

# Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older

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**PURPOSE** The prognosis of elderly patients with diffuse large B-cell lymphoma (DLBCL) is worse than that of young patients. An attenuated dose of chemotherapy—cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-miniCHOP)—is a good compromise between efficacy and safety in very elderly patients. In combination with R-CHOP (R2-CHOP), lenalidomide has an acceptable level of toxicity and may mitigate the negative prognosis of the non-germinal center B-cell-like phenotype. The Lymphoma Study association conducted a multicentric, phase III, open-label, randomized trial to compare R-miniCHOP and R2-miniCHOP.

**PATIENTS AND METHODS** Patients of age 80 years or older with untreated DLBCL were randomly assigned into the R-miniCHOP21 group or the R2-miniCHOP21 group for six cycles and stratified according to CD10 expression and age. The first cycle of rituximab was delivered by IV on D1 after a prephase and then delivered subcutaneously on D1 of cycles 2-6. Lenalidomide was delivered at a dose of 10 mg once daily on D1-D14 of each cycle. The primary end point was overall survival (OS).

**RESULTS** A total of 249 patients with new DLBCL were randomly assigned (127 R-miniCHOP and 122 R2-miniCHOP). The median age was 83 years (range, 80-96), and 55% of the patients were classified as non-GCB. The delivered dose for each R-miniCHOP compound was similar in both arms. Over a median follow-up of 25.1 months, the intention-to-treat analysis revealed that R2-miniCHOP did not improve OS (2-year OS 66% in R-miniCHOP and 65.7% in R2-miniCHOP arm,  $P = .98$ ) in the overall population or in the non-GCB population. Grade 3-4 adverse events occurred in 53% of patients with R-miniCHOP and in 81% of patients with R2-miniCHOP.

**CONCLUSION** The addition of lenalidomide to R-miniCHOP does not improve OS. Rituximab delivered subcutaneously was safe in this population.

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## INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, and its incidence steadily increases with age. Approximately 40% of patients with DLBCL are older than 70 years. Despite the development of the anti-CD20 antibody in combination with chemotherapy, the prognosis of elderly patients with newly diagnosed DLBCL is worse than that of young patients. Comorbidities and physiological organ function impairment often lead to unmanageable toxicities and limit optimal chemotherapy. An attenuated dose of chemotherapy (cyclophosphamide, doxorubicin,

vincristine, and prednisone, referred to as mini-CHOP) with a conventional dose of anti-CD20, that is, rituximab (R) or ofatumumab, has been evaluated by the LYSA group in two phase II trials and is considered a good compromise between efficacy and safety in patients older than 80 years.<sup>1-3</sup> In this setting, the 2-year overall survival (OS) varied from 59% to 65%. Toxicities were manageable, as most events occurred during the first two cycles. A prephase containing a short course of vincristine and prednisone eventually improves outcome in this frail population.<sup>1,4-6</sup> Although there is no specific histological DLBCL subtype in very elderly patients, it is currently well-recognized that the

## ASSOCIATED CONTENT

See accompanying editorial on page 1193

## Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

How to improve the current standard attenuated dose of immunochemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab [R-mini-CHOP]) to treat patients older than 80 years with newly diagnosed diffuse large B-cell lymphoma (DLBCL)?

### Knowledge Generated

The addition of lenalidomide to R (sub/cutaneous)-miniCHOP schema does not improve overall survival (OS) irrespective of germinal center B-cell-like/activated B-cell-like status and results in more adverse events. Albuminemia is, with staging, the most significant factor related to OS, independent of the International Prognostic Index and geriatric scales.

### Relevance

Rituximab delivered subcutaneously with miniCHOP remains a gold standard in very elderly patients with DLBCL and led to a 2-year OS of 66%. Albuminemia can be used as a simple and strong prognostic marker.

frequency of the two main molecular-defined subtypes, namely, germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, differs according to patient age. Additionally, an increase in the ABC subtype prevalence during the aging of patients with DLBCL has been widely reported, even if its clinical and prognostic relevance among patients older than 80 years remains unclear.<sup>7</sup> Many strategies have been proposed to more specifically target the ABC DLBCL subtype and attenuate its unfavorable outcome. Lenalidomide is an oral immunomodulatory drug with complex and pleiotropic immunologic and antiproliferative activities in B-cell lymphomas.<sup>8</sup> Lenalidomide demonstrated activity in xenograft models of ABC DLBCL by down-regulating the BCR-NFκB pathway through inhibition of IRF4 and Cereblon.<sup>9</sup> In combination with R-CHOP (R2-CHOP), lenalidomide has acceptable levels of toxicity and may mitigate the negative prognosis of the non-GCB phenotype.<sup>7,10-14</sup> It has also been suggested that the clinical benefit of lenalidomide monotherapy in patients with DLBCL was more evident in the gene-expression profiling (GEP)-defined ABC population.<sup>15</sup> On the basis of these data, we designed a randomized phase III clinical trial to determine the tolerance and efficacy of the R2-miniCHOP regimen in comparison to R-miniCHOP in patients older than 80 years with newly diagnosed DLBCL.

