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ORIGINAL REPORT

Risk Factors and Outcomes for Patients With Follicular Lymphoma Who Had Histologic Transformation After Response to First-Line Immunochemotherapy in the PRIMA Trial

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ABSTRACT

Purpose
To study the outcome of histologic transformation (HT) in a large prospective cohort of patients with follicular lymphoma (FL) who previously responded to immunochemotherapy.

Patients and Methods
After a median 6-year follow-up of 1,018 randomly assigned patients from the PRIMA trial, disease progression was observed in 463 patients, 194 of whom had histologic documentation.

Results
Forty patients had histology consistent with HT, and 154 had untransformed FL (median time to recurrence, 9.6 *v* 22.8 months, respectively; $P = .018$). Thirty-seven percent of biopsies performed during the first year of follow-up showed HT corresponding to 58% of all HTs. Altered performance status, anemia, high lactate dehydrogenase level, "B" symptoms, histologic grade 3a, and high Follicular Lymphoma International Prognostic Index scores at diagnosis were identified as HT risk factors. Response (complete *v* partial) to immunochemotherapy or rituximab maintenance had no impact on the risk of HT. After salvage treatment, patients with HT had less frequent complete response (50.3% *v* 67.4%; $P = .03$) and more disease progression (28.2% *v* 9.6%; $P < .001$) than patients without HT. Estimated overall survival for the patients with HT was poorer (median, 3.8 *v* 6.4 years; hazard ratio, 3.9; 95% CI, 2.2 to 6.9). Autologous stem cell transplantation improved the outcomes of patients with HT (median overall survival, not reached *v* 1.7 years) but not of patients with persistent FL histology.

Conclusion
HT in patients with FL who previously responded to immunochemotherapy is an early event associated with a poor outcome that may deserve intensive salvage with autologous stem cell transplantation. These data emphasize the necessity for biopsy at the first recurrence of FL.

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INTRODUCTION

Follicular lymphoma (FL) is the most common indolent form of non-Hodgkin lymphoma, and it is characterized by heterogeneous clinical evolution. Histologic transformation (HT) is the culmination of a series of biologic events leading to aggressive lymphoma; it is histologically defined by the documentation of increased numbers of large cells that eliminate the follicular structure, the most frequent manifestation being diffuse large B-cell lymphoma (DLBCL).[1] If HT is suspected because of the presence of several clinical characteristics, then histologic documentation[2] remains the gold standard for diagnosis. The overall rate of transformation reported in patients with FL ranges from 16% to 60%, depending on the number of serial biopsies and the duration of follow-up in the different historical series.[3-8] Annual incidence has been estimated at approximately 3% in various reports.[8-10] Previously associated with a poor prognosis,[8-10] this dismal outcome may be improved by the introduction of rituximab.[11] Recent retrospective and registry studies have

suggested that the risk of HT might be slightly lower in the rituximab era, and median overall survival (OS) has also improved.[12-15] However, these retrospective reports include heterogeneous populations of symptomatic and asymptomatic patients who received a variety of first-line treatment strategies.

The PRIMA (Primary Rituximab and Maintenance) trial was a randomized phase III trial that evaluated the impact of maintenance with rituximab in symptomatic patients with FL who were treated with an induction regimen of rituximab chemotherapy. After a median follow-up of more than 6 years, the maintenance strategy with rituximab significantly improved progression-free survival (PFS) but not OS.[16] The objectives of this analysis were to evaluate the incidence of HT at first recurrence in the PRIMA patient cohort, to study the risk factors (at diagnosis) associated with this event, and to assess the outcomes of these patients.

PATIENTS AND METHODS

PRIMA was a prospective phase III trial that included patients with high tumor burden FL by the Groupe d'Etude des Lymphomes Folliculaires criteria[17] recruited between 2004 and 2007. Patients with histologic grades 1, 2, or 3a FL, according to the WHO classification, were included. Diagnostic biopsies were centrally reviewed. Patients received six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone and two additional doses of rituximab (n = 885 patients), or eight cycles of rituximab plus cyclophosphamide, vincristine, and prednisone (n = 272 patients), or six cycles of rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (n = 45 patients). At the end of induction, patients with responsive disease (complete response [CR] or partial response [PR]) were randomly allocated to 2 years of maintenance with rituximab (every 2 months) or observation. A total of 1,018 patients were randomly assigned: 513 in the observation arm and 505 in the rituximab maintenance arm. One patient was excluded from the analysis after a histologic review of the initial diagnostic material showed DLBCL. This study included the 1,017 randomly assigned patients in CR or PR after the induction regimen. The rate of HT at recurrence was originally defined as a secondary end point of the study protocol, with HT defined (according to WHO criteria) as progression to high-grade lymphoma (namely, DLBCL or Burkitt lymphoma) with more large cells associated with loss of the follicular structure.

