

Rituximab-CHOP With Early Rituximab Intensification for Diffuse Large B-Cell Lymphoma: A Randomized Phase III Trial of the HOVON and the Nordic Lymphoma Group (HOVON-84)

Pieterella Johanna Lugtenburg, MD, PhD¹; Peter de Nully Brown, MD, PhD²; Bronno van der Holt, PhD³; Francesco A. D'Amore, MD, PhD⁴; Harry R. Koene, MD, PhD⁵; Eva de Jongh, MD⁶; Rob Fijnheer, MD, PhD⁷; Joost W. van Esser, MD, PhD⁸; Lara H. Böhmer, MD⁹; Johannes F. Pruijt, MD, PhD¹⁰; Gregor E. Verhoef, MD, PhD¹¹; Mels Hoogendoorn, MD, PhD¹²; Memis Y. Bilgin, MD, PhD¹³; Marcel Nijland, MD, PhD¹⁴; Nicole C. van der Burg-de Graauw, MD¹⁵; Margreet Oosterveld, MD, PhD¹⁶; Kon-Siong G. Jie, MD, PhD¹⁷; Thomas Stauffer Larsen, MD, PhD¹⁸; Marjolein W. van der Poel, MD, PhD, MSc¹⁹; Maria B. Leijds, MD²⁰; Matthijs H. Silbermann, MD²¹; Marinus van Marwijk Kooy, MD, PhD²²; Aart Beeker, MD, MBA²³; Marie J. Kersten, MD, PhD²⁴; Jeanette K. Doorduijn, MD, PhD¹; Lidwine W. Tick, MD, PhD²⁵; Rolf E. Brouwer, MD, PhD²⁶; King H. Lam, MD, PhD¹; Coreline N. Burggraaff, MD²⁷; Bart de Keizer, MD, PhD²⁸; Anne I. Arens, MD²⁹; Daphne de Jong, MD, PhD³⁰; Otto S. Hoekstra, MD, PhD²⁷; and Josée M. Zijlstra-Baalbergen, MD, PhD²⁷

abstract

PURPOSE Immunotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has become standard of care for patients with diffuse large B-cell lymphoma (DLBCL). This randomized trial assessed whether rituximab intensification during the first 4 cycles of R-CHOP could improve the outcome of these patients compared with standard R-CHOP.

PATIENTS AND METHODS A total of 574 patients with DLBCL age 18 to 80 years were randomly assigned to induction therapy with 6 or 8 cycles of R-CHOP-14 with (RR-CHOP-14) or without (R-CHOP-14) intensification of rituximab in the first 4 cycles. The primary end point was complete remission (CR) on induction. Analyses were performed by intention to treat.

RESULTS CR was achieved in 254 (89%) of 286 patients in the R-CHOP-14 arm and 249 (86%) of 288 patients in the RR-CHOP-14 arm (hazard ratio [HR], 0.82; 95% CI, 0.50 to 1.36; $P = .44$). After a median follow-up of 92 months (range, 1-131 months), 3-year failure-free survival was 74% (95% CI, 68% to 78%) in the R-CHOP-14 arm versus 69% (95% CI, 63% to 74%) in the RR-CHOP-14 arm (HR, 1.26; 95% CI, 0.98 to 1.61; $P = .07$). Progression-free survival at 3 years was 74% (95% CI, 69% to 79%) in the R-CHOP-14 arm versus 71% (95% CI, 66% to 76%) in the RR-CHOP-14 arm (HR, 1.20; 95% CI, 0.94 to 1.55; $P = .15$). Overall survival at 3 years was 81% (95% CI, 76% to 85%) in the R-CHOP-14 arm versus 76% (95% CI, 70% to 80%) in the RR-CHOP-14 arm (HR, 1.27; 95% CI, 0.97 to 1.67; $P = .09$). Patients between ages 66 and 80 years experienced significantly more toxicity during the first 4 cycles in the RR-CHOP-14 arm, especially neutropenia and infections.

CONCLUSION Early rituximab intensification during R-CHOP-14 does not improve outcome in patients with untreated DLBCL.

J Clin Oncol 38:3377-3387. © 2020 by American Society of Clinical Oncology

INTRODUCTION

The overall survival (OS) of patients with diffuse large B-cell lymphoma (DLBCL) has improved significantly since the addition of rituximab to standard 3-week cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP-21) or dose-dense 2-week CHOP (R-CHOP-14).^{1,2} No significant benefits have been shown for R-CHOP-14 versus R-CHOP-21, and these regimens are currently standard treatments

worldwide.^{3,4} However, approximately 40% of patients experience primary refractory disease or relapse, which is often fatal.^{5,6} Therefore, further improvement of first-line therapy is needed.

The dose and schedule of rituximab in the R-CHOP combination are largely empirically determined on historical grounds. Few phase II studies have explored variations of the rituximab schedule in combination with CHOP in elderly patients with DLBCL.^{7,8} In a single

ASSOCIATED

CONTENT

Appendix

Protocol

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

Accepted on June 22, 2020 and published at ascopubs.org/journal/jco on July 30, 2020; DOI <https://doi.org/10.1200/JCO.19.03418>

CONTEXT

Key Objective

Diffuse large B-cell lymphoma (DLBCL) is a curable disease. However, 40% of patients are refractory to or relapse after treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Several single-arm phase II studies in elderly patients with DLBCL have explored variations of the rituximab schedule in combination with CHOP and have reported a better outcome for patients with poor prognosis. Our randomized study examined whether rituximab intensification during the first 4 cycles of 2-week R-CHOP could improve the outcome of untreated patients with DLBCL compared with standard 2-week R-CHOP.

Knowledge Generated

Intensification of rituximab during the first 4 cycles of 2-week R-CHOP did not improve complete remission rate, progression-free survival, or overall survival. Patients between ages 66 and 80 years experienced more neutropenia and infections during rituximab intensification.

Relevance

R-CHOP remains the standard treatment for DLBCL. Novel therapies are needed to improve the outcome of these patients.

study in which patients were treated with rituximab administered in shorter intervals at the beginning of treatment and over a prolonged period of time, a better outcome for patients with poor prognosis with International Prognostic Index (IPI) score of 3 to 5 compared with historical controls was reported.⁸ The same group reported significantly reduced rituximab clearance in elderly women compared with elderly men.⁹ During standard R-CHOP-14 treatment, serum levels of rituximab show a gradual increase up to cycle 5, reaching a plateau thereafter.¹⁰ The lag time of 5 cycles may result in suboptimal rituximab serum levels, especially early during treatment. Therefore, treatment outcome may be improved through intensification of rituximab during the first 4 cycles by providing a steeper increase to the optimal therapeutic serum level as well as reaching a higher serum concentration within the large therapeutic window of rituximab.^{11,12}

To assess the efficacy of early rituximab intensification during first-line treatment in patients with DLBCL, we performed a prospective randomized phase III study to compare standard R-CHOP-14 with R-CHOP-14 combined with 4 extra administrations of rituximab during the first 4 induction cycles. Patients in complete remission (CR) after induction treatment were randomly assigned a second time between observation and rituximab maintenance. Here, we present the final analysis of the induction random assignment, including long-term follow-up data with a data cutoff of October 16, 2019.

PATIENTS AND METHODS

Patient Population

The HOVON-84 (Haemato Oncology Foundation for Adults in the Netherlands) study was an investigator-initiated prospective randomized phase III study conducted among 68 participating centers in the Netherlands, Denmark, and

Belgium. The study was approved by the institutional review boards at all centers. Eligibility included previously untreated, biopsy-confirmed, CD20+ DLBCL according to local pathology and Ann Arbor stage II to IV. Patients between age 18 and 65 years and with an age-adjusted IPI score of 1 to 3 and patients between age 66 and 80 years and an age-adjusted IPI score of 0 to 3 were eligible. Central pathology review was performed as part of quality control (HOVON Pathology Facility and Biobank). CNS involvement, testicular DLBCL, primary mediastinal B-cell lymphoma, transformed indolent lymphoma, any solid malignancy in the preceding 5 years, and illnesses precluding study treatment rendered patients ineligible.

Computed tomography (CT) scanning and bone marrow biopsies were minimum mandatory staging procedures. Baseline ¹⁸F-fluorodeoxyglucose positron emission tomography (PET) scans were recommended but not mandated.

Random Assignment

After providing written informed consent, patients were randomly allocated to receive either R-CHOP-14 (arm A) or R-CHOP-14 with intensification of rituximab in the first 4 cycles (RR-CHOP-14; arm B). Random assignment was stratified by center, age group (18-65 v 66-80 years), and age-adjusted IPI score using a minimization procedure, ensuring balance within each stratum and overall balance.

Treatment and Response Assessment

The R-CHOP-14 regimen consisted of 14-day cycles of intravenous cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (maximum, 2 mg), and rituximab 375 mg/m² on day 1 and prednisone 100 mg once daily on days 1 to 5, for a total of 8 cycles.¹³ Pegfilgrastim was administered on day 2 of each cycle. Patients randomly assigned to arm B received extra intravenous

rituximab 375 mg/m² on day 8 of the first 4 cycles (RR-CHOP-14). Initially, inclusion was limited to elderly patients (age 66-80 years). In July 2009, the protocol was amended to also include patients age 18 to 65 years. At the same time, because of the results of the RICOVER-60 trial, the number of CHOP-14 cycles for patients age 66 to 80 years was reduced to 6, whereas the number of rituximab cycles was maintained at 8.² Details regarding prephase and supportive measures during treatment are provided in the Appendix (online only). Consolidation radiotherapy was not allowed.

