original reports abstract

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

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

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% *v* 17.5%; $P = .026$) and longer IRC-assessed PFS (median, 9.5 *v* 3.7 months; hazard ratio [HR], 0.36, 95% CI, 0.21 to 0.63; $P < .001$) and OS (median, 12.4 *v* 4.7 months; HR, 0.42; 95% CI, 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.

J Clin Oncol 38:155-165. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying article on page 166

Appendix

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

Accepted on September 24, 2019 and published at ascopubs.org/journal/jco on November 6, 2019: DOI https://doi.org/10.1200/JCO.19.00172

Clinical trial information: NCT02257567

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 third-line 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 antibody-drug conjugate delivering monomethyl auristatin E

(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 monotherapy[16] 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 platinum-based regimens. Obinutuzumab, an alternative CD20-targeted agent designed to promote greater antibody-dependent 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 (ClinicalTrials.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 transplantation-ineligible 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 ≥ 18 years were eligible if they had biopsy-confirmed R/R DLBCL (excluding transformed lymphoma) after ≥ 1 prior line of therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, grade ≤ 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 (≤ 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/m^2 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/m^2 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 21-day cycles.

Assessments and End Points

Primary end points were safety and tolerability (phase Ib) and CR rate of pola-BR versus BR (phase II), as measured by [^{18}F]fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) using modified Lugano Response Criteria[22] (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,

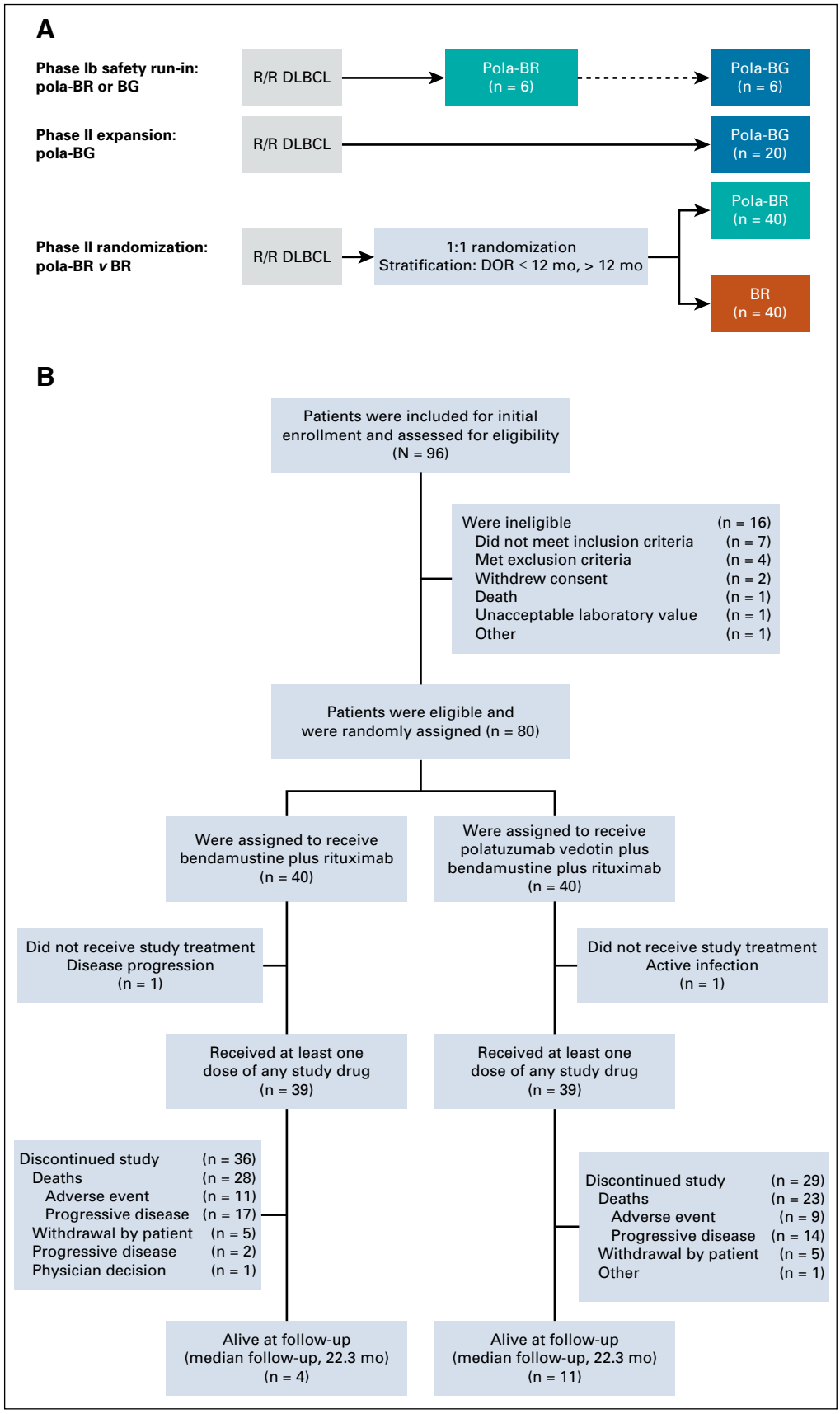

FIG 1. (A) Study schema. (B) CONSORT diagram for randomly assigned cohort. BG, bendamustine-obinutuzumab; BR, bendamustine-rituximab; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; mo, month; pola, polatuzumab vedotin; pola-BG, polatuzumab vedotin combined with bendamustine-obinutuzumab; 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 ± 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 ≥ 85% likelihood of observing ≥ 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) CIs. Time-to-event end points, including DOR, PFS, and OS, were summarized as median survival time estimated using Kaplan–Meier methodology with 95% Greenwood's CIs. 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 IRC-assessed 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 ≥ 22.5 months) without additional therapy. At last follow-up, 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

TABLE 1. Baseline 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 (≥ 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.

