original report

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

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abstract

PURPOSE Ibrutinib has shown activity in non–germinal center B-cell diffuse large B-cell lymphoma (DLBCL). This double-blind phase III study evaluated ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in untreated non–germinal center B-cell DLBCL.

PATIENTS AND METHODS Patients were randomly assigned at a one-to-one ratio to ibrutinib (560 mg per day orally) plus R-CHOP or placebo plus R-CHOP. The primary end point was event-free survival (EFS) in the intent-to-treat (ITT) population and the activated B-cell (ABC) DLBCL subgroup. Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

RESULTS A total of 838 patients were randomly assigned to ibrutinib plus R-CHOP (n = 419) or placebo plus R-CHOP (n = 419). Median age was 62.0 years; 75.9% of evaluable patients had ABC subtype disease, and baseline characteristics were balanced. Ibrutinib plus R-CHOP did not improve EFS in the ITT (hazard ratio [HR], 0.934) or ABC (HR, 0.949) population. A preplanned analysis showed a significant interaction between treatment and age. In patients age younger than 60 years, ibrutinib plus R-CHOP improved EFS (HR, 0.579), PFS (HR, 0.556), and OS (HR, 0.330) and slightly increased serious adverse events (35.7% *v* 28.6%), but the proportion of patients receiving at least six cycles of R-CHOP was similar between treatment arms (92.9% *v* 93.0%). In patients age 60 years or older, ibrutinib plus R-CHOP worsened EFS, PFS, and OS, increased serious adverse events (63.4% *v* 38.2%), and decreased the proportion of patients receiving at least six cycles of R-CHOP (73.7% *v* 88.8%).

CONCLUSION The study did not meet its primary end point in the ITT or ABC population. However, in patients age younger than 60 years, ibrutinib plus R-CHOP improved EFS, PFS, and OS with manageable safety. In patients age 60 years or older, ibrutinib plus R-CHOP was associated with increased toxicity, leading to compromised R-CHOP administration and worse outcomes. Further investigation is warranted.

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ASSOCIATED CONTENT

See accompanying Editorial on page 1267

Appendix

Data Supplements

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

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma, accounting for up to 40% of lymphoma cases worldwide.[1] It is highly heterogeneous, with variable pathogenesis and cell of origin.[2] Although gene expression profiling (GEP) methods classify DLBCL into molecular subtypes (germinal center B cell–like [GCB], activated B cell–like [ABC], and unclassified),[2,3] routine use of GEP is not common in the clinical setting. Immunohistochemical methods have been developed to classify DLBCL into the binary of GCB and non-GCB (which includes ABC and unclassified by GEP) subtypes, with the Hans algorithm most commonly used.[4]

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy is the standard front-line treatment of DLBCL.[5,6] Depending on local practice guidelines, R-CHOP is typically administered for six or eight cycles[5,6]; treatment adherence is important for optimal outcomes.[7] Although R-CHOP cures approximately 60% of patients,[8] outcomes remain poor for those who do not

achieve complete remission or develop disease relapse,[8] with a median overall survival (OS) of less than 1 year after progression during first-line treatment.[9] Despite the development and testing of innovative therapies, none has outperformed R-CHOP in almost two decades.[10,11]

Ibrutinib, a first-in-class oral covalent inhibitor of Bruton's tyrosine kinase (BTK), has been approved for several B-cell malignancies in the United States, the European Union, and other countries.[12,13] A phase I/II study evaluated single-agent ibrutinib in relapsed and refractory DLBCL and demonstrated preferential activity in ABC DLBCL, which is sensitive to BTK-dependent B-cell receptor signaling inhibition, with an overall response rate (ORR) of 37%.[14] In a phase I study, ibrutinib plus R-CHOP was safe in patients with untreated B-cell lymphoma, including DLBCL.[15] Here, we aimed to determine if the addition of ibrutinib to R-CHOP would improve efficacy in untreated patients with non-GCB or ABC DLBCL.

PATIENTS AND METHODS

Patients

Eligible patients were age 18 years or older, with previously untreated non-GCB DLBCL confirmed by Hans-based immunohistochemistry (Dako pharmDx™ Kit; Dako/Agilent, Santa Clara, CA) at a central laboratory (IQVIA, Durham, NC). Available tumor samples were retrospectively analyzed for ABC subtype using GEP (HTG EdgeSeq DLBCL Cell of Origin Assay; HTG Molecular Diagnostics, Tucson, AZ).[16] Eligibility criteria included stage II to IV measurable disease, revised International Prognostic Index score of 1 or higher, Eastern Cooperative Oncology Group performance status of 2 or lower, absolute neutrophil count of 1,000 cells or more per μL, and platelets of 75,000 cells or more per μL, unless bone marrow involvement was present. Exclusion criteria included known CNS lymphoma, primary mediastinal lymphoma, history of indolent lymphoma or HIV, and active hepatitis B or C virus.

Study Design and Treatments

This randomized double-blind placebo-controlled multicenter phase III study was conducted in 28 countries across North America, Europe, Asia, Latin America, and Australia (Appendix, online only).

Patients were randomly assigned to the ibrutinib plus R-CHOP or placebo plus R-CHOP arm at a one-to-one ratio to receive R-CHOP (intravenous rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 [maximum total, 2 mg], and oral prednisone [or equivalent] 100 mg) with either ibrutinib (560 mg per day orally) or placebo in a 21-day cycle for six or eight cycles, per institutional guidelines. Study treatment was administered on day 1 of cycle one until day 21 of the last cycle. Infection and cytopenia prophylaxis was not mandated but permitted per local standards; granulocyte colony-stimulating factor was used at investigator discretion. Treatment dosing modification or discontinuation was managed per prespecified guidelines (Appendix).

Random assignment was based on a computer-generated preplanned schedule, balanced by permuted blocks and stratified by revised International Prognostic Index (1 to 2 *v* 3 to 5), region (United States or Western Europe *v* rest of world), and prespecified R-CHOP cycle numbers (six *v* eight).

The study was approved by the institutional review board or independent ethics committee at each participating institution and conducted in accordance with ethical principles defined by the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. An independent data monitoring committee reviewed safety and risk/benefit. All patients provided informed consent.

Study End Points and Assessments

The primary end point was investigator-assessed event-free survival (EFS), defined as time from random assignment to disease progression, relapse after complete response (CR), initiation of subsequent disease-specific therapy for positron emission tomography–positive or biopsy-proven residual disease after six or more cycles of R-CHOP, or any-cause death in the intent-to-treat (ITT) population (non-GCB by immunohistochemistry). According to a protocol amendment implemented approximately 4 years after study initiation, primary analysis was also performed in the ABC (by GEP) population. Secondary end points included progression-free survival (PFS), defined as time from random assignment to progression, relapse, or death, CR rate, and OS in the ITT population.

Response was assessed by investigators using computed tomography (CT) per Revised Response Criteria for Malignant Lymphoma.[17] Whole-body positron emission tomography was recommended (but not mandated) at baseline and was required at the end of treatment. Adverse events (AEs) were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).[18]

Statistical Analysis

Because DLBCL is potentially curable, the statistical plan factored in both cure rate improvement, assuming a cure rate of 40% for the control arm, and risk reduction among uncured patients. The study was designed to show ibrutinib plus R-CHOP as superior to placebo plus R-CHOP in EFS with 90% power to demonstrate an increase of 10% or more in cure rate and 25% risk reduction among uncured patients with a planned sample size of approximately 800 patients. Hypothesis testing for EFS was performed for both ITT and ABC populations using the Song and Chi[19] method, which included a two-stage procedure to control overall type I error (Appendix).

EFS, PFS, and OS were compared between arms using the stratified log-rank test and Cox proportional hazards model. Survival distribution was estimated using the Kaplan-Meier product-limit method. CR rates were compared using the Cochran-Mantel-Haenszel χ^2 test (for relative risk) and logistic regression analysis (for odds ratio), adjusted for stratification factors.

Preplanned exploratory analyses in subgroups with various prognostic and predictive factors were conducted using a Cox proportional hazards model (Appendix). If an interaction demonstrated statistical significance (one-sided $P < .10$), additional post hoc analyses on EFS, PFS, and OS would be performed to examine the nature of treatment comparisons within each subgroup stratum. All *P* values for exploratory analyses are nominal.

RESULTS

Patient Characteristics and Treatment

Between October 2013 and November 2015, 838 patients with non-GCB DLBCL were randomly assigned and included in the ITT analysis (ibrutinib plus R-CHOP, n = 419; placebo plus R-CHOP, n = 419; Fig 1). Baseline characteristics were similar between arms. Median age was 62.0 years. ABC subtype was confirmed in 567 (75.9%) of 747 evaluable patients and was balanced between two treatment arms (77.0% *v* 74.8%; Table 1). Median time from diagnosis to treatment was 27 days. Median follow-up was 34.8 months. More patients discontinued all treatment components in the ibrutinib plus R-CHOP than placebo plus R-CHOP arm (22.4% *v* 13.6%); AEs were the most common reason (12.2% *v* 5.3%; Appendix Table A1, online only).

