original reports

Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412

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abstract

PURPOSE Lenalidomide combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (R2CHOP) in untreated diffuse large B-cell lymphoma (DLBCL) has shown promising activity, particularly in the activated B-cell–like (ABC) subtype. Eastern Cooperative Oncology Group (ECOG)-ACRIN trial E1412 was a randomized phase II study comparing R2CHOP versus R-CHOP in untreated DLBCL.

PATIENTS AND METHODS Patients with newly diagnosed DLBCL, stage II bulky-IV disease, International Prognostic Index (IPI) ≥ 2, and ECOG performance status ≤ 2 were eligible and randomly assigned 1:1 to R2CHOP versus R-CHOP for six cycles. Tumors were analyzed using the NanoString Lymph2Cx for cell of origin. The primary end point was progression-free survival (PFS) in all patients with the co-primary end point of PFS in ABC-DLBCL. Secondary end points included overall response rate (ORR), complete response (CR) rate, and overall survival (OS).

RESULTS Three hundred forty-nine patients were enrolled; 280 patients (145 R2CHOP and 135 R-CHOP) were evaluable: 94 were ABC-DLBCL, 122 germinal center B-cell–like-DLBCL, 18 unclassifiable, and 46 unknowns. Baseline characteristics were well-balanced between arms, and the median age was 66 (range, 24-92); 70% of patients had stage IV disease; 34%, 43%, and 24% had IPI 2, 3, and 4 or 5, respectively. Myelosuppression was more common in the R2CHOP arm. The ORR and CR rate were 92% and 68% in R-CHOP and 97% ($P = .06$) and 73% ($P = .43$) in the R2CHOP arm, respectively. The median follow-up was 3.0 years; R2CHOP was associated with a 34% reduction in risk of progression or death versus R-CHOP (hazard ratio [HR], 0.66 95% CI, 0.43 to 1.01) and 3-year PFS of 73% versus 61%, one-sided $P = .03$, and an improvement in OS (83% and 75% at 3 years; HR, 0.67; one-sided $P = .05$). The PFS HR for R2CHOP was 0.67 for ABC-DLBCL, one-sided $P = .1$.

CONCLUSION In this signal-seeking study, the addition of lenalidomide to R-CHOP (R2CHOP) improved outcomes in newly diagnosed DLBCL including patients with ABC-DLBCL.

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ASSOCIATED CONTENT

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Protocol

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

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INTRODUCTION

Approximately 40% of patients with diffuse large B-cell lymphoma (DLBCL) will relapse after initial chemoimmunotherapy, the majority of which will succumb to the disease.[1-3] Consequently, improving frontline therapy in DLBCL has been a focus of intense effort in the last decade.[4] Much of the effort has focused on recognizing the molecular heterogeneity of DLBCL. Gene expression profiling (GEP) identifies three cell-of-origin (COO) subtypes: activated B-cell–like (ABC), germinal center B-cell–like (GCB), and unclassifiable subtypes, of which ABC subtype was shown to be associated with worse outcomes in retrospective studies.[5]

Lenalidomide has single-agent activity in relapsed and refractory DLBCL,[6,7] and it can be safely combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (R2CHOP) without affecting the dose intensity of chemoimmunotherapy. R2CHOP showed promising results in single-arm phase II studies, particularly in non-GCB-DLBCL.[8,9]

Based on these results, the Eastern Cooperative Oncology Group (ECOG) developed a randomized phase II study (E1412) comparing R2CHOP with R-CHOP in patients with newly diagnosed DLBCL. The design of E1412 had three principal goals. The first was to evaluate the activity of lenalidomide with R-CHOP in all

CONTEXT

Key Objective

The addition of novel agents to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and selection of patients based on cell of origin (COO) have been postulated as the best ways to improve outcomes in diffuse large B-cell lymphoma (DLBCL). Lenalidomide has been a prime candidate for addition to R-CHOP (R2CHOP).

Knowledge Generated

R2CHOP has been tested in two independent randomized trials: a phase III study (ROBUST) in activated B-cell–like (ABC)-DLBCL and a phase II study (E1412) in all DLBCL regardless of COO, allowing recruitment without the delay of patients with rapidly progressive disease. E1412 also used a higher lenalidomide dose among other differences.

Although E1412 showed the potential benefit of adding lenalidomide to R-CHOP, considering it was a signal-seeking study and a larger ROBUST study did not show any benefit, the results seen in E1412 are not practice changing.

Relevance

The E1412 results provide impetus to study lenalidomide and novel lenalidomide analogues and highlight the importance of trial design when incorporating biomarkers in frontline studies.

patients with DLBCL, regardless of molecular subtype. Preclinical studies of lenalidomide suggested preferential direct cytotoxicity in ABC subtype. However, lenalidomide could have a potential impact on other mechanisms such as immunomodulation and enhancing antibody-dependent cytotoxicity in GCB subtype.[10] Indeed, lenalidomide shows activity in GCB subtype in a relapsed or refractory (R/R)-DLBCL, albeit less so than in ABC subtype.[7] Interestingly, the benefit of lenalidomide as maintenance after R-CHOP was seen primarily in the GCB subtype, suggesting a different mechanism of action in GCB subtype.[11] The second goal was to maximize synergy with chemoimmunotherapy early in the cycle while allowing hematological recovery. A higher dose of lenalidomide (25 mg) was selected for days 1-10 of a 21-day cycle based on data from phase I and single-arm phase II studies.[8,12] Most of the data regarding single activity of lenalidomide in the R/R-DLBCL were based on a 25 mg daily dose.[6,7] The third goal was to facilitate easy enrollment of patients in a large intergroup study without delay. We therefore elected not to use real-time biomarker selection for COO to assess patient eligibility. Centers participating in the study were allowed to use local laboratory and pathology to determine eligibility, and the study assumed that some of the patients would be rendered ineligible after central pathology review. Here, we present the results of the E1412 study.

