Brentuximab Vedotin Combination for Relapsed Diffuse Large B-Cell Lymphoma

Nancy L. Bartlett, MD[1]; Uwe Hahn, MD[2]; Won-Seog Kim, MD, PhD[3]; Isabelle Fleury, MD[4]; Kamel Laribi, MD[5]; Juan-Miguel Bergua, MD[6]; Krimo Bouabdallah, MD[7]; Nicholas Forward, MSc, MD, FRCPC[8]; Fontanet Bijou, MD[9]; David MacDonald, MD[10]; Craig A. Portell, MD[11]; Herve Ghesquieres, MD, PhD[12]; Grzegorz Nowakowski, MD[13]; Christopher A. Yasenchak, MD[14]; Monica Patterson, PharmD[15]; Linda Ho, MD[15]; Evelyn Rustia, MD[15]; Michelle Fanale, MD[15]; Fei Jie, PhD[15]; and Jeong-A Kim, MD[16]

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ABSTRACT

PURPOSE In patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), brentuximab vedotin (BV) as monotherapy or combined with either lenalidomide (Len) or rituximab (R) has demonstrated efficacy with acceptable safety. We evaluated the efficacy and safety of BV + Len + R versus placebo + Len + R in patients with R/R DLBCL.

METHODS ECHELON-3 is a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial comparing BV + Len + R with placebo + Len + R in patients with R/R DLBCL. Patients received BV or placebo once every 3 weeks, Len once daily, and R once every 3 weeks. The primary end point was overall survival (OS), and secondary end points included investigator-assessed progression-free survival (PFS) and objective response rate (ORR). A prespecified interim analysis was performed after 134 OS events, with two-sided $P = .0232$ as the efficacy boundary.

RESULTS Patients (N = 230) were randomly assigned to receive BV + Len + R (n = 112) or placebo + Len + R (n = 118). Two patients in the placebo arm did not receive treatment. With a median follow-up of 16.4 months, the median OS was 13.8 months with BV + Len + R versus 8.5 months with placebo + Len + R (hazard ratio, 0.63 [95% CI, 0.45 to 0.89]; two-sided $P = .009$). The median PFS was 4.2 months with BV + Len + R versus 2.6 months with placebo + Len + R (hazard ratio, 0.53 [95% CI, 0.38 to 0.73]; two-sided $P < .001$). The ORR was 64% ([95% CI, 55 to 73]; two-sided $P < .001$) with BV + Len + R and 42% (95% CI, 33 to 51) with placebo + Len + R; complete response rates were 40% and 19%, respectively. Treatment-emergent adverse events (AEs) occurred in 97% of patients in both arms. In both arms, the most common treatment-emergent AEs were neutropenia, thrombocytopenia, diarrhea, and anemia.

CONCLUSION BV + Len + R demonstrated a statistically significant survival benefit with a manageable safety profile in heavily pretreated patients with R/R DLBCL.

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BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for approximately 30% of NHLs diagnosed annually.[1] Although the majority of patients with DLBCL are cured with standard first-line chemoimmunotherapy, approximately 40% have relapsed or refractory (R/R) disease.[2-4] Chimeric antigen receptor (CAR) T-cell therapy shifted the management of DLBCL in the second-line setting, but use may be limited by administration logistics, cost, and toxicity profile.[2,5] The US Food and Drug Administration recently approved bispecific therapies for third-line DLBCL treatment on the basis of promising response rates, including in R/R disease following stem-cell transplant (SCT) or CAR T-cell therapy.[5-7] Unmet need exists for patients with R/R DLBCL who are ineligible for or experience relapse after these recent advancements.

Brentuximab vedotin (BV) is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated via a protease-cleavable linker to the microtubule-disrupting drug monomethyl auristatin E.[8] BV is currently approved for R/R Hodgkin lymphoma and has shown clinical efficacy in previous R/R DLBCL studies.[9-11] A phase 2 BV monotherapy study reported an objective response rate (ORR) of 44%, with responses observed across variable CD30 expression levels.[10] Moreover, BV combined with rituximab (R), a monoclonal anti-CD20 antibody, demonstrated a comparable ORR of

CONTEXT

Key Objective

This phase 3 ECHELON-3 primary interim analysis compared the efficacy and safety of brentuximab vedotin versus placebo in combination with lenalidomide and rituximab (BV + Len + R *v* placebo + Len + R) for patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

Knowledge Generated

BV combined with Len + R demonstrated significant improvements in overall survival (OS; 37% reduced risk of death), progression-free survival (PFS; 47% reduced risk of disease progression or death), and objective response rate (64% *v* 42%). BV + Len + R demonstrated a favorable benefit-risk balance in third-line or later R/R DLBCL, with significant but manageable toxicities consistent with the safety profiles of the individual drugs.

Relevance *(J.W. Friedberg)*

The activity of BV and impact on OS in this setting is surprising, with increased complete response but short PFS. BV + Len + R may be considered as a bridging therapy for patients with R/R DLBCL prior to chimeric antigen receptor-T or other more definitive options, and future studies should explore molecular subsets toward a predictive biomarker.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

46%.[2,10] Lenalidomide (Len), an immunomodulatory agent, showed encouraging activity in R/R DLBCL, with efficacy outcomes favoring non–germinal center B-cell subtypes in a few studies.[12,13] Len + R had favorable outcomes in various NHLs and offers older patients a chemotherapy-free alternative.[14,15] In a phase 1 dose-expansion study, patients with R/R DLBCL receiving BV + Len, who were ineligible for or experienced relapse after SCT, had ORR and complete response (CR) rates of 57% and 35%, respectively; BV + Len had a tolerable safety profile.[16]

ECHELON-3 (ClinicalTrials.gov identifier: NCT04404283) was initiated to compare BV + Len + R with placebo + Len + R in patients with R/R DLBCL who received ≥2 lines of therapy and were pretreated with or ineligible for SCT or CAR T-cell therapy.[17] In the previously reported safety run-in portion of ECHELON-3 (N = 10), the ORR was 70% with BV + Len + R.[17] Here, results from the prespecified interim analysis of the randomized portion are reported.

METHODS

Trial Design

ECHELON-3 is a randomized, double-blind, placebo-controlled, active-comparator, multicenter, phase 3 study comparing the efficacy and safety of BV + Len + R with those of placebo + Len + R in patients with R/R DLBCL. This international study was conducted in 14 countries; 98 sites screened patients, and patients were enrolled at 88 sites.

The study design included a safety run-in and a randomized portion.[17] A safety monitoring committee reviewed data from the first six patients after completion of one cycle of open-label BV + Len + R in the safety run-in period, which enrolled a total of 10 patients. No new safety signals were identified; therefore, the committee approved the random assignment.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and the policy of the trial sponsor(s) on bioethics and human biological samples. Patients provided written informed consent.

Patients

Adult patients with R/R DLBCL with eligible subtypes, including transformed DLBCL, were enrolled. Patients must have received ≥2 previous lines of systemic therapy, be ineligible for hematopoietic SCT or CAR T-cell therapy, and have an Eastern Cooperative Oncology Group performance status of ≤2. Full eligibility criteria are provided in the Data Supplement (online only).

Random Assignment and Treatment

Patients were randomly assigned 1:1 to receive BV + Len + R or placebo + Len + R. Patients were stratified by CD30 expression (positive [≥1%] *v* negative [<1%]), cell of origin (germinal center B cell or non–germinal center B cell), previous treatment with CAR T-cell therapy (received or not), and previous hematopoietic SCT therapy (received or not).