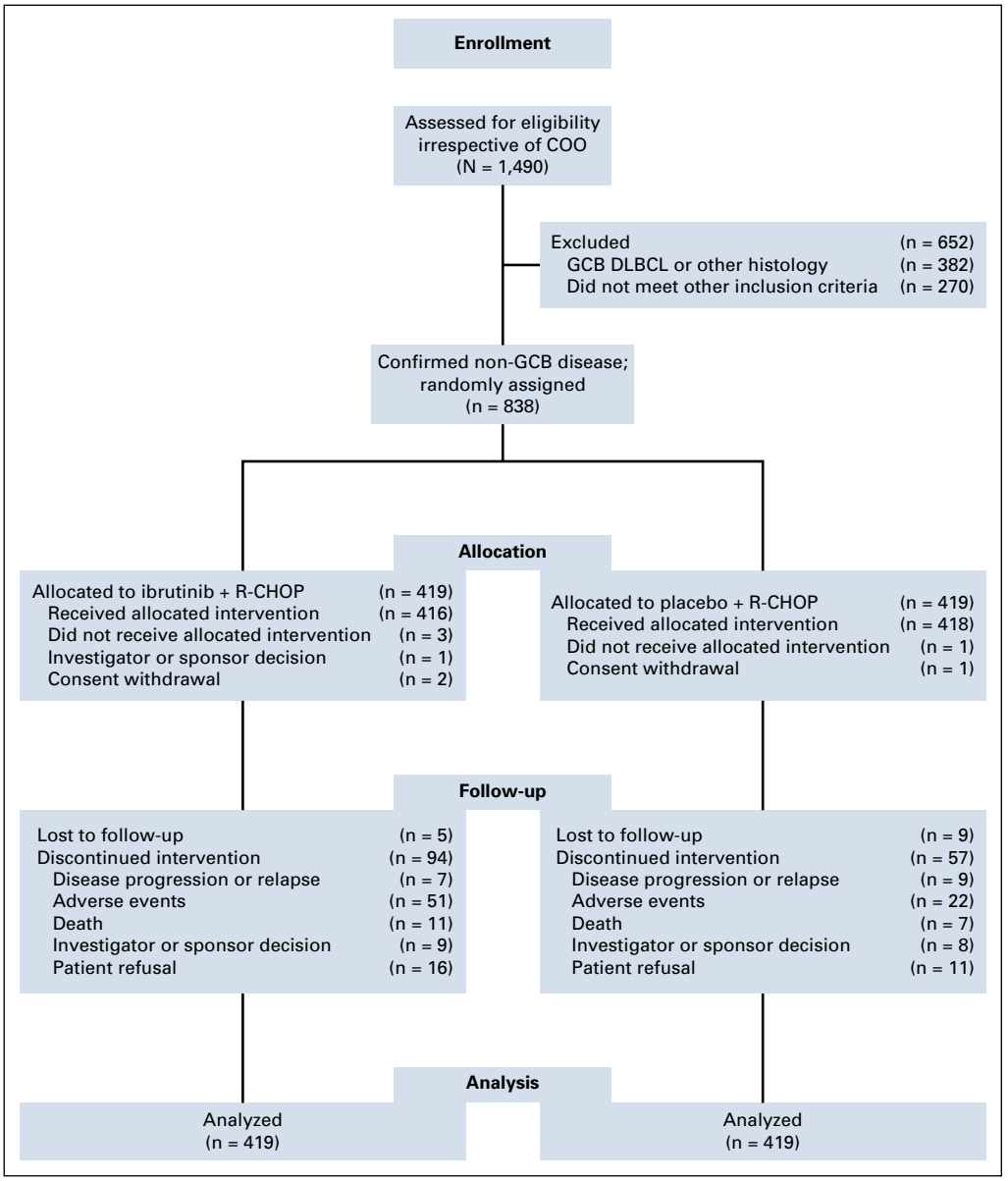

FIG 1. Patient disposition. Random assignment was stratified by revised International Prognostic Index (1 to 2 *v* 3 to 5), region (United States/Western Europe *v* rest of world), and prespecified rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) cycle number (six *v* eight). COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal B cell–like.

TABLE 1. Patient Baseline Demographic and Clinical Characteristics

Characteristic	No. (%) Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)
Age, years		
Median	63.0	61.0
Range	19-88	19-87
< 60	156 (37.2)	186 (44.4)
≥ 60	263 (62.8)	233 (55.6)
Sex		
Female	198 (47.3)	193 (46.1)
Male	221 (52.7)	226 (53.9)
Region (used in stratification)		
United States/Western Europe	131 (31.3)	131 (31.3)
Rest of the world	288 (68.7)	288 (68.7)
Ethnicity		
Hispanic or Latino	17 (4.1)	13 (3.1)
Not Hispanic or Latino	388 (92.6)	396 (94.5)
Unknown	3 (0.7)	4 (1.0)
Not reported	11 (2.6)	6 (1.4)
Race		
White	237 (56.6)	250 (59.7)
Black or African American	4 (1.0)	4 (1.0)
Asian	166 (39.6)	160 (38.2)
American Indian or Alaska Native	2 (0.5)	1 (0.2)
Other	1 (0.2)	1 (0.2)
Not reported	7 (1.7)	2 (0.5)
Multiple	2 (0.5)	1 (0.2)
Geographic region		
United States	40 (9.5)	36 (8.6)
Canada	12 (2.9)	9 (2.1)
Europe	185 (44.2)	204 (48.7)
Latin America	11 (2.6)	6 (1.4)
Asia	159 (37.9)	156 (37.2)
Oceania	12 (2.9)	8 (1.9)
Time from initial diagnosis to random assignment, days		
Mean	30.7	32.0
SD	23.96	25.47
Median	27.0	26.0
Range	4-302	6-349
Baseline stage of DLBCL at entry		
I	0	1 (0.2)
II	101 (24.1)	103 (24.6)
III	130 (31.0)	118 (28.2)
IV	188 (44.9)	197 (47.0)
Baseline lymphoma symptoms	175 (41.8)	195 (46.5)
Bone marrow involvement*	50 (11.9)	43 (10.3)
ECOG performance status		
0	190 (45.3)	187 (44.6)
1	191 (45.6)	170 (40.6)
2	38 (9.1)	62 (14.8)
Bulky tumor (long axis ≥ 10 cm)	60 (14.3)	59 (14.1)
No. of extranodal sites		
0	138 (32.9)	122 (29.1)
1	151 (36.0)	141 (33.7)
> 1	130 (31.0)	156 (37.2)
IPI/R-IPI score index number		
0	0	0
1	97 (23.2)	110 (26.3)
2	139 (33.2)	128 (30.5)
3	125 (29.8)	112 (26.7)
4	54 (12.9)	56 (13.4)
5	4 (1.0)	13 (3.1)
Elevated LDH	234 (55.8)	220 (52.5)
No. of planned treatment cycles (used in stratification)		
6	246 (58.7)	246 (58.7)
8	173 (41.3)	173 (41.3)
GEP subtype†		
ABC	285 (77.0)	282 (74.8)
Unclassified	28 (7.6)	23 (6.1)
GCB	57 (15.4)	72 (19.1)

Abbreviations: ABC, activated B cell-like; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell–like; GEP, gene expression profiling; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI, revised International Prognostic Index; SD, standard deviation.

*Bone marrow involvement is defined as any baseline aspirate or biopsy result of histology positive or histology negative/indeterminate that is confirmed positive by immunohistochemistry or flow cytometry.

†GEP was conducted after non-GCB enrichment by immunohistochemistry. Samples were evaluable in 370 patients for ibrutinib plus R-CHOP and 377 patients for placebo plus R-CHOP. Patients with missing samples (ibrutinib plus R-CHOP, n = 9; placebo plus R-CHOP, n = 4) or test failure (ibrutinib plus R-CHOP, n = 40; placebo plus R-CHOP, n = 38) were not included in the analysis.

Efficacy

Ibrutinib plus R-CHOP did not improve EFS versus placebo plus R-CHOP in the ITT (hazard ratio [HR], 0.934; 95% CI, 0.726 to 1.200; $P = .5906$) or ABC population (HR, 0.949; 95% CI, 0.704 to 1.279; $P = .7311$; Fig 2). Furthermore, addition of ibrutinib did not increase PFS (HR, 0.917; 95% CI, 0.710 to 1.183; $P = .5027$), OS (HR, 0.991; 95% CI, 0.712 to 1.380; $P = .9593$; Fig 2; Appendix Table A2, online only), or ORR (89.3% *v* 93.1%; $P = .0515$), including CR rates (67.3% *v* 68.0%; $P = .8229$) versus placebo plus R-CHOP in the ITT population (Appendix Table A3, online only). EFS and PFS results were similar. CNS relapse occurred in 2.4% and 3.8% patients in the ibrutinib plus R-CHOP and placebo plus R-CHOP arms, respectively.

Subgroup Analysis by Age

In preplanned subgroup analyses, age and elevated lactate dehydrogenase were associated with favorable outcomes in EFS, but lactate dehydrogenase failed to demonstrate robustness across all end points (Appendix Fig A1, online only). Exploratory analysis showed an interaction between treatment effect (EFS, PFS, and OS) and age as a continuous ($P = .0365$) or categorical variable (age younger than 60 *v* 60, 62, or 65 years or older; P = .0087, .0054, and .0239, respectively; Appendix Table A4, online only), with patients age younger than 65 years showing a more favorable outcome versus those age 65 years or older, which was confirmed by multivariable analysis. A post hoc analysis using different age cutoffs showed more precisely that ibrutinib plus R-CHOP was associated with benefit in patients age younger than 60 years but worsened outcomes in those age 60 years or older (Fig 3).

