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Prognostic Significance of *MYC* Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium

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PURPOSE *MYC* rearrangement (*MYC*-R) occurs in approximately 10% of diffuse large B-cell lymphomas (DLBCLs) and has been associated with poor prognosis in many studies. The impact of *MYC*-R on prognosis may be influenced by the *MYC* partner gene (immunoglobulin [IG] or a non-IG gene). We evaluated a large cohort of patients through the Lunenburg Lymphoma Biomarker Consortium to validate the prognostic significance of *MYC*-R (single-, double-, and triple-hit status) in DLBCL within the context of the *MYC* partner gene.

METHODS The study cohort included patients with histologically confirmed DLBCL morphology derived from large prospective trials and patient registries in Europe and North America who were uniformly treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone therapy or the like. Fluorescence in situ hybridization for the *MYC, BCL2, BCL6,* and IG heavy and light chain loci was used, and results were correlated with clinical outcomes.

RESULTS A total of 5,117 patients were identified of whom 2,383 (47%) had biopsy material available to assess for *MYC*-R. *MYC*-R was present in 264 (11%) of 2,383 patients and was associated with a significantly shorter progression-free and overall survival, with a strong time-dependent effect within the first 24 months after diagnosis. The adverse prognostic impact of *MYC*-R was only evident in patients with a concurrent rearrangement of *BCL2* and/or *BCL6* and an IG partner (hazard ratio, 2.4; 95% CI, 1.6 to 3.6; *P* < .001).

CONCLUSION The negative prognostic impact of *MYC*-R in DLBCL is largely observed in patients with *MYC* double hit/triple-hit disease in which *MYC* is translocated to an IG partner, and this effect is restricted to the first 2 years after diagnosis. Our results suggest that diagnostic strategies should be adopted to identify this high-risk cohort, and risk-adjusted therapeutic approaches should be refined further.

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INTRODUCTION

MYC rearrangement (*MYC*-R) occurs in approximately 10% to 15% of diffuse large B-cell lymphomas (DLBCLs), and several studies have suggested an inferior progression-free survival (PFS) and overall survival (OS) compared with patients without *MYC*-R.[1-9] For large B-cell lymphomas that carry *MYC* and *BCL2* and/or *BCL6* translocations (double-hit [DH]/triple-hit [TH] lymphoma), the current WHO classification now includes a new entity termed high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement, which has been associated with a poor prognosis after standard treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[10,11] As a consequence, fluorescence in situ hybridization (FISH) testing for *MYC*-R, followed by *BCL2* and *BCL6* loci if *MYC*-R is present, has become routine practice in many institutions, and the presence of *MYC*-DH/TH often triggers a distinct, sometimes more intensive therapeutic approach.

However, many questions about the role of *MYC*-R remain. The negative prognostic implication of a single-hit (SH) *MYC*-R has been reported variably. In addition, the partner gene associated with *MYC*-R, which can be either an immunoglobulin (IG) heavy

chain or light chain or a non-IG locus,[12] may affect outcome.[3] Given the relatively small sample sizes in previous studies, the prognostic impact of *MYC*-SH and *MYC*-DH/TH within the context of the *MYC* translocation partner (*MYC*-IG *v MYC*-non-IG) in DLBCL has been reported inconsistently. Similarly, the prognostic implication of DH lymphoma with *MYC*-R and *BCL6* rearrangement is also controversial.[3,10,13-15] The Lunenburg Lymphoma Biomarker Consortium (LLBC) set out to address these questions in a large cohort of patients with DLBCL who were uniformly treated with R-CHOP or R-CHOP–like immunochemotherapy within prospective clinical trials and population-based settings.

METHODS

DLBCL Cohorts

The LLBC compiled a cohort of patients with de novo, CD20+ DLBCL treated with curative intent with R-CHOP or R-CHOP–like immunochemotherapy, including patients enrolled in prospective clinical trials (The Lymphoma Study Association [LYSA]: LNH01-5B and LNH03-B[16-19]; German Study Group for High-Grade Non-Hodgkin's Lymphoma: RICOVER[20] and MegaCHOEP[21]; Hemato-Oncology Foundation for Adults in the Netherlands [HOVON]: HOVON 46 and HOVON 84) and from population-based registries with available clinical data (Leeds/Haematological Malignancy Research Network [United Kingdom], Barts Cancer Institute [United Kingdom], Stanford Cancer Institute [United States], and BC Cancer [Canada]). Diagnostic samples were reviewed by expert hematopathologists within each of the contributing LLBC groups and classified according to the current WHO classification.[11] Of note, aggressive B-cell lymphomas with morphologic features other than that of DLBCL (ie, intermediate morphology between Burkitt lymphoma and DLBCL or blastoid appearance) were not included in the current study. The study was approved by the ethics committees of all participating groups.