Response at the end of induction treatment was assessed using PET-CT scans.^{14,15} Patients with progressive disease on CT scan after 4 cycles went off protocol. The interim PET scan after 4 cycles was performed for observational purposes only. All PET-CT scans were centrally reviewed by the HOVON Imaging Group according to standard procedures as previously described¹⁶ using Deauville score (DS) for visual assessment.¹⁵ Scores of 1 to 3 were interpreted as complete metabolic response, and scores of 4 to 5 were consistent with partial metabolic response or progressive disease. CT scans of neck, chest, abdomen, and pelvis were required at 6, 12, 18, and 24 months after completion of induction treatment. Severity of adverse events was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Sample Size Calculation and Statistical Analysis

This trial was designed to compare CR rates on induction treatment between R-CHOP-14 and RR-CHOP-14 (first randomization; R1) and compare failure-free survival (FFS) from second randomization (R2) between no further treatment and rituximab maintenance. The sample size for R1 was 575 patients, accrued over 5 years, with a power of 86% to detect an improvement in CR rate from 77% to 87%. Additional sample size calculation details are provided in the Appendix. The primary end point for R1 was CR on induction. Logistic regression analysis with adjustment for age group (18-65 v ≥ 66-80 years) and age-adjusted IPI score (0 v 1 v 2 v 3; categorical) was applied for the primary analysis, and odds ratios and 95% CIs were determined, with *P* values < .05 considered statistically significant. Secondary end points were best response on protocol treatment, adverse events, FFS, progression-free survival (PFS), and OS from R1 and disease-free survival (DFS) from CR. For the survival end points, the hazard ratios (HRs) and 95% CIs were determined using univariable and multivariable Cox regression analyses. Kaplan-Meier curves by treatment arm were generated to illustrate survival.

All analyses were performed according to the intention-to-treat (ITT) principle. However, patients initially randomly assigned but considered ineligible in retrospect based on information that should have been available before random assignment were excluded from the respective analyses

(modified ITT). The proportion of patients with specific adverse events was compared between arms post hoc using the χ^2 test or Fisher's exact test, whichever was appropriate. All reported *P* values are 2 sided and were not adjusted for multiple testing. Additional details on statistical methods and survival end point definitions are provided in the Appendix.

RESULTS

Study Patients

Between November 14, 2007, and April 6, 2012, 600 patients were enrolled. Twenty-six patients (R-CHOP-14 arm, *n* = 14; RR-CHOP-14 arm, *n* = 12) were considered ineligible in hindsight and excluded from all analyses because of diagnosis other than DLBCL at study entry according to local pathology (*n* = 12), stage I disease (*n* = 4), absence of age-adjusted IPI risk factors (*n* = 4), CNS involvement (*n* = 2), absence of measurable disease (*n* = 1), heart disease (*n* = 1), administrative error (*n* = 1), or missing data (*n* = 1). Of 574 patients included in the modified ITT analysis, 286 individuals were allocated to the R-CHOP-14 arm and 288 were assigned to the RR-CHOP-14 arm (Fig 1). Central pathology review was available for 522 (91%) of 574 eligible patients, and diagnosis of CD20+ DLBCL according to the 2008 WHO classification was confirmed for 492 (94%) of 522 patients. Baseline characteristics of patients were well balanced between arms (Table 1; Appendix Table A1, online only).

Treatment

At least 6 cycles were received by 269 (94%) of 286 patients in the R-CHOP-14 arm and 261 (91%) of 288 patients in the RR-CHOP-14 arm; 151 patients (53%) received 7 to 8 cycles of R-CHOP-14, compared with 158 (55%) in the RR-CHOP-14 arm (Fig 1). The median total dose received and median relative dose-intensities achieved for cyclophosphamide (98%) and doxorubicin (98%) were similar in the R-CHOP-14 and RR-CHOP-14 arms. However, for vincristine, in patients age 66 to 80 years, the median total dose and median relative dose-intensities were 12.0 versus 10.0 mg (*P* = .015) and 92% versus 85% (*P* = 0.083) for the R-CHOP-14 and RR-CHOP-14 arms, respectively.

Efficacy Outcomes

There was no statistically significant difference in the primary end point of CR rate on induction between the 2 treatment arms. CR was achieved in 254 patients (89%) in the R-CHOP-14 arm and in 249 (86%) in the RR-CHOP-14 arm (HR, 0.82; 95% CI, 0.50 to 1.36; *P* = .44; adjusted for age and age-adjusted IPI score). Also, CR rates for patients age < 66 years (90% v 85%) and patients age ≥ 66 years (88% v 88%) were not different per treatment arm.

After a median follow-up of 92 months (range, 1-131 months) in the 364 patients still alive, the median FFS and

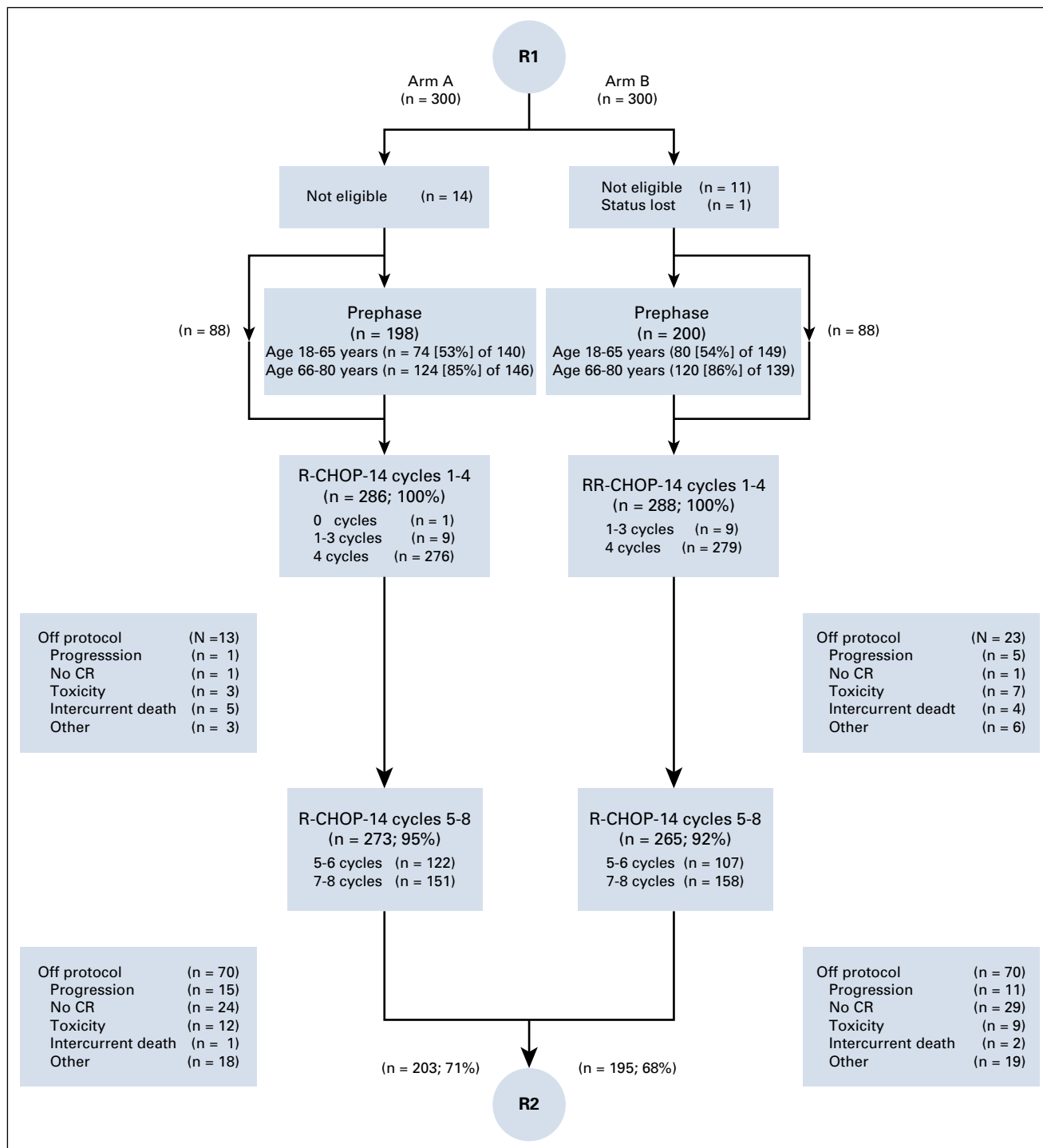


FIG 1. CONSORT diagram of induction treatment of patients with diffuse large B-cell lymphoma in the HOVON-84 non-Hodgkin lymphoma trial by treatment arm. CR, complete remission; R1, induction randomization; R2, maintenance randomization; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, prednisone (arm B).

median PFS were not reached in the R-CHOP-14 arm and were both 101 months in the RR-CHOP-14 arm, and the median DFS and OS had not been reached in either arm. The 3-year FFS rate was 74% (95% CI, 68% to 78%) in the R-CHOP-14 arm versus 69% (95% CI, 63% to 74%) in

the RR-CHOP-14 arm (HR, 1.26; 95% CI, 0.98 to 1.61; $P = .07$; adjusted for age group and age-adjusted IPI score; Fig 2A); FFS rates at 5 years were 68% (95% CI, 62% to 73%) and 62% (95% CI, 56% to 67%), respectively. PFS at 3 years was 74% (95% CI, 69% to 79%)

TABLE 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	No. (%)	
	R-CHOP-14 (n = 286)	RR-CHOP-14 (n = 288)
Sex		
Male	145 (51)	154 (53)
Female	141 (49)	134 (47)
Age, years		
Median	66	65
Range	18-80	31-80
≤ 65	140 (49)	149 (52)
> 65	146 (51)	139 (48)
WHO performance status		
0-1	254 (89)	251 (87)
2	30 (10)	36 (13)
Unknown	2 (1)	1 (0)
Ann Arbor stage		
II	53 (18)	61 (21)
III	88 (31)	89 (31)
IV	145 (51)	138 (48)
B symptoms	112 (39)	120 (42)
LDH > ULN	183 (64)	196 (68)
Bulky disease (> 10 cm)	83 (29)	85 (30)
BM involvement	30 (10)	36 (13)
Age-adjusted IPI risk group		
Low	22 (8)	24 (8)
Low-intermediate	107 (37)	93 (33)
High-intermediate	132 (46)	147 (51)
High	25 (9)	24 (8)
Histology (central review)		
DLBCL	251 (88)	244 (85)
Other diagnosis or unclassified ^a	11 (4)	16 (6)
Not reviewed	25 (8)	28 (10)
Phenotype ^b		
Germinal center	124 of 200 (62)	107 of 177 (60)
Nongerminal center	76 of 200 (38)	70 of 177 (40)
MYC rearrangement	14 of 104 (13)	5 of 73 (7)
MYC SH	4 of 14	1 of 5
MYC plus <i>BCL2</i> and/or <i>BCL6</i> ^c	10 of 14	4 of 5

Abbreviations: BM, bone marrow; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B); SH, single hit; ULN, upper limit of normal.

