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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

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ASSOCIATED CONTENT

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Data Supplements

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The study was coordinated by Alliance/Cancer and Leukemia Group B (CALGB). Participating groups included Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, National Surgical Adjuvant Breast and Bowel Project, and SWOG.

abstract

PURPOSE Alliance/CALGB 50303 (NCT00118209), an intergroup, phase III study, compared dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as frontline therapy for diffuse large B-cell lymphoma.

PATIENTS AND METHODS Patients received six cycles of DA-EPOCH-R or R-CHOP. The primary objective was progression-free survival (PFS); secondary clinical objectives included response rate, overall survival (OS), and safety.

RESULTS Between 2005 and 2013, 524 patients were registered; 491 eligible patients were included in the final analysis. Most patients (74%) had stage III or IV disease; International Prognostic Index (IPI) risk groups included 26% IPI 0 to 1, 37% IPI 2, 25% IPI 3, and 12% IPI 4 to 5. At a median follow-up of 5 years, PFS was not statistically different between the arms (hazard ratio, 0.93; 95% CI, 0.68 to 1.27; $P = .65$), with a 2-year PFS rate of 78.9% (95% CI, 73.8% to 84.2%) for DA-EPOCH-R and 75.5% (95% CI, 70.2% to 81.1%) for R-CHOP. OS was not different (hazard ratio, 1.09; 95% CI, 0.75 to 1.59; $P = .64$), with a 2-year OS rate of 86.5% (95% CI, 82.3% to 91%) for DA-EPOCH-R and 85.7% (95% CI, 81.4% to 90.2%) for R-CHOP. Grade 3 and 4 adverse events were more common ($P < .001$) in the DA-EPOCH-R arm than the R-CHOP arm, including infection (16.9% *v* 10.7%, respectively), febrile neutropenia (35.0% *v* 17.7%, respectively), mucositis (8.4% *v* 2.1%, respectively), and neuropathy (18.6% *v* 3.3%, respectively). Five treatment-related deaths (2.1%) occurred in each arm.

CONCLUSION In the 50303 study population, the more intensive, infusional DA-EPOCH-R was more toxic and did not improve PFS or OS compared with R-CHOP. The more favorable results with R-CHOP compared with historical controls suggest a potential patient selection bias and may preclude generalizability of results to specific risk subgroups.

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INTRODUCTION

In 2002, the first of three trials established rituximab (R) plus CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP refers to the combination regimen) as frontline standard of care for diffuse large B-cell lymphoma (DLBCL).[1-5] The 3-year event-free survival (EFS) rate ranged from 53% in patients age 60 years or older with high-risk features to 79% in patients 18 to 60 years old with a low-risk International Prognostic Index (IPI).[3,4] Less favorable outcomes for patients with recurrent DLBCL[6] prompted efforts to improve first-line approaches and biomarkers to identify high-risk patients.

National Cancer Institute (NCI) investigators modified the CHOP regimen and developed the 96-hour infusional dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) combination. Rationale included evidence of less tumor resistance with prolonged exposure to natural products, less cardiac toxicity with prolonged doxorubicin administration, and maximization of dose intensity by pharmacodynamic dose adjustment on the basis of each cycle's neutrophil nadir.[7,8] The initial DA-EPOCH study in untreated DLBCL reported a 62-month progression-free survival (PFS) rate of 70% and overall survival (OS) rate of 73%, better results than

with CHOP.[8] Rituximab was added to DA-EPOCH, resulting in a 12-month PFS rate of 85%.[9,10] A phase II, multicenter trial of DA-EPOCH-R in DLBCL by Cancer and Leukemia Group B (CALGB) confirmed the regimen could be safely and accurately administered in community settings, with outcomes (5-year time-to-progression rate, 81%) similar to NCI data.[11] A phase III trial comparing R-CHOP with DA-EPOCH-R in frontline therapy of DLBCL (a collaboration between the NCI and the US Intergroup) was coordinated by CALGB (now part of the Alliance for Clinical Trials) and activated in 2005. We report clinical outcomes with a median follow-up of 5 years. Additional primary and secondary objectives will be reported separately.

PATIENTS AND METHODS

Study Design and Patients

Alliance/CALGB 50303 compared DA-EPOCH-R with R-CHOP in a 1:1 randomization. Eligible patients included untreated DLBCL (including morphologic variants centroblastic, immunoblastic, T-cell/histiocyte rich, and anaplastic), primary mediastinal large B-cell lymphoma (PMBCL), and intravascular large B-cell lymphoma confirmed by central pathology review. Patients with underlying indolent lymphoma in the bone marrow or in a biopsy specimen were excluded. Before registration, limited field radiation or fewer than 10 days of glucocorticoid treatment for urgent disease complications (eg, cord compression) were allowed. Additional eligibility criteria included age at least 18 years, stage II to IV DLBCL (or stage I PMBCL), Eastern Cooperative Oncology Group performance status 0 to 2, left ventricular ejection fraction rate greater than 45%, absolute neutrophil count (ANC) greater than 1,000/μL, platelet count greater than 100,000/μL, creatinine level not more than 1.5 mg/dL, and bilirubin level not more than 2 mg/dL. Patients with known CNS disease or HIV were excluded.

