Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory follicular lymphoma: a phase Ib/II study

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Abstract

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma. Despite treatment advances that have improved outcomes for patients with relapsed or refractory (R/R) FL, many patients still die from progressive disease or treatment-related toxicities. In the phase Ib/II GO29365 study (clinicaltrials.gov 02257567), the safety and efficacy of polatuzumab vedotin plus bendamustine and rituximab (Pola-BR) *versus* bendamustine and rituximab (BR) alone, and polatuzumab vedotin plus bendamustine and obinutuzumab (Pola-BG) as a single-arm cohort were evaluated in patients with R/R FL. Following the phase Ib safety run-in, patients were randomized 1:1 to receive Pola-BR or BR alone in the phase II stage; a separate non-randomized Pola-BG cohort was examined in the phase Ib/II expansion stage. Primary endpoints included safety and tolerability (phase Ib) and positron emission tomography complete response (PET-CR) rate by independent review committee (phase II). Overall, 112 patients were enrolled (phase Ib safety run-in: Pola-BR, N=6; phase II randomized cohort: Pola-BR, N=39; BR, N=41; phase Ib/II expansion cohort: Pola-BG, N=26). PET-CR rates were 66.7% (phase Ib safety run-in, Pola-BR); 69.2% (phase II randomized, Pola-BR); 63.4% (phase II randomized, BR); and 65.4% (phase Ib/II expansion Pola-BG). There was a higher occurrence of cytopenias with Pola-BR and Pola-BG than with BR; serious adverse events were more frequent with Pola-BR (61.4%) and Pola-BG (46.2%) than with BR (29.3%). Overall, this analysis does not demonstrate a benefit of adding Pola to BR or BG regimens for patients with R/R FL.

Introduction

Follicular lymphoma (FL) is an indolent B-cell lymphoma that accounts for 20% of all non-Hodgkin lymphomas.[1] Although improved patient outcomes were observed with the introduction of anti-CD20 monoclonal antibodies, FL remains an incurable disease and patients frequently require multiple lines of treatment.[2] Despite the available standard treatment options for relapsed or refractory (R/R) FL, patients often die due to progressive disease (PD) or treatment-related toxicities.[3,4] For these reasons, new therapeutic options are needed.

Polatuzumab vedotin is an antibody-drug conjugate (ADC) that targets CD79b to deliver a microtubule inhibitor, monomethyl auristatin E (MMAE), to malignant B cells.[5-7] Once internalized in the cell, MMAE binds to microtubules and prevents cell division, thereby inducing apoptosis.[8] Polatuzumab vedotin in combination with bendamustine

and rituximab (Pola-BR) has received approval from the European Medicines Agency and United States Food and Drug Administration for patients with R/R diffuse large B-cell lymphoma (DLBCL) based on data from the pivotal phase Ib/II GO29365 study (clinicaltrials.gov 02257567).[9-11] Furthermore, obinutuzumab-chemotherapy combination demonstrated superiority compared with rituximab-chemotherapy in patients with previously untreated FL in the phase III GALLIUM study (clinicaltrials.gov 01332968).[12] Improved progression-free survival (PFS) with obinutuzumab *versus* rituximab has been demonstrated across the most commonly used chemotherapy backbones, including bendamustine.[13]

Here, we present efficacy and safety data from patients with R/R FL enrolled in the GO29365 study. The cohorts included in this analysis are patients who received Pola-BR *versus* bendamustine and rituximab (BR) alone, and a single-arm expansion cohort of polatuzumab vedotin in combination with bendamustine and obinutuzumab (Pola-BG).

Methods

Trial conduct

This international, multicenter, open-label, phase Ib/II GO29365 study evaluated the safety, tolerability, and efficacy of Pola-BR, BR, and Pola-BG in patients with R/R FL or R/R DLBCL. Safety and efficacy results have been previously reported for the DLBCL cohorts.[14,15] This analysis includes the R/R FL cohorts only.

The study protocol was approved by applicable ethics committees and institutional review boards in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki.[16] All patients provided informed consent. An Independent Review Committee (IRC), including board-certified radiologists and an oncologist experienced in malignant lymphoma, assessed all patients for end-of-treatment (EOT) response based on imaging and bone marrow biopsy results during the phase II part of the study.

Patient population

Eligible patients were aged ≥18 years with histologically confirmed R/R FL (grade 1, 2 or 3a), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Patients had received ≥1 prior therapy for FL and were considered relapsed or refractory to their last treatment. Patients who had received prior bendamustine were considered eligible if they had a response duration of ≥1 year following treatment. Patients were excluded if they had received treatment with any monoclonal antibodies, radioimmunoconjugate, or ADC within five half-lives or four weeks (whichever was longer) prior to cycle (C) 1, day (D) 1 of the study regimen. Full details of the inclusion and exclusion criteria are shown in *Online Supplementary Table S1*.

Study design

The study comprised a phase Ib safety run-in stage of Pola-BR and Pola-BG, followed by a phase II randomized stage to evaluate Pola-BR *versus* BR, and a phase II expansion stage to evaluate Pola-BG (Figure 1), which was recruited in parallel with the randomized cohort. Patients were randomized 1:1, and stratified by duration of response to prior therapy (≤12 months *vs*. >12 months) and disease burden (high *vs*. low, as defined by the Groupe d'Étude des Lymphomes Folliculaires criteria[17]). Patients were treated for up to six 28-day cycles and received the regimens above with dosing of intravenous (IV) bendamustine 90 mg/m^2 on D2 and D3 of C1, and D1 and D2 of subsequent cycles; IV rituximab 375 mg/m^2 on D1 of each cycle; IV obinutuzumab 1,000 mg on D1, D8 and D15 of C1 and D1 of subsequent cycles; and IV polatuzumab vedotin 1.8 mg/kg on D2 of C1 and D1 of subsequent cycles.

Primary prophylaxis against neutropenia with granulocyte-colony stimulating factor was required during each cycle of therapy, according to American Society of Clinical Oncology guidelines[18] or institutional standards at each site. Also, antiviral and antipneumocystis prophylaxis was

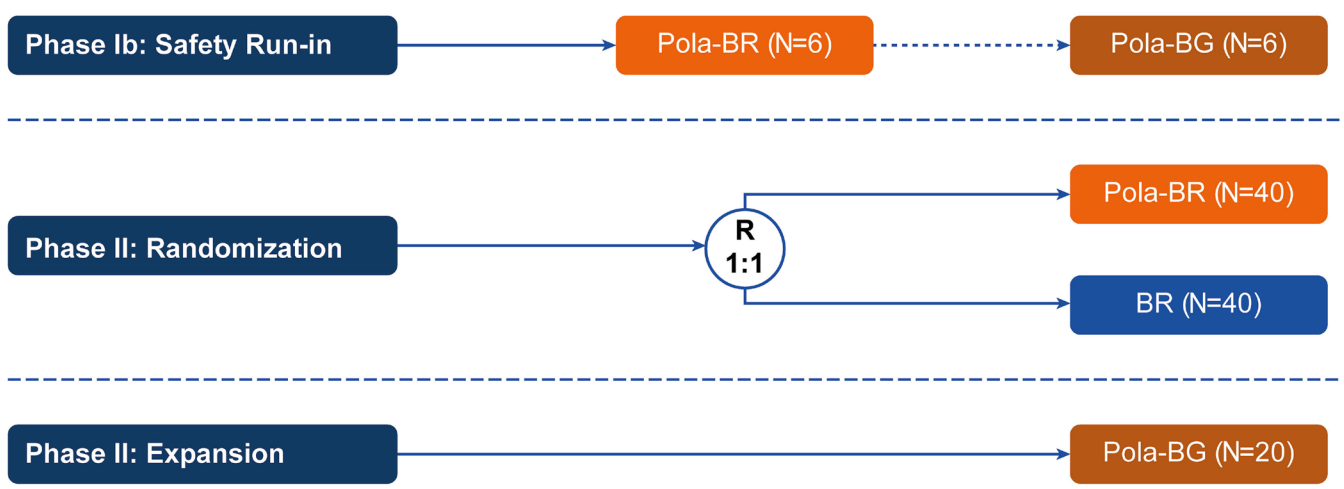

Figure 1. GO29365 study design: follicular lymphoma cohorts. BG: bendamustine plus obinutuzumab; BR: bendamustine plus rituximab; Pola: polatuzumab vedotin; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; N: number; R: randomization.