## PATIENTS AND METHODS

### Study Design and Patients

SENIOR is a multicentric, phase III, open-label, randomized trial for patients of age 80 years or older with previously untreated CD20 + DLBCL. Eligibility criteria included stages II-IV, measurable disease, a revised International Prognostic Index (IPI) score of 1 or higher, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or lower. The exclusion criteria were known CNS lymphoma or meningeal involvement, cardiac dysfunction assessed by isotopic or echotomographic measure, or renal

insufficiency assessed by creatinine clearance lower than 40 mL/min (minimal residual disease).

Eligible patients were randomly assigned 1:1 to standard R-miniCHOP or R2-miniCHOP on a 21-day cycle for six cycles. Patients were stratified in each arm according to CD10 expression (local assessment with a threshold of positivity of 30%) and age ( $\leq 85$  years or  $> 85$  years). Patients provided written informed consent before enrollment. This study was approved by an independent research ethics committee and performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, the Declaration of Helsinki (1996), and local regulatory requirements and laws. An independent Data and Safety Monitoring Committee (DSMC) reviewed safety and risk and/or benefit throughout the clinical trial at planned intervals.

### Treatment Procedure

All patients received prephase treatment with vincristine (1 mg total dose given once intravenously 1 week before cycle 1 [day - 7]) and oral prednisone (60 mg/m<sup>2</sup> once daily total dose, days - 7 to - 1) before the first cycle of R/R2-miniCHOP. R-MiniCHOP consisted of rituximab 375 mg/m<sup>2</sup> intravenously once on day 1 and then 1,400 mg total dose subcutaneously once on day 1 of cycles 2-6, 25 mg/m<sup>2</sup> once on day 1 of doxorubicin, 400 mg/m<sup>2</sup> once on day 1 of cyclophosphamide, and 1 mg once on day 1 of vincristine, and 40 mg/m<sup>2</sup> of oral prednisone once daily on days 1-5. Lenalidomide was given at a dose of 10 mg once daily TD on D1 to D14 every 3 weeks with venous thrombosis prophylaxis (aspirin or low-molecular-weight heparin; Data Supplement, online only).

### Cell of Origin Classification

Available tumor samples were retrospectively classified for the cell of origin (COO) subtypes (namely, GCB, ABC, and unclassified) by central laboratory GEP of formalin-fixed paraffin-embedded biopsy tissue using Lymph2CX assay

**TABLE 1.** Clinical and Biological Features of the SENIOR Cohort

Characteristic	R-miniCHOP n = 127 (%)	R2-miniCHOP n = 122 (%)	Total N = 249 (%)
Sex			
Male	56 (44)	57 (46)	113 (45)
Age (year)			
80-85	95 (75)	93 (76)	188 (75.5)
> 85	32 (25)	29 (24)	61 (24.5)
Ann Arbor stage			
I-II	22 (17)	16 (13)	38 (15)
III-IV	105 (83)	106 (87)	211 (85)
Performance status (ECOG)			
0-1	91 (72)	95 (78)	186 (75)
2	36 (28)	27 (22)	63 (25)
IPI			
Missing	1	3	4
0-2	32 (25)	33 (28)	65 (26.5)
3-5	94 (75)	86 (72)	180 (73.5)
CD10 expression (IHC)			
Negative	79 (62)	79 (65)	158 (63.5)
Positive	48 (38)	43 (35)	91 (36.5)
Phenotype (Hans algorithm)			
GCB	41 (40)	54 (50)	95 (45)
Non-GCB	62 (60)	55 (50)	117 (55)
Missing data	24	13	37
Phenotype (Lymph2CX)			
GCB or unclassified	39 (50)	44 (58)	83 (54)
ABC	38 (50)	33 (42)	71 (46)
Missing data	50	45	95
MYC expression (IHC)	41/72 (57)	45/76 (59)	86/148 (58)
BCL2 expression (IHC)	90/100 (90)	90/102 (89)	180/202 (89)
MYC or BCL2 double expressor	39/68 (57)	40/70 (57)	79/138 (57)
MYC rearrangement (FISH)	9/83 (11)	13/86 (15)	22/169 (13)
BCL2 rearrangement (FISH)	19/83 (23)	16/82 (19)	35/165 (21)
BCL6 rearrangement (FISH)	21/85 (25)	18/83 (21)	39/168 (23)
Double or triple hits (FISH)	6/116 (5)	5/118 (4)	11/223 (5)

NOTE. BCL2/MYC protein expression was determined according to standard IHC methods and thresholds (> 50% and > 40%, respectively). *MYC/BCL6/BCL2* rearrangements were determined as previously reported.<sup>28</sup>

