ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

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ABSTRACT

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is typically treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, only 60% of patients are cured with R-CHOP. Polatuzumab vedotin is an antibody–drug conjugate targeting CD79b, which is ubiquitously expressed on the surface of malignant B cells.

METHODS

We conducted a double-blind, placebo-controlled, international phase 3 trial to evaluate a modified regimen of R-CHOP (pola-R-CHP), in which vincristine was replaced with polatuzumab vedotin, as compared with standard R-CHOP, in patients with previously untreated intermediate-risk or high-risk DLBCL. Patients 18 to 80 years of age were randomly assigned in a 1:1 ratio to receive six cycles of either pola-R-CHP or R-CHOP, plus two cycles of rituximab alone. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival and safety.

RESULTS

Overall, 879 patients underwent randomization: 440 were assigned to the pola-R-CHP group and 439 to the R-CHOP group. After a median follow-up of 28.2 months, the percentage of patients surviving without progression was significantly higher in the pola-R-CHP group than in the R-CHOP group (76.7% [95% confidence interval (CI), 72.7 to 80.8] vs. 70.2% [95% CI, 65.8 to 74.6] at 2 years; stratified hazard ratio for progression, relapse, or death, 0.73 by Cox regression; 95% CI, 0.57 to 0.95; P=0.02). Overall survival at 2 years did not differ significantly between the groups (88.7% [95% CI, 85.7 to 91.6] in the pola-R-CHP group and 88.6% [95% CI, 85.6 to 91.6] in the R-CHOP group; hazard ratio for death, 0.94; 95% CI, 0.65 to 1.37; P=0.75). The safety profile was similar in the two groups.

CONCLUSIONS

Among patients with previously untreated intermediate-risk or high-risk DLBCL, the risk of disease progression, relapse, or death was lower among those who received pola-R-CHP than among those who received R-CHOP. (Funded by F. Hoffmann–La Roche/Genentech; POLARIX ClinicalTrials.gov number, NCT03274492.)

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A list of investigators in the POLARIX trial is provided in the Supplementary Appendix, available at NEJM.org.

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Diffuse large B-cell lymphoma (DLBCL) is the most common form of lymphoma.[1] The addition of rituximab, an anti-CD20 monoclonal antibody, to the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) has yielded substantial improvement in patient outcomes.[2,3] Although most patients (depending on prognostic factors) can be cured with rituximab plus CHOP (R-CHOP), up to 40% of patients will have disease that is refractory to this treatment or will have a relapse after an initial response.[4,5] To improve treatment outcomes with R-CHOP, numerous approaches have been attempted in randomized trials, including intensification of chemotherapy[6-8] or rituximab (by increasing the doses or the number of cycles or by shortening the interval between cycles),[9] the addition of maintenance therapy,[10,11] the use of a second-generation anti-CD20 monoclonal antibody,[12] or incorporation of novel agents.[13,14] These trials have not shown a meaningful improvement in outcomes, and R-CHOP remains the standard first-line treatment for DLBCL.[4,15]

CD79b is a subunit of a heterodimer transmembrane component of the B-cell antigen receptor involved in cell signaling and is ubiquitously expressed on the surface of mature B-cell lymphomas, including DLBCL.[16,17] Polatuzumab vedotin is an antibody–drug conjugate composed of an anti-CD79b monoclonal antibody[18] conjugated by a protease-cleavable linker to monomethyl auristatin E, a potent microtubule inhibitor.[16,19] Polatuzumab vedotin has shown efficacy in patients with relapsed or refractory DLBCL, both as a single agent (with an overall response of 52%)[20] and in combination with rituximab.[21] In a recent randomized trial involving patients with relapsed or refractory DLBCL, the addition of polatuzumab vedotin to bendamustine and rituximab resulted in significantly longer overall survival than treatment with bendamustine and rituximab alone.[22]

In a phase 1b–2 trial in which polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) was investigated as first-line therapy for DLBCL, 89% of the patients had an overall response and 77% had a complete response. Vincristine was excluded from the regimen owing to the risk of overlapping neurologic toxic effects with polatuzumab vedotin.[23] We conducted the phase 3 POLARIX trial to evaluate the efficacy and safety of pola-R-CHP, as compared with R-CHOP, in patients with previously untreated DLBCL.