Immunohistochemistry and FISH Analysis

Immunohistochemical stains for MYC (clone EP121, also known as Y69; Epitomics, Burlingame, CA) and BCL2 (clone 124; Dako, Glostrup, Denmark) were performed on paraffin sections of tumors assembled in a tissue microarray (TMA) format (0.6-mm core diameter in duplicate) according to standard protocols and scored in 10% increments. DLBCL with 40% or greater MYC expression and 50% or greater BCL2 expression were designated dual-expressor DLBCL. Additional subgroups included DLBCL with MYC less than 40%/BCL2 less than 50%, MYC less than 40%/BCL2 greater than 50%, and MYC greater than 40%/BCL2 less than 50% expression. FISH assays (either on whole sections at the time of diagnosis or on the same TMAs) to detect breakpoints in the *MYC*, *BCL2*, and *BCL6* loci (break-apart probes from Abbott Molecular, Des Plaines, IL) underwent interlaboratory testing among all participating groups before the study and demonstrated very high rates of concordance (data not shown). DLBCL cases that had a breakpoint in the *MYC* locus were tested further for breaks in the *BCL2* and *BCL6* loci. In addition, *MYC*-R cases were tested for *MYC*/IG heavy chain fusion (Zytomed, Berlin, Germany) and, if negative, for *MYC*-IG kappa and *MYC*-IG light chain double-color fusion.[22] This strategy allowed for the assignment of patients with DLBCL to the following groups: DLBCL without *MYC*-R, *MYC*-SH (IG), *MYC*-SH (non-IG), *MYC*-DH/TH (IG), and *MYC*-DH/TH (non-IG). Cell of origin (COO) was assigned using the Hans algorithm[23] and/or gene expression–based assays.[24]

Statistical Analysis

The primary objective of the study was to validate the prognostic relevance of *MYC*-SH and *MYC*-DH/TH status within the context of the *MYC* translocation partner (*MYC*-IG *v MYC*-non-IG) in patients with DLBCL morphology. PFS was defined as the time between diagnosis and the first event, including death as a result of any cause or progression of disease (with or without treatment response). OS was defined as the time between diagnosis and death as a result of any cause. For PFS and OS, patients were censored at the latest date known to be alive. Variables were summarized by numbers and percentages (excluding missing values) for categorical data and by the mean and standard deviation and median and quartiles for quantitative data. The prognostic impact of *MYC* variables defined as rearranged (yes/no), including breakpoint in the *BCL2* and/or *BCL6* loci (yes/no), and IG partnership (IG *v* non-IG) on 5-year PFS and 5-year OS were estimated using the Kaplan-Meier method. PFS and OS curves were compared using the log-rank test. Median follow-up time was estimated using a reverse Kaplan-Meier estimator.[25,26] Cox proportional hazards regression was used to assess the association of the *MYC* variables and outcome. The models were stratified for the source of data (clinical trials or registries). Univariable and multivariable models were used to estimate hazard ratios (HRs) and their 95% CIs. Multivariable models included the International Prognostic Index (IPI) as the main confounder. The IPI was considered in two categories (low, 0 to 2; high, 3 to 5). The proportional hazard assumption was tested with Schoenfeld residuals.[27] Whenever relevant, the proportional hazard assumption was alleviated by dividing the time scale in agreement with the residuals' smoothing curves. A time-dependent effect was introduced for the corresponding variables that estimated effects before and after a given threshold. All *P* values less than 5% were considered statistically significant. All analyses were performed using R statistical software.[28] The hazard rate was estimated using cubic splines implemented in the survPen package.[29,30]

RESULTS

Patient Cohort

In total, 5,117 patients who met the criteria outlined in the Methods were identified. Of these, 2,383 patients (1,003

from clinical trials and 1,380 from registries) had available tissue samples suitable for TMA cores with evaluable FISH results for *MYC*-R and complete clinical data and represent the study cohort (Fig 1; Table 1). The study cohort was largely representative of the overall cohort, with no major discernible biases except for minor, nonsignificant differences in median age, IPI low versus high, Eastern Cooperative Oncology Group performance status, number of extranodal sites, and median follow-up. Within the study cohort, median age was 65.7 years (interquartile range, 55.7-73.6 years), and median follow-up time was 74.7 months (95% CI, 73 to 76.7 months). Survival curves of patients from each contributing group are shown in the Data Supplement.

FISH Results

Of the 2,383 study patients with DLBCL, 264 (11%) had an *MYC*-R, a proportion comparable with previously published data.[1,31] In 53 of the 264 patients, *BCL2* and/or *BCL6* rearrangement status could not be determined, and in 69 of

264 patients, the *MYC* partner gene (IG or non-IG) could not be assessed because of limited material or failure in one of the IG heavy or light chain FISH assays. Figure 1 shows the distribution of patients according to FISH results. Within the cohort of patients with full data on *MYC*-R and *BCL2* and *BCL6* rearrangements (n = 211), 72 (34%) had *MYC*-SH, 82 (39%) had *MYC*-DH with *BCL2*, 31 (15%) had *MYC*-DH with BCL6, and 26 (12%) had *MYC*-TH. Within the cohort of patients with available data on *MYC* partner gene status (n = 196), 107 (55%) had *MYC*-IG and 88 (45%) had *MYC*-non-IG. Details for patients within each contributing group are listed in Data Supplement.