Among patients age younger than 60 years, baseline characteristics were similar between arms (Appendix Table A5, online only). Ibrutinib plus R-CHOP improved EFS (HR, 0.579; 95% CI, 0.380 to 0.881), PFS (HR, 0.556; 95% CI,

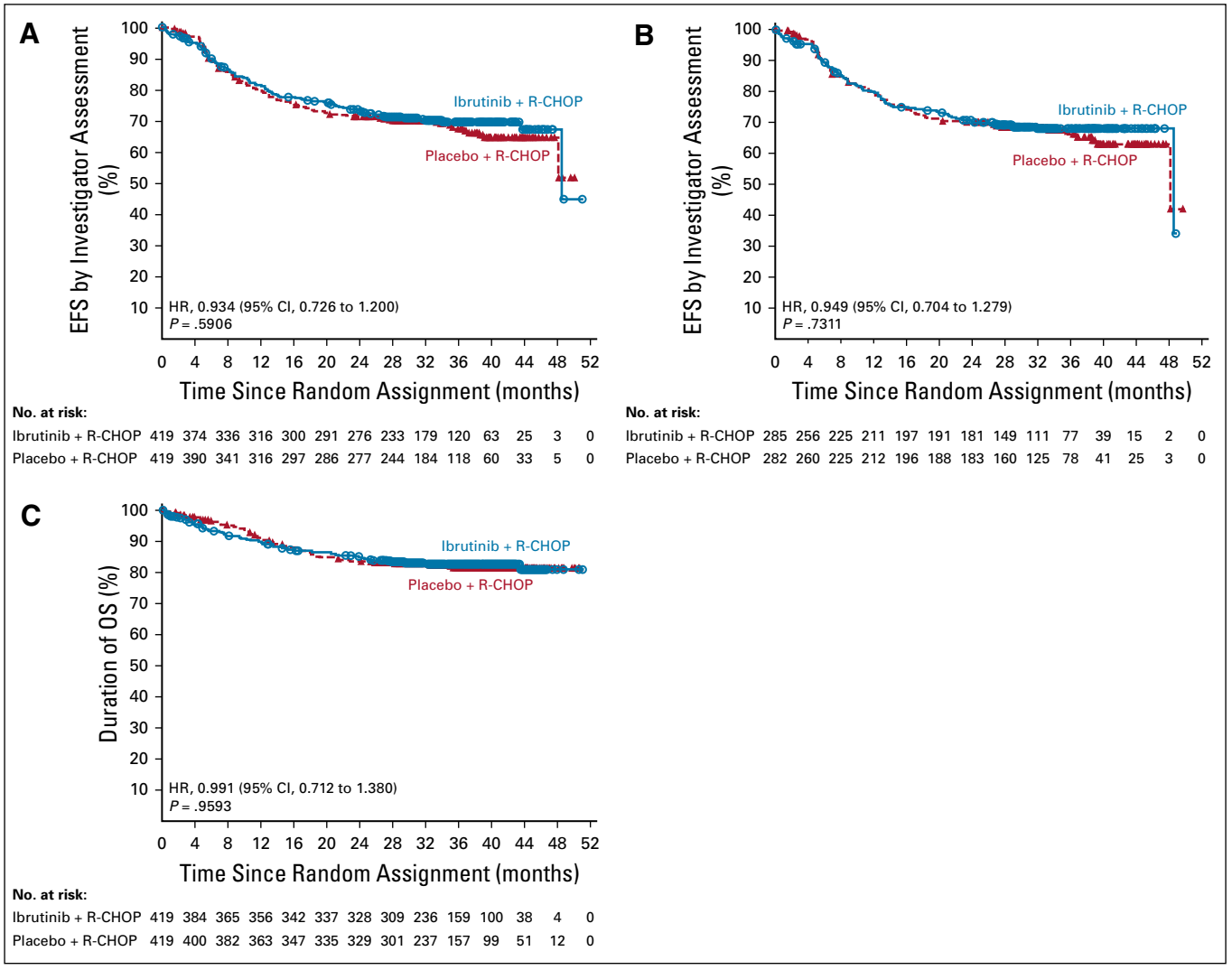

FIG 2. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS). (A) Investigator-assessed EFS, intent-to-treat (ITT) population. (B) Investigator-assessed EFS, activated B cell–like population. (C) OS, ITT population. HR, hazard ratio; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

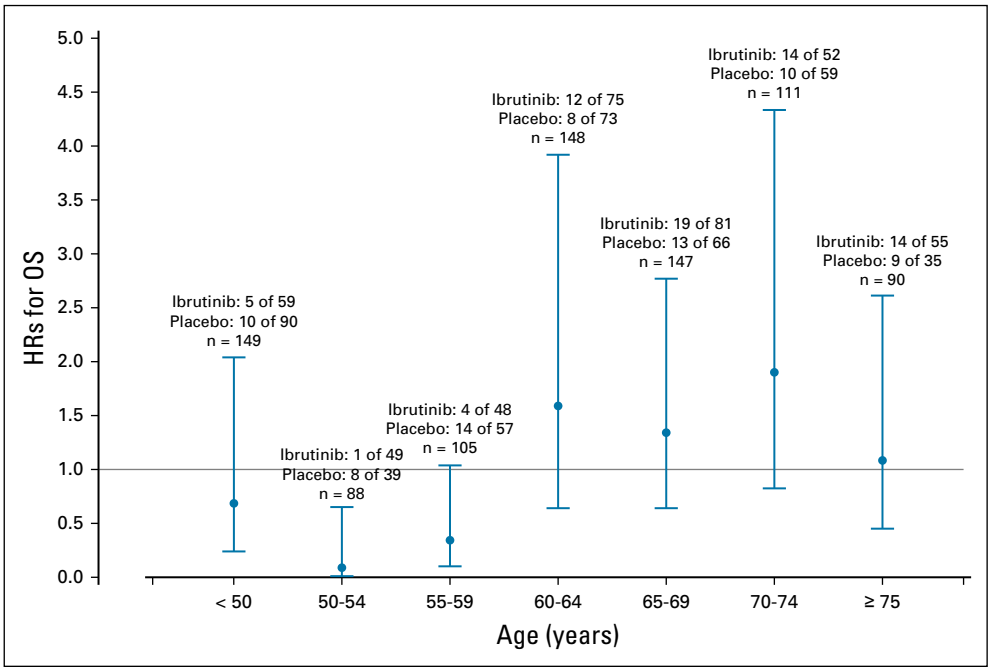

FIG 3. Hazard ratios (HRs) of overall survival (OS) by different discrete age groups. Bars indicate 95% CIs.

0.359 to 0.860), and OS (HR, 0.330; 95% CI, 0.162 to 0.673) versus placebo plus R-CHOP (Table 2; Fig 4). EFS, PFS, and OS rates at 36 months were also higher in the ibrutinib plus R-CHOP than placebo plus R-CHOP arm. ORR was similar between arms (93.6% *v* 94.6%) in younger patients, with a slightly higher CR rate (71.2% *v* 69.9%) and increased rate of durable partial response longer than 6 months (57.1% *v* 34.8%; Appendix Table A3) in the ibrutinib plus R-CHOP arm. A similar trend with age was seen in patients age younger than 60 years with ABC DLBCL.

Subgroup analyses in patients age younger than 60 years showed that EFS benefit was consistent across most subgroups for baseline factors (Appendix Fig A2, online only). After disease progression, subsequent disease-specific therapies were generally balanced between arms in the ITT population and by 60-year age cutoff (Appendix Table A6, online only).

Among patients age 60 years or older, EFS (HR, 1.228; 95% CI, 0.887 to 1.699), PFS (HR, 1.200; 95 CI, 0.866 to 1.664), and OS (HR, 1.440; 95% CI, 0.963 to 2.152) were worse in the ibrutinib plus R-CHOP versus placebo plus R-CHOP arm (Table 2; Fig 4). Similar outcomes were seen in patients age 60 years or older with ABC DLBCL.

Safety

In all patients, all-grade (100% *v* 99.0%) and grade 3 or higher treatment-emergent AEs (89.9% *v* 87.1%) were similar across arms (Appendix Table A7, online only). However, more serious AEs (SAEs) were reported in the ibrutinib plus R-CHOP than in the placebo plus R-CHOP arm (53.1% *v* 34.0%), particularly febrile neutropenia, diarrhea, cytopenia, and pneumonia (Table 3), as were AEs leading to treatment discontinuation (31.5% *v* 13.6%). Rates of R-CHOP discontinuation (any component) as a result of AEs were also higher in the ibrutinib plus R-CHOP arm (26.7% *v* 11.7%), most often because of lung infection (1.4% *v* 0.5%), pneumonia (1.0% *v* 0.7%), and peripheral neuropathy (4.1% *v* 1.4%). Rate of treatment discontinuation because of progressive disease was 1.7% versus 2.1% in the ibrutinib plus R-CHOP versus placebo plus R-CHOP arm. SAEs and AEs leading to treatment discontinuation increased with older age in both arms but were more pronounced in the ibrutinib plus R-CHOP versus placebo plus R-CHOP arm (Appendix Fig A3, online only). Rates of all-cause deaths were similar (16.3% *v* 17.0%) between arms. In the ibrutinib plus R-CHOP and placebo plus R-CHOP arms, rates of AEs leading to death were 4.3% and 2.9%, respectively, including 1.2% and 0.7% rates of death resulting from infections, whereas rates of death resulting from disease progression were 7.5% and 11.0%, respectively.

In patients age younger than 60 years, the any-grade AE rate was 100% in both arms. Grade 3 or higher treatment-emergent AE rates (87.7% *v* 85.9%) were similar between arms, but more SAEs (35.7% *v* 28.6%; Table 3) and AEs leading to R-CHOP discontinuation (12.3% and 7.6%) were noted in the ibrutinib plus R-CHOP versus placebo plus R-CHOP arm. Among patients age 60 years or older, all-grade (100.0% *v* 98.3%) and grade 3 or higher AEs (91.2% *v* 88.0%) were also similar between arms. There

TABLE 2. Efficacy of Ibrutinib Plus R-CHOP by Age

	ITT				ABC			
	Age < 60 Years		Age ≥ 60 Years		Age < 60 Years		Age ≥ 60 Years	
Survival	Ibrutinib + R-CHOP (n = 156)	Placebo + R-CHOP (n = 186)	Ibrutinib + R-CHOP (n = 263)	Placebo + R-CHOP (n = 233)	Ibrutinib + R-CHOP (n = 90)	Placebo + R-CHOP (n = 115)	Ibrutinib + R-CHOP (n = 195)	Placebo + R-CHOP (n = 167)
EFS								
HR	0.579		1.228		0.532		1.229	
95% CI	0.380 to 0.881		0.887 to 1.699		0.307 to 0.922		0.849 to 1.780	
P	.0099		.2153		.0223		.2739	
No. of events	34	64	84	65	19	41	66	50
36-month EFS rate, %	75.4	64.6	66.0	69.6	76.9	64.5	64.0	67.1
95% CI, %	67.0 to 81.9	56.6 to 71.6	59.6 to 71.6	62.7 to 75.6	66.1 to 84.6	54.4 to 72.9	56.5 to 70.6	58.4 to 74.3
PFS								
HR	0.556		1.200		0.438		1.186	
95% CI	0.359 to 0.860		0.866 to 1.664		0.244 to 0.784		0.817 to 1.722	
P	.0075		.2731		.0043		.3680	
No. of events	31	61	82	65	16	41	64	50
36-month PFS rate, %	77.4	66.3	66.8	69.6	80.5	64.5	65.1	67.0
95% CI, %	69.1 to 83.7	58.3 to 73.1	60.5 to 72.4	62.6 to 75.5	70.1 to 87.6	54.4 to 72.9	57.6 to 71.6	58.4 to 74.3
OS								
HR	0.330		1.440		0.345		1.383	
95% CI	0.162 to 0.673		0.963 to 2.152		0.138 to 0.862		0.881 to 2.170	
P	.0013		.0739		.0170		.1570	
No. of events	10	32	59	40	6	20	47	32
36-month OS rate, %	93.2	80.9	76.6	81.7	92.8	80.9	74.5	79.3
95% CI, %	87.7 to 96.3	73.9 to 86.2	70.8 to 81.4	75.8 to 86.3	84.7 to 96.7	71.9 to 87.3	67.6 to 80.2	71.9 to 85.0