Methods

Trial Conduct

The POLARIX trial is a randomized, double-blind, placebo-controlled, international phase 3 trial. The protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review board or ethics committee at each participating institution. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki.[24] All the patients provided written informed consent. The trial was sponsored by F. Hoffmann–La Roche/Genentech and was designed by the sponsor in collaboration with the Lymphoma Study Association. An independent data and safety monitoring committee reviewed safety data on a regular basis during the conduct of the trial. The first draft of the manuscript was written primarily by one academic author and one author employed by the sponsor; medical writing assistance was funded by the sponsor. All the authors reviewed the data and contributed to the preparation of the final version of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

Patients

Patients were eligible for inclusion if they were 18 to 80 years of age, had CD20-positive DLBCL,[25] had not received previous treatment for lymphoma, had an Eastern Cooperative Oncology Group performance status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability), had a baseline International Prognostic Index (IPI)[26] score between 2 and 5 (on a 5-level prognostic scale, with higher numbers indicating a poorer prognosis), and had adequate hematologic, renal, hepatic, and cardiac function, regardless of the cell of origin or the presence of rearrangements in *MYC*, *BCL2*, *BCL6*, or a combination of these. Key exclusion criteria were a history of indolent lymphoma, a contraindication to any component of R-CHOP, previous receipt of

anthracycline agents, and known central nervous system (CNS) involvement. Details of the eligibility criteria and trial methods are provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND BLINDING

Eligible patients were randomly assigned in a 1:1 ratio to receive pola-R-CHP or R-CHOP. The doses and treatment schedules used are described below and in further detail in the protocol. Randomization was stratified according to IPI score (2 vs. 3 to 5), status with respect to bulky disease (present [one or more lesions ≥7.5 cm in greatest dimension] vs. absent), and geographic region (Western Europe, the United States, Canada, and Australia vs. Asia vs. rest of world). The investigator, sponsor, and patients were unaware of the treatment assignments. Details of the randomization procedure and blinding are provided in the protocol.

TREATMENT

Eight 21-day cycles of treatment were planned. During the first six cycles, patients received either pola-R-CHP or R-CHOP. On day 1 of each cycle, patients received either intravenous polatuzumab vedotin at a dose of 1.8 mg per kilogram of body weight and a placebo matching intravenous vincristine (pola-R-CHP group) or a placebo matching polatuzumab vedotin and intravenous vincristine at a dose of 1.4 mg per square meter of body-surface area (maximum of 2 mg) (R-CHOP group), plus intravenous doses of rituximab (375 mg per square meter), cyclophosphamide (750 mg per square meter), and doxorubicin (50 mg per square meter). All the patients also received oral prednisone at a dose of 100 mg once daily on days 1 through 5 of each of the first six cycles. During cycles 7 and 8, patients in both groups received rituximab monotherapy at a dose of 375 mg per square meter.

CNS prophylaxis with intrathecal chemotherapy was permitted, in accordance with institutional practice guidelines. The use of granulocyte colony-stimulating factor (G-CSF) was required during the first six cycles of treatment for primary prophylaxis against neutropenia. The administration of consolidative radiotherapy to initial sites of bulky disease or extranodal sites was permitted at the discretion of the investigator. In such cases, radiotherapy had to be planned before randomization and was given after end-of-treatment assessments, as described in the Supplementary Appendix. Details of the management of dose interruptions, dose modifications, discontinuations of polatuzumab vedotin and vincristine, and any other permitted treatments are provided in the protocol.

END POINTS AND ASSESSMENTS

The primary efficacy end point was investigator-assessed progression-free survival as calculated in a time-to-event analysis, in which investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Key secondary end points, which were examined hierarchically,[27] were investigator-assessed event-free survival (as assessed in a time-to-event analysis, in which an event was defined as investigator-assessed disease progression or relapse, death from any cause, initiation of any treatment for lymphoma that was not specified in the protocol, or biopsy-confirmed residual disease after treatment completion); positron-emission tomography and computed tomography (PET-CT)–based complete response at the end of treatment as determined by blinded independent central review; and overall survival. Details regarding the hierarchical testing are described further in the Supplementary Appendix. An additional secondary end point, which was not subject to hypothesis testing, was investigator-assessed disease-free survival as evaluated in a time-to-event analysis. The analysis of disease-free survival included patients who had a best overall response of complete response and was therefore based on a subgroup of patients that was defined after randomization. Details of the methods regarding additional secondary and exploratory end points are provided in the protocol. The primary safety objective was to compare the incidence of adverse events in the two treatment groups. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 24.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Lugano classification response criteria for lymphoma[28] were used by the investigators to perform tumor assessments, as well as by the independent central review committee to evaluate end-of-treatment response on the basis of PET-CT. CT and PET-CT were required at baseline and at treatment completion; CT, PET-CT, or both were

planned after cycle 4 and during surveillance (i.e., every 6 months for the next 24 months, then every 12 months for the next 36 months). Cell-of-origin assessment, immunohistochemical analysis of BCL2 and MYC protein expression, and fluorescence in situ hybridization to detect *MYC*, *BCL2*, and *BCL6* rearrangements were performed at central laboratories (see the Supplementary Appendix).

STATISTICAL ANALYSIS

With the exception of the analysis of investigator-assessed disease-free survival (described above), the efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomization. The safety analysis population included all patients who received at least one dose of any of the trial drugs.

The primary analyses reported here were performed after 228 events (disease progression, relapse, or death) had occurred and all patients had been enrolled in the trial for at least 24 months. These analyses included the primary analyses of progression-free survival, event-free survival, and complete response, as well as the interim analysis of overall survival.