Clinical Characteristics and Outcome of *MYC*-R DLBCL

Patient characteristics are listed in Table 1. Compared with patients with DLBCL without *MYC*-R, patients with DLBCL with *MYC*-R were slightly older (*P* = .027), were more likely to have stage III/IV disease (*P* = .009), had a poorer Eastern Cooperative Oncology Group performance status (*P* = .006) and were more likely to have numerous extranodal sites
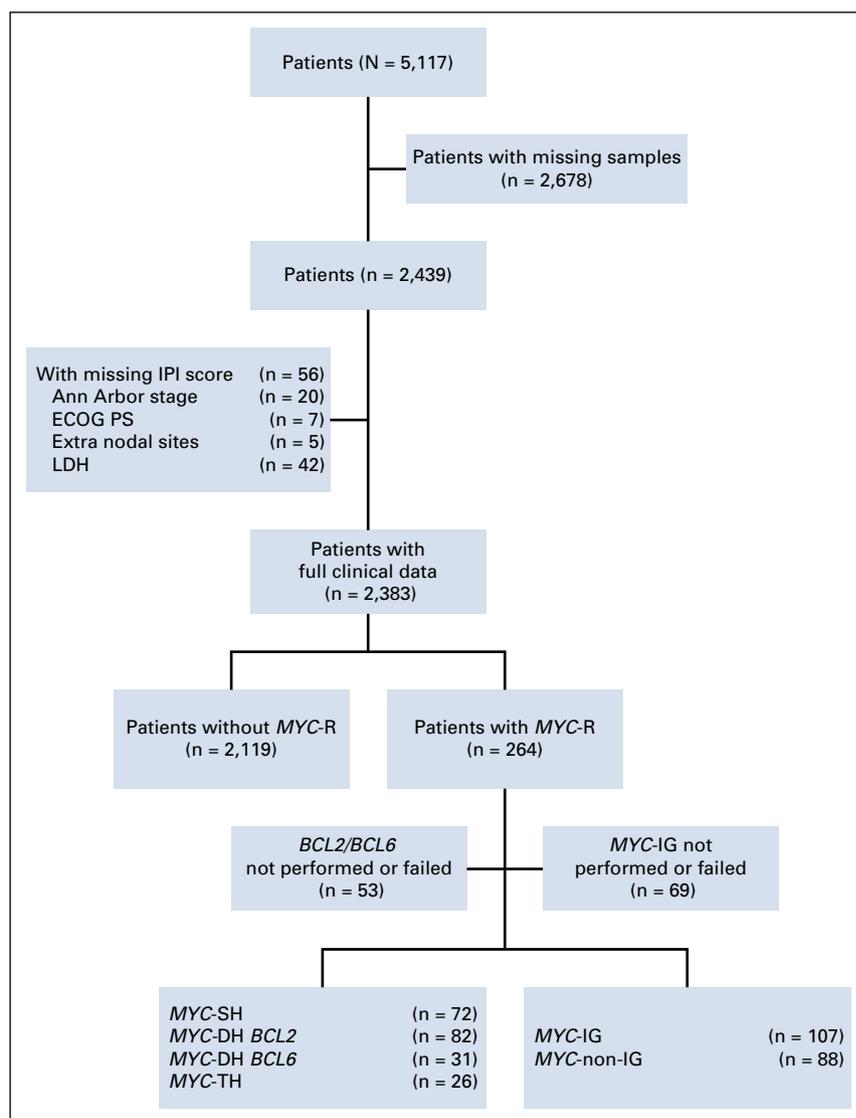

FIG 1. Flowchart of the diffuse large B-cell lymphoma study cohort. DH, double hit; ECOG PS, Eastern Cooperative Oncology Group performance status; IG, immunoglobulin; IPI, International Prognostic Index; LDH, lactate dehydrogenase; *MYC*-R, *MYC* rearrangement; SH, single hit; TH, triple hit.

TABLE 1. Clinical and Biologic Characteristics of the DLBCL Study Cohort

	Patients, No. (%)		
Characteristic	**All**	**Without *MYC*-R**	**With *MYC*-R**
No. of patients	2,383	2,119 (88.9)	264 (11.1)
Data source			
Registries	1,380 (57.9)	1,215 (57.3)	165 (62.5)
Trials	1,003 (42.1)	904 (42.7)	99 (37.5)
IPI score			
0-2	1,374 (57.7)	1,250 (59.0)	124 (47.0)
3-5	1,009 (42.3)	869 (41.0)	140 (53.0)
Missing	0	0	0
Age, years			
≤ 60	798 (33.5)	726 (34.3)	72 (27.3)
> 60	1,584 (66.5)	1,392 (65.7)	192 (72.7)
Missing	1	1	0
Ann Arbor stage			
I/II	938 (39.7)	854 (40.6)	84 (32.1)
III/IV	1,425 (60.3)	1,247 (59.3)	178 (67.9)
Missing	20	18	2
ECOG performance status			
≤ 1	1,933 (81.3)	1,736 (82.2)	197 (74.9)
1	443 (18.6)	377 (17.8)	66 (25.1)
Missing	7	6	1
No. of extra nodal sites			
≤ 1	1,797 (75.6)	1,618 (76.5)	179 (67.8)
1	581 (24.4)	496 (23.5)	85 (32.2)
Missing	5	5	0
Lactate dehydrogenase			
Normal	1,042 (45.5)	957 (46.9)	85 (34.1)
Elevated	1,248 (54.5)	1,084 (53.1)	164 (65.9)
Missing	93	78	15
MYC			
Negative	2,119 (92.8)	2,119 (100)	
SH (IG)	40 (1.7)		40 (27.2)
DH/TH (IG)	54 (2.4)		54 (36.7)
SH (non-IG)	17 (0.7)		17 (11.6)
DH/TH (non IG)	53 (2.3)		53 (36.0)
Missing	100		100
Death			
Yes	1,536 (65.1)	819 (60.3)	717 (71.8)
No	822 (34.9)	540 (39.7)	282 (28.2)
Progression			
No	1,347 (58.6)	716 (53.5)	631 (65.7)
Yes	950 (41.4)	623 (46.5)	330 (34.3)