PATIENTS AND METHODS

This prospective randomized multicenter phase II study was conducted as a US Intergroup Study led by ECOG-ACRIN with participation of SWOG and Alliance and supported by NCI. This study was approved by the IRB at respective participating institutions, and all patients provided written study consent.

Patients

Eligible patients were adults (≥ 18 years) with newly diagnosed, untreated, histologically proven DLBCL, measurable, stage II bulky (> 10 cm) to IV, ECOG performance status 0-2, and International Prognostic Index (IPI) 2-5. Patients with severe systemic symptoms or compressive disease were allowed treatment with up to 1 mg/kg/day prednisone for ≤ 7 days before beginning the study treatment. Adequate organ function was required: absolute neutrophil count (ANC) > 1,500/μL, platelet count > 100,000/μL, total bilirubin < 1.5 times upper limit of normal (ULN) (if bilirubin was > 1.5 × ULN, the direct bilirubin must have been normal), alkaline phosphatase ≤ 3 × ULN, aspartate transferase ≤ 3 × ULN (unless evidence of liver involvement, than < 5 times normal), creatinine ≤ 2 × ULN (or creatinine clearance > 30 mL/min), and left ventricular ejection fraction of > 45%.

Exclusion criteria included: known CNS lymphoma, history of deep venous thrombosis or embolism, or known thrombophilia (unless willing to be on full anticoagulation—Warfarin or low-molecular-weight heparin) if randomly assigned to the R2CHOP arm, and AIDS-related conditions (other than the presenting DLBCL).

Central Pathology Review

Patients were required to have histologically and immunophenotypically confirmed DLBCL expressing CD20 by central pathology review based on WHO criteria at the time of study initiation.[13] Patients with transformed lymphoma and composite lymphoma in the diagnostic tissue (concomitant DLBCL and follicular lymphoma or another low-grade lymphoma component) were excluded, as were patients with primary mediastinal large B-cell lymphoma. Patients with tumors of DLBCL morphology and *MYC* translocation alone or in combination with *BCL2* and/or *BCL6* translocations by fluorescence in situ hybridization (FISH) (so-called double-hit and triple-hit lymphomas) were eligible; *MYC* FISH testing before study enrollment was not required. In the original study design, the central pathology review was conducted after study entry. However, after enrollment of 208 patients, high ineligibility rate by

central pathology review (74 of 208 or 35% of patients) primarily because of composite histology and alternative diagnosis (n = 47) and/or inadequate tissue or its quality for central confirmation of diagnosis (n = 27) became apparent. The study was amended to require rapid real-time pathology review for eligibility, thereby reducing ineligibility as described elsewhere.[14] In brief, a real-time central pathology review was performed within 48 hours and centers were allowed to enroll patients only if a combined morphologic and immunophenotypic diagnosis of DLBCL was confirmed by study pathologists (step 0). Following this amendment, 214 patients were screened and 147 patients were enrolled. Importantly, this requirement did not affect the median time from diagnosis to treatment (an important prognostic variable)[15]; it was 21 days before and after the institution of the real-time pathology eligibility requirement.

Cell-of-Origin Assessment

Paraffin-embedded tumor tissues from the initial biopsies were analyzed for COO by the NanoString Lymph2Cx GEP assay[16] performed centrally (D.W.S.).

Treatment and Supportive Care

Patients received R-CHOP21 (one dose each of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 all on day 1, and prednisone 100 mg/m^2 once a day on days 1-5 of each cycle every 21 days $\times$ 6 cycles). Patients in the R2CHOP arm, in addition to RCHOP21, received 25 mg of lenalidomide daily days 1-10 of each cycle. All patients received prophylactic G-CSF (pegfilgrastim or filgrastim per local practice), and patients taking lenalidomide received aspirin 325 mg once a day as thromboembolism prophylaxis. Patients unable to take aspirin or with history of thrombosis or pulmonary embolism were required to be on full anticoagulation. Antiemetics, tumor lysis prophylaxis, and other supportive care were applied per local practice. ANC and platelet count $\geq$ 1,500/μL and $\geq$ 75,000/μL at the time of retreatment were required, respectively. Lenalidomide was not held or reduced midcycle regardless of ANC nadir unless ANC was $<$ 500/μL $>$ 7 days and/or platelet nadir was below 10,000/μL or $<$ 25,000/μL for 7 days to maintain dose intensity of lenalidomide.

Statistical Analysis

Patients were randomly assigned 1:1 and stratified by IPI (2 of 3 *v* 4 of 5) and age ($<$ 60 *v* $\geq$ 60 years old) to R2CHOP21 versus R-CHOP for six cycles (Fig 2A). The primary end point was progression-free survival (PFS) defined as the occurrence of progression or death from the time of random assignment. With anticipated 289 evaluable patients (102 ABC-DLBCL), the study was designed to have 89% power at one-sided 0.1 significance level with 89 PFS events for detecting a hazard ratio (HR) of 0.59 in all patients and 81% power at one-sided 0.125 significance level with 40 PFS events for an HR of 0.52 in ABC-DLBCL. Secondary end points included overall response rate (ORR), complete response (CR) rate,[17] and overall survival (OS). Cochran-Mantel-Haenszel (CMH) test was used to compare ORR and CR rate stratified on IPI and age. Kaplan-Meier method was used to estimate PFS and OS, and stratified log-rank test and Cox model were used to compare between arms and estimate HR. All randomly assigned patients who were eligible and received the study treatment were deemed evaluable and included in the primary analysis. Intent-to-treatment analysis, which excludes only pathology ineligible patients, was conducted as the secondary analysis. One-sided *P*-values were reported for PFS and OS end points per study design. Two-sided *P*-values were presented for all other efficacy end points and all safety outcomes (Appendix Table A1, online only).