The cumulative incidence of HT was evaluated and compared with the cumulative incidence of recurrences with confirmed ongoing FL histology. The time to first recurrence with FL or HT was defined as the time from the date of random assignment to the date of first recurrence with FL histology or HT. To assess the pretreatment risk factors for transformation, the initial characteristics of patients with biopsies that showed HT were compared with those of patients without HT (ie, corresponding to the patients with biopsies that showed persistent FL histology and those without disease progression [CONSORT diagram; Fig 1]). In further exploratory analyses, the clinical outcomes of patients with HT were then evaluated and compared with the outcomes of patients who had a recurrence and conserved FL histology. The OS from random assignment was calculated from the date of random assignment to the date of death related to any cause or to the date of last follow-up for patients still alive. The OS from the first recurrence was calculated from the time of first recurrence or HT to the date of death related to any cause or to the date of last follow-up for the patients still alive. Statistical analyses were performed with SAS v9.2 software (SAS Institute, Cary, NC).

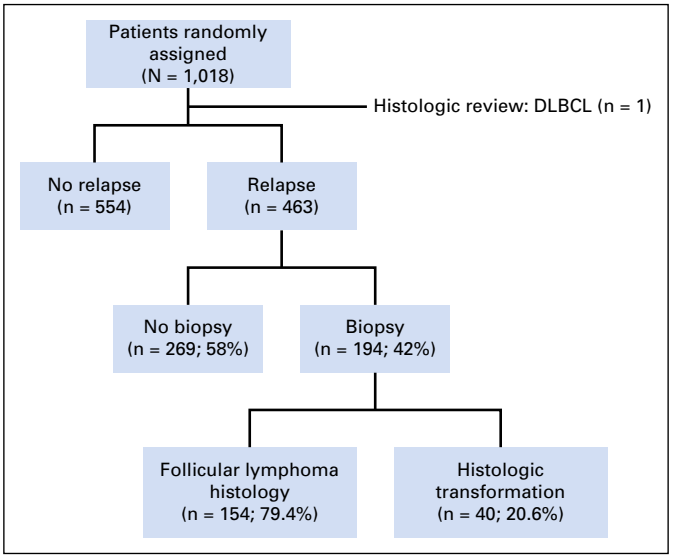

Fig 1. CONSORT diagram. DLBCL, diffuse large B-cell lymphoma.

RESULTS

Incidence of HT

After a median follow-up of 73 months, a total of 463 patients experienced disease recurrence or progression (45.5% of the randomly assigned patients); 194 of these patients (42%) underwent biopsy at first progression. Data regarding the decision to perform a biopsy or not and its site are unavailable. The patients with and without biopsies had comparable initial clinical characteristics, except for less frequent anemia (19.7% in the biopsy group *v* 29.9% in the nonbiopsy group; $P = .011$; Appendix Table A1, online only). Among the 194 biopsies performed, 40 had HT (20.6%), and 154 had FL histology. During the first year, 66 of 144 relapsing patients had a biopsy: 42 (63.6%) showed FL and 24 (36.4%) showed HT. More than half (58%) of the total documented cases of HT occurred within the first year of follow-up, with a median time of 9.7 months from random assignment. This timing was significantly shorter than the time to progression for patients with FL histology documentation (median, 22.9 months; log-rank test $P = .017$). At 6 years after induction, the cumulative incidence of documented HT was 4.1% versus 15.9% for the incidence of documented progression with FL histology. These results do not consider the group of patients who did not have a biopsy. The distribution of the cumulative incidence over time seemed to differ between the patients with documented FL histology recurrence and HT (Appendix Figure A1, online only). It increased sharply for HT during the first year after induction treatment (58% of all cases of documented HT), whereas it increased linearly for FL histology relapses over the first 6 years. Indeed, 36.4% of the biopsies performed during the first year after random assignment demonstrated HT compared with 11.8% of the biopsies performed after 1 to 5 years of follow-up.

At first recurrence, patients with HT more frequently manifested a new site of disease involvement (80%; 32 of 40) compared with the patients with FL histology (60.4%; 93 of 154; $P = .02$).

They also more frequently had extranodal disease (55% [22 of 40] *v* 45% [69 of 154]; $P = .2$), although this was not statistically significant.