Patients received BV 1.2 mg/kg or placebo intravenously once every 3 weeks, Len 20 mg orally once daily, and R 375 mg/m^2

intravenously once every 3 weeks in 21-day cycles. Subcutaneous R (1,400 mg) was permitted from cycle 2 onward. Prophylaxis with granulocyte colony-stimulating factors was required at all treatment cycles in both arms and administered per institutional guidelines. Treatment was allowed until disease progression or unacceptable toxicity.

Trial End Points and Assessments

The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), ORR, CR rate, and duration of response (DOR) per Lugano classification,[18] as determined by the investigator; adverse events (AEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; and OS in the CD30-positive subgroup. Exploratory efficacy end points included association of CD30 expression with ORR and PFS.

To assess disease response, positron emission tomography and computed tomography scans were required at baseline, every 6 weeks for the first 48 weeks, and every 12 weeks thereafter. If a patient achieved positron emission tomography–based metabolic CR, only computed tomography was required for disease surveillance in subsequent assessments until radiographic disease progression.

Statistical Analysis

Efficacy analyses were performed in the intention-to-treat analysis set, which included all randomly assigned patients regardless of the actual treatment received. The safety analysis set included all patients who received ≥1 dose of any study drug.

The primary end point of OS was defined as time from random assignment to death due to any cause. A target sample size of approximately 170 events from 225 patients was chosen to provide power to reject the null hypothesis of no difference in OS between the treatment arms. Prespecified interim analysis of OS for both efficacy and futility was performed by an independent data monitoring committee after 134 OS events. At the interim analysis, a hazard ratio of >1.1 was used as the nonbinding futility boundary; two-sided $P = .0232$ was used as the O'Brien-Fleming efficacy boundary to maintain overall type I error at a two-sided .05. On rejection of the null hypothesis for the primary end point during interim analysis, secondary end points of PFS and ORR were tested using a fixed-sequence approach. The Kaplan-Meier method was used to estimate OS and PFS in each treatment arm. Reverse Kaplan-Meier was used to estimate median duration of follow-up for OS. The stratified log-rank test was used to test the null hypothesis of no difference between the treatment arms. Patients who were alive were censored for OS at the last known alive date or the data cutoff, whichever was earlier. For PFS, patients were censored at their most recent tumor assessment if they initiated a new anticancer therapy, experienced a PFS event after two or more missed visits, or did not have a PFS event. Patients without any postbaseline response assessments were censored at the randomization date. As the efficacy boundary was crossed during the interim analysis, it is considered the primary analysis. The final analysis will occur when approximately 170 OS events have been observed and will be descriptive.

RESULTS

Patients

From April 2021 to November 2023, 230 patients were randomly assigned to receive BV + Len + R (n = 112) or placebo + Len + R (n = 118). Two patients in the placebo arm did not receive treatment (Fig 1). Baseline characteristics were generally balanced between the BV + Len + R and placebo + Len + R arms: median age (74 *v* 70 years), CD30-positive status (32% each), germinal center B-cell origin (46% each), median previous systemic therapy lines (three each), and previous CAR T-cell therapy received (29% *v* 30%) (Table 1). The majority of patients were refractory to initial treatment for DLBCL and the most recent previous therapy (57% with BV + Len + R *v* 54% with placebo + Len + R, and 88% with BV + Len + R *v* 81% with placebo + Len + R, respectively). Additionally, of the patients who received previous CAR-T, the majority were CAR-T refractory (28/32, 88% with BV + Len + R *v* 28/35, 80% with placebo + Len + R). At data cutoff (January 22, 2024), treatment was ongoing in 22 patients (20%) in the BV + Len + R arm and 14 patients (12%) in the placebo + Len + R arm.

Efficacy

By data cutoff, 134 patients (58%) had died (58 [52%] in the BV + Len + R arm and 76 [64%] in the placebo + Len + R arm). The median duration of follow-up for OS was 15.5 months (95% CI, 12.2 to 18.1) in the BV + Len + R arm and 18.9 months (95% CI, 12.2 to 23.2) in the placebo + Len + R arm. Risk of death was reduced by 37% with BV + Len + R compared with placebo + Len + R (stratified hazard ratio, 0.63 [95% CI, 0.45 to 0.89]; two-sided $P = .009$); the median OS was 13.8 months (95% CI, 10.3 to 18.8) and 8.5 months (95% CI, 5.4 to 11.7), respectively (Fig 2A). The prespecified boundary for efficacy was crossed. The hazard ratio for OS favored BV + Len + R across most prespecified subgroups, including cell of origin, previous CAR T-cell therapy, and CD30 expression, and in the nonprespecified subgroup of primary refractory disease (Fig 2B; Data Supplement, Table S1).

BV + Len + R significantly reduced the risk of disease progression or death by 47% compared with placebo + Len + R (hazard ratio, 0.53 [95% CI, 0.38 to 0.73]; two-sided $P < .001$), leading to a median PFS of 4.2 months (95% CI, 2.9 to 7.1) and 2.6 months (95% CI, 1.4 to 3.1), respectively (Fig 3A). The median PFS for patients with complete and partial responses with BV + Len + R was 21.5 months (95%