required from initiation of study treatment until ≥6 months after completion of treatment.

Study assessments and endpoints

The primary endpoints were safety and tolerability (phase Ib), and IRC-assessed [^{18}F]fluorodeoxyglucose-positron emission tomography-computed tomography (PET-CT) complete response (CR) rate using modified Lugano Response Criteria[19] 6-8 weeks after C6, D1 or last dose of study medication (phase II). Secondary endpoints included objective response at EOT and best objective response. Exploratory endpoints included efficacy outcomes by biomarker status (including CD79b expression, which is presented in this analysis), investigator (INV)-assessed duration of response (DOR), PFS, event-free survival, and overall survival (OS). Responses were assessed by CT or PET-CT after C3 (interim) and at EOT (primary response assessment). Follow-up CT scans were performed every six months until PD or patient withdrawal, or for up to approximately two years after completing study treatment. Patients who were in remission after two years of scans were not required to continue surveillance imaging in this study.

Results

Patient population

Between February 3, 2015 and September 20, 2016, 112 patients with R/R FL were enrolled into separate arms of the GO29365 study as follows: phase Ib safety run-in (Pola-BR, N=6), phase II randomized cohort (Pola-BR, N=39; BR, N=41), phase Ib/II expansion cohort (Pola-BG, N=26).

Patients' demographics and baseline characteristics are described in Table 1. Patients in all treatment groups had received a similar number of lines of prior treatment, with more than half of patients receiving ≥2 lines. Refractory status to last therapy was also similar between treatment groups, although fewer patients in the Pola-BG group had PD within 24 months of initiation of the first anti-lymphoma treatment with chemoimmunotherapy (POD24) (Table 1). High

Table 1. Baseline patients' characteristics.

	Phase Ib safety run-in	Phase II randomized		Phase Ib/II expansion
	Pola-BR N=6	Pola-BR N=39	BR N=41	Pola-BG N=26
Median age in years (range)	68 (54-73)	65 (37-74)	63 (39-80)	62 (37-86)
Age ≥65 years, N (%)	5 (83.3)	20 (51.3)	17 (41.5)	10 (38.5)
Male, N (%)	2 (33.3)	21 (53.8)	18 (43.9)	14 (53.8)
ECOG PS score, N (%) 0 1 2 Unknown	 3 (50.0) 3 (50.0) 0 0	 20 (51.3) 15 (38.5) 3 (7.7) 1 (2.6)	 28 (68.3) 8 (19.5) 5 (12.2) 0	 16 (61.5) 10 (38.5) 0 0
Ann Arbor stage III/IV, N (%)	6 (100)	33 (84.6)	34 (82.9)	21 (80.8)
FLIPI score ≥3, N (%)	2 (33.3)	24 (61.5)	16 (39.0)	14 (53.8)
Bulky disease (≥7.5 cm), N (%)	2 (33.3)	6 (15.4)	5 (12.2)	4 (15.4)
Extranodal disease, N (%)	4 (66.7)	19 (48.7)	24 (58.5)	14 (53.8)
Median number of prior therapies (range) 1 line, N (%) 2 lines, N (%) ≥3 lines, N (%)	2 (1-3) 2 (33.3) 2 (33.3) 2 (33.3)	2 (1-5) 18 (46.2) 9 (23.1) 12 (30.8)	2 (1-5) 20 (48.8) 7 (17.1) 14 (34.1)	2 (1-7) 10 (38.5) 5 (19.2) 9 (34.6)
Prior bendamustine, N (%)	0	2 (5.1)	6 (14.6)	4 (15.4)
Prior stem cell transplant, N (%)	1 (16.7)	4 (10.3)	2 (4.9)	3 (11.5)
Refractory to last therapy,* N (%)	3 (50.0)	17 (43.6)	18 (43.9)	11 (42.3)
Refractory to last anti-CD20, N (%)	1 (16.7)	12 (30.8)	18 (43.9)	9 (34.6)
POD24 status,† N (%)	2 (33.3)	14 (35.9)	10 (24.4)	3 (11.5)

BR: bendamustine plus rituximab; ECOG PS: Eastern Cooperative Oncology Group performance status; FLIPI: Follicular Lymphoma International Prognostic Index; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab. *No response or progression within 6 months of last treatment.†POD24: progression of disease within 24 months of initial diagnosis. Defined as progression of disease within 24 months of initiation of first anti-lymphoma treatment with chemoimmunotherapy.

levels of CD79b protein expression (H-score ≥200 or ≥2) were observed in 97/100 (97.0%) patients with FL across all cohorts in this analysis.

At the clinical cut-off date (October 21, 2021), median duration of follow up was: phase Ib safety run in (Pola-BR), 74.8 months (95% confidence interval [CI]: 70.3-not evaluable [NE]); phase II randomized (Pola-BR), 62.4 months (95% CI: 60.8-64.5), (BR), 60.4 months (95% CI: 59.4-62.4); phase Ib/II expansion (Pola-BG), 65.0 months (95% CI: 61.6-65.4).

Efficacy

Efficacy outcomes in the FL cohorts are summarized in Table 2. Similar IRC-assessed PET-CR rates were observed across treatment arms at the primary response assessment: phase Ib safety run-in (Pola-BR) 66.7% (4/6 patients); phase II randomized (Pola-BR) 69.2% (27/39), (BR) 63.4% (26/41); phase Ib/II expansion (Pola-BG) 65.4% (17/26).

Among patients who responded to treatment (CR or partial response), median INV-assessed DOR was 16.4 months in the phase II randomized Pola-BR group *versus* 18.1 months in the BR group and was not reached in the phase Ib/II expansion Pola-BG group (*Online Supplementary Figure S1*).

In the phase II randomized cohort, median INV-assessed PFS was 18.5 months (95% CI: 15.9-30.4) in the Pola-BR arm and 17.8 months (95% CI: 12.5-35.0) in the BR arm (Figure 2A). In the phase Ib/II expansion (Pola-BG) arm, median INV-assessed PFS was 40.5 months (95% CI: 23.1-NE) (Figure 2B). Median OS was not reached in either the phase II randomized Pola-BR or BR arms (Figure 2C) or the phase Ib/II expansion Pola-BG arm (Figure 2D). INV-assessed PFS and OS rates by baseline risk factors are shown in Figure 3A and B. INV-assessed PFS and OS were generally similar between patients receiving Pola-BR or BR across the subgroups included.