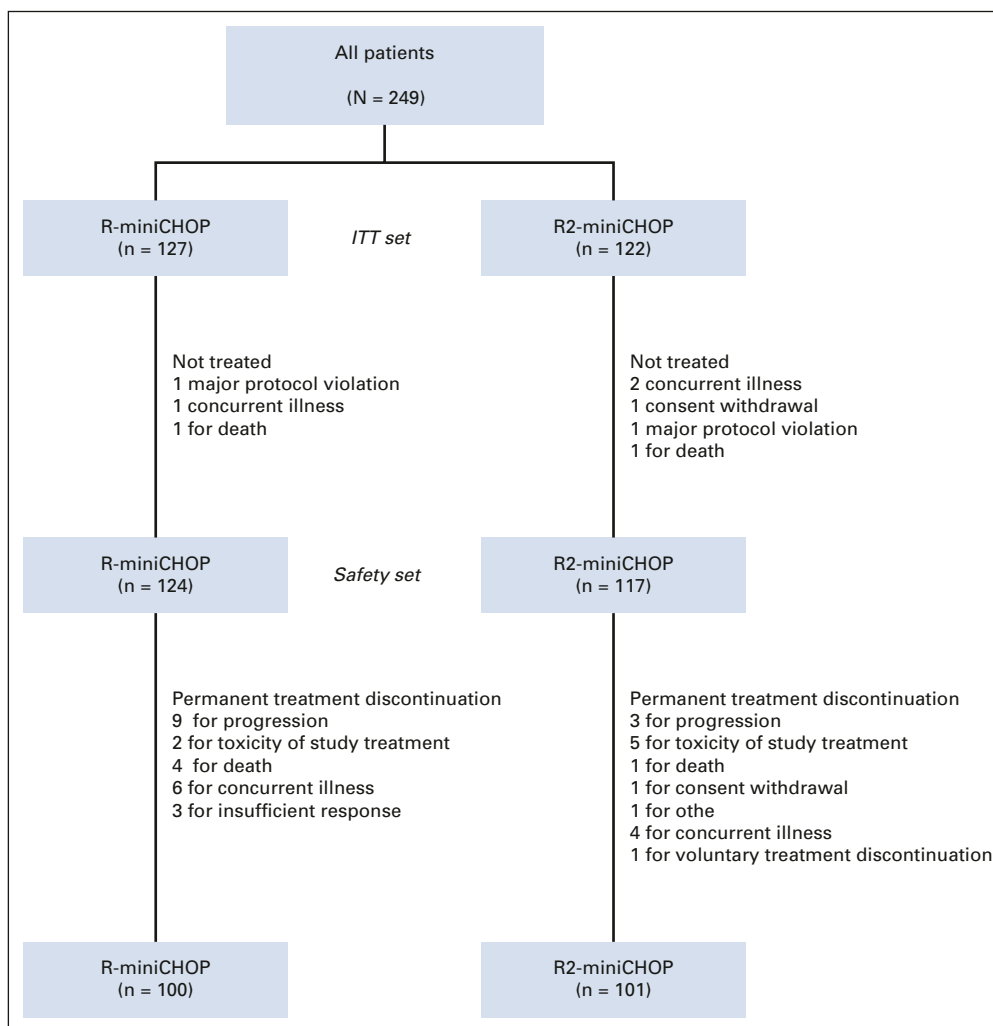
Abbreviations: ABC, activated B-cell-like; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell-like; IHC, immunohistochemistry; IPI, International Prognostic Index.

(NanoString Technologies, Seattle, WA).<sup>16</sup> Hans-based immunohistochemistry (IHC) classification (CD10, BCL6, and MUM1) was retrospectively performed by the central review platform to define GCB and non-GCB subtypes<sup>17</sup>.

### Primary and Secondary End Points and Assessments

Primary efficacy analyses were conducted in the intention-to-treat (ITT) population, defined as all patients who were

randomly assigned, regardless of whether they received treatment. The primary end point was OS. Secondary end points were progression-free survival (PFS), event-free survival (EFS), duration of response (DOR) for complete responders and unconfirmed complete responders (CR/CRu), response rate at the end of the treatment, and the differential efficacy of the R2-miniCHOP according to the GCB/non-GCB IHC phenotype.



**FIG 1.** Patient disposition. ITT, intention-to-treat; R-miniCHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; R2-miniCHOP, R-miniCHOP plus lenalidomide.

Responses were assessed by investigators using computed tomography according to published criteria in 1999.<sup>18</sup> Bone marrow biopsy was not mandatory. Adverse events (AEs) were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). A geriatric status assessment was performed at baseline using the instrumental activities of daily living (IADL) scale, the Cumulative Illness Rating Scale-Geriatric (CIRSG), the Mini Nutritional Assessment (MNA), and G8 scoring.<sup>19-21</sup>

### Statistical Analysis

The primary end point was the OS. Using a one-arm survival sample size, we designed the trial to have 80% power to detect an increase from 59% to 74% in the 2-year OS at the overall 5% significance level in favor of the experimental arm, leading to the inclusion of a total of 250 patients. A Cox regression model was used to assess the effect of prognostic factors on OS in multivariate analyses. EFS, PFS, and OS were compared between arms using the

stratified log-rank test and Cox proportional hazards model. Survival distribution was estimated using the Kaplan-Meier product-limit method. CR rates were compared using the 95% CI according to the Pearson-Clopper method. All statistical analyses were performed in SAS (version 9.3, Cary, NC) by the investigators of the LYSARC statistical office.