RESULTS

Patient Characteristics and Disposition

Between August 2013 and January 2017, 349 patients were enrolled and randomly assigned in the study. Twelve patients did not start planned treatment (seven in the R2CHOP arm and five in the R-CHOP arm) because of consent withdrawal (n = 5), ineligibility (n = 5), death (n = 1), and the need to start alternative therapy urgently (n = 1). The safety analysis population included all 337 treated patients, 166 in the R2CHOP arm and 171 in the R-CHOP arm. Fifty-four patients were deemed ineligible for efficacy evaluation secondary to central pathology review exclusion because of lack of material either for confirmation of local diagnosis or for ancillary studies required by the study or to ineligible diagnoses. Three patients were deemed ineligible because of not meeting other eligibility criteria (Fig 1).

Two hundred eighty patients (145 in R2CHOP and 135 in R-CHOP) were evaluable (eligible and treated) for efficacy analysis. Baseline patient characteristics were balanced between arms with a median age of 66 (range, 24-92). The majority of patients had relatively high-risk disease: 96% had stage III or IV, 46% had $\geq$ 2 extra-nodal site involvement, and 24% had a high IPI of 4 or 5 (Table 1). The clinical characteristics were also balanced in the patients with ABC analyzed for co-primary end point (Table 1). The median time from diagnosis to treatment was 21 days (21 days in R2CHOP and 19 days in the R-CHOP arm); only 22% of patients were treated more than 31 days from diagnosis (Appendix Fig A2, online only).

COO Analysis

COO analysis was attempted in all patients with available material by Lymph2Cx, and the results were obtained for 234 patients of 280 evaluable patients: 122 patients (52%) had GCB-DLBCL, 94 (40%) had ABC-DLBCL, and 18 (8%) were unclassifiable (Table 1). COO by GEP was unable to be assessed in 46 of 280 (16%) evaluable patients because of insufficient material (n = 34), low RNA quantity (n = 10), or low RNA quality (n = 2).

Efficacy

The ORR and CR rate were 92% and 68% in R-CHOP and 97% (*P* = .06) and 73% (*P* = .43) in R2CHOP arms,

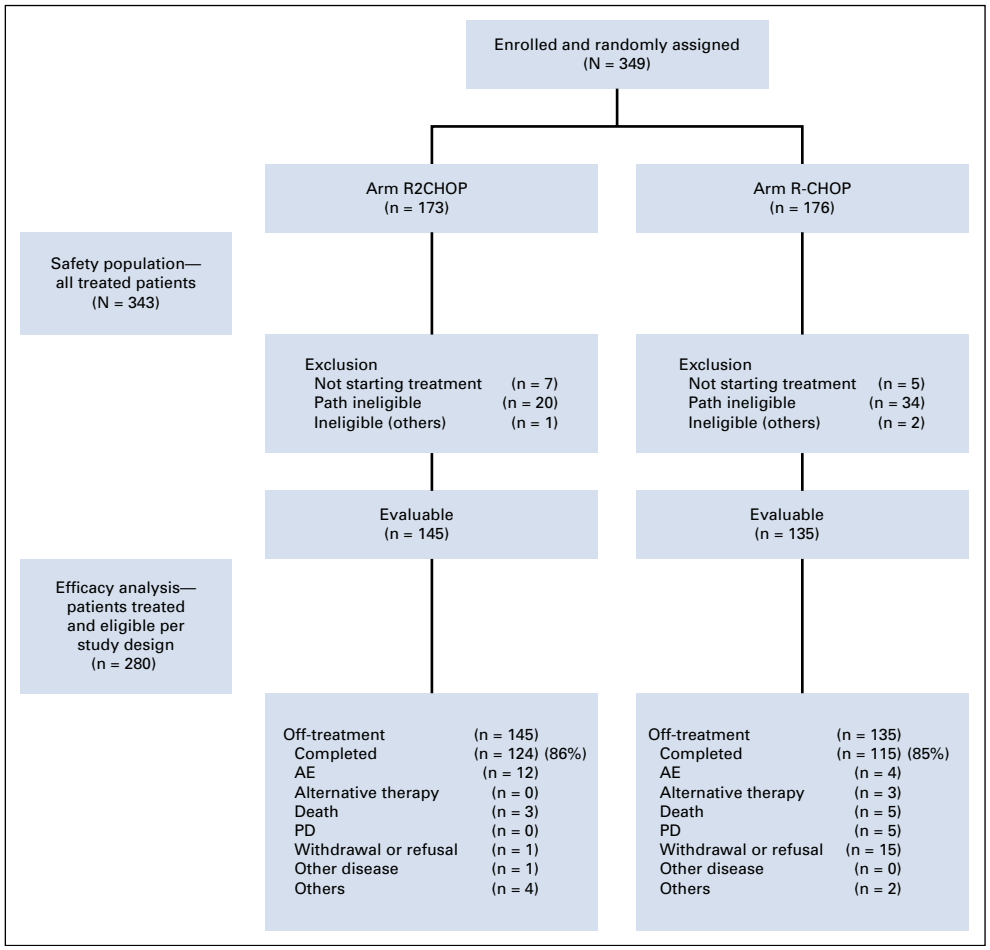

FIG 1. E1412 CONSORT diagram. AE, adverse event; PD, progression of disease; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