For the primary efficacy end point of investigator-assessed progression-free survival, under the assumption of a hazard ratio of 0.69, we estimated that a sample of 875 patients would result in a total of 228 events. This would provide the trial with 80% power at a one-sided (2.5%) significance level (or equivalently, a two-sided [5.0%] significance level) to detect a risk of disease progression, relapse, or death that was lower by at least 23% (the minimum detectable difference; hazard ratio, 0.77) with pola-R-CHP than with R-CHOP. The null hypothesis would be rejected if the one-sided P value from a log-rank test was less than 0.025, with the conclusion that progression-free survival was higher among patients who received pola-R-CHP than among those who received R-CHOP. The Kaplan–Meier method was used to estimate progression-free survival in each treatment group. Estimates of the treatment effect were expressed as hazard ratios and corresponding 95% confidence intervals and were derived with the use of a stratified Cox proportional-hazards analysis. In patients who were progression-free at the time of data cutoff, progression-free survival data were censored at the date of the last disease assessment. For patients who had no tumor assessment after the baseline assessment or who had postbaseline assessment results that could not be evaluated for response, progression-free survival data were censored at the date of randomization. All P values are two-sided and are presented only for end points that were tested in a hierarchical manner. The proportional-hazards assumption for progression-free survival was evaluated with the use of the method proposed by Grambsch and Therneau,[29] and no evidence suggested violation of the proportionality assumption. Detailed statistical methods are described in the statistical analysis plan and in the Supplementary Appendix.

RESULTS

PATIENTS

Overall, 1063 patients were screened for eligibility. Between November 14, 2017, and June 27, 2019, a total of 879 patients underwent randomization: 440 were assigned to the pola-R-CHP group and 439 to the R-CHOP group (the intention-to-treat population) (Fig. 1). The safety population included 435 patients in the pola-R-CHP group and 438 patients in the R-CHOP group. The demographic and clinical characteristics of the two groups were similar at baseline (Table 1 and Table S1 in the Supplementary Appendix). The median age of the overall patient population was 65 years (range, 19 to 80). Stratification factors (IPI score, presence or absence of bulky disease, and geographic region) and centrally evaluated subtypes of DLBCL were balanced between the two groups. The median time between diagnosis, which was defined by the date of biopsy, and the initiation of treatment was similar in the two groups (26 days in the pola-R-CHP group and 27 days in the R-CHOP group) (Table 1).

TREATMENT EXPOSURE

Most of the patients received all six doses of the active agents of polatuzumab vedotin or vincristine (91.7% and 88.5% in the pola-R-CHP and R-CHOP groups, respectively); 88.0% and 85.9% of the patients in the pola-R-CHP and R-CHOP groups, respectively, received all eight cycles of treatment (Fig. 1). The median relative dose intensities (the proportions of administered doses relative to planned doses) of rituximab, doxorubicin, and cyclophosphamide were greater than 99% in both treatment groups.

In total, 11 patients (2.5%) in the pola-R-CHP group and 18 patients (4.1%) in the R-CHOP group received preplanned radiotherapy after completion of the trial treatment, as allowed according to the protocol. A total of 72 patients (16.4%) in the pola-R-CHP group and 86 patients (19.6%) in the R-CHOP group received CNS prophylaxis (Table S2).

EFFICACY

Primary End Point

At the time of data cutoff (June 28, 2021), after a median follow-up of 28.2 months (range, 0.1 to 43.4), the risk of progression, relapse, or death was significantly lower in the pola-R-CHP group than in the R-CHOP group (stratified hazard ratio, 0.73; 95% confidence interval [CI], 0.57 to 0.95; P=0.02) (Table 2 and Fig. 2A). Milestone analysis showed that the percentage of patients surviving without progression at 2 years was 6.5 percentage points higher in the pola-R-CHP group than in the R-CHOP group (76.7% [95% CI, 72.7 to 80.8] vs. 70.2% [95% CI, 65.8 to 74.6]).

The results of an exploratory subgroup analysis of progression-free survival varied according to demographic and disease characteristics. No-