## RESULTS

### Patient Characteristics

From August 20, 2014, to September 13, 2017, 249 patients enrolled in the study were randomly assigned at a 1:1 ratio to R-miniCHOP (n = 127) or R2-miniCHOP (n = 122). Baseline characteristics are summarized in Table 1. A total of 212 DLBCL were classified according to IHC (85%), of which 55% were non-GCB and treated with R-miniCHOP (62 of 103, 60%) and R2-miniCHOP (55 of 109, 50%). The Lymph2CX molecular COO classification was obtained in 154 cases (62%) (Table 1).

## Treatment Delivery

Forty-eight (19%) patients discontinued treatment. Patient disposition is summarized in the CONSORT diagram shown in Figure 1. The median diagnosis-to-treatment interval was 33 days (range, 8-89) in the R-miniCHOP arm and 35 days (range, 0-154) in the R2-miniCHOP arm (Data Supplement).

In the safety set population ( $n = 241$ ), the six planned cycles were delivered in 80% and 86% of patients in R-miniCHOP and R2-miniCHOP, respectively. Seventy-five percent of patients received  $\geq 75\%$  of the planned dose of lenalidomide. Twenty (17%) patients experienced a dose reduction, 17 (85%) of which were due to AEs. The dose of lenalidomide decreased constantly over the six cycles and was reduced by 25% or more in 20% of patients (Data Supplement). Twenty out of 117 (17.1%) patients stopped permanently lenalidomide during planned treatment.

## Primary Objective

With a median follow-up of 25.1 months, the ITT analysis revealed that the primary end point of OS was not significantly different between the two arms (HR, 0.99; 95% CI, 0.65 to 1.5;  $P = .98$ , Fig 2). The 2-year OS was 66% (95% CI, 56.4 to 74.0) in the R-miniCHOP arm and 65.7% (95% CI, 55.6 to 74.1) in the R2-miniCHOP arm.

Among treated patients, 42 (34%) deaths occurred in the R-miniCHOP arm (29 for lymphoma progression) and 43 (37%) in the R2-miniCHOP arm (24 for lymphoma progression). Causes of death are provided in the Data Supplement.

## Secondary Objectives

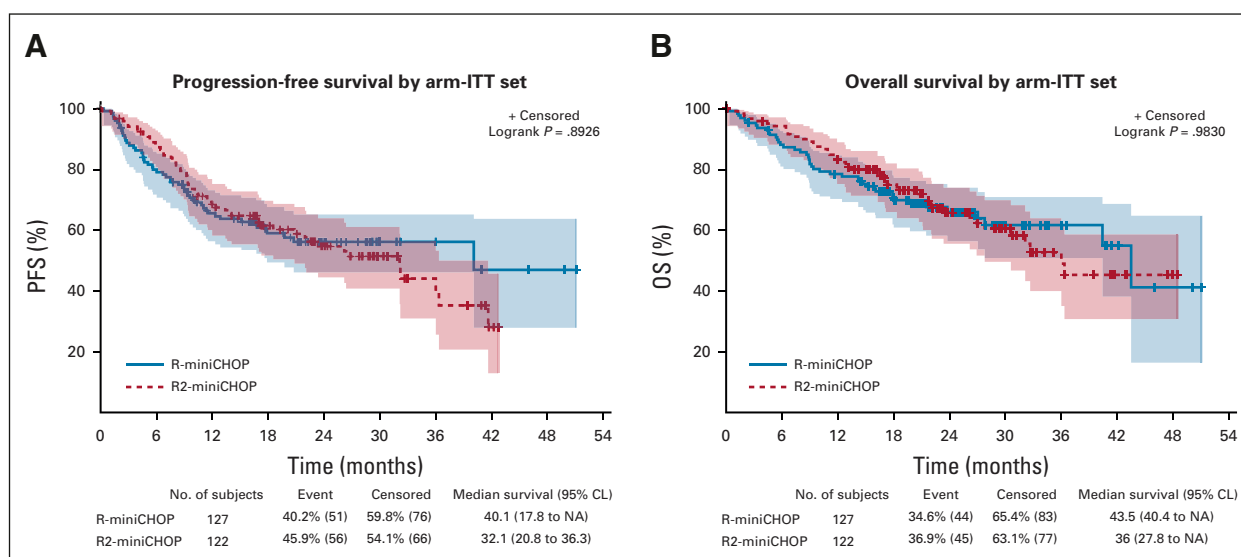
The 2-year PFS was 56.2% (95% CI, 46.2 to 65.1) in the R-miniCHOP group and 54.8% (95% CI, 44.6 to 63.9) in

