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ORIGINAL REPORT

Young Patients With Non–Germinal Center B-Cell–Like Diffuse Large B-Cell Lymphoma Benefit From Intensified Chemotherapy With ACVBP Plus Rituximab Compared With CHOP Plus Rituximab: Analysis of Data From the Groupe d'Etudes des Lymphomes de l'Adulte/Lymphoma Study Association Phase III Trial LNH 03-2B

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ABSTRACT

Purpose
To determine whether any tumor biomarkers could account for the survival advantage observed in the LNH 03-2B trial among patients with diffuse large B-cell lymphoma (DLBCL) and low-intermediate risk according to the International Prognostic Index when treated with dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) compared with standard rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP).

Patients and Methods
Using immunohistochemistry, expression of CD10, BCL6, MUM1, MYC, and BCL2 and coexpression of MYC/BCL2 were examined. The interaction effects between each biomarker and treatment arm on survival were studied in a restricted model and a full model incorporating clinical parameters.

Results
Among the 379 patients analyzed in the trial, 229 tumors were evaluable for germinal center B-cell–like (GCB)/non-GCB subclassification according to the Hans algorithm. Among all the biomarkers, only the interaction between the Hans algorithm and the treatment arm was significant for progression-free survival (PFS) and overall survival (OS) in univariable (PFS, $P = .04$; OS, $P = .01$) and multivariable (PFS, $P = .03$; OS, $P = .01$) analyses. Non-GCB tumors predicted worse PFS (hazard ratio [HR], 3.21; 95% CI, 1.29 to 8.00; $P = .01$) and OS (HR, 6.09; 95% CI, 1.37 to 27.03; $P = .02$) among patients treated with R-CHOP compared with patients who received R-ACVBP, whereas there were no significant survival differences between these regimens among patients with GCB tumors.

Conclusion
The survival benefit related to R-ACVBP over R-CHOP is at least partly linked to improved survival among patients with non-GCB DLBCL. Therefore, the Hans algorithm could be considered a theragnostic biomarker for selecting young patients with DLBCL who can benefit from an intensified R-ACVBP immunochemotherapy regimen.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common adult lymphoma, accounting for 25% of all lymphoid neoplasms.[1] Most patients are now treated with anthracycline-containing regimens with the addition of the anti-CD20 antibody, a combination that leads to cure in approximately 50% to 80% of patients according to the International Prognostic Index (IPI).[2-5] The first-line treatment is crucial,

because the estimate of progression-free survival (PFS) at 3 years is only 23% when the disease is refractory to immunochemotherapy with rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP).[6] Important issues remain unresolved, such as the optimum rituximab dose and schedule and the optimum chemotherapy regimen. Dose-intensification related to R-CHOP did not show any benefit with an R-CHOP 14-day cycle regimen versus an R-CHOP 21-day cycle regimen in two recent phase III trials.[7,8] Findings from the multicenter, randomized, phase III, first-line LNH 03-2B trial indicated that compared with R-CHOP, intensified immunochemotherapy with the rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) regimen in addition to subsequent consolidation improves the survival of patients age 18 to 59 years with DLBCL with low-intermediate risk according to the IPI; the findings included 3-year estimates of PFS and overall survival (OS) of 87% and 92% with R-ACVBP versus 73% and 84% with R-CHOP, respectively.[9] Because hematologic and mucosal toxicity are increased in patients treated with R-ACVBP, it is critical to better define which patients are more likely to benefit from this intensive chemotherapy. This improvement in survival compared with R-CHOP could depend on tumor biology, tumor volume, pharmacokinetics, or pharmacogenomics. Considering tumor biology, the cell of origin (COO) classification defined by gene expression profiling (GEP) differentiates germinal center B-cell–like (GCB) from activated B-cell (ABC) DLBCL.[10-12] Different oncogenic events have been linked to these subtypes, and tumor cells responded differentially to the CHOP and R-CHOP regimens according to the oncogenic pathways activated, with a poorer OS in ABC-like DLBCL.[10-13] This COO classification in DLBCL has been translated on paraffin-embedded tissues via the combined immunostaining of CD10, BCL6, and MUM1/IRF4 using the Hans algorithm.[14] This algorithm, which is most widely used clinically, has been confirmed as one with the highest concordance with the GEP (86%)[15] and was also associated with poorer survival in patients with non-GCB DLBCL who were treated with R-CHOP[15,16]; however, this result was not reproducible in many groups.[17-20] Other biomarkers such as MYC and/or BCL2 overexpression analyzed using immunohistochemistry[21-23] have been shown to identify distinct subgroups of patients with poor prognosis when treated with R-CHOP and who could thus benefit from alternative regimens. The aim of our study was to determine whether any of these biomarkers could account for the advantage of survival observed in patients included in trial LNH 03-2B when treated with R-ACVBP compared with R-CHOP.