respectively. The median follow-up was 3.0 years. The study met its prespecified primary and co-primary end points. R2CHOP was associated with 34% reduction in risk of progression or death compared with R-CHOP, an HR of 0.66 with one-sided 90% CI < 0.88 (95% CI, 0.43 to 1.01), and *P* (one-sided) = .03 (Fig 2A). The 1-, 2-, and 3-year PFS was 84% versus 73%, 76% versus 69%, and 73% versus 62% for R2CHOP versus R-CHOP, respectively. OS was also superior with R2CHOP versus R-CHOP with a 3-year OS of 83% versus 75% (one-sided *P* = .05), respectively (Fig 2B). Analysis of PFS by COO using GEP showed improved outcome with R2CHOP in the 94 patients with ABC (HR = 0.64; one-sided 90% CI upper limit, 1.01; two-sided 95% CI, 0.31 to 1.29; one-sided *P* = .1) (Fig 3A). In the 122 patients with GCB, the HR was 0.82 (one-sided 90% CI upper limit, 1.27; two-sided 95% CI, 0.43 to 1.59) (Fig 3C). The subset analysis of PFS showed that R2CHOP was associated with a benefit in most groups (Fig 4). However, the power of analysis was limited by a relatively small number of patients in most subgroups. Outcomes in the intend to treat population and in patients age < 60 and ≥ 60 years are shown in Appendix Table A1 and Appendix Figure A2.

Safety and Dose Modifications

Adverse events (AEs) were largely as expected with R-CHOP. Significantly different rates of grade ≥ 3 AEs between R2CHOP and R-CHOP arms were found for diarrhea (6% *v* 1%, *P* = .005), anemia (29% *v* 20%, *P* = .03), febrile neutropenia (25% *v* 14%, *P* = .003), thrombocytopenia (34% *v* 13%, *P* < .001), and electrolyte abnormalities (5% *v* 2%, *P* = .06), respectively (Table 2). 86% and 85% of patients completed the intended six cycles of therapy in R2CHOP and R-CHOP arms, respectively. AEs were the reason for discontinuation of intended treatment in 12 (8%) patients in the R2CHOP arm (discontinuation of lenalidomide alone in seven and R-CHOP and lenalidomide in five) and four (3%) patients in the R-CHOP arm (discontinuation of R-CHOP). There were nine treatment-related deaths, two in the R2CHOP arm (lung infection, n = 2) and seven in the R-CHOP arm (lung

TABLE 1. Patient Characteristics

		All Patients (n = 280)		ABC-DLBCL (n = 94)	
	All (n = 280)	R2CHOP (n = 145)	R-CHOP (n = 135)	R2CHOP (n = 44)	R-CHOP (n = 50)
Age (years): median (range)	66 (24-92)	67 (24-88)	66 (37-92)	67 (24-88)	67 (37-80)
Time Dx to Rx (d): median (range)	21 (1-134)	21 (1-111)	19 (2-134)	21 (5-83)	19 (2-134)
Sex—male: n (%)	170 (61)	94 (65)	76 (56)	30 (68)	21 (42)
Stage III and/or IV: n (%)	271 (97)	141 (97)	130 (96)	44 (100)	47 (97)
Bulky disease ≥ 7 cm: n (%)	119 (43)	60 (41)	59 (43)	13 (30)	22 (44)
Extra nodal sites ≥ 2: n (%)	128 (46)	65 (45)	63 (47)	17 (40)	16 (32)
ECOG PS: n (%)					
0	103 (37)	56 (39)	47 (35)	18 (41)	17 (34)
1-2	177 (63)	89 (61)	88 (65)	26 (59)	33 (66)
IPI: n (%)					
2	95 (34)	49 (33)	45 (34)	16 (36)	22 (44)
3	119 (42)	63 (43)	57 (42)	19 (43)	20 (40)
4-5	66 (24)	33 (23)	33 (24)	9 (20)	8 (16)
Cell of origin: n					
ABC	94	44	50		
GCB	122	66	56		
Unclassified	18	9	9		
Unknown	46	26	20		

Abbreviations: ABC, activated B-cell–like; DLBCL, diffuse large B-cell lymphoma; Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell–like; IPI, International Prognostic Index; PS, performance status; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP; Rx, treatment.

infection n = 1, sepsis or febrile neutropenia n = 5, and adult respiratory distress syndrome n = 1). To date, there have been 19 secondary neoplasms: 12 in the R2CHOP arm and seven in the R-CHOP arm (Appendix Table A2, online only).

DISCUSSION

Lenalidomide has long been a prime candidate to be combined with chemoimmunotherapy in frontline therapy of DLBCL based on its novel mechanisms of activity, single-agent

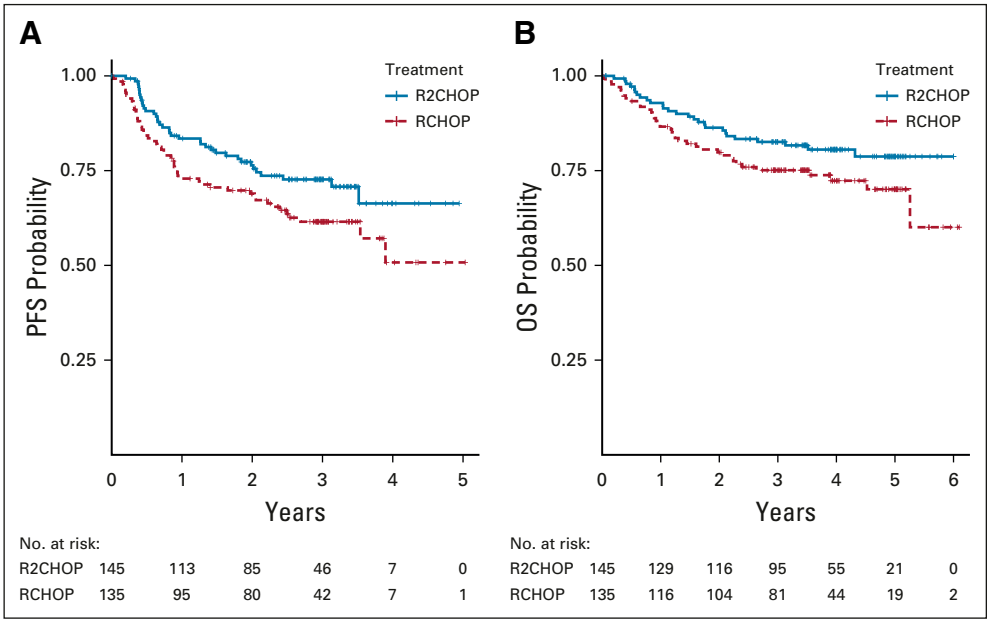

FIG 2. Kaplan-Meier estimate of (A) PFS for all patients, n = 280 and (B) OS for all patients, n = 280. OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