Abbreviations: DH, double hit; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IG, immunoglobulin; IPI, International Prognostic Index; *MYC*-R, *MYC* rearrangement; SH, single hit; TH, triple hit.

(P = .002) and an elevated lactate dehydrogenase level (P < .001; Table 1). Overall, the presence of *MYC*-R was a predictor of inferior PFS and OS (Figs 2A and 2B). Of note, a time-dependent effect on outcome for *MYC*-R was noted, with the strongest impact within the first 2 years after diagnosis (PFS: HR, 1.7 [95% CI, 1.4 to 2.1]; OS: HR, 2.1 [95% CI, 1.7 to 2.7]). Beyond 24 months, the negative impact of *MYC*-R was not observed for either PFS (HR, 0.7; 95% CI, 0.4 to 1.2) or OS (HR, 0.8; 95% CI, 0.5 to 1.4). The negative prognostic impact of *MYC*-R was independent of the variables within the IPI (PFS: HR, 1.6 [95% CI, 1.3 to 2.0]; OS: HR, 2.0 [95% CI, 1.6 to 2.5]).

We next analyzed the impact of *MYC*-SH versus *MYC*-DH/TH on clinical outcome. As expected, DLBCL with *MYC*-DH/TH had inferior PFS and OS compared with DLBCL without *MYC*-R (Figs 2C and 2D). Again, there was a strong effect on outcome only within the first 2 years after diagnosis (PFS: HR, 1.8 [95% CI, 1.3 to 2.4]; OS: HR, 2.4 [95% CI, 1.8 to 3.3]). Of note, within the group with *MYC*-R DLBCL, the presence of *MYC*-SH affected neither PFS (HR, 1.2; 95% CI, 0.8 to 1.7) nor OS (HR, 1.3; 95% CI, 0.9 to 2.0). On multivariable analysis, including the IPI score (low/high), presence of *MYC*-SH and *MYC*-DH/TH, and the time interval before and after 24 months postdiagnosis, only the IPI and presence of *MYC*-DH/TH (as a variable before 24 months) were significant predictors of PFS (both P < .001; Table 2), whereas the presence of *MYC*-SH was not significant (P = .25). Multivariable analysis that evaluated predictors of OS demonstrated similar findings.

DLBCL With *MYC*-DH Involving *BCL6*

In patients with DLBCL morphology, *MYC*-DH that involves *BCL6* is less commonly encountered than *MYC*-DH/TH with *BCL2*, and studies have yielded controversial results about its clinical relevance in view of small cohort sizes.[3,10,12-15] Our study cohort included 31 patients with *MYC*-DH with *BCL6* rearrangement, and we found no evidence of a difference in outcome (PFS, OS) compared with patients with *MYC*-DH with *BCL2* rearrangement or those with the presence of an *MYC*-TH constellation (Fig 3).

Prognostic Implications of the *MYC*-R Partner (IG *v* Non-IG)

