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abstract

PURPOSE Patients with transplantation-ineligible relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) fare poorly, with limited treatment options. The antibody-drug conjugate polatuzumab vedotin targets CD79b, a B-cell receptor component.

METHODS Safety and efficacy of polatuzumab vedotin with bendamustine and obinutuzumab (pola-BG) was evaluated in a single-arm cohort. Polatuzumab vedotin combined with bendamustine and rituximab (pola-BR) was compared with bendamustine and rituximab (BR) in a randomly assigned cohort of patients with transplantation-ineligible R/R DLBCL (primary end point: independent review committee [IRC] assessed complete response [CR] rate at the end of treatment). Duration of response, progression-free survival (PFS), and overall survival (OS) were analyzed using Kaplan–Meier and Cox regression methods.

RESULTS Pola-BG and pola-BR had a tolerable safety profile. The phase Ib/II pola-BG cohort (n = 27) had a CR rate of 29.6% and a median OS of 10.8 months (median follow-up, 27.0 months). In the randomly assigned cohort (n = 80; 40 per arm), pola-BR patients had a significantly higher IRC-assessed CR rate (40.0% v17.5%; P = .026) and longer IRC-assessed PFS (median, 9.5 v 3.7 months; hazard ratio [HR], 0.36, 95% Cl, 0.21 to 0.63; P < .001) and OS (median, 12.4 v 4.7 months; HR, 0.42; 95% Cl, 0.24 to 0.75; P = .002; median follow-up, 22.3 months). Pola-BR patients had higher rates of grade 3-4 neutropenia (46.2% v 33.3%), anemia (28.2% v 17.9%), and thrombocytopenia (41% v 23.1%), but similar grade 3-4 infections (23.1% v 20.5%), versus the BR group. Peripheral neuropathy associated with polatuzumab vedotin (43.6% of patients) was grade 1-2 and resolved in most patients.

CONCLUSION Polatuzumab vedotin combined with BR resulted in a significantly higher CR rate and reduced the risk of death by 58% compared with BR in patients with transplantation-ineligible R/R DLBCL.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) represents approximately 25% of all newly diagnosed patients with non-Hodgkin lymphoma.^{1,2} Although DLBCL is often curable, 30%-40% of patients are refractory to, or relapse after treatment with, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemoimmunotherapy, the current standard of care.^{3,4} Higher treatment failure rates are observed in poor-risk subgroups, including activated B-cell–like (ABC) and MYC/ BCL2 double-expressor lymphomas (DEL).^{5,6}

Platinum-based salvage therapy followed by high-dose chemotherapy and autologous stem-cell transplantation (ASCT) can cure 30%-40% of patients with relapsed/refractory (R/R) disease able to undergo this therapy.^{7,8} However, prognosis is poor for most patients with R/R DLBCL who are ineligible for ASCT because of age, comorbidity, or inadequate response

to salvage chemotherapy and for those who relapse after ASCT, with a median overall survival (OS) of approximately 6 months.⁸ Currently, there is no standard of care in this setting, and treatment options include gemcitabine and/or platinum-based therapies, as well as bendamustine and rituximab (BR).9 Recently, CD19-directed chimeric antigen receptor (CAR) T-cell therapy was approved for use in the thirdline or later setting in the United States and Europe.^{10,11} Although CAR T-cell therapy appears promising, generalized use is restricted by lack of effective bridging therapies, treatment toxicity, and limited access because of high cost and need for specialized centers. Therefore, significant unmet medical need remains for patients with transplantation-ineligible R/R DLBCL, including those who experienced ASCT treatment failure.

Polatuzumab vedotin is a CD79b-targeted antibodydrug conjugate delivering monomethyl auristatin E

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(MMAE), a microtubule inhibitor.^{12,13} CD79b is a signaling component of the B-cell receptor located on normal B cells and most mature B-cell malignancies, including > 95% of DLBCL.^{14,15} Polatuzumab vedotin demonstrated encouraging activity in R/R DLBCL as monotherapy¹⁶ and combined with an anti-CD20 monoclonal antibody,¹⁷ yielding overall response rates (ORRs) of 13%-56%. However, complete response (CR) rates are low (0%-15%), prompting combination with additional agents. BR has been evaluated in patients with transplantation-ineligible R/R DLBCL, with median progression-free survival (PFS) of 3.6-6.7 months.^{18,19} Given the limited treatment options in this setting, combining polatuzumab vedotin with BR (pola-BR) was considered rational and avoided the risk of overlapping neurotoxicity that could occur with platinumbased regimens. Obinutuzumab, an alternative CD20targeted agent designed to promote greater antibodydependent cellular cytotoxicity and increased direct B-cell death compared with rituximab,^{20,21} was considered a promising agent to evaluate in combination with polatuzumab vedotin and bendamustine. However, this trial was designed before availability of GOYA trial (Clinical-Trials.gov identifier: NCT01287741) results, when obinutuzumab combinations in DLBCL were of greater interest.³

We report a phase Ib/II trial evaluating polatuzumab vedotin combined with bendamustine and obinutuzumab (pola-BG), and of pola-BR versus BR alone, in transplantationineligible R/R DLBCL, including patients who experienced treatment failure with prior ASCT. Results from a cohort of patients with follicular lymphoma (FL) will be reported separately.

METHODS

Trial Conduct

This international, multicenter, open-label, phase Ib/II trial (GO29365; ClinicalTrials.gov identifier: NCT02257567), approved by the institutional review board at each participating site, was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

The study was designed with input from investigators and sponsored by Genentech and F. Hoffmann-La Roche. All authors reviewed the data, vouch for the completeness and accuracy of the results and the trial's fidelity to the Protocol, reviewed the manuscript, and agreed on its submission for publication. Editorial support was funded by F. Hoffmann-La Roche.

Patients

Patients aged \geq 18 years were eligible if they had biopsyconfirmed R/R DLBCL (excluding transformed lymphoma) after \geq 1 prior line of therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, grade \leq 1 peripheral neuropathy (PN), and were considered transplantation ineligible by the treating physician or experienced treatment failure with prior ASCT. Double- and triple-hit lymphomas were not excluded. Complete eligibility and exclusion criteria are available in the Protocol.

Trial Design

The phase Ib safety run-in included 6 pola-BR–treated patients and 6 pola-BG–treated patients (Fig 1A). The phase II portion included an expansion cohort evaluating pola-BG (21 patients) and a randomly assigned cohort (80 patients: 40 per treatment arm) comparing pola-BR with BR alone, stratified by duration of response (DOR) to last prior therapy (\leq 12 months v > 12 months; Fig 1A). Cohorts treated with pola-BG in the safety and expansion phases were combined.

All patients received bendamustine 90 mg/m² intravenously (IV) on days 2 and 3 of cycle 1 and then days 1 and 2 of subsequent cycles, and either rituximab IV (375 mg/m² on day 1 of each cycle) or obinutuzumab IV (1,000 mg on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles). Those treated with polatuzumab vedotin received 1.8 mg/kg IV on day 2 of cycle 1 and day 1 of subsequent cycles. Patients were treated for up to six 21day cycles.

Assessments and End Points

Primary end points were safety and tolerability (phase lb) and CR rate of pola-BR versus BR (phase II), as measured by [¹⁸F]fluorodeoxyglucose positron emission tomographycomputed tomography (PET-CT) using modified Lugano Response Criteria²² (Appendix, online only) at the end of treatment (EOT; 6-8 weeks after cycle 6 day 1 or last dose of study treatment) by an independent review committee (IRC). If no scans were performed, the IRC considered the patient missing or unevaluable and he or she was treated as a nonresponder. Secondary end points included ORR at EOT, best overall response, DOR, and PFS as assessed by the IRC. Exploratory end points included biomarker evaluation of efficacy by cell of origin (COO), determined by either NanoString (NanoString Technologies, Seattle, WA) or Hans criteria, and immunohistochemical staining for DEL, investigator-assessed (INV) DOR and PFS, and OS.

Responses were assessed by CT, PET-CT, and bone marrow examination (if required to confirm CR) after 3 cycles (interim) and at EOT (primary response assessment). Follow-up CT scans were performed every 6 months for 2 years or until progressive disease (PD) or patient withdrawal.

The National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) was used to assess and grade all adverse events (AEs) throughout the study. All AEs, including serious AEs (SAEs), were reported from cycle 1 day 1 until 90 days after last dose of study drug,



FIG 1. (A) Study schema. (B) CON-SORT diagram for randomly assigned cohort. BG, bendamustine-obinutuzumab; BR, bendamustine-rituximab; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; mo, month; pola, polatuzumab vedotin; pola-BG, polatuzumab vedotin; pola-BG, polatuzumab vedotin; combined with bendamustine-obinutuzumab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab; R/R, relapsed/refractory. regardless of relationship to treatment. All SAEs were reported indefinitely.

Biomarkers

Methodology for exploratory biomarker evaluation of CD79b expression, COO, and DEL is described in the Appendix.

Statistical Analysis

A sample size of 12 patients was planned for the phase Ib safety run-in portion (6 pola-BR; 6 pola-BG). The study could proceed to phase II if < 33.3% of patients in each cohort experienced safety events. The sample size of the phase II randomly assigned cohort was determined based on an assumed 25% difference in CR rate from 40% in BR to 65% in pola-BR, allowing exclusion of zero as the lower boundary of the 95% exact Clopper–Pearson CI of the difference in CR rate (CI, 3.8% to 46.2%), with a margin of error not exceeding \pm 17%. For the phase II safety assessment, the sample size of 20 patients in the expansion arm and 40 patients in each of the randomized arms provided a \geq 85% likelihood of observing \geq 1 AE based on true incidence rates of 10% and 5%, respectively.