A fresh (frozen) tumor biopsy specimen was required before registration. When necessary, a repeated study biopsy (excisional or core needle) was required, unless not feasible (and exception granted by study chairs). If fresh tissue was unavailable, stained and unstained slides or blocks were requested. Tissue was prioritized for primary and secondary molecular correlates and for central pathology review. Immunohistochemistry for BCL-2 (DAKO 124; Agilent, Santa Clara, CA) and MYC (Ventana Y69; Roche, Tucson, AZ) expression and fluorescence in situ hybridization (FISH) testing for *MYC*, *BCL2*, and *BCL6* rearrangements were not preplanned but were performed centrally on patients with available material.

Participants provided institutional review board–approved informed consent in accordance with federal and institutional guidelines. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured through data review by the Alliance Statistics and Data Center and the study chairperson following Alliance policies.

Treatment

R-CHOP and DA-EPOCH-R administration was planned every 21 days for six cycles. Dosing, escalation and de-escalation of DA-EPOCH-R on the basis of nadir ANC and platelet count are as previously reported[8] and described in the Data Supplement for this report. Patients with more than one extranodal site and elevated lactate dehydrogenase level, or bone marrow involvement were to receive CNS prophylaxis with intrathecal methotrexate, 12 mg on day 1 or day 2 of cycles 3 through 6. Consolidative radiotherapy (RT) was prohibited. Required ancillary medications for both regimens included a proton pump inhibitor, stool softeners, and, for patients positive for hepatitis B surface antigen, lamivudine 100 mg per day. *Pneumocystis* prophylaxis was required with DA-EPOCH-R. Filgrastim was required on days 6 through 15 of DA-EPOCH-R or until ANC was greater than 5,000/μL after nadir; pegfilgrastim was allowed with study chair approval. In the R-CHOP arm, filgrastim or pegfilgrastim was initiated if a patient experienced an ANC of less than 500/μL, febrile neutropenia with the previous cycle, or at physician discretion.

Efficacy and Safety Measures

The investigator determined response according to the 1999 International Working Group response criteria.[12] End-of-treatment (EOT) positron emission tomography (PET)–computed tomography (CT) was recommended for patients with partial response, complete response (CR), or CR unconfirmed (CRu). Baseline, postcycle 2, and EOT PET were only required for patients participating in the optional imaging companion study (CALGB 580603). If an EOT PET was performed, either as standard of care or in the companion study, results were incorporated into the response determination with a negative PET-defined as uptake less than or equal to the mediastinal blood pool (Data Supplement). Adverse events were reported according to the revised NCI Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The primary clinical end point was PFS, measured from randomization to progression, relapse, or death from any cause, whichever occurred first. Secondary clinical objectives included comparisons of response rate, OS, and toxicity. The protocol required up to 5 years of follow-up. The initial sample size was 478, assuming a 3-year PFS of 55% in the R-CHOP arm, a hazard ratio (HR) of 0.65 for DA-EPOCH-R versus R-CHOP detectable with 90% power, a two-sided α 0.05 log-rank test, and a 10% ineligibility rate. Sample size was increased to 523 owing to lower than expected participation in the companion imaging study, CALGB 580603.

Final analysis was initially planned after 242 PFS events; however, as a result of significantly fewer events than predicted, the Data and Safety Monitoring Board recommended release of the data in July 2016, after 167 PFS events. All analyses were based on modified intent to treat, including eligible patients randomly assigned to treatment, and were performed with SAS, version 9.4. The primary end point was assessed between arms using unadjusted Cox models and Cox models stratified by IPI. Statistical tests reported were two-sided and $P < .05$ was used to declare statistical significance for the primary end point. No planned clinical subset analyses were in the protocol and all analyses beyond the primary end points should be considered post hoc. Additional statistical details are included in the Data Supplement.

RESULTS

Patients

From 2005 to 2013, 524 patients were randomly assigned to R-CHOP or DA-EPOCH-R (Fig 1). Data cutoff occurred on November 11, 2017. Of 491 eligible patients (93.7%), 250 were assigned to R-CHOP and 241 to DA-EPOCH-R. Median time from diagnosis to registration and initiation of therapy was 18 days and 21 days, respectively. Ten patients (n = 6 in the R-CHOP arm and n = 4 in the DA-EPOCH-R arm) never started the assigned treatment (one died before starting and nine refused or withdrew) but were included in the intent-to-treat analysis. One of five expert hematopathologists reviewed pathology centrally on 429 patients (82.0%) and 18 (3.4%) were excluded (Fig 1). The principal investigator reviewed diagnostic biopsy reports for all cases not centrally reviewed to confirm DLBCL. Fifteen patients (2.9%) were excluded during case evaluations (Fig 1). The study arms were well balanced for baseline characteristics (Table 1; Data Supplement). Most patients had stage III or IV disease (74.0%) with IPI risk group distribution as follows: 0 to 1, 26.0%; 2, 37.0%; 3, 25.0%; and 4 to 5, 12.0%. In terms of age, 19.0% of patients (n = 93) were at least 70 years old and 2.6% (n = 13) were 80 years or older. As allowed, seven patients received short-course local RT and 35 patients received corticosteroids briefly before initiating protocol therapy.