Abbreviations: ABC, activated B cell–like; EFS, event-free survival; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

were more SAEs in the ibrutinib plus R-CHOP than placebo plus R-CHOP arm (63.4% *v* 38.2%); febrile neutropenia, neutropenia, pneumonia, diarrhea, and lung infection were most common (Table 3). Notably, in the ibrutinib plus R-CHOP arm (*v* the placebo plus R-CHOP arm), AEs leading to R-CHOP discontinuation were increased to a greater extent among patients age 60 years or older (35.1% *v* 15.0%) relative to patients age younger than 60 years. In older patients, although serious atrial fibrillation occurred only in the ibrutinib plus R-CHOP arm, the rate (3.1%) was consistent with prior reports of atrial fibrillation with ibrutinib (4.2%).[20]

Aspergillus infection was reported only in patients age 60 years or older. Bronchopulmonary aspergillosis occurred in four (1.0%) and two patients (0.5%) in the ibrutinib plus R-CHOP and placebo plus R-CHOP arms, respectively; cerebral aspergillosis occurred in two patients (0.4%) in the ibrutinib plus R-CHOP arm.

Prophylactic granulocyte colony-stimulating factor use was balanced between arms in patients younger than 60 years and those age 60 years or older, whereas secondary antibiotic prophylaxis (administered 5 days or more after first dose of study drug) was higher in the ibrutinib plus R-CHOP arm (Appendix Table A8, online only).

Treatment Exposure

In all patients, the proportion of patients receiving at least six cycles of R-CHOP (any component) was lower in the ibrutinib plus R-CHOP than placebo plus R-CHOP arm (80.8% *v* 90.7%). The decreased R-CHOP exposure was primarily seen in older patients in the ibrutinib plus R-CHOP arm. In patients age 60 years or older, the proportion of patients receiving six cycles or more of R-CHOP was lower in the ibrutinib plus R-CHOP arm than the placebo plus R-CHOP arm (73.7% *v* 88.8%; Appendix Table A9, online

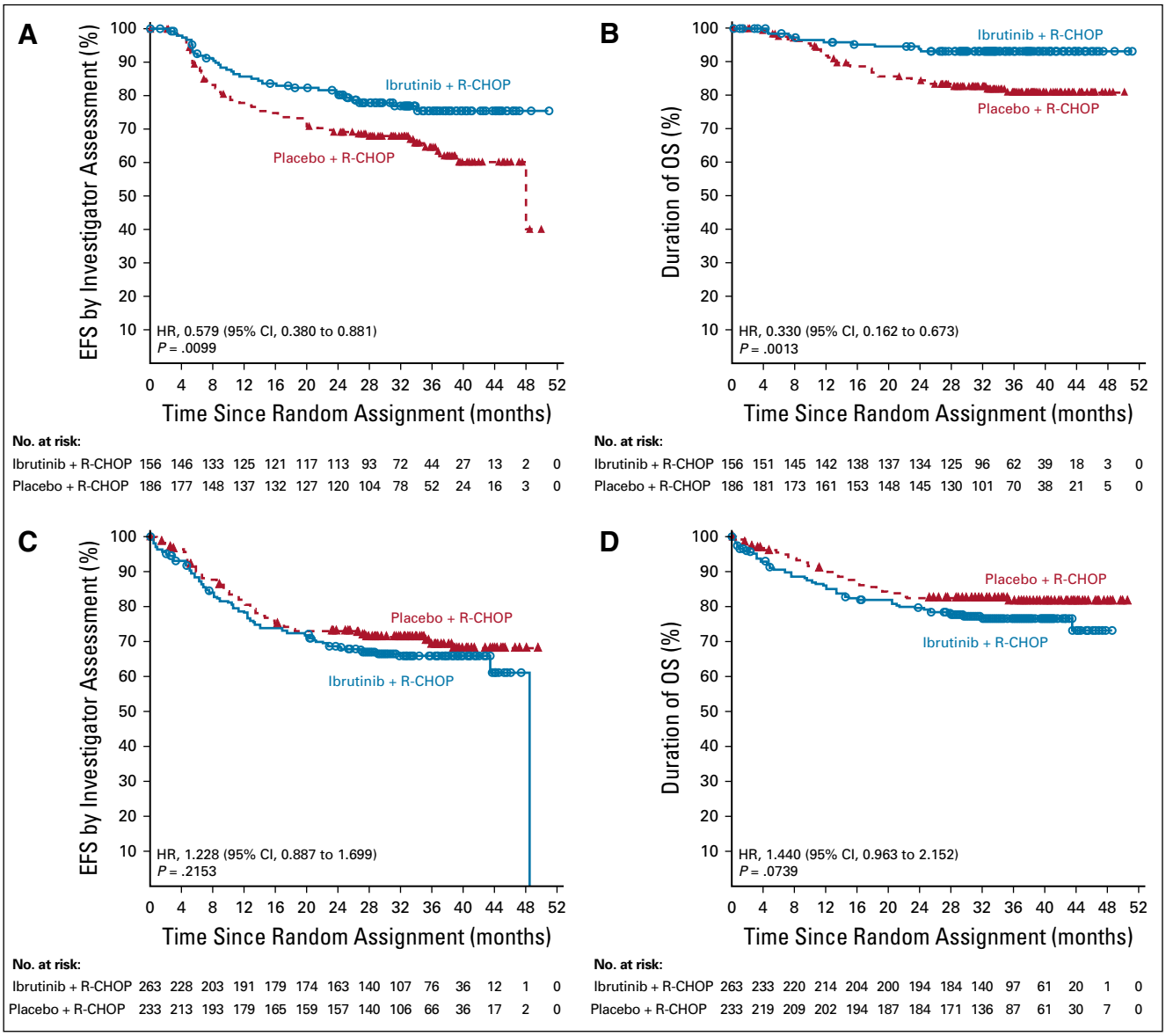

FIG 4. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS) by cutoff of age 60 years in the intent-to-treat population. (A) EFS, age younger than 60 years (n = 342). (B) OS, age younger than 60 years (n = 342). (C) EFS, age 60 years or older (n = 496). (D) OS, age 60 years or older (n = 496). HR, hazard ratio; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

only) but was similar between arms in patients younger than 60 years (92.9% *v* 93.0%).

DISCUSSION

In the non-GCB population and ABC subpopulation, addition of ibrutinib to R-CHOP did not improve efficacy in patients with untreated DLBCL. However, preplanned subgroup analysis discovered a significant interaction between treatment and age. Exploratory analysis showed that in patients age younger than 60 years, ibrutinib plus R-CHOP was associated with prolonged EFS, PFS, and OS. The risk profile for ibrutinib plus R-CHOP was age dependent. Although SAE rates were higher in the ibrutinib plus R-CHOP arm versus the placebo plus R-CHOP arm in both younger and older patients, R-CHOP exposure was not affected in patients younger than age 60. In contrast, in patients age 60 years or older, addition of ibrutinib increased rates of SAEs and AEs leading to R-CHOP discontinuation, which compromised treatment exposure and likely decreased efficacy. The observed differential efficacy according to age was likely a result of poor ibrutinib plus R-CHOP tolerance in older patients.

Median follow-up was nearly 3 years (34.8 months), which is appropriate to evaluate outcomes, given the strong correlation between 24-month EFS and long-term survival.[21] Outcomes with placebo plus R-CHOP were similar

TABLE 3. Treatment-Emergent SAEs Occurring in 2% or More of Patients in the Safety Population and by Cutoff of Age 60 Years

	No. (%)					
	Safety Population		< 60 Years		≥ 60 Years	
SAE	Ibrutinib + R-CHOP (n = 416)	Placebo + R-CHOP (n = 418)	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
Overall	221 (53.1)	142 (34.0)	55 (35.7)	53 (28.6)	166 (63.4)	89 (38.2)
Febrile neutropenia	78 (18.8)	44 (10.5)	22 (14.3)	17 (9.2)	56 (21.4)	27 (11.6)
Diarrhea	15 (3.6)	4 (1.0)	1 (0.6)	2 (1.1)	14 (5.3)	2 (0.9)
Neutropenia	17 (4.1)	13 (3.1)	2 (1.3)	4 (2.2)	15 (5.7)	9 (3.9)
Pneumonia*	28 (6.7)	14 (3.3)	6 (3.9)	4 (2.2)	22 (8.4)	10 (4.3)
Anemia	15 (3.6)	5 (1.2)	3 (1.9)	2 (1.1)	12 (4.6)	3 (1.3)
Atrial fibrillation	13 (3.1)	1 (0.2)	2 (1.3)	1 (0.5)	11 (4.2)	0
Lung infection*	14 (3.4)	7 (1.7)	1 (0.6)	2 (1.1)	13 (5.0)	5 (2.1)
Pyrexia	12 (2.9)	11 (2.6)	3 (1.9)	4 (2.2)	9 (3.4)	7 (3.0)
Dehydration	8 (1.9)	2 (0.5)	1 (0.6)	0	7 (2.7)	2 (0.9)
Sepsis	7 (1.7)	3 (0.7)	0	0	7 (2.7)	3 (1.3)
Pneumonitis*	6 (1.4)	3 (0.7)	4 (2.6)	2 (1.1)	2 (0.8)	2 (0.9)
Thrombocytopenia	9 (2.2)	1 (0.2)	0	0	9 (3.4)	1 (0.4)
Interstitial lung disease*	7 (1.7)	4 (1.0)	4 (2.6)	2 (1.1)	3 (1.1)	2 (0.9)

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SAE, serious adverse event.