Risks Factors for HT

The initial clinical characteristics of the 40 patients with HT were compared with those of the 708 patients without HT (154 with persistent FL histology at first recurrence and 554 without recurrence). As shown in Table 1, the patients with HT more frequently had a histologic grade of 3a, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2, a hemoglobin level < 12 g/dL, a lactate dehydrogenase (LDH) level above the upper limit of normal, the presence of "B" symptoms, and a Follicular Lymphoma International Prognostic Index (FLIPI) score > 2 at study entry (pretreatment) compared with the other patients. In a multivariate analysis that included parameters with a P value $< .2$, only an ECOG PS ≥ 2 and hemoglobin < 12 g/dL

Table 1. Initial Clinical and Biological Characteristics at the Time of FL Diagnosis Among Patients With and Without HT in the PRIMA Trial

	Patients With Available Data				
	No Transformation (n = 708)*		HT (n = 40)		
Characteristic	No.	%	No.	%	*P*
Age, years					.84
Range	23-81		33-77		
Mean	56		56.5		
Median	57		57		
Sex					.19
Female	358	50.6	16	40	
Male	350	49.4	24	60	
FL grade					.02
1	304	43	8	20	
2	255	36	19	47	
3	148	21	13	33	
ECOG performance status					< .001
0-1	689	97.3	34	85	
2-4	19	2.7	6	15	
B symptoms					.042
Yes	211	29.8	18	45	
No	497	70.2	22	55	
No. of extranodal sites					.33
Range	0-7		0-6		
Mean	1.4		1.6		
Median	1		1		
No. of nodal sites					.29
Range	0-9		1-9		
Mean	5		5.4		
Median	5		6		
> 4	370	52.3	23	57.5	.518
Bulky disease					.27
Yes	330	47.4	22	56.4	
No	366	52.6	17	43.6	
Ann Arbor stage					.11
I-II	81	11.4	1	2.5	
III-IV	627	88.6	39	97.5	
Anemia, g/dL					< .001
< 12	127	17.9	16	40	
≥ 12	581	82.1	24	60	
LDH					.029
≤ ULN	488	69	21	52.5	
> ULN	219	31	19	47	
FLIPI score					.007
0-1	176	24.9	3	7.5	
2	252	35.6	12	30	
3-5	279	39.5	25	62.5	
Albumin, g/L					.105
< 35	48	8.4	6	18.2	
≥ 35	524	91.6	27	81.8	
B_2 microglobulin, mg/L					.605
< 3	481	72.9	25	69.4	
≥ 3	179	27.1	11	30.6	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HT, histologic transformation; LDH, lactate dehydrogenase; ULN, upper limit of normal.
*The 708 patients without HT corresponded to the 554 patients without relapse and the 154 patients with recurrence and biopsy showing FL histology.

were independently associated with HT: hazard ratio (HR) of 5.6 (95% CI, 1.7 to 17.7) for ECOG PS and HR of 3.7 (95% CI, 1.4 to 9.7) for anemia. With the limitation of modest patient numbers, the induction regimen (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, rituximab plus cyclophosphamide, vincristine, and prednisone, or rituximab plus fludarabine, cyclophosphamide, and mitoxantrone) did not seem to influence the risk of transformation (data not shown). Among the 708 patients without HT, 382 (54%) had received rituximab maintenance, and among the 40 patients with HT, only 16 (40%) had received rituximab maintenance. In addition, the quality of the response to the induction regimen was comparable between the two groups: 42.5% of patients with HT had CR, 30% had unconfirmed CR (CRu), and 27.5% had PR compared with 42.2%, 31.6%, and 25.3%, respectively, for patients without HT (P = .98).

Outcomes of Patients With HT

To analyze the outcomes of the patients with HT, we compared their outcomes with those of patients with FL histology at recurrence. Among the patients with a biopsy showing FL, 135 (87.7%) received therapy after the first recurrence, whereas among the patients with HT, 39 (97.5%) underwent treatment. The treatments used (Table 2) included chemotherapy and anti-CD20 immunotherapy for the majority of the patients with HT who underwent DLBCL-like intensive regimens. The patients with FL histology received various treatments, including radiation alone, rituximab alone, and rituximab chemotherapy. Patients with HT were less likely to achieve CR or CRu (50.3% *v* 67.4%; P = .03; Table 3) and more patients frequently had progressive disease under salvage therapy (28.2% *v* 9.6%; P < .001) than those with FL histology. They also had shorter survival from recurrence than the 154 patients with FL histology (median OS, 3.8 *v* 6.4 years; HR, 3.9; 95% CI, 2.2 to 6.9; P < .001; Fig 2). This was also true when considering only those patients with disease progression within 12 months of immunochemotherapy (P = .007). After salvage therapy, among the 40 patients with HT, 17 (42%) underwent consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT). These 17 patients had an improved OS rate (not reached [NR] *v* 1.7 years; Fig 3A) compared with the 23 who could not reach ASCT or were not referred to ASCT. Among the patients with FL histology at recurrence, 44 (28%) underwent salvage therapy followed by ASCT. ASCT had no impact on OS (Fig 3B) of the relapsing patients with FL histology. To limit bias, we performed the same analysis by excluding patients who had an early progression after salvage (with a 6-month landmark analysis) and who were older than age 65 years—an age potentially considered the limit for transplantation eligibility. Results were similar: ASCT had no impact on OS in the population of patients relapsing with FL (median OS, 6.4 years [95% CI, 4.7 to 6.4 years] *v* NR [95% CI, NR to NR] for the 42 and 59 patients who were treated with or without ASCT, respectively), whereas patients with HT and age younger than 65 years who received an ASCT (n = 16) had a longer OS than those who did not (n = 9; median OS, NR [95% CI, 3.8 to NR] *v* 1.7 years [95% CI, 0.5 to NR]). Among the 40 patients with HT at recurrence, 16 received rituximab maintenance after induction treatment. This prolonged rituximab exposure did not seem to have an adverse impact on their response to salvage treatment or their outcomes (median OS for the 16 patients was 4.9 years [95% CI, 1.4 to 6.5 years] *v* NR [95% CI, 3.4 years to NR]; P = .159, for the 24 patients who did not receive maintenance).