PATIENTS AND METHODS

Patient Selection

Three hundred eighty patients with previously untreated de novo CD20$^+$ DLBCL were enrolled onto the Groupe d'Etudes des Lymphomes de l'Adulte/Lymphoma Study Association (LYSA) LNH 03-2B trial. LNH 03-2B was an open-label randomized trial comparing dose-intense R-ACVBP with subsequent consolidation versus standard R-CHOP. Patients were eligible if they were age 18 to 59 years and had only one adverse prognostic factor, as defined by the age-adjusted IPI (increased lactate dehydrogenase [LDH], Ann Arbor stage III or IV, Eastern Cooperative Oncology Group performance status of 2 to 4). Details regarding the design and data management of the LNH 03-2B trial have been published.[9] This study complied with all provisions of the Declaration of Helsinki and was performed in accordance with good clinical practice guidelines. All of the patients provided written informed consent to participate and to provide tissue material for review and biologic studies.

Morphology

A central review was performed by at least two pathologists from LYSA (D.C. and T.J.M.) to confirm the diagnosis of CD20$^+$ DLBCL according to the WHO classification. A central pathology review was completed for 344 patients (91%), confirming DLBCL diagnosis in 156 patients (90%) in the R-ACVBP group and 161 patients (94%) in the R-CHOP group. In total, 25 patients were considered as having the primary mediastinal large B-cell lymphoma (PMBL) subtype. Tissue microarrays (TMAs) containing three representative 0.6-mm cores of routinely processed tissues from patients with DLBCL were prepared (Beecher Instruments, Silver Spring, MD). Only patients with DLBCL and large tumor tissue blocks (excluding needle biopsies) were selected for TMA. The quality of each tissue core was evaluated for morphology using hematoxylin and eosin staining, and the percentage of CD20$^+$ tumor cells was evaluated using CD20 immunostaining. In addition, we added patients included in the LNH 03-2B trial without TMA but with at least five unstained slides in the LYSA tissue bank available for additional immunohistochemistry after central pathologic review.

Immunohistochemistry

Paraffin-embedded, 3-μm-thick sections (either from TMA or unstained slides) were subjected to antigen retrieval and antibody staining. The immunoperoxidase stains were performed on a Benchmark Ultra automated stainer (Roche Ventana, Tucson, AZ) using Ultraview Universal diaminobenzidine detection kits and optimized protocols for CD10, BCL6, MUM1, BCL2, and MYC staining (Appendix Table A1, online only). The COO classification was based on the Hans algorithm using CD10, BCL6, and MUM1 expression with cutoff levels of 30%.[14] The presence of CD10$^+$ stromal cells or neutrophils was considered a positive internal control along with the nuclear staining of reactive lymphoid cells for BCL6, MUM1, and MYC or cytoplasmic staining for BCL2. In the absence of an internal positive control, immunostains were considered nonevaluable. The tissue core with the highest percentage of tumor cell staining was considered for analysis. GCB/non-GCB scoring was evaluated by two pathologists (T.J.M. and D.C.) with consensus agreement using a two-head microscope in case of discordance. MYC and BCL2 were scored by two pathologists (J.B. and C.C.-B.), and the thresholds used were in accordance with published thresholds, such as 40% for MYC and 50% or 70% for BCL2.[21,22]

Statistical Analysis

Patient characteristics and response rates were compared using the χ^2 or Fisher's exact test, depending on the number of observations. PFS was measured from the date of random assignment to the date of disease progression, relapse, or death from any cause. OS was measured from the date of random assignment to the date of death from any cause. PFS and OS were analyzed using the log-rank test and expressed as Kaplan-Meier plots. Interactions between the treatment arm and biomarkers were evaluated in a restricted model, which considered only the treatment arm and the biomarker tested, and in a full model, which was adjusted for clinical parameters. Multivariable analyses were performed using the Cox proportional hazards regression model. Differences between the results of comparative tests were considered significant at a two-sided $P < .05$. Statistical analyses were performed using SAS 9.1.3 software (SAS Institute, Cary, NC) by the LYSA Research Clinic Statistical Office investigators and two authors (J.P.J. and N.M.).