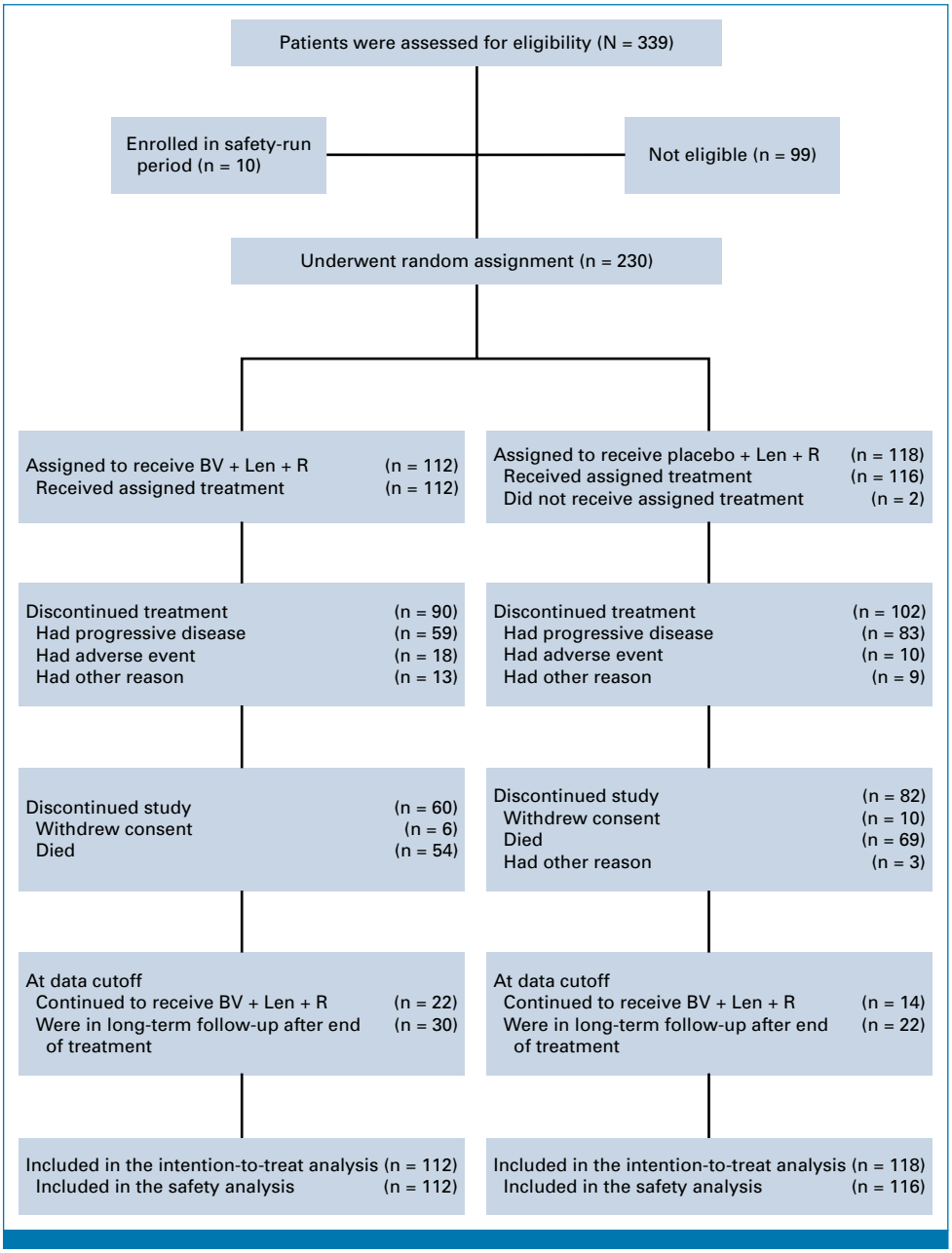


FIG 1. Enrollment, random assignment, and follow-up. A total of 339 patients were assessed for eligibility, and 230 patients were randomly assigned to receive BV + Len + R or placebo + Len + R. The intention-to-treat population included all randomly assigned patients, and the safety population included patients who received ≥1 dose of the study treatment. BV, brentuximab vedotin; Len, lenalidomide; R, rituximab.

CI, 12.6 to not evaluable) and 4.1 months (95% CI, 2.9 to 4.9), respectively (Appendix Fig A1, online only). PFS improvement with BV + Len + R was consistent across most prespecified subgroups, including CD30 expression and the nonprespecified subgroup of primary refractory disease (Fig 3B; Data Supplement, Table S1).

ORR by investigator was significantly higher with BV + Len + R versus placebo + Len + R (64% [95% CI, 55 to 73] *v* 42% [95% CI, 33 to 51]; two-sided $P < .001$). Consistent improvements in ORR and CR rates were observed regardless of CD30 expression or cell of origin (Data Supplement, Table S2). The median DOR was 8.3 months (95% CI, 4.2 to 15.3) with BV + Len + R and 3 months (95% CI, 2.8 to 5.4) with placebo + Len + R (Appendix Fig A2). CR rates were higher with BV + Len + R versus placebo + Len + R (40% *v* 19%). The median duration of CR was 18.9 months (95% CI, 11.1 to not evaluable) with BV + Len + R and not evaluable (95% CI, 2.8 to not evaluable) with placebo + Len + R; the median time to CR was 1.58 months (range, 1.2-7.3) and 1.61 months

TABLE 1. Patient Characteristics at Baseline (intention-to-treat population)

Characteristic	BV + Len + R (n = 112)	Placebo + Len + R (n = 118)
Median age, years (range)	74 (29-87)	70 (21-89)
Age category, No. (%)		
<65 years	33 (29)	42 (36)
≥65 years	79 (71)	76 (64)
Sex, No. (%)		
Male	60 (54)	70 (59)
Female	52 (46)	48 (41)
Race, No. (%)		
American Indian or Alaska Native	0	1 (1)
Asian	28 (25)	32 (27)
White	65 (58)	56 (47)
Other	0	1 (1)
Unknown	1 (1)	0
Not reported	18 (16)	28 (24)
Ethnicity, No. (%)		
Hispanic, Latino, or of Spanish origin	4 (4)	5 (4)
Non-Hispanic, Latino, or of Spanish origin	90 (80)	84 (71)
Unknown	0	1 (1)
Not reportable	18 (16)	28 (24)
ECOG performance status, No. (%)		
0	42 (38)	41 (35)
1	58 (52)	64 (54)
2	12 (11)	13 (11)
Extranodal disease involvement at baseline, No. (%)		
No involvement	25 (22)	33 (28)
1 site	31 (28)	30 (25)
>1 site	56 (50)	55 (47)
Ann Arbor stage at baseline, No. (%)		
Stage I	14 (13)	7 (6)
Stage II	15 (13)	13 (11)
Stage III	14 (13)	33 (28)
Stage IV	69 (62)	65 (55)
International Prognostic Index score at enrollment, No. (%)		
<3	45 (40)	47 (40)
≥3	67 (60)	71 (60)
Elevated lactate dehydrogenase level at study entry, No. (%)		
Yes	67 (60)	76 (64)
No	44 (39)	39 (33)
Unknown	1 (1)	3 (3)
Bulky disease at study entry, No. (%)		
Yes	16 (14)	35 (30)
No	95 (85)	82 (69)
Unknown	1 (1)	1 (1)
CD30 status, No. (%)		
Positive (≥1%)	36 (32)	38 (32)
Negative (<1%)	76 (68)	80 (68)
Cell of origin, No. (%)		
GCB	51 (46)	54 (46)
Non-GCB	61 (54)	64 (54)
DLBCL, not otherwise specified, No. (%)	63 (56)	64 (54)
Transformed DLBCL, No. (%)	32 (29)	27 (23)
Median lines of systemic therapy (range)	3 (2-8)	3 (2-7)
Lines of systemic therapy received in DLBCL setting, No.		
Mean (SD)	2.73 (1.24)	2.76 (1.06)
Median (range)	2 (0-7)	3 (1-7)
Most common previous systemic therapies received, No. (%)		
Anthracycline	110 (98)	115 (97)
Anti-CD20 antibody	110 (98)	114 (97)
CAR T-cell therapy	32 (29)	35 (30)
Bispecific antibody	14 (13)	20 (17)
Autologous stem-cell transplant	10 (9)	18 (15)
Disease primary refractory to initial DLBCL therapy, No. (%)[a]	64 (57)	64 (54)
Disease refractory to last previous DLBCL therapy, No. (%)[a]	98 (88)	96 (81)

Abbreviations: BV, brentuximab vedotin; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell; Len, lenalidomide; R, rituximab.

[a]Relapsed or refractory status is derived from previous therapy data. Refractory is defined as no response or a response lasting <6 months from the last treatment end date. Relapsed is defined as a response lasting ≥6 months from the last treatment end date.

(range, 0.7-4.6), respectively. At data cutoff, responses were ongoing in 30 patients with BV + Len + R and 16 patients with placebo + Len + R (Data Supplement, Table S3). Of those patients, 16 and 13 patients, respectively, were continuing to receive all three treatments, including patients with reduced doses of BV or Len.

The most common subsequent treatments following BV + Len + R were anti-CD20 therapies, bispecific antibodies, and antibody-drug conjugates (Data Supplement, Table S4).