The safety-evaluable population comprised patients who received ≥ 1 dose of any study treatment. Efficacy analyses were performed based on the intent-to-treat principle (ie, all randomly assigned patients were analyzed according to their treatment assignment at the time of randomization or at study entry for nonrandomly assigned patients). The intent-to-treat population included all patients with DLBCL by investigator/site pathology. Additional efficacy analyses were conducted for the population of patients with DLBCL according to central pathology review (performed retrospectively to classify patients by WHO 2016 criteria) who received ≥ 1 dose of any study treatment.

Response rates were reported as percentages with associated 95% Clopper-Pearson (ie, exact binomial) Cls. Time-toevent end points, including DOR, PFS, and OS, were summarized as median survival time estimated using Kaplan-Meier methodology with 95% Greenwood's Cls. Differences in response rate and time-to-event end points between the pola-BR and BR arms were compared for exploratory purposes and reported as absolute differences and hazard ratios (HRs) using stratified Wilson and Cox regression methods, respectively. Multiple Cox regression analyses were conducted for OS and PFS, adjusting for potential prognostic factors and baseline characteristics (Ann Arbor stage, ECOG performance status, and bulky disease for OS; Ann Arbor stage and ECOG performance status for PFS; and International Prognostic Index [IPI] score for both OS and PFS). All reported P values are 2 sided.

RESULTS

Patients

Between October 15, 2014, and June 10, 2016, 113 patients with transplantation-ineligible R/R DLBCL were

enrolled. The safety run-in included 12 patients (6 pola-BR; 6 pola-BG). The phase II pola-BG cohort enrolled 21 and treated 20 patients. For the phase II randomly assigned cohort, 40 patients per arm were enrolled, and 39 patients per arm were treated (Fig 1B). Demographics and disease characteristics are shown in Table 1. Although patients receiving BR were slightly older (median age, 71 years v 67 years), baseline characteristics of the randomly assigned patients were generally balanced. The median number of prior lines of therapy was 2, with most patients refractory to the last treatment (75% pola-BR; 85% BR).

Two patients in the intent-to-treat randomly assigned cohort were determined by central pathology review to have FL and Burkitt's lymphoma. By investigator and site pathology, all patients had a DLBCL diagnosis. No double-/triple-hit lymphomas were confirmed by central pathology.

Efficacy

Response rates at EOT and median time-to-event end points are shown in Table 2. In the phase Ib pola-BR arm, EOT IRC-assessed CR rate was 50% (3/6), with all 3 patients remaining in remission at a median follow-up of 37.6 months (DOR, > 28.9 to ≥ 38.2 months). One nonresponder received subsequent therapy and remained alive at the time of data cutoff; 2 died as a result of PD. In the combined phase Ib/II pola-BG cohort, the EOT IRCassessed CR rate was 29.6%. At a median follow-up of 27.0 months, median PFS (IRC) and OS were 6.3 and 10.8 months, respectively. Two patients proceeded to consolidative stem-cell transplantation (SCT; 1 autologous and 1 allogeneic). Four patients (15%) had documented responses lasting at least 20 months (range, > 20.7 to \geq 22.5 months) without additional therapy. At last followup, 8 patients remained alive, 17 had died (12 PD; 5 AEs), and 2 discontinued the study (1 physician decision; 1 AE).

The primary analysis for the randomly assigned cohort showed significantly higher IRC-assessed CR rates at EOT with pola-BR versus BR (40.0% v 17.5%; P = .026; Table 2), with > 90% concordance between the IRC and investigator. Best OR and CR rates were also higher with pola-BR versus BR (Table 2). Discrepancies in PD assessments between the IRC and the investigator were mainly due to INV assessment of clinical progression without confirmatory scans, which were required for IRC assessment. Such patients were considered missing/not evaluable by the IRC (Appendix Table A1, online only).

After a median follow-up of 22.3 months, PFS (Figs 2A and 2B), OS (Fig 2C), and DOR were significantly improved with pola-BR versus BR. Consistent benefit in risk reduction was seen for IRC- and INV-assessed PFS (IRC: HR, 0.36; 95% CI, 0.21 to 0.63; P < .001; INV: HR, 0.34; 95% CI, 0.20 to 0.57; P < .001) and for DOR (IRC: HR, 0.47; 95% CI, 0.19 to 1.14; INV: HR, 0.44, 95% CI, 0.20 to 0.95), although IRC-assessed DOR did not reach statistical significance. IRC assessments of DOR and PFS were longer than INV

TARIE 1 Bacolino Characteristics

TADLE T. Daseline Characteristics	Phase Ib Safety Run-In	Phase Ib/II Expansion	Phase II Randomized		
Characteristic	Pola-BR $(n = 6)$	Pola-BG (n = 27)*	Pola-BR ($n = 40$)	BR (n = 40)	
Median age, years (range)	65 (58-79)	66 (26-86)	67 (33-86)	71 (30-84)	
Male sex	4 (66.7)	16 (59.3)	28 (70)	25 (62.5)	
ECOG PS score†					
0-1	6 (100)	22 (81.5)	33 (82.5)	31 (77.5)	
2	0	4 (14.8)	6 (15.0)	8 (20.0)	
WHO 2016 Classification (central pathology review)‡					
DLBCL, NOS	6 (100)	26 (96.3)	38 (95.0)	40 (100.0)	
ABC	4 (66.7)	9 (33.3)	19 (47.5)	19 (47.5)	
GCB	1 (16.7)	11 (40.7)	15 (37.5)	17 (42.5)	
Primary mediastinal (thymic) large B-cell lymphoma	0	1 (3.7)	0	0	
Burkitt lymphoma	0	0	1 (2.5)	0	
Follicular lymphoma	0	0	1 (2.5)	0	
Primary reason for transplantation ineligibility					
Age	1 (16.7)	9 (33.3)	13 (32.5)	19 (47.5)	
Comorbidities	0	2 (7.4)	1 (2.5)	1 (2.5)	
Performance status	0	0	0	2 (5.0)	
Insufficient response to salvage therapy	2 (33.3)	10 (37.0)	12 (30.0)	9 (22.5)	
Insufficient CD34+ cells collected	0	1 (3.7)	0	0	
Failed prior transplantation	0	2 (7.4)	10 (25.0)	6 (15.0)	
Patient refused	2 (33.3)	1 (3.7)	2 (5.0)	2 (5.0)	
Other	1 (2.5)	2 (7.4)	2 (5.0)	1 (2.5)	
Ann Arbor stage III/IV	4 (66.7)	23 (85.2)	34 (85)	36 (90)	
International Prognostic Index score at enrollment					
0	0	1 (3.7)	0	0	
1	1 (16.7)	2 (7.4)	9 (22.5)	3 (7.5)	
2	3 (50.0)	4 (14.8)	9 (22.5)	8 (20.0)	
3	2 (33.3)	11 (40.7)	13 (32.5)	12 (30.0)	
4	0	8 (29.6)	8 (20.0)	12 (30.0)	
5	0	1 (3.7)	1 (2.5)	5 (12.5)	
Bulky disease (\geq 7.5 cm)	1 (16.7)	7 (25.9)	10 (25.0)	15 (37.5)	
Stratification factor					
DOR of last treatment ≤ 12 months	5 (83.3)	23 (85.2)	32 (80)	33 (82.5)	
Lines of prior therapy, median (range)	2 (1-2)	2 (1-5)	2 (1-7)	2 (1–5)	
1	2 (33.3)	6 (22.2)	11 (27.5)	12 (30)	
2	4 (66.7)	9 (33.3)	11 (27.5)	9 (22.5)	
≥ 3	0	12 (44.4)	18 (45.0)	19 (47.5)	
Prior bone marrow transplantation	0	2 (7.4)	10 (25.0)	6 (15.0)	
Prior bendamustine	0	2 (7.4)	1 (2.5)	0	
Prior anti-CD20 agent	6 (100)	27 (100)	39 (97.5)	40 (100)	
Refractory to last prior therapy§	5 (83.3)	23 (85.2)	30 (75.0)	34 (85.0)	

NOTE. Data are no. (%) unless otherwise specified. High-dose chemotherapy with autologous stem-cell transplantation was counted as 1 line of therapy.

Abbreviations: ABC, activated B-cell–like; BR, bendamustine-rituximab; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell–like; NOS, not otherwise specified; pola-BG, polatuzumab vedotin combined with bendamustine-obinutuzumab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab. *Phase Ib and II cohorts combined.

 \pm ECOG PS score was unknown for two patients in the phase II randomized cohort (pola-BR, n = 1; BR, n = 1) and one patient in the phase Ib/II expansion cohort (pola-BG).

‡Central pathology review incorporated results of NanoString cell of origin when available.

§Definition of refractory: no response or progression within 6 months of last treatment.