RESULTS

Among the 379 patients analyzed in the study, 287 lymphomas were immunostained and 229 (80%) could be classified using the Hans algorithm classification on the entire population of TMA and unstained slides (Fig 1). A total of 175 DLBCLs were derived from the TMA, and 54 other cases were derived from the available unstained slides. There were no significant differences in the clinical characteristics or outcomes of these selected series (age, sex, "B" symptoms, performance status, stage, LDH, number of extranodal sites, bulky

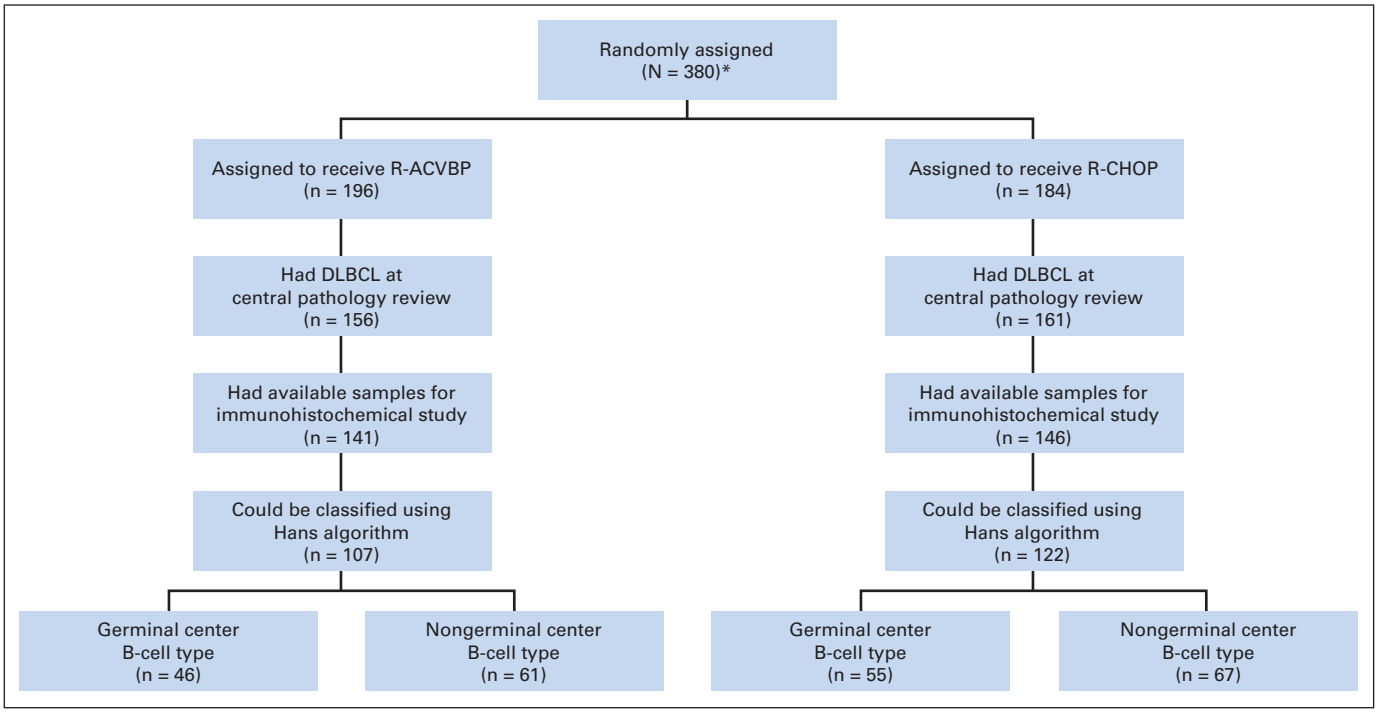

Fig 1. CONSORT diagram. Trial profile and cell of origin data. (*) One patient withdrew consent before treatment, and 379 patients were included in the intent-to-treat population. DLBCL, diffuse large B-cell lymphoma; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, followed by a consolidation phase consisting of methotrexate, rituximab, ifosfamide, etoposide, and cytarabine; R-CHOP, standard rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

mass, bone marrow involvement, complete remission, 3-year PFS, and 3-year OS) compared with the entire LNH 03-2B population, with the exception of the number of extranodal sites, which is not a parameter of the age-adjusted IPI factor used for the stratification of the LNH 03-2B trial (Table 1; Appendix Table A2, online only). One hundred seven patients were treated with R-ACVBP, and 122 patients were treated with R-CHOP.