^aAppendix Table A1.

^bBased on standard Hans criteria.

^cAccording to WHO classification 2016; now classified as high grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements.

in the R-CHOP-14 arm versus 71% (95% CI, 66% to 76%) in the RR-CHOP-14 arm (HR, 1.20; 95% CI, 0.94 to 1.55; $P = .15$; adjusted for age group and age-adjusted IPI score; Fig 2B); the 5-year PFS rates were 69% (95% CI, 63% to 74%) and 64% (95% CI, 58% to 69%), respectively. Among patients who had achieved CR on protocol treatment, the 3-year DFS rate from date of CR was 81% (95% CI, 76% to 85%) in the R-CHOP-14 arm versus 76% (95% CI, 70% to 81%) in the RR-CHOP-14 arm (HR, 1.24; 95% CI, 0.93 to 1.65; $P = .15$; adjusted for age group and age-adjusted IPI score; Fig 2C); the 5-year DFS rates were 75% (95% CI, 69% to 80%) and 70% (95% CI, 64% to 75%), respectively. OS at 3 years was 81% (95% CI, 76% to 85%) in the R-CHOP-14 arm versus 76% (95% CI, 70% to 80%) in the RR-CHOP-14 arm (HR, 1.27; 95% CI, 0.97 to 1.67; $P = .09$; adjusted for age group and age-adjusted IPI score; Fig 2D); the 5-year OS rates were 77% (95% CI, 71% to 81%) and 69% (95% CI, 63% to 74%), respectively.

A total of 210 patients died, 96 in the R-CHOP-14 arm (lymphoma related, $n = 41$; treatment related, $n = 9$; intercurrent death, $n = 8$; secondary malignancies, $n = 11$; other reasons, $n = 15$; and unknown causes, $n = 12$) and 114 in the RR-CHOP-14 arm (lymphoma related, $n = 56$; treatment related, $n = 10$; intercurrent death, $n = 10$; secondary malignancies, $n = 11$; other reasons, $n = 11$; and unknown causes, $n = 16$).

Planned subgroup analyses showed that the impact of RR-CHOP-14 versus R-CHOP-14 on FFS, PFS, DFS, and OS was not different between subgroups of age (18-65 v 66-80 years), sex (male v female), or age-adjusted IPI score (low v low-intermediate v high-intermediate v high). Post hoc analyses showed similar results for subgroups according to DLBCL phenotype. Figure 3 and Appendix Figures A1 and A2 (online only) show the Kaplan-Meier PFS curves for these subgroups.

Results of the multivariable analyses of individual prognostic factors for the survival end points FFS, PFS, and OS are listed in Table 2 (and for DFS in Appendix Table A2, online only). The HRs for both treatment arms were similar compared with those in the analyses with adjustment for only age group and age-adjusted IPI score, confirming that survival was not improved in either subgroup in the RR-CHOP-14 arm. The only statistically significant prognostic factor was age 66 to 80 years.

PET-CT Assessment

PET-CT scans were visually assessed using the 5-point DS; DSs 1 to 3 were regarded as negative and DSs 4 to 5 as positive. A total of 496 end-of-treatment (EOT) PET scans were centrally reviewed. In 417 patients (84%), the EOT PET-CT scans were negative, and 79 patients (16%) had positive EOT PET scans. The estimated 2-year PFS rate in patients with EOT PET-positive scans was 46%

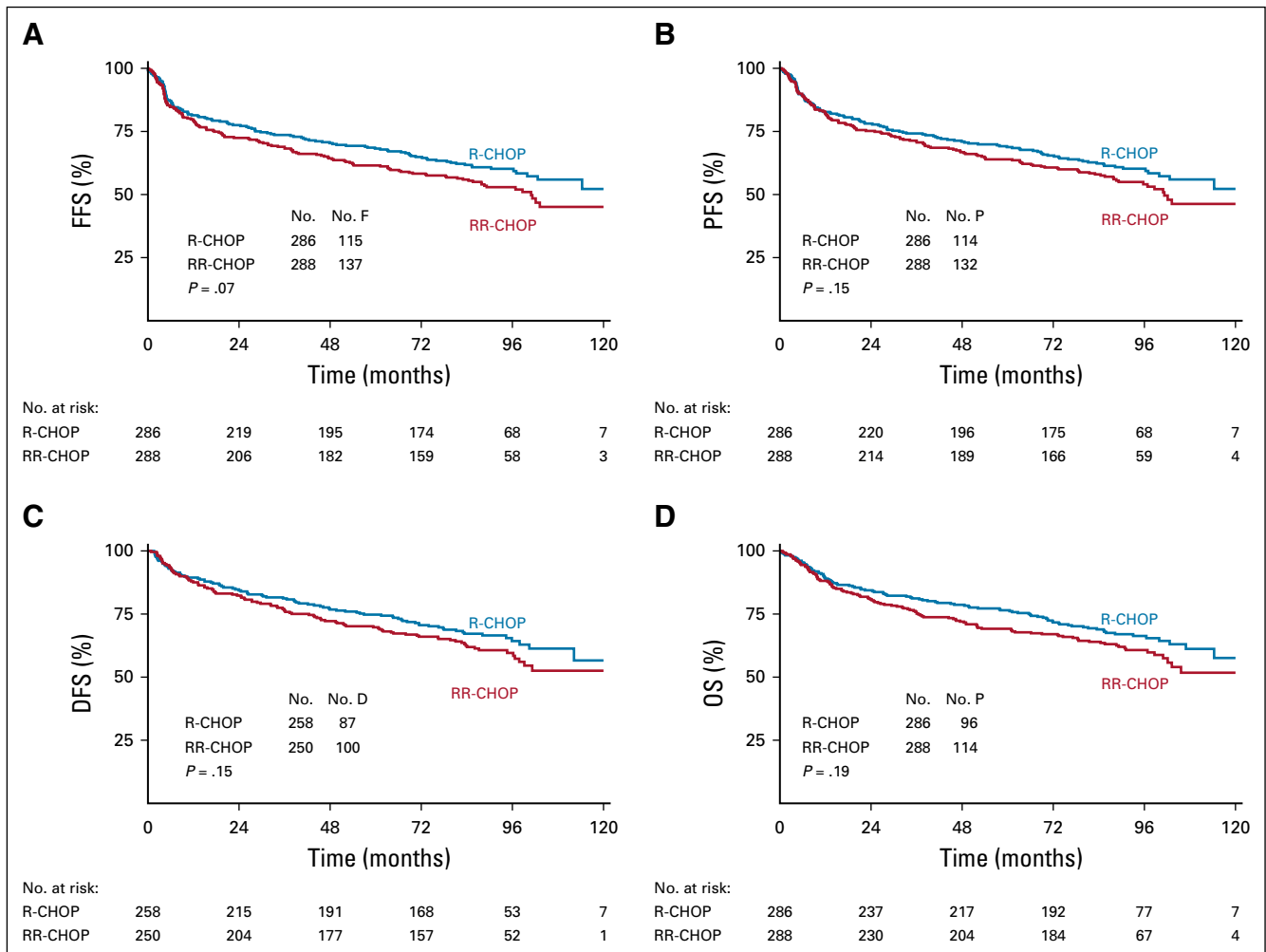


FIG 2. Kaplan-Meier survival curves according to assigned treatment arm. (A) Failure-free survival (FFS), (B) progression-free survival (PFS), (C) disease-free survival (DFS) from complete remission, and (D) overall survival (OS). All P values by Cox logistic regression (adjusted). D, death; F, no complete remission, relapse, or death; P, progression, relapse, or death; R, relapse or death; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

(95% CI, 36% to 57%) versus 88% (95% CI, 85% to 92%) in those with EOT PET-negative scans ($P < .001$). The 2-year OS rate was 58% (95% CI, 47% to 69%) for patients with EOT PET-positive scans and 94% (95% CI, 91% to 96%) for those with EOT PET-negative scans. Corresponding positive and negative predictive values for 2-year PFS were 53% (95% CI, 42% to 64%) and 89% (95% CI, 85% to 91%) for EOT PET scans, respectively.

Rituximab Pharmacokinetics

Rituximab trough serum levels increased after each subsequent treatment cycle during the first 4 cycles and reached a plateau at cycles 5 to 8 in both treatment arms. Rituximab trough serum levels were systematically higher in the RR-CHOP-14-treated patients than in R-CHOP-treated patients (Appendix Figure A3, online only).