*On the basis of MedDRA (version 20.0), lung infection/pneumonia were coded under system organ class term "infections and infestations"; pneumonitis and interstitial lung disease were coded under "respiratory, thoracic, and mediastinal disorders."

in the ITT population and various subgroups and were generally comparable to those reported in other randomized controlled trials of R-CHOP in non-GCB or ABC DLBCL (3-year PFS rate, 67% to 70%),[10,11] although different study design, patient population, and end point analyses among trials may affect results. Although increased age is considered a negative prognostic factor in DLBCL, older fit patients who can tolerate full-dose R-CHOP may achieve outcomes similar to those seen in younger patients. According to the Kaplan-Meier survival curves (Fig 4), older and younger patients in the placebo plus R-CHOP arm demonstrated comparable survival benefit.[22] In patients younger than age 60, ibrutinib plus R-CHOP versus placebo plus R-CHOP improved EFS and OS despite similar ORR, confirming that CR alone was not a predictor of long-term outcome in DLBCL.

On the basis of the hypothesis that adding ibrutinib to R-CHOP would improve the outcome of ABC DLBCL,[14] immunohistochemistry was used to select non-GCB DLBCL in the ITT population to enrich for the ABC subtype. GEP showed that 75.9% of patients had ABC DLBCL, confirming enrichment for ABC over the general DLBCL population.[16] Although this demonstrates the limitations of cell-of-origin subtyping by immunohistochemistry, it is consistent with published concordance of approximately 80% between immunohistochemistry- and GEP-based methods.[16] Interestingly, in younger patients, ibrutinib plus R-CHOP showed similar benefit in the non-GCB population and ABC subgroup, suggesting ibrutinib plus R-CHOP may also benefit patients beyond ABC DLBCL. This is consistent with recent findings that BTK-dependent B-cell receptor signaling is present in a subset of non-ABC DLBCL,[15] and unclassified DLBCL could respond to ibrutinib.[14,23]

In patients age 60 years or older, rates of SAEs, including febrile neutropenia, pneumonia, diarrhea, and lung infection, were notably higher in the ibrutinib plus R-CHOP than the placebo plus R-CHOP arm. Older patients in the ibrutinib plus R-CHOP arm were also more likely to discontinue R-CHOP because of peripheral neuropathy, infections, and GI AEs, whereas cardiac events, including atrial fibrillation, did not seem to increase treatment discontinuation.

Treatment discontinuation was not explained by altered ibrutinib pharmacokinetics with R-CHOP in this study. In a phase I study, pharmacokinetic analysis did not reveal an interaction between ibrutinib and vincristine.[15] In this study, vincristine pharmacokinetics were not altered, and ibrutinib pharmacokinetics were similar to those of single-agent ibrutinib reported in other studies (Appendix Table A10, online only; Appendix Fig A4, online only; Appendix "Pharmacokinetic Analysis," online only).[15,24]

The interaction between age and treatment was an unexpected finding in this study, which confounded result interpretation. Randomized studies, although considered the gold standard for assessing treatment benefit, must rely on generally equivalent toxicity across major characteristics such as age. However, in our study, ibrutinib plus R-CHOP increased toxicity in patients age 60 years or older, leading to premature R-CHOP discontinuation and inferior outcomes. Therefore, it is important to separate the potential benefit of

ibrutinib, which is indicated in younger patients, from its adverse effect when combined with R-CHOP in older patients; this may be attributable to multiple factors, including impaired immune responses leading to increased infections.[25] Additionally, DLBCL subtype analysis, determined by immunohistochemistry at central laboratories, prolonged the time from tumor biopsy to random assignment. Median time from diagnosis to treatment of 27 days was longer than that seen in clinical practice, particularly for the ABC DLBCL subgroup, which may have excluded patients necessitating immediate treatment. Therefore, the outcome in the overall population was better than anticipated, suggesting an enrollment bias toward more physically fit patients and patients with better prognosis, a common observation in clinical studies.[26] Despite the optimal outcome in the entire non-GCB DLBCL population, an improvement in younger patients was observed for ibrutinib plus R-CHOP. Ibrutinib plus R-CHOP was associated with treatment benefit in most subgroups, except for patients from the United States and Western Europe, but the event number was too small to draw any conclusions. Although unlikely, the impact of genotype variation across regions or age groups cannot be excluded and warrants further investigation.

For the past 20 years, R-CHOP has remained the standard treatment for previously untreated DLBCL.[5] Insights into DLBCL pathobiology have led to trials evaluating targeted agents combined with R-CHOP within DLBCL subtypes, several of which have been recently completed or are ongoing, but none of which has reported a definitive benefit in the ABC subgroup.[8,11,27] In our trial, ibrutinib plus R-CHOP seemed to improve EFS and OS in younger patients with non-GCB DLBCL to an extent not previously noted, with a trend toward improvement in the more specific ABC DLBCL population. This aligns with the hypothesis that BTK-dependent nuclear factor κB signaling inhibition by ibrutinib may augment the cytotoxic effects of chemotherapeutic agents.[14,28] Unfortunately, older patients could not tolerate ibrutinib plus R-CHOP. Real-world data show that older patients with DLBCL are more likely to receive compromised R-CHOP regimens or alternative chemotherapies,[29] and in our study, the addition of ibrutinib seemed to worsen treatment tolerance. These results, although obtained from post hoc analyses, indicate the influence of age on treatment tolerability and outcome with ibrutinib plus R-CHOP. These results are hypothesis generating and therefore represent an area for further investigation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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APPENDIX

Participating Sites

The study was conducted at 181 sites in 28 countries or regions: People's Republic of China, the United States, Japan, Russia, Turkey, Italy, Poland, the United Kingdom, Czech Republic, Korea, Israel, Canada, Australia, Ukraine, Republic of China, Belgium, Finland, Germany, Brazil, Spain, Denmark, France, Hungary, Norway, the Netherlands, Mexico, Argentina, and Sweden.

Dosing Guidelines

The start of a new treatment cycle may be delayed on a weekly basis until recovery from toxicity. If toxicity persists after a 2-week cycle delay related to a specific drug, the offending drug withholding should continue while the remaining drugs should be resumed. If rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy is delayed, study drug (ibrutinib or placebo) treatment should be continued as initially planned during the delay phase. If the study drug is delayed or withheld, any remaining study treatment (ie, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may be continued. If the delay in the initiation of a new treatment cycle is longer than 3 weeks because of insufficient recovery from toxicity (with all drugs withheld), the patient should discontinue study participation.

R-CHOP component dose adjustments and discontinuation were based on the prescribing information. Study drug was held for any unmanageable, potentially study drug–related grade 3 or higher toxicity for up to 21 consecutive days. Study drug was discontinued permanently if toxicity lasted more than 21 days. No dose escalation (more than four capsules per day [ie, more than 560 mg]) was allowed for the study drug in this study.

Statistical Analysis

The study population was differentiated as two subgroups (curable *v* noncurable) to factor patient curability into the estimation of study power. Sample size was determined using simulation studies, with the study cutoff being planned at 30 months after 800 patients were randomly assigned.

Simulation studies were conducted in the overall population based on the following assumptions:

- A one-to-one random assignment ratio between two treatment arms.
- Enrollment of approximately 800 patients (approximately 400 patients per treatment arm)
- Assuming the cure rate for the control arm (placebo plus R-CHOP) was 40% and the targeted cure rate of improvement was 10% for the active treatment arm ibrutinib plus R-CHOP (ie, the cure rate for ibrutinib plus R-CHOP was 50%), median event-free survival (EFS) was assumed to be 15 years for cured patients.
- Among those patients not cured, a targeted hazard ratio of 0.75 was assumed. This corresponds to a 4-month increase in median EFS for the active treatment arm (ibrutinib plus R-CHOP) relative to the control arm (placebo plus R-CHOP), assuming median EFS for the control arm (placebo plus R-CHOP) was 12 months.
- Dropout rate was 5%.
- One interim analysis was to be performed when approximately 270 EFS events were available for superiority testing at a significance level of .002 (one sided).

This statistical method can capture statistically significant between-group differences resulting from a wide range of clinical outcomes.

The Song and Chi[19] method was performed as a two-stage testing procedure. At stage one, if the *P* value associated with the weighted statistic Z1 was less than .04, then we proceeded to stage two for testing both the intent-to-treat (ITT) population (based on log-rank test instead of weighted testing statistic Z1) and the target subgroup (activated B cell–like [ABC] population by gene expression profiling) at the α level of .05 separately. If the *P* values for the weighted statistic Z1 at stage one were $\geq$ .04 and $<$ .2, then the ABC population would be tested at the corresponding significance level for the ABC population. The significance level for the ABC population was calculated to control the family-wise error rate of .05 by incorporating the correlation between Z1 and Z2 (standardized test statistic for the ABC population by gene expression profiling). If significance was shown in the target subgroup (ABC population), then the ITT population could be retested at the significance level of .05 using a standard log-rank test.

In the preplanned exploratory subgroup analyses, assessed prognostic and predictive factors included demographic factors (age, sex, race, region, and intended number of treatment cycles), disease characteristics (revised International Prognostic Index score, lactate dehydrogenase level, normal left ventricular ejection fraction, bone marrow involvement, number of measurable lesions at baseline, bulky disease, number of assessable lesions at baseline, number of extranodal sites, hepatic impairment, and renal impairment), and laboratory values (creatinine clearance, albumin, platelet, hemoglobin, and absolute neutrophil count).