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TABLE 2. Summary of Efficacy Outcomes

	Phase Ib Safety Run-In	Phase Ib/II Expansion	Phase II Randomized		
Outcome	Pola-BR $(n = 6)$	Pola-BG (n = 27)*	Pola-BR ($n = 40$)	BR (n = 40)	
End of treatment					
IRC, objective response	3 (50.0)	11 (40.7)	18 (45.0)	7 (17.5)	
Complete response	3 (50.0)	8 (29.6)	16 (40.0)	7 (17.5)	
Partial response	0	3 (11.1)	2 (5.0)	0	
Stable disease	0	2 (7.4)	6 (15.0)	1 (2.5)	
Progressive disease	1 (16.7)	6 (22.2)	8 (20.0)	10 (25.0)	
Missing or unevaluable [†]	2 (33.3)	8 (29.6)	8 (20.0)	22 (55.0)	
INV-assessed objective response	3 (50.0)	10 (37.0)	19 (47.5)	7 (17.5)	
Complete response	2 (33.3)	9 (33.3)	17 (42.5)	6 (15.0)	
Partial response	1 (16.7)	1 (3.7)	2 (5.0)	1 (2.5)	
Stable disease	0	0	1 (2.5)	0	
Progressive disease	3 (50.0)	10 (37.0)	12 (30.0)	26 (65.0)	
Missing or unevaluable	0	7 (25.9)	8 (20.0)	7 (17.5)	
Best responses (INV)					
Objective response	3 (50.0)	16 (59.3)	28 (70.0)	13 (32.5)	
Complete response	2 (33.3)	11 (40.7)	23 (57.5)	8 (20.0)	
Partial response	1 (16.7)	5 (18.5)	5 (12.5)	5 (12.5)	
Stable disease	0	2 (7.4)	1 (2.5)	2 (5.0)	
Progressive disease	3 (50.0)	6 (22.2)	7 (17.5)	22 (55.0)	
Missing or unevaluable	0	3 (11.1)	4 (10.0)	3 (7.5)	
Best responses (IRC)					
Objective response	3 (50.0)	13 (48.1)	25 (62.5)	10 (25.0)	
Complete response	3 (50.0)	10 (37.0)	20 (50.0)	9 (22.5)	
Partial response	0	3 (11.1)	5 (12.5)	1 (2.5)	
Stable disease	2 (33.3)	5 (18.5)	5 (12.5)	9 (22.5)	
Progressive disease	1 (16.7)	4 (14.8)	6 (15.0)	8 (20.0)	
Missing or unevaluable	0	5 (18.5)	4 (10.0)	13 (32.5)	
Median duration of response, months (95% CI)					
IRC	NE (NE)	28.4 (15.0 to 31.9)	12.6 (7.2 to NE)	7.7 (4.0 to 18.9)	
INV assessed	NE (NE)	28.4 (3.0 to 31.9)	10.3 (5.6 to NE)	4.1 (2.6 to 12.7)	
Median progression-free survival, months (95% CI)					
IRC	NE (5.6 to NE)	6.3 (3.5 to 30.4)	9.5 (6.2 to 13.9)	3.7 (2.1 to 4.5)	
INV assessed	NE (1.8 to NE)	5.4 (2.8 to 30.4)	7.6 (6.0 to 17.0)	2.0 (1.5 to 3.7)	
Median overall survival, months (95% CI)	NE (5.6 to NE)	10.8 (5.8 to 33.8)	12.4 (9.0 to NE)	4.7 (3.7 to 8.3)	

NOTE. Data are no. (%) unless otherwise specified.

Abbreviations: BR, bendamustine-rituximab; INV, investigator; IRC, independent review committee; NE, not estimable; pola-BG, polatuzumab vedotin combined with bendamustine-rituximab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

*Phase Ib and II cohorts combined.

†Reasons for unevaluable patients are provided in the Appendix (Table A1).

assessments due primarily to a lag in obtaining confirmatory scans or not performing scans required for IRC review after INV-determined clinical progression.

OS was significantly improved in the pola-BR arm, with risk of death reduced by 58% (HR, 0.42; 95% CI, 0.24 to 0.75;

P = .002) and a longer median OS with pola-BR (12.4 months; 95% Cl, 9.0 to not evaluable) compared with BR alone (4.7 months; 95% Cl, 3.7 to 8.3 months; Fig 2C). Eleven pola-BR-treated patients and 4 BR-treated patients remained alive in follow-up. Post hoc subgroup analyses demonstrated consistent survival benefit across all clinical



FIG 2. (A) Progression-free survival by independent review committee. (B) Progression-free survival by investigator. (C) Overall survival of polatuzumab vedotin combined with bendamustine-rituximab (pola-BR) compared with bendamustine-rituximab (BR). (D) Forest plot of overall survival according to clinical and biologic characteristics. Values are based on an unstratified analysis. WHO classification was by central pathology review that incorporated results from NanoString Technologies for cell-of-origin determination when available. ABC, activated B-cell–like; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; GCB, germinal center B-cell–like; IPI, International Prognostic Index; ph, phase; ref, refractory; yr, year.

and biological subgroups examined (Fig 2D; Appendix Fig A1, online only). Importantly, patients benefited regardless of refractory status and number of prior lines of therapy, although sample sizes were small and statistical significance could not be established.

Multiple Cox regression analyses showed that after adjusting for potential prognostic factors and baseline characteristics, the treatment effects on survival of pola-BR

remained consistent with the primary analysis. For investigator-assessed PFS, the adjusted HR was between 0.34 (95% CI, 0.20 to 0.58; P < .001) and 0.38 (95% CI, 0.22 to 0.64; P < .001), whereas for IRC-assessed PFS, the adjusted HR was between 0.37 (95% CI, 0.21 to 0.66; P < .001) and 0.40 (95% CI, 0.23 to 0.70; P = .001). For OS, the adjusted HR was between 0.43 (95% CI, 0.24 to 0.78; P = .005) and 0.46 (95% CI, 0.26 to 0.82; P = .008).

D			BR (Pl (n = 4	h II) Ю)		Pola-BR (I (n = 40	Ph II))				
Baseline risk factors	Total No.	No.	Events	Median (months)	No.	Events	Median (months)	HR	95% CI	Pola-BR (Ph II)	BR (Ph II)
All patients	80	40	28	4.7	40	23	12.4	0.42	0.24 to 0.74	ц Т	
Age group, years										i i	
< 65	31	14	9	3.8	17	10	10.6	0.47	0.19 to 1.19	⊢ - þ	•
≥ 65 Cau	49	26	19	5.1	23	13	13.9	0.39	0.19 to 0.79		
Male	53	25	18	45	28	18	12 1	0 54	0 28 to 1 06		
Female	27	15	10	4.7	12	5	-	0.24	0.08 to 0.72		
Race						Ū		0.2.1	0100100112		
American Indian or Alaska Native	1	1	1	3.4	-	-	-	-	-		
Asian	10	4	0	-	6	2	-	> 999.99	0.00 to – 🛛 🗲		>
Black or African American	3	-	-	-	3	2	4.4	-	-	i	
White	57	31	23	4.7	26	15	12.6	0.40	0.21 to 0.77	 	
Unknown	9	4	4	4.1	5	4	9.0	0.26	0.05 to 1.49		-
Baseline ECOG PS	14	0	7	1.6	e	4	26	0.20	0 10 to 1 51		
≥ 2 0 or 1	14 64	0 21	/ 21	1.0	22	4	2.0	0.39	0.10 to 1.51		
Ann Arbor stage at study entry	04	51	21	5.5	55	15	13.5	0.45	0.23 10 0.80		
Stage III/IV	70	36	26	3.9	34	21	11.5	0.37	0.21 to 0.68	⊢┥	
Stage I/II	10	4	2	_	6	2	-	0.70	0.10 to 4.98		
Bulky disease										i	
Yes	25	15	12	3.7	10	7	11.8	0.50	0.19 to 1.31	┝─┼┓─┤	-
No	55	25	16	5.3	30	16	13.9	0.43	0.21 to 0.86		
Ref to last prior anti-cancer therapy										i	
Yes	64	34	24	3.9	30	19	9.5	0.48	0.26 to 0.89		
No	16	6	4	8.3	10	4	-	0.32	0.08 to 1.33	• • • • • • • •	-
Lines of prior anti-lymphoma therapy			00	0.0	00	10	11 5	0.47	0.05 1.0.00	. <u>i</u> .	
≥ Z 1	5/	28 12	20	3.8 5.0	29	18	11.5	0.47	0.25 to 0.89		
IPI at study entry	23	12	0	5.5		5		0.20	0.08 10 0.32		
> 3	51	29	22	3.9	22	15	10.5	0.44	0.22 to 0.86		
< 3	29	11	6	6.0	18	8	_	0.55	0.19 to 1.58		
Duration of response to prior anti-lymphoma therapy											
> 12 months	14	6	4	13.3	8	3	-	0.41	0.09 to 1.83		
≤ 12 months	66	34	24	3.9	32	20	10.5	0.43	0.23 to 0.79	⊢ ‡→	
Extranodal involvement at study entry											
Yes	56	29	21	3.9	27	18	11.5	0.43	0.22 to 0.82	⊢ ∎1	
No	24	11	7	8.4	13	5	-	0.37	0.12 to 1.18		1
Prior bone marrow transplant	10	~	•	5.0	10	0	10.0	0.70	0.40.1.0.05		
Yes	16	54	3	5.3	10	6 17	13.9	0.73	0.18 to 2.95		1
WHO 2016 DI BCL status	64	34	25	4.5	30	17	11.0	0.38	0.20100.72		
ABC	38	19	15	4.7	19	12	12.8	0.34	0.15 to 0.74		
GCB	32	17	12	3.8	15	11	8.9	0.56	0.24 to 1.29		-
									1/100	1	

FIG 2. (Continued).

Seven pola-BR patients (18%) had ongoing DOR of > 20 months (range, > 20.0 to ≥ 22.5 months) and remained in complete remission at last follow-up. One patient underwent consolidative allogeneic SCT; the other 6 received no additional therapy. Only 2 BR patients (5%) remained in follow-up without progression; both received consolidative therapy (1 allogeneic SCT and the other radiation). Overall, efficacy results for the as-treated DLBCL population (according to central pathology review, excluding the 2 patients with FL or Burkitt's lymphoma) were similar to those of the intent-to-treat population, as summarized in Appendix Table A2 (online only).