Finally, the OS rate of the 269 patients who did not undergo biopsy at recurrence was slightly higher than that for the 194 patients who underwent biopsy, although the difference was not significant (median OS, NR *v* 6.4 years for the group of patients without and with biopsy, respectively; HR, 1.46; 95% CI, 0.99 to 2.22; *P* = .056; Appendix Figure A2, online only).

Table 2. Salvage Type Therapy at Recurrence, According to Biopsy Results

	Treated Patients			
	With FL Histology (n = 135)		With HT (n = 39)	
Type of Therapy	No.	%	No.	%
Chemotherapy	113	83.7	37	95
Radiotherapy	14	10.4	8	20.5
Immunotherapy	116	85.9	28	71.8
Radioimmunotherapy	13	9.6	0	
ASCT	44	32.6	17	43.6
Allotransplant	2		1	

NOTE. Among the patients with a biopsy showing follicular lymphoma (FL), 135 (87.7%) were treated after the first recurrence, 112 (83%) of whom were treated immediately after the recurrence. Among the patients with histologic transformation (HT), 39 (97.5%) received treatment, 35 (89.7%) of whom received treatment immediately after the documentation of HT (four patients received treatment between 3 and 12 months after the HT documentation, and one patient did not receive any treatment). The principal immunochemotherapy regimen was rituximab plus dexamethasone, cytarabine, and oxaliplatin (R-DHAOX) for patients with FL and those with HT; other regimens included rituximab plus bendamustine or rituximab plus fludarabine and cyclophosphamide (R-FC) for relapsing patients with FL histology; less commonly used regimens consisted of rituximab plus etoposide, cytarabine, steroid, and platinum (R-ESHAP) or rituximab plus etoposide, ifosfamide, and carboplatin (R-ICE) for patients with HT. ASCT, autologous stem-cell transplantation.

Table 3. Response to Salvage Therapy, According to Biopsy Results

	FL Histology (n = 135)		HT (n = 39)	
Type of Response	No.	%	No.	%
CR/CRu	91	67.4	20	50.3
PR	19	14.1	5	12.8
Stable	7	5.2	2	5.1
Progressive	13	9.6	11	28.2
Not evaluated	5	3.7	1	2.6

NOTE. Nineteen patients in the follicular lymphoma (FL) group and one patient in the histologic transformation (HT) group did not undergo salvage treatment. Abbreviations: CR, complete response; CRu, unconfirmed CR; PR, partial response.

DISCUSSION

This study reports on the incidence, risk factors, and outcomes of patients with HT of high tumor burden FL who responded to a rituximab chemotherapy regimen. The originality of this report is represented by the inclusion of well-characterized patients who were homogenously treated and followed in a prospective clinical trial, whereas other reports have included patients with various