Subsequent therapies

New anti-lymphoma therapy (NALT) data in the FL cohorts are shown in Table 3. Patients did not receive maintenance treatment as part of this regimen. One patient proceeded to receive chimeric antigen receptor T-cell therapy in the phase II randomized Pola-BR arm. In total, 9 patients received subsequent stem cell transplants (5 autologous, 4 allogeneic): one in the phase Ib safety run-in Pola-BR arm, one in the phase 1b safety run-in Pola-BG arm, 4 in the phase II randomized BR arm, one in the phase II randomized Pola-BR arm, and 2 in the Pola-BG expansion arm.

Safety

A summary of patient safety across the three treatment

Table 2. Summary of efficacy outcomes.

	Phase Ib safety run-in	Phase II randomized		Phase Ib/II expansion
	Pola-BR N=6	Pola-BR N=39	BR N=41	Pola-BG N=26
End-of-treatment response,* N (%), 95% CI				
IRC assessed				
ORR (CR/PR)	5 (83.3), 35.9-99.6	30 (76.9), 60.7-88.9	30 (73.2), 57.1-85.8	23 (88.5), 69.9-97.6
CR	4 (66.7), 22.3-95.7	27 (69.2), 52.4-83.0	26 (63.4), 46.9-77.9	17 (65.4), 44.3-82.8
Investigator-assessed				
ORR (CR/PR)	5 (83.3), 35.9-99.6	31 (79.5), 63.5-90.7	33 (80.5), 5.1-91.2	23 (88.5), 69.9-97.6
CR	4 (66.7), 22.3-95.7	25 (64.1), 47.2-78.8	26 (63.4), 46.9-77.9	18 (69.2), 48.2-85.7
Best overall response† (INV), N (%), 95% CI				
ORR (CR/PR)	6 (100.0), 54.1-100.0	35 (89.7), 75.8-97.1	37 (90.2), 76.9-97.3	24 (92.3), 74.9-99.1
CR	5 (83.3), 35.9-99.6	30 (76.9), 60.7-88.9	27 (65.9), 49.4-79.9	21 (80.8), 60.7-93.5
Duration of response (INV)				
Patients with event, N (%)	4/6 (66.7)	28/35 (80.0)	24/37 (64.9)	9/24 (37.5)
Median in months (95% CI)	36.3 (16.1-NE)	16.4 (14.0-27.8)	18.1 (13.3-39.6)	NE (22.9-NE)
Progression-free survival (INV)				
Patients with event, N (%)	4 (66.7)	30 (76.9)	27 (65.9)	11 (42.3)
Median in months (95% CI)	38.9 (18.4-NE)	18.5 (15.9-30.4)	17.8 (12.5-35.0)	40.5 (23.1-NE)
48-month landmark, % (95% CI)	50.0 (10.0-90.0)	20.4 (7.1-33.6)	28.5 (13.4-43.5)	46.5 (22.3-70.8)
Overall survival				
Patients with event, N (%)	2 (33.3)	16 (41.0)	11 (26.8)	5 (19.2)
Median in months (95% CI)	NE	NE	NE	NE
60-month landmark, % (95% CI)	83.3 (53.5-100.0)	59.1 (43.2-75.1)	69.4 (54.2-84.7)	80.0 (64.3-95.8)

BG: bendamustine plus obinutuzumab; BR: bendamustine plus rituximab; CI: Confidence Interval; CR: complete response; CT: computed tomography; INV: investigator-assessed; IRC: independent review committee; N: number; NE: not evaluable; ORR: objective response rate; PET: positron emission tomography; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab; PR: partial response. *At primary response assessment by PET. †By PET-CT or CT.

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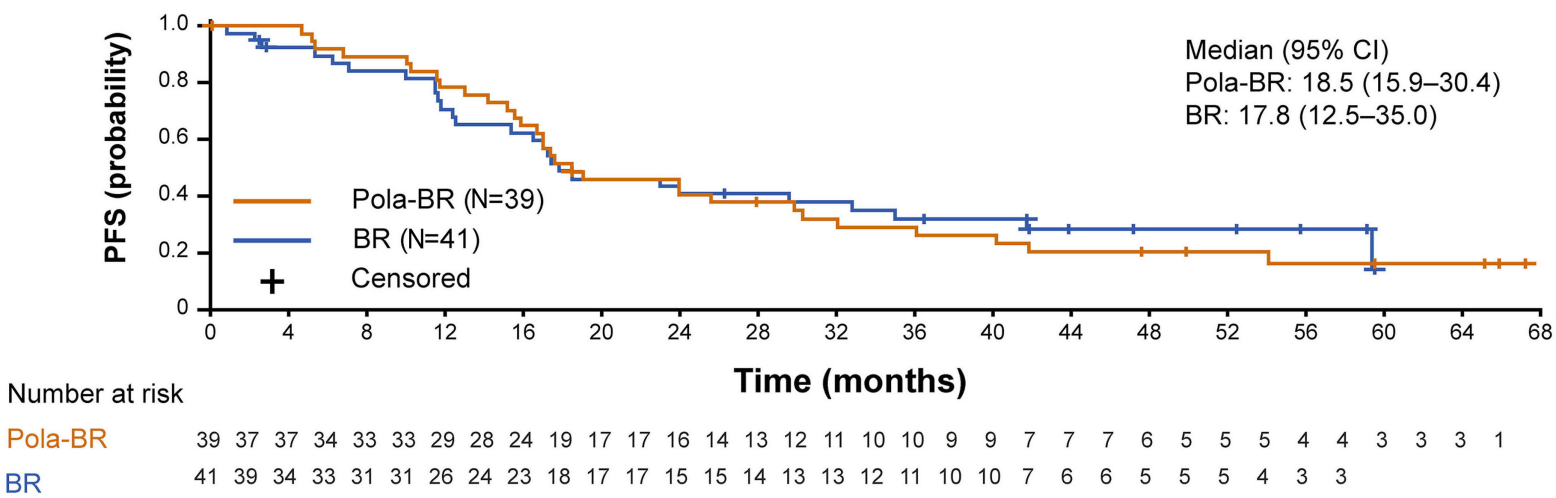

Number at risk

Pola-BR	39	37	37	34	33	33	29	28	24	19	17	17	16	14	13	12	11	10	10	9	9	7	7	7	6	5	5	5	4	4	3	3	3	1
BR	41	39	34	33	31	31	26	24	23	18	17	17	15	15	14	13	13	12	11	10	10	7	6	6	5	5	5	4	3	3				