Safety

In the phase Ib pola-BR and phase Ib/II pola-BG cohorts, treatment delivery and AEs were similar to the phase II randomized pola-BR arm (Appendix). Among randomly assigned patients, the treatment completion rate was higher in the pola-BR arm compared with BR (46.2% v

23.1%), as was the median number of completed cycles (5 v3), primarily due to a higher rate of PD in the BR arm. In the randomly assigned cohort, 53.8% of pola-BR patients and 38.5% of BR patients had treatment delays (Appendix Table A3, online only). PD resulted in treatment discontinuation in 53.8% and 15.4% of patients treated with BR and pola-BR, respectively. AEs were the most common reason for discontinuation of pola-BR (33.3%; Appendix Table A3). In both arms, the most common reason for bendamustine dose reduction was cytopenias (4 pola-BR; 3 BR).

The most common all-grade and grade 3-4 AEs are shown in Table 3. Although rates of grade 3-4 anemia and thrombocytopenia were higher with pola-BR, transfusion rates were similar between pola-BR and BR (red cells: 25.6% v 20.5%; platelets: 15.4% v 15.4%). Grade 3-4 neutropenia was higher with pola-BR (46.2% v 33.3%), but grade 3-4 infections and infestations were similar

TABLE 3. Adverse Events in Patients	Treated With Pola-BR	Compared With BR
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	Pola-BR	(n = 39)*	BR (n = 39)*			
Adverse Event	All Grades, No. (%)	Grades 3-4, No. (%)	All Grades, No. (%)	Grades 3-4, No. (%)		
Blood and lymphatic system of	disorders					
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)		
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)		
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)		
Lymphopenia	5 (12.8)	5 (12.8)	0	0		
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)		
GI disorders						
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)		
Nausea	12 (30.8)	0	16 (41.0)	0		
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)		
General disorders and admini	istration site conditions					
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)		
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0		
Metabolism and nutrition disc	orders					
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0		
Peripheral neuropathy						
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0		

NOTE. Shown are all-grade adverse events occurring in \geq 20% of patients and grade 3-4 adverse events in \geq 10% of patients (safetyevaluable). Preferred terms are shown within each System Organ Class with the exception of peripheral neuropathy.

Abbreviations: BR, bendamustine-rituximab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

*One patient in each group did not receive the study treatment and so was excluded from the safety-evaluable population.

†Includes peripheral motor neuropathy, peripheral sensory neuropathy, decreased vibratory sense, hypoesthesia, paresthesia.

in both arms (23.1% pola-BR; 20.5% BR). Use of granulocyte-colony stimulating factor (GCSF) was permitted per investigator's discretion. For pola-BR versus BR, 71.8% versus 61.5% of patients received at least 1 dose of GCSF.

Overall incidence of PN was 43.6% (17/39) in pola-BR patients (11 grade 1; 6 grade 2), with resolution in 10 patients and improvement in 1 patient at clinical cutoff. PN was the only reason for polatuzumab vedotin dose reduction, which occurred in 2 patients (5.1%; both grade 2 PN), and in both cases, the PN resolved.

Fatal AEs occurred in 9 pola-BR patients and 11 BR patients, with infection being the most common cause (4 pola-BR; 4 BR). Many fatal AEs occurred after PD (Appendix).

Biomarkers: CD79b, COO, and DEL

Among 83 patient samples stained, 80 (96.4%) had detectable CD79b (immunohistochemistry [IHC] H-score 1-300 or 1⁺-3⁺). RNA assessments demonstrated measurable expression of CD79b in all samples, including 3 that were negative by IHC (Appendix Fig A2, online only). No relationship was observed between levels of CD79b expression and clinical outcome for both response rate and time-to-event clinical end points, including PFS and OS (Appendix Figs A3-A5, online only). COO assessment was performed in 107 patient samples, with 97 evaluable. COO distribution was 46.4% ABC, 47.4% germinal center B-cell–like (GCB), and 6.2% unclassifiable. In the randomly assigned cohort, improved outcome with pola-BR was observed in both ABC and GCB subgroups (Appendix Table A4; Appendix Fig A6, online only).

DEL status was assessed in 62 patient samples, with 41.9% identified as DEL. In the randomly assigned cohort, improved outcome with pola-BR was observed in both DEL and non-DEL patients (Appendix Table A5; Appendix Fig A7, online only).

DISCUSSION

Patients with transplantation-ineligible R/R DLBCL, including those who experienced treatment failure with ASCT, have dismal outcomes with limited therapeutic options. In this randomized comparison, treatment with pola-BR resulted in a significantly improved CR rate, PFS, and OS compared with BR alone. BR-treated patients fared poorly despite 13 patients receiving additional therapy after progression, highlighting the limitation of currently available agents. To our knowledge, this is the first randomized trial demonstrating an OS benefit in patients with transplantation-ineligible R/R DLBCL.

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OS was significantly longer in patients receiving pola-BR compared with BR alone (median, 12.4 months v 4.7 months). All subgroups examined appeared to benefit, including refractory patients and those who received multiple prior lines of therapy. Benefit was seen regardless of age, performance status, IPI score, and the presence of bulky disease. Furthermore, biomarker studies suggest that pola-BR benefited patients regardless of COO or DEL status. Ubiquitous expression of CD79b was confirmed, with no correlation noted between CD79b expression level and response. Although the independent contribution of bendamustine to overall efficacy cannot be measured, the 40% CR rate observed with pola-BR was notably higher than the 15% reported previously with polatuzumab vedotin in combination with an anti-CD20 monoclonal antibody.¹⁷ Achievement of CR has been associated with improved outcomes in DLBCL, and the higher CR rate observed may partly explain the durable responses seen in some patients receiving pola-BR, 7 (18%) of whom remained disease free.

The CR rate was 30% and 40% in the pola-BG and pola-BR arms, respectively. The modest number of patients in the pola-BG cohort made estimation of the true CR rate difficult; however, there was no indication of benefit of obinutuzumab over rituximab in this setting. Similarly, the GOYA trial (NCT01287741) did not demonstrate superiority of obinutuzumab over rituximab in front-line DLBCL.³

PN is a recognized toxicity associated with MMAE-based antibody-drug conjugates and was closely monitored during this study. Although many patients had prior exposure to vincristine or platinum agents, the majority of PN observed was low grade and reversible, requiring dose reduction or delay in relatively few patients. A higher rate of grade 3-4 cytopenias was observed with pola-BR versus

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Laurie H. Sehn, BC Cancer Centre for Lymphoid Cancer, 600 West 10th Ave, Vancouver, BC, V5Z 4E6 Canada; e-mail: lsehn@bccancer.bc.ca. BR, but this did not result in a higher risk of infection or need for transfusion.

The phase II design and modest sample size are potential limitations of the study; nonetheless, a clear and significant PFS and OS benefit was observed with pola-BR. Although this study examined pola-BR as a stand-alone therapy, the high CR rates and prolonged disease control observed suggest it may provide an important bridge to further consolidative therapies, including SCT or CAR T-cell therapy. Additional research into the feasibility and safety of this approach is warranted. CAR T-cell therapy is a promising treatment for patients with R/R DLBCL, but its generalized use has been limited by the inability to achieve timely and sufficient disease control in patients with rapidly evolving disease to enable them to proceed to CAR T-cell treatment. Availability of an effective novel agent, such as polatuzumab vedotin, may enable more patients to receive CAR T-cell therapy in the R/R setting. Conversely, not all patients with R/R DLBCL are suitable for CAR T-cell therapy because of its toxicity, including cytokine release syndrome and neurologic events, and specialized care requirements. Pola-BR may offer a valuable treatment option that is readily deliverable to a wider population of patients.

Pola-BR represents a novel, effective therapeutic regimen to address the unmet need of patients with transplantationineligible R/R DLBCL. Only 25% of pola-BR-treated patients had received prior ASCT; therefore, definitive conclusions on this combination's efficacy in the post-ASCT setting cannot currently be determined. Additional evaluation of polatuzumab vedotin with other agents in the R/R setting is ongoing, as is a phase III trial evaluating the substitution of polatuzumab vedotin for vincristine in R-CHOP for patients with untreated DLBCL (POLARIX; ClinicalTrials.gov identifier: NCT03274492).

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Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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Expanded Methods

Modified Lugano. Modifications to the Lugano 2014 Classification were as follows: (1) an assessment of complete response (CR) based solely on imaging modalities without confirmatory bone marrow testing was classified as a partial response (PR) for patients with bone marrow involvement or unknown status at baseline; (2) a PR (by independent review committee [IRC] only) required a partial metabolic response by [18F]fluorodeoxyglucose positron emission tomography and either a CR or PR by computed tomography; otherwise, the response per the modified Lugano 2014 criteria was classified as stable disease. However, because of an error, IRC had the PR modification, but the investigator did not.

Expanded Safety Results

Phase Ib polatuzumab vedotin in combination with bendamustine plus rituximab. Of the 6 patients treated in the phase Ib polatuzumab vedotin in combination with bendamustine plus rituximab (pola-BR) arm, the most common adverse events (AEs) occurring in \geq 1 patient were decreased appetite, decreased weight, diarrhea, hypocalcemia, pneumonia, pyrexia, thrombocytopenia (all 33.3%), hypokalemia and nausea (both 50%), and fatigue (66.7%). The following grade 3-4 AEs occurred in 1 patient: febrile neutropenia, pneumonia, and thrombocytopenia. Only 1 patient received granulocyte colony-stimulating factor (GCSF). No grade 5 AEs occurred.