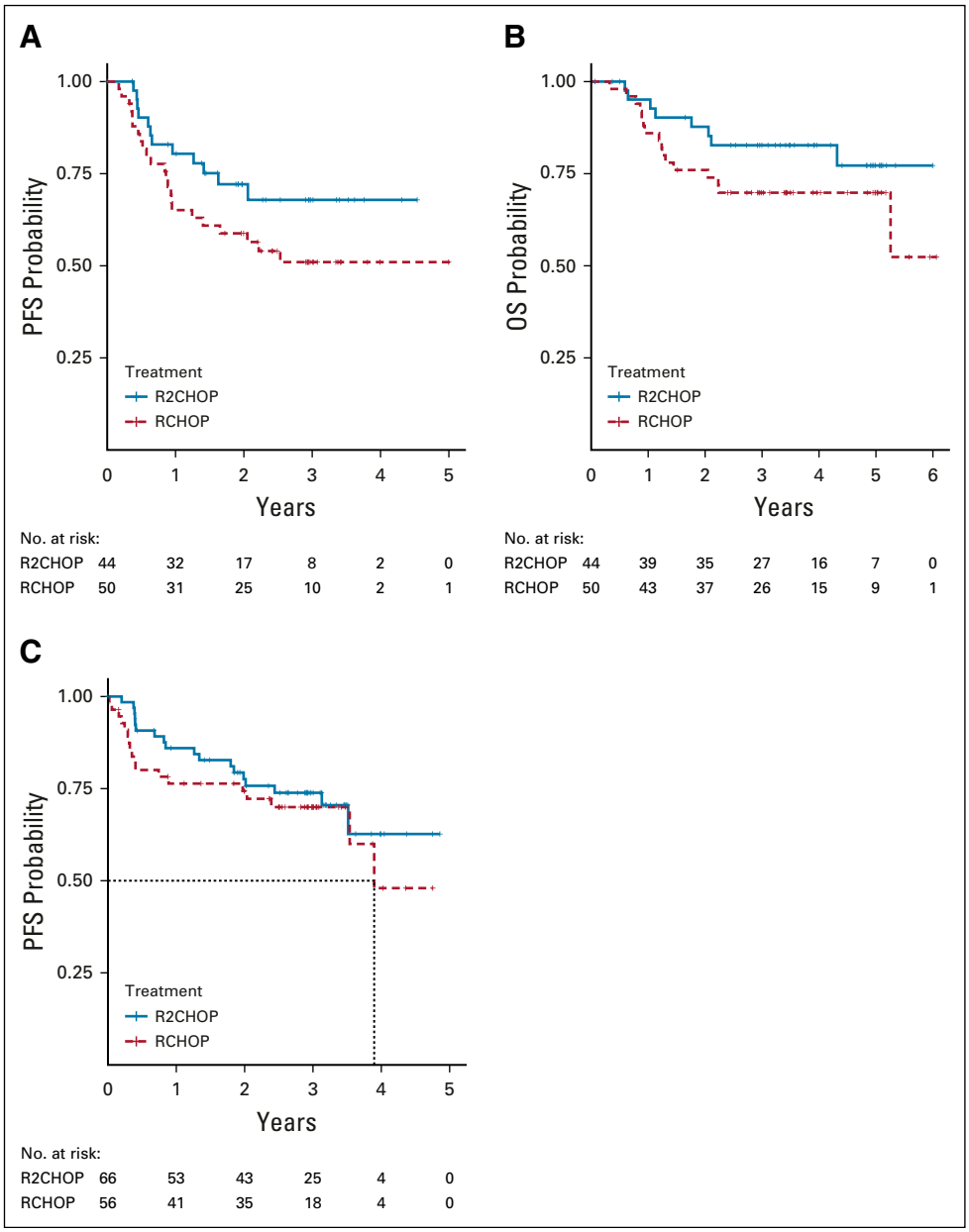

FIG 3. Kaplan-Meier estimate of (A) PFS in patients with ABC, n = 94; (B) OS for patients with ABC; and (C) PFS in patients with GCB. ABC, activated B-cell–like; GCB, germinal center B-cell–like; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

activity, synergy with rituximab and chemotherapy, and modest toxicity profile allowing safe combination with R-CHOP. Single arm phase II studies combining lenalidomide with R-CHOP show promising results in patients with newly diagnosed and untreated DLBCL, particularly in the ABC subtype.[4,8,9]

In the current randomized study, the addition of lenalidomide to R-CHOP resulted in a 34% reduction in risk of progression or death in all comers when compared with R-CHOP alone and in the co-primary end point of improved PFS in ABC subtype of DLBCL. Subset analysis showed mostly consistent benefit from adding lenalidomide across the clinical subsets, albeit small numbers of patients in each subgroup warrant caution in interpretation. A subset analysis from a randomized phase III study of ibrutinib plus R-CHOP versus R-CHOP (PHOENIX) in patients with non-GCB DLBCL suggested better outcomes in patients < 60 years of age.[18] A similar subset analysis of E1412 demonstrated trend toward more pronounced benefit from addition of lenalidomide in younger patients (Fig 4, Fig A2) with less toxicity than in older patients (Appendix Tables A3