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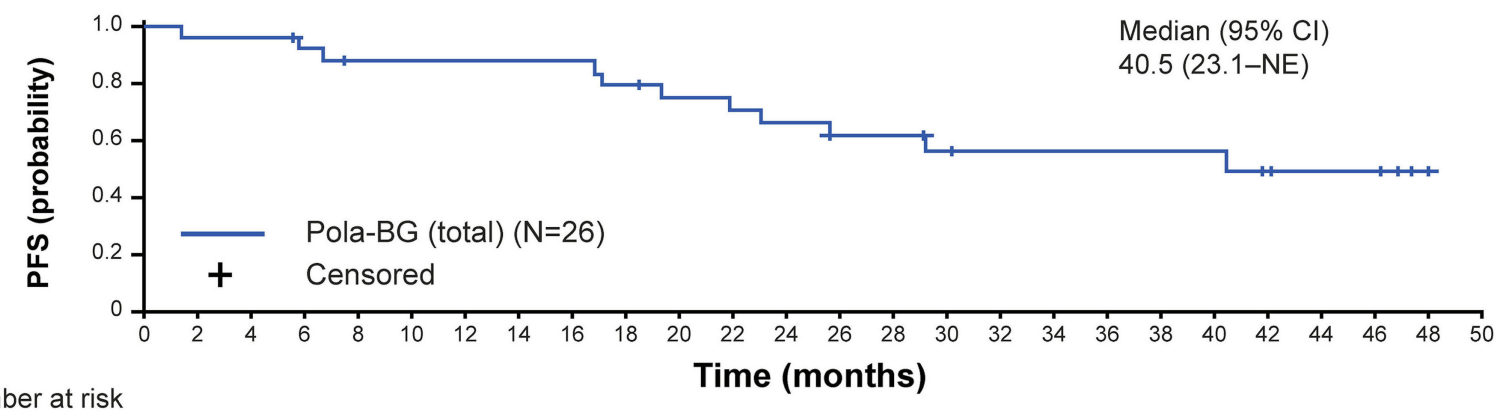

Number at risk

Pola-BG	26	25	25	23	21	21	21	21	21	19	17	16	15	12	12	10	8	8	8	8	8	6	5	5	1											

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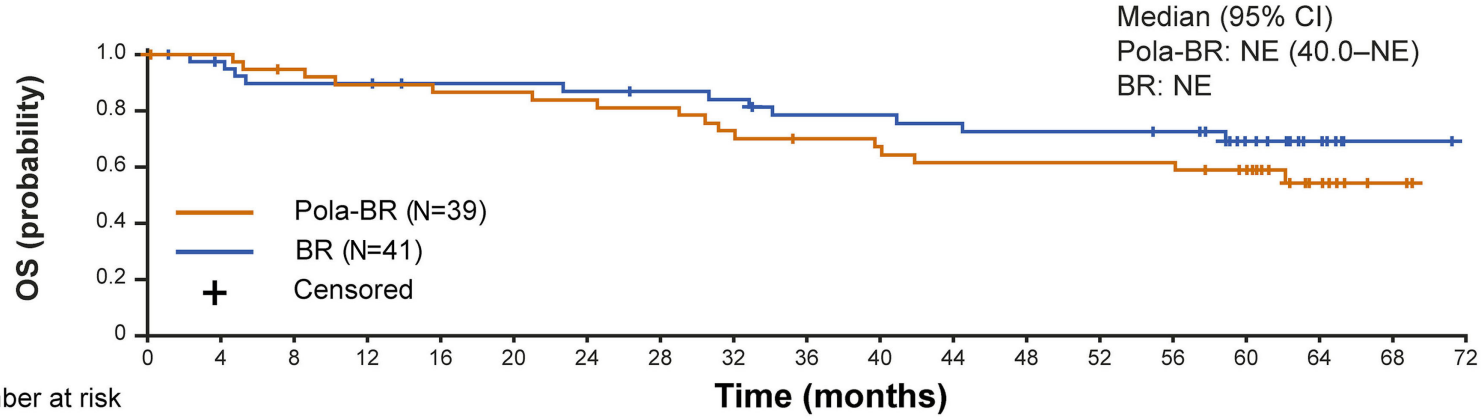

Number at risk

Pola-BR	39	38	38	36	35	34	33	33	32	32	32	31	31	30	30	29	27	26	25	25	24	22	22	22	22	22	22	22	22	20	19	13	8	3	2	
BR	41	40	38	35	35	35	35	33	33	33	33	33	32	32	31	31	30	28	27	27	27	26	26	25	25	25	25	25	25	24	22	15	11	7	1	1	1

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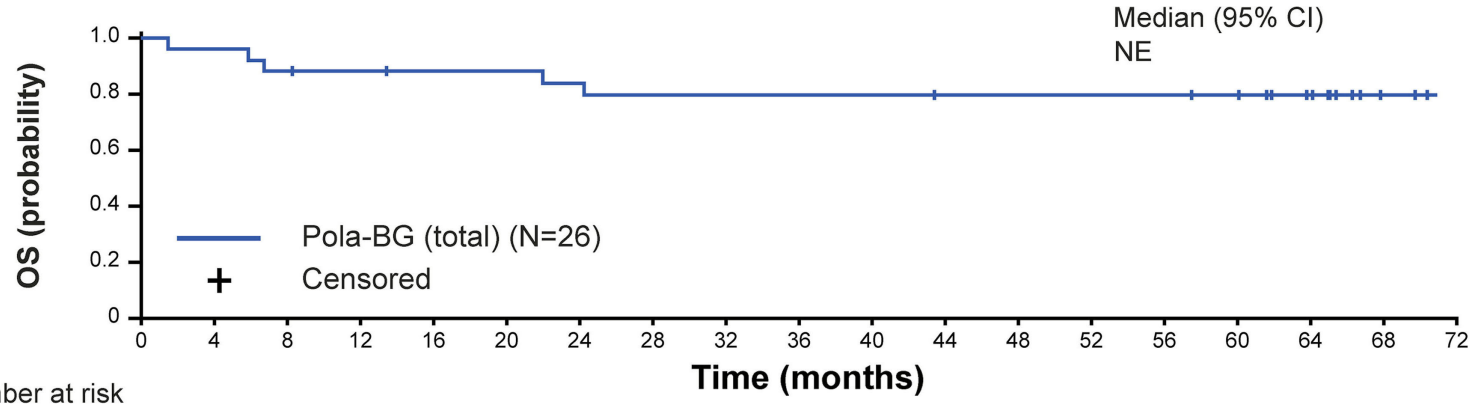