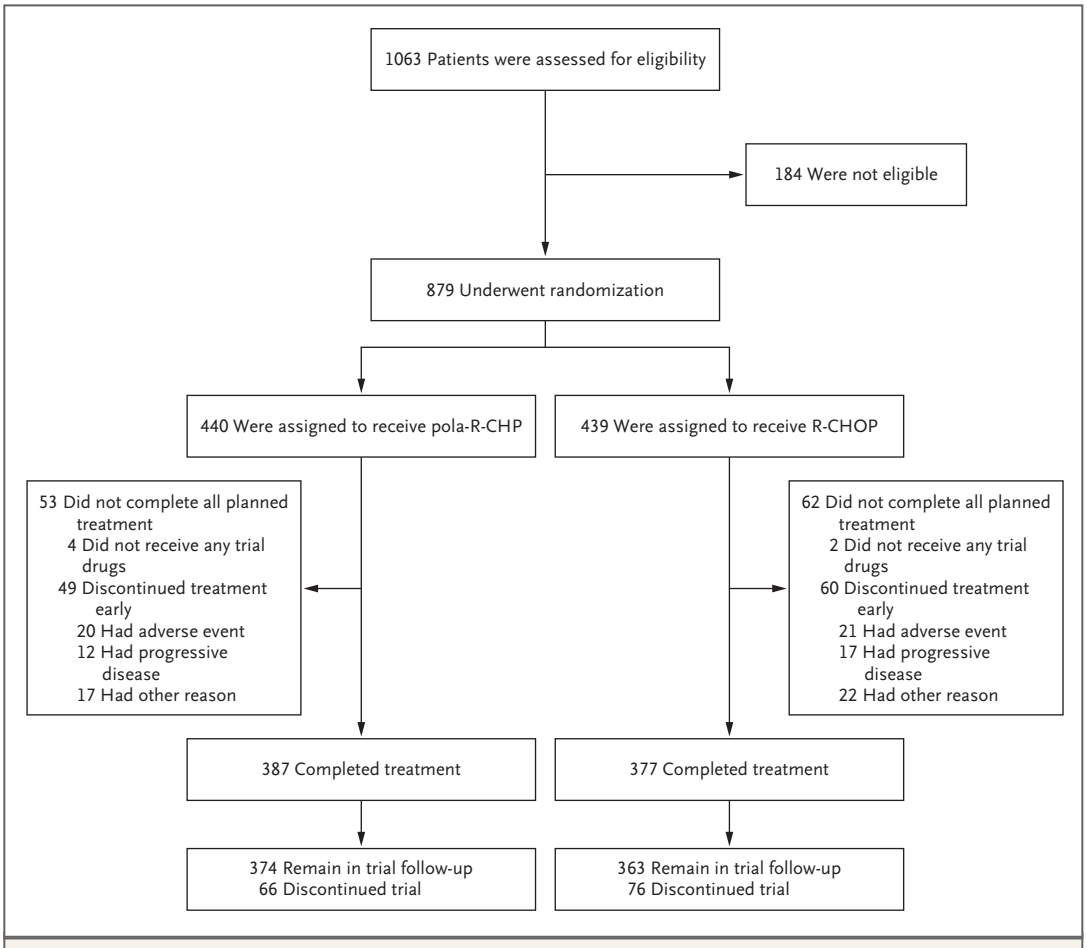

Figure 1. Enrollment, Randomization, and Follow-up.

The most common eligibility criteria that patients did not meet were an International Prognostic Index score between 2 and 5 (23 patients), the availability of archival or freshly collected tumor tissue before trial enrollment (22 patients), a signed written informed consent form (19 patients), and the presence of previously untreated CD20-positive diffuse large B-cell lymphoma (19 patients). In the pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone) group, the reasons for not receiving treatment were physician decision (2 patients), patient withdrawal (1 patient), and exclusion criteria identified (1 patient). In the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) group, the reasons for not receiving treatment were patient withdrawal and other cancer identified (1 patient each).

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Pola-R-CHP (N=440)	R-CHOP (N=439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)
ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

* A complete list of the demographic and clinical characteristics at baseline is provided in Table S8. IQR denotes interquartile range; pola-R-CHP polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; and R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
† This variable was a stratification factor.
‡ Stages range from I to IV, with higher stages indicating more extensive disease.
§ Bulky disease was defined as the presence of one or more lesions that were 7.5 cm or larger in greatest dimension.
¶ Patients were to have a baseline Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability). ECOG performance status was not reported for 1 patient in the R-CHOP group.
‖ The lactate dehydrogenase level was not reported for 3 patients in the pola-R-CHP group and for 1 patient in the R-CHOP group.
** An International Prognostic Index (IPI) score indicates low (0 or 1), low–intermediate (2), high–intermediate (3), or high (4 or 5) risk of a poor outcome on the basis of a scoring system that gives one point for each of the following risk factors: age older than 60 years, 1 or more extranodal areas of disease, an ECOG performance status score of 2 or higher, a lactate dehydrogenase level above the upper limit of the normal range, and Ann Arbor stage III or IV disease.
†† Testing was performed at a central laboratory. Assessments of the cell-of-origin subtype were performed with the use of the NanoString Lymph2Cx assay. Immunohistochemical analysis of MYC and BCL2 protein expression was performed for the assessment of double-expressor lymphoma. Tests for the presence of rearrangements in *MYC*, *BCL2*, *BCL6*, or a combination of these were performed for the assessment of double-hit and triple-hit lymphoma. Percentages are based on the population of patients who had centrally reported results; patients who did not have baseline tumor-tissue samples or who had test failures were not included.

table subgroups that did not show a clear benefit with pola-R-CHP included patients 60 years of age or younger, patients with the germinal-center B-cell–like subtype of DLBCL, patients who had bulky disease, and patients who had lower IPI scores (Fig. S1).