Among all of the clinical parameters, the presence of a bulky mass was the only parameter predicting a poor OS ($P = .007$); however, it did not predict a poor PFS. A total of 101 tumors (44%) were classified as GCB, and 128 tumors (56%) were classified as non-GCB according to the Hans algorithm. Seventy-six tumors (44%) were BCL2 positive and 95 tumors (56%) were BCL2 negative using the 70% threshold; 95 tumors were BCL2 positive using the 50% threshold. Forty-seven tumors (27%) were MYC positive and 127 tumors (73%) were MYC negative using the 40% threshold. Twenty-eight tumors (17%) were MYC and BCL2 positive (70% threshold for BCL2). Neither any single immunohistochemical marker nor the Hans algorithm or MYC-/BCL2-positive combination significantly affected PFS or OS in the entire population. PFS and OS did not differ between the GCB and non-GCB profile in the overall population ($P = .90$ and $P = .68$, respectively; Figs 2A and 2B). However, our aim was to determine whether any immunohistochemical tumor biomarkers could potentially account for the survival advantage observed in favor of R-ACVBP in the LNH 03-2B trial. Therefore, we tested the interaction between the treatment arm and all of the biomarkers considering PFS and OS. We tested this interaction using both a restricted model (including only the treatment arm and the tested biomarker) and a full model (adjusted for clinical parameters, such as the presence of a bulky mass, LDH level, and stage). MYC expression (40% threshold), BCL2 expression (50% or 70% threshold), and MYC (40%) and BCL2 (50% or 70%) coexpression did not significantly interact with the treatment arm for either PFS or OS, in either the restricted or full models (Table 2). In addition, the log-rank curves did not find any relevant thresholds for MYC and/or BCL2 interacting with the treatment arm for either PFS or OS (Data Supplement). However, regarding the GCB/non-GCB phenotype according to the Hans algorithm, the interaction was significant for PFS and OS, both in the restricted model (PFS, $P = .04$; OS, $P = .01$) and the full model (PFS, $P = .03$; OS, $P = .01$), and there was a poorer survival rate among patients with non-GCB tumors treated with R-CHOP than those treated with R-ACVBP (Table 3). The interaction in the multivariable analysis was still significant when patients with PMBL were excluded (PFS, $P = .02$; OS, $P = .01$).

The estimated hazard ratios (HRs) between R-CHOP and R-ACVBP were significant among patients with non-GCB tumors both for PFS (HR, 3.21; 95% CI, 1.29 to 8.00; $P = .01$) and OS (HR, 6.09; 95% CI, 1.37 to 27.03; $P = .02$), whereas there were no significant survival differences between these regimens among patients with GCB tumors. As illustrated by the log-rank curves (Figs 2C and 2D), there was no difference in PFS and OS between R-ACVBP and R-CHOP among patients with GCB tumors ($P = .84$ and $P = .33$, respectively). However, PFS and OS were significantly longer among non-GCB patients treated with R-ACVBP compared with those treated with R-CHOP (3-year PFS rate, 93%; 95% CI, 82% to 97.3% *v* 74%; 95% CI, 61% to 83%; $P = .0074$; 3-year OS rate, 97%; 95% CI, 87% to 99% *v* 83%; 95% CI, 71% to 91%; $P = .0067$; Figs 2E and 2F). The median follow-up time for survival analyses did not differ between the 379 patients included in the trial and the 229 patients with the COO phenotype (PFS, 43.7 months; 95% CI, 40.8 to 45.7 months *v* 43.6 months; 95% CI, 40.3 to 47.3 months; OS,

Table 1. Demographic and Clinical Characteristics of the Selected Population Compared With the Nonselected LNH 03-2B Population