Double expressor (DE) status was determined centrally in 270 patients (55.0%), of whom 42 patients (15.6%) were classified as DE (BCL-2 ≥ 50% and MYC ≥ 40%). *MYC*, *BCL-2*, and *BCL-6* rearrangements were determined centrally by FISH on available tissue. *MYC* rearrangement data were available on 249 patients (50.7%), of whom 13 (5.2%) were positive for rearrangements, six in the R-CHOP arm and seven in the DA-EPOCH-R arm. Of the 13 *MYC* rearranged cases, three had rearrangements of *BCL-2* and/or *BCL-6* (double hit) and 10 had incomplete DE data.

Treatment

All six treatment cycles were completed by 88.0% of the R-CHOP and 82.0% of the DA-EPOCH-R group. Reasons for

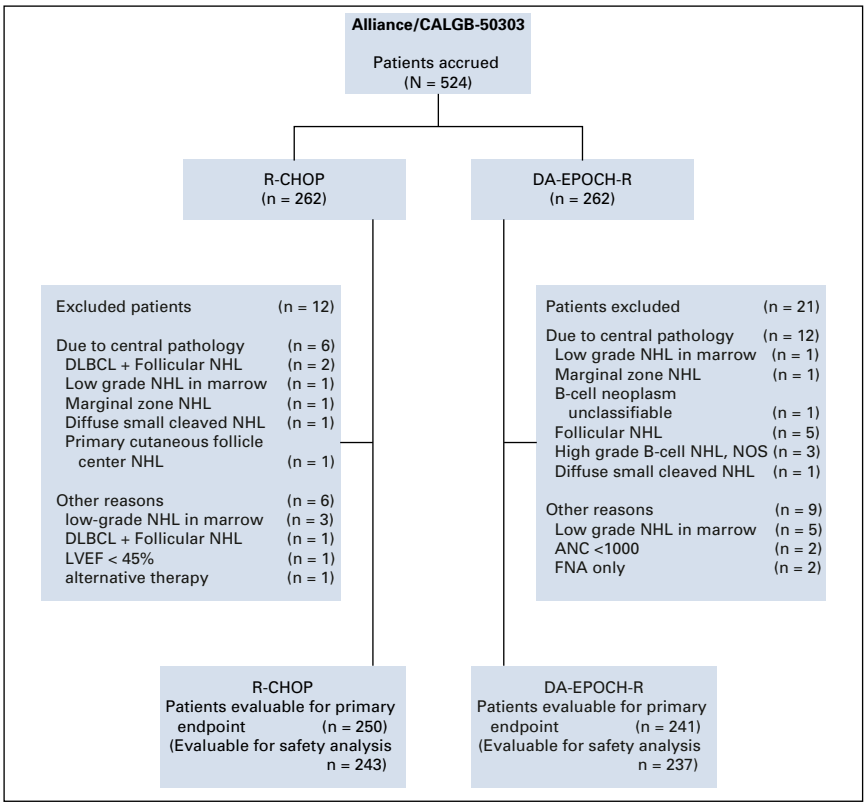

FIG 1. CONSORT diagram. ANC, absolute neutrophil count; CALGB, Cancer and Leukemia Group B; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; FNA, fine-needle aspirate; LVEF, left ventricular ejection fraction; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 1. Characteristics of Eligible Patients

Characteristic	Treatment Received		P
	R-CHOP (n = 250)	DA-EPOCH-R (n = 241)	
Sex			.7630†
Missing	1	0	
Male	133 (53.4)	132 (54.8)	
Female	116 (46.6)	109 (45.2)	
Age, years			.8567*
No. (no. missing)	247 (3)	239 (2)	
Median	58.0	58.0	
Range	18.0-86.0	19.0-84.0	
Age group, years			.9579†
Missing	3	2	
18-60	141 (57.1)	137 (57.3)	
> 60	106 (42.9)	102 (42.7)	
ECOG PS			.2069†
Missing	1	0	
0	101 (40.6)	113 (46.9)	
1	119 (47.8)	96 (39.8)	
2	29 (11.6)	32 (13.3)	
Extranodal disease (≥ 1 site)	64 (25.7)	68 (28.2)	.5308†
Stage			.6654†
Missing	7	5	
I	7 (2.9)	6 (2.5)	
II	53 (21.8)	48 (20.3)	
III	71 (29.2)	60 (25.4)	
IV	112 (46.1)	122 (51.7)	
IPI risk group			.6047†
Missing	9	6	
Low	64 (26.6)	59 (25.1)	
Low-intermediate	93 (38.6)	83 (35.3)	
High-intermediate	60 (24.9)	61 (26.0)	
High	24 (10.0)	32 (13.6)	

NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Kruskal-Wallis test.