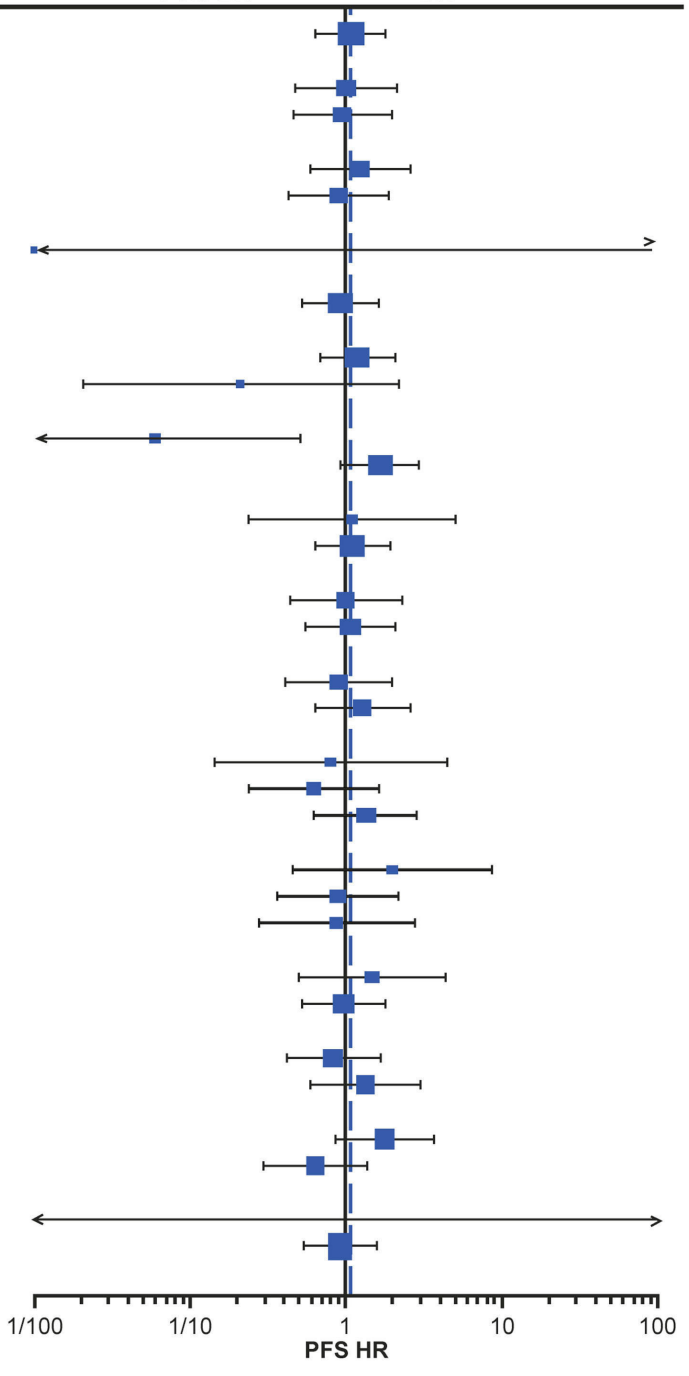
Number at risk

Pola-BG	26	25	25	24	23	22	22	21	21	21	21	20	20	19	19	19	19	19	19	19	19	19	18	18	18	18	18	18	18	17	17	13	12	5	2	1

Figure 2. Kaplan-Meier curves of investigator-assessed progression-free and overall survival. (A) Progression-free survival (PFS) in randomized polatuzumab vedotin (Pola) plus bendamustine and rituximab (Pola-BR) and bendamustine plus rituximab (BR) arms. (B) PFS in phase Ib/II expansion (Pola-BR plus bendamustine and obinutuzumab [Pola-BG]) arm. (C) Overall survival (OS) in randomized Pola-BR and bendamustine plus rituximab (BR) arms. (D) OS in phase Ib/II expansion (Pola-BG) arm. CI: Confidence Interval; N: number; NE: not evaluable.

A

Baseline risk factors	N	BR (N=41) N	BR (N=41) PFS events, N	BR (N=41) Median PFS, months	Pola-BR (N=39) N	Pola-BR (N=39) PFS events, N	Pola-BR (N=39) Median PFS, months	HR	95% CI
All patients	80	41	27	17.8	39	30	18.5	1.07	0.64–1.80
Age (years)									
<65	43	24	14	17.8	19	13	24.0	1.01	0.47–2.15
≥65	37	17	13	18.5	20	17	17.3	0.95	0.46–1.97
Sex									
Male	39	18	12	17.8	21	17	17.4	1.22	0.58–2.56
Female	41	23	15	24.0	18	13	22.0	0.90	0.43–1.91
Ethnicity									
Asian	3	2	1	10.0	1	0	-	<0.01	NE
Black or African American	1	-	-	-	1	1	19.1	-	-
White	66	33	24	17.3	33	25	17.4	0.92	0.53–1.62
Baseline ECOG PS									
0–1	71	36	24	23.0	35	28	18.8	1.19	0.69–2.06
≥2	8	5	3	7.1	3	2	15.2	0.21	0.02–2.17
Ann Arbor stage at study entry									
Stage I/II	13	7	7	17.1	6	2	-	0.06	<0.01–0.51
Stage III/IV	67	34	20	29.6	33	28	17.0	1.66	0.93–2.96
Bulky disease									
Yes	11	5	3	32.8	6	4	20.4	1.10	0.24–5.08
No	69	36	24	17.8	33	26	18.5	1.10	0.63–1.92
Refractory to last prior anti-lymphoma therapy									
Yes	35	18	11	17.5	17	12	18.4	1.00	0.44–2.28
No	45	23	16	23.0	22	18	18.5	1.07	0.54–2.10
N of lines of prior anti-lymphoma therapy									
1	38	20	12	23.0	18	13	32.1	0.90	0.41–1.98
≥2	42	21	15	17.5	21	17	17.2	1.27	0.63–2.58
FLIPI score at study entry									
0–1	12	7	4	17.5	5	2	-	0.80	0.14–4.44
2	28	18	12	23.0	10	7	36.1	0.62	0.24–1.59
3–5	40	16	11	18.5	24	21	16.7	1.34	0.64–2.80
FL grade at study entry									
Grade 1	13	6	3	41.9	7	5	15.6	1.98	0.46–8.45
Grade 2	29	14	6	15.5	15	12	17.9	0.89	0.37–2.13
Grade 3a	18	9	9	24.0	9	6	24.0	0.87	0.28–2.71
POD24 status									
Yes	24	10	5	17.3	14	10	21.2	1.47	0.50–4.32
No	56	31	22	18.5	25	20	17.6	0.97	0.53–1.77
DOR to prior anti-lymphoma therapy									
>12 months	41	22	17	17.8	19	16	17.4	0.83	0.42–1.67
≤12 months	39	19	10	18.5	20	14	18.8	1.33	0.59–3.02
Extranodal involvement at study entry									
Yes	43	24	14	29.6	19	16	16.8	1.76	0.85–3.65
No	37	17	13	17.1	20	14	30.4	0.64	0.30–1.37
Prior bone marrow transplant									
Yes	6	2	1	59.4	4	4	11.9	NE	NE
No	74	39	26	17.5	35	26	19.1	0.92	0.53–1.59



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Baseline risk factors	N	BR (N=41) N	BR (N=41) OS events, N	BR (N=41) Median OS, months	Pola-BR (N=39) N	Pola-BR (N=39) OS events, N	Pola-BR (N=39) Median OS, months	HR	95% CI
All patients	80	41	11	-	39	16	-	1.53	0.71–3.30
Age (years)									
<65	43	24	2	-	19	7	-	4.80	1.00–23.1
≥65	37	17	9	44.4	20	9	-	0.77	0.31–1.95
Sex									
Male	39	18	6	-	21	8	-	1.20	0.42–3.45
Female	41	23	5	-	18	8	-	1.95	0.64–5.96
Ethnicity									
Asian	3	2	0	-	1	0	-	-	-
Black or African American	1	-	-		1	0	-	-	-
White	66	33	10	-	33	16	62.1	1.62	0.74–3.58
Baseline ECOG PS									
0–1	71	36	9	-	35	14	-	1.67	0.72–3.87
≥2	8	5	2	-	3	2	39.7	0.82	0.11–6.00
Ann Arbor stage at study entry									
Stage I/II	13	7	2	-	6	0	-	<0.01	NE
Stage III/IV	67	34	9	-	33	16	62.1	1.94	0.86–4.39
Bulky disease									
Yes	11	5	2	-	6	3	-	1.21	0.20–7.25
No	69	36	9	-	33	13	-	1.56	0.67–3.66
Refractory to last prior anti-lymphoma therapy									
Yes	35	18	5	-	17	5	-	0.83	0.24–2.86
No	45	23	6	-	22	11	62.1	2.37	0.87–6.41
N of lines of prior anti-lymphoma therapy									
1	38	20	4	-	18	7	-	2.20	0.64–7.51
≥2	42	21	7	-	21	9	-	1.14	0.43–3.07
FLIPI score at study entry									
0–1	12	7	1	-	5	0	-	<0.01	NE
2	28	18	3	-	10	2	-	1.03	0.17–29.92
3–5	40	16	7	-	24	14	41.9	1.32	0.53–3.28
FL grade at study entry									
Grade 1	13	6	1	-	7	4	51.1	3.32	0.37–29.92
Grade 2	29	14	5	-	15	4	-	0.66	0.18–2.46
Grade 3a	18	9	3	-	9	4	-	1.59	0.35–7.16
POD24 status									
Yes	24	10	1	-	14	4	-	2.68	0.30–24.08
No	56	31	10	-	25	12	62.1	1.51	0.65–3.50
DOR to prior anti-lymphoma therapy									
>12 months	41	22	7	-	19	11	56.1	2.14	0.83–5.52
≤12 months	39	19	4	-	20	5	-	1.01	0.27–3.77
Extranodal involvement at study entry									
Yes	43	24	7	-	19	10	62.1	1.91	0.73–5.03
No	37	17	4	-	20	6	-	1.23	0.35–4.36
Prior bone marrow transplant									
Yes	6	2	0	-	4	2	-	NE	NE
No	74	39	11	-	35	14	-	1.39	0.63–3.07