Characteristic	Nonselected Population (n = 150) No. of Patients	%	Selected Population (n = 229) No. of Patients	%	*P*
Median age, years	47		48		.997
Sex					.09
Male	97	65	128	56	
Female	53	35	101	44	
"B" symptoms					.06
No	100	67	173	76	
Yes	50	33	56	25	
Performance status					.25
< 2	150	100	227	99	
≥ 2	0	0	2	1	
Stage					.07
I-II	59	39	112	49	
III-IV	91	61	117	52	
LDH					.23
≤ Normal	90	60	123	54	
> Normal	60	40	106	46	
No. of extranodal sites					.01
≤ 1	101	67	180	79	
> 1	49	33	49	21	
Mass > 10 cm					.07
No	110	73	185	81	
Yes	40	27	43	19	
Bone marrow biopsy					.17
Negative	121	83	199	88	
Positive	24	17	26	12	
Complete remission (after induction)	51	36	94	41	.75
Complete remission (at end of treatment)	70	47	141	62	.06
3-Year PFS, %	80.3		80.7		.74*
3-Year OS, %	88.1		90.1		.33*
Completed treatment					.36
Yes	126	84	200	87	
No	24	16	29	13	
Treatment arm					.02
R-ACVBP	89	59	107	47	
R-CHOP	61	41	122	53	

Abbreviations: LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP, rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.
*Log-rank *P* value.

44.2 months; 95% CI, 41.7 to 46.8 months *v* 43 months; 95% CI, 40.8 to 46.8 months, respectively). Considering the 25 patients with PMBL, 17 were classified as non-GCB subtype using the Hans algorithm. Among the 15 patients with PMBL treated with R-CHOP, three patients experienced relapse/progression, whereas no relapse/progression was observed among the 10 patients with PMBL treated with R-ACVBP.

DISCUSSION

Our aim was to determine whether the difference in patient survival observed between the R-ACVBP and R-CHOP arms in the LNH 03-2B trial was associated with the COO established via immunohistochemistry according to the Hans algorithm or with MYC and/or BCL2 overexpression. We did not observe any significant interaction effects on survival between the treatment arm and MYC and/or BCL2 overexpression, suggesting that the expression of these two proteins in tumor cells did not differentially modify the sensitivity of the tumor cells to these two chemotherapy regimens. In this series of young patients with DLBCL and one factor on the age-adjusted IPI, BCL2/MYC overexpression was not associated with a poor outcome, although this overexpression has been clearly demonstrated as prognostic in previous series of patients with DLBCL treated with R-CHOP.[21,22] The low number of MYC-/BCL2-positive samples (n = 28) could explain the limited statistical power for identifying any survival differences. In addition, MYC-/BCL2-positive DLBCLs are prevalent in 63% to 76% of tumors of the ABC[21] or non-GCB DLBCL[22] subtype; the different response to treatment in our series observed for the non-GCB subtype could have been an additional factor underlying the absence of a strong effect when considering the entire study population (R-CHOP and R-ACVBP).

In contrast, we found a significant interaction effect on both PFS and OS between the treatment arm and the Hans algorithm. Although this study was an unplanned secondary analysis of the trial, there was a striking difference both in PFS and OS among patients with non-GCB DLBCL when treated with R-ACVBP versus when treated with R-CHOP, suggesting that the observed survival advantage is at least partially linked to tumor cell biology. R-CHOP is a drug combination that has greater success against GCB tumors compared with ABC-like tumors. The Hans algorithm is the WHO classification recommended algorithm to differentiate GCB from non-GCB tumor cells via immunohistochemistry,[1] and it correlates well (86% concordance) with GEP.[15] The dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab regimen has been evaluated in terms of COO classification, and it shows better PFS and OS among patients with GCB tumors compared with those with non-GCB tumors in both single- and multi-institutional settings, suggesting preferential targeting in the treatment of oncogenic pathways activated in GCB tumors.[24,25]

