10	11	1.00
Serum albumin < 3.5 g/dL (n = 99)†	5	5	6	1.00
ECOG performance status > 1	2	2	0	.093
FLIPI (n = 104)†				.891
0-1	55	53	51	
2	38	36	37	
3-5	11	11	12	
FLIPI2 (n = 89)†				.390
0	21	24	20	
1-2	54	61	57	
3-5	14	16	23	

Abbreviations: B2M, β_2-microglobulin; ECOG, Eastern Cooperative Oncology Group; ENS, extranodal sites; ESR, erythrocyte sedimentation rate; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; FLIPI2, Follicular Lymphoma International Prognostic Index 2; Hb, hemoglobin; LDH, lactate dehydrogenase; LoDLIN, longest diameter of largest involved node; UNL, upper normal limit; W&W, watch and wait.

*P values for categorical variables calculated using Fisher's exact test or χ^2 test; P values for continuous variables calculated using Mann-Whitney U test.

†Number indicates patients in W&W group with available data.

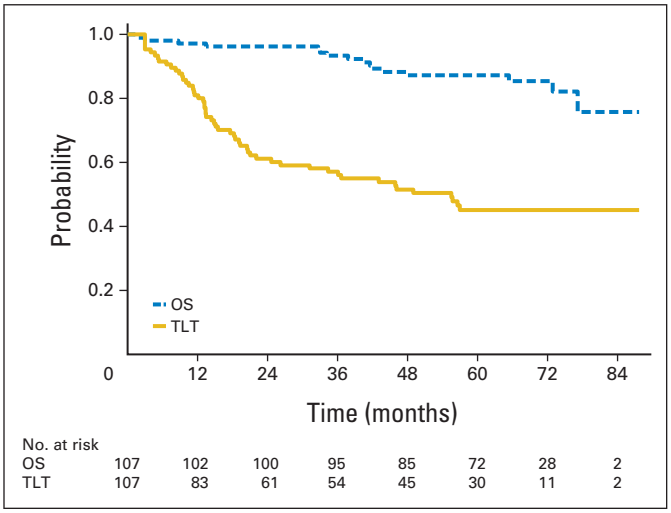

Fig 1. Time to initiation of a lymphoma treatment (TLT) and overall survival (OS) of the 107 patients with no initial treatment (watch and wait).

Various treatments were given after progression. Overall, 37 (71%) of 52 patients for whom treatment details were provided received rituximab either alone (n = 7) or in combination with chemotherapy (n = 30). Of the 50 patients assessable for response, 30 (60%) achieved a complete response, 11 (22%) achieved a partial response, five (10%) achieved a response less than partial response requiring additional therapy according to the responsible physician, and four (8%) experienced progression on treatment.

Finally, we compared the FFTF of the W&W cohort with that of the group of 242 patients from the F2-study who initially received rituximab-containing treatment despite having a low tumor burden according to GELF criteria (Table 1). There was no difference in terms of prognosis according to the FLIPI and FLIPI2 criteria between these two groups.

The FFTF curves of these two groups are shown in Figure 3. The 4-year FFTF rates were 69% (95% CI, 61% to 76%) for the initially treated group and 79% (95% CI, 69% to 85%) for the W&W group.

As seen in Table 1, some variables seemed to be imbalanced between patients in the W&W group and treated patients, including Ann Arbor stage, serum hemoglobin level, longest diameter of involved lymph nodes, number of nodal sites, and age taken as a continuous variable. By controlling for the confounding covariates, an HR of 0.63 (95% CI, 0.36 to 1.09) between patients in the W&W group and treated patients was obtained, and the FFTF of treated patients approached that of the W&W cohort, with no significant difference between the two groups ($P = .103$).

In addition, lactate dehydrogenase levels and the number of extranodal sites of involvement were imbalanced between the two groups of patients (Table 1). Nevertheless, these variables have not been taken into account for controlling because the unfavorable profile was reported for the W&W group.

Overall, at a median follow-up of 64 months, five patients (5%) experienced transformation to aggressive non-Hodgkin lymphoma, two during the W&W no treatment period and three after progression. There was no difference in the incidence of histologic transformation between patients who were initially treated and W&W patients (data not shown). Of the 107 W&W patients, 16 patients have died, nine after progression (lymphoma in three patients, treatment-related toxicity in three patients, other disease in one patient, and unknown cause in two patients) and seven without initiation of lymphoma treatment (lymphoma in two patients, infection in one patient, other disease in two patients, and unknown cause in two patients). Five-year OS was 87% (95% CI, 79% to 92%). No difference in OS was observed between patients initially treated (88%; 95% CI, 82% to 92%) and W&W patients (87%; 95% CI, 79% to 92%).