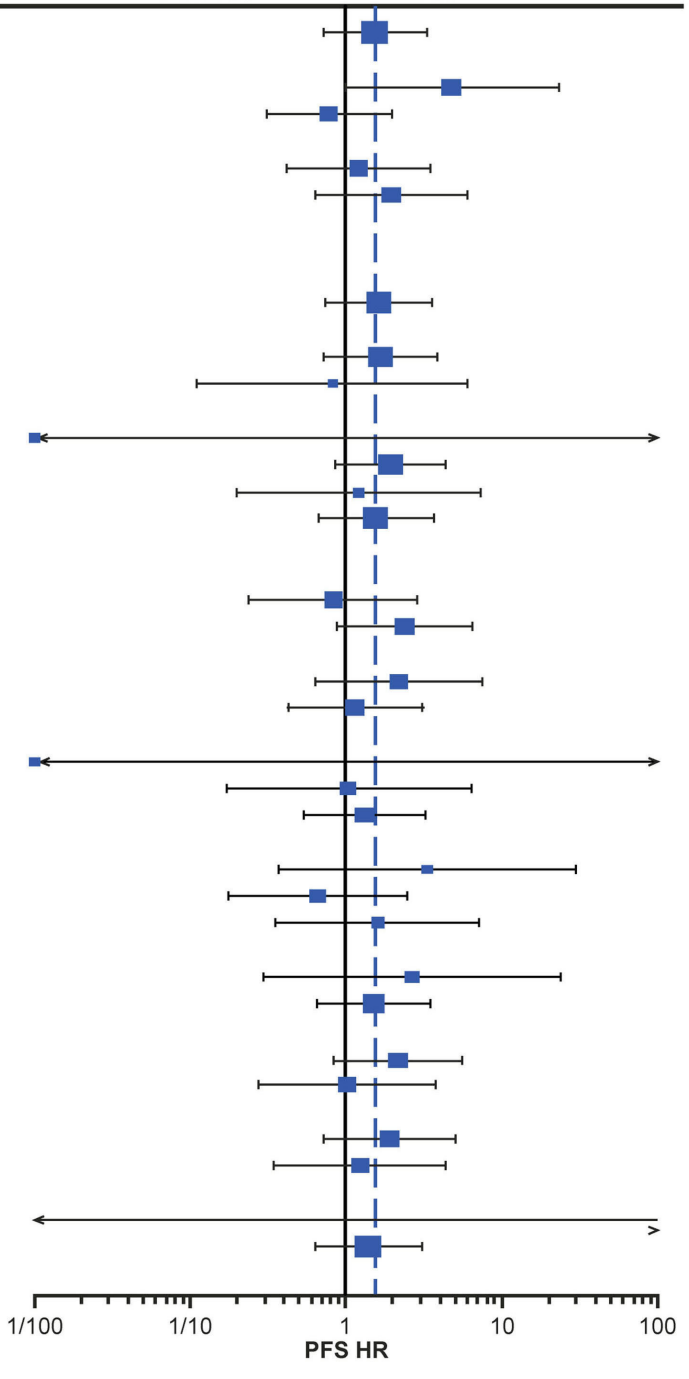

Figure 3. Forest plot showing the effects of baseline variables on investigator-assessed progression-free and overall survival in patients in the phase II randomized cohort treated with polatuzumab vedotin plus bendamustine and rituximab or bendamustine plus rituximab. (A) Progression-free survival (PFS). (B) Overall survival (OS). BR: bendamustine plus rituximab; CI: Confidence Interval; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; HR: hazards ratio; N: number; POD24: progression within 24 months of treatment; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; NE: not evaluable.

arms is presented in Table 4. The median number of treatment cycles completed was 5 (range: 1-6) in the Pola-BR arm, 3 (range: 1-6) with BR, and 6 (range: 1-6) with Pola-BG (*Online Supplementary Table S2*). Adverse events (AE) were the main cause of treatment discontinuation across all arms. Median duration on treatment was 4.7 months in all treatment arms. The most common all-grade and grade 3-4 AE are summarized in Table 5; infections and cytopenias were the most common. In the randomized groups, rates of all-grade and grade 3-4 neutropenia, febrile neutropenia, and anemia were greater with Pola-BR than with BR, and all-grade and grade 3-4 thrombocytopenia was greater with BR than with Pola-BR. Rates of all-grade non-hematologic AE were generally higher with Pola-BR than with BR (Table 5).

Serious AE (SAE) were observed in 27/44 (61.4%) patients who received Pola-BR, 12/41 (29.3%) patients who received BR, and 12/26 (46.2%) patients who received Pola-BG. SAE were mostly infections and infestations: Pola-BR group N=16 (including pneumonia, N=7); BR group, N=6; Pola-BG group, N=7. In the Pola-BR group, 7 patients had SAE categorized as blood and lymphatic disorders.

Peripheral neuropathy (PN) was reported in 19/44 (43.2%) patients in the Pola-BR group, 11/41 (26.8%) patients in the BR group, and 14/26 (53.8%) patients in the Pola-BG group. PN was mostly grade 1-2 in all treatment groups; grade 3 PN was reported in one patient (gait disturbance; unresolved at time of patient's death) in the Pola-BR group and one patient (hypoesthesia; resolved 19 days after onset) in the Pola-BG group. PN was mostly resolved by the data cut-off date (PN resolved in 13/19 [68.4%] patients in the Pola-BR group, 8/11 [72.7%] in the BR group, and 10/14 [71.4%] in the Pola-BG group). Dose reductions due to PN were reported in one and 2 patients in the Pola-BR and Pola-BG groups, respectively; dose interruption due to PN was reported in one patient, in the Pola-BG group.

Secondary malignancies were reported in 4/41 (9.8%) patients in the Pola-BR group (endometrial cancer, acute myeloid leukemia, colon cancer, and Hodgkin lymphoma [each N=1]), 7/41 (17%) patients in the BR group (basal cell carcinoma, gastrointestinal adenocarcinoma [each N=2], pancreatic carcinoma, rectal cancer, squamous cell carcinoma of the skin [each N=1]), and 1/26 (4%) patient in the Pola-BG group (endometrial adenocarcinoma).