the experimental arm. The 2-year EFS was 50.7% (95% CI, 40.8 to 59.8) in the R-miniCHOP arm and 53.1% (95% CI, 43 to 62.2) in the experimental arm. No significant difference between the standard and experimental arms was observed regarding PFS (HR, 1.027, 95% CI, 0.7 to 1.5,  $P = .89$ , Fig 2) and EFS (HR, 0.93, 95% CI, 0.65 to 1.34,  $P = .70$ ). The median DOR was not reached in the R-miniCHOP arm (95% CI 40.1 to not applicable) and was 36 months (95% CI 26.3 to not applicable) in the R2-miniCHOP (HR, 1.27, 95% CI, 0.77 to 2.07,  $P = .34$ ). The ORR assessed by investigators at the end of treatment was 73% in the R-miniCHOP arm (95% CI, 64.6% to 80.7%) and 82% in the R2-miniCHOP arm (95% CI, 75% to 89%). CR/CRu was achieved in 53% of R-miniCHOP patients and in 58% of R2-miniCHOP patients.

## Safety and Toxicity

The safety population included 241 patients (124 R-miniCHOP and 117 R2-miniCHOP). Of these, 87 who received R-miniCHOP (70%) and 101 who received R2-miniCHOP (86%) displayed any-grade AE. Compared with standard R-miniCHOP, more patients who received R2-miniCHOP had at least one grade 3-4 AEs. The increased rate of grade 3-4 AEs with R2-miniCHOP was attributable primarily to increased grade 3 or 4 neutropenia (32% v 18% patients,  $P = .01$ ) with similar GCSF support usage (data not shown). The most common grade 3-4 AEs and fatal AEs are provided in Table 2.

No deep venous thrombosis (DVT) but one pulmonary embolism (PE) was reported in the standard arm. DVT and PE occurred in six (5.1%) and seven patients (6%) treated with R2-miniCHOP, respectively. Three patients with PE treated with R2-miniCHOP did not receive mandatory antithrombotic prophylaxis.



**FIG 2.** (A) PFS and (B) OS in the intent-to-treat (ITT) population ( $N = 249$ ) according to treatment arm. OS, overall survival; PFS, progression-free survival.

**TABLE 2.** AEs and SAEs According to Treatment Arm

Adverse Event	R-miniCHOP (n = 124)	R2-miniCHOP (n = 117)
Total no. of AEs	292	390
Any grade (patients)	87 (70%)	101 (86%)
No. of AEs per patient: median (q1-q3)	2 (0-4)	2 (1-5)
Total no. of grade 3-4 AEs	216 (74%)	324 (83%)
Grade 3-4 AEs (patients)	71 (57%)	95 (81%)
Neutropenia	22 (18%)	38 (35%)
Anemia	7 (5%)	11 (9%)
Thrombocytopenia	1 (0.8%)	9 (7.6%)
Febrile neutropenia	1 (0.8%)	4 (3.4%)
Infections	10 (8%)	16 (13.5%)
DVT	0 (0%)	6 (5%)
PE	1 (0.8%)	7 (6%)
Vascular disorders (arterial)	2 (1.5%)	6 (5%)
Grade 5 (fatal) no.	7 (5.6%)	8 (6.8%)
Total no. of SAEs	76	113
Infections and infestations	12 (9.7%)	17 (14.5%)
Respiratory and mediastinal disorders	4 (3.2%)	13 (11.1%)
GI disorders	8 (6.5%)	6 (5.1%)
General disorders	6 (4.8%)	8 (6.8%)
Injury and procedural complications	4 (3.2%)	7 (6%)
Cardiac and vascular disorders	3 (2.4%)	6 (5.1%)
Metabolism and nutrition disorders	2 (1.6%)	4 (3.4%)
Musculoskeletal tissue disorders	1 (0.8%)	5 (4.3%)
Renal and urinary disorders	2 (1.6%)	4 (3.4%)
Nervous system disorders	2 (1.6%)	3 (2.6%)
Psychiatric disorders	2 (1.6%)	1 (0.9%)
Skin disorders	0 (0%)	1 (0.9%)
Hepatobiliary disorders	1 (0.8%)	0 (0%)

Abbreviations: AE, adverse event; DVT, deep venous thrombosis; PE, pulmonary embolism; SAE, severe adverse event.

Secondary primary malignancies (SPMs) were reported in eight (6.5%) patients in the R-miniCHOP arm and in 11 (9%) patients in the R2-miniCHOP arm (Data Supplement).

### Clinical Prognostic Factors

In univariate analyses, IPI score, stage, and serum albumin and lymphocyte count were predictive of survival (Table 3). Conversely, LDH, age (> or < 85 years), and monocyte count were not predictive of survival. Among geriatric and nutritional assessment tools, both an IADL score < 4 and an MNA score < 12 were predictive of shorter survival. Conversely, G8 and CIRSG did not correlate with survival (Table 3 and Data Supplement). Regarding the clinical impact of COO subtyping, Hans' algorithm delineation was not predictive of the outcome in the overall population or

according to treatment arm (Fig 3). Similarly, CD10 expression was not predictive of survival in the overall population or according to treatment arm (Data Supplement). In contrast, in the subpopulation (n = 154, 62%) molecularly defined by Lymh2CX, the ABC subtype was related to an unfavorable outcome compared with the non-ABC subtype. However, no difference was observed in the ABC subtype according to the treatment arm (Fig 3). In a multivariate analysis incorporating IPI, albuminemia, IADL, lymphocyte count, and GCB/ABC status, only albuminemia < 35 g/L was predictive of the OS in the overall population and according to treatment arm (Table 4).