Secondary End Points

The analysis of investigator-assessed event-free survival showed that the relative risk of events was lower in the pola-R-CHP group than in the R-CHOP group (2-year event-free survival, 75.6% [95% CI, 71.5 to 79.7] and 69.4% [95% CI, 65.0 to 73.8%], respectively; hazard ratio for event or death, 0.75; 95% CI, 0.58 to 0.96; P=0.02) (Table 2 and Fig. 2B). The percentage of patients who had a complete response at the end of treatment, as determined by blinded central review, did not differ significantly between the two groups (78.0% in the pola-R-CHP group and 74.0% in the R-CHOP group; P=0.16). However, the analysis of investigator-assessed disease-free survival indicated that patients who received pola-R-CHP and had a complete response as the best response (Table S3) were more likely to have persistence of remission than those who received R-CHOP and had a complete response (hazard ratio for relapse or death, 0.70; 95% CI, 0.50 to 0.98) (Table 2 and Fig. 2C). Overall survival did not differ significantly between the groups (Table 2 and Fig. 2D). Disease progression or relapse with CNS involvement was reported in 13 patients (3.0%) in the pola-R-CHP group and in 12 patients (2.7%) in the R-CHOP group (Table S2).

Subsequent Treatment for Lymphoma

At the time of data cutoff, 99 of the 440 patients (22.5%) in the pola-R-CHP group and 133 of the 439 patients (30.3%) in the R-CHOP group had received at least one subsequent course of therapy for lymphoma that was not specified in the protocol (Table S4). The percentage of patients receiving radiotherapy (preplanned or unplanned) was lower in the pola-R-CHP group than in the R-CHOP group (9.3% vs. 13.0%), as was the percentage of patients receiving systemic therapy (17.0% vs. 23.5%), including stem-cell transplantation (3.9% vs. 7.1%) and chimeric antigen receptor (CAR) T-cell therapy (2.0% vs. 3.6%). After disease progression, unblinding was permitted for individual patients, and 8 patients (all in the R-CHOP group) received polatuzumab vedotin as part of a subsequent therapy.

SAFETY

The overall safety profile was generally similar in the pola-R-CHP and R-CHOP groups, with mostly similar types and incidences of adverse events of both any grade and grade 3 or 4 reported in the two groups (Table 3). No new safety signals were detected, and the safety profile of pola-R-CHP was consistent with the known safety profiles of the individual drugs.

The most common adverse events of grade 3 or 4 were neutropenia (28.3% in the pola-R-CHP group and 30.8% in the R-CHOP group), febrile neutropenia (13.8% and 8.0%, respectively), and anemia (12.0% and 8.4%, respectively). Although the incidence of febrile neutropenia was higher among patients who received pola-R-CHP than among those who received R-CHOP, the percentages of patients who had infections of grade 3 or 4 were similar (15.2% in the pola-R-CHP group and 12.6% in the R-CHOP group), as were the percentages of patients who discontinued at least one of the drugs in the trial regimen (2.1% and 2.3%, respectively) or had dose reductions (1.8% and 2.5%, respectively) because of either infections or neutropenia. Primary prophylaxis with G-CSF was reported in 90.1% of the patients in the pola-R-CHP group and in 93.2% of the patients in the R-CHOP group. Serious adverse events were reported in 34.0% of the patients who received pola-R-CHP and in 30.6% of the patients who received R-CHOP (Table 3). Adverse events that resulted in death (i.e., adverse events of grade 5) were reported in 13 patients in the pola-R-CHP group and in 10 patients in the R-CHOP group; these events were primarily related to infections (pneumonia in 4 patients and 3 patients, respectively, and sepsis in 1 patient and 3 patients, respectively) (Table S5).

Overall, 27 patients (6.2%) in the pola-R-CHP group and 29 patients (6.6%) in the R-CHOP group had adverse events that led to discontinuation of at least one of the drugs in the trial regimen. Among these patients, 19 (4.4%) in the pola-R-CHP group discontinued polatuzumab vedotin because of adverse events, and 22 (5.0%) in the R-CHOP group discontinued vincristine because of adverse events; both drugs were mainly associated with neurologic events. Dose reductions of a trial drug owing to an adverse event occurred in 9.2% of the patients who received pola-R-CHP and in 13.0% of those who received R-CHOP.

The incidence of peripheral neuropathy did

Table 2. Efficacy (Intention-to-Treat Population).