We analyzed the impact of the *MYC*-R partner gene (IG *v* non-IG) on PFS and OS. Among patients with *MYC*-R, only those with *MYC*-DH/TH in which *MYC* was rearranged with an IG partner (*MYC*-IG) demonstrated inferior outcome (Fig 4). The early effect was again evident in the analysis (PFS: HR, 2.9 [95% CI, 2.0 to 4.3]; OS: HR, 3.6 [95% CI, 2.5 to 5.4]) within 24 months after diagnosis. Patients with *MYC*-SH (either IG or non-IG) and those with MYC-DH/TH non-IG had an outcome comparable with those with DLBCL without *MYC*-R (*MYC* negative). In multivariable Cox proportional hazards regression models for PFS and OS that included the various MYC subgroups, the time-dependent effect and the IPI demonstrated a significant impact of the
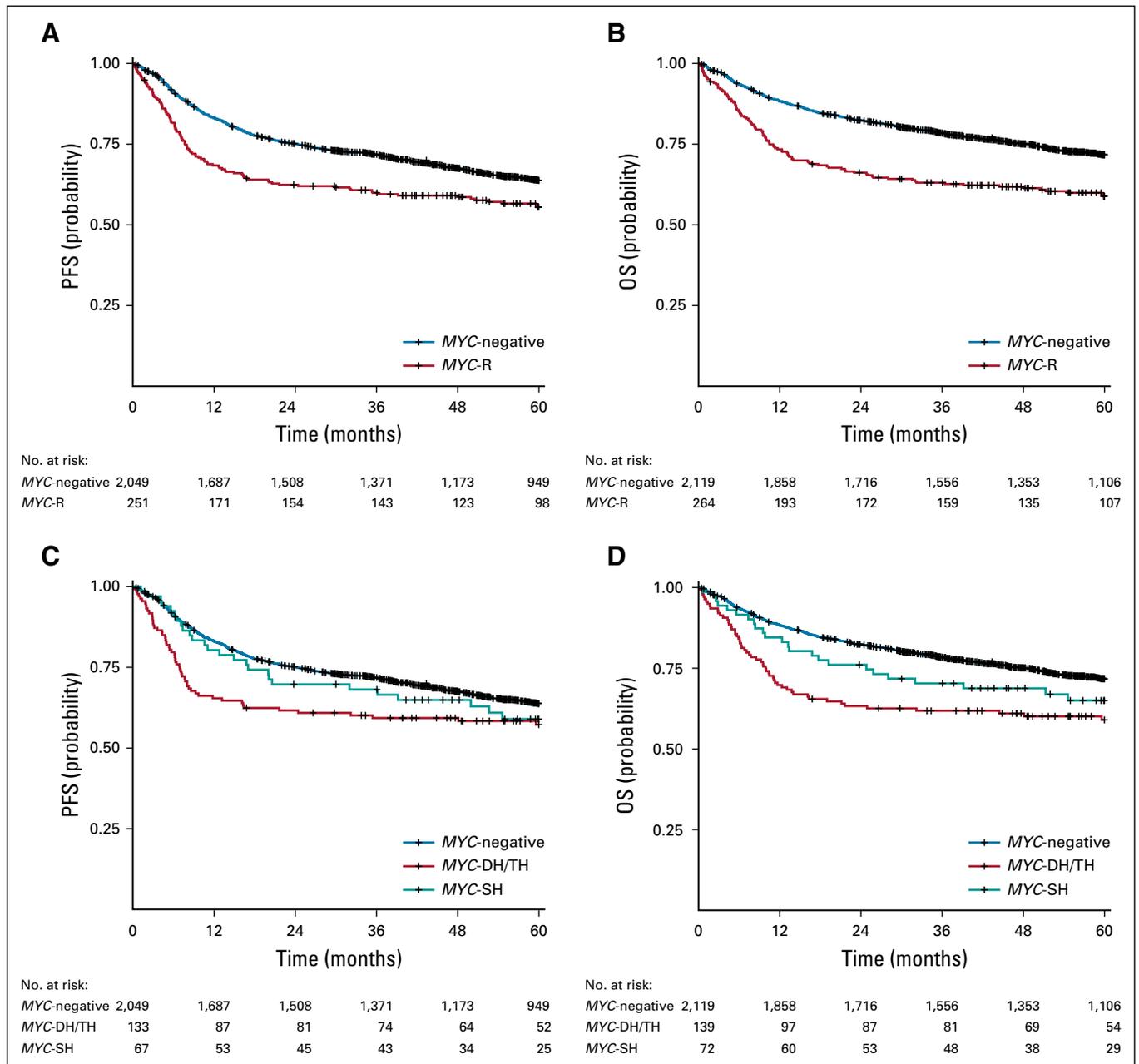
FIG 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) according to MYC-rearrangement (*MYC*-R); (B) overall survival (OS) according to *MYC*-R; (C) PFS according to *MYC* single-hit (SH), double-hit (DH), or triple-hit (TH) constellation; and (D) OS according to *MYC*-SH, -DH, or -TH constellation.

MYC-DH/TH (IG) constellation ($P < .001$) and the IPI ($P < .001$), whereas all other variables were not significant (Table 2).

Impact of MYC and BCL2 Expression and COO on Outcome

A total of 1,414 patients with DLBCL with available immunohistochemical expression status of the MYC and BCL2 proteins were available for analysis. Survival curves (PFS, OS) for the four subgroups (with and without including patients with *MYC*-DH/TH) are shown in the Data Supplement. In accordance with numerous published studies, dual-expressor DLBCL (40% or greater MYC expression and 50% or greater BCL2 expression) had an inferior outcome (overall log-rank $P < .001$). The COO assignment using the Hans algorithm (with and without including patients with MYC-DH/TH) was prognostic in the entire cohort (n = 1,919) and within the groups of clinical trial and registry patients separately (n = 698 and 1,221, respectively). In line with previous results, *MYC*-R was more frequent in germinal center B-cell–like (GCB) DLBCL (16.6%) compared with non-GCB DLBCL (6.3%; $P < .001$), and patients with *MYC*-DH that involved BCL2 and those with *MYC*-TH almost exclusively fell into the GCB