### DISCUSSION

To the best of our knowledge, we report the first randomized phase III study dedicated to patients with DLBCL of age

**TABLE 3.** Univariate analyses of prognostic factors for OS

Variable	2-Year OS	HR (95% CI)	Log-Rank <i>P</i>
IPI (0-2 v 3-5)	80.61% v 60.88%	2.26 (1.25 to 4.08)	<b>.0054</b>
Ann Arbor stage (II-III v IV)	82.54% v 59.91%	2.12 (1.2 to 3.76)	<b>.0083</b>
LDH (normal v > UL)	70.7% v 63.5%	1.28 (0.81 to 2.03)	.2808
Hans score (non-GC v GC)	68.93% v 59.86%	1.32 (0.84 to 2.07)	.2345
Nanostring (non-ABC v ABC)	74.26% v 63.11%	1.77 (1.01 to 3.11)	<b>.0438</b>
G8 score ( $\leq 14$ v $> 14$ )	67.59% v 70.41%	0.94 (0.47 to 1.88)	.8555
IADL scale (4 v $< 4$ )	74.98% v 58.99%	1.69 (1.09 to 2.64)	<b>.0179</b>
MNA (normal v malnourished)	63.89% v 74.58%	0.57 (0.35 to 0.94)	<b>.0245</b>
CIRSG ( $< 7$ v $\geq 7$ )	67.22% v 67.02%	1.12 (0.7 to 1.77)	.6406
Monocyte count ( $\leq 0.7$ v $> 0.7$ G/L)	64.82% v 66.39%	0.90 (0.59 to 1.38)	.6336
Lymphocyte count ( $< 1$ v $\geq 1$ G/L)	59.06% v 69.45%	0.66 (0.43 to 1)	<b>.049</b>
Albumin ( $\leq 35$ v $> 35$ g/L)	78.1% v 52.07%	2.51 (1.6 to 3.92)	<b>&lt; .0001</b>

NOTE. Bold indicates statistically significant *P* values.

Abbreviations: ABC, activated B-cell-like; CIRSG, Cumulative Illness Rating Scale-Geriatric; GC, Germinal Center B-cell-like; HR, hazard ratio; IADL, instrumental activities of daily living; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MNA, mini-nutritional assessment; OS, overall survival; UL, upper limit.

over 80 years. In this challenging setting, we have proven that a large prospective study is possible. We showed no survival advantage for the R2-miniCHOP arm compared with the standard arm. With a median follow-up of 25 months and a 2-year OS of 66%, we replicated the results in terms of survival at 2 years recently obtained in LYSA trials 03-7B (59%, CI 95%, 49 to 67) and 09-7B (64.7%, CI 95%, 55 to 73).<sup>1,2</sup>