DISCUSSION

Here we report on the course of FL in a subgroup of patients from the prospective observational F2-study, the database from which the

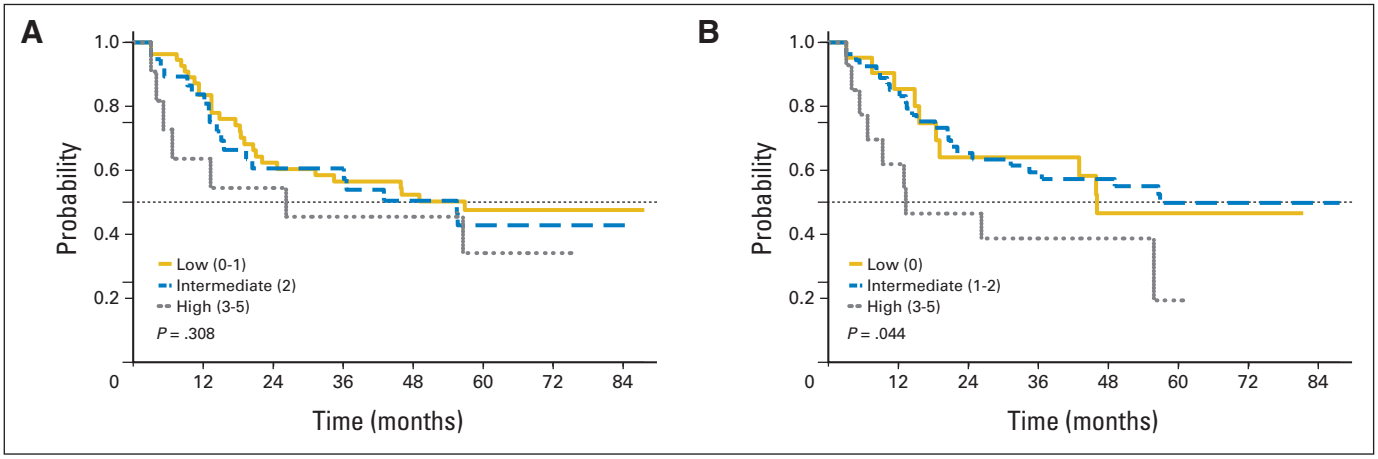

Fig 2. Time to initiation of a lymphoma treatment stratified by (A) Follicular Lymphoma International Prognostic Index (FLIPI; low/intermediate *v* high, $P = .308$) and (B) FLIPI2 (low/intermediate *v* high, $P = .044$).

FLIPI2 prognostic index was derived. All patients from participating centers were registered, but some patients were not initially treated. These patients were excluded in the previously reported PFS analysis of the FLIPI2 study[12] because PFS with or without treatment cannot be simultaneously analyzed. One hundred twenty patients (11% of the F2 cohort) were not treated within 3 months of diagnosis, and 107 of these patients make up the study group for this report.

This large, international, prospective study shows that W&W remains a management therapeutic option in patients with FL in the rituximab era. Our analysis confirms that deferring treatment in patients with a good prognosis is a safe choice that does not have deleterious effects on both FFTF and long-term survival. It is to be stressed that, using FFTF, W&W was not considered as a first-line treatment; similarly, treatment start was not counted as an event for W&W patients because it is part of the initial strategy, which is to postpone active treatment until symptoms occur. We believe that the adoption of FFTF allows a better assessment of treatment efficacy when W&W is considered because it takes into account events that have the same meaning in the two groups.

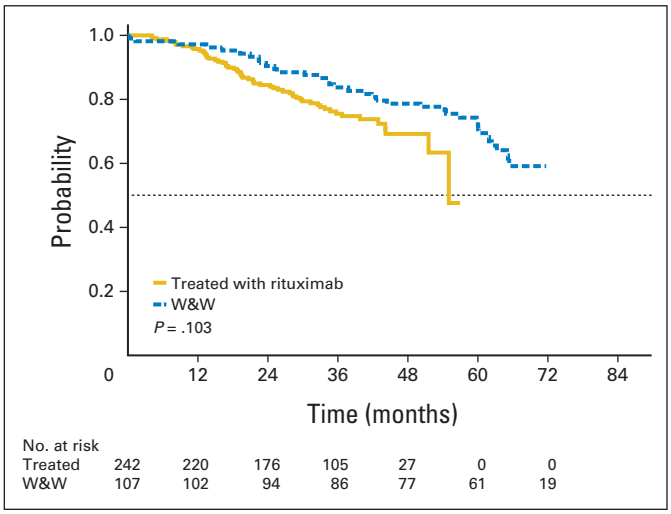

Fig 3. Freedom from treatment failure of the watch and wait (W&W) cohort (n = 107) and the subgroup of initially treated patients with good prognosis characteristics (n = 242).