†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.

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-obinutuzumab; 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% CI, 9.0 to not evaluable) compared with BR alone (4.7 months; 95% CI, 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

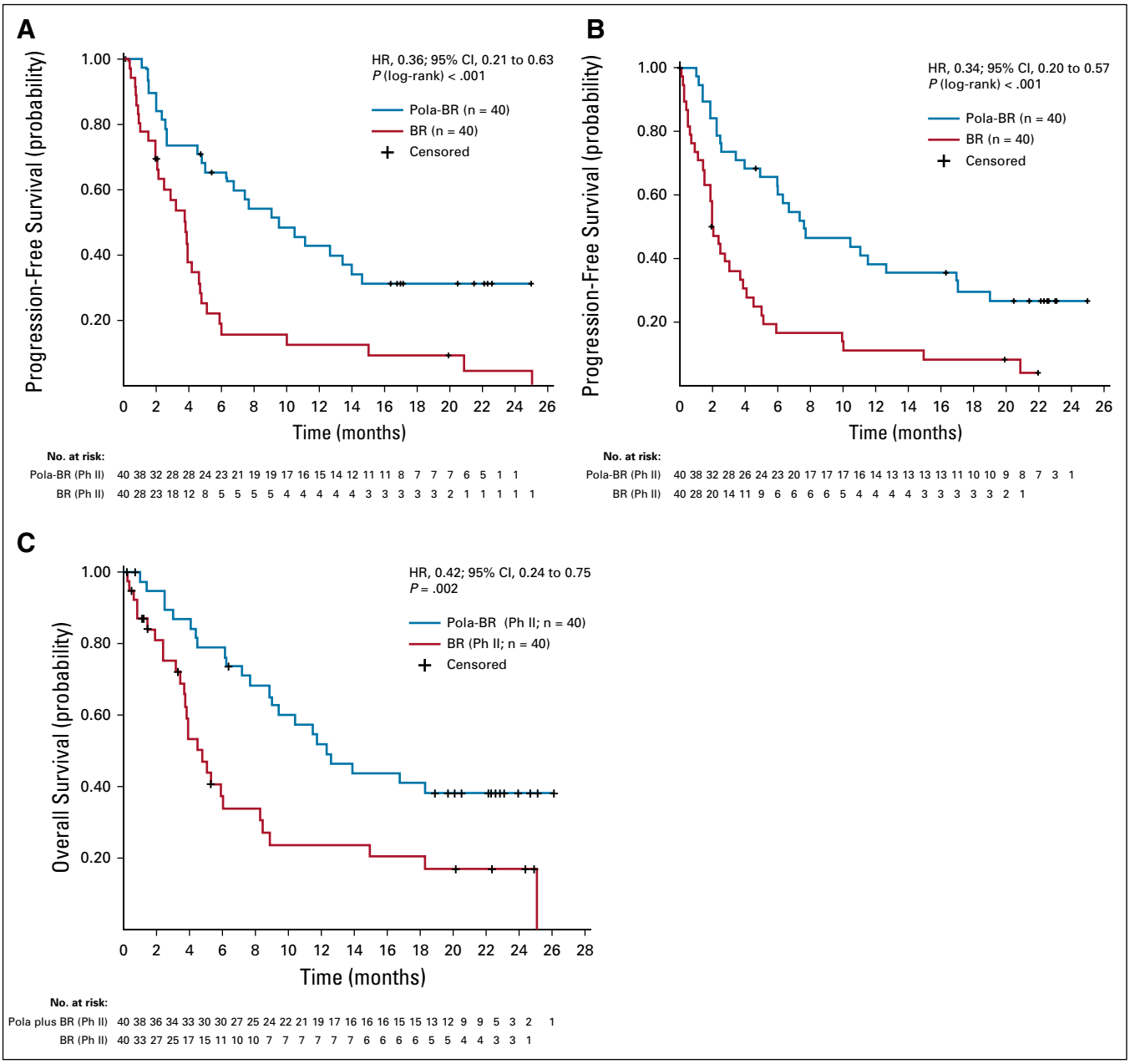

FIG 2. (A) Progression-free survival by independent review committee. (B) Progression-free survival by investigator. (C) Overall survival of polatuzumab vedotin combined with bendamustine-rituximab (pola-BR) compared with bendamustine-rituximab (BR). (D) Forest plot of overall survival according to clinical 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; $P = .008$).