†χ^2 test.

early discontinuation included disease progression (R-CHOP, 2.8%; DA-EPOCH-R, 1.3%), adverse events (R-CHOP, 2.0%; DA-EPOCH-R, 6.3%), death (R-CHOP, 1.6%; DA-EPOCH-R, 2.5%), patient withdrawal after initiating treatment (R-CHOP, 1.2%; DA-EPOCH-R, 2.9%), patient withdrawal before beginning protocol treatment (R-CHOP, 2.4%; DA-EPOCH-R, 1.7%), alternative therapy (R-CHOP, 0.8%; DA-EPOCH-R, 1.3%), and other or missing reasons (R-CHOP, 1.6%; DA-EPOCH-R, 2.9%). The maximum dose level (DL) achieved with DA-EPOCH-R was DL1 in 25.3%, DL2 in 19.8%, DL3 in 24.5%, DL4 in 16.5%, and greater than DL4 in 13.9%. Intrathecal methotrexate prophylaxis was administered in 19.8% of the R-CHOP group and 27.0% of the DA-EPOCH-R group ($P = .060$). Of patients in the R-CHOP group, 64.2% received growth factor support at least once, including 54 (22.2%) who initiated filgrastim with cycle 1.

Efficacy. Across arms, at median follow-up of 5.2 years (interquartile range, 4.8-5.4), 159 patients had a PFS event and 109 patients died. There was no statistically significant difference in PFS between arms (DA-EPOCH-R HR, 0.93, 95% CI, 0.68 to 1.27; $P = .65$; Fig 2). Two-year and 5-year PFS rates for R-CHOP were 75.5% and 66.0%, respectively, and for DA-EPOCH-R, 78.9% and 68.0% respectively (Table 2). These results were consistent when stratified by IPI (DA-EPOCH-R HR, 0.84; 95% CI, 0.61 to 1.15; $P = .27$). OS was similar (DA-EPOCH-R HR, 1.09, 95% CI, 0.75 to 1.59; $P = .64$; Fig 3) with 5-year OS rates of 78.5% for R-CHOP and 77.5% for DA-EPOCH-R. The overall response rate was 88.0% (CR/Cru, 59.6%) in the R-CHOP group and 86.7% (CR/Cru, 58.5%) in the DA-EPOCH-R group ($P = .67$).

The 2- and 5-year PFS rates for all patients was 77.1% (95% CI, 73.5 to 81) and 67.1% (95% CI, 62.8 to 71.6), respectively, with a 5-year OS rate of 78.0% (95% CI, 74.3 to 81.9). Patients older than 60 years had inferior PFS compared with younger patients (HR, 1.43; 95% CI, 1.04 to 1.95; $P = .026$) with a 2-year PFS rate of 75.2% (95% CI, 69.5 to 81.4) versus 78.9% (95% CI, 74.2 to 83.9), respectively, and 5-year PFS rate of 62% (95% CI, 55.5 to 69.2) versus 71.3% (95% CI, 65.9 to 77.2), respectively. CNS relapse occurred in 18 patients (3.7%); six had received intrathecal prophylaxis. PFS was strongly associated with IPI ($P < .001$); the 2-year PFS rate was 91.7% (95% CI, 86.9 to 96.8) for IPI 0 to 1; 76.5% (95% CI, 70.4 to 83.2) for IPI 2; 70.7% (95% CI, 63 to 79.4) for IPI 3; and 62.2% (95% CI, 50.7 to 76.4) for IPI 4 to 5 (Data Supplement). Among 270 patients with DE data, PFS was inferior (HR, 1.75; 95% CI, 1.03 to 2.98; $P = .037$) for DE-positive patients (n = 42) compared with 228 DE-negative patients (Data Supplement).

Subgroup analysis. Figure 4 shows the post hoc comparison of PFS by arm in subgroups of standard clinical features, including age, lactate dehydrogenase level, Eastern Cooperative Oncology Group performance status, extranodal disease, stage, and IPI risk group. No adjustment for multiple comparisons is reported for these post hoc analyses and the study was not powered for these comparisons. PFS was higher in the DA-EPOCH-R arm in the highest risk IPI (ie, IPI 4 to 5) subgroup (HR, 0.46; 95% CI, 0.21 to 1.01; unadjusted $P = .052$) as well as when grouping patients with IPI 3 to 5 together (HR, 0.63, 95% CI, 0.41 to 0.99, unadjusted $P = .041$; Data Supplement).