Table 3. Number of patients who received new anti-lymphoma therapy: safety-evaluable population.

	Phase Ib safety run-in	Phase II randomized		Phase Ib/II expansion
	Pola-BR N=6	Pola-BR N=38	BR N=41	Pola-BG N=26
Patients with ≥1 NALT, N (%)	2 (33.3)	24 (63.2)	23 (56.1)	8 (30.8)
N of systemic therapy regimens received*	4	71	78	19
Patients who received ≥1 systemic therapy, N (%) Stem cell transplant, N (%) CAR T-cell therapy, N (%)	2 (33.3) 1 (16.7) 0 (0.0)	24 (63.2) 0 (0.0) 1 (2.6)	23 (56.1) 3 (7.3) 0 (0.0)	8 (30.8) 2 (7.7) 0 (0.0)

BR: bendamustine plus rituximab; CAR: chimeric antigen receptor; N: number; NALT: new anti-lymphoma therapy; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab. *Includes any monotherapy, multi-drug, or cell-based regimen.

Table 4. Safety summary in the follicular lymphoma cohorts.

	Phase II randomized		Phase Ib/II expansion
	Pola-BR N=38	BR N=41	Pola-BG N=26
Total N of events	664	402	521
Patients with ≥1 AE, N (%) Grade 5 Grade 3-4 Serious AE Leading to treatment discontinuation Leading to treatment dose delay/interruption Leading to dose reduction	38 (100) 8 (21.1) 31 (81.6) 25 (65.8) 9 (23.7) 17 (44.7) 8 (21.1)	41 (100) 4 (9.8) 26 (63.4) 12 (29.3) 5 (12.2) 11 (26.8) 3 (7.3)	26 (100) 2 (7.7) 21 (80.8) 12 (46.2) 6 (23.1) 13 (50.0) 5 (19.2)

AE: adverse event; BR: bendamustine plus rituximab; N: number; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab.

Grade 5 AE were observed in 8 (18.2%) patients who received Pola-BR, 4 (9.8%) patients who received BR, and 2 (7.7%) patients who received Pola-BG. Three of the events were considered by the investigator to be related to study treatment, one in each cohort. The majority of the deaths (9/14; 64%) occurred more than 90 days after the last dose of study drug. Eight patients experienced the event following PD or after initiating NALT. Grade 5 infections and infestations included pneumonia (N=1, Pola-BR), sepsis (N=1, BR), SARS-CoV-2 infection-induced pneumonia (N=1, Pola-BR), septic shock (N=1, BR), and progressive multifocal leukoencephalopathy (N=1, Pola-BG). A summary of all deaths in the safety-evaluable population is shown in *Online Supplementary Table S3*.

Discussion

In this study, efficacy outcomes were generally consistent across treatment groups. High IRC-assessed PET-CR rates were observed in all treatment arms at EOT (Table 2) and were comparable to results reported in the GADOLIN (bendamustine + obinutuzumab) and AUGMENT (lenalidomide + rituximab) trials.[20,21] Furthermore, overall response rate and best overall responses were similar across treatment arms.

In the randomized arms, time-to-event endpoints were similar in patients treated with Pola-BR and BR. Notably, despite five years of follow up, the median DOR was not reached for the Pola-BG arm. The median PFS was twice as long for patients in the Pola-BG group than in the Pola-BR group, although patients were not randomized between these arms and the 95% CI for DOR and PFS overlapped. In this small cohort, there was a lower proportion of patients in the Pola-BG group with POD24, and the median age was lower, compared with patients in the Pola-BR arm, which may explain the longer median PFS with Pola-BG *versus* Pola-BR. The efficacy benefits previously reported with polatuzumab vedotin in the R/R DLBCL cohorts of this study[9] were not observed in this current analysis of patients with R/R FL. As expected, higher objective response and CR rates were observed with the triplet combination of Pola+BR than with the doublet combination of Pola+R reported in the phase II ROMULUS study (clinicaltrials.gov 01691898), in which the objective response rate for patients with FL was 70% (95% CI: 47-88), and the CR rate was 45% (95% CI: 23-68).[22] However, differences in study design and patient populations limit the value of cross-trial comparisons.
Hematologic toxicities were more frequent in the Pola-BR group than in the BR or Pola-BG groups. For example, higher rates of grade 3/4 neutropenia were observed with

Table 5. Summary of the most common adverse events.

	Phase II randomized				Phase Ib/II expansion	
	Pola-BR N=38		BR N=41		Pola-BG N=26	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
Blood and lymphatic disorders, N (%)*						
Neutropenia	17 (44.7)	12 (31.6)	11 (26.8)	8 (19.5)	8 (30.8)	8 (30.8)
Febrile neutropenia	6 (15.8)	6 (15.8)	2 (4.9)	2 (4.9)	2 (7.7)	2 (7.7)
Thrombocytopenia	4 (10.5)	1 (2.6)	8 (19.5)	4 (9.8)	5 (19.2)	3 (11.5)
Anemia	6 (15.8)	4 (10.5)	5 (12.2)	0 (0.0)	3 (11.5)	1 (3.8)
Lymphopenia	3 (7.9)	3 (7.9)	3 (7.3)	3 (7.3)	3 (11.5)	3 (11.5)
Non-hematologic disorders, N (%)†						
Infections (SOC)	31 (81.6)	14 (36.8)	20 (48.8)	4 (9.8)	19 (73.1)	6 (23.1)
Nausea	22 (57.9)	0 (0.0)	13 (31.7)	0 (0.0)	16 (61.5)	0 (0.0)
Fatigue	16 (42.1)	2 (5.3)	13 (31.7)	0 (0.0)	16 (61.5)	2 (7.7)
Diarrhea	16 (42.1)	4 (10.5)	9 (22.0)	0 (0.0)	14 (53.8)	1 (3.8)
Constipation	10 (26.3)	0 (0.0)	8 (19.5)	0 (0.0)	11 (42.3)	0 (0.0)
Decreased appetite	10 (26.3)	0 (0.0)	5 (12.2)	0 (0.0)	8 (30.8)	1 (3.8)
Pyrexia	9 (23.7)	1 (2.6)	5 (12.2)	1 (2.4)	4 (15.4)	0 (0.0)
Pneumonia	9 (23.7)	7 (18.4)	3 (7.3)	1 (2.4)	2 (7.7)	0 (0.0)
Headache	8 (21.1)	0 (0.0)	5 (12.2)	0 (0.0)	7 (26.9)	0 (0.0)
Asthenia	8 (21.1)	2 (5.3)	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	7 (18.4)	0 (0.0)	8 (19.5)	1 (2.4)	13 (50.0)	0 (0.0)
Dyspnea	4 (10.5)	0 (0.0)	4 (9.8)	0 (0.0)	9 (34.6)	0 (0.0)
Alopecia	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)	0 (0.0)
Peripheral neuropathy	6 (15.8)	0 (0.0)	5 (12.2)	0 (0.0)	6 (23.1)	0 (0.0)
Upper respiratory tract infection	3 (7.9)	0 (0.0)	8 (19.5)	1 (2.4)	6 (23.1)	0 (0.0)

AE: adverse event; BR: bendamustine plus rituximab; Pola-BR: polatuzumab vedotin plus bendamustine and rituximab; Pola-BG: polatuzumab vedotin plus bendamustine and obinutuzumab; SOC: system organ class. *Most common blood and lymphatic system disorder AE defined as incidence ≥10% (any grade) in any treatment group. †Most common non-hematologic disorder AE defined as incidence ≥20% (any grade) in any treatment group.