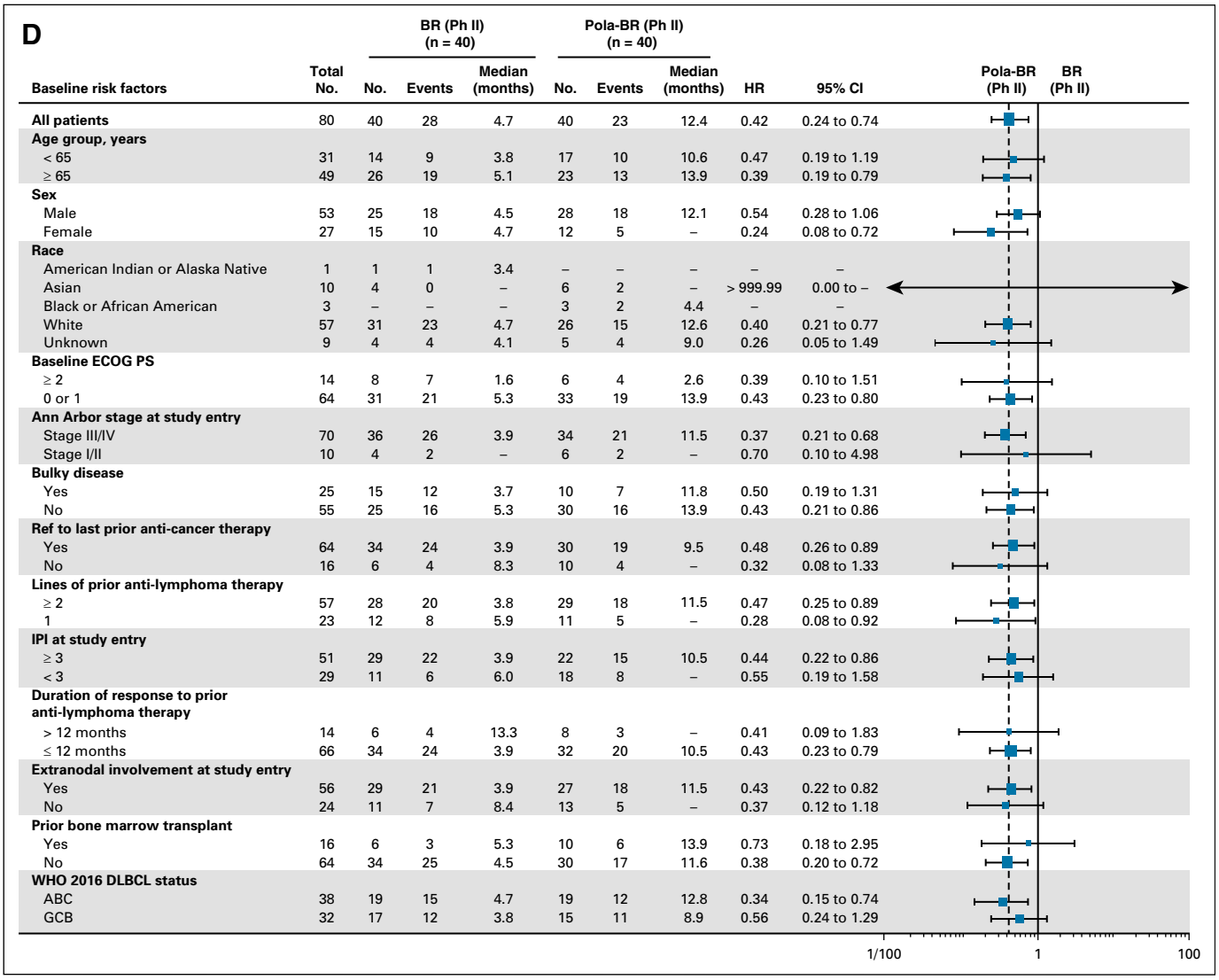

FIG 2. (Continued).

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 *v* 3), 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

	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 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 administration 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 disorders				
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 ≥ 20% of patients and grade 3-4 adverse events in ≥ 10% of patients (safety-evaluable). 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.

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 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 transplantation-ineligible 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).

AFFILIATIONS

[1]BC Cancer Centre for Lymphoid Cancer and The University of British Columbia, Vancouver, British Columbia, Canada
[2]City of Hope, Duarte, CA
[3]Winship Cancer Institute of Emory University, Atlanta, GA
[4]University of Colorado, Aurora, CO
[5]Nottingham University Hospitals, Nottingham, United Kingdom
[6]Prince of Wales Hospital and University of NSW, Sydney, NSW, Australia
[7]Jewish General Hospital, Montreal, Quebec, Canada
[8]Seoul National University Hospital, Seoul, South Korea
[9]Samsung Medical Center, Seoul, South Korea
[10]Ankara University, Ankara, Turkey
[11]Genentech, South San Francisco, CA
[12]F. Hoffman-La Roche, Mississauga, Ontario, Canada
[13]Memorial Sloan Kettering Cancer Center, New York, NY

CORRESPONDING AUTHOR

Laurie H. Sehn, BC Cancer Centre for Lymphoid Cancer, 600 West 10th Ave, Vancouver, BC, V5Z 4E6 Canada; e-mail: lsehn@bccancer.bc.ca.

PRIOR PRESENTATION

Presented at the 2016 American Society of Hematology (ASH) Annual Meeting, December 3-6 2016, San Diego, CA; 2017 European Hematology Association (EHA) Annual Meeting, June 22-25 2017, Madrid, Spain; 2017 ASH Annual Meeting, December 9-12 2017, Atlanta, GA; 2018 EHA Annual Meeting, June 14-17 2018, Stockholm, Sweden; 2018 ASCO Annual Meeting, June 1-5 2018, Chicago, IL; and 2018 ASH Annual Meeting, December 1-4 2018, San Diego, CA.

SUPPORT

Supported by F. Hoffmann-La Roche and Genentech (GO29365).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00172.

AUTHOR CONTRIBUTIONS

Conception and design: Laurie H. Sehn, Christopher R. Flowers, Andrew McMillan, Jamie Hirata, Elicia Penuel, Ji Cheng, Grace Ku, Matthew J. Matasar

Provision of study materials or patients: Laurie H. Sehn, Alex F. Herrera, Christopher R. Flowers, Manali K. Kamdar, Andrew McMillan, Mark Hetzberg, Sarit Assouline, Tae Min Kim, Won Seog Kim, Muhit Ozcan, Matthew J. Matasar

Collection and assembly of data: Laurie H. Sehn, Alex F. Herrera, Christopher R. Flowers, Manali K. Kamdar, Andrew McMillan, Sarit Assouline, Tae Min Kim, Won Seog Kim, Muhit Ozcan, Jamie Hirata, Elicia Penuel, Ji Cheng, Grace Ku, Matthew J. Matasar

Data analysis and interpretation: Laurie H. Sehn, Alex F. Herrera, Christopher R. Flowers, Manali K. Kamdar, Andrew McMillan, Mark Hertzberg, Sarit Assouline, Tae Min Kim, Won Seog Kim, Jamie Hirata, Elicia Penuel, Joseph N. Paulson, Ji Cheng, Grace Ku, Matthew J. Matasar

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the participating patients and their families, and the research nurses, study coordinators, and operations staff. Additional assistance was provided by Brandon Croft, PharmD, Will Harris, MS, and Lawrence Lu, MD, employees of Genentech. Third-party editorial assistance, under the direction of the authors, was provided by Rachel Hubbard, MSc, of Gardiner-Caldwell Communications and was funded by F. Hoffmann-La Roche.