Phase Ib/II polatuzumab vedotin in combination with bendamustine plus obinutuzumab. In the combined phase Ib/II polatuzumab vedotin with bendamustine and obinutuzumab (pola-BG) cohort, patients received a median of 4 cycles, with 42.3% of patients completing all treatment cycles. Overall, this was similar to pola-BR. The median dose intensity adjusted for dose modification and dose delay was approximately 99%-100% for all components. Bendamustine was dose reduced in 26.9% (7/26) of patients. The most common reasons for bendamustine dose reduction were neutropenia (15.4%) and fatigue/ asthenia (7.7%). One patient had 1 dose reduction for both neutropenia and fatigue (same cycle). The most common reasons for treatment delay were cytopenias (neutropenia or thrombocytopenia; 23.1%) and infection (15.4%). GCSF was used in 65.4% of patients. Two patients had treatment delays for transaminitis and 1 patient for peripheral neuropathy (PN).

The most common AEs occurring in at least 20% of patients were diarrhea (61.5%), fatigue (53.8%), nausea (53.8%), constipation (42.3%), decreased appetite (42.3%), pyrexia (42.3%), thrombocytopenia (30.8%), neutropenia (26.9%), anemia (19.2%), vomiting (34.6%), and hypokalemia (23.1%). The most commonly reported grade 3-4 AEs that occurred in at least 10% of patients were neutropenia (26.9%), thrombocytopenia (23.1%), febrile neutropenia

(11.5%), anemia (11.5%), nausea (11.5%), and fatigue (11.5%). Grade 3-4 infections occurred in 23.1% of patients.

All-grade PN occurred in 38.5% of patients, with 15.4% being grade \geq 2. Two patients reported grade 3 muscular weakness, although 1 was consistent with progression of disease. Two patients withdrew from all study treatments: 1 because of grade 2 PN and the other because of grade 3 muscular weakness.

There were 5 fatal AEs. Three of the fatal AEs were infections (pneumonia, fungal pneumonia, and sepsis). The other 2 were myelodysplastic syndrome (occurring 2 years after subsequent autologous transplantation) and general physical health deterioration.

Fatal AEs in pola-BR versus bendamustine plus rituximab. Three fatal AEs (pneumonia, hemoptysis, and pulmonary edema) in the pola-BR group and 4 (cerebrovascular accident, sepsis [2], and pneumonia) in the bendamustine plus rituximab (BR) group occurred within 35 days of treatment. Fatal AEs occurring during follow-up (including in the setting of PD) were pola-BR (distributive shock [PD], pneumonia [PD], renal failure [PD], intracranial hemorrhage [PD], herpetic encephalitis, and sepsis); BR (multiple-organ dysfunction [2 patients, both PD], cerebral hemorrhage [PD], leukoencephalopathy [PD], sepsis [PD], cardiac failure, and unexplained death).

Treatment delay and dose reductions in the pola-BG and pola-BR cohorts. Among the 45 patients who received pola-BR, treatment was delayed in 57.8% of patients (Appendix Table A3). Polatuzumab vedotin dose was reduced in 3 patients (6.7%). Among the 26 patients who received pola-BG, there were no dose reductions in polatuzumab vedotin, whereas 12 patients (46.2%) required a delay.

Expanded Biomarkers Methods

CD79b. CD79b tumor cell protein expression was assessed by immunohistochemistry (IHC) in central lab using the AT107-2 (Serotec, Oxford, UK) antibody and the Ventana Benchmark XT platform and was scored using staining intensity (0-3+). Additionally, the range of expression was evaluated with greater granularity by assessing continuous measurements of H-scores, a weighted scoring system that takes into account the percentage of tumor cells with 0, 1, 2, or 3+ staining intensity and ranges from 0 to 300. The H-score was calculated for staining of tumor cells using the following formula: H-score = (% at 0) × 0 + (% at 1+) × 1 + (% at 2+) × 2 + (% at 3+) × 3. Thus, this score produces a continuous variable that ranges from 0 to 300. Cells with H-score staining greater than 0 were considered positive.

In addition to a potential effect of the presence or absence of CD79b on activity by polatuzumab vedotin, the potential effects of different levels of CD79b expression were evaluated. The Subgroup Treatment Effect Pattern (STEP) plot approach was used to evaluate the relationship between CD79b expression and polatuzumab vedotin treatment effect in the patients with R/R DLBCL in phase II comparing pola-BR with BR. Window sizes of 25% and step-size increments of 5% were employed, and 95% CIs were displayed. To account for many ties in H-score, noise randomly drawn from a normal distribution was added.

Cell of origin. Samples were sent to Labcorp, where the NanoString LST assay was performed. If cell-of-origin (COO) classification by NanoString LST was not available (eg, because of tissue availability), COO was classified by central pathology review (HistoGeneX) with IHC using the Hans algorithm using local pathology reports. Non-GCB by Hans was counted as activated B-cell–like in analyses.

MYC/BCL2 double expression. IHC was performed at Ventana using the investigational-use-only B-cell lymphoma 2 (*BCL2*; 124) mouse antibody and *MYC* (Y69) IHC assays on the Ventana Benchmark XT platform. *MYC* IHC overexpression was defined as \geq 40% tumor nuclei as positive stains, and *BCL2* overexpression was defined as \geq 50% tumor cells with cytoplasmic staining intensity of \geq 2+.