The better survival observed in the this study among patients with non-GCB tumors when treated with R-ACVBP compared with R-CHOP suggests that oncogenic events specific to non-GCB tumor cells, the hallmark being nuclear factor-κB (NF-κB) activation,[26] can be better targeted with R-ACVBP and a consolidation regimen than with R-CHOP. Compared with R-CHOP, we believe that the benefit of R-ACVBP in the non-GCB subtype is associated with the better ability of this regimen to avoid the persistence of an NF-κB–addicted chemotherapy-resistant niche, which can explain the better PFS and OS, because the clinical response at the end of the treatment did not differ. Indeed, in murine models of aggressive B-cell lymphoma (Eμ-*Myc*) after treatment with DNA-damaging agents such as cyclophosphamide, high NF-κB activity (associated with the *IκBα* expression level) is associated with a relapse-prone pattern.[27] Interestingly, methotrexate suppresses NF-κB activation through the inhibition of IκBα phosphorylation and degradation,[29] and it has also been shown to enhance irradiation-induced cell death in natural killer/T-cell lymphoma cell lines through the suppression of NF-κB activation.[30] The consolidation regimen of R-ACVBP started with two cycles of methotrexate followed by four cycles of rituximab, ifosfamide, and etoposide and two cycles of cytarabine. Therefore, we might suggest that in