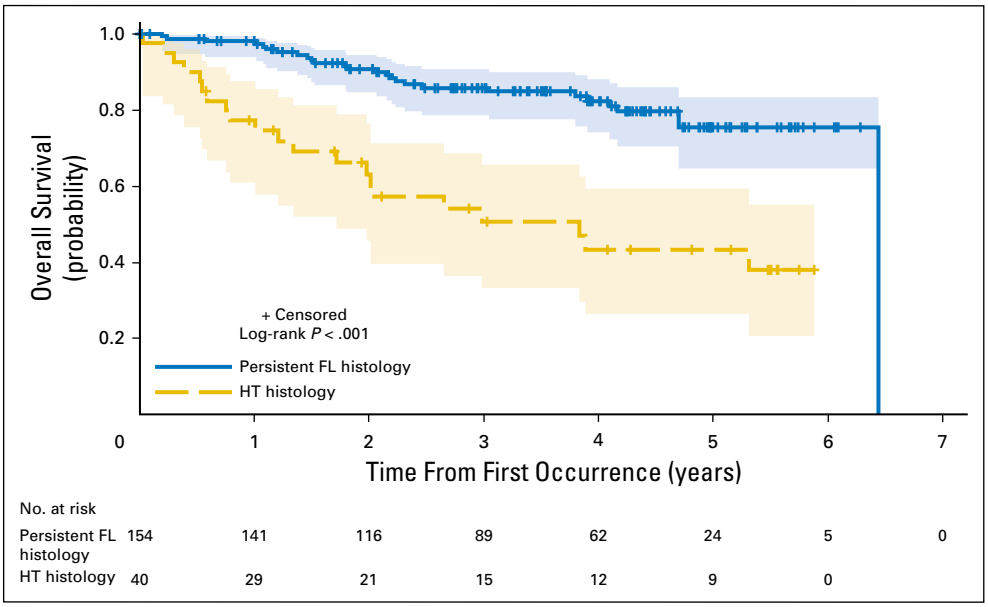

Fig 2. Overall survival (OS) of 194 patients with documentation of histologic transformation (HT) or persistent follicular lymphoma (FL) after first recurrence in the PRIMA trial, according to transformation status. Patients with HT histology had a shorter median OS (n = 40; median, 3.8 years; 95% CI, 1.7 years to not reached [NR]) than patients with FL histology (n = 154; median, 6.4 years; 95% CI, NR to NR; hazard ratio, 3.9; 95% CI, 2.2 to 6.9; $P < .001$). Among patients who progressed within 12 months, those with HT histology had a shorter OS (n = 23; median, 2 years; 95% CI, 0.8 years to NR) than those with FL histology (n = 41; median, 6.4 years; 95% CI, 4.7 to 6.4 years; $P = .007$).

initial management strategies. Furthermore, only the first disease progression event was considered in this study as opposed to other studies that have reported on late HT events after multiple disease relapses.

In this study, HT at first progression remained a relatively uncommon event that typically occurred soon after the end of induction treatment, whereas the risk of progression with FL histology seemed to be linear over time (up to 6 years of follow-up). Interestingly, more than half of the transformations were documented during the first year after induction, which represents a third of the biopsies performed during that period versus 11.8% being documented during the next 4 years. The recurrence kinetic strengthens the importance of performing a biopsy for any relapse within the first year of follow-up. Link et al[13] reported that HT incidence seemed to diminish after 5 years of follow-up and that it was consistent throughout 1 to 5 years, with an overall incidence of 10.7% at 5 years, which is similar to our results. This different temporal pattern might be at least partially explained by the inclusion of different populations: asymptomatic patients with FL at diagnosis were included in the US study by Link et al,[13] whereas our study only considered the HT occurring in patients with high tumor burden and who had responded to initial immunochemotherapy. The median time to transformation was also shorter in our study (ie, 9 months from the end of induction) than in studies that included symptomatic and asymptomatic patients with FL at diagnosis (40 and 33 months, respectively[10,12]).

A current challenge in managing patients with FL is to identify (at the time of diagnosis) those at high risk of treatment failure and poor outcomes.[18] This group of patients may include those with a higher risk of HT, which emphasizes the need to identify the risk factors for transformation. Despite the recent progress made in deciphering the molecular features of HT,[19-21] clinical features remain the only routinely available method for identifying risk factors. In our population, ECOG PS, anemia, high LDH level, presence of B symptoms, high FLIPI score, and histologic grade 3a at diagnosis were associated with a higher incidence of HT at recurrence. ECOG PS and anemia were the only independent factors in multivariate analysis. Before the rituximab era, advanced Ann Arbor stage, low serum albumin level (< 35 g/L), high β_2-microglobulin (> 3 mg/L), and a high FLIPI score at diagnosis appeared to be risk factors for HT.[8-10] In more recent reports, increased LDH, ECOG PS > 1, B symptoms, more than one extranodal site, and FLIPI score at diagnosis were associated with the risk of HT.[12-14] It would be interesting to further merge large clinical series obtained in the rituximab era to define a score that might identify these patients at risk for HT at diagnosis. In addition, for patients who demonstrate clinical risk factors for HT at the time of their initial diagnosis, it may be helpful to track occult transformation, perhaps even repeating a biopsy (eventually guided with positron emission tomography-computed tomography scans) to optimize initial management.

The influences of initial patient management and the response to the induction regimen on risk of transformation have also been debated. It remains unclear whether patients who are initially managed with watchful waiting have a higher risk of HT.[9,13,14,17,22] In the PRIMA trial and in reports of other studies,[13,14] no difference in HT was observed according to the different induction regimen used, whereas one study[10] suggested that there is a diminished risk in patients treated with an anthracycline. Older reports have suggested that failure to achieve CR was associated with a higher risk of transformation.[8] In this report, the quality of response (CR *v* PR) did not have a significant impact on the incidence of transformation. Finally, rituximab maintenance reduced the overall risk of lymphoma progression and therefore the number of patients with HT ($P = .08$). But given the limited number of patients with HT, the sample size does not allow us to establish whether rituximab maintenance had an impact on the risk of HT among patients with disease progression.

