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 ^{18}F-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/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (maximum, 2 mg), and rituximab 375 mg/m^2 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/m^2 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 described[16] 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 $v \geq$ 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 $\geq$ 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

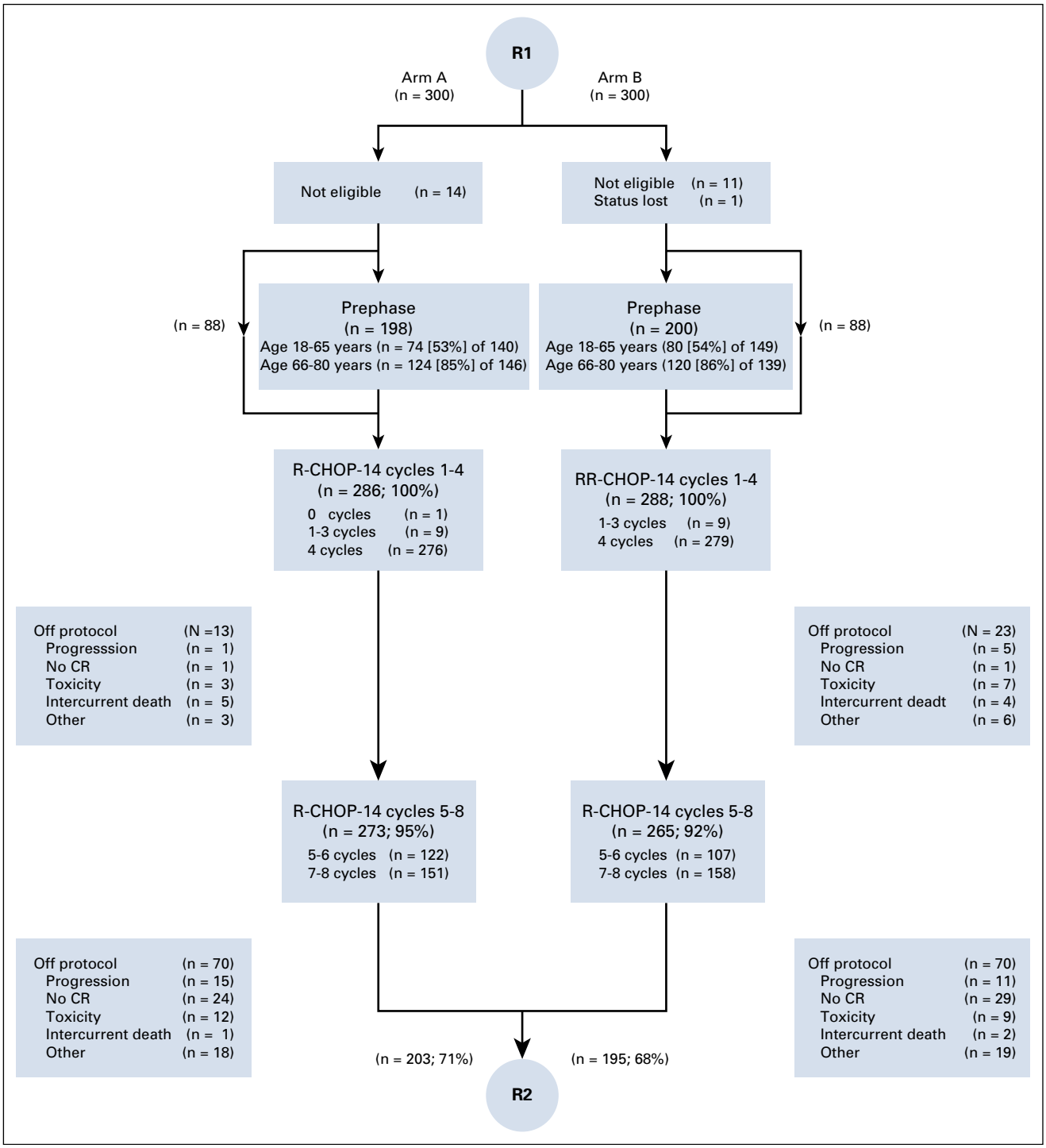

FIG 1. CONSORT diagram of induction treatment of patients with diffuse large B-cell lymphoma in the HOVON-84 non-Hodgkin lymphoma trial by treatment arm. CR, complete remission; R1, induction randomization; R2, maintenance randomization; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, 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)	No. (%) 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 *BCL2* and/or *BCL6*[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.