Safety

All-causality treatment-emergent AEs of any grade and grade ≥3 occurred in 109 (97%) and 99 patients (88%) receiving BV + Len + R and 113 (97%) and 89 patients (77%)

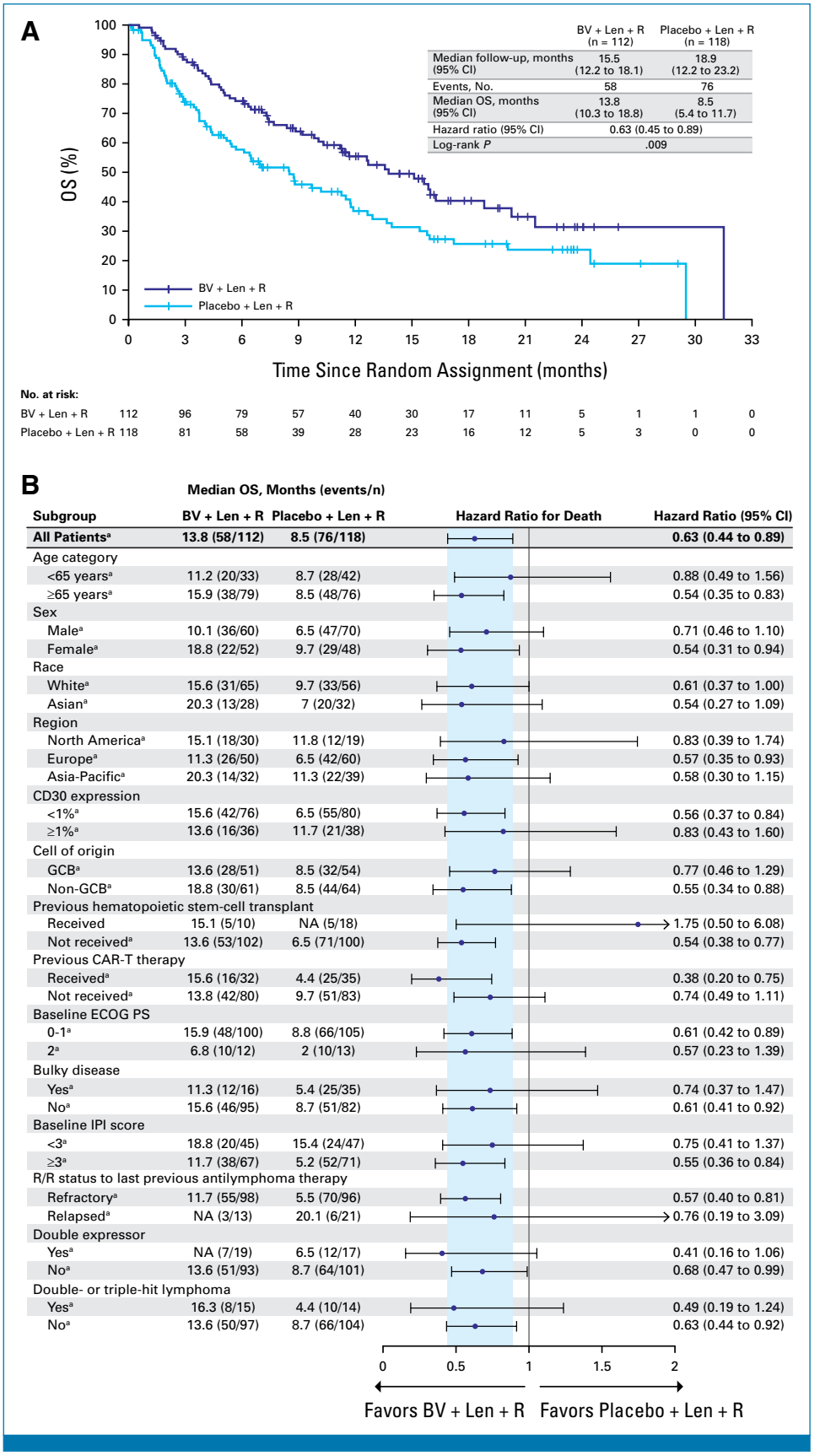


FIG 2. OS in the intention-to-treat population. (A) Shows the Kaplan-Meier estimates of OS in the intention-to-treat population. The median OS was significantly longer with BV + Len + R. Tick marks on the curves indicate censoring of data. (B) Shows a subgroup analysis (continued on following page)

FIG 2. (Continued). of OS. [a]Subgroup with hazard ratio for death of <1. BV, brentuximab vedotin; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index; Len, lenalidomide; NA, not available; OS, overall survival; R, rituximab; R/R, relapsed or refractory.

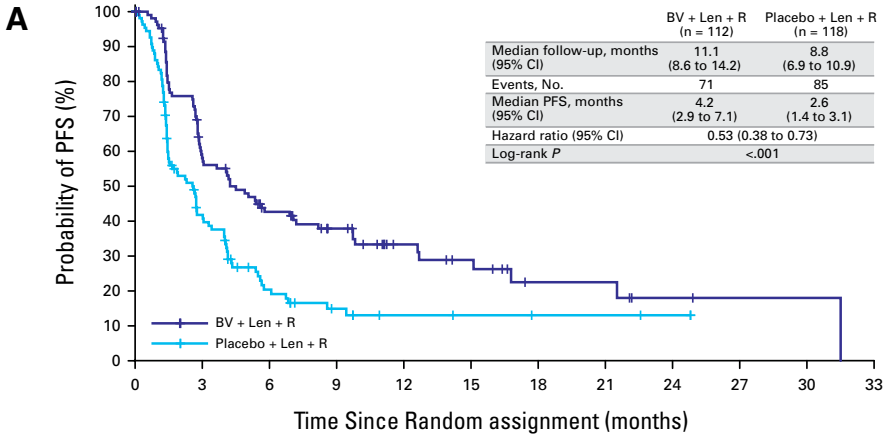
receiving placebo + Len + R (Table 2; Data Supplement, Table S5). The most common treatment-emergent AEs (≥25% in either arm; BV + Len + R *v* placebo + Len + R) were neutropenia (46% *v* 32%), thrombocytopenia (32% *v* 22%), diarrhea (31% *v* 23%), and anemia (29% *v* 27%). The most frequent grade ≥3 treatment-emergent AEs (BV + Len + R *v* placebo + Len + R) were neutropenia (43% *v* 28%), thrombocytopenia (25% *v* 19%), and anemia (22% *v* 21%). Febrile neutropenia occurred in 9% of patients in both treatment arms. Patients receiving BV + Len + R versus placebo + Len + R experienced more frequent treatment-emergent peripheral neuropathy, including any-grade (31% *v* 24%) and grade 3 events (6% *v* 2%); however, most events were grade 1/2 (25% *v* 22%; Data Supplement, Table S6). Of these patients, seven (20%) of 35 had resolved or improved peripheral neuropathy with BV + Len + R versus 12 (43%) of 28 with placebo + Len + R (Data Supplement, Table S7). Serious treatment-emergent AEs occurred in 67 patients (60%) receiving BV + Len + R versus 58 patients (50%) receiving placebo + Len + R, with pneumonia (11% *v* 5%), COVID-19 (7% *v* 5%), COVID-19 pneumonia (7% *v* 3%), and febrile neutropenia (6% *v* 5%) being the most common (Data Supplement, Table S8). Overall, 58 total deaths were reported in the BV + Len + R arm and 74 in the placebo + Len + R arm; treatment-emergent AEs led to 13 (12%) and nine deaths (8%) in the respective arms, mostly due to COVID-19–related events (4% *v* 3%; Data Supplement, Table S9).