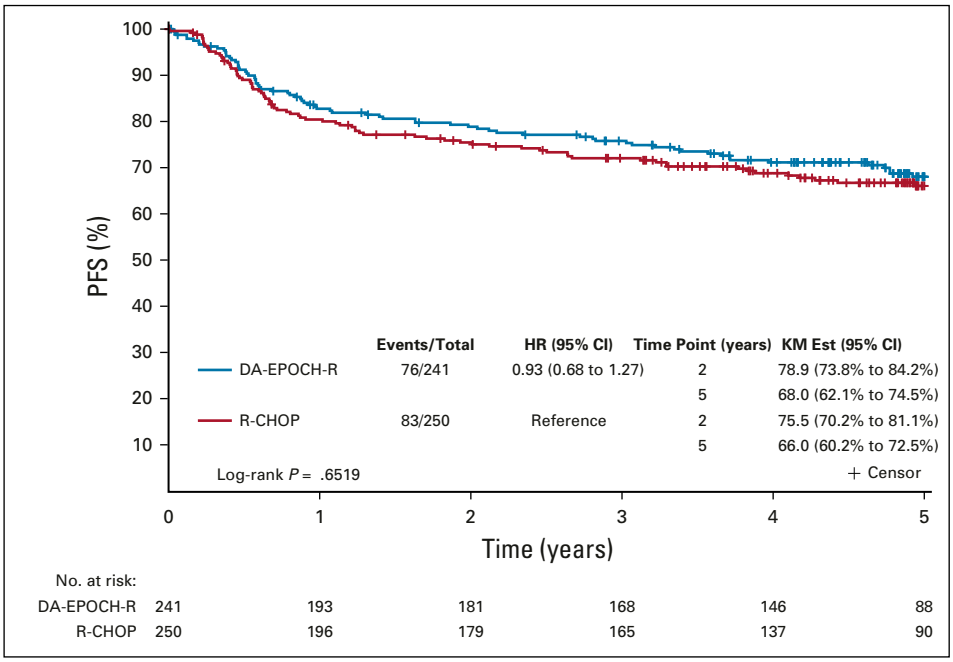

FIG 2. Progression-free survival (PFS) by treatment arm. Kaplan-Meier PFS estimate of all patients by treatment arm in years since random assignment. There was no statistically significant difference in PFS between arms ($P = .6519$). DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HR, hazard ratio; KM Est, KM, Kaplan-Meier estimate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

However, no difference in OS was observed in this subgroup (Data Supplement). No meaningful difference in PFS or OS between arms for any of the other subgroups was demonstrated.

CNS relapse occurred in 4.0% of patients (n = 10) treated with R-CHOP and 3.3% (n = 8) treated with DA-EPOCH-R. Compliance with protocol-specified CNS prophylaxis was not captured precisely. However, there was no clear impact of prophylaxis on CNS relapse in our limited data set (Data Supplement).

Among 35 patients with PMBCL, PFS events occurred in three of 20 patients treated with R-CHOP and two of 15 patients treated with DA-EPOCH-R. No patients with PMBCL received RT. There was no difference in PFS or OS for 42 patients with DE phenotype who received R-CHOP (n = 22) versus DA-EPOCH-R (n = 20; Data Supplement). Progression or death occurred in seven of 13 patients with *MYC* rearrangement: four of seven treated with DA-EPOCH-R and three of six treated with R-CHOP.

Safety. The safety analysis population comprised eligible patients with available toxicity data (n = 480). There were five (2.1%) treatment-related deaths per arm (causes in R-CHOP arm: infection [n = 2], cardiac [n = 1], CNS hemorrhage [n = 1], unknown [n = 1]; causes in DA-EPOCH-R

TABLE 2. Progression-Free Survival for All Patients and According to Treatment Arm

Parameter	Event/Total	Hazard Ratio (95% CI)*	Survival Estimates (95% CI), %†	*P*
All patients	159/491		2 Years: 77.1 (73.5 to 81.0)	
			3 Years: 73.9 (70.1 to 77.9)	
			5 Years: 67.1 (62.8 to 71.6)	
Treatment arm				.6519‡
DA-EPOCH-R	76/241	0.93 (0.68 to 1.27)	2 Years: 78.9 (73.8 to 84.2)	
			3 Years: 75.8 (70.5 to 81.5)	
			5 Years: 68.0 (62.1 to 74.5)	
R-CHOP	83/250	Reference	2 Years: 75.5 (70.2 to 81.1)	
			3 Years: 72.0 (66.6 to 77.9)	
			5 Years: 66.0 (60.2 to 72.5)	

Abbreviations: DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Cox model.

†Kaplan-Meier method.

‡Log-rank test.