Pharmacokinetic Analysis

Pharmacokinetic samples from the ITT population were available from 726 patients: 358 in the ibrutinib plus R-CHOP arm and 368 in the placebo plus R-CHOP arm (87%). Appendix Figure A4 shows observed ibrutinib concentrations measured in our study superimposed on those from earlier studies (CLL3001 [ClinicalTrials.gov identifier: NCT01611090], PCYC 1112 [NCT01578707], PCYC 1115 [NCT01722487], PCYC 1117 [NCT01744691], PCYC 1102 [NCT01105247], PCYC 1104 [NCT01236391], MCL2001 [NCT01599949], MCL3001 [NCT01646021], and PCYC 04753 [NCT00849654]) using a previously developed pharmacokinetic model for ibrutinib.

There was substantial overlap between the observed ibrutinib plasma concentrations and the predicted values based on the previous pharmacokinetic model, indicating that the pharmacokinetics of ibrutinib in our study were consistent with those seen in previous assessments. Average area under the plasma concentration-time curve from time 0 to 24 hours at steady state was 620 ng $\times$ h/mL (standard deviation, 356 ng $\times$ h/mL), consistent with the weighted average of 654 ng $\times$ h/mL (standard deviation, 477 ng $\times$ h/mL) calculated for three studies (PCYC 1104, MCL2001, and MCL3001) in patients with mantle cell lymphoma who also received a 560-mg daily dose as monotherapy (Appendix Table A10). Average area under the concentration-time curve was 25.6% higher in patients age 60 years or older, also consistent with the observations in patients with mantle cell lymphoma. Post hoc analyses of vincristine exposure indicated a similar exposure between the treatment arms, confirming the earlier phase I (DBL1002) finding that an interaction between vincristine and ibrutinib was absent.

Data Sharing Statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

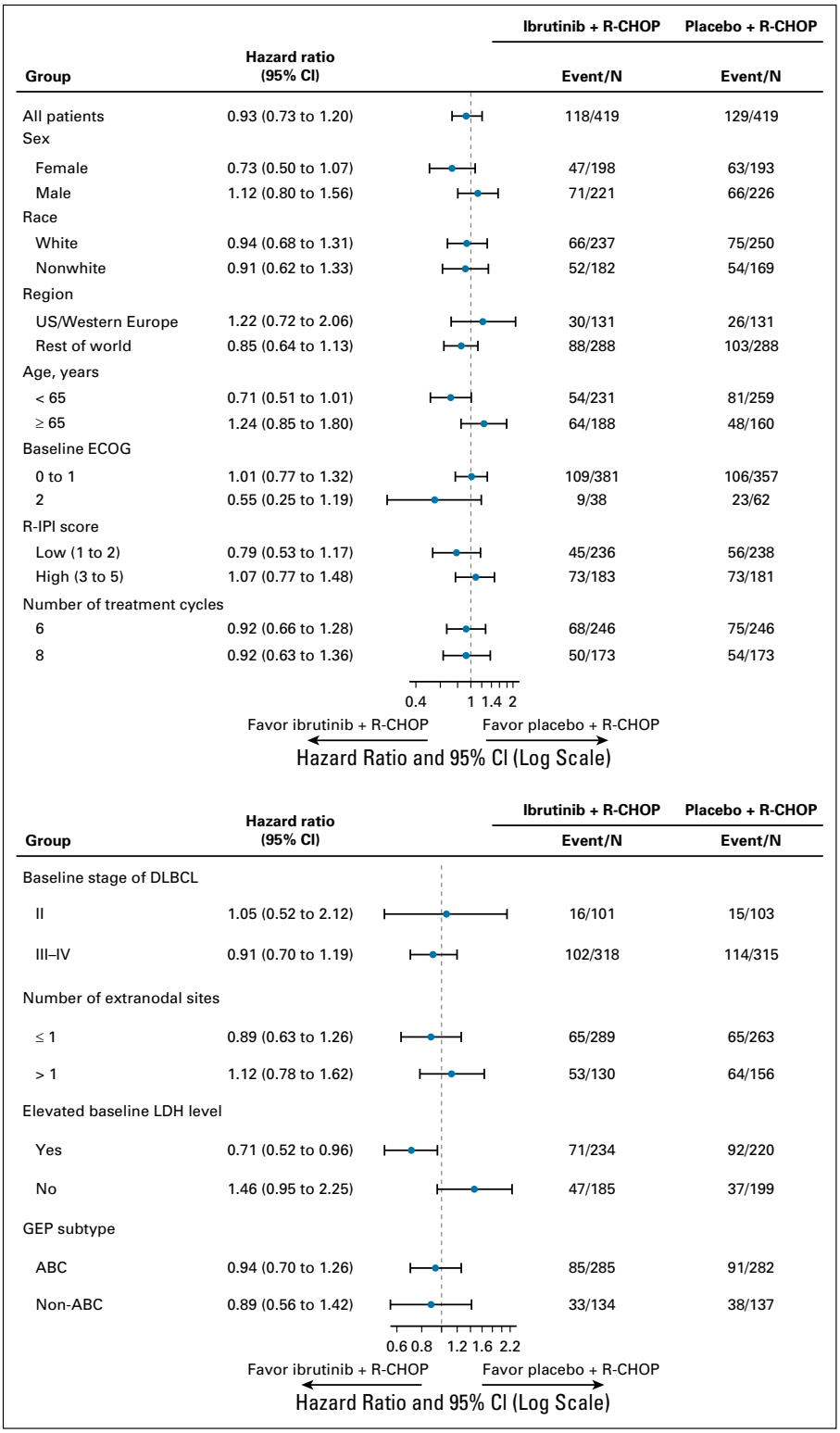

FIG A1. Subgroup analysis of event-free survival (EFS) in the intent-to-treat (ITT) population. ABC, activated B cell–like; ECOG, Eastern Cooperative Oncology Group; GEP, gene expression profiling; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI, Revised International Prognostic Index.

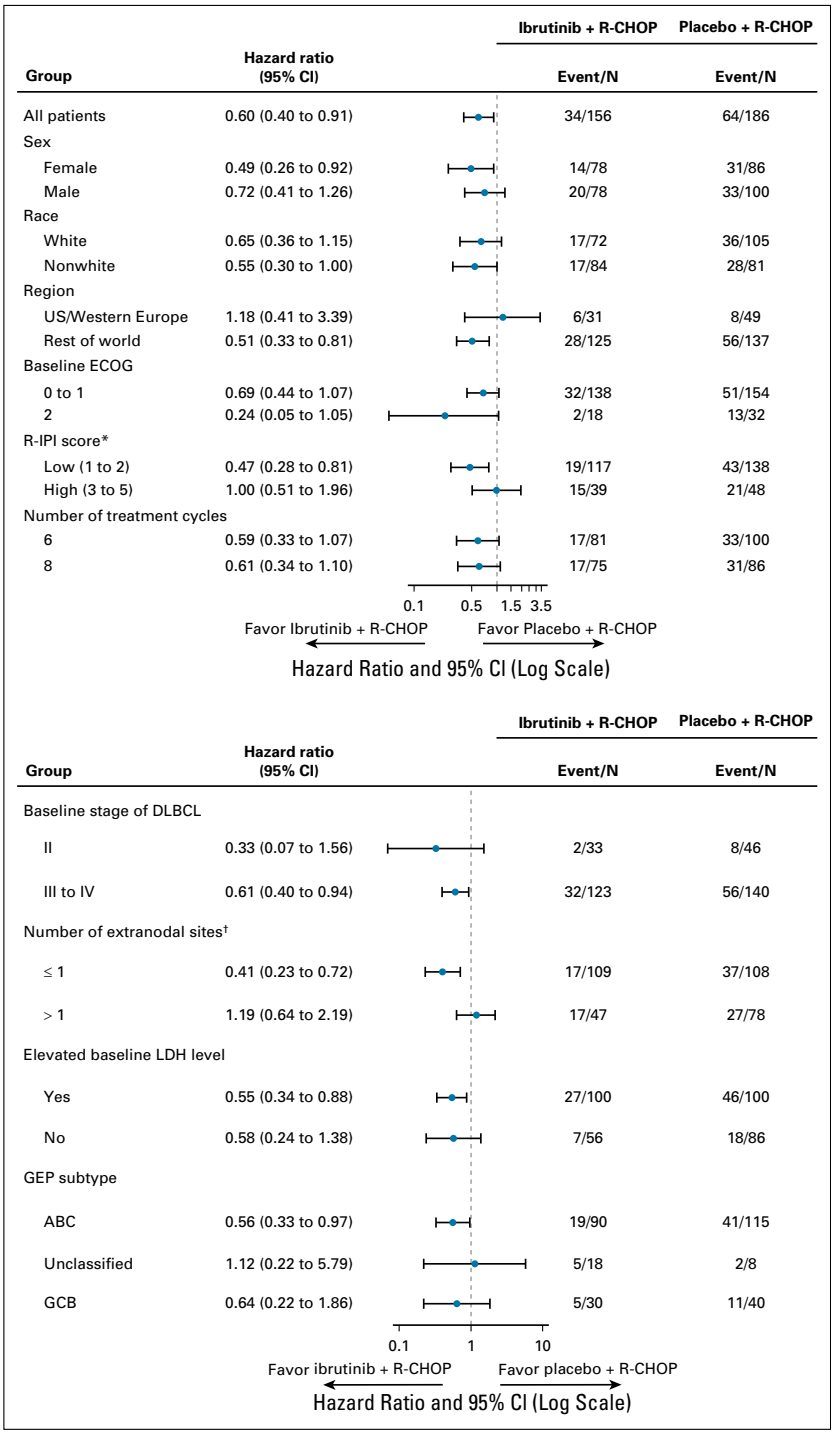

FIG A2. Subgroup analysis of event-free survival (EFS) in patients age younger than 60 years. ABC, activated B cell–like; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell–like; GEP, gene expression profiling; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI, Revised International Prognostic Index. (*) No patient had an R-IPI score of 5 because all patients were age younger than 60 years. (†) More than one extranodal lesion showed a hazard ratio of >1, but the CI was wide because of small event size.