REFERENCES

1. Armitage JO, Weisenburger DD: New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 16:2780-2795, 1998
2. Swerdlow SH, Campo E, Harris NL, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Volume 2 (rev ed 4). Lyon, France, International Agency for Research on Cancer, 2017
3. Vitolo U, Trněný M, Belada D, et al: Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol 35:3529-3537, 2017
4. Coiffier B, Lepage E, Brière J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002
5. Scott DW, Mottok A, Ennishi D, et al: Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fix paraffin-embedded tissue biopsies. J Clin Oncol 33:2848-2856, 2015
6. Johnson NA, Slack GW, Savage KJ, et al: Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 30:3452-3459, 2012
7. Gisselbrecht C, Glass B, Mounier N, et al: Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 28:4184-4190, 2010
8. Crump M, Neelapu SS, Farooq U, et al: Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. Blood 130: 1800-1808, 2017
9. National Comprehensive Cancer Network: NCCN guidelines for diffuse large B-cell lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
10. Neelapu SS, Locke FL, Bartlett NL, et al: Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377:2531-2544, 2017
11. Schuster SJ, Bishop MR, Tam CS, et al: Primary analysis of JULIET: A global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Blood 130:577, 2017
12. Okazaki M, Luo Y, Han T, et al: Three new monoclonal antibodies that define a unique antigen associated with prolymphocytic leukemia/non-Hodgkin's lymphoma and are effectively internalized after binding to the cell surface antigen. Blood 81:84-94, 1993
13. Bai RL, Pettit GR, Hamel E: Binding of dolastatin 10 to tubulin at a distinct site for peptide antimitotic agents near the exchangeable nucleotide and vinca alkaloid sites. J Biol Chem 265:17141-17149, 1990
14. Dornan D, Bennett F, Chen Y, et al: Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood 114:2721-2729, 2009
15. Pfeifer M, Zheng B, Erdmann T, et al: Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia 29:1578-1586, 2015
16. Palanca-Wessels MCA, Czuczman M, Salles G, et al: Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: A phase 1 study. Lancet Oncol 16:704-715, 2015
17. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol 6:254-265, 2019
18. Ohmachi K, Niitsu N, Uchida T, et al: Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 31:2103-2109, 2013
19. Vacirca JL, Acs PI, Tabbara IA, et al: Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 93:403-409, 2014
20. Mössner E, Brünker P, Moser S, et al: Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 115:4393-4402, 2010
21. Herter S, Herting F, Mundigl O, et al: Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther 12:2031-2042, 2013
22. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3068, 2014

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Laurie H. Sehn
Honoraria: Amgen, Apobiologix, AbbVie, Celgene, F. Hoffmann-La Roche, Gilead Sciences, Janssen-Ortho, Karyopharm Therapeutics, Kite Pharma, Lundbeck, Merck, Genentech, Seattle Genetics, Takeda, Teva, TG Therapeutics, AstraZeneca, Acerta Pharma, Morphosys
Consulting or Advisory Role: Celgene, AbbVie, Seattle Genetics, TG Therapeutics, Janssen, Amgen, Genentech, Gilead Sciences, Lundbeck, Amgen, Apobiologix, Karyopharm Therapeutics, Kite Pharma, Merck, Takeda, Teva, TG Therapeutics, AstraZeneca, Acerta Pharma, MorphoSys, F. Hoffmann-La Roche
Research Funding: F. Hoffmann-La Roche (Inst)

Alex F. Herrera
Consulting or Advisory Role: Bristol-Myers Squibb, Merck, Kite Pharma, Seattle Genetics
Research Funding: Pharmacyclics (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Genentech (Inst), Kite Pharma, Immune Design (Inst), AstraZeneca (Inst), Seattle Genetics (Inst), Gilead Sciences (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Christopher R. Flowers
Consulting or Advisory Role: Bayer, Gilead Sciences, Spectrum Pharmaceuticals, AbbVie, Celgene, Denovo Biopharma, BeiGene, AstraZeneca, Karyopharm Therapeutics, Pharmacyclics/Janssen, Genentech, MEI Pharma
Research Funding: Acerta Pharma (Inst), Onyx (Inst), Janssen Oncology (Inst), Gilead Sciences (Inst), Celgene (Inst), TG Therapeutics (Inst), Genentech (Inst), Pharmacyclics (Inst), AbbVie (Inst), Immune Design (Inst), BeiGene (Inst), Millennium (Inst)
Travel, Accommodations, Expenses: Gilead Sciences, Celgene, Genentech

Manali K. Kamdar
Consulting or Advisory Role: AstraZeneca, Celgene, Pharmacyclics/Janssen
Speakers' Bureau: Seattle Genetics

Andrew McMillan
Honoraria: Genentech, Celgene, BMS, MSD Oncology, Novartis, AbbVie
Consulting or Advisory Role: Celgene (I)
Speakers' Bureau: Genentech
Research Funding: Pfizer, Genentech (Inst)
Travel, Accommodations, Expenses: Genentech, Celgene, Takeda

Mark Hertzberg
Honoraria: BMS, Takeda, Genentech
Consulting or Advisory Role: MSD, Janssen, Roche
Travel, Accommodations, Expenses: Takeda