Adverse Events

We analyzed safety for all patients who received at least 1 administration of study treatment. The proportion of patients with at least 1 adverse or serious adverse event did not differ between the R-CHOP-14 and RR-CHOP-14 arms. The most common grade 3 and 4 adverse events were cytopenias and infections (Table 3). During the first 4 cycles, patients between ages 66 and 80 years experienced significantly more toxicity in the RR-CHOP-14 arm, especially neutropenia and infections (Table 4).

Seventeen grade 5 adverse events were reported during induction, 9 in the R-CHOP-14 arm and 8 in the RR-CHOP-14 arm. The main cause of death was infection (4 patients in each arm). Other causes of death in the R-CHOP-14 arm were small-bowel perforation ($n = 2$), sudden death ($n = 2$), and progressive multifocal

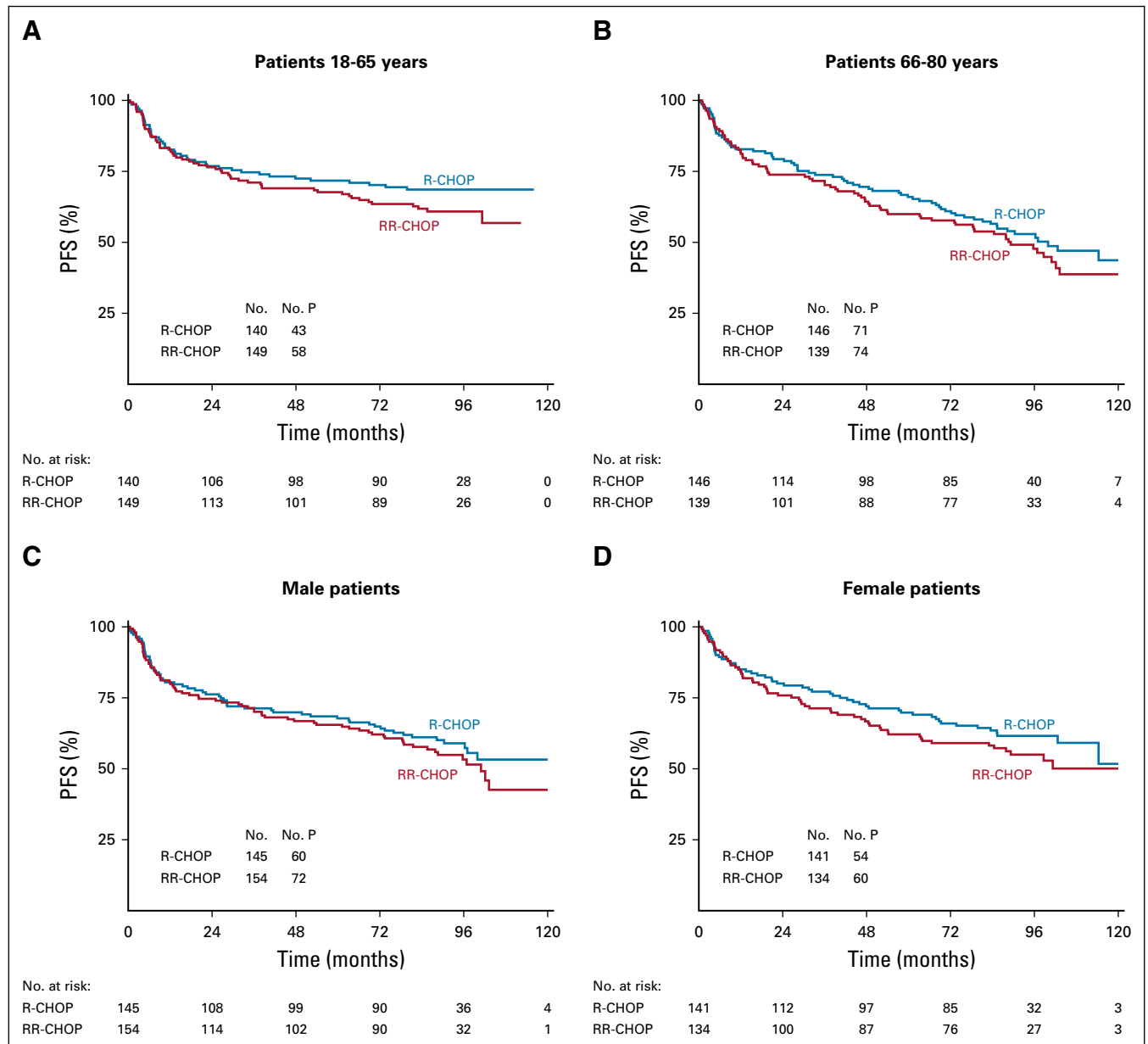


FIG 3. Progression-free survival (PFS) by treatment arm within subgroups: (A) age 18 to 65 years, (B) age 66 to 80 years, (C) male patients, and (D) female patients. P, progression, relapse, or death; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

leukoencephalopathy ($n = 1$). In the RR-CHOP-14 arm, other causes of death were myocardial infarction ($n = 1$), GI bleeding ($n = 1$), small-bowel perforation ($n = 1$), and cardiac arrhythmia ($n = 1$).

DISCUSSION

The primary objective of achieving a significantly superior CR rate with RR-CHOP-14 treatment as compared with standard R-CHOP-14 treatment was not met. RR-CHOP-14 treatment also did not improve FFS, PFS, DFS, or OS.

In DLBCL, rapid tumor control is critical to improve outcome by avoiding development of refractory disease on or after R-CHOP, because patients with refractory disease have poor prognosis.¹⁷ Several phase II studies have explored optimization of rituximab for the treatment of DLBCL. In the DENSE-R-CHOP-14 trial, early dose-intensification of rituximab in combination with R-CHOP-14 was tested in 124 elderly patients with DLBCL.⁷ In this study, 4 additional rituximab administrations were added during the first 3 weeks. Compared with a historical control population (RICOVER-60 population), no differences in outcome were

TABLE 2. Multivariable Analysis of Prognostic Factors for FFS, PFS, and OS

Factor	FFS			PFS			OS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
RR-CHOP-14 arm	1.25	0.98 to 1.61	.08	1.20	0.93 to 1.54	.16	1.25	0.95 to 1.65	.10
Age \geq 66 years	1.57	1.21 to 2.03	.001	1.58	1.21 to 2.04	.001	1.78	1.33 to 2.36	< .001
Age-adjusted IPI score ^a	1.09	0.81 to 1.46	.57	1.12	0.84 to 1.51	.44	1.17	0.85 to 1.61	.35
Female sex	0.80	0.63 to 1.04	.09	0.85	0.66 to 1.09	.20	0.80	0.61 to 1.05	.11
WHO performance score ^b	1.02	0.82 to 1.28	.84	1.04	0.83 to 1.30	.76	1.12	0.88 to 1.44	.35
LDH > ULN	1.51	1.00 to 2.30	.051	1.46	0.96 to 2.23	.08	1.49	0.94 to 2.37	.09
B symptoms	1.12	0.86 to 1.46	.42	1.13	0.87 to 1.49	.36	1.08	0.80 to 1.44	.62
Bulky disease	1.05	0.79 to 1.38	.75	0.93	0.70 to 1.24	.63	0.85	0.62 to 1.15	.29
BM involvement	1.21	0.84 to 1.75	.30	1.19	0.82 to 1.72	.36	0.98	0.65 to 1.49	.93

Abbreviations: BM, bone marrow; FFS, failure-free survival; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B); ULN, upper limit of normal.

^aAnalyzed as low ν low-intermediate ν high-intermediate ν high.

^bAnalyzed as WHO 0 ν 1 ν 2.

observed for the whole population. Subgroup analysis revealed that patients with high-intermediate and high IPI scores had higher CR/unconfirmed CR (CRu) rates after rituximab intensification, but this did not translate into better survival outcome. A high rate of grade 3 and 4 infectious complications was reported, which improved after mandatory prophylaxis with acyclovir and cotrimoxazole was instituted. In the SMARTE-R-CHOP-14 study, a prolonged exposure time of rituximab using a loading schedule of 2 rituximab administrations before the first CHOP cycle and 3 additional rituximab administrations after completion

of R-CHOP was investigated in 189 elderly patients with DLBCL.⁸ Compared with the RICOVER-60 population, survival outcome was not significantly better for the complete study population, and subgroup analysis showed that patients with high-intermediate and high IPI scores had higher CR/CRu rates and better 3-year PFS (71% ν 59%) and OS (80% ν 67%) rates. Elderly male patients showed a significantly faster rituximab clearance than elderly female patients, resulting in a shorter rituximab serum elimination half-life, lower serum levels, and shorter rituximab exposure times.^{8,10} Because in the RICOVER-60 study elderly male patients seemed to benefit to a lesser extent from addition of rituximab to CHOP than elderly female patients, an increased dose of 500 mg/m² of rituximab for male patients and the standard dose of 375 mg/m² for female patients were investigated in 271 elderly patients with DLBCL in the SEXIE-R-CHOP-14 study.^{2,18} No survival differences were found, and the authors concluded that the increased rituximab dose may have abrogated the negative effect in elderly male patients. These phase II studies in elderly patients with DLBCL supported the notion that patients with DLBCL with poor prognosis would be most likely to benefit from adapted rituximab schedules.