Α			BR (Pr (n = 4	II) 0)		Pola-BR ((n = 4	(Ph II) 0)				
Baseline risk factors	Total No.	No.	Events	Median (months)	No.	Events	Median (months)	HR	95% CI	Pola-BR (Ph II)	BR (Ph II)
All patients	80	40	35	2.0	40	27	7.6	0.37	0.22 to 0.62		()
Age group, years < 65 ≥ 65	31 49	14 26	12 23	2.0 2.1	17 23	11 16	6.3 10.8	0.43 0.33	0.19 to 0.99 0.17 to 0.65		
Sex Male Female	53 27	25 15	22 13	2.0 2.8	28 12	20 7	7.5 10.4	0.39 0.36	0.21 to 0.73 0.14 to 0.92		
Race American Indian or Alaska Native	1	1	1	1.9	6	4	19.0	-	- 0 10 to 2 10		
Black or African American White	10 3 57	4	27	2.1	3 26	4 2 17	2.3	0.46	- 0.19 to 0.65		-
Unknown Baseline ECOG PS	9	4	4	2.4	5	4	7.7	0.38	0.07 to 2.18		-
≥ 2 0 or 1	14 64	8 31	8 27	0.9 2.1	6 33	4 23	2.3 7.7	0.39 0.39	0.10 to 1.51 0.22 to 0.69		•
Ann Arbor stage at study entry Stage III/IV Stage I/II	70 10	36 4	33 2	2.0	34 6	25 2	6.7	0.30 0.70	0.17 to 0.52 0.10 to 4.98		
Yes	25	15	14	1.9	10	8	7.6	0.56	0.23 to 1.39	<u>i</u>	•
Ref to last prior anti-cancer therapy Yes	64	34	30	1.9	30	22	6.0	0.41	0.23 to 0.73		
No Lines of prior anti-lymphoma therapy	16	6	5	5.1	10	5	19.0	0.26	0.07 to 0.97		
≥ 2 1 IPI at study entry	57 23	28 12	25 10	2.0 3.9	29 11	22 5	-	0.46	0.26 to 0.83 0.02 to 0.50		_
≥3 <3	51 29	29 11	27 8	2.0 2.5	22 18	17 10	6.2 10.4	0.35 0.48	0.19 to 0.67 0.10 to 1.23		
Duration of response to prior anti-lymphoma therapy	14	6	л	7 5	0	4		0.47	0 11 to 1 00		_
> 12 months ≤ 12 months Extranodal involvement at study entry	66	34	31	1.9	32	23	6.3	0.47	0.19 to 0.58	-	-
Yes No	56 24	29 11	28 7	2.0 2.5	27 13	18 9	6.3 17.0	0.30 0.58	0.16 to 0.56 0.21 to 1.57	÷	-
Yes No	16 64	6 34	4 31	3.6 2.0	10 30	8 19	6.9 7.7	0.86 0.30	0.26 to 2.88 0.16 to 0.54		
WHO 2016 DLBCL status ABC GCB	38 32	19 17	18 16	2.2 1.9	19 15	13 12	9.1 3.4	0.27 0.44	0.12 to 0.57 0.20 to 0.97	, i	
Ref to first prior anti-cancer therapy Yes	48	27	23	1.9	21	16	4.9	0.46	0.24 to 0.89		
No	32	13	12	4.5	19	11	17.1	0.33	0.15 to 0.77	1/100 1	
В			BR (Ph	II)		Pola-BR (Ph II)			1/100	100
_	-		(n = 4	0)		(11 = 4	0)				
Baseline risk factors	Total No.	No.	Events	Median (months)	No.	Events	Median (months)	HR	95% Cl	Pola-BR (Ph II)	BR (Ph II)
Baseline risk factors All patients Ace group, years	Total No. 80	No . 40	Events 32	Median (months) 3.7	No . 40	Events 25	Median (months) 9.5	HR 0.38	95% Cl 0.22 to 0.66	Pola-BR (Ph II)	BR (Ph II)
Baseline risk factors All patients Age group, years < 65 2 65	Total No. 80 31 49	No. 40 14 26	Events 32 10 22	Median (months) 3.7 3.2 3.7	No. 40 17 23	Events 25 11 14	Median (months) 9.5 7.4 11.9	HR 0.38 0.43 0.36	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72	Pola-BR (Ph II)	BR (Ph II)
Baseline risk factors All patients < 65 ≥ 65 Sex Male Eemale	Total No. 80 31 49 53 27	No. 40 14 26 25 15	(n = 4 Events 32 10 22 21 11	Median (months) 3.7 3.2 3.7 2.8 4.0	No. 40 17 23 28 12	Events 25 11 14 19 6	Median (months) 9.5 7.4 11.9 7.5 10.4	HR 0.38 0.43 0.36 0.38 0.38	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.14 to 1.04	Pola-BR (Ph II)	BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female Race American Indian or Alaska Native	Total No. 80 31 49 53 27	No. 40 14 26 25 15	(n = 4 Events 32 10 22 21 11	Median (months) 3.7 3.2 3.7 2.8 4.0	No. 40 17 23 28 12 -	Events 25 11 14 19 6	Median (months) 9.5 7.4 11.9 7.5 10.4	HR 0.38 0.43 0.36 0.38 0.38	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.14 to 1.04	Pola-BR (Ph II) 	BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female American Indian or Alaska Native Asian Black or African American	Total No. 80 31 49 53 27 1 10 3 57	No. 40 14 26 25 15 1 4 -	(n = 4 Events 32 10 22 21 11 11 2 	Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2 2.8	No. 40 17 23 28 12 - 6 3 26	Events 25 11 14 19 6 - 2 2 2	Median (months) 9.5 7.4 11.9 7.5 10.4 - - 2.4 0.5	HR 0.38 0.43 0.36 0.38 0.38 0.38	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.4 to 1.72 0.05 to 2.48	Pola-BR (Ph II) +	BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female Race American Indian or Alaska Native Asian Black or African American White Unknown Evon Becelon EFCO BE	Total No. 80 31 49 53 27 1 10 3 57 9	No. 40 14 25 15 1 4 - 31 4	Image: Non-Section 1 Image: No	Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2 - 3.8 3.7	No. 40 17 23 28 12 - 6 3 26 5	Events 25 11 14 19 6 - 2 2 17 4	Median (months) 9.5 7.4 11.9 7.5 10.4 - - - 2.4 9.5 9.0	HR 0.38 0.43 0.36 0.38 0.38 0.38 - 0.34 - 0.39 0.14	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.14 to 1.04 		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 265 Sex Male Female Race American Indian or Alaska Native Asian Black or African American White Unknown Baseline ECOG PS 2 0 0 r 1	Total No. 80 31 49 53 27 1 10 3 57 9 14 64	No. 40 14 26 25 15 1 4 - 31 4 8 31	Image: 10 minipage 32 10 minipage 21 11 1 25 4 7 25	Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2 	No. 40 17 23 28 12 - 6 3 26 5 6 33	Events 25 11 14 19 6 - 2 17 4 21	Median (months) 9.5 7.4 11.9 7.5 10.4 - 2.4 9.0 2.5 10.4	HR 0.38 0.43 0.36 0.38 0.38 - 0.34 - 0.39 0.14 0.39 0.39	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.14 to 1.04 		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female Race Asian Black or African American White Unknown Baseline ECOG PS < 2 2 0 or 1 Stage II/V Stage	Total No. 80 31 49 53 27 1 10 3 57 9 14 64 70 10	No. 40 14 25 15 1 4 - 31 4 8 31 36 4	(n = 4 Events 32 10 22 21 11 1 2 25 4 7 25 30 2	Jong Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2 - 3.8 3.7 0.9 3.8 3.2 3.4 3.7 3.8 3.7 3.8 3.7 3.8 3.7 3.8	No. 40 17 23 28 12 - 6 3 26 5 6 33 26 5 6 33 34 6	Image: Constraint of the second sec	Median (months) 9.5 7.4 11.9 7.5 10.4 - 2.4 9.5 9.0 2.5 9.0 2.5 10.4	HR 0.38 0.43 0.36 0.38 0.38 0.38 0.38 0.38 0.39 0.14 0.39 0.39 0.39 0.36 0.53	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.20 to 0.72 0.05 to 2.48 0.20 to 0.73 0.01 to 1.31 0.10 to 1.51 0.21 to 0.63 0.07 to 3.81		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 ≥ 65 Sex Male Female Race American Indian or Alaska Native Asian Black or African American White Unknown Baseline ECOG PS ≥ 2 0 or 1 Ann Arbor stage at study entry Stage I/I Stage I/I Bulky disease Yos	Total 80 31 49 53 27 1 10 3 57 9 14 64 70 10 25 55	No. 40 14 25 15 15 1 4 - 31 4 8 31 4 8 31 36 4 15 25	(n = 4 Events 32 10 22 21 11 1 2 - - 25 4 7 25 30 2 13 19	Jong Median (months) 3.7 3.2 3.7 3.2 3.7 2.8 4.0 1.9 11.2 -	No. 40 17 23 28 12 - 6 3 26 5 6 33 34 6 10 30	Events 25 11 14 19 6 - 2 2 17 4 21 23 2 7 18	J Median (months) 9.5 7.4 11.9 7.5 7.4 10.4 - 2.4 9.0 2.5 10.4 9.0 - 7.6 10.4 9.0 - 7.6 10.4 9.0	HR 0.38 0.43 0.36 0.38 0.38 0.38 0.34 0.39 0.34 0.39 0.39 0.39 0.35 0.52 0.36	95% Cl 0.22 to 0.66 0.18 to 0.72 0.18 to 1.07 0.18 to 0.72 0.20 to 0.72 0.20 to 0.72 0.74 to 1.73 0.07 to 1.31 0.20 to 0.63 0.27 to 0.81 0.20 to 0.63 0.07 to 3.81 0.20 to 1.36 0.21 to 0.71		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female Rec Asian Black or African American White Unknown Baseline ECOG PS < 2 0 or 1 Stage III/ Stage III	Total 80 31 49 53 27 1 10 3 57 9 14 64 70 10 25 55 64 16	No. 40 14 26 25 15 1 4 - 31 4 31 4 31 31 4 31 36 4 15 25 34 6	In = 4 Events 32 10 22 21 11 1 2 - 25 4 7 25 30 2 13 19 28 4	Jong Median (months) 3.7 3.2 3.7 3.2 3.7 3.2 3.7 3.2 3.7 3.2 3.7 3.2 3.7 3.2 3.7 3.8 3.7 3.8 3.7 3.8 3.7 9.3.8 3.2 14.9 2.6 3.9 2.8 5.5	No. 40 17 23 28 12 - 6 3 26 5 6 33 26 5 6 33 34 6 10 30 30 10	Events 25 11 14 19 6 - 2 2 17 4 21 23 2 7 18 20 5	Median (months) 9.5 7.4 11.9 7.5 0.4 - - 2.4 9.5 9.0 2.5 9.0 2.5 9.0 - 7.6 10.4	HR 0.38 0.43 0.38 0.38 0.38 0.38 0.38 0.39 0.14 0.39 0.39 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.39 0.39 0.36 0.39 0.39 0.36 0.39 0.36 0.39 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.39 0.36 0.56 0.	