Variable	Pola-R-CHP (N=440)	R-CHOP (N=439)	Hazard Ratio (95% CI)	P Value
Progression-free survival*				
Patients who died or had progression or relapse — no. (%)	107 (24.3)	134 (30.5)	0.73 (0.57–0.95)	0.02
Earliest event — no.				
Death	19	20		
Progression or relapse	88	114		
Estimate at 1 year (95% CI) — %	83.9 (80.4–87.4)	79.8 (75.9–83.6)		
Estimate at 2 years (95% CI) — %	76.7 (72.7–80.8)	70.2 (65.8–74.6)		
Event-free survival*				
Patients who died, had progression or relapse, or had other events — no. (%)†	112 (25.5)	138 (31.4)	0.75 (0.58–0.96)	0.02
Earliest event — no.				
Death	18	20		
Progression or relapse	86	106		
Other†	8	12		
Estimate at 2 years (95% CI) — %	75.6 (71.5–79.7)	69.4 (65.0–73.8)		
Response status at treatment completion‡				
Overall response — no. (%)	376 (85.5)	368 (83.8)		
Complete response	343 (78.0)	325 (74.0)		
Partial response	33 (7.5)	43 (9.8)		
Stable disease — no. (%)	8 (1.8)	6 (1.4)		
Progressive disease — no. (%)	22 (5.0)	28 (6.4)		
Not evaluated or data missing — no. (%)	34 (7.7)	37 (8.4)		
Overall survival				
Patients who died — no. (%)	53 (12.0)	57 (13.0)	0.94 (0.65–1.37)	0.75
Estimate at 2 years (95% CI) — %	88.7 (85.7–91.6)	88.6 (85.6–91.6)		
Disease-free survival§				
No. of patients who could be evaluated¶	381	363		
Patients who died or had relapse — no. (%)	62 (16.3)	79 (21.8)	0.70 (0.50–0.98)	
Earliest event — no.				
Death	8	13		
Relapse	54	66		

* Events of progression or relapse were assessed by the investigator.
† Other events are subsequent therapy for lymphoma or biopsy-confirmed residual disease after treatment.
‡ Response was assessed by an independent central review committee.
§ Events of relapse were assessed by the investigator.
¶ Patients who had a best response of complete response at any time during the trial could be evaluated for disease-free survival; see Table S3.

not differ significantly between the treatment groups (Table S6). Peripheral neuropathy of any grade was reported in 52.9% of the patients who received pola-R-CHP and in 53.9% of those who received R-CHOP, and peripheral neuropathy of grade 2 or higher was reported in 13.8% and 16.7% of the patients, respectively. The median time to the onset of any neuropathy was 2.3 months in the pola-R-CHP group and 1.9 months in the R-CHOP group; the median time to resolution of any neuropathy was 4.0 months and 4.6 months, respectively. Very few patients discontinued any treatment because of peripheral neuropathy (0.2% in the pola-R-CHP group and

0.9% in the R-CHOP group). The percentage of patients who had peripheral neuropathy that led to dose reduction was lower among those who received polatuzumab vedotin than among those who received vincristine (4.4% vs. 8.0%).

DISCUSSION

Treatment with pola-R-CHP showed a significant progression-free survival benefit over the commonly prescribed regimen R-CHOP in patients with previously untreated DLBCL. In this population of patients who had either intermediate-risk or high-risk disease, in which approximately one third of the patients had activated B-cell–like subtype DLBCL and almost two thirds had a baseline IPI score between 3 and 5, treatment with pola-R-CHP resulted in a risk of disease progression, relapse, or death that was 27% lower (stratified hazard ratio, 0.73; 95% CI, 0.57 to 0.95; P=0.02) than that with R-CHOP. Progression-free survival at 2 years was 76.7% in the