In our study, trough rituximab levels were indeed consistently higher during the first 4 cycles in the RR-CHOP-14 arm than in the R-CHOP-14 arm, and they remained higher during further treatment. However, this did not translate into better short- or long-term outcome for the complete study population. Also, exploratory subgroup analyses for different age groups, age-adjusted IPI risk groups, and sexes could not identify any subgroup that might benefit from rituximab intensification. Our randomized phase III study differs in some essential aspects from the phase II studies. The study populations were not comparable; in our study, both young and elderly patients with DLBCL were

TABLE 3. Grade 3-4 Adverse Events During Cycles 1-8 in All Patients

Adverse Event	No. (%)			
	R-CHOP-14 (n = 285)		RR-CHOP-14 (n = 288)	
	Grade 3	Grade 4	Grade 3	Grade 4
All toxicity	70 (25)	127 (45)	70 (24)	146 (51)
Neutropenia	23 (8)	91 (32)	29 (10)	107 (37)
Febrile neutropenia	—	3 (1)	—	1 (0)
Anemia	44 (15)	11 (4)	49 (17)	5 (2)
Thrombocytopenia	13 (5)	19 (7)	20 (7)	16 (6)
Infection	57 (20)	13 (5)	64 (22)	7 (2)
Neurologic toxicity	38 (13)	2 (1)	37 (13)	3 (1)
GI	36 (13)	4 (1)	31 (11)	6 (2)
Cardiac toxicity	11 (4)	—	11 (4)	3 (1)

NOTE. Data are No. of patients (%) with an event. Patients could have the same type of event more than once.

Abbreviations: R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

TABLE 4. Grade 3-4 Adverse Events During Cycles 1-4 in Patients Age 18-65 Versus 66-80 Years

Adverse Event	No. (%)							
	Age 18-65 Years				Age 66-80 Years			
	R-CHOP-14 (n = 140)		RR-CHOP-14 (n = 149)		R-CHOP-14 (n = 145)		RR-CHOP-14 (n = 139)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
All toxicity ^a	30 (21)	42 (30)	32 (21)	46 (31)	26 (18)	58 (40)	23 (17)	78 (56)
Neutropenia ^b	12 (9)	33 (24)	10 (7)	38 (26)	6 (4)	41 (28)	14 (10)	48 (35)
Febrile neutropenia	—	1 (1)	—	—	—	1 (1)	—	1 (1)
Anemia	11 (8)	3 (2)	11 (7)	2 (1)	21 (14)	4 (3)	18 (13)	3 (2)
Thrombocytopenia	2 (1)	5 (4)	5 (3)	2 (1)	7 (5)	6 (4)	7 (5)	5 (4)
Infection ^c	13 (9)	3 (2)	17 (11)	1 (1)	23 (16)	4 (3)	30 (22)	4 (3)
Neurologic toxicity	5 (4)	—	8 (5)	—	11 (8)	—	8 (6)	—
GI	15 (11)	1 (1)	5 (3)	—	14 (10)	—	17 (12)	3 (2)
Cardiac toxicity	1 (1)	—	—	—	2 (1)	—	7 (5)	2 (1)

NOTE. Data are No. of patients (%) with an event. Patients could have the same type of event more than once.

Abbreviations: R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

^aIn patients age 66-80 years: grade 4, 40% v 56% ($P = .007$); grade 3-4, 58% v 73% ($P = .009$).

^bIn patients age 66-80 years: grade 4, 28% v 35% ($P = .26$); grade 3-4, 32% v 45% ($P = .04$).

^cIn patients 66-80 years: grade 4, 3% v 3% ($P = 1.00$); grade 3-4, 19% vs 25% ($P = .23$).

included, whereas the phase II studies included elderly patients only and included a broader spectrum of aggressive B-cell lymphoma diagnoses. In our phase III study, staging and response evaluation was based on PET-CT, whereas it was based on CT scanning only in the phase II studies. Lastly, the schedules for rituximab intensification differed to some extent. However, from these studies, it may be concluded that dose-intensification within a standard R-CHOP regimen is insufficient to improve outcome for patients with DLBCL. Tout et al¹⁹ demonstrated that rituximab exposure is influenced by baseline metabolic tumor volume (MTV) and suggest that outcome might improve when the rituximab dose is individualized according to the MTV. This interesting hypothesis needs to be confirmed in a prospective trial.

For the past 2 decades, R-CHOP has remained the standard treatment for previously untreated DLBCL, and it has

proven exceedingly difficult to improve on this baseline.²⁰ To date, neither next-generation anti-CD20 monoclonal antibodies, such as obinutuzumab or ofatumumab, nor approaches adding targeted therapy based on molecular subtypes of DLBCL, such as bortezomib, ibrutinib, or lenalidomide in ABC/non-GCB subgroups, have proven successful.^{6,21-24} More recent developments in chemo-immunotherapy using antibody-drug conjugates (eg, polatuzumab vedotin), bispecific antibodies (eg, anti-CD3 × anti-CD20), immune checkpoint inhibitors, and CAR T-cell therapy may reveal new opportunities, and novel insights into DLBCL biology may provide essential information for meaningful patient selection for such treatments.^{25,26} Our phase III study shows that early rituximab intensification in patients with untreated DLBCL during R-CHOP-14 does not improve outcome.

AFFILIATIONS

¹Erasmus MC Cancer Institute, Rotterdam, the Netherlands

²Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark

³Haemato Oncology Foundation for Adults in the Netherlands (HOVON) Data Center, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

⁴Aarhus University Hospital, Aarhus, Denmark

⁵St Antonius Hospital, Nieuwegein, the Netherlands

⁶Albert Schweitzer Hospital, Dordrecht, the Netherlands

⁷Meander MC, Amersfoort, the Netherlands

⁸Amphia Hospital, Breda, the Netherlands

⁹Haga Teaching Hospital, The Hague, the Netherlands

¹⁰Jeroen Bosch Hospital, 's Hertogenbosch, the Netherlands

¹¹University Hospitals Leuven, Leuven, Belgium

¹²Medical Center Leeuwarden, Leeuwarden, the Netherlands

¹³Admiraal de Ruijter Hospital, Goes, the Netherlands

¹⁴University Medical Center Groningen, Groningen, the Netherlands

¹⁵Bravis Hospital, Roosendaal, the Netherlands

¹⁶Canisius Wilhelmina Hospital, Nijmegen, the Netherlands

¹⁷Zuyderland Medical Center, Heerlen, the Netherlands

¹⁸Odense University Hospital, Odense, Denmark

¹⁹Maastricht University MC, Maastricht, the Netherlands

²⁰Maastad Hospital, Rotterdam, the Netherlands

²¹Tergooi Hospitals, Hilversum, the Netherlands

²²Isala Hospital, Zwolle, the Netherlands

²³Spaarne Gasthuis, Hoofddorp, the Netherlands

²⁴Amsterdam UMC, AMC, Amsterdam, the Netherlands

²⁵Maxima Medical Center, Eindhoven, the Netherlands

²⁶Reinier de Graaf Hospital, Delft, the Netherlands

²⁷Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

²⁸UMC Utrecht, Utrecht, the Netherlands

²⁹Radboud UMC, Nijmegen, the Netherlands

³⁰HOVON Pathology Facility and Biobank, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

CORRESPONDING AUTHOR

Pieterella Johanna Lugtenburg, MD, PhD, Department of Hematology, Erasmus MC Cancer Institute, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands; e-mail: p.lugtenburg@erasmusmc.nl.

PRIOR PRESENTATION

Presented orally at the 57th Annual Meeting of the American Society of Hematology, Orlando, FL, December 5-8, 2015; 52nd ASCO Annual Meeting, Chicago, IL, June 3-7, 2016; and 21st Congress of the European Hematology Association, Copenhagen, Denmark, June 9-12, 2016.

SUPPORT

The funding sources had no role in design, data collection, data analysis, or interpretation of the findings. Supported by Grant No. CKTO 2006-14 from the Dutch Cancer Society, which funded clinical data management, and by Roche Nederland, which funded the pharmacokinetic and clinical studies and supplied the off-label rituximab.

CLINICAL TRIAL INFORMATION

NTR1014; 2006-005174-42

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.03418>.

REFERENCES

- Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 346:235-242, 2002
- Pfreundschuh M, Schubert J, Ziepert M, et al: Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60). *Lancet Oncol* 9:105-116, 2008
- Delarue R, Tilly H, Mounier N, et al: Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): A randomised phase 3 trial. *Lancet Oncol* 14:525-533, 2013
- Cunningham D, Hawkes EA, Jack A, et al: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: A phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet* 381:1817-1826, 2013
- Vaidya R, Witzig TE: Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. *Ann Oncol* 25:2124-2133, 2014
- van Imhoff GW, McMillan A, Matasar MJ, et al: Ofatumumab versus rituximab salvage chemioimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The ORCHARD study. *J Clin Oncol* 35:544-551, 2017
- Murawski N, Pfreundschuh M, Zeynalova S, et al: Optimization of rituximab for the treatment of DLBCL (I): Dose-dense rituximab in the DENSE-R-CHOP-14 trial of the DSHNHL. *Ann Oncol* 25:1800-1806, 2014
- Pfreundschuh M, Poeschel V, Zeynalova S, et al: Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): Extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the German high-grade non-Hodgkin lymphoma study group. *J Clin Oncol* 32:4127-4133, 2014 [Erratum: *J Clin Oncol* 33:1991, 2015]
- Pfreundschuh M, Müller C, Zeynalova S, et al: Suboptimal dosing of rituximab in male and female patients with DLBCL. *Blood* 123:640-646, 2014
- Müller C, Murawski N, Wiesen MHJ, et al: The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. *Blood* 119:3276-3284, 2012
- Keating M, O'Brien S: High-dose rituximab therapy in chronic lymphocytic leukemia. *Semin Oncol* 27:86-90, 2000 (suppl 12)
- O'Brien SM, Kantarjian H, Thomas DA, et al: Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J Clin Oncol* 19:2165-2170, 2001
- Pfreundschuh M, Trümper L, Kloess M, et al: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. *Blood* 104:634-641, 2004