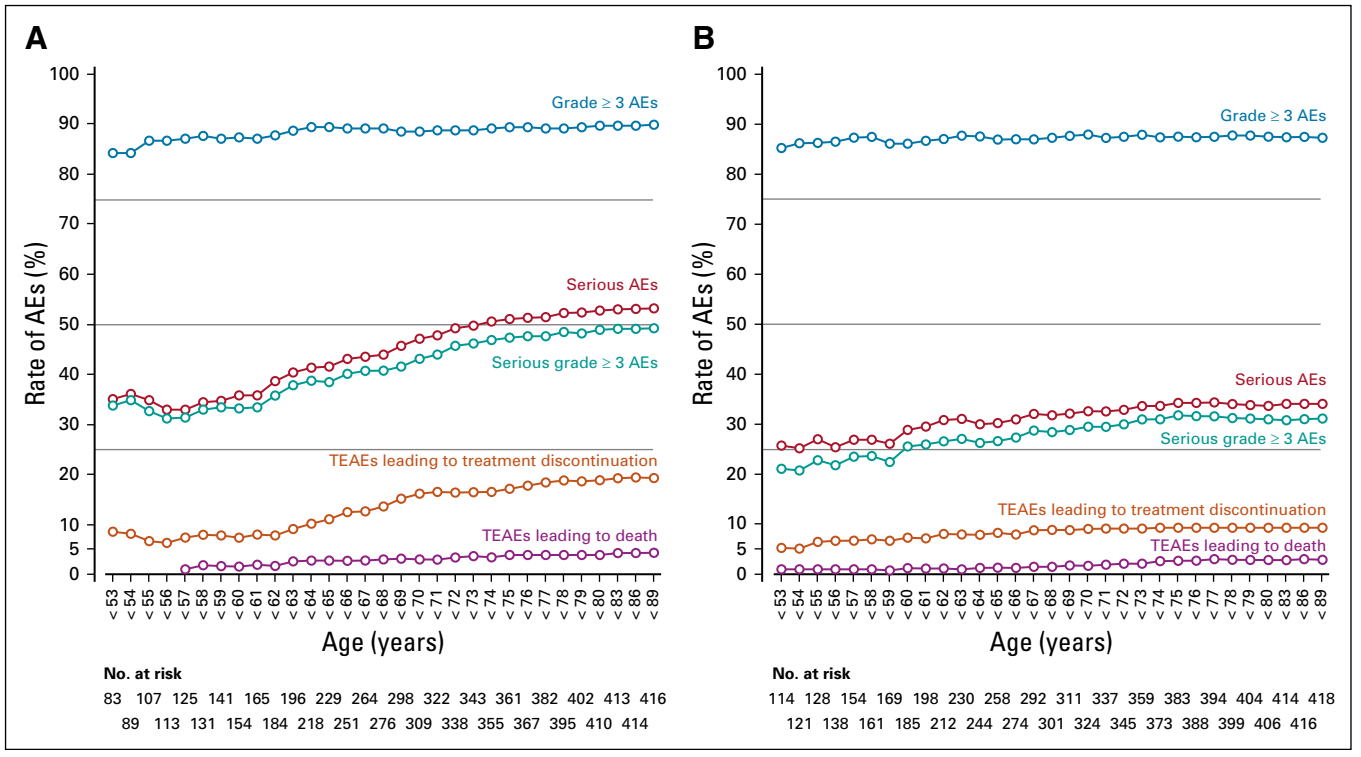

FIG A3. Adverse event (AE) rate by age cutoffs. (A) Ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. (B) Placebo plus R-CHOP arm. TEAEs, treatment-emergent AEs.

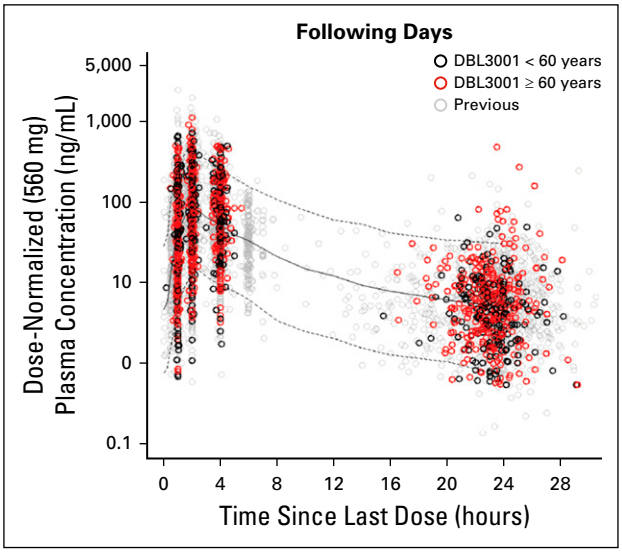

FIG A4. Steady-state ibrutinib concentrations by age. Solid line represents median; dashed lines represent fifth and 95th percentiles. In previous studies, ibrutinib was administered at the following doses: chronic lymphocytic leukemia: ibrutinib 420 mg per day, CLL3001, PCYC 1112, PCYC 1115, PCYC 1117, and PCYC 1102; mantle cell lymphoma: ibrutinib 560 mg per day, PCYC 1104, MCL2001, and MCL3001; miscellaneous doses, PCYC 04753.

TABLE A1. Patient Disposition

Disposition	No. (%)		
	Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)	Total (N = 838)
Did not receive any study treatment	3 (0.7)	1 (0.2)	4 (0.5)
Reasons for no study treatment received			
Adverse event	0	0	0
Lost to follow-up	0	0	0
Investigator or sponsor decision	1 (0.2)	0	1 (0.1)
Withdrawal of consent to treatment	0	0	0
Withdrawal of consent to study	2 (0.5)	1 (0.2)	3 (0.4)
Completed assigned 6 or 8 cycles of all study treatment	322 (76.8)	361 (86.2)	683 (81.5)
Discontinued all treatment	94 (22.4)	57 (13.6)	151 (18.0)
Reason for treatment discontinuation			
Progressive disease or relapse	7 (1.7)	9 (2.1)	16 (1.9)
Adverse event	51 (12.2)	22 (5.3)	73 (8.7)
Death	11 (2.6)	7 (1.7)	18 (2.1)
Investigator or sponsor decision	9 (2.1)	8 (1.9)	17 (2.0)
Patient refuses further treatment	16 (3.8)	11 (2.6)	27 (3.2)

Abbreviation: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A2. Survival Outcomes (36 months) in ITT Population

Outcome	% (95% CI)	
	Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)
EFS rate	69.6 (64.6 to 74.0)	67.4 (62.3 to 72.0)
No. of events	118	129
PFS rate	70.8 (65.9 to 75.2)	68.1 (63.0 to 72.7)
No. of events	113	126
OS rate	82.8 (78.6 to 86.2)	81.4 (77.1 to 85.0)
No. of events	69	72

Abbreviations: EFS, event-free survival; ITT, intent to treat; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A3. Best Response Rates in ITT Population and by Age

	No. (%)					
	ITT		Age < 60 Years		Age ≥ 60 Years	
Response	Ibrutinib + R-CHOP (n = 419)	Placebo + R-CHOP (n = 419)	Ibrutinib + R-CHOP (n = 156)	Placebo + R-CHOP (n = 186)	Ibrutinib + R-CHOP (n = 263)	Placebo + R-CHOP (n = 233)
Overall	374 (89.3)	390 (93.1)	146 (93.6)	176 (94.6)	228 (86.7)	214 (91.8)
Complete response	282 (67.3)	285 (68.0)	111 (71.2)	130 (69.9)	171 (65.0)	155 (66.5)
Partial response	92 (22.0)	105 (25.1)	35 (22.4)	46 (24.7)	57 (21.7)	59 (25.3)
Stable disease	2 (0.5)	4 (1.0)	1 (0.6)	2 (1.1)	1 (0.4)	2 (0.9)
Progressive disease	9 (2.1)	8 (1.9)	5 (3.2)	4 (2.2)	4 (1.5)	4 (1.7)

NOTE. Patients who died before first response assessment were considered nonresponders.
Abbreviations: ITT, intent to treat; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A4. Treatment (EFS, PFS, and OS) Effect and Age Interaction

Treatment Effect and Age (years) Interaction	*P*
Age × treatment (age as continuous variable)	.0365
Age < 60 × treatment	.0087
Age < 62 × treatment	.0054
Age < 65 × treatment	.0239

Abbreviations: EFS, event-free survival; OS, overall survival; PFS, progression-free survival.