The patients with HT had a poorer OS rate than the relapsing patients with FL histology. Among the patients with HT, the median OS rate from first relapse was 3.8 years compared with more than 6 years for the patients with FL histology, which

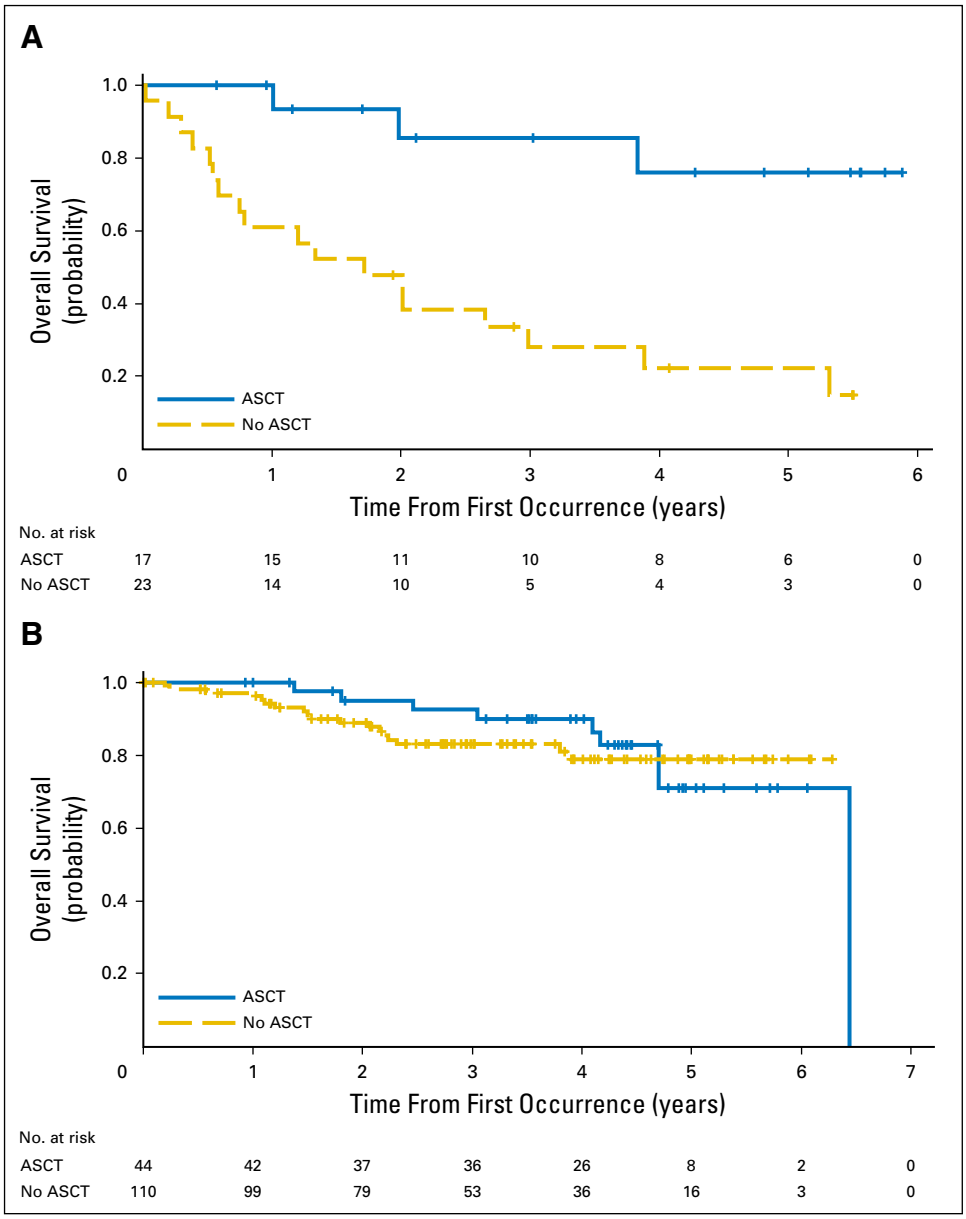

Fig 3. Overall survival (OS) of patients with a first recurrence according to histology (histologic transformation [HT] (A) versus follicular lymphoma [FL] (B) at first recurrence) and according to treatment with or without autologous stem cell transplantation (ASCT) after salvage therapy. OS was calculated from first recurrence. (A) Among the 40 patients with HT, 17 had an ASCT and an improved OS estimate (median, not reached [NR]; 95% CI, 3.8 years to NR) compared with the 23 who could not reach ASCT or were not referred for ASCT (median, 1.7 years; 95% CI, 0.6 to 3 years). (B) Among the 154 patients with FL histology at recurrence, 44 (28%) had an ASCT. ASCT had no impact on the OS estimate of relapsing patients with FL histology. Median OS was 6.4 years (95% CI, 4.7 to 6.4 years) for those who received an ASCT and was not reached for those who did not receive an ASCT.