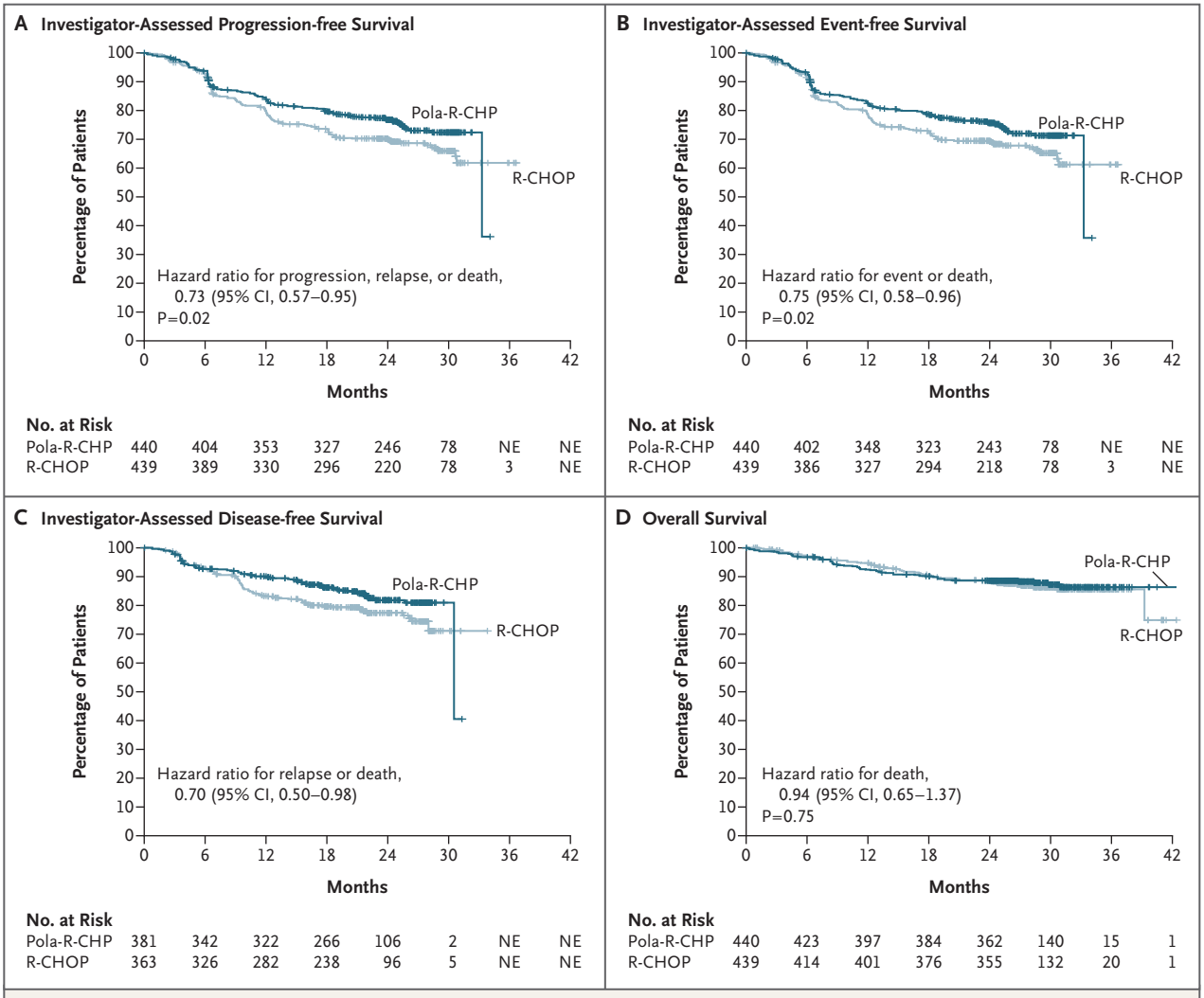

Figure 2. Kaplan–Meier Estimates of Efficacy End Points.

In the analysis of investigator-assessed progression-free survival, investigator-assessed disease progression and disease relapse or death from any cause were counted as events. In the analysis of investigator-assessed event-free survival, an event was defined as investigator-assessed disease progression or relapse, death from any cause, initiation of any antilymphoma treatment that was not specified in the protocol, or biopsy-confirmed residual disease after treatment completion. In the analysis of investigator-assessed disease-free survival, investigator-assessed disease relapse or death from any cause were counted as events. Tick marks indicate censored data. NE denotes not able to be evaluated.

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

* Shown are the most common adverse events, which were defined as adverse events of any grade that occurred in at least 12% of the patients in either treatment group. These adverse events are *Medical Dictionary for Regulatory Activities*, version 24.0, preferred terms. Adverse events of any grade were reported in 426 patients (97.9%) in the pola-R-CHP group and in 431 patients (98.4%) in the R-CHOP group; adverse events of grade 3 or higher in 264 (60.7%) and 262 (59.8%), respectively; serious adverse events in 148 (34.0%) and 134 (30.6%), respectively; and adverse events of grade 5 in 13 (3.0%) and 10 (2.3%), respectively.

† Peripheral neuropathy includes the following preferred terms from the system organ class of peripheral neuropathy: peripheral neuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, ear paresthesia, peroneal nerve palsy, and skin burning sensation.

pola-R-CHP group, as compared with 70.2% in the R-CHOP group.

Although this trial was not designed or powered to compare progression-free survival in patient subgroups, the observed heterogeneity in the treatment effect of pola-R-CHP across subgroups needs to be assessed in future trials. Because CD79b is ubiquitously expressed on the surface of mature B-cell lymphoid cancers, it is expected that pola-R-CHP would be active in mature B-cell lymphomas such as DLBCL and its subtypes, including newly identified genetic subgroups.[30-33] In our trial, point estimates that suggested a benefit with pola-R-CHP among the various patient subgroups evaluated were observed in patients older than 60 years of age, in patients who had an IPI score between 3 and 5, and in patients with the activated B-cell–like subtype of DLBCL. Conversely, subgroups that did not show a clear benefit were patients 60 years of age or younger, those who had lower IPI scores, those who had bulky disease, and those who had the germinal-center B-cell–like subtype of DLBCL.

Among the key secondary end points, event-free survival was significantly higher with pola-R-CHP than with R-CHOP, and although the percentage of patients who had a complete response did not differ significantly between the groups, remissions appeared to be more durable with pola-R-CHP than with R-CHOP. The median follow-up in this trial was 28.2 months, which was not long enough to observe any effect of the

progression-free survival benefit on overall survival. However, other studies have indicated that progression-free survival and 2-year event-free survival are often surrogates for overall survival in patients with DLBCL.[34-36] The lack of a significant difference between the two groups in overall survival in our trial may also be explained by the advent of new, effective treatments for relapsed or refractory DLBCL in recent years.