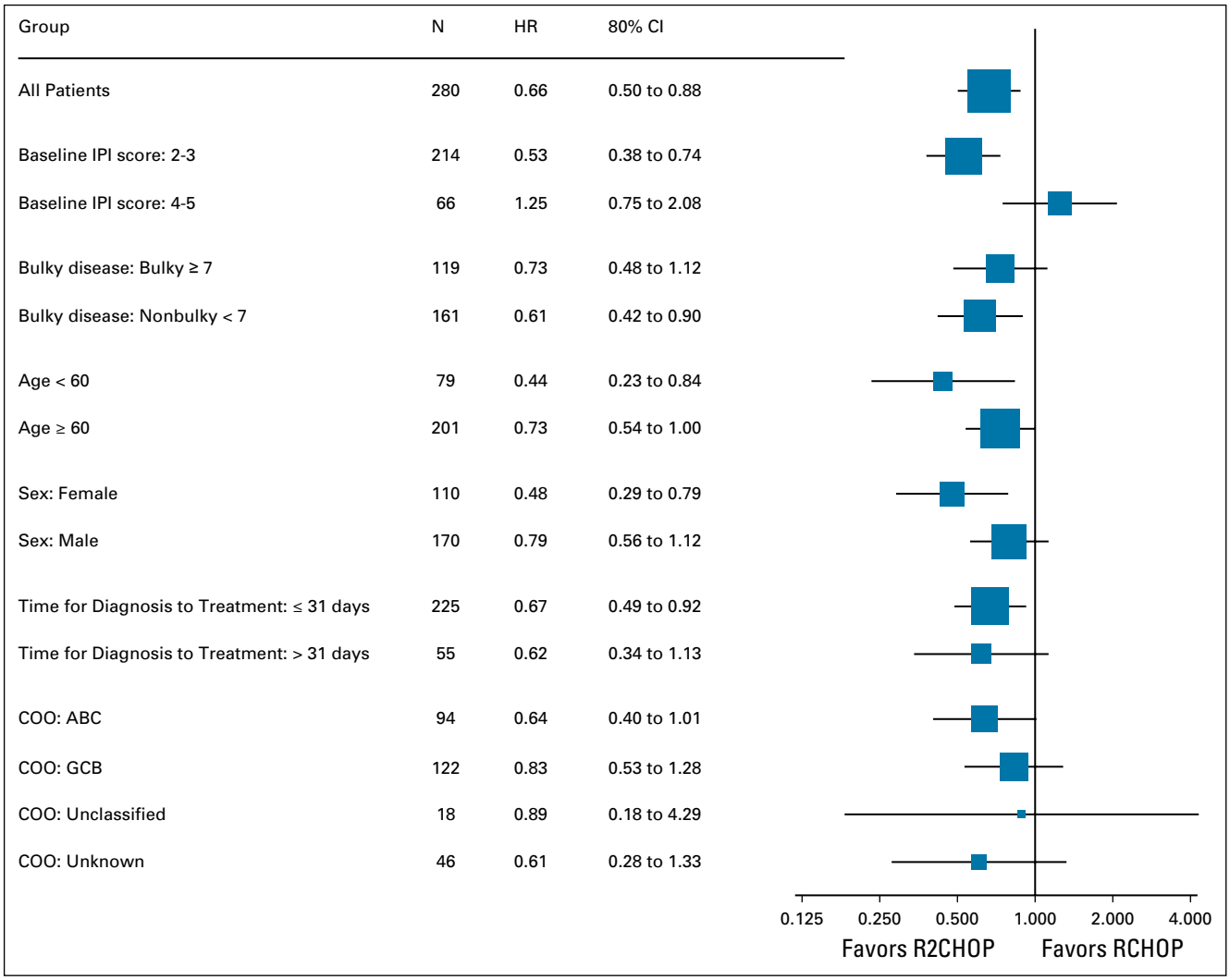

FIG 4. Forest plot of treatment effect (HR, 80% CI) within subsets of interest. ABC, activated B-cell–like; COO, cell of origin; GCB, germinal center B-cell–like; HR, hazard ratio; IPI, International Prognostic Index.

and A4, online only); however, a small number of patients limit interpretation of this finding.

The E1412 study was designed as a signal-seeking study to be validated in a further phase III study and to test the best platform for future studies. The recently presented phase III ROBUST study,[19] evaluating R2CHOP versus R-CHOP plus placebo, was not designed as the validation study for E1412 because it was conducted at the same time and with several major differences. Important differences between E1412 and ROBUST were the targeted patient population, lenalidomide dose and schedule, and the ability to promptly enroll high-risk patients, with E1412 being a smaller study with wider confidence intervals.[19,20] Although these differences could have played a role in the discordant results of both trials, the experience with E1412 allows one to draw important implications for future frontline studies in DLBCL. The study was designed to allow for accrual of high-risk, rapidly progressing patients based on local laboratories and local pathology review, but later changed to a rapid central pathology review for patient enrollment. The initial design was based on emerging evidence that time from diagnosis to treatment is a critical variable and that complicated trials with central review of biomarkers or other baseline data are biased toward patients who can wait, and such patients tend to have better outcomes.[15] The strategy applied in E1412, allowing local laboratory parameters to assess eligibility criteria, local pathology, and utilization of an integral yet not real-time biomarker, as well as allowing pretreatment with steroids in symptomatic patients, was successful in overcoming some of the obstacles for enrollment of rapidly progressing and sick patients with the median time from diagnosis to treatment of 21 days. Because of this strategy, the study was designed to compensate for some initially enrolled patients found to be ineligible by central pathology review, either because of not meeting diagnostic criteria or because of sites unable to submit adequate