Sarit Assouline
Stock and Other Ownership Interests: Knight Pharmaceuticals
Honoraria: Janssen Oncology, Pfizer
Consulting or Advisory Role: AbbVie, Roche Canada, Genentech
Speakers' Bureau: Pfizer, Janssen, Bristol-Myers Squibb
Research Funding: Roche Canada (Inst), Takeda (Inst), Epizyme (Inst), Gilead Sciences (Inst), Astex Pharmaceuticals (Inst), Janssen (Inst), BeiGene (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Roche Canada

Tae Min Kim
Research Funding: AstraZeneca

Muhit Ozcan
Honoraria: Takeda, Amgen, Bristol-Myers Squibb
Research Funding: Janssen, Celgene, Takeda, Bayer, Merck, Archigen Biotech, Roche, Pharmacyclics
Travel, Accommodations, Expenses: Takeda, Sanofi, Roche, Bristol-Myers Squibb, Abdi Ibrahim, Amgen, Janssen

Jamie Hirata
Employment: Genentech
Stock and Other Ownership Interests: Roche

Elicia Penuel
Employment: Genentech
Stock and Other Ownership Interests: Genentech

Joseph N. Paulson
Employment: Genentech
Stock and Other Ownership Interests: Roche

Ji Cheng
Employment: Hoffmann-La Roche

Grace Ku
Employment: Genentech
Stock and Other Ownership Interests: Genentech
Consulting or Advisory Role: Exelixis (I), AstraZeneca (I), Aligos (I), BMS (I)

Matthew J. Matasar
Stock and Other Ownership Interests: Merck
Honoraria: Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacyclics, Janssen, Seattle Genetics
Consulting or Advisory Role: Genentech, Bayer, Merck, Juno Therapeutics, Roche, Teva, Rocket Medical, Seattle Genetics, Daiichi Sankyo
Research Funding: Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacyclics, Janssen, Rocket Medical, Seattle Genetics
Travel, Accommodations, Expenses: Genentech, Roche, Seattle Genetics, Bayer

No other potential conflicts of interest were reported.

APPENDIX

List of Investigators

Australia: S. Opat, M. Hertzberg, P. Giri, N. Wickham
Canada: L.H. Sehn, S. Assouline, I. Fleury, D. Macdonald
Czech Republic: M. Trněný J. Mayer, D. Belada, R. Hajek
France: G. Salles, G. Cartron, H. Tilly, O. Casasnovas, S. Le Gouill, N. Morineau, E. Nicolas-Virelizier
Germany: R. Liersch, H. Sayer
Hungary: A. Rosta, J. Demeter, A. Illes
Italy: A. Pinto, G. Rossi, F. Salvi, A. De Crescenzo
Republic of Korea: W.S. Kim, T.M. Kim
Netherlands: W. Stevens
Spain: F. Bosch Albareda, A. Lopez Guillermo, M.A. Canales Albendea, D. Caballero Barrigon, F. Cruz Vicente
Turkey: M. Ozcan, G.H. Ozsan, M. Sonmez, M. Turgut
United Kingdom: A. McMillan, J. Radford, A. Davies
United States: A.F. Herrera, A. Mehta, M.J. Matasar, K. Sivarajan, C.R. Flowers, M. Kamdar, J. Suh, W Harb, J. Pagel, J. Chandler, M. de Oliveira, N. Ghosh, E. McGuire

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 ≥ 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 ≥ 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 ≥ 40% tumor nuclei as positive stains, and *BCL2* overexpression was defined as ≥ 50% tumor cells with cytoplasmic staining intensity of ≥ 2+.