TABLE A5. Baseline Characteristics in Patients Age Younger Than 60 Years

Characteristic	No. (%)	
	Ibrutinib + R-CHOP (n = 156)	Placebo + R-CHOP (n = 186)
Age, years		
Median	52.0	50.0
Range	19-59	19-59
Sex		
Female	78 (50.0)	86 (46.2)
Male	78 (50.0)	100 (53.8)
Ethnicity		
Hispanic or Latino	6 (3.8)	6 (3.2)
Not Hispanic or Latino	148 (94.9)	178 (95.7)
Unknown	0	1 (0.5)
Not reported	2 (1.3)	1 (0.5)
Race		
White	72 (46.2)	105 (56.5)
Black or African American	2 (1.3)	1 (0.5)
Asian	77 (49.4)	77 (41.4)
American Indian or Alaska Native	2 (1.3)	1 (0.5)
Other	1 (0.6)	0
Not reported	1 (0.6)	1 (0.5)
Multiple	1 (0.6)	1 (0.5)
Region (used in stratification)		
United States/Western Europe	31 (19.9)	49 (26.3)
Rest of the world	125 (80.1)	137 (73.7)
Geographic region		
United States	7 (4.5)	17 (9.1)
Canada	4 (2.6)	2 (1.1)
Europe	60 (38.5)	85 (45.7)
Latin America	6 (3.8)	3 (1.6)
Asia	75 (48.1)	75 (40.3)
Oceania	4 (2.6)	4 (2.2)
Time from initial diagnosis to random assignment, days		
Median	22.0	25.0
Range	6-98	6-349
Baseline stage of DLBCL at entry		
II	33 (21.2)	46 (24.7)
III	50 (32.1)	55 (29.6)
IV	73 (46.8)	85 (45.7)
Baseline lymphoma symptoms	69 (44.2)	89 (47.8)
Bone marrow involvement*	24 (15.4)	17 (9.1)
ECOG performance status		
0	80 (51.3)	92 (49.5)
1	58 (37.2)	62 (33.3)
2	18 (11.5)	32 (17.2)
Bulky tumor (long axis ≥ 10 cm)	21 (13.5)	30 (16.1)
Number of extranodal sites		
0	54 (34.6)	45 (24.2)
1	55 (35.3)	63 (33.9)
> 1	47 (31.0)	78 (41.9)
IPI/R-IPI score index number		
1	61 (39.1)	73 (39.2)
2	56 (35.9)	65 (34.9)
3	35 (22.4)	39 (21.0)
4	4 (2.6)	9 (4.8)
Elevated LDH	100 (64.1)	100 (53.8)
Planned No. of treatment cycles (used in stratification)		
6	81 (51.9)	100 (53.8)
8	75 (48.1)	86 (46.2)
GEP subtype		
ABC	90 (57.7)	115 (61.8)
Unclassified	18 (11.5)	8 (4.3)
GCB	30 (19.2)	40 (21.5)
Unknown†	17 (10.9)	20 (10.8)
Missing‡	1 (0.6)	3 (1.6)

Abbreviations: ABC, activated B cell–like; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell–like; GEP, gene expression profiling; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-IPI, revised International Prognostic Index.

*Bone marrow involvement was defined as any baseline aspirate or biopsy result of histology positive or histology negative/indeterminate that was confirmed positive by immunohistochemistry or flow cytometry.

†Sample available but unable to be classified because of failed testing.

‡Sample unavailable.

TABLE A6. Subsequent Disease-Specific Therapies in Safety Population and by Age

	No. (%)					
	Safety Population		Age < 60 Years		Age ≥ 60 Years	
Therapy	Ibrutinib + R-CHOP (n = 416)	Placebo + R-CHOP (n = 418)	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
High-dose therapy and/or stem cell transplantation	19 (4.6)	19 (4.5)	11 (7.1)	15 (8.1)	8 (3.1)	4 (1.7)
Anticancer surgery	2 (0.5)	6 (1.4)	0	2 (1.1)	2 (0.8)	4 (1.7)
Anticancer radiotherapy	9 (2.1)	10 (2.4)	3 (1.9)	5 (2.7)	6 (2.3)	5 (2.1)
Anticancer systemic therapy	69 (16.6)	86 (20.6)	25 (16.2)	40 (21.6)	44 (16.8)	46 (19.7)

Abbreviation: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A7. Treatment-Emergent AEs in Safety Population

	No. (%)					
	Ibrutinib + R-CHOP (n = 416)			Placebo + R-CHOP (n = 418)		
AE	All Grades	Grade 3 to 4	Grade 5	All Grades	Grade 3 to 4	Grade 5
Overall	416 (100.0)	356 (85.6)	18 (4.3)	414 (99.0)	352 (84.2)	12 (2.9)
Neutropenia	218 (52.4)	212 (51.0)	0	249 (59.6)	242 (57.9)	0
Anemia	179 (43.0)	84 (20.2)	0	116 (27.8)	44 (10.5)	0
Nausea	172 (41.3)	13 (3.1)	0	137 (32.8)	3 (0.7)	0
Diarrhea	155 (37.3)	23 (5.5)	0	83 (19.9)	3 (0.7)	0
Fatigue	141 (33.9)	21 (5.0)	0	102 (24.4)	1 (0.2)	0
Constipation	112 (26.9)	2 (0.5)	0	110 (26.3)	1 (0.2)	0
WBC count decreased	108 (26.0)	93 (22.4)	0	104 (24.9)	92 (22.0)	0
Febrile neutropenia	106 (25.5)	106 (25.5)	0	62 (14.8)	62 (14.8)	0
Thrombocytopenia	105 (25.2)	58 (13.9)	0	54 (12.9)	22 (5.3)	0
Neutrophil count decreased	101 (24.3)	92 (22.1)	0	81 (19.4)	78 (18.7)	0
Vomiting	96 (23.1)	14 (3.4)	0	59 (14.1)	4 (1.0)	0
Pyrexia	92 (22.1)	2 (0.5)	0	73 (17.5)	9 (2.2)	0
Platelet count decreased	85 (20.4)	44 (10.6)	0	38 (9.1)	14 (3.3)	0
Hypokalemia	77 (18.5)	33 (7.9)	0	23 (5.5)	5 (1.2)	0
Peripheral sensory neuropathy	77 (18.5)	15 (3.6)	0	63 (15.1)	3 (0.7)	0
Leukopenia	71 (17.1)	65 (15.6)	0	74 (17.7)	64 (15.3)	0
Alopecia	69 (16.6)	0	0	106 (25.4)	0	0
Stomatitis	66 (15.9)	5 (1.2)	0	47 (11.2)	3 (0.7)	0
Neuropathy peripheral	65 (15.6)	13 (3.1)	0	35 (8.4)	4 (1.0)	0
Decreased appetite	64 (15.4)	6 (1.4)	0	52 (12.4)	3 (0.7)	0
Cough	55 (13.2)	1 (0.2)	0	47 (11.2)	0	0
Edema peripheral	47 (11.3)	2 (0.5)	0	30 (7.2)	0	0
Pneumonia	46 (11.1)	27 (6.5)	1 (0.2)	20 (4.8)	11 (2.6)	1 (0.2)
Lymphocyte count decreased	44 (10.6)	40 (9.6)	0	42 (10.0)	36 (8.6)	0
Insomnia	39 (9.4)	2 (0.5)	0	43 (10.3)	1 (0.2)	0
Headache	29 (7.0)	2 (0.5)	0	43 (10.3)	0	0

Abbreviations: AE, adverse event; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A8. Primary Prophylactic, Secondary Prophylactic, and Overall Use (Prophylactic or Therapeutic) of G-CSF, Antibiotics, Antivirals, and Antifungals

	No. (%)					
	Overall Population		Age < 60 Years		Age ≥ 60 Years	
Therapy	Ibrutinib + R-CHOP (n = 416)	Placebo + R-CHOP (n = 418)	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 232)
G-CSF						
Primary*	100 (24.0)	88 (21.1)	22 (14.3)	29 (15.7)	78 (29.8)	59 (25.3)
Secondary†	175 (42.1)	179 (42.8)	65 (42.2)	75 (40.5)	110 (42.0)	104 (44.6)
Overall	361 (86.8)	356 (85.2)	127 (82.5)	155 (83.8)	234 (89.3)	201 (86.3)
Antibiotics						
Primary*	105 (25.2)	96 (23.0)	26 (16.9)	30 (16.2)	79 (30.2)	66 (28.3)
Secondary†	83 (20.0)	60 (14.4)	33 (21.4)	28 (15.1)	50 (19.1)	32 (13.7)
Overall	322 (77.4)	270 (64.6)	110 (71.4)	110 (59.5)	212 (80.9)	160 (68.7)
Antivirals						
Primary*	69 (16.6)	71 (17.0)	21 (13.6)	39 (21.1)	48 (18.3)	32 (13.7)
Secondary†	31 (7.5)	28 (6.7)	10 (6.5)	13 (7.0)	21 (8.0)	15 (6.4)
Overall	135 (32.5)	128 (30.6)	44 (28.6)	61 (33.0)	91 (34.7)	67 (28.8)
Antifungals						
Primary*	2 (0.5)	4 (1.0)	0	1 (0.5)	2 (0.8)	3 (1.3)
Secondary†	5 (1.2)	4 (1.0)	2 (1.3)	2 (1.1)	3 (1.1)	2 (0.9)
Overall	42 (10.1)	28 (6.7)	11 (7.1)	9 (4.9)	31 (11.8)	19 (8.2)

Abbreviations: G-CSF, granulocyte colony-stimulating factor; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Prophylactic therapy use within 5 days of first dose of study drug.
†Prophylactic therapy use beyond 5 days of first dose of study drug.

TABLE A9. Extent of Drug Exposure by Age

	No. (%)			
	Age < 60 Years		Age ≥ 60 Years	
No. of Cycles Received	Ibrutinib + R-CHOP (n = 154)	Placebo + R-CHOP (n = 185)	Ibrutinib + R-CHOP (n = 262)	Placebo + R-CHOP (n = 233)
Ibrutinib/placebo				
< 6	16 (10.4)	15 (8.1)	84 (32.1)	31 (13.3)
≥ 6	138 (89.6)	170 (91.9)	178 (67.9)	202 (86.7)
R-CHOP (any one or more components)				
< 6	11 (7.1)	13 (7.0)	69 (26.3)	26 (11.2)
≥ 6	143 (92.9)	172 (93.0)	193 (73.7)	207 (88.8)

Abbreviation: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE A1O. Ibrutinib $AUC_{0\text{-}24h}$ in DBL3001 and Previous Studies With Ibrutinib (560 mg per day) Monotherapy and by Age

	$AUC_{0\text{-}24h}$ * (mg × h/L)		
Study	**Overall**	**Age < 60 Years**	**Age ≥ 60 Years**
Study DBL3001	N = 357	n = 127	n = 230
Median	535	499	575
Minimum	83.3	83.3	116
Maximum	2059	1185	2059
Mean	619	531	667
SD	364	263	401
Studies PCYC 1104, MCL2001, MCL3001	N = 302	n = 62	n = 240
Median	544	466	556
Minimum	77.0	77.0	89.0
Maximum	3781	1460	3781
Mean	654	530	686
SD	477	309	507

Abbreviations: $AUC_{0\text{-}24h}$, area under the concentration-time curve from time 0 to 24 hours; SD, standard deviation.
*$AUC_{0\text{-}24h}$ was derived as apparent oral clearance of 560 mg per day.