[a]Appendix Table A1.

[b]Based on standard Hans criteria.

[c]According 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%

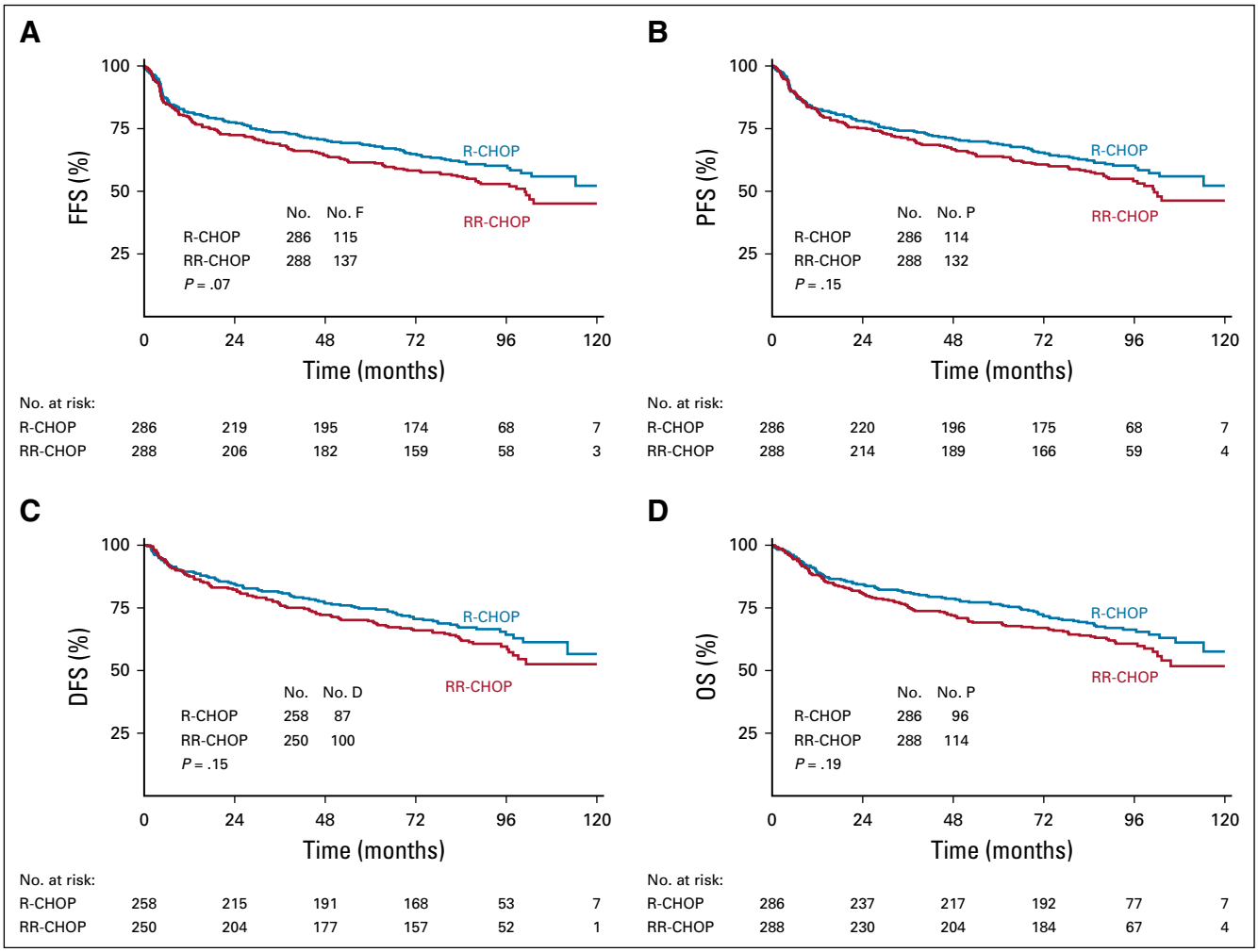

FIG 2. Kaplan-Meier survival curves according to assigned treatment arm. (A) Failure-free survival (FFS), (B) progression-free survival (PFS), (C) disease-free survival (DFS) from complete remission, and (D) overall survival (OS). All *P* values by Cox logistic regression (adjusted). D, death; F, no 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