TABLE 2. Common (> 5%) Treatment-Related Toxicities and Toxicities of Special Interest, Grade 3 or More (Safety Population, N = 337)

	Treatment Arm					
	R2CHOP (n = 166)			R-CHOP (n = 171)		
	Grade			Grade		
	3	4	5	3	4	5
Toxicity Type	%	%	%	%	%	%
Anemia	25	4	—	18	2	—
Febrile neutropenia	20	5	—	11	1	1
Fatigue	10	—	—	6	—	—
Sepsis	—	7	—	—	4	2
Lung infection	5	1	1	4	—	1
Neutropenia	9	51	—	12	42	—
Thrombocytopenia	14	20	—	4	9	—
Hypokalemia	5	1	—	1	1	—
Hyponatremia	5	—	—	4	—	—
Hypophosphatemia	5	—	—	1	—	—
Generalized muscle weakness	5	—	—	2	—	—
Rash maculopapular	2	—	—	—	—	—
Thromboembolic event	3	1	—	2	—	—

Abbreviations: R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

tissue to verify diagnosis and assess COO. In E1412, ineligibility because of these factors was 35% before amendment (20% because of composite DLBCL or alternative diagnosis, and 15% because of site unable to submit diagnostic tissue for retrospective review, despite study eligibility criteria requiring confirmation that tissue is available for central pathology review and biomarker assessment). This high ineligibility rate by central pathology review resulted in the development of a rapid registration step 0 real-time central pathology review that was able to be performed without a negative impact on the time from diagnosis to treatment. The experience with step 0 rapid central pathology review in E1412 as US intergroup study was published elsewhere, demonstrating the feasibility of this approach.[14]

There are two broad strategies of incorporating new agents into R-CHOP model: to extend duration of targeted agent exposure or to maximize exposure early in the cycle.[4] E1412 used the latter approach to maximize synergy with chemoimmunotherapy early in the cycle while allowing hematological recovery. The dose of lenalidomide was 25 mg daily, which was supported by effectiveness in R/R-DLBCL.[6,7] This strategy of a higher dose but administered for only 10 of the 21 days was indeed successful in E1412, and while associated with a higher incidence of neutropenia, febrile neutropenia, and thrombocytopenia, these toxicities did not result in an increase in rates of treatment-related deaths or bleeding complications. Overall treatment discontinuations did not differ between arms, and while 12 (9%) patients discontinued study treatment because of AEs in R2CHOP, this number included seven patients who discontinued lenalidomide only—representing only 5% of treated patients. Although optimal dose versus duration of exposure may depend on the experimental agent added to R-CHOP, R2CHOP in E1412 provides an example of the incorporation of a potentially myelosuppressive agent early in the cycle at doses shown to be effective in relapse and refractory setting. Although the number of secondary malignancies was small, careful further follow-up is required in this regard.

E1412 was designed with co-primary end point of improvement of PFS in ABC-DLBCL, as preclinical studies and single-arm trials indicated that this population is particularly likely to benefit from the addition of lenalidomide.[8] Indeed, the improvement of outcomes in patients with the ABC subtype had the largest impact on the overall positive study results. It is now established that DLBCL subtypes defined by COO are themselves molecularly heterogenous with different underlying genetic changes.[21,22] Recently published data from a single-arm R2CHOP study identified a specific molecular signature linked to the benefit from the addition of lenalidomide to R-CHOP that was seen in both ABC and GCB subtypes of DLBCL, albeit enriched in the ABC subtype.[23] This observation is consistent with the clinical results in E1412 and supports the notion that COO appears to be inadequate to support a precision medicine approach in DLBCL. Although further molecular studies evaluating mutation

clusters and other molecular markers associated with benefit of lenalidomide in E1412 are ongoing, E1412 demonstrates both feasibility and the need for evaluation of the effects of new therapy in all molecular subsets of DLBCL while allowing for a co-primary end point in a molecular subset of highest interest.

In summary, the ECOG-ACRIN E1412 study demonstrated a potential clinical benefit of adding lenalidomide to R-CHOP in newly diagnosed patients regardless of COO and in patients with ABC-DLBCL. This benefit was consistent across subgroups and translated to OS benefit of R2CHOP. No new safety signals were observed. Although the E1412 results are not practice changing, considering its signal-seeking nature and conflicting results from phase III ROBUST study, these results support further studies of lenalidomide and/or novel lenalidomide analogues in frontline therapy of DLBCL.

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Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412

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APPENDIX

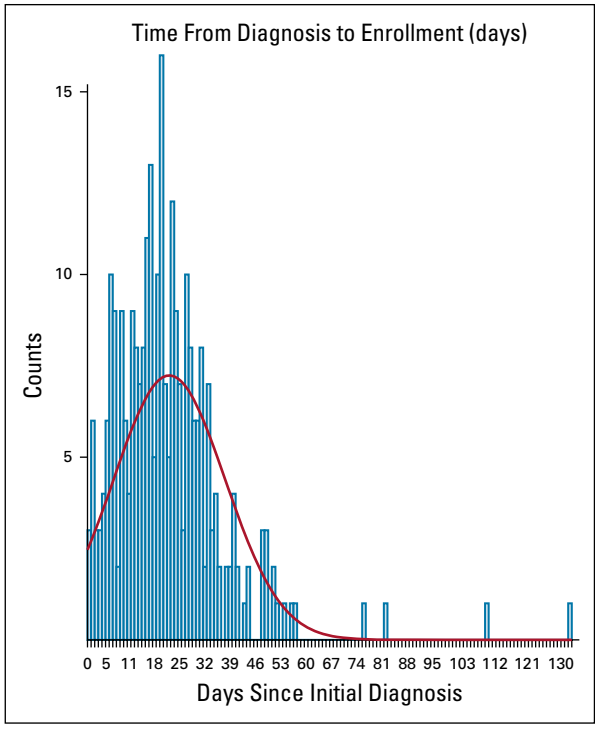

FIG A1. Time from diagnosis to treatment in E1412.