AUTHOR CONTRIBUTIONS

Conception and design: Pieterella Johanna Lugtenburg, Lara H. Böhmer, Gregor E. Verhoef, Kon-Siong G. Jie, Marinus van Marwijk Kooy, Marie J. Kersten, Jeanette K. Doorduyn, Rolf E. Brouwer, Otto S. Hoekstra, Josée M. Zijlstra-Baalbergen

Provision of study material or patients: Pieterella Johanna Lugtenburg, Eva de Jongh, Joost W. van Esser, Johannes F. Pruijt, Gregor E. Verhoef, Mels Hoogendoorn, Memis Y. Bilgin, Marcel Nijland, Kon-Siong G. Jie, Marjolein W. van der Poel, Matthijs H. Silbermann, Aart Beeker, Lidwine W. Tick, Rolf E. Brouwer, King H. Lam

Collection and assembly of data: Pieterella Johanna Lugtenburg, Peter de Nully Brown, Francesco D'Amore, Harry R. Koene, Eva de Jongh, Rob Fijnheer, Joost W. van Esser, Lara H. Böhmer, Johannes F. Pruijt, Mels Hoogendoorn, Memis Y. Bilgin, Nicole C. van der Burg-de Graauw, Margreet Oosterveld, Kon-Siong G. Jie, Thomas Stauffer Larsen, Maria B. Leijts, Matthijs H. Silbermann, Aart Beeker, Marie J. Kersten, Jeanette K. Doorduyn, Lidwine W. Tick, King H. Lam, Coreline N. Burggraaff, Bart de Keizer, Daphne de Jong, Otto S. Hoekstra, Josée M. Zijlstra-Baalbergen

Data analysis and interpretation: Pieterella Johanna Lugtenburg, Peter de Nully Brown, Bronno van der Holt, Rob Fijnheer, Gregor E. Verhoef, Marcel Nijland, Kon-Siong G. Jie, Thomas Stauffer Larsen, Marjolein W. van der Poel, Jeanette K. Doorduyn, Coreline N. Burggraaff, Anne I. Arens, Daphne de Jong, Otto S. Hoekstra, Josée M. Zijlstra-Baalbergen

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We acknowledge all local data managers and the HOVON Data Center trial team for trial management and central data management. We thank the members of the data and safety monitoring board, E. Brusamolino (Pavia, Italy), B. Coiffier (deceased; Lyon, France), and statistician W.C.J. Hop (deceased; Rotterdam, the Netherlands) for their contribution to the conduct of the study and also thank all collaborators and patients who participated in this study.

14. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *J Clin Oncol* 32:3059-3068, 2014
15. Barrington SF, Mikhaeel NG, Kostakoglu L, et al: Role of imaging in the staging and response assessment of lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol* 32:3048-3058, 2014
16. Burggraaf CN, Cornelisse AC, Hoekstra OS, et al: Interobserver agreement of interim and end-of-treatment ¹⁸F-FDG PET/CT in diffuse large B-cell lymphoma (DLBCL): Impact on clinical practice and trials. *J Nucl Med* 59:1831-1836, 2018
17. Crump M, Neelapu SS, Farooq U, et al: Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood* 130:1800-1808, 2017 [Erratum: *Blood* 131:587-588, 2018]
18. Pfreundschuh M, Murawski N, Zeynalova S, et al: Optimization of rituximab for the treatment of DLBCL: Increasing the dose for elderly male patients. *Br J Haematol* 179:410-420, 2017
19. Tout M, Casasnovas O, Meignan M, et al: Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: A Lymphoma Study Association report. *Blood* 129:2616-2623, 2017
20. Tilly H, Gomes da Silva M, Vitolo U, et al: Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26:v116-v125, 2015 (suppl 5)
21. Vitolo U, Trněný M, Belada D, et al: Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. *J Clin Oncol* 35:3529-3537, 2017
22. Davies A, Cummin TE, Barrans S, et al: Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): An open-label, randomised, phase 3 trial. *Lancet Oncol* 20:649-662, 2019
23. Younes A, Sehn LH, Johnson P, et al: Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol* 37:1285-1295, 2019
24. Vitolo U, Witzig TE, Gascoyne RD, et al: Robust: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematol Oncol* 37, 2019 (suppl 2; abstr 005)
25. Chapuy B, Stewart C, Dunford AJ, et al: Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med* 24:679-690, 2018 [Errata: *Nat Med* 24:1290-1291, 2018; *Nat Med* 24:1292, 2018]
26. Schmitz R, Wright GW, Huang DW, et al: Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med* 378:1396-1407, 2018

ASCO® Career Center

Search for Oncology Career Opportunities

Visit the ASCO Career Center today to:

- View oncology jobs in your specialty area
- Upload your resume
- Sign up for job alerts
- Get career advice and tips

You can also attend the annual ASCO Career Fair at the ASCO Annual Meeting.

ASCO Career Center is also available via iPhone app. Search jobs at **careercenter.asco.org**

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Rituximab-CHOP With Early Rituximab Intensification for Diffuse Large B-Cell Lymphoma: A Randomized Phase III Trial of the HOVON and the Nordic Lymphoma Group (HOVON-84)**

The following represents disclosure information provided by the author of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Pieterella Johanna Lugtenburg

Consulting or Advisory Role: Takeda Pharmaceuticals, Servier, Roche/Genentech, Genmab, Celgene

Research Funding: Takeda Pharmaceuticals (Inst), Servier (Inst)

Travel, Accommodations, Expenses: Celgene

Peter de Nully Brown

Consulting or Advisory Role: Roche, Novartis

Francesco A. D'Amore

Honoraria: Servier (Inst), Takeda Pharmaceuticals (Inst)

Consulting or Advisory Role: Nordic Nanovector (Inst), Kyowa Hakko Kirin (Inst), Takeda Pharmaceuticals (Inst)

Research Funding: Servier (Inst)

Johannes F. Pruijt

Consulting or Advisory Role: Roche

Kon-Siong G. Jie

Research Funding: Leo-Pharma, Pfizer

Thomas Stauffer Larsen

Consulting or Advisory Role: Novartis, Bristol Myers Squibb

Travel, Accommodations, Expenses: Novartis

Marjolein W. van der Poel

Consulting or Advisory Role: Takeda Pharmaceuticals

Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Daiichi Sankyo

Marinus van Marwijk Kooy

Consulting or Advisory Role: BMS Netherlands

Marie J. Kersten

Honoraria: Novartis, Kite, Roche

Consulting or Advisory Role: Novartis, Kite, Miltenyi Biotec (Inst), Takeda Pharmaceuticals (Inst)

Travel, Accommodations, Expenses: Novartis, Kite, Roche, Celgene

Jeanette K. Doorduijn

Travel, Accommodations, Expenses: Roche, Celgene

Rolf E. Brouwer

Stock and Other Ownership Interests: Celgene, Bristol Myers Squibb, Gilead Sciences

No other potential conflicts of interest were reported.

APPENDIX

Prephase Treatment and Supportive Measures During R-CHOP-14 Treatment

Prephase treatment. A prephase treatment before the start of study treatment was mandatory in all elderly patients (age 66-80 years) and was left at the discretion of the treating physician in young patients (age 18-65 years). The prephase treatment consisted of a 5-day course of 100 mg of prednisone once daily.

Allopurinol. Allopurinol was applied according to local practices. The dose should have been adapted if the creatinine clearance was decreased.

Prednisone tapering. A gradual reduction of the prednisone dose was recommended to prevent marked fatigue after prompt discontinuation of prednisone. Prednisone 50 mg could be administered on day 6, 25 mg on day 7, and 10 mg on day 8. For patients complaining of fatigue after tapering of prednisone, hydrocortisone 20 mg orally in the morning and 10 mg orally at 1200 was recommended.

Prophylaxis of infection. *Pneumocystis jiroveci* and herpes infection prophylaxis was mandatory in all patients. This consisted of oral cotrimoxazol 480 mg once daily and oral valaciclovir 500 mg twice per day, starting with the prephase treatment until 4 weeks after the last rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP-14) cycle.

Intrathecal prophylaxis for CNS relapse was at the discretion of the treating physician.

Sample Size Calculation

The sample size was calculated to have a sufficient number of patients available for the second randomization (R2); thereafter, the statistical power for the first randomization (R1) was determined. To detect with 80% power an improvement in failure-free survival (FFS) from R2 with a hazard ratio (HR) of 0.60 (2-sided significance level, $\alpha = 0.05$), 126 events were required. Assuming a proportional hazard for young versus elderly patients of 0.62, an accrual period of 5 years, and 2 years of follow-up after the last patient was included in the maintenance randomization, this would require 395 patients (young, $n = 174$; elderly, $n = 221$). Therefore, 575 patients should be included in this trial, resulting in a power of 86% to detect an improvement in complete remission (CR) rate from 77% to 87%.

Statistical Methods

The primary end point for R1 was CR on induction. Patient treatment was considered a success if CR was achieved during or after induction treatment. All other patient treatments were considered a failure. Logistic regression analysis with adjustment for age group (18-65 ν \geq 66-80 years) and age-adjusted International Prognostic Index (IPI) score (0 ν 1 ν 2 ν 3; categorical) was applied for the primary analysis, and odds ratios and 95% CIs were determined, with P values $< .05$ considered statistically significant.

Secondary end points were best response on protocol treatment, adverse events, FFS, progression-free survival (PFS) and overall survival (OS) from R1, and disease-free survival (DFS) from CR. FFS was defined as time from R1 to no CR on protocol, relapse, or death, whichever came first. PFS was calculated from R1 to progression, relapse, or death, whichever came first. OS was determined from R1 to death resulting from any cause. Patients still alive at last contact were censored. DFS was measured from date of CR to relapse or death, whichever came first.