The median duration of treatment was 3.6 months (range, 0.5-26.4) with BV + Len + R and 2 months (range, 0.1-26.6) with placebo + Len + R (Data Supplement, Table S10). Treatment-emergent AEs led to dose modifications of any study treatment and overall treatment discontinuation in 85 (76%) and 17 patients (15%) receiving BV + Len + R, respectively, and 56 (48%) and 10 patients (9%) receiving placebo + Len + R (Data Supplement, Table S11). Treatment-emergent AEs led to dose modifications of BV or placebo, Len, and R in 70 (63%), 81 (72%), and 67 patients (60%) receiving BV + Len + R and 40 (34%), 53 (46%), and 36 patients (31%) receiving placebo + Len + R, respectively. In the BV + Len + R and placebo + Len + R arms, Len dose modifications were mainly due to neutropenia (28 [25%] and 18 [16%]) and thrombocytopenia (19 [17%] and 12 [10%]). Treatment-emergent AEs led to BV or placebo discontinuations in 22 patients (20%) receiving BV + Len + R and 11 patients (9%) receiving placebo + Len + R (Data Supplement, Table S12). Safety summary and dose modifications were also adjusted for treatment exposure (Data Supplement, Table S13).

DISCUSSION

In patients with R/R DLBCL, BV + Len + R versus placebo + Len + R demonstrated significant improvements in OS (37% reduced risk of death), PFS (47% reduced risk of disease progression or death), and ORR (64% *v* 42%). Survival benefit was observed across most subgroups, including high-risk subgroups, such as age ≥65 years, International Prognostic Index score ≥3, and previous CAR T-cell therapy. The patient population enrolled in ECHELON-3 is reflective of current real-world practice, as 29% of patients received previous CAR T-cell therapy, 15% received previous bispecific antibodies, and 12% received previous SCT. Although almost 70% of patients were CD30-negative, BV + Len + R resulted in benefit regardless of CD30 expression. These results support BV + Len + R as a potential option for patients with R/R DLBCL following ≥2 previous treatments, including patients with R/R disease or those who are ineligible for other treatment options such as SCT, CAR T-cell therapy, or bispecific antibodies.

Prognosis is poor in patients with R/R DLBCL who have exhausted multiple treatment lines, and no standard of care currently exists.[2,19] Before the availability of CAR T-cell therapies and bispecific antibodies, a large, pooled, retrospective study (SCHOLAR-1) showed dismal results for patients with refractory DLBCL, with a median OS of 6.3 months.[19] CD19-directed CAR T-cell therapies have shown high ORR (52%-87%) and CR rates (40%-74%), leading to regulatory approvals in the second-line setting.[5,20-22] Despite the impressive response rates that CAR T-cell therapies offer, not all patients will respond, and some patients will relapse after treatment. A recently published real-world study reported 5-year PFS of 29% with CAR T-cell therapy, highlighting the need for additional options for this patient population.[23] Bispecific antibodies demonstrated high ORR (42%-63%) and CR rates (24%-40%), with 78%-85% of CRs ongoing at 12 months, which led to approval in the third-line setting.[5-7,24] However, many patients fail to respond to or experience disease progression after treatment with bispecific antibodies, and there is no optimal treatment for these patients or for those who fail CAR T-cell therapy. Additionally, these recent advancements using T-cell engager therapies are limited by administration logistics and associated toxicities, such as cytokine release syndrome and neurotoxicity, making them not suitable for all patients. On the basis of the ECHELON-3 results, BV + Len + R may be a treatment option for a broad range of patients in the outpatient setting, including those ineligible for the aforementioned therapies.



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Subgroups	Median PFS, Months (events/n) BV + Len + R	Placebo + Len + R	Hazard Ratio (95% CI)
All Patients[a]	**4.2 (71/112)**	**2.6 (85/118)**	**0.53 (0.38 to 0.73)**
Age category			
<65 years[a]	2.9 (25/33)	1.4 (33/42)	0.69 (0.41 to 1.17)
≥65 years[a]	5.7 (46/79)	2.8 (52/76)	0.48 (0.32 to 0.72)
Sex			
Male[a]	2.9 (41/60)	2.2 (54/70)	0.56 (0.37 to 0.85)
Female[a]	7.2 (30/52)	3.3 (31/48)	0.55 (0.33 to 0.92)
Race			
White[a]	5.1 (41/65)	2.7 (37/56)	0.54 (0.34 to 0.86)
Asian[a]	9.7 (16/28)	2.8 (24/32)	0.51 (0.27 to 0.97)
Region			
North America[a]	4.1 (22/30)	1.4 (12/19)	0.65 (0.32 to 1.34)
Europe[a]	3.6 (31/50)	1.5 (44/60)	0.48 (0.30 to 0.77)
Asia-Pacific[a]	9.7 (18/32)	3 (29/39)	0.50 (0.28 to 0.91)
CD30 expression			
<1%[a]	3.1 (49/76)	1.9 (57/80)	0.57 (0.38 to 0.84)
≥1%[a]	6.9 (22/36)	2.7 (28/38)	0.49 (0.28 to 0.86)
Cell of origin			
GCB[a]	4.2 (33/51)	2.8 (38/54)	0.55 (0.34 to 0.89)
Non-GCB[a]	4.5 (38/61)	1.9 (47/64)	0.52 (0.33 to 0.80)
Previous hematopoietic stem cell transplant			
Received	5.4 (6/10)	5.6 (10/18)	1.00 (0.36 to 2.79)
Not received[a]	4.2 (65/102)	1.5 (75/100)	0.46 (0.33 to 0.64)
Previous CAR-T therapy			
Received[a]	3 (21/32)	1.4 (25/35)	0.41 (0.22 to 0.76)
Not received[a]	5.1 (50/80)	2.8 (60/83)	0.58 (0.40 to 0.85)
Baseline ECOG PS			
0-1[a]	5.7 (60/100)	2.7 (75/105)	0.50 (0.35 to 0.70)
2[a]	1.5 (11/12)	1.1 (10/13)	0.59 (0.25 to 1.42)
Bulky disease			
Yes[a]	3.1 (12/16)	1.9 (26/35)	0.67 (0.33 to 1.36)
No[a]	4.9 (59/95)	2.6 (59/82)	0.51 (0.35 to 0.74)
Baseline IPI score			
<3[a]	5.4 (29/45)	2.8 (32/47)	0.60 (0.36 to 1.00)
≥3[a]	3.6 (42/67)	1.5 (53/71)	0.49 (0.32 to 0.73)
R/R to last previous antilymphoma therapy			
Refractory[a]	4.1 (66/98)	1.5 (74/96)	0.51 (0.36 to 0.71)
Relapsed[a]	15.1 (5/13)	5.6 (10/21)	0.29 (0.08 to 0.98)
Double expressor			
Yes[a]	6.4 (10/19)	2.6 (12/17)	0.55 (0.23 to 1.27)
No[a]	4.2 (61/93)	2.6 (73/101)	0.52 (0.37 to 0.74)
Double- or triple-hit lymphoma			
Yes[a]	4.1 (9/15)	1.5 (9/14)	0.36 (0.13 to 0.97)
No[a]	4.5 (62/97)	2.6 (76/104)	0.56 (0.40 to 0.78)

FIG 3. PFS in the intention-to-treat population. (A) Shows the Kaplan-Meier estimates of investigator-assessed PFS in the intention-to-treat population. The median PFS was significantly longer with BV + Len + R. Tick marks on the curves indicate censoring of data. (continued on following page)

FIG 3. (Continued). (B) Shows subgroup analysis of PFS. [a]Subgroup with hazard ratio for disease progression or death of <1. BV, brentuximab vedotin; CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index; Len, lenalidomide; PFS, progression-free survival; R, rituximab.