Expanded Efficacy Results

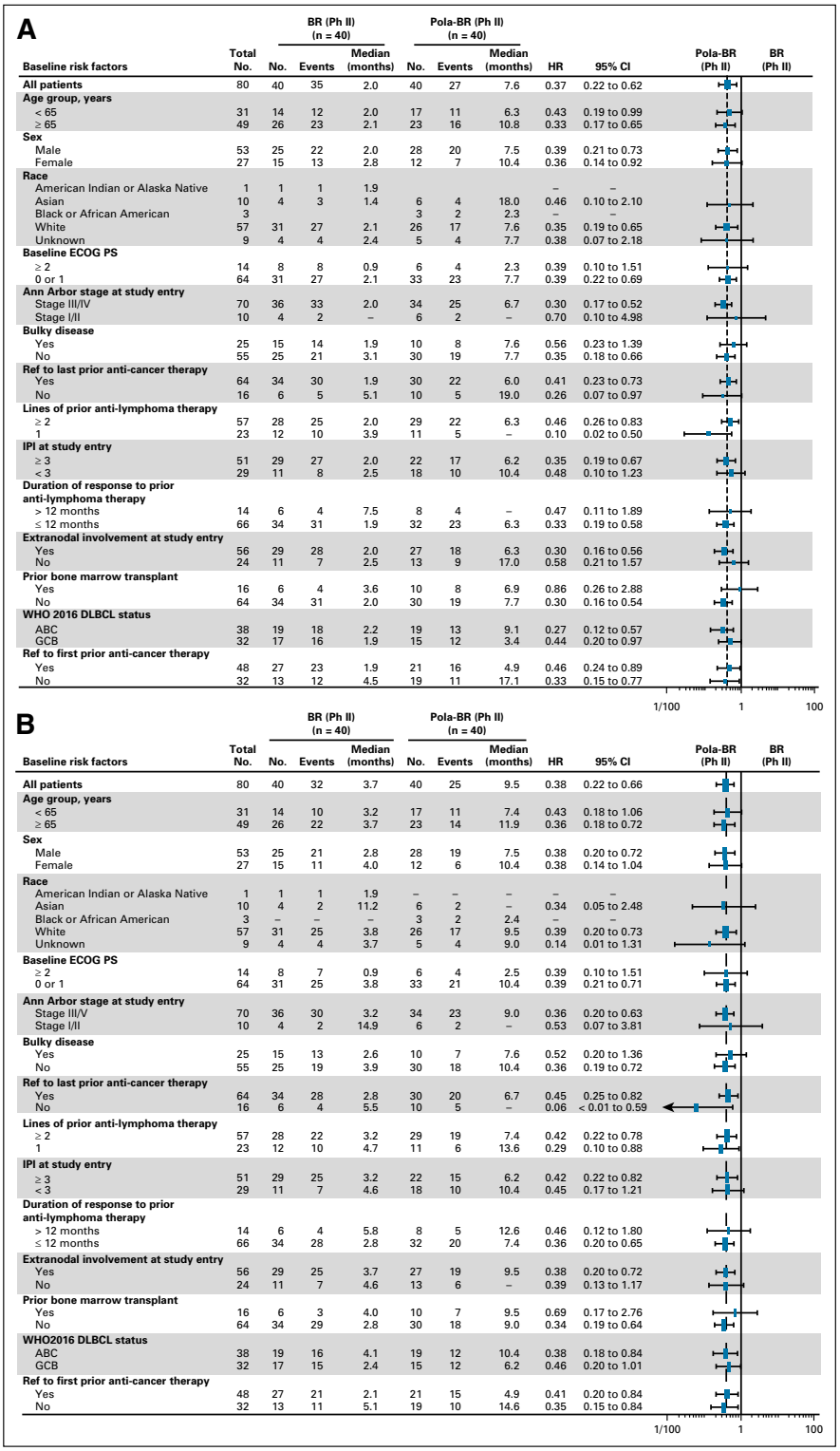

FIG A1. Forest plot for progression-free survival by (A) investigator and (B) independent review committee (IRC) in patients treated with polatuzumab vedotin combined with bendamustine-rituximab (pola-BR) or bendamustine-rituximab (BR). ABC, activated B-cell–like; DLBCL, diffuse B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; IPI, International Prognostic Index; ph, phase; ref, refractory.

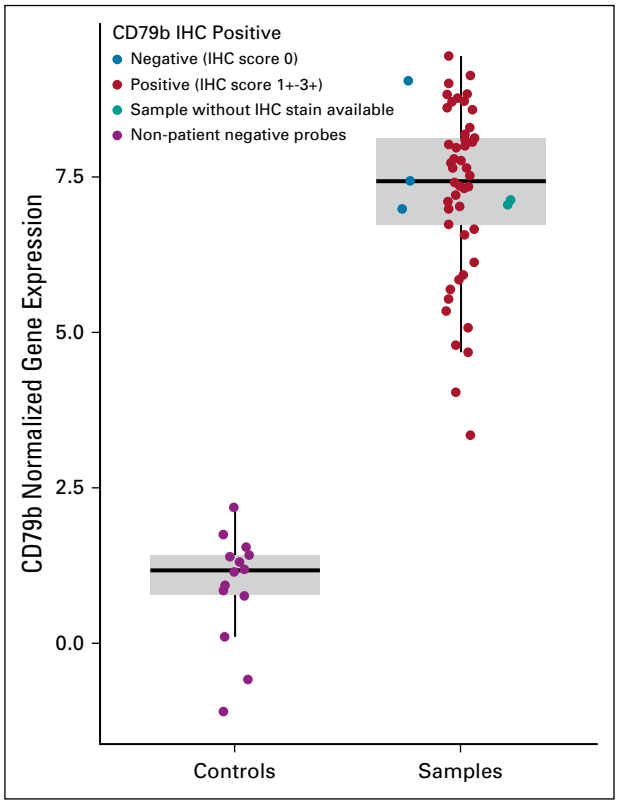

FIG A2. CD79b gene expression. Of the 3 samples with undetectable CD79b by immunohistochemistry (IHC), parallel RNA assessments showed measurable expression significantly above background levels inconsistent with the IHC data. Each point represents an individual sample or negative control probes. Gene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

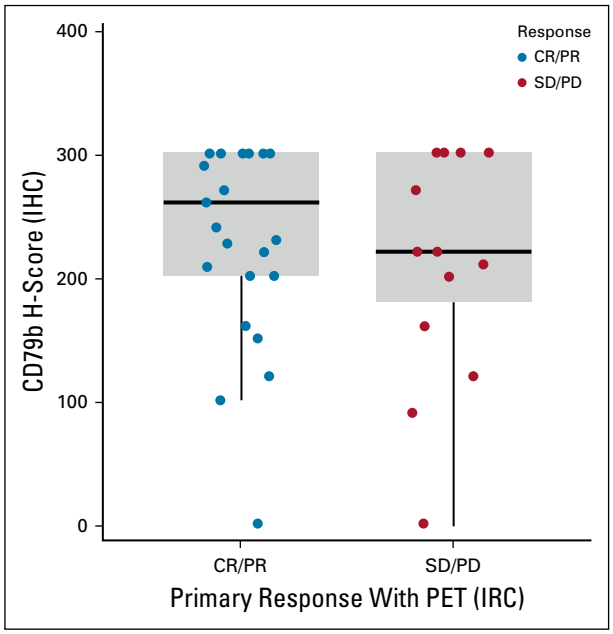

FIG A3. CD79b protein expression (immunohistochemistry [IHC] H-scores) in patients with relapsed/refractory diffuse large B-cell lymphoma treated with polatuzumab vedotin–based therapy relative to responses at end of treatment (independent review committee [IRC] assessed). There was no significant difference 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.