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.20 to 0.72 0.14 to 1.04 0.05 to 2.48 0.00 to 1.51 0.21 to 0.71 0.07 to .63 0.07 to .63 0.07 to .63 0.19 to 0.72 0.25 to 0.82 0.01 to 10.72		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 < 65 Sex Male Female Race American Indian or Alaska Native Asian Black or African American White Unknown Baseline ECOG PS ≥ 2 0 or 1 Ann Arbor stage at study entry Stage I/I) Stage I/I) Bulky disease Yes No Ref to last prior anti-cancer therapy Yes No	Total 80 31 49 53 1 10 357 14 70 255 64 57	No. 40 14 25 15 15 1 4 - 31 4 8 31 36 4 15 25 34 6 28	In = 4 Events 32 10 22 21 11 1 2 - 25 4 7 25 30 2 13 19 28 4 22 21	Jong Median (months) 3.7 3.2 3.7 3.2 3.7 3.7 2.8 4.0 1.9 11.2 3.8 3.7 0.9 3.8 3.2 14.9 14.9 2.6 3.9 2.8 5.5 3.2 3.47 3.7	No. 40 17 23 28 12 - 6 3 26 5 6 33 26 5 5 6 33 34 6 10 30 30 10 29	III	Jordian (months) 9.5 7.4 7.5 10.4 - 2.4 9.0 - 7.6 10.4 6.7 - 7.6 10.4	HR 0.38 0.43 0.36 0.38 0.39 0.34 0.39 0.36 0.52 0.36 0.45 0.45	95% Cl 0.22 to 0.66 0.18 to 0.72 0.18 to 0.72 0.20 to 0.72 0.20 to 0.73 0.01 to 1.31 0.20 to 0.33 0.07 to 3.81 0.20 to 0.63 0.07 to 3.81 0.20 to 1.36 0.19 to 0.72 < 0.01 to 0.59 < 0.01 to 0.59		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 Sex Male Female Race Asian Black or African American White Unknown Baseline ECOG PS ≥ 2 0 or 1 Stage II/V Stage II/V Stage II/V Stage II/I Bulky disease Yes No Elites of prior anti-lymphoma therapy Yes 1 IPI at study entry ≥ 3	Total 80 31 49 53 27 1 10 377 14 64 57 25 64 57 23 51	No. 40 14 25 15 1 - 31 4 31 4 31 4 31 36 4 15 25 34 6 28 12 29	Image: Non-Section 1 Image: No	Jong Median (months) 3.7 3.2 3.7 3.2 3.7 2.8 4.0 1.1 1.12 -	No. 40 17 23 28 12 - 6 3 26 5 6 33 26 5 6 33 34 6 10 30 30 10 29 11 22	Image: mail of the second se	or Median (months) 9.5 7.4 7.5 10.4 - 2.4 9.0 2.5 10.4 9.0 7.6 10.4 9.7 7.6 10.4 9.7 7.6 10.4 6.7 7.4 7.6 13.6 6.2 6.2	HR 0.38 0.43 0.36 0.38 0.38 0.39 0.14 0.39 0.36 0.35 0.36 0.37 0.39 0.36 0.52 0.36 0.45 0.45 0.45 0.45 0.42	95% Cl 0.22 to 0.66 0.18 to 1.06 0.18 to 0.72 0.14 to 1.04 0.05 to 2.48 0.00 to 1.51 0.21 to 0.71 0.07 to 3.61 0.20 to 1.51 0.20 to 1.51 0.20 to 1.51 0.20 to 1.36 0.19 to 0.72 0.07 to 3.81 0.20 to 1.36 0.19 to 0.72 0.00 to 0.59 0.25 to 0.82 < 0.01 to 0.59 0.22 to 0.82 0.01 to 0.59 0.22 to 0.82 0.01 to 0.59 0.22 to 0.82		BR (Ph II)
Baseline risk factors All patients Age group, years < 65 ≥ 65 Sex Male Female Race Asian Black or African American White Unknown Baseline ECOG PS ≥ 0 or 1 Ann Arbor stage at study entry Stage II/V	Total 80 31 49 53 27 1 3 57 14 70 10 25 64 57 51	No. 40 14 25 15 1 4 - 3 1 4 8 31 36 4 15 25 34 6 28 12 29 11	Image: 1 Image: 2	Jong Median (months) 3.7 3.2 3.7 3.2 3.7 2.8 4.0 1.1 1.12 3.8 3.7 0.9 3.8 3.2 14.9 2.6 3.9 2.8 5.5 3.2 4.7 3.2 4.6	No. 40 17 23 28 12 - 6 3 26 5 6 33 26 5 6 33 34 6 10 30 30 10 29 11 22 18	0 = 0 Events 25 11 14 19 6 - 2 2 7 17 4 4 21 23 2 7 18 20 5 19 6 15 10	or Median (months) 9.5 7.4 11.9 7.5 10.4 - 2.4 9.5 10.4 - 2.5 10.4 9.0 - 7.6 10.4 6.7 - 7.4 13.6 6.2 10.4	HR 0.38 0.43 0.36 0.38 0.38 0.39 0.39 0.39 0.36 0.52 0.36 0.42 0.42 0.42	95% Cl 0.22 to 0.66 0.18 to 1.02 0.18 to 0.72 0.14 to 1.04 0.05 to 2.48 0.20 to 0.72 0.20 to 0.73 0.01 to 1.51 0.21 to 0.71 0.20 to 0.53 0.07 to 3.81 0.20 to 0.82 0.07 to 3.81 0.20 to 0.82 0.07 to 3.81 0.22 to 0.82 0.01 to 1.86 0.22 to 0.82 0.10 to 0.88 0.22 to 0.88 0.17 to 1.21	₽ġġ₽₿ (₽ħ ₽) 	BR (Ph II)
Baseline risk factors All patients Age group, years < 65	Total 80 31 49 53 1 0 37 10 37 9 14 64 70 10 25 64 57 23 51 29 14	No. 40 14 25 15 1 -31 31 4 31 34 6 28 12 29 11 6 34	$\begin{array}{c} (1) = 4 \\ \hline \textbf{Events} \\ 32 \\ 10 \\ 22 \\ 21 \\ 11 \\ 1 \\ 2 \\ 25 \\ 4 \\ 7 \\ 5 \\ 30 \\ 2 \\ 13 \\ 19 \\ 28 \\ 4 \\ 22 \\ 10 \\ 28 \\ 4 \\ 22 \\ 10 \\ 28 \\ 4 \\ 28 \\ 28 \\ 4 \\ 28 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 1$	Jong Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2 -	No. 40 17 23 28 12 - 6 3 26 5 5 6 33 26 6 5 3 34 6 33 34 6 10 30 10 29 11 22 18 8 32	u = v Events 25 11 14 19 6 - 2 2 2 7 17 4 4 1 2 3 2 7 18 20 5 19 6 10 5 20	Jording Median (months) 9.5 7.4 7.5 10.4 - - 2.4 9.0 2.5 10.4 9.0 - 7.6 10.4 10.4 - 7.6 10.4 6.2 10.4 12.6 6.2 12.6 7.4	HR 0.38 0.43 0.36 0.38 0.38 0.39 0.39 0.36 0.52 0.36 0.45 0.42 0.42 0.42 0.45	95% Cl 0.22 to 0.72 0.18 to 1.06 0.18 to 1.06 0.18 to 1.07 0.20 to 0.72 0.20 to 0.72 0.20 to 1.33 0.07 to 3.81 0.20 to 1.36 0.19 to 0.73 0.20 to 1.36 0.19 to 0.72 < 0.01 to 0.83 0.22 to 0.82 0.22 to 0.78 0.22 to 0.78 0.10 to 0.83 0.22 to 0.78 0.22 to 0.78 0.10 to 0.83 0.22 to 0.78 0.10 to 0.83 0.22 to 0.82 0.22 to 1.80 0.22 to 1.80 0.22 to 1.80 0.21 to 1.81 0.21 to 1.81 0.21 to 1.81 0.21 to 1.81	┍╞╛╝ ╒╆ ╞╆ ╞╆ ┲ ┲ ┲ ┣ ╊ ┲ ╊ ┲ ╊ ┲ ┲ ┲ ┲ ┲ ┲	BR (Ph II)
Baseline risk factors All patients Age group, years < 65 Sex Male Female Race American Indian or Alaska Native Asian Black or African American White Unknown Baseline ECOG PS ≥ 2 0 or 1 Ann Arbor stage at study entry Stage I/I Bulky disease Yes No Ref to last prior anti-cancer therapy Yes No Ref to last prior anti-dymphoma therapy ≥ 1 IPI at study entry ≥ 3 < 3 Duration of response to prior anti-lymphoma therapy > 1 IPI at study entry > 3 < 3 Duration of response to prior anti-lymphoma therapy > 12 months > 12 months < 12 months < 12 months	Total 80 31 49 53 1 10 37 14 64 16 57 25 64 16 57 23 51 29 14 66 57 23 51 24	No. 40 14 26 15 1 - 31 4 - 31 4 - 31 4 - 31 4 - 31 4 - 31 4 - 31 36 4 5 34 6 34 6 34 6 34 6 34 6 34 6 34 6 34 6 34 6 34 6 34 6 34 6	(i) = 4 Events 32 10 22 21 11 1 2 25 4 7 25 4 25 7 28 4 28 4 28 25 7 25 7 28 4 28 25 7 25 25 26 27 27 27 27 27 27 27 27 27 27	Jong Median (months) 3.7 3.2 3.7 2.8 4.0 1.9 11.2	No. 40 17 23 28 12 - 6 32 6 33 34 6 10 30 10 30 10 29 11 22 18 8 32 27 13	(1) = Events 25 11 14 19 6 - 2 2 17 4 4 21 23 2 7 18 20 5 19 6 15 10 5 20 19 6 15 20 10 19 10 10 10 10 10 10 10 10 10 10	J Median (months) 9.5 7.4 7.5 10.4 - - 2.4 9.0 2.5 10.4 9.0 - 7.6 10.4 9.0 - 7.6 10.4 6.7 - 7.4 10.4 10.4 - 7.4 - 9.5 -	HR 0.38 0.43 0.38 0.33 0.34 0.39 0.14 0.39 0.363 0.52 0.36 0.45 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.42 0.43	95% Cl 0.22 to 0.86 0.18 to 1.06 0.18 to 1.07 0.18 to 1.07 0.05 to 2.48 0.20 to 0.72 0.14 to 1.04 0.05 to 2.48 0.20 to 0.73 0.01 to 1.31 0.10 to 1.51 0.20 to 0.63 0.07 to 3.81 0.20 to 0.63 0.07 to 3.81 0.20 to 0.63 0.19 to 0.72 0.25 to 0.82 < 0.01 to 0.59 0.22 to 0.78 0.10 to 0.88 0.22 to 0.78 0.10 to 0.88 0.22 to 0.78 0.10 to 0.88 0.22 to 0.82 0.11 to 1.21 0.12 to 1.80 0.20 to 0.85 0.20 to 0.85 0.20 to 0.72 0.13 to 0.77 0.13 to 0.78 0.12 to 0.81 0.20 to 0.85 0.20 to 0.75 0.13 to 0.78 0.13 to 0.78 0.13 to 0.78 0.21 to 0.71 0.12 to 0.85 0.22 to 0.85 0.22 to 0.85 0.22 to 0.78 0.13 to 0.78 0.21 to 0.71 0.12 to 1.80 0.20 to 0.85 0.20 to 0.75 0.13 to 0.78 0.13 to 0	Pola-BR (Ph II) + ++ ++ + + ++ ++ ++ ++ ++ ++ ++ ++ ++	BR (Ph II)
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FIG A1. Forest plot for progression-free survival by (A) investigator and (B) independent review committee (IRC) in patients treated with polatuzumab vedotin combined with bendamustine-rituximab (pola-BR) or bendamustine-rituximab (BR). ABC, activated B-cell–like; DLBCL, diffuse B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; IPI, International Prognostic Index; ph, phase; ref, refractory.