strengthens the necessity of performing a biopsy at the first recurrence of FL. Importantly, prolonged treatment with rituximab (ie, maintenance after induction regimen) did not have an impact on the OS of the HT patients after relapse. The OS after HT appears to be comparable to that in other reports from the rituximab era[13,14,23] (5-year OS, 48% to 50%), thereby confirming the improvement achieved in the rituximab era. However, this outcome appears to be inferior to that observed for newly diagnosed patients with DLBCL. The median OS rate after relapse in this study (3.6 years) seems to be similar to the OS rate of relapsed patients with DLBCL who are eligible for transplantation, as reported in the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study (median OS, approximately 4 years).[24]

As shown here, when achievable, ASCT seems to improve the outcomes of HT patients; however, this result was not observed in patients with persistent FL histology at progression. The efficacy of ASCT has also been reported in other studies[25-29] but not in the recent US study by Link et al.[13] Only patients who responded and were adequately fit were eligible for ASCT, which biases the interpretation of these data and the potential benefit of ASCT. When reported, the transplantation rate among initial eligible patients was approximately 50% to 60%.[30-33] A retrospective comparison of young patients who did not undergo ASCT for a reason other than progression still shows good results, with an OS rate comparable to or slightly inferior to that of grafted patients.[23,30]

Our study has some limitations. We analyzed only those patients who were randomly assigned in the PRIMA trial after responding to induction therapy. The study population was therefore selected, thus limiting wider applicability of the findings. For instance, among the 86 patients who did not respond to induction therapy, 31 had a biopsy: 23 biopsies showed FL and eight (26%) showed HT. These patients were not followed as per

protocol and therefore are not reported here. Given the multicentric nature of the study, a central review of biopsies performed at first recurrence was not possible, but all individual patient medical records and pathologic reports were carefully reviewed. When estimating the risk factors for HT, the patients who did not undergo new biopsies were not considered, but this population likely includes patients with and without transformation, and their exclusion avoids further confounding factors.

In conclusion, this report of HT among a cohort of high-tumor burden patients with FL who were treated with immunochemotherapy shows that HT is a relatively uncommon event that remains associated with a poor prognosis. The cumulative incidence was significant within the first year and then diminished compared with the incidence of FL relapse, which continuously increased. Management after the first progression indicates that there may be a benefit from ASCT for patients with HT, whereas this strategy was not associated with a better OS rate for patients with persistent FL histology at first progression. Our results further emphasize the need to perform a new biopsy at the time of first progression in patients with FL. Although intensive treatment may represent a good option for younger patients and those who are eligible for ASCT, the remaining population still represents a group of patients with an unmet medical need.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Clémentine Sarkozy, Gilles Salles, Hervé Tilly
Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: Clémentine Sarkozy, John Seymour, Gilles Salles, Hervé Tilly
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk Factors and Outcomes for Patients With Follicular Lymphoma Who Had Histologic Transformation After Response to First-Line Immunochemotherapy in the PRIMA Trial

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Appendix

Table A1. Comparison of Initial Clinical and Biological Characteristics of Patients With a First Recurrence in the PRIMA Trial Who Had a Histologic Documentation (biopsy) and Those Who Did Not.

Characteristic	No Histologic Documentation (n = 269), No. (%)		Histologic Documentation (n = 194), No. (%)		Test
Age, years					Wilcoxon $P = .8$
Mean (SD)	55.8 (11.58)		55.7 (12.60)		
Median	57.0		57.0		
Sex					χ^2 $P = .5$
Female	111	(41.3)	86	(44.3)	
Male	158	(58.7)	108	(55.7)	
Initial pathology diagnosis					
FL grade 1	117	(43.5)	72	(37.1)	
FL grade 2	89	(33.1)	78	(40.2)	
FL grade 3	3	(1.1)	1	(0.5)	
FL grade 3A	28	(10.4)	16	(8.2)	
NA	32		27		
ECOG performance status					χ^2 $P = .4$
0	172	(63.9)	115	(59.3)	
1	86	(32.0)	67	(34.5)	
2	11	(4.1)	12	(6.2)	
3	0	(0.0)	0	(0.0)	
4	0	(0.0)	0	(0.0)	
Extranodal sites					Wilcoxon $P = .8$
N	269		194		
Mean (SD)	1.7 (1.33)		1.8 (1.39)		
Median	2.0		2.0		
Nodal area					Wilcoxon $P = .2$
No.	269		194		
Mean (SD)	6.0 (2.68)		5.8 (2.49)		
Median	7.0		6.0		
Hemoglobin, g/dL					χ^2 $P = .011$
< 12	53	(19.7)	58	(29.9)	
≥ 12	216	(80.3)	136	(70.1)	
Albumin, g/L					χ^2 $P = .4$
< 35	18	(8.3)	17	(10.4)	
≥ 35	200	(91.7)	147	(89.6)	
NA	51		30		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; NA, not available; SD, standard deviation.