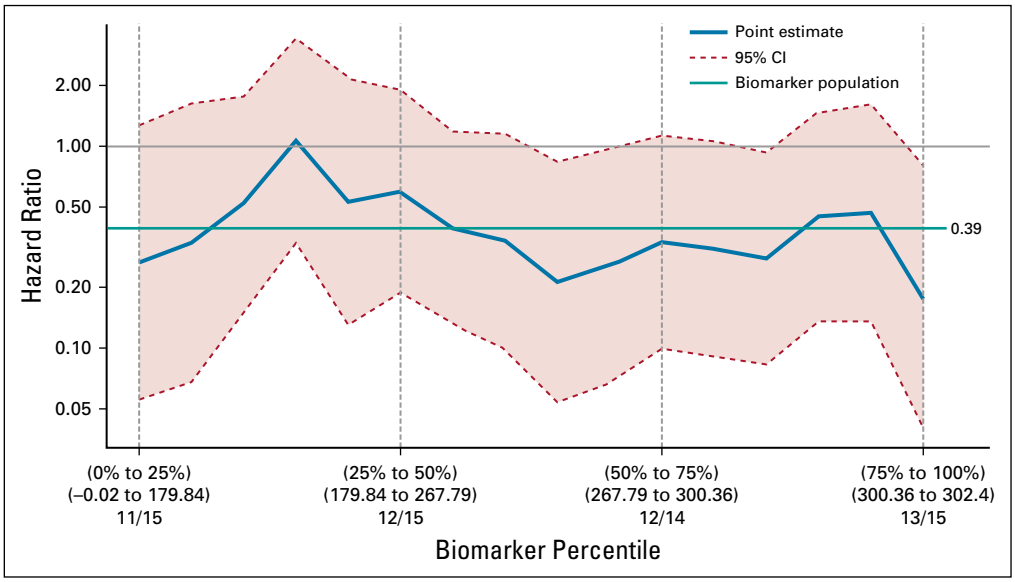

FIG A4. Polatuzumab vedotin (pola) treatment effect as seen across the range of CD79b expression for investigator-assessed progression-free survival (PFS). Subgroup Treatment Effect Pattern (STEP) plot for the phase II patients with relapsed/refractory diffuse large B-cell lymphoma comparing pola-bendamustine 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% CIs 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).

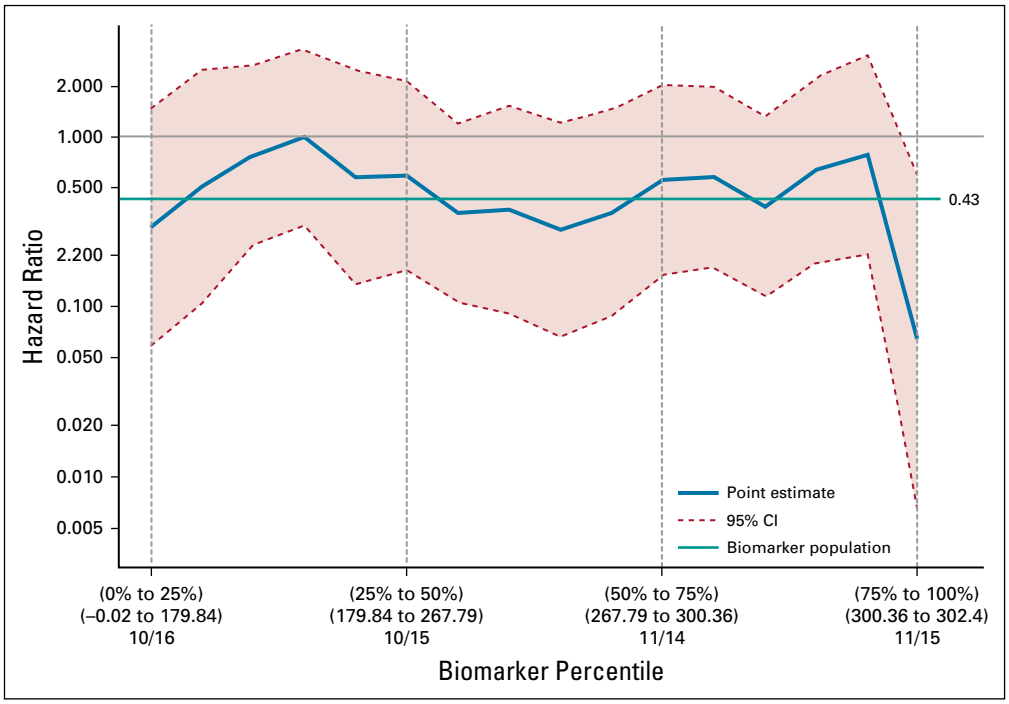

FIG A5. Polatuzumab vedotin (pola) treatment effect as seen across the range of CD79b expression for overall survival (OS). Subgroup Treatment Effect Pattern (STEP) plot for the phase II patients with relapsed/refractory diffuse large B-cell lymphoma comparing pola-bendamustine and rituximab with bendamustine 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).