Other combinations have demonstrated efficacy in patients with R/R DLBCL.[25-29] Loncastuximab tesirine, an anti-CD19 antibody and alkylating cytotoxin conjugate, demonstrated ORR and CR rates of 48% and 25%, respectively, and a median OS of 9.5 months.[28-30] Various combinations of polatuzumab vedotin, a CD79b-targeted antibody-drug conjugate, have demonstrated efficacy in patients with R/R DLBCL.[25-27] Polatuzumab vedotin combined with bendamustine and R showed ORR and CR rates of 70% and 58%, respectively, and a median OS of 12.4 months, leading to its approval for R/R DLBCL treatment after ≥2 previous therapies.[25,26,31] In the phase 2 L-MIND study, which excluded primary refractory disease, >3 previous lines of therapy, high-risk cytogenetics, and previous CD19-directed therapy, Len combined with tafasitamab, an anti-CD19 monoclonal antibody, demonstrated an ORR of 58% and OS of 33.5 months.[32,33] Half of the patients had only one previous line of therapy.[32] In a real-world retrospective study in 178 patients with R/R DLBCL, the ORR was 31%, the median PFS was 1.9 months, and the median OS was 6.5 months.[34] ECHELON-3 enrolled high-risk patients (median of three previous therapies compared with two in the polatuzumab vedotin and L-MIND studies, and allowed primary refractory DLBCL) but demonstrated similar efficacy, with ORR and CR rates of 64% and 40%, respectively, and a median OS of 13.8 months.

In contrast to previous studies, which indicated that Len favors non–germinal center B-cell subtypes[13] and that BV targets only CD30-expressing cells,[8] BV + Len + R provided clinical benefit regardless of CD30 status or cell of origin. The multimodal mechanism of action of BV includes effects on the tumor microenvironment through bystander effect and T-reg depletion in addition to direct CD30-mediated cell death.[10] The combination of Len with BV may enhance immune-mediated mechanisms of action that are independent of CD30 expression. The benefit observed with BV + Len + R may be attributed to overlapping mechanisms of

TABLE 2. Most Common Treatment-Emergent Adverse Events (safety population)

	BV + Len + R (n = 112), No. (%)		Placebo + Len + R (n = 116), No. (%)	
Patients	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	109 (97)	99 (88)	113 (97)	89 (77)
Neutropenia	52 (46)	48 (43)	37 (32)	32 (28)
Thrombocytopenia	36 (32)	28 (25)	25 (22)	22 (19)
Diarrhea	35 (31)	5 (4)	27 (23)	2 (2)
Anemia	32 (29)	25 (22)	31 (27)	24 (21)
Fatigue	27 (24)	7 (6)	20 (17)	3 (3)
COVID-19	26 (23)	8 (7)	18 (16)	6 (5)
Asthenia	24 (21)	4 (4)	14 (12)	3 (3)
Peripheral sensory neuropathy	22 (20)	5 (4)	9 (8)	0
Pneumonia	19 (17)	12 (11)	8 (7)	6 (5)
Constipation	19 (17)	2 (2)	21 (18)	0
Decreased appetite	19 (17)	1 (1)	11 (9)	0
Nausea	17 (15)	1 (1)	19 (16)	1 (1)
Pyrexia	17 (15)	2 (2)	17 (15)	1 (1)
Hypokalemia	15 (13)	6 (5)	9 (8)	3 (3)
Febrile neutropenia	10 (9)	10 (9)	11 (9)	11 (9)
Neutrophil count decreased	9 (8)	9 (8)	7 (6)	7 (6)
COVID-19 pneumonia	8 (7)	8 (7)	4 (3)	4 (3)

NOTE. The safety population included all patients who received any amount of the trial drug. Treatment-emergent adverse events that occurred in ≥15% of patients in either treatment arm or grade ≥3 events that occurred in ≥5% of patients in either treatment arm are included. Treatment-emergent adverse events are newly occurring or worsening within the safety reporting period (after the first dose of study treatment and within 30 days after the last dose of BV or Len or 110 days after the last dose of R, whichever was later). Events are sorted by decreasing frequency in the BV + Len + R arm.
Abbreviations: BV, brentuximab vedotin; Len, lenalidomide; R, rituximab.

action, which contribute to a synergistic immunomodulatory effect with this combination.[34,35]

ECHELON-3 supports a positive benefit-to-risk ratio for BV + Len + R for R/R DLBCL, with significant but manageable toxicities consistent with the safety profiles of the individual drugs. Differences in some safety end points between the treatment arms are likely attributable to longer duration of treatment in the BV + Len + R group (five cycles with BV + Len + R *v* three cycles with placebo + Len + R). However, effect on quality of life was not included as part of this interim analysis due to low compliance with patient-reported outcomes assessments.[10,12,36] Consistent with the known safety profile of BV,[10] the incidence of any-grade treatment-emergent peripheral neuropathy was higher with BV + Len + R (31%) than placebo + Len + R (24%), with 16% experiencing grade 1 events in both arms. Similar incidence of peripheral neuropathy (31%) was observed with polatuzumab vedotin combined with bendamustine and R, whereas a lower incidence (18%) was reported with polatuzumab vedotin combined with Len and R.[25,27] In ECHELON-3, the incidence of peripheral neuropathy was higher with BV + Len + R, but longer follow-up is needed to assess duration and severity. At the time of this analysis, 20% of peripheral neuropathy events experienced by patients receiving BV + Len + R were resolved or improved.

Key limitations of this trial include that although the primary end point of OS was evaluated by an independent data monitoring committee, key secondary end points, including PFS and ORR, were not. The follow-up period was also relatively short, potentially affecting censoring for time-to-event end points, although continued follow-up is ongoing. Although the efficacy results appear well positioned in the treatment landscape, detailed efficacy analyses by number of previous lines of therapy received are not available. Additionally, although previous exposure to CAR T-cell therapy was evaluated as a subgroup, and OS and PFS appear promising, information such as time from CAR T-cell therapy to enrollment and efficacy for those refractory to CAR T-cell therapy is not available. Efficacy analyses on the basis of previous exposure to CAR T-cell therapy are ongoing. We also acknowledge that the continuous dosing of Len in both arms rather than a 21-day on, 7-day off dosing regimen could have contributed to a higher level of AEs, including hematologic AEs.

In conclusion, ECHELON-3 is the first randomized controlled study to demonstrate survival benefit in patients with R/R DLBCL in the third-line or later setting; efficacy was observed across high-risk subgroups. ECHELON-3 could potentially affect the treatment landscape for R/R DLBCL by supporting the use of BV + Len + R in this patient population.

AFFILIATIONS

[1]Division of Oncology, Washington University School of Medicine, Siteman Cancer Center, St Louis, MO
[2]Haematology Unit, Royal Adelaide Hospital, Adelaide, Australia
[3]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea
[4]Hôpital Maisonneuve-Rosemont, Institut Universitaire d'Hématologie-Oncologie et de Thérapie Cellulaire, Université de Montréal, Montréal, QC, Canada
[5]Department of Hematology, Centre Hospitalier Le Mans, Le Mans, France
[6]Hospital San Pedro de Alcantara, Cáceres, Spain
[7]Service d'Hematologie Clinique et Therapie Cellulaire, CHU Haut-Leveque, Pessac, France
[8]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada
[9]Centre de Lutte Contre le Cancer (CLCC)—Institut Bergonié, Bordeaux, France
[10]Division of Hematology, The Ottawa Hospital, Ottawa, ON, Canada
[11]UVA Comprehensive Cancer Center, University of Virginia, Charlottesville, VA
[12]Hematology Department, Hôpital Lyon Sud—HCL, Lyon, France
[13]Division of Hematology, Mayo Clinic, Rochester, MN
[14]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR
[15]Pfizer Inc, Bothell, WA
[16]St Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea

CORRESPONDING AUTHOR

Nancy L. Bartlett, MD; e-mail: nbartlet@wustl.edu.