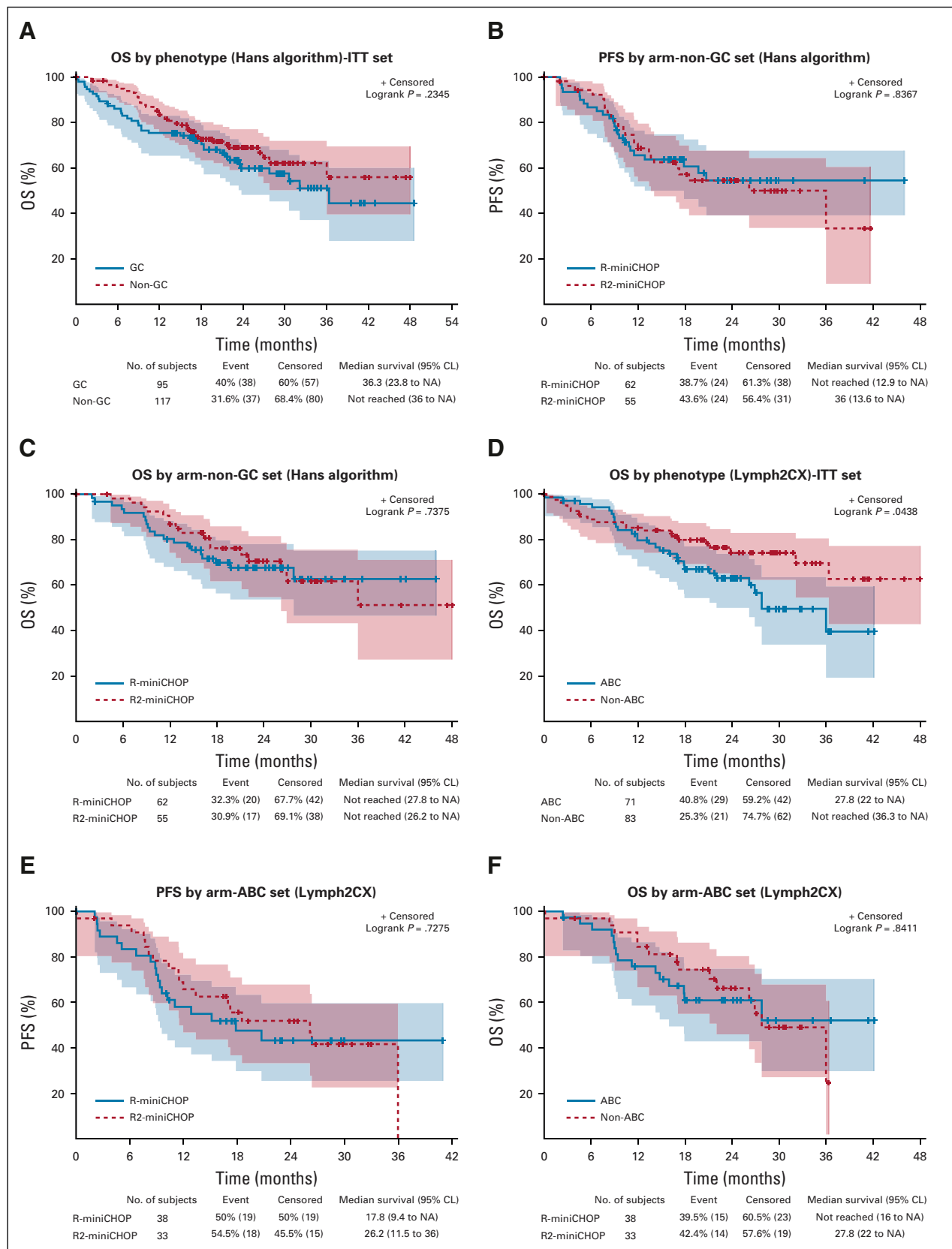
In this trial, we failed to reject the null hypothesis. Several explanations can be put forward to explain this result. The proposed treatment regimen might not be adequate and brings insufficient doses of lenalidomide to the patient. In this category of very elderly patients, the dose of 10 mg once daily D1-D14 (ie, 140 mg/cycle) has been proposed and is accompanied by significant additional toxicity, suggesting that a higher dose would probably not have been properly tolerated. Different clinical trials have proposed different regimens, but they involved younger patients. In the phase III ROBUST trial for ABC DLBCLs (median age of 65 years), lenalidomide 15 mg once daily was combined with standard R-CHOP from D1 to D15 (225 mg/cycle).<sup>22</sup> In the phase II randomized ECOG-ACRIN trial (E1412) comparing R2-CHOP and R-CHOP, patients with DLBCL (median age, 66 years [range, 24-92]) received lenalidomide at a dose of 25 mg once daily from D1 to D10 (250 mg/cycle) in the experimental arm.<sup>23</sup>

Identical to our study, the ROBUST trial did not demonstrate an advantage to the use of lenalidomide in combination with RCHOP in patients with ABC DLBCL. Overall, the ROBUST study did not meet the primary end point of PFS for R2-CHOP versus placebo/R-CHOP.<sup>22</sup>

Conversely, the preliminary results of the ECOG-ACRIN trial suggest an advantage in terms of PFS for the R2-CHOP arm with significantly different rates of grade  $> 3$  AEs between arms.<sup>23</sup> In the SENIOR trial, we showed a significant decrement in the planned doses of lenalidomide over the cycles, suggesting that we did not achieve sufficient doses for a large number of patients who were analyzed in ITT.

These results may suggest that the treatment regimen proposed in the SENIOR trial was inadequate to deliver a sufficient dose of lenalidomide. A strategy based on the use of lenalidomide in maintenance after RCHOP had been explored in the REMARC trial but failed to show an improvement of OS in patients of age 60 to 80 years.<sup>24</sup>

The toxicity of the R2 miniCHOP combination could have strongly affected the final result of the trial. Indeed, in a strategy based on the combination of drug X with R-CHOP at full or reduced dose, toxicity is a major obstacle, particularly in elderly subjects. In the Phoenix trial comparing R-CHOP versus RCHOP plus ibrutinib, the advantage of adding ibrutinib was only observed in patients under 60 years of age. A decrease in the dose intensity of R-CHOP was thus observed in elderly patients treated with R-CHOP plus ibrutinib in the Phoenix trial and could explain the lack of benefit of the combination.<sup>25</sup> In the SENIOR trial, the very high number of toxicities and comorbidities inherent to this population may lead to negating the beneficial effect of the experimental drug even if the dose intensity of R-miniCHOP received was equivalent in both arms. The use of the subcutaneous form of rituximab did not seem to affect the high frequency of side effects related to R2miniCHOP, and subcutaneous rituximab is effective and safe in very elderly



**FIG 3.** OS and PFS according to COO status determined by IHC (A-C), by Lymph2CX (D-F) in the overall population (A and D), and according to treatment arm (B, C, E, and F). COO, cell of origin; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival.