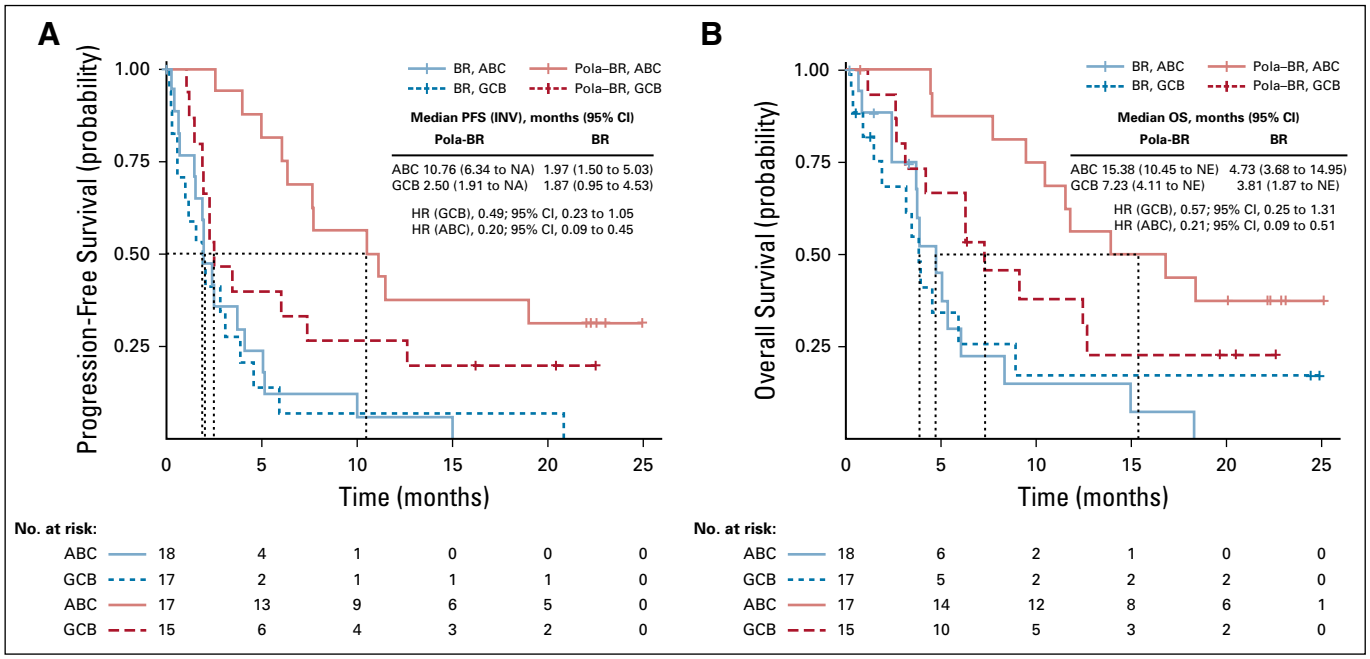

FIG A6. (A) Progression-free survival (PFS) by investigator (INV) and (B) overall survival (OS) in patients with activated B-cell–like (ABC) and germinal center B-cell–like (GCB) diffuse large B-cell lymphoma. BR, bendamustine-rituximab; HR, hazard ratio; NE, not estimable; pola-BR, polatuzumab vedotin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

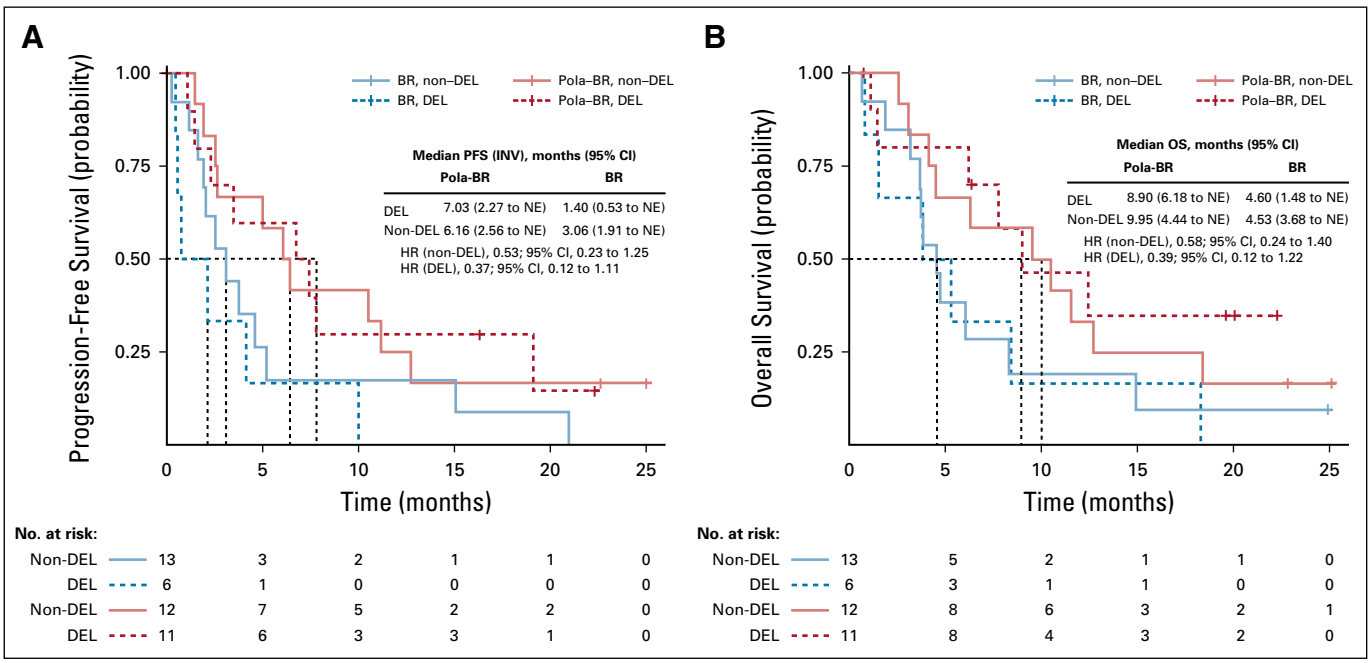

FIG A7. (A) Progression-free survival (PFS) by investigator (INV) and (B) overall survival (OS) in patients with double-expressor lymphoma (DEL) and non-DEL diffuse large B-cell lymphoma. BR, bendamustine-rituximab; HR, hazard ratio; pola-BR, polatuzumab vedotin combined with bendamustine-rituximab.

TABLE A1. Reasons for "Not Evaluable" at EOT

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
EOT CT performed without PET§	1

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).

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)
P	.03	
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)	
P	< .01	
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)	
P	< .01	
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	< .001	

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.

TABLE A3. Summary of Treatment Exposure (safety-evaluable population)

	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.

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

	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)

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 Without 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.