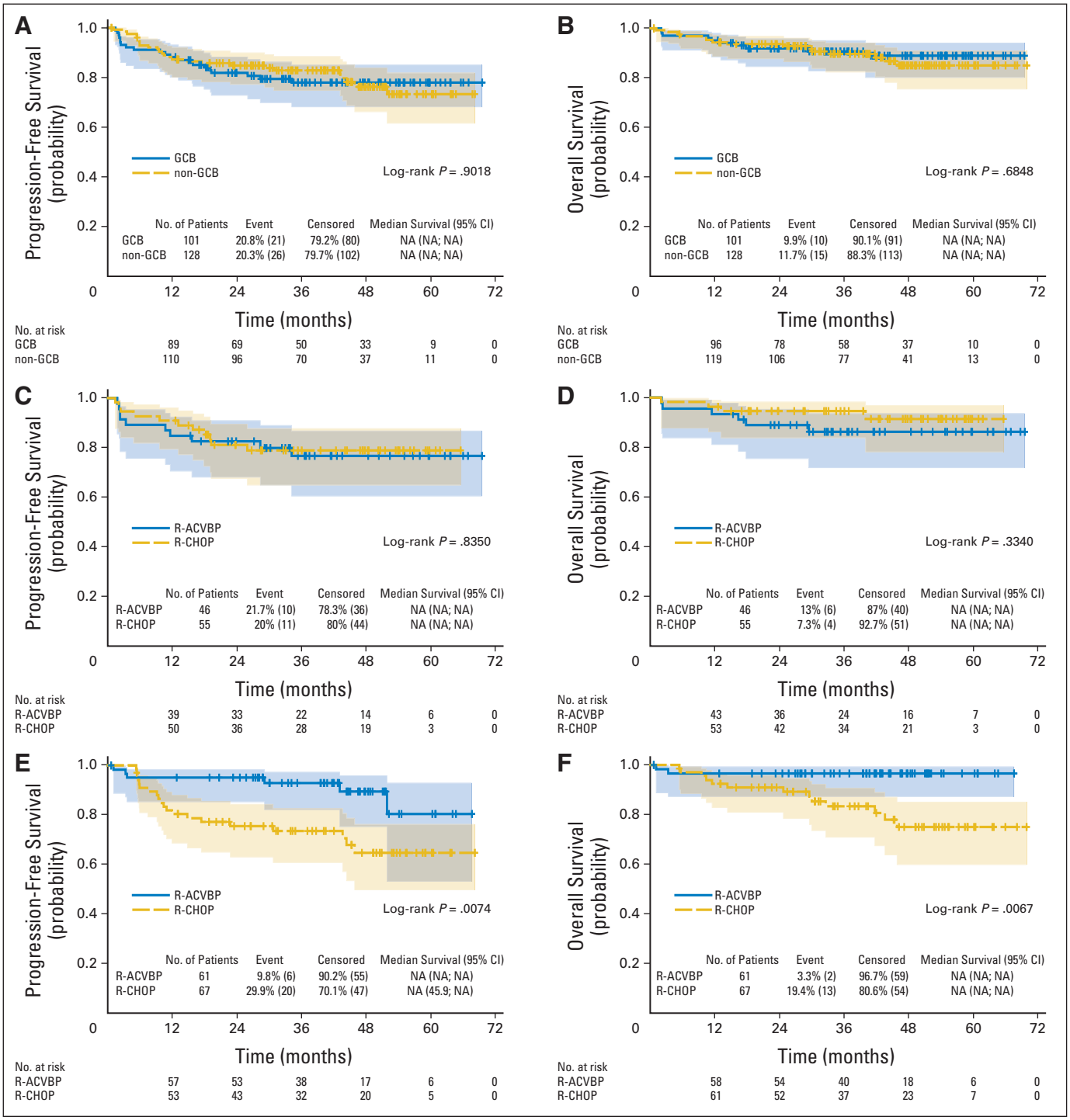

Fig 2. Kaplan-Meier estimates of progression-free survival and overall survival according to (A and B) germinal center B-cell–like (GCB)/non-GCB subtype, (C and D) among patients with GCB tumors according to treatment arm, and (E and F) among patients with non-GCB tumors according to treatment arm. NA, not available; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, followed by a consolidation phase consisting of methotrexate, rituximab, ifosfamide, etoposide, and cytarabine; R-CHOP, standard rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

the consolidation regimen of R-ACVBP, methotrexate suppressed the major oncogenic pathway activated in non-GCB DLBCL NF-κB–addicted cells, most likely allowing the sensitization of this chemotherapy-resistant niche to new genotoxic drugs (ifosfamide, etoposide, cytarabine), whereas this was not the case when using four additional cycles of R-CHOP in the other arm. The additional observation that R-CHOP in a 14-day cycle was not associated with better survival when compared with R-CHOP in a 21-day cycle in two recently published phase III trials[7,8] suggests that dose-intensity does not play a major role. The efficiency of targeting NF-κB in non-GCB DLBCL has been suggested by a phase I/II study of 40 previously untreated patients with de novo DLBCL using bortezomib plus R-CHOP.[31] The results of

Table 2. Interaction Between Biomarker Expression Determined via Immunohistochemistry and the Treatment Arm

Parameter	Interaction HR	95% CI	*P*
Interaction between treatment arm and GCB/non-GCB (Hans algorithm)			
PFS	3.73	1.07 to 13.06	.04
OS	11.67	1.65 to 82.36	.01
Interaction between treatment arm and BCL2 (50%*)			
PFS	1.27	0.30 to 5.45	.75
OS	1.06	0.15 to 7.52	.95
Interaction between treatment arm and BCL2 (70%*)			
PFS	2.66	0.63 to 11.24	.18
OS	2.71	0.37 to 20.09	.33
Interaction between treatment arm and MYC (40%*)			
PFS	1.15	0.21 to 6.27	.87
OS	0.58	0.04 to 8.12	.68
Interaction between treatment arm and MYC (40%*)/BCL2 (50%*)			
PFS	0.88	0.12 to 6.23	.90
OS	1.15	0.06 to 22.55	.93
Interaction between treatment arm and MYC (40%*)/BCL2 (70%*)			
PFS	1.48	0.18 to 12.22	.72
OS	†	†	.20‡

Abbreviations: GCB, germinal center B-cell like; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Threshold considered when analyzing the biomarker.
†Interaction parameter not estimable because of a lack of events in one subgroup arm.
‡Likelihood ratio test of the models with and without the interaction term. The interaction parameter quantifies the heterogeneity of HRs between treatment arms according to the marker status by estimating the ratio of these two HRs. For example, an interaction HR of 3.73 for the Hans algorithm signifies that the HR between the rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone (R-CHOP) arm and rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) arm is 3.73-fold higher for the non-GCB subtype compared with the GCB subtype.

Table 3. Multivariable Analysis of Progression-Free Survival and Overall Survival

Parameter	Hazard Ratio	95% CI	*P*
Progression-free survival			
Mass > 10 cm, yes	1.83	0.94 to 3.57	.08
Interaction between treatment arm and Hans algorithm	4.26	1.21 to 15.05	.02
LDH > normal	1.54	0.53 to 4.52	.43
Stage III-IV	1.03	0.34 to 3.11	.96
No. of extranodal sites > 1	1.68	0.78 to 3.61	.19
R-CHOP *v* R-ACVBP for GCB patients	0.75	0.31 to 1.81	.52
R-CHOP *v* R-ACVBP for non-GCB patients	3.21	1.29 to 8.00	.01
Overall survival			
Mass > 10 cm, yes	3.35	1.43 to 7.89	.01
Interaction between treatment arm and Hans algorithm	13.38	1.87 to 95.74	.01
LDH > normal	0.88	0.20 to 3.85	.86
Stage III-IV	0.59	0.13 to 2.68	.50
No. of extranodal sites > 1	1.71	0.56 to 5.20	.35
R-CHOP *v* R-ACVBP for GCB patients	0.46	0.13 to 1.65	.23
R-CHOP *v* R-ACVBP for non-GCB patients	6.09	1.37 to 27.03	.02

Abbreviations: GCB, germinal center B-cell like; LDH, lactate dehydrogenase; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP, rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

current phase II and III studies evaluating bortezomib combined with R-CHOP will shed light on the potential benefit of this NF-κB pathway inhibitor in patients with non-GCB or ABC-like DLBCL.