**TABLE 4.** Multivariate Analyses of Prognostic Factors for OS

Variable	HR (95% CI)	P
IPI (0-2 v 3-5)	0.94 (0.43 to 2.04)	.871
Non-ABC v ABC (Lymph2CX)	1.14 (0.68 to 1.92)	.614
IADL scale	0.72 (0.44 to 1.18)	.193
MNA (normal v malnourished)	1.16 (0.67 to 2.03)	.596
Ann Arbor stage (II-III v IV)	2.01 (0.94 to 4.32)	.073
Lymphocyte count (< 1 v ≥ 1 G/L)	0.80 (0.50 to 1.30)	.373
Albumin (≤ 35 v > 35 g/L)	2.08 (1.25 to 3.57)	<b>.005</b>

NOTE. Bold indicates statistically significant *P* values.

Abbreviations: ABC, activated B-cell-like; HR, hazard ratio; IADL, instrumental activities of daily living; IPI, international prognostic index; MNA, Mini Nutritional Assessment; OS, overall survival.

patients with DLBCL, as previously reported in younger patients with FL or DLBCL.<sup>26</sup>

The negative results of the study could also be due to the unexpectedly low proportion of ABC DLBCL subtypes in this population of very elderly patients, a subtype in which lenalidomide is believed to be particularly effective.<sup>7</sup> Despite stratification based on CD10 staining, only 50% were finally classified as non-GCB in the R2-miniCHOP arm using the Hans algorithm and 42% were classified as ABC using L2CX technology, suggesting that too few ABC DLBCL may not demonstrate a survival advantage for R2-miniCHOP. However, to date, there is no formal evidence that lenalidomide is a particularly effective drug in patients with ABC DBCLs, contrary to in vitro data.

The long-term follow-up of R2-CHOP21 in DLBCL was recently reported in the merged two independent phase II trials conducted by the Mayo clinic and FIL. A total of 112 patients with a median age of 69 years were analyzed with a median follow-up of 5.1 years.<sup>14</sup> The cumulative incidence of primary secondary malignancies at 5 years was 0.9% for therapy-related secondary acute leukemia and/or myelodysplastic syndromes and 5.4% for other tumors. In the SENIOR trial, with a shorter follow-up of 25 months, SPMs were numerically similar between the two arms (eight patients in the standard arm and 11 patients in the experimental arm) but seem to be qualitatively different.

Given the demographics of the population, improving the effectiveness of treatment and the survival of patients over 80 years of age with DLBCL is still a major challenge in 2020. The SENIOR trial highlights and confirms a certain number of prognostic factors that make it possible to identify the most fragile patients for whom standard chemotherapy based on immunochemotherapy does not seem to be adequate, even after a prephase has been performed in all patients.

Among these factors, albuminemia is, with staging, the most significant factor, independent of the IPI, MNA score,

or IADL scale. These data confirm those of LYSA Trial 03-7B and suggest that this parameter should lead to changes in the therapeutic strategy of these high-risk patients and lead to the development of alternative chemo-free strategies.<sup>2</sup>

In our cohort, although Hans' algorithm does not seem to confirm the prognostic value of the GCB/non-GCB phenotype, the molecular classification carried out in a subgroup seems to confirm the pejorative prognostic value of the ABC phenotype. This suggests that the understanding of the molecular specificities of DLBCL in the very elderly, independent of the intrinsic fragility linked to the geriatric context, is an important area for improvement in the management of these patients.<sup>27</sup>

In conclusion, the SENIOR study is the first prospective phase III trial in patients older than 80 years with newly diagnosed DLBCL. The addition of lenalidomide to the R-miniCHOP schema does not improve OS irrespective of GCB/ABC status and results in more AEs. Rituximab delivered subcutaneously was safe and well-tolerated in this very elderly population, showing a similar efficacy with historic R-miniCHOP data. In three consecutive trials dedicated to DLBCL > 80 years, our group confirmed that R-miniCHOP led to 2-year OS rates from 59% to 66%. New therapeutic strategies are needed to improve such results.

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This study was designed by the LYSA scientific committee. All logistical aspects of this study were managed by the LYSARC. Data were collected by LYSARC and analyzed by LYSARC and the PI and Co-PI. Celgene and Roche provided lenalidomide (Revlimid) and rituximab (Mabthera), respectively. Celgene supports the cost of NanoString experiments. The PI and Co-PI were responsible for data interpretation and writing of the report. All authors had full access to the data in this study, and the corresponding author had final responsibility for the decision to submit the manuscript for publication.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Subcutaneous Rituximab-MiniCHOP Compared With Subcutaneous Rituximab-MiniCHOP Plus Lenalidomide in Diffuse Large B-Cell Lymphoma for Patients Age 80 Years or Older**

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