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FIG A2. CD79b gene expression. Of the 3 samples with undetectable CD79b by immunohistochemistry (IHC), parallel RNA assessments showed measurable expression significantly above background levels inconsistent with the IHC data. Each point represents an individual sample or negative control probes. Gene expression levels are median normalized as defaulted in the NanostringQCPro Bioconductor R-package.



FIG A3. CD79b protein expression (immunohistochemistry [IHC] H-scores) in patients with relapsed/refractory diffuse large B-cell lymphoma treated with polatuzumab vedotin–based therapy relative to responses at end of treatment (independent review committee [IRC] assessed). There was no significant difference in expression between responders and nonresponders (P = .69; Wilcoxon rank-sum test with continuity correction). CR, complete response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.



FIG A4. Polatuzumab vedotin (pola) treatment effect as seen across the range of CD79b expression for investigatorassessed progression-free survival (PFS). Subgroup Treatment Effect Pattern (STEP) plot for the phase II patients with relapsed/refractory diffuse large B-cell lymphoma comparing pola-bendamustine and rituximab with bendamustine and rituximab shows that there was no association between CD79b expression and pola treatment effect. The STEP plot shows the hazard ratios and 95% Cls from overlapping subpopulations of patients grouped by a sliding window of CD79b immunohistochemistry H-score values for investigator-assessed PFS. The result was robust to different draws (data not shown).



FIG A5. Polatuzumab vedotin (pola) treatment effect as seen across the range of CD79b expression for overall survival (OS). Subgroup Treatment Effect Pattern (STEP) plot for the phase II patients with relapsed/refractory diffuse large B-cell lymphoma comparing pola-bendamustine and rituximab with bendamustine and rituximab. It shows hazard ratios (HRs) and 95% CIs from overlapping subpopulations of patients grouped by a sliding window of CD79b immunohistochemistry H-score values for OS. In the STEP plot, we see a consistent HR that has natural variability around the "overall" HR of 0.43 in the biomarker-evaluable population. The result was robust to different draws (data not shown).



FIG A6. (A) Progression-free survival (PFS) by investigator (INV) and (B) overall survival (OS) in patients with activated B-cell–like (ABC) and germinal center B-cell–like (GCB) diffuse large B-cell lymphoma. BR, bendamustine-rituximab; HR, hazard ratio; NE, not estimable; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.



FIG A7. (A) Progression-free survival (PFS) by investigator (INV) and (B) overall survival (OS) in patients with double-expressor lymphoma (DEL) and non-DEL diffuse large B-cell lymphoma. BR, bendamustine-rituximab; HR, hazard ratio; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

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TABLE A1. Reasons for "Not Evaluable" at EOT Rea

Reason	No. of Patients
Phase I pola-BR	
No EOT scan performed (PD by INV at interim, SD by IRC)	2
Phase I/II pola-BG	
Clinical progression, no scan performed	3
No EOT scan performed because of AE	1
Scan not received by IRC (PD by INV)	1
Scan considered unevaluable by IRC	3
Phase II randomized BR	
Clinical progression, no scan performed	14
No EOT scan performed; interim scan PD by INV and SD by IRC	4
No EOT scan performed; death from AE	2
No scans performed in study; withdrew from study	2*
Phase II randomized pola-BR	
No EOT scan performed due to AE	3
No EOT scan for IRC	1†
No scans in study; withdrew from study	2‡
EOT scan unevaluable by IRC	1

1

EOT CT performed without PET§

Abbreviations: AE, adverse event; BR, bendamustine and rituximab; CT, computed tomography; EOT, end of treatment; INV, investigator; IRC, independent review committee; PD, progressive disease; PET, positron emission tomography; pola-BG, polatuzumab vedotin combined with bendamustine-obinutuzumab; pola-BR, polatuzumab vedotin combined with bendamustine and rituximab; PR, partial response; SD, stable disease.

*One patient was not treated, as was determined by investigator to be rapidly progressing and withdrew from study.

†No EOT scan; on interim scan, investigator-assessed PD, but IRC-assessed SD. No additional scans were performed.

‡One patient was found no longer eligible just before treatment, was not treated, and withdrew.

\$CT showed PR by both investigator and IRC; however, all responses required PET to be considered at EOT, unless it showed progression (then CT alone was acceptable). Scan was performed approximately 8 weeks after 2 cycles (discontinued because of AE).

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TABLE A2. Summary of Efficacy Outcomes in the As-Treated DLBCL Population (according to central pathology review)

	Phase II Randomized				
Outcome	Pola-BR (n = 37)	BR (n = 39)			
End of treatment					
IRC, objective response	16 (43.2)	7 (17.9)			
Complete response	15 (40.5)	7 (17.9)			
Р	EO.	}			
Partial response	1 (2.7)	0			
Stable disease	6 (16.2)	1 (2.6)			
Progressive disease	8 (21.6)	10 (25.6)			
Missing or unevaluable	7 (18.9)	21 (53.8)			
INV assessed, objective response	17 (45.9)	7 (17.9)			
Complete response	15 (40.5)	6 (15.4)			
Partial response	2 (5.4)	1 (2.6)			
Stable disease	1 (2.7)	0			
Progressive disease	12 (32.4)	26 (66.7)			
Missing or unevaluable	7 (18.9)	6 (15.4)			
Best responses (INV)					
Objective response	26 (70.3)	13 (33.3)			
Complete response	21 (56.8)	8 (20.5)			
Partial response	5 (13.5)	5 (12.8)			
Stable disease	1 (2.7)	2 (5.1)			
Progressive disease	7 (18.9)	22 (56.4)			
Missing or unevaluable	3 (8.1)	2 (5.1)			
Best responses (IRC)					
Objective response	23 (62.2)	10 (25.6)			
Complete response	19 (51.4)	9 (23.1)			
Partial response	4 (10.8)	1 (2.6)			
Stable disease	5 (13.5)	9 (23.1)			
Progressive disease	6 (16.2)	8 (20.5)			
Missing or unevaluable	3 (8.1)	12 (30.8)			
Median duration of response, months, (95% CI)					
IRC assessed	10.9 (5.7 to NE)	7.7 (4.0 to 18.9)			
INV assessed	9.0 (5.6 to NE)	4.1 (2.6 to 12.7)			
Median progression-free survival, months, (95% CI)					
IRC assessed	9.0 (4.9 to 13.4)	3.7 (2.1 to 4.5)			
HR (95% CI)	0.38 (0.22	to 0.65)			
Р). >)1			
INV assessed	7.4 (4.9 to 12.6)	2.0 (1.5 to 3.7)			
HR (95% CI)	0.35 (0.21	to 0.60)			
Р). >)1			
Median overall survival, months (95% CI)	11.8 (8.9 to NE)	4.7 (3.7 to 8.3)			
HR (95% CI)	0.45 (0.26	to 0.80)			
P	0. >	01			

NOTE. Data are no. (%) unless otherwise specified.

Abbreviations: BR, bendamustine-rituximab; HR, hazard ratio; INV, investigator; IRC, independent review committee; NE, not estimable; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

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TABLE A3.	Summary of	Treatment	Exposure	(safety-evaluable	population)
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	Phase Ib Safety Run-In	Phase Ib/II Expansion	Phase II Randomized		
Treatment Exposure	Pola-BR $(n = 6)$	Pola-BG ($n = 26$)	Pola-BR ($n = 39$)	BR (n = 39)	
Median no. of cycles completed (range)	4.5 (2-6)	4 (1-6)	5 (1-6)	3 (1-6)	
Completed 6 cycles	2 (33.3)	11 (42.3)	18 (46.2)	9 (23.1)	
Discontinued treatment					
Progressive disease	3 (5)	6 (23.1)	6 (15.4)	21 (53.8)	
Lack of efficacy	0	0	1 (2.6)	1 (2.6)	
AE	1 (16.7)	6 (23.1)	13 (33.3)	4 (10.3)	
Other	0	3 (11.5)	1 (2.6)	4 (10.3)	
Pola dose reduction	0	0	2 (5.1)	_	
Bendamustine dose reduction	1 (16.7)	7 (26.9)	5 (12.8)	4 (10.3)	
Treatment delay	2 (33.3)	11 (42.3)	21 (53.8)	15 (38.5)	
Median dose intensity, % (range)*					
Pola	98 (91-100)	89 (54-105)	93 (58-109)	—	
Bendamustine	97 (81-98)	94 (55-137)	91 (84-98)	93 (63-102)	
Rituximab or obinutuzumab	97 (88-100)	95 (77-100)	91 (70-103)	93 (45-101)	

NOTE. Data are no. (%) unless otherwise specified.

Abbreviations: AE, adverse event; BR, bendamustine-rituximab; pola, polatuzumab vedotin; pola-BG, polatuzumab vedotin combined with bendamustine-obinutuzumab; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

*Dose intensity: percentage of planned dose received in cycles delivered.

	ABC, No. (%)		GCB,	No. (%)	
Response	Pola-BR (n = 17)	BR (n = 18)	Pola-BR (n = 15)	BR (n = 17)	
CR	8 (47.1)	2 (11.1)	4 (26.7)	2 (11.8)	
PR	2 (11.8)	0	1 (6.7)	0	
SD	0	0	0	0	
PD	5 (29.4)	15 (83.3)	8 (53.3)	11 (64.7)	
NE	2 (11.8)	1 (5.6)	2 (13.3)	4 (23.5)	

 TABLE A4.
 Response Rates (investigator assessed) at End of Treatment, by COO

 ABC. No. (%)
 GCB. No. (%)

Abbreviations: ABC, activated B-cell–like; BR, bendamustine-rituximab; COO, cell of origin; CR, complete response; GCB, germinal center B-cell–like; NE, not estimable; PD, progressive disease; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab; PR, partial response; SD, stable disease.

TABLE A5.	Response Rates (investigator assessed) at End of Treatment in Patients	
With and W	ithout DEL Treated With Pola-BR Compared With BR	

	DEL, No. (%)		Non-DEL, No. (%)	
Response	Pola-BR (n = 11)	BR (n = 6)	Pola-BR (n = 12)	BR (n = 13)
CR	4 (36.4)	1 (16.7)	4 (33.3)	2 (15.4)
PR	1 (9.1)	0	1 (8.3)	0
SD	0	0	0	0
PD	2 (18.2)	5 (83.3)	6 (50.0)	9 (69.2)
NE	4 (36.4)	0	1 (8.3)	2 (15.4)

Abbreviations: BR, bendamustine-rituximab; CR, complete response; DEL, double-expressor lymphoma; NE, not estimable; PD, progressive disease; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab; PR, partial response; SD, stable disease.