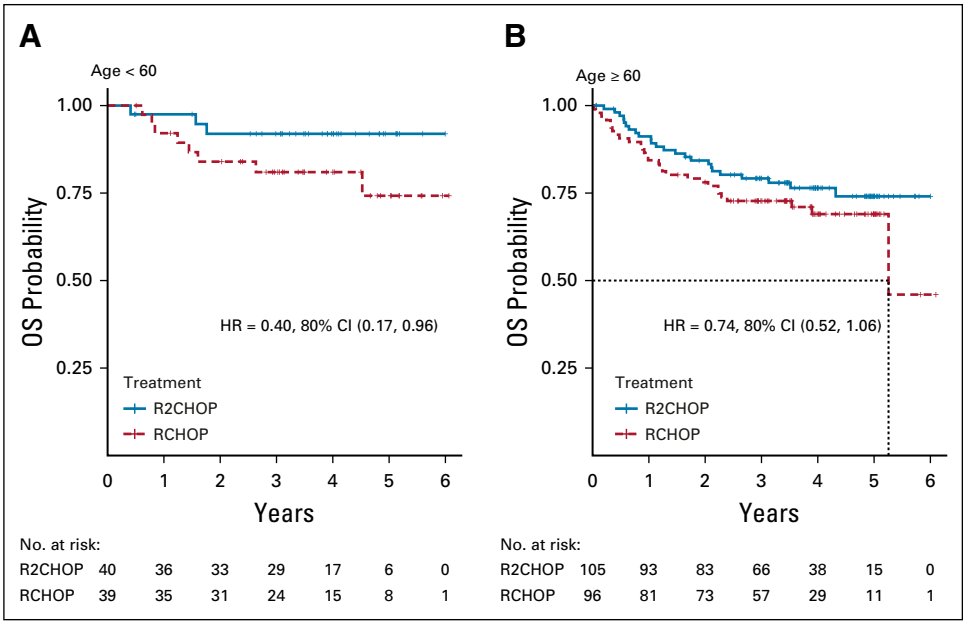

FIG A2. OS in patients age ≥ 60. HR, hazard ratio; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

TABLE A1. PFS and OS Outcomes in the ITT Population Analysis

	PFS		OS	
R2CHOP *v* R-CHOP	**All Patients**	**ABC Subset**	**All Patients**	**ABC Subset**
Stratified HR (80% CI)	0.70 (0.54 to 0.92)	0.61 (0.39 to 0.96)	0.72 (0.53 to 0.99)	0.57 (0.32 to 0.99)
Stratified one-sided *P*	.045	.1	.1	.1

Abbreviations: ABC, activated B-cell–like; HR, hazard ratio; ITT, intent-to-treatment; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

TABLE A2. List of Second Primary Cancer by Treatment Arms

	Treatment		
	R2CHOP	**R-CHOP**	**All**
	n	**n**	**n**
Second cancer			
AML	3	0	3
Bladder and urinary tract	0	1	1
Breast	2	2	4
Liver, gall bladder, and bile duct	0	1	1
Lung cancer	2	0	2
Myelodysplastic syndrome	1	0	1
Non–small-cell lung cancer	1	0	1
Others	2	1	3
Pancreas adenocarcinoma or others	0	1	1
Skin cancer not melanoma	1	1	2
All	12	7	19

Abbreviations: AML, acute myeloid leukemia; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide plus R-CHOP.

TABLE A3. Common AE (≥ 5%) Among n = 93 Treated Patients of Age < 60

	Treatment				
	A-R2CHOP (n = 45)			B-CHOP (n = 48)	
	Grade			Grade	
	3	4	5	3	4
Toxicity Type	%	%	%	%	%
Anemia	9	2	0	8	0
Febrile neutropenia	9	7	0	8	2
Hyperglycemia	4	0	0	6	0
Hypokalemia	7	0	0	0	0
Neutrophil count decreased	11	27	0	13	38
Platelet count decreased	4	11	0	2	0
Worst grade	36	27	2[a]	21	44

Abbreviations: AE, adverse event; B-CHOP, bleomycin, cytoxan, hydroxydaunomycin, oncovin, and prednisone; R2CHOP, lenalidomide plus R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).

[a]Case with grade 5 lung infection.

TABLE A4. Common AE (≥ 5%) Among n = 244 Treated Patients of Age ≥ 60

	Treatment				
	A-R2CHOP (n = 121)			A-R2CHOP (n = 123)	
	Grade			Grade	
	3	4	5	3	4	5
Toxicity Type	%	%	%	%	%	%
Anemia	31	5	0	22	3	0
Dehydration	5	0	0	3	0	0
Diarrhea	8	0	0	1	0	0
Fatigue	12	0	0	9	0	0
Febrile neutropenia	24	5	0	11	1	1
Generalized muscle weakness	7	0	0	2	0	0
Hypokalemia	5	1	0	2	1	0
Hyponatremia	7	0	0	5	0	0
Hypophosphatemia	6	0	0	2	0	0
Lung infection	7	1	0	5	0	1
Neutrophil count decreased	8	60	0	12	44	0
Platelet count decreased	17	24	0	4	12	0
Sepsis	0	7	0	0	3	3
Thromboembolic event	4	1	0	2	0	0
Urinary tract infection	5	0	0	1	0	0
Worst grade	16	65	1	16	48	6

Abbreviations: AE, adverse event; R2CHOP, lenalidomide plus R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).