TABLE 2. Multivariable Cox Proportional Hazards Regression Models for *MYC*-SH and *MYC*-DH/TH DLBCL (Model 1) and for *MYC* Variables, Including IG/Non-IG Partners (Model 2)

Model	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1				
MYC-negative	1		1	
MYC-DH/TH before 24 months	1.67 (1.25 to 2.23)	**< .001**	2.20 (1.64 to 2.96)	**< .001**
MYC-DH/TH after 24 months	0.42 (0.17 to 1.02)	.055	0.44 (0.18 to 1.08)	.073
MYC-SH	1.22 (0.82 to 1.80)	.25	1.45 (0.96 to 2.18)	.077
IPI low	1		1	
IPI high	2.51 (2.18 to 2.90)	**< .001**	2.83 (2.41 to 3.32)	**< .001**
Model 2				
MYC-negative	1		1	
MYC-DH/TH (IG) before 24 months	2.43 (1.65 to 3.58)	**< .001**	3.04 (2.05 to 4.60)	**< .001**
MYC-DH/TH (IG) after 24 months	0.45 (0.11 to 1.81)	.26	0.71 (0.23 to 2.21)	.55
Other*	1.04 (0.74 to 1.48)	.91	1.24 (0.87 to 1.77)	.24
IPI low	1		1	
IPI high	2.52 (2.18 to 2.91)	**< .001**	2.82 (2.40 to 3.32)	**< .001**

NOTE. Boldface indicates significance at *P* < .05.

Abbreviations: DH, double hit; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; IG, immunoglobulin; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; SH, single hit; TH, triple hit.

*Other = *MYC*-SH (IG), *MYC*-SH (non-IG), and *MYC*-DH/TH (non-IG).

DLBCL subgroup, whereas those with *MYC*-DH that involved BCL6 were found in both COO subgroups. *MYC*-SH DLBCL that occurred in the non-GCB subgroup tended to have an inferior outcome compared with *MYC*-SH DLBCL in the GCB subgroup (*P* = .076 for OS).

DISCUSSION

Our study addresses a number of open questions about *MYC* translocations in aggressive B-cell lymphomas with DLBCL morphology. The 2017 WHO revision[11] established a new category of high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangement. This decision was influenced by emerging data from studies that demonstrated inferior survival of patients with aggressive B-cell lymphomas that carry an *MYC* translocation either alone or in combination with a *BCL2* and/or *BCL6* translocation.[2-9] As a consequence, the routine work-up of aggressive B-cell non-Hodgkin lymphoma (B-NHL) at many institutions now includes FISH testing for *MYC*-R and, if positive, for *BCL2* and *BCL6* loci. However, several unanswered issues remain. First, the diagnosis of high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangement includes various morphologies (Burkitt-like morphology, blastoid appearance, and DLBCL morphology). Some studies suggest that the negative prognostic impact of an *MYC*-DH/TH constellation in aggressive B-NHL with DLBCL morphology is less pronounced compared with lymphomas with other morphologies.[3,31] Second, the prognostic role of the *MYC* translocation partner (IG *v* non-IG) has been

investigated in only a few and relatively small studies that included aggressive B-NHL with different morphologies as well as transformed lymphomas.[5,12,32,33] A pivotal study by Copie-Bergman et al[3] that focused on aggressive B-NHL with DLBCL morphology treated uniformly in prospective clinical trials of the French Study Group of Adult Lymphoma/LYSA suggested that the negative prognostic impact of *MYC*-R correlated with the *MYC* translocation partner (IG *v* non-IG), although the number of DLBCLs that showed *MYC* translocation with an IG or non-IG partner was relatively small (n = 24 and 26, respectively). With the inclusion of these DLBCLs from the French Study Group of Adult Lymphoma/LYSA, our study now comprises 94 DLBCL tumors with *MYC*-R to an IG gene locus and 70 with *MYC*-R to a non-IG locus, which is the largest series in our knowledge reported to date.

In this study, the LLBC, whose members represent leading trial groups or registries in Europe and North America, addressed some of the existing controversies. Of note, we focused on aggressive B-NHLs with DLBCL morphology that were treated uniformly with an R-CHOP or R-CHOP–like therapy. A uniform and thorough FISH strategy (in particular for the light-chain loci) included an interlaboratory validation procedure among the participating centers before the pooling of the clinical and FISH data.