At a time when ongoing phase III trials are aiming to improve R-CHOP by adding lenalidomide[32] or a Bruton's tyrosine kinase inhibitor[33] to the treatment regimen for non-GCB patients, the observation of increased survival in this specific population when using a conventional regimen such as R-ACVBP could offer an attractive comparison. The potentially important role of the consolidation regimen in the sensitization of NF-κB–addicted chemotherapy-resistant tumor cells to DNA damage–induced cell death has to be proven ex vivo and could further diminish the impact of the nonavailability of vindesine in the United States, which is used during the induction regimen of R-ACVBP. It might also be of interest to evaluate multiagent chemotherapy regimens using methotrexate and cytarabine in an alternating fashion (eg, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cytarabine plus methotrexate [R-Hyper-CVAD/MA] or rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/rituximab, etoposide, ifosfamide, cytarabine [R-CODOX-M/R-IVAC]) for the treatment of non-GCB DLBCL. Clinical follow-up in the few patients with PMBL in our series (mainly classified as non-GCB using the Hans algorithm) might suggest that R-ACVBP is more active than R-CHOP, but this concept has to be demonstrated in a larger series. In conclusion, our study suggests that R-ACVBP could be preferentially selected for non-GCB tumors in young patients with DLBCL of low-intermediate risk. This observation suggests the use of the Hans algorithm, which is widely applied by pathologists, as a theragnostic biomarker for management of first-line DLBCL in clinical practice; it has also been suggested for use with relapsing DLBCL.[34]

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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Table A1. Antibodies Used and Protocols for Immunohistochemistry

Antibody	Clone	Source*	Incubation and Dilution	Antigen Retrieval	Amplification
CD10	56C6	Novocastra	2 hours, 1/25	CC1 buffer; pH 8.4; 92 minutes; 95°C	4 minutes/4 minutes
BCL6	PG-B6p	Dako	2 hours, 1/5	CC1 buffer; pH 8.4; 92 minutes; 95°C	4 minutes/4 minutes
MUM1	Mum1p	Dako	2 hours, 1/20	CC1 buffer; pH 8.4; 92 minutes; 95°C	4 minutes/4 minutes
BCL2	129	Dako	2 hours, 1/25	CC1 buffer; pH 8.4; 92 minutes; 95°C	4 minutes/4 minutes
MYC	Y69	Epitomics (Clinisciences)	32 minutes, 1/100	CC1 buffer; pH 8.4; 92 minutes; 95°C	4 minutes/4 minutes

*Novocastra, Newcastle, United Kingdom; Dako, Glostrup, Denmark; Epitomics, Burlingame, CA.

Table A2. Baseline Demographic and Clinical Characteristics of Non-GCB Patients Treated With R-ACVBP or R-CHOP

Characteristic	No. of Patients		*P*
	R-ACVBP (n = 61)	R-CHOP (n = 67)	
Sex			.39
Male	32	30	
Female	29	37	
Median age, years	42	48	.45
Performance status			—
> 2	61	67	
≥ 2	0	0	
Stage			.79
I-II	35	40	
II-IV	26	27	
"B" symptoms			.36
No	42	51	
Yes	19	16	
Mass > 10 cm			.80
No	49	55	
Yes	12	12	
No. of extranodal sites			.31
≤ 1	54	55	
> 1	7	12	
LDH			.94
≤ Normal	26	29	
> Normal	35	38	
Bone marrow			.42
Not involved	55	61	
Involved	3	6	
Response after induction			.54
CR/CRu	44	45	
No CR/CRu	17	22	
Response at the end of treatment			.39
CR/CRu	51	52	
No CR/CRu	10	15	
Treatment completion			.02
Yes	49	63	
No	12	4	

Abbreviations: CR/CRu, complete remission/complete remission unconfirmed; GCB, germinal center B-cell like; LDH, lactate dehydrogenase; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP, rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.