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A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-02242. Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

AUTHOR CONTRIBUTIONS

Conception and design: Nancy L. Bartlett, Grzegorz Nowakowski, Christopher A. Yasenchak, Monica Patterson, Linda Ho, Evelyn Rustia, Michelle Fanale, Fei Jie
Administrative support: Juan-Miguel Bergua
Provision of study materials or patients: Nancy L. Bartlett, Uwe Hahn, Isabelle Fleury, Kamel Laribi, Juan-Miguel Bergua, Krimo Bouabdallah, Nicholas Forward, Fontanet Bijou, David MacDonald, Craig A. Portell, Herve Ghesquieres, Grzegorz Nowakowski, Jeong-A Kim
Collection and assembly of data: Nancy L. Bartlett, Uwe Hahn, Won-Seog Kim, Juan-Miguel Bergua, Krimo Bouabdallah, Nicholas Forward, Fontanet Bijou, David MacDonald, Craig A. Portell, Herve Ghesquieres, Grzegorz Nowakowski, Christopher A. Yasenchak, Monica Patterson, Linda Ho, Evelyn Rustia, Michelle Fanale, Fei Jie, Jeong-A Kim
Data analysis and interpretation: Nancy L. Bartlett, Uwe Hahn, Isabelle Fleury, Kamel Laribi, Nicholas Forward, Craig A. Portell, Grzegorz Nowakowski, Christopher A. Yasenchak, Monica Patterson, Linda Ho, Evelyn Rustia, Michelle Fanale, Fei Jie, Jeong-A Kim
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Brentuximab Vedotin Combination for Relapsed Diffuse Large B-Cell Lymphoma

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Nancy L. Bartlett
Consulting or Advisory Role: Roche/Genentech, Foresight Diagnostics, Kite, a Gilead company, Genmab/AbbVie, Pfizer/Seagen
Research Funding: Seagen (Inst), Forty Seven (Inst), Janssen (Inst), Pharmacyclics (Inst), Millennium (Inst), ADC Therapeutics (Inst), Autolus (Inst), Roche/Genentech (Inst), Bristol Myers Squibb/Celgene, Kite, a Gilead company, Genmab/AbbVie (Inst)

Uwe Hahn
Honoraria: AstraZeneca

Won-Seog Kim
Research Funding: Sanofi, Boryung, BeiGene

Isabelle Fleury
Consulting or Advisory Role: AbbVie, AstraZeneca, BeiGene, Celgene, Gilead Sciences, Incyte, Janssen, Merck, Novartis, Roche, Seagen
Speakers' Bureau: AbbVie, BeiGene, Gilead Sciences, Incyte, Seagen

Kamel Laribi
Consulting or Advisory Role: BeiGene, AbbVie, Takeda, Pfizer, Novartis
Research Funding: AstraZeneca, AbbVie

Juan-Miguel Bergua
Stock and Other Ownership Interests: Genomic Health, Roche Pharma AG
Consulting or Advisory Role: Daiichi Sankyo, CEPLENE
Speakers' Bureau: Roche/Genentech (Inst), Jazz Pharmaceuticals
Research Funding: DAIHI (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Sandoz, Roche Pharma AG, AbbVie

Krimo Bouabdallah
Honoraria: Roche, Takeda Science Foundation, AbbVie, Kite/Gilead, Sandoz-Novartis, BeiGene
Consulting or Advisory Role: Roche, Takeda, Kite/Gilead, BeiGene, Sandoz, Lilly
Travel, Accommodations, Expenses: Roche, Takeda, Kite/Gilead, BeiGene

Nicholas Forward
Honoraria: BeiGene, AstraZeneca, Roche, Seattle Genetics/Astellas
Consulting or Advisory Role: AbbVie, AstraZeneca, BeiGene, IMV, Bristol Myers Squibb/Celgene, Janssen, Kite/Gilead, Novartis, Pfizer, Roche, Seattle Genetics/Astellas, Servier, Incyte
Research Funding: ADC Therapeutics (Inst), AstraZeneca (Inst), Astellas Pharma (Inst), IMV (Inst), Merck (Inst), MorphoSys (Inst), Seagen (Inst)
Travel, Accommodations, Expenses: ApoPharma

David MacDonald
Honoraria: AbbVie, AstraZeneca, BeiGene, Kite/Gilead, Pfizer, Roche Canada, Seagen/Astellas

Craig A. Portell
Consulting or Advisory Role: BeiGene, Aptitude Health, Janssen, Targeted Oncology, Merck, AbbVie, AstraZeneca, Curio Science, Carden Jennings
Research Funding: BeiGene (Inst), Acerta Pharma (Inst), TG Therapeutics (Inst), AbbVie (Inst), Kite, a Gilead company (Inst), Xencor (Inst), Seagen (Inst), VelosBio (Inst), AstraZeneca (Inst), Prelude Therapeutics (Inst), Loxo/Lilly (Inst), Merck (Inst)

Herve Ghesquieres
Honoraria: Gilead Sciences, Roche, AbbVie
Consulting or Advisory Role: Gilead Sciences, Roche
Travel, Accommodations, Expenses: AbbVie, Pierre Fabre

Grzegorz Nowakowski
Consulting or Advisory Role: Celgene (Inst), MorphoSys (Inst), Genentech (Inst), Selvita, Debiopharm Group, Kite/Gilead, TG Therapeutics, Kymera, Karyopharm Therapeutics, Ryvu Therapeutics, Bantam Pharmaceutical, Bristol Myers Squibb/Celgene, AbbVie, Genmab, Roche Pharma AG (Inst)
Research Funding: Celgene (Inst), NanoString Technologies (Inst), MorphoSys (Inst)

Christopher A. Yasenchak
Stock and Other Ownership Interests: Karyopharm Therapeutics
Consulting or Advisory Role: Pfizer, BeiGene, GlaxoSmithKline, Bristol Myers Squibb/Celgene
Travel, Accommodations, Expenses: Pfizer

Monica Patterson
Employment: Pfizer, Scorpion Therapeutics

Linda Ho
Employment: Seagen, Pfizer
Stock and Other Ownership Interests: Pfizer, Seagen
Research Funding: Pfizer, Seagen
Travel, Accommodations, Expenses: Seagen, Pfizer

Evelyn Rustia
Employment: Seagen, Pfizer, Gilead Sciences
Stock and Other Ownership Interests: Seagen, Gilead Sciences

Michelle Fanale
Employment: Seagen, Pfizer
Stock and Other Ownership Interests: Seagen, Pfizer