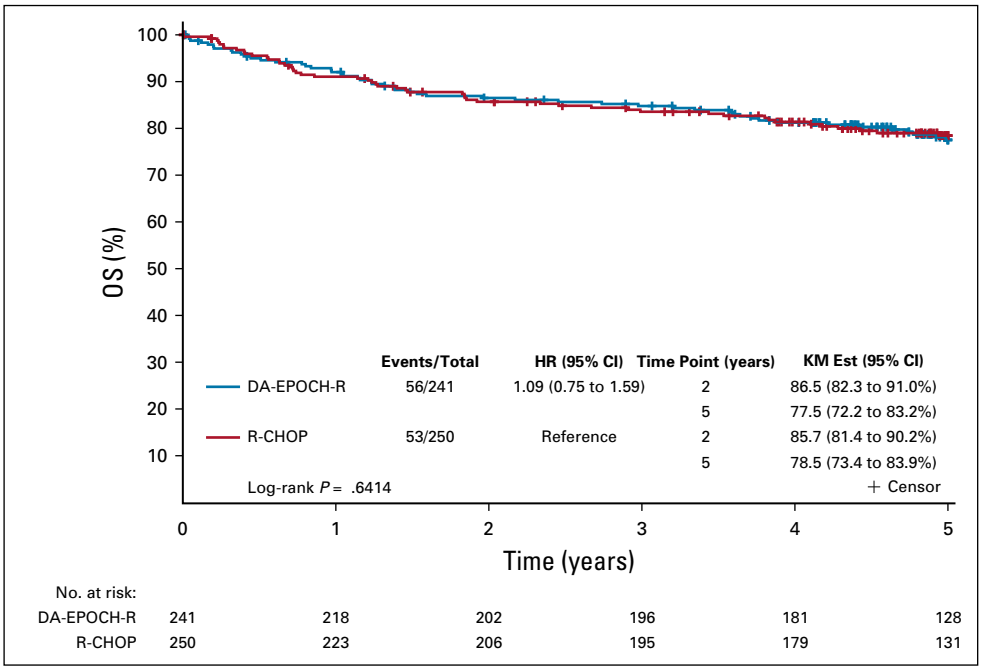

FIG 3. Overall survival (OS) by treatment arm. Kaplan-Meier OS estimate of all patients by treatment arm in years since random assignment. The 5-year OS was similar between the R-CHOP and DA-EPOCH-R arms ($P = .6414$). DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HR, hazard ratio; KM Est, KM, Kaplan-Meier estimate; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

arm: infection [n = 2], cardiac [n = 1], sudden death [n = 1], multiorgan failure [n = 1]). Grade 3 to 5 treatment-related events occurred in 98.3% of patients in the DA-EPOCH-R arm and 78.2% in the R-CHOP arm ($P < .001$). Overall grade 3 to 4, treatment-related hematologic (97.5% *v* 73.7%; $P < .001$) and nonhematologic (72.2% *v* 43.2%; $P < .001$) adverse events were more frequent in the DA-EPOCH-R arm. Table 3 lists selected toxicities that the investigator deemed at least possibly related to treatment and were significantly different between arms. Late cardiac events occurred in six patients in the R-CHOP arm (n = 5 left ventricular systolic dysfunction, n = 1 atrial fibrillation) and two patients in the DA-EPOCH-R arm (n = 1 myocardial infarction with heart failure, n =1 atrial fibrillation). Two patients receiving DA-EPOCH-R and one receiving R-CHOP died of secondary acute myeloid leukemia.

DISCUSSION

This randomized trial compared the efficacy of R-CHOP to the more intensive, infusional DA-EPOCH-R in patients with untreated DLBCL. Despite greater toxicity and complexity, there was no improvement in PFS, OS, or response rate with DA-EPOCH-R. In post hoc subset analyses, patients with IPI 3 to 5 who received DA-EPOCH-R had improved PFS (HR = 0.63, 95% CI: 0.41 to 0.99; unadjusted $P = 0.041$) compared with patients in the R-CHOP arm; however, the subset analysis was unplanned and not powered, and the significance of the unadjusted *P* value must be tempered in light of multiple comparisons. There was no difference between arms in OS (HR, 0.78; 95% CI, 0.47 to 1.32; unadjusted $P = .36$) in this subgroup.

The trial design of Alliance/CALGB 50303 assumed a 55% 3-year PFS rate in the R-CHOP arm and targeted a HR of 0.65 for DA-EPOCH-R compared with R-CHOP. The observed 3-year PFS rate for R-CHOP in our study was significantly better, at 72% (95% CI, 66.6% to 77.9%). By comparison, in the broad-based population cohort of the Mayo/Iowa Molecular Epidemiology Resource, the 3-year EFS rate was 61% (95% CI, 57% to 64%) for 686 patients with stage II to IV DLBCL or PMBCL treated with R-CHOP, suggesting enrollment of patients with better outcomes than similar IPI risk–stratified patients outside of trials.[13] The median time from diagnosis-to-treatment initiation was 21 days for Alliance/CALBG 50303 versus 15 in the Mayo/Iowa Molecular Epidemiology Resource study; longer diagnosis-to-treatment initiation is associated with more favorable clinical characteristics and better outcomes, and may reflect under enrollment of higher-risk patients (ie, poor performance status, rapidly progressive disease) in the 50303 trial, because of the inability to delay treatment to meet trial enrollment requirements.[14] Furthermore, the requirement for fresh tissue on the 50303 trial for molecular profiling may have exacerbated this effect. Other prospective trials have reported similar issues, such as the PYRAMID trial (NCT00931918) in patients with nongerminal center B-cell–like DLBCL, with a 2-year PFS rate with R-CHOP of 78%, compared with the historically reported 30% to 40% in this subgroup.[15,16] This unintended enrichment for favorable patients could mask any benefit of a new combination in higher-risk patients.