Pola-BR than with BR or Pola-BG, resulting in higher rates of febrile neutropenia and infections. SAE were also higher in the Pola-BR group; febrile neutropenia and pneumonia were the most frequently reported SAE. In this analysis, safety results were found to be consistent with the known safety profiles of polatuzumab vedotin, bendamustine, obinutuzumab, and rituximab.[10,11] However, the rate of PN in the BR group (11/41; 26.8%) was surprising, since PN is not typically associated with BR.[23,24] PN reported during the study was mostly grade 1-2 in all treatment groups, and in the BR group, nine out of eleven (81.8%) patients with PN experienced grade 1 events. Despite higher rates of AE, there was no difference in rates of treatment discontinuation between the study arms.

Baseline characteristics, including number of prior therapies and refractory status, were generally balanced between treatment arms, except for some characteristics associated with a better prognosis in the Pola-BG arm. These characteristics included younger median age, lower POD24 rate, patients with ECOG PS 0-1, and a longer duration from initial diagnosis and time since last treatment in the Pola-BG group than in the Pola-BR and BR groups. Among baseline variables, Ann Arbor stage I/II disease and prior autologous stem cell transplant appeared to be associated with more favorable outcomes with Pola-BR *versus* BR alone, although patient numbers in some of the subgroups were too small to draw definitive conclusions.

As most patients with FL experience relapse, and duration of response typically diminishes with subsequent lines of treatment, safer and more effective treatment options are needed.[25] Adding polatuzumab vedotin to rituximab results in improved efficacy compared with rituximab monotherapy;[22,26] however, a similar add-on benefit was not observed when combining Pola+BR. One potential rationale for the lack of benefit observed when adding polatuzumab vedotin to bendamustine combined with an anti-CD20 agent may be related to the considerable activity of bendamustine in patients with FL.[20] In the current study, adding polatuzumab vedotin to BR did not improve on the already high response rates observed with BR/BG alone. The combination of polatuzumab vedotin plus rituximab could be a well-tolerated option in some patients with R/R FL who may not be candidates for bendamustine-based chemotherapy regimens. A limitation of this study was the modest sample size for all three study arms, in particular, the Pola-BG arm, in which only 26 patients were enrolled. Also, inclusion of patients who had previously received bendamustine with a response duration of ≥1 year (~10% of the population) could be considered a limitation, given the known negative impact of bendamustine on bone marrow.[27]

In conclusion, no difference in efficacy was observed between Pola-BR and BR, although higher rates of cytopenias and SAE were reported in patients who received Pola-BR *versus* BR alone. This analysis does not demonstrate a benefit of adding Pola to BR regimens for patients with R/R FL.

Disclosures

CRF reports consultancy for AbbVie, Bayer, BeiGene, Celgene, DenovoBiopharma, Foresight Diagnostics, Genentech Inc., F. Hoffmann-La Roche Ltd., Genmab, Gilead, Karyopharm, Pharmacyclics/Janssen, SeaGen, and Spectrum; research funding from 4D, AbbVie, Acerta, Adaptimmune, Allogene, Amgen, Bayer, Celgene, Cellectis, EMD, Gilead, F. Hoffmann-La Roche Ltd., Genentech Inc., Guardant, Iovance, Janssen Pharmaceutical, Kite, Morphosys, Nektar, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, Ziopharm, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, and V Foundation, Cancer Prevention and Research Institute of Texas: CPRIT Scholar in Cancer Research; and receives Foresight Diagnostics and NPower stock options. MJM reports consultancy for ADC Therapeutics, AstraZeneca, Bayer, Daiichi Sankyo, Epizyme, F. Hoffmann-La Roche Ltd., Genentech Inc., IMV Therapeutics, Juno Therapeutics, Karyopharm, Merck, MEI Pharma, Rocket Medical, Seattle Genetics, TG Therapeutics, Teva, and Bayer; research funding from AstraZeneca, Bayer, Genentech Inc., IGM Biosciences, Janssen, Pharmacyclics, F. Hoffmann-La Roche Ltd., and Seattle Genetics; honoraria from ADC Therapeutics, Bayer, Daiichi Sankyo, Epizyme, IMV Therapeutics, Janssen, MEI Pharma, Pharmacyclics, Genentech Inc., F. Hoffmann-La Roche Ltd., and Seattle Genetics; and receives Merck stocks. AFH reports consultancy for BMS, Genentech Inc., Merck, Seattle Genetics, AstraZeneca, Karyopharm, ADC Therap, Takeda, Tubulis, Regeneron, Genmab, Pfizer, Caribou, AbbVie and Adicet Bio; and research funding from Bristol Myers Squibb, Genentech Inc., Merck, Seattle Genetics, Kite Pharma, Gilead, AstraZeneca, and ADC Therapeutics. MH reports advisory board participation and honoraria for F. Hoffmann-La Roche Ltd., Takeda, Otsuka, BeiGene, Gilead, Janssen, Novartis, and Mundipharma. SA reports consultancy for Genentech Inc., F. Hoffmann-La Roche Ltd., Astra Zeneca, Novartis, BMS, Jazz, Gilead, Amgen, BeiGene, AbbVie, and Paladin; research funding for Novartis; and honoraria from Genentech Inc., F. Hoffmann-La Roche Ltd., Astra Zeneca, Novartis, BMS, Jazz, Gilead, Amgen, BeiGene, AbbVie, and Paladin. JD reports consultancy for AbbVie, BMS, Janssen-Cilag, Novartis, Pfizer, Takeda; and honoraria for Pfizer. AMc reports honoraria from F. Hoffmann-La Roche Ltd., Takeda, Amgen, and Prosthetics; and has served on speakers' bureaux for F. Hoffmann-La Roche Ltd. AM reports research funding from Incyte, Takeda, Forty Seven Inc./Gilead, Juno Pharmaceuticals/BMS, Celgene/BMS, Innate Pharmaceuticals, Seattle Genetics, TG Therapeutics, Affimed, Merck, Kite/Gilead, F. Hoffmann La-Roche Ltd., Genentech Inc., I-MAB; consultancy for Gilead, AstraZeneca, Pharmacyclics, Seattle Genetics, Incyte, Morphosys/Incyte, TG Therapeutics, Kyowa Kirin, Novartis, BMS, BeiGene; and has served on speakers' bureaux for Gilead, AstraZeneca, Pharmacyclics, Seattle Genetics, Incyte, Morphosys/Incyte, Kyowa Kirin, BMS, BeiGene. SO reports consultancy for AbbVie, AstraZeneca, BeiGene, CSL Behring,

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Contributions

JH, LM, CRF and LHS designed the clinical study and interpreted clinical data. AY contributed to the statistical analysis. LM and CRF wrote the manuscript with input and approval of the final version from all co-authors. All authors collected and analyzed the data, reviewed the data, provided critical review of the manuscript, confirmed the completeness and accuracy of the results and the trial's fidelity to the protocol, and agreed on its submission for publication.

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Data-sharing statement

For eligible studies, qualified researchers may request access to individual patient level clinical data through a data request platform. At the time of writing, this request platform is Vivli. https://go.roche.com/data_sharing. For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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