Fei Jie
Employment: Pfizer

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APPENDIX

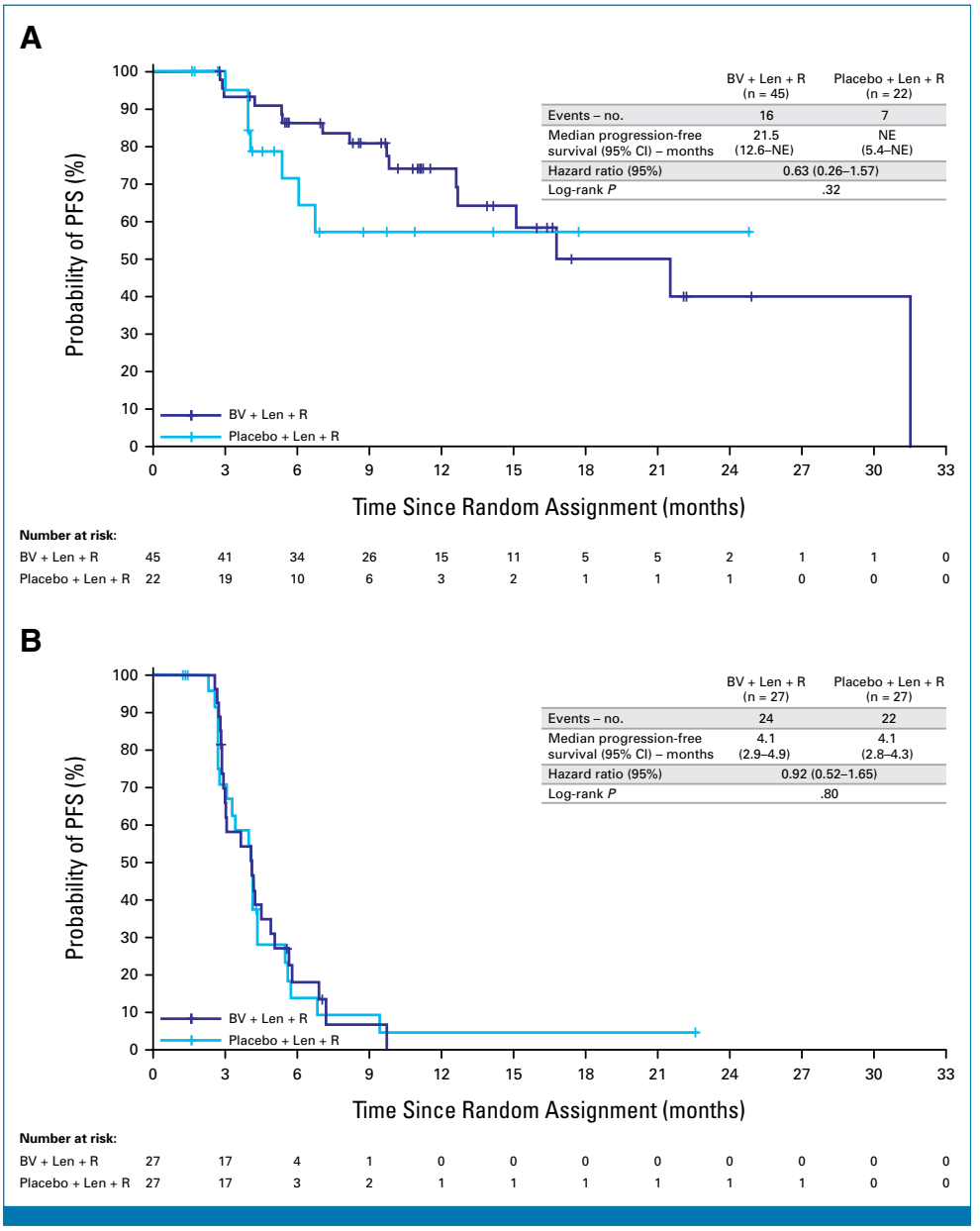

FIG A1. PFS in patients with complete or partial response. Kaplan-Meier estimates of investigator-assessed PFS (A) in patients who achieved complete response, and (B) in patients who achieved a partial response. Tick marks on the curves indicate censoring of data. BV, brentuximab vedotin; Len, lenalidomide; NE, not evaluable; PFS, progression-free survival; R, rituximab.

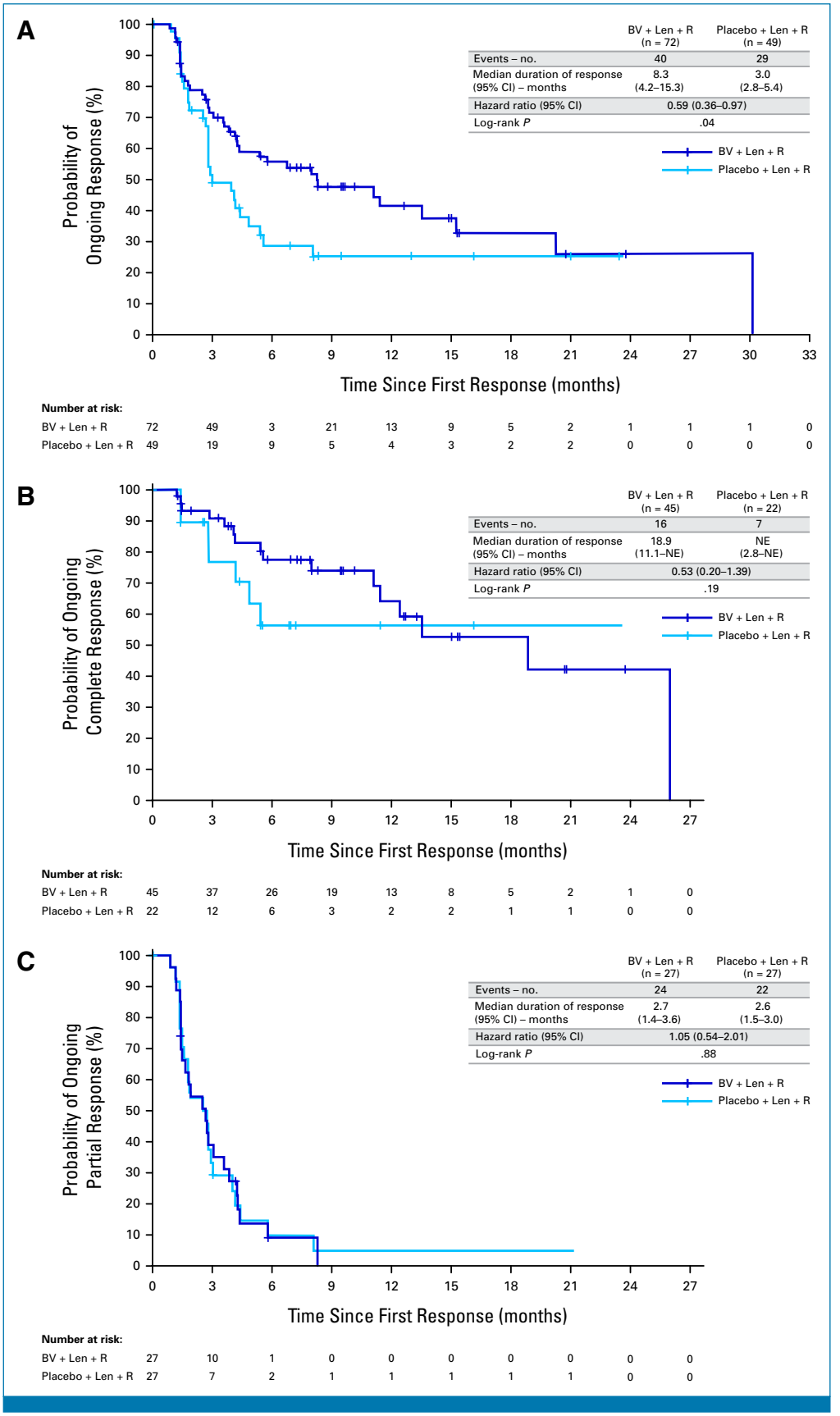

FIG A2. DOR in the intent-to-treat population. Kaplan-Meier estimates of DOR in evaluable patients per Lugano classification,[18] as determined by the investigator. (A) DOR (complete or partial) in the intent-to-treat population. (B) Duration of complete response in evaluable patients. (continued on following page)

FIG A2. (Continued). (C) Duration of partial response in evaluable patients. Tick marks on the curves indicate censoring of data. BV, brentuximab vedotin; DOR, duration of response; Len, lenalidomide; NE, not evaluable; R, rituximab.