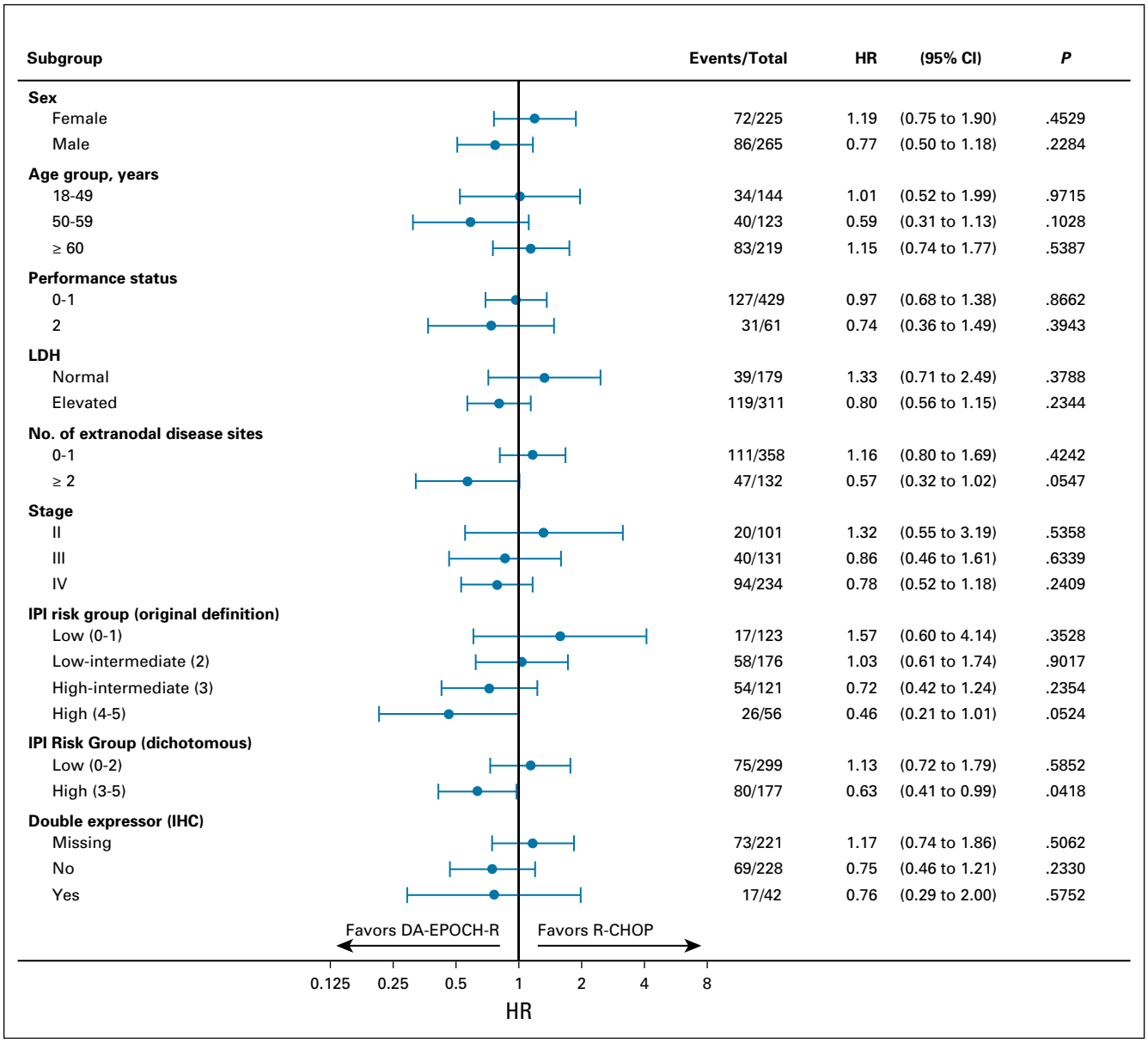

FIG 4. Progression-free survival (PFS) by subset analysis. Post hoc comparison of PFS by arm in subgroups of standard clinical features, including age, LDH level, Eastern Cooperative Oncology Group performance status, extranodal disease, stage, and IPI risk group. PFS was higher in the DA-EPOCH-R arm in the highest risk IPI (4-5) subgroup (unadjusted $P = .0524$). No meaningful difference in PFS between arms for any of the other subgroups was demonstrated. DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HR, hazard ratio; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Since initiation of Alliance/CALGB 50303, an NCI phase II study of DA-EPOCH-R in PMBCL reported an EFS rate of 93% in 51 patients with a median 5 years of follow-up.[17] A retrospective, multicenter study reported an 86% 3-year EFS rate in 156 patients with PMBCL receiving DA-EPOCH-R.[18] In a second retrospective study of PMBCL, DA-EPOCH-R (n = 76 patients) and R-CHOP (n = 56 patients) had 2-year PFS rates of 85% and 76%, respectively ($P = .28$).[19] Consolidative RT was given to 59% of patients receiving R-CHOP. There was no statistical difference ($P = .38$) in 2-year PFS rate between the R-CHOP plus RT group (95%) and R-CHOP alone (88%). Alliance/CALGB 50303 registered only 35 patients with PMBCL, possibly reflecting investigator concern with randomization to R-CHOP without radiation. There was no difference in outcomes in this small subset.