The proportion of patients with specific adverse events was compared between arms post hoc using the χ^2 test or Fisher's exact test, whichever was appropriate.

For the survival end points, the HRs and 95% CIs were determined using univariable and multivariable Cox regression analyses. Multivariable Cox regression analysis was primarily aimed at evaluating the impact of adjustment on the HRs and 95% CIs of treatment arms,

rather than at evaluating the prognostic value of individual covariates, and included: treatment arm, age (18-65 ν \geq 66-80 years), sex (male ν female), age-adjusted IPI stage (low ν low-intermediate ν high-intermediate ν high; continuous), WHO performance (0 ν 1 ν 2; continuous), lactate dehydrogenase (normal ν elevated), B symptoms (no ν yes), bulky mass (no ν yes), and bone marrow involvement (no ν yes), as specified in the statistical analysis plan. Because the number of patients with missing data was low (ie, 3 of 574 eligible patients [1%]), the multivariable Cox regression analyses were restricted to patients with complete data. Kaplan-Meier curves by treatment arm were generated to illustrate survival.

All analyses were performed according to the intention-to-treat (ITT) principle. However, patients initially randomly assigned but considered ineligible in retrospect based on information that should have been available before random assignment were excluded from the respective analyses (modified ITT).

Two interim analyses were planned after the inclusion of 200 and 400 evaluable patients, primarily to guard against unfavorable results in the experimental arm, and the results were presented confidentially to an independent data and safety monitoring board. All reported P values are 2 sided and were not adjusted for multiple testing.

Rituximab Pharmacokinetics

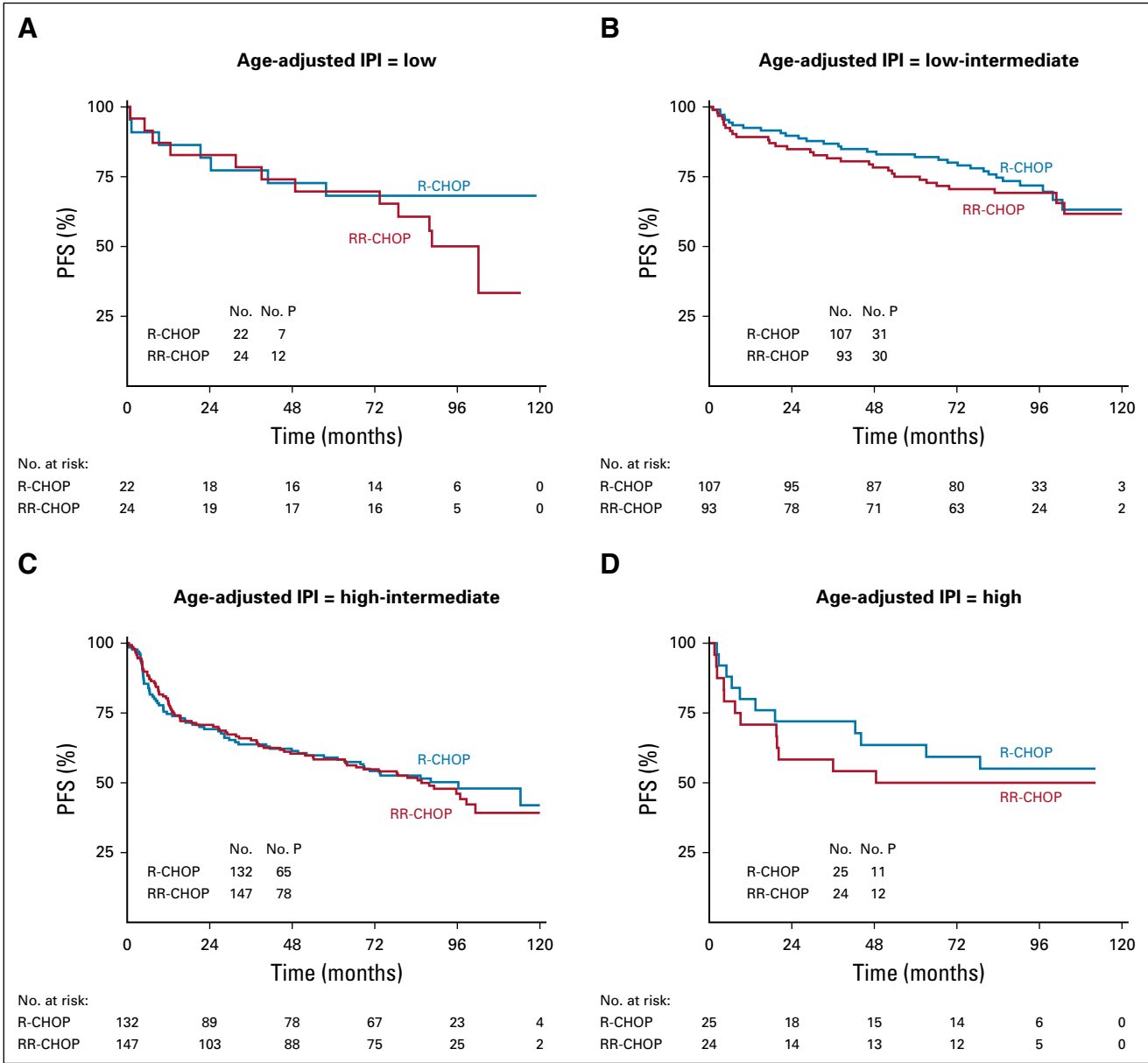
Rituximab pharmacokinetics were evaluated in 6 patients in the R-CHOP-14 arm and 4 patients in the RR-CHOP-14 (R-CHOP-14 with intensification of rituximab in the first 4 cycles) arm during the induction phase. Thirty to 60 minutes before each rituximab infusion, 5 mL of blood was drawn, and samples were centrifuged at 1,000 g for 10 minutes at room temperature and stored at -20°C until shipping on dry ice for analysis. Rituximab serum levels were measured by enzyme-linked immunosorbent assay at Xendo Laboratories (Groningen, the Netherlands).

Participating Hospitals and Principal Investigators

The following is a full list of the study sites and principal investigators who participated in the HOVON-84 study: P. Zachee, ZNA Stuivenberg, Antwerpen, Belgium; G.E.G. Verhoef, University Hospitals Leuven, Leuven, Belgium; J. Madsen, Aalborg Hospital, Aalborg, Denmark; F.A. D'Amore, Aarhus University Hospital, Aarhus, Denmark; P. Brown, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; P.B. Hansen, Herlev Hospital, Herlev, Denmark; S. Pulczynski, Regionshospital, Holstebro, Denmark; T. Stauffer Larsen, Odense University Hospital, Odense, Denmark; B. Himmelstrup, Zealand University Hospital, Roskilde, Denmark; T. Plesner, Vejle Hospital, Vejle, Denmark; H. Larsen, Regionshospitalet, Viborg, Denmark; B. Himmelstrup, Zealand University Hospital, Roskilde, Denmark; T. Plesner, Vejle Hospital, Vejle, Denmark; H. Larsen, Regionshospitalet, Viborg, Denmark; H.P.J. Visser, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands; B.W. Schot, Ziekenhuisgroep Twente, Almelo, the Netherlands; R. Fijnheer, Meander MC, Amersfoort, the Netherlands; G.J. Timmers, Amstelland Hospital, Amstelveen, the Netherlands; M.J. Kersten, Amsterdam UMC, location AMC, Amsterdam, the Netherlands; J.M. Zijlstra-Baalbergen, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands; J.W. Baars, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands; A.M. de Kreuk, Sint Lucas Andreas Hospital, Amsterdam, the Netherlands; W.E. Terpstra, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; M. Soesan, Slotervaart Hospital, Amsterdam, the Netherlands; C.G. Schaar, Gelre Hospitals, Apeldoorn, the Netherlands; E.J.M. Mattijssen, Hospital Rijnstate, Arnhem, the Netherlands; L.M. Faber, Rode Kruis Hospital, Beverwijk, the Netherlands; J.W.J. van Esser, Amphibia Hospital, Breda, the Netherlands; R.F.J. Schop, IJsselland Hospital, Capelle aan den IJssel, the Netherlands; R.E. Brouwer, Reinier de Graaf Hospital, Delft, the Netherlands; L.Th. Vlasveld, Bronovo Hospital, The Hague, the Netherlands; L.H. Böhmer, Haga Teaching Hospital, The Hague, the Netherlands; C. Westerhuis-Siemes, Deventer Hospitals, Deventer, the Netherlands; H.S. Noordzij-Nooteboom, Van Weel Bethesda Hospital, Dirksland, the Netherlands; E. de Jongh, Albert Schweitzer Hospital,

Dordrecht, the Netherlands; G.A. Velders, Gelderse Vallei Hospital, Ede, the Netherlands; L.W. Tick, Maxima Medical Center, Eindhoven, the Netherlands; M.R. Schaafsma, Medisch Spectrum Twente, Enschede, the Netherlands; Y. Bilgin, Admiraal de Ruyter Hospital, Goes, the Netherlands; M.A. Davidis-Van Schoonhoven, Beatrix Hospital, Gorinchem, the Netherlands; H. Levenga, Groene Hart Hospital, Gouda, the Netherlands; A.W.G. van der Velden, Martini Hospital, Groningen, the Netherlands; M. Nijland, University Medical Center Groningen, Groningen, the Netherlands; P.W.G. van der Linden, Kennemer Gasthuis, Haarlem, the Netherlands; K.S.G. Jie, Zuyderland Medical Center, Heerlen, the Netherlands; J.F.M. Pruijt, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands; M.H. Silbermann, Tergooi Hospitals, Hilversum, the Netherlands; A. Beeker, Spaarne Hospitals, Hoofddorp, the Netherlands; M. Hoogendoorn, Medical Center Leeuwarden, Leeuwarden, the Netherlands; W.A.F. Marijt, Leiden University Medical Center, Leiden, the Netherlands; D. van Lammeren-Venema, IJsselmeer Hospital, Lelystad, the Netherlands; M.W.M. van der Poel, Maastricht University Medical Center, Maastricht, the Netherlands; H.R. Koene, St. Antonius Hospital, Nieuwegein, the Netherlands; M. Oosterveld,

Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands; W.B.C. Stevens, RadboudUMC, Nijmegen, the Netherlands; M.H.W. van de Poel, Laurentius Hospital, Roermond, the Netherlands; N.C.H.P. van der Burg-de Graauw, Bravis Hospital, Roosendaal, the Netherlands; M.B.L. Leijds, Maasstad Hospital, Rotterdam, the Netherlands; P.J. Lugtenburg and J.K. Doorduijn, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; H.C.T. van Zaanen, Franciscus Gasthuis, Rotterdam, the Netherlands; F. de Boer, Ikazia Hospital, Rotterdam, the Netherlands; N. Durdu-Rayman, Franciscus Vlietland Hospital, Schiedam, the Netherlands; R.J.W. van Kampen, Orbis Medical Center, Sittard-Geleen, the Netherlands; E.J.M.M. van de Weijert, Ruwaard van Putten Hospital, Spijkenisse, the Netherlands; C.M.A. Henkens, Rivierenland Hospital, Tiel, the Netherlands; M.F. Durian, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands; M.C. Minnema, University Medical Center Utrecht, Utrecht, the Netherlands; M.E.P. Smeets, Beatrix Hospital, Winterswijk, the Netherlands; K.G. van der Hem, Zaans Medical Center, Zaandam, the Netherlands; and M. van Marwijk Kooy, Isala Hospital, Zwolle, the Netherlands.



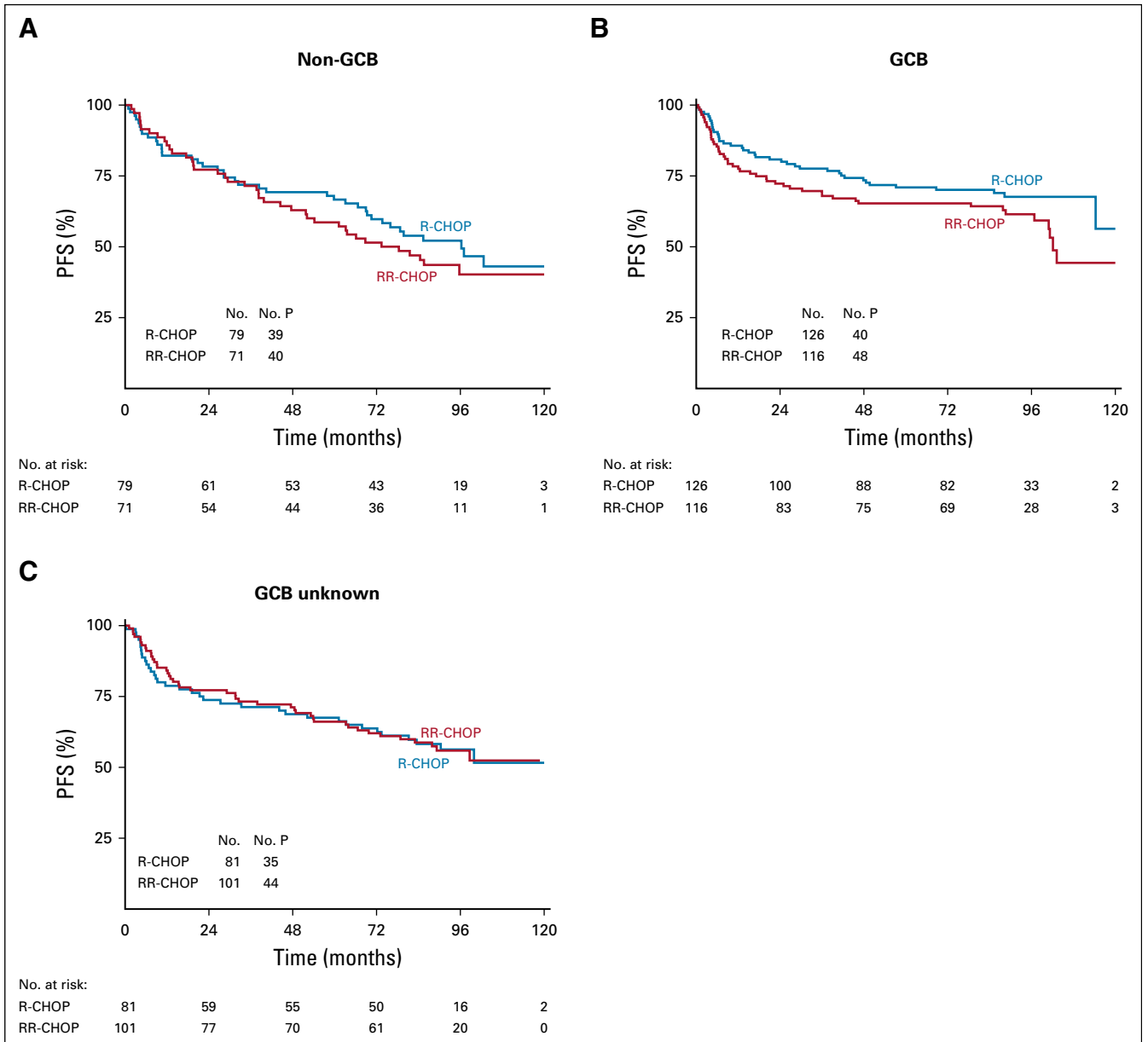


FIG A2. Progression-free survival (PFS) by treatment arm for diffuse large B-cell lymphoma phenotype: (A) non-germinal center B cell (GCB), (B) GCB, and (C) GCB unknown. P, progression, relapse, or death; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

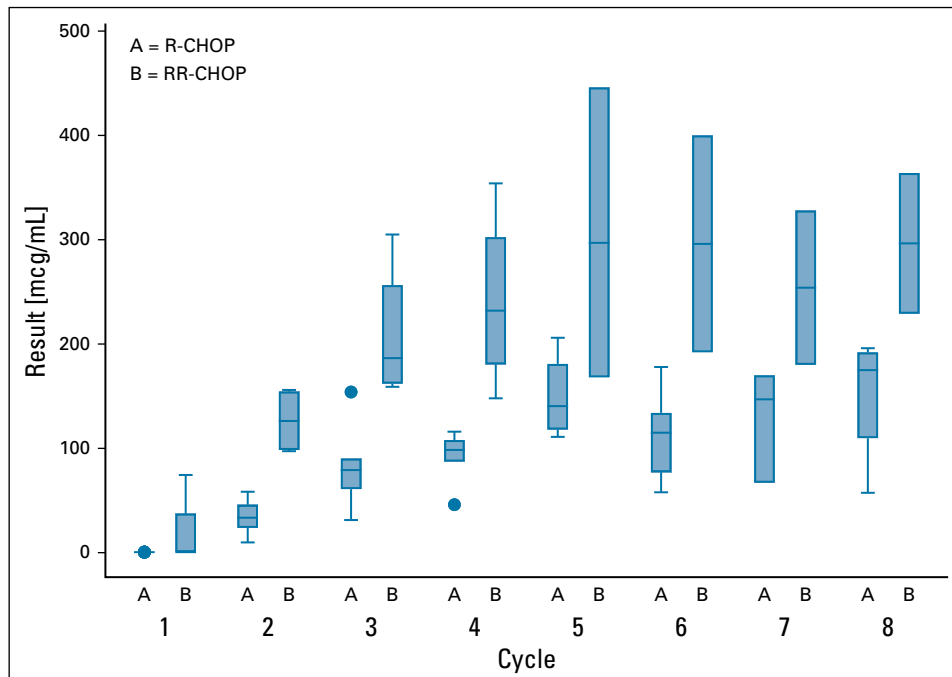


FIG A3. Rituximab trough serum levels. A, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm A); B, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B).

TABLE A1. Central Pathology Review Category for Other Diagnosis or Unclassifiable

Histology	No. of Patients
Indolent B-cell lymphoma	8
Transformed follicular lymphoma	6
B-cell lymphoma unclassifiable	6
Angioimmunoblastic T-cell lymphoma	2
Transformed nodular lymphocyte-predominant Hodgkin lymphoma	1
Poor-quality sample	4

TABLE A2. Multivariable Analysis of Prognostic Factors for DFS From CR

Factor	HR	95% CI	P
RR-CHOP-14 arm	1.24	0.93 to 1.66	.14
Age \geq 66 years	1.77	1.30 to 2.40	< .001
Age-adjusted IPI score ^a	1.14	0.81 to 1.60	.45
Female sex	1.02	0.76 to 1.37	.89
WHO performance score ^b	0.99	0.76 to 1.28	.92
LDH > ULN	1.50	0.93 to 2.42	.10
B symptoms	1.04	0.76 to 1.42	.82
Bulky disease	0.94	0.68 to 1.31	.72
BM involvement	1.34	0.89 to 2.03	.16

Abbreviations: BM, bone marrow; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; RR-CHOP, rituximab on days 1 and 8 of first 4 cycles and day 1 of remaining cycles plus cyclophosphamide, doxorubicin, vincristine, and prednisone (arm B); ULN, upper limit of normal.

^aAnalyzed as low v low-intermediate v high-intermediate v high.

^bAnalyzed as WHO 0 v 1 v 2.