The number of patients who were not initially treated is lower than that reported in other cohort studies. For instance, in the National LymphoCare Study conducted in the United States between 2004 and 2007, 17.7% of 2,728 patients were not initially treated.[17] The lower number reported in our population may be related to usual treatment approaches in some geographical areas (predominance of European patients in our subgroup) and/or to the safety profile of rituximab treatment.

Although progression was, by far, the most frequently reported reason for initiating a treatment in all of these studies including ours, we cannot confirm that the progression fulfilled the criteria as defined by Cheson et al.[18] Because toxicity of modern FL treatments is lower than that of past regimens, a mild increase in lymph node size or an increased number of involved sites on a positron emission tomography scan may have led the responsible physician to consider that the disease was progressive and to initiate a treatment. Furthermore, patients are currently aware of all treatment approaches for their disease, and their demand differs from that of patients diagnosed more than 20 years ago. Conversely, a few patients with progression according to the criteria of Cheson et al[18] could have been still observed without treatment. The discussion with patients and their close family of a no treatment policy is more and more complex given the fact that treatment of FL is increasingly more effective and less toxic, leading to remarkably prolonged survival in many patients.

Among patients for whom W&W can be proposed, our study suggests that there is a subgroup of patients who will require treatment within a short time (ie, those at high risk according to the FLIPI2 prognostic model). Except for specific patients (eg, elderly patients or patients with severe comorbidities), initiating treatment immediately for these patients would seem more reasonable than proposing a watchful period that will most probably last a short time.

Our analysis demonstrates that initial W&W does not have negative effects on outcome in patients with disseminated FL and a low tumor burden in the rituximab era. However, this strategy is probably less commonly used initially, and treatment is initiated earlier than in the past. Recently, Ardeshna et al[10] presented the preliminary results of

the prospective, randomized RWW (Rituximab—Watch and Wait) trial (ClinicalTrials.gov identifier: NCT00112931) comparing W&W strategy (arm A) versus rituximab administered for 4 weeks (arm B) versus rituximab for 4 weeks followed by rituximab maintenance every 2 months for 2 years (arm C) in patients with advanced-stage, asymptomatic, nonbulky FL. They demonstrated that time to initiation of new therapy was 33 months in the W&W arm, whereas the median time was not yet reached in the rituximab arms at 4 years. Because the characteristics of the patients in our study and in the trial by Ardeshna et al[10] were different and criteria for initiating treatment were not the same, it is speculative to compare the 33-month median time to initiation of therapy in the trial by Ardeshna et al[10] with the 55-month median time in our study. Furthermore, there was a highly significant difference in 3-year PFS between all three arms (33%, 60%, and 81% in arms A, B, and C, respectively; $P < .001$ for each of the rituximab arms *v* the W&W arm). The authors concluded that upfront rituximab followed by maintenance may become the standard of care for this subset of patients. However, this conclusion could be challenged by the fact that OS is not statistically different among the arms and the fact that their end point of first lymphoma treatment in the observation arm (arm A) and second lymphoma treatment in the treatment arms (arms B and C) is not a valid comparison and should not at this point inform practice patterns in FL. A more appropriate comparison would have been FFTF or time to second lymphoma treatment and OS. Because OS is not different in their first report, we await these latter analyses.

The National LymphoCare Study group recently reported on the outcome of the subgroup of patients with advanced-stage FL selected among all registered in the project.[19] This cohort included 237 patients managed with initial W&W and 1,500 patients who received immediate therapy. In the W&W group, 146 patients were later assigned to treatment, either with rituximab alone or in combination. The authors found that the median PFS times after first active treatment were 42 and 55 months when rituximab was given at diagnosis and after W&W, respectively. These results support our findings that deferring treatment is not detrimental. In contrast, median PFS after rituximab given in combination was shorter when administered in patients initially managed expectantly (37 months) compared with patients treated at diagnosis (71 months). However, clinical features and prognosis were different between these two groups. There was no difference in OS whether patients were treated at diagnosis or after initial W&W.

In conclusion, our data in a prospective and well-analyzed database that reflects actual practice suggest that there is no difference in outcome between patients who were observed and patients who were treated initially. Our cohort study provides additional information relevant to the important issue of management of patients with FL in the current era and suggests that observation remains an appropriate approach in asymptomatic patients with low–tumor burden FL. The long-term follow-up of the RWW trial by Ardeshna et al[10] and other clinical trials comparing W&W with other new treatments (eg, radioimmunotherapy, new anti-CD20 monoclonal antibodies) are clearly warranted.

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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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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