Patients with DLBCL with *MYC*-rearrangement (*MYC*$^+$), especially those with concomitant *BCL2* or *BCL6*

TABLE 3. Selected Treatment-Related Toxicities That Differed by Treatment Arm

CTCAE Toxicity Grade	Treatment			
	R-CHOP (n = 243)*	DA-EPOCH-R (n = 237)*	Total (n = 480)*	P†
3/4/5 AE				<.001
No	53 (21.8)	4 (1.7)	57 (11.9)	
Yes	190 (78.2)	233 (98.3)	423 (88.1)	
3/4 Hematologic				<.001
No	64 (26.3)	6 (2.5)	70 (14.6)	
Yes	179 (73.7)	231 (97.5)	410 (85.4)	
3/4 Nonhematologic				<.001
No	138 (56.8)	66 (27.8)	204 (42.5)	
Yes	105 (43.2)	171 (72.2)	276 (57.5)	
3/4 Infection				.0494
No	217 (89.3)	197 (83.1)	414 (86.3)	
Yes	26 (10.7)	40 (16.9)	66 (13.8)	
3/4 Febrile neutropenia				<.001
No	200 (82.3)	154 (65.0)	354 (73.8)	
Yes	43 (17.7)	83 (35.0)	126 (26.3)	
3/4 Mucositis				.0017
No	238 (97.9)	217 (91.6)	455 (94.8)	
Yes	5 (2.1)	20 (8.4)	25 (5.2)	
1/2 Neuropathy				<.001
No	128 (52.7)	82 (34.6)	210 (43.8)	
Yes	115 (47.3)	155 (65.4)	270 (56.3)	
3/4 Neuropathy				<.001
No	235 (96.7)	193 (81.4)	428 (89.2)	
Yes	8 (3.3)	44 (18.6)	52 (10.8)	

NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: AE, adverse event; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Excludes 10 patients who did not initiate treatment and one patient in the R-CHOP arm without toxicity data submitted.

†χ^2 *P* value.

rearrangements (double hit), have a worse prognosis; the British Columbia Cancer Agency reported a 5-year PFS rate of 31% with R-CHOP for the 8.8% of patients with *MYC*$^+$ DLBCL versus 66% in the *MYC*$^-$ cohort (*P* = .006).[20] In marked contrast, results of a multicenter phase II study of DA-EPOCH-R in 53 patients with *MYC*$^+$ DLBCL demonstrated a 4-year EFS rate of 71% in all patients and 73.4% for patients with double-hit DLBCL.[21] Coexpression of MYC and BCL2 proteins in DLBCL has also been associated with poor outcomes.[22-25] In our study, the lower incidence of the DE phenotype (15.6%) compared with the literature again likely reflects a more favorable patient population.[26] We found no differences by treatment arm in the *MYC* rearranged or patients with the DE phenotype, though, again, this subset was of insufficient size for statistical comparison. On the basis of encouraging phase II results with DA-EPOCH-R in patients with double-hit and Burkitt lymphoma compared with historical R-CHOP data, the results of Alliance/CALGB 50303 should not discourage use of DA-EPOCH-R in these settings.[21,22]

In summary, the primary end point of PFS was not different among patients treated with DA-EPOCH-R compared with those treated with standard R-CHOP. Unfortunately, those with the greatest unmet need are not well represented. Whether patients with high-risk IPI, high-grade double-hit and DE lymphomas, or PMBCL may benefit from DA-EPOCH-R cannot be answered from our study, because of the subset size and statistical caveats. These limitations reflect challenges in current clinical trial design.[16,27]

We now understand DLBCL is even more heterogeneous than appreciated when this trial was designed. Recent work on the genetic drivers as well as the exome and transcriptome of DLBCL highlights its heterogeneity.[28-30] Therefore, the National Clinical Trials Network is planning a precision medicine approach to identify molecular subsets of DLBCL and determine if specific chemotherapy platforms and/or targeted agents offer differential benefit.[31] A primary focus is on patients with translocated or expressed *BCL2/MYC* who are treated with the BCL2 inhibitor venetoclax, with either R-CHOP or DA-EPOCH-R, depending upon FISH and DE status. Future studies may benefit from steps allowing more rapid initiation of treatment, such as prephase or permitted standard cycle 1 therapy, thus facilitating inclusion of high-risk patients.

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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

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