In our large cohort of 2,383 patients with DLBCL, we confirm the strong negative prognostic impact of the
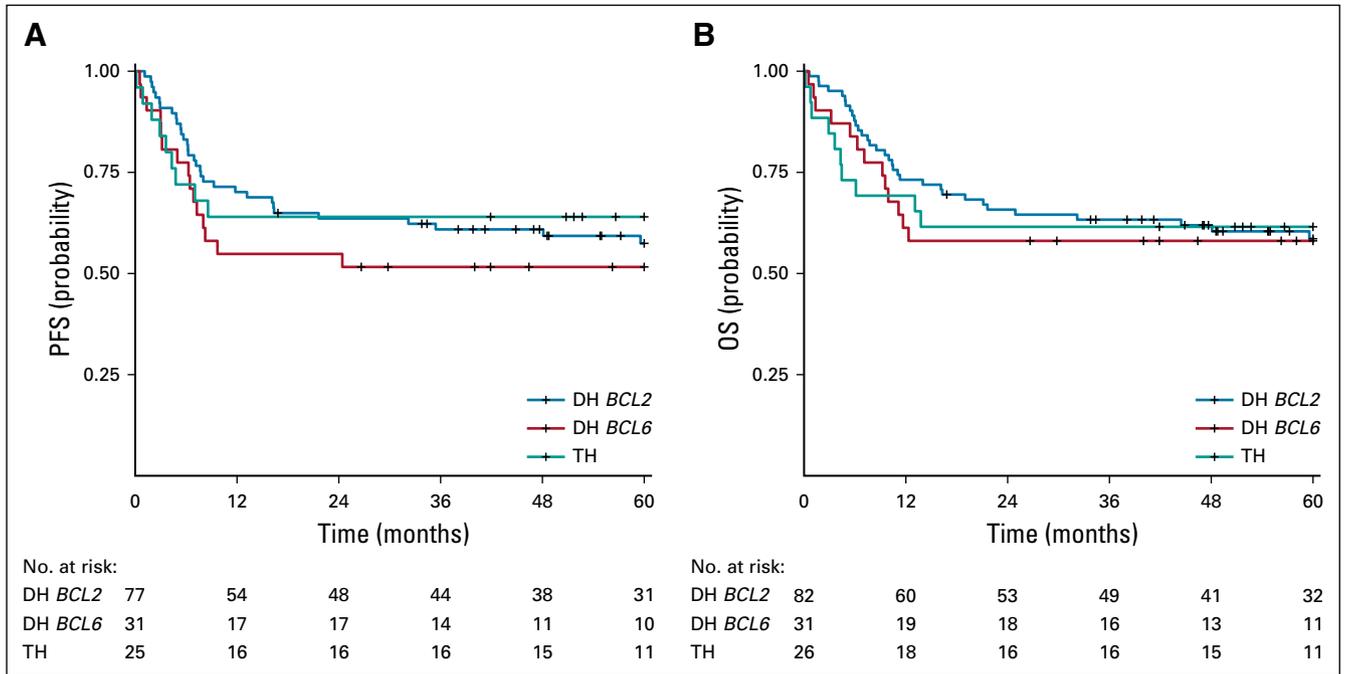
FIG 3. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) for patients with diffuse large B-cell lymphoma with rearranged *MYC* with associated breaks in *BCL2* or *BCL6* or both loci (double hit [DH]/triple hit [TH]; overall log-rank *P* = .38 and .62, respectively).

presence of *MYC*-R on survival. By statistically analyzing time-dependent effects, we demonstrated that this impact was only evident within the first 2 years after the diagnosis. Thus, the survival probability of patients with *MYC*-R DLBCL who survived for at least 2 years did not differ from those with DLBCL without *MYC*-R. This 2-year effect was also

evident in DLBCL with an *MYC*-SH and *MYC*-DH/TH constellation when analyzed separately. However, although *MYC*-DH/TH DLBCL clearly showed decreased PFS and OS, the negative impact of *MYC*-SH was negligible and not statistically significant. These data suggest that little justification exists for altering initial therapeutic approaches in
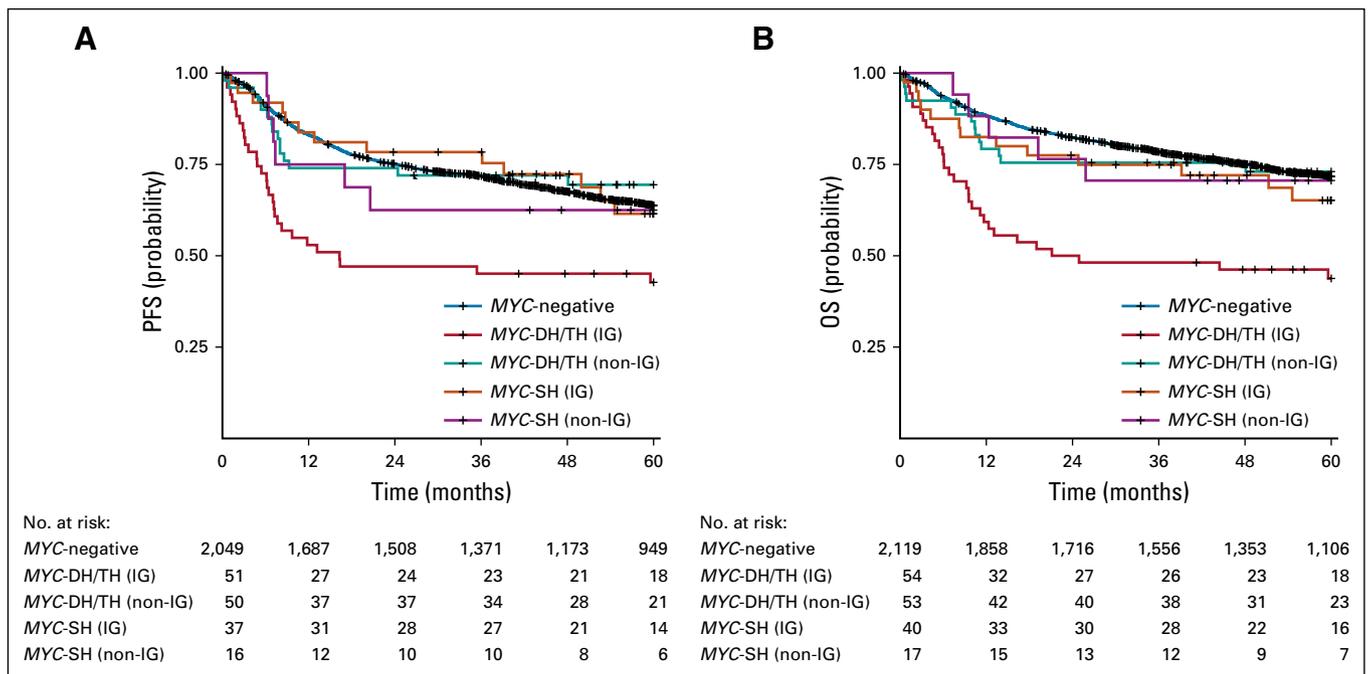