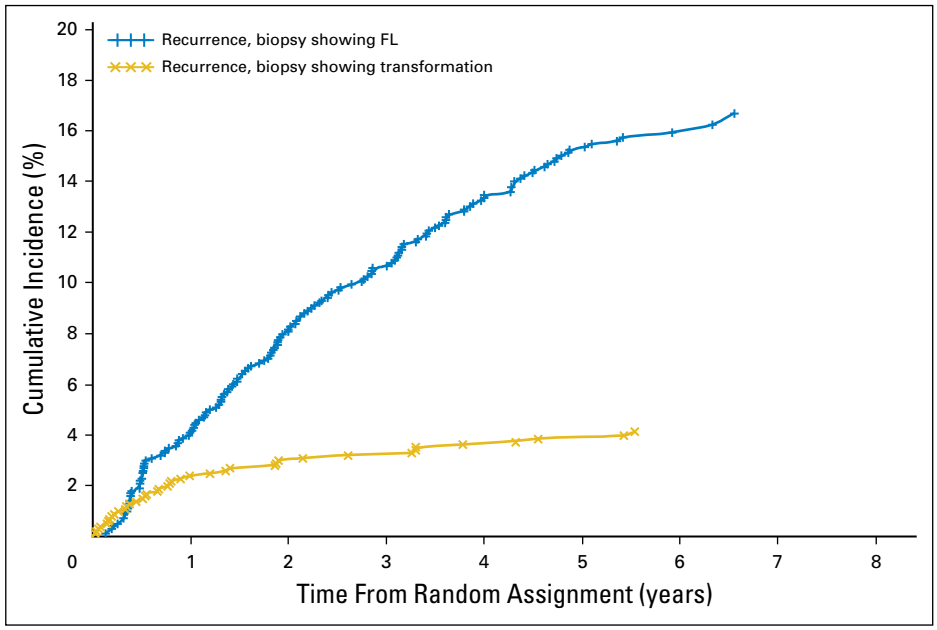
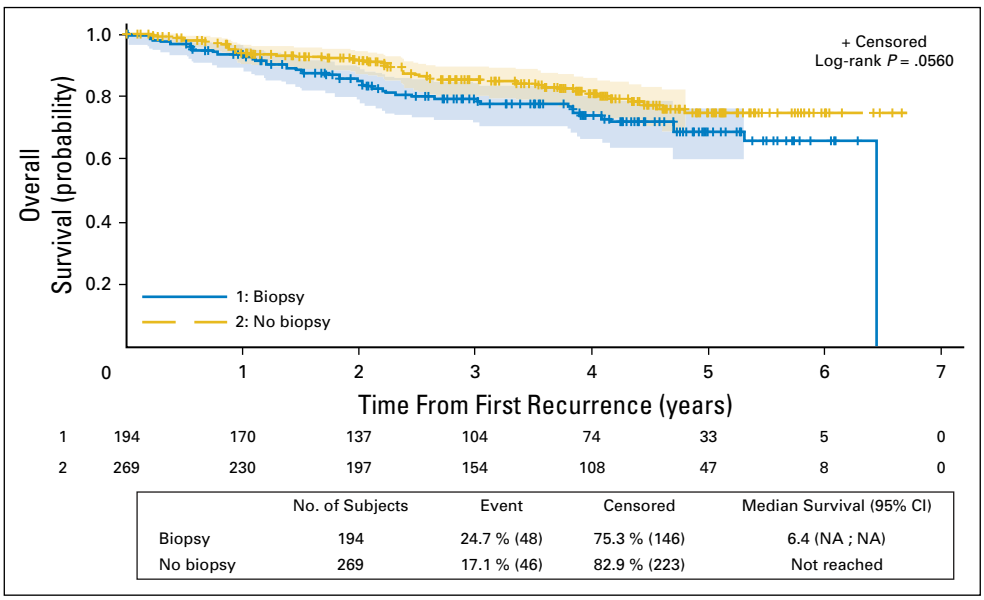


Fig A1. Cumulative incidence of a documented histological transformation or persistent follicular lymphoma (FL) at first recurrence in the PRIMA trial, among patients in the maintenance intent-to-treat population who experienced disease progression.



	No. of Subjects	Event	Censored	Median Survival (95% CI)
Biopsy	194	24.7 % (48)	75.3 % (146)	6.4 (NA ; NA)
No biopsy	269	17.1 % (46)	82.9 % (223)	Not reached

Fig A2. Overall survival from random assignment of patients with a first recurrence in the PRIMA trial and according to the existence of biopsy at relapse.