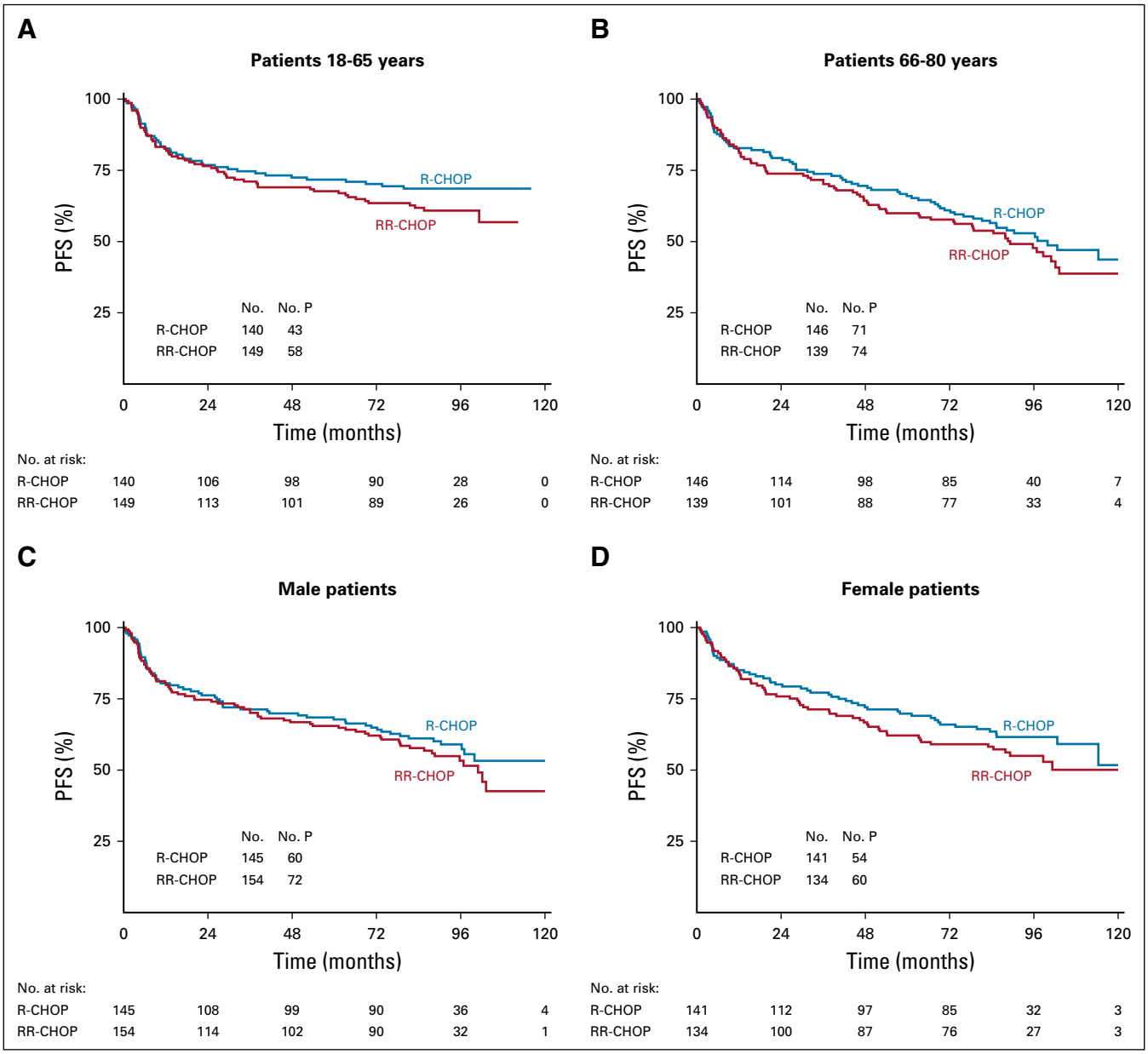

FIG 3. Progression-free survival (PFS) by treatment arm within subgroups: (A) age 18 to 65 years, (B) age 66 to 80 years, (C) male patients, and (D) female patients. P, progression, relapse, or death; R-CHOP, rituximab on day 1 of each cycle plus cyclophosphamide, doxorubicin, vincristine, and prednisone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