FIG 4. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) for patients with diffuse large B-cell lymphoma without *MYC* rearrangement (*MYC*-negative), patients with *MYC* single hit (SH; immunoglobulin [IG]), *MYC*-SH (non-IG), *MYC* double hit/triple hit (DH/TH; IG), or *MYC*-DH/TH (non-IG).

patients with DLBCL whose tumors carry an *MYC* translocation alone (*MYC*-SH). However, for *MYC*-DH/TH DLBCL, the major negative prognostic impact and 2-year effect support the practice of optimizing first-line treatment approaches to achieve maximum complete response rates because salvage treatment at relapse is not effective.[34]

Of note, our study provides additional evidence that the survival rate for patients with *MYC*-DH/TH lymphoma with DLBCL morphology may be significantly better (approximately 60% after 5 years) compared with those with *MYC*-DH/TH lymphoma with Burkitt-like or blastoid morphology.[5,32,34,35] This finding supports the statement in the updated WHO classification[11] that the morphology of the tumor cells should be provided in the pathology report when the diagnosis of a high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement is made. Potential consequences of this morphologic information for treatment purposes, however, remain unclear. Furthermore, the outcomes are superior to those previously reported for tumors with DLBCL morphology treated with R-CHOP.[10] This likely reflects a historic selection bias in FISH testing of patients with high-risk features that was mitigated in the current study by applying FISH to all tumors.

Our data also contribute to the open question of whether DLBCL with *MYC*-R and *BCL6* rearrangement differ clinically from *MYC/BCL2* or *MYC/BCL2/BCL6* rearrangement.[3,10,12-15] Differences could be expected because *MYC/BCL6*-positive DLBCL at least partially falls into the group of activated B-cell DLBCL, whereas DLBCL with *MYC/BCL2* or *MYC/BCL2/BCL6* rearrangement almost exclusively belongs in the group of GCB DLBCL.[1] Our series of 31 patients with DLBCL with an *MYC/BCL6* double represents, in our knowledge, the largest number of such patients reported to

date and shows no differences in clinical features, including IPI factors or survival outcomes compared with other *MYC*-DH/TH DLBCLs.

Our study also confirms a prior report that the type of the *MYC* translocation partner (IG *v* non-IG) has a prognostic impact. Non-IG translocation partners of *MYC* in aggressive B-cell lymphomas include *PAX5*, *BCL6*, and *IKAROS*, among many others.[36] Whether the juxtaposition of *MYC* to enhancers of these genes has different biologic consequences compared with the juxtaposition of *MYC* to IG enhancers is not well studied.[3,12] Also unclear is whether the *MYC* translocation partner affects the recently established DH gene expression or molecular high-grade signatures.[37,38] Our data strongly suggest that patients with DLBCL in which *MYC* is rearranged to a non-IG partner do not differ in outcomes from those with DLBCL without *MYC*-R. Of note, this also holds true for patients with *MYC*-DH/TH DLBCL in which the *MYC* partner is a non-IG gene. The finding that only patients with DLBCL-DH/TH in which *MYC* is rearranged to an IG partner have significantly worse PFS and OS might have two major implications. First, future FISH strategies in DLBCL may have to include the IG light-chain loci in cases where *MYC* is rearranged, and second, risk-adjusted therapeutic approaches in DLBCL may be needed only for *MYC*-DH/TH cases in which *MYC* is rearranged to an IG partner. Because the large impact of this genetic constellation seems to be restricted to the first 2 years after diagnosis, emphasis should be given to optimizing first-line treatment and consolidation after complete remission. Thus, the MYC effect is a compelling biologic contributor to the 2-year event-free survival/PFS effect seen in many prospective studies of DLBCL that was proposed and further validated as a surrogate end point in several large studies.[39,40]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prognostic Significance of *MYC* Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium

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