The relatively short follow-up provides limited data confirming the expected plateau in the progression-free survival curve. DLBCL is characterized by an early risk of relapse followed by a distinct plateau in the survival curve that indicates a high probability of cure. Late relapses are unusual. On the basis of previous treatment results,[34-36] it is expected that the remissions that have lasted at least 2 years will be durable. The data from this trial do not yet confirm that the remissions associated with pola-R-CHP treatment will be durable. Whether such a conclusion can be drawn can be determined only with longer follow-up.

In this double-blind trial, drug delivery was not impeded by the replacement of vincristine with polatuzumab vedotin. The delivery of rituximab, doxorubicin, and cyclophosphamide was maintained, with median relative dose intensities of greater than 99% in both treatment groups. Moreover, the percentage of patients who received all the planned doses of polatuzumab vedotin was slightly higher than the percentage who received all the planned doses of vincristine (91.7% in the pola-R-CHP group and 88.5% in the R-CHOP group), and fewer patients in the pola-R-CHP group than in the R-CHOP group had adverse events that led to dose reductions.

The occurrence of peripheral neuropathy is expected in patients treated with antibody–drug conjugates containing monomethyl auristatin E and has been described in a study of single-agent polatuzumab vedotin[20] and in studies of polatuzumab vedotin in combination with other agents.[21-23] In this trial, the majority of cases of peripheral neuropathy were grade 1. Moreover, the incidence and severity of peripheral neuropathy were similar in the two treatment groups. These results are similar to those observed in the ECHELON-2 trial, in which another antibody–drug conjugate combination — brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone — was compared with CHOP in patients with T-cell lymphoma.[37] Although the incidence of febrile neutropenia was higher among patients who received pola-R-CHP than among those who received R-CHOP in our trial (14.3% vs. 8.0%), this finding did not translate into a higher overall incidence of infection, treatment discontinuation, or dose reductions and was similar to the percentages reported in recent R-CHOP trials (9.0% to 15.2%).[12-14]

Several groups of patients were not included in the current trial: those with lymphoma arising from previously diagnosed indolent lymphoma, those with a primary mediastinal lymphoma, and those older than 80 years of age. A phase 3 trial investigating an age-adapted combination of pola-R-CHP with dose-attenuated chemotherapy in the older patient population is ongoing (ClinicalTrials.gov number, NCT04332822).

Among patients with DLBCL, first-line treatment with the pola-R-CHP combination evaluated in the current trial showed a progression-free survival benefit over the R-CHOP regimen at 2 years and had a similar safety profile.

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APPENDIX

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REFERENCES

1. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-59.
2. 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 2002;346:235-42.
3. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013-22.
4. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med 2021;384:842-58.
5. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-8.
6. 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 2013;381:1817-26.
7. 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 2013;14:525-33.
8. Bartlett NL, Wilson WH, Jung S-H, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol 2019;37:1790-9.
9. Lugtenburg PJ, de Nully Brown P, van der Holt B, et al. 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). J Clin Oncol 2020;38:3377-87.
10. Jaeger U, Trneny M, Melzer H, et al. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica 2015;100:955-63.
11. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2017;35:2473-81.
12. 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 2017;35:3529-37.
13. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol 2021;39:1317-28.
14. 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 2019;37:1285-95.
15. Goy A. Succeeding in breaking the R-CHOP ceiling in DLBCL: learning from negative trials. J Clin Oncol 2017;35:3519-22.
16. Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood 2009;114:2721-9.
17. Pfeifer M, Zheng B, Erdmann T, et al. Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia 2015;29:1578-86.
18. Okazaki M, Luo Y, Han T, Yoshida M, Seon BK. Three new monoclonal antibodies that define a unique antigen associated with prolymphocytic leukemia/non-Hodgkin's lymphoma and are effectively internalized after binding to the cell surface antigen. Blood 1993;81:84-94.
19. Polson AG, Yu S-F, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. Blood 2007;110:616-23.
20. Palanca-Wessels MCA, Czuczman M, Salles G, et al. Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. Lancet Oncol 2015;16:704-15.
21. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol 2019;6(5):e254-e265.
22. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38:155-65.
23. Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin in combina-

tion with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. Lancet Oncol 2019;20:998-1010.
24. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
25. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
26. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987-94.
27. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.
28. 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 2014;32:3059-68.
29. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26.
30. 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 2018;24:679-90.
31. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
32. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med 2018;378:1396-407.
33. Ennishi D, Jiang A, Boyle M, et al. Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma. J Clin Oncol 2019;37:190-201.
34. Maurer MJ, Ghesquières H, Jais J-P, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. J Clin Oncol 2014;32:1066-73.
35. Maurer MJ, Habermann TM, Shi Q, et al. Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials. Ann Oncol 2018;29:1822-7.
36. Shi Q, Schmitz N, Ou F-S, et al. Progression-free survival as a surrogate end point for overall survival in first-line diffuse large B-cell lymphoma: an individual patient-level analysis of multiple randomized trials (SEAL). J Clin Oncol 2018;36:2593-602.
37. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-40.