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A phase 2 study of polatuzumab vedotin + bendamustine + rituximab in relapsed/refractory diffuse large B-cell lymphoma

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Abstract

Polatuzumab vedotin (pola) is a CD79b-targeted antibody-drug conjugate delivering a potent antimitotic agent (monomethyl auristatin E) to B cells. This was an open-label, single-arm study of pola 1.8 mg/kg, bendamustine 90 mg/m^2, rituximab 375 mg/m^2 (pola + BR) Q3W for up to six cycles in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who received ≥1 prior line of therapy and were ineligible for autologous stem cell transplantation (ASCT) or experienced treatment failure with prior ASCT. Primary endpoint was complete response rate (CRR) at the end of the treatment (EOT) by positron emission tomography–computed tomography (PET-CT) using modified Lugano Response Criteria. Secondary endpoints included efficacy, safety, and pharmacokinetics. Thirty-five patients (median age 71 [range 46-86] years) were enrolled. Twenty-three (66%) patients had refractory disease, and 23 (66%) had ≥2 prior lines of therapy. At a median follow-up of 5.4 (0.7-11.9) months, patients received a median of five treatment cycles. CRR was 34.3% (95% confidence interval [CI] 19.1-52.2) at EOT. Overall response rate was 42.9% at EOT, and median progression-free survival was 5.2 months (95% CI 3.6-not evaluable). Median overall survival was not reached. No fatal adverse events (AEs) were observed. Grade 3-4 AEs were mainly hematological: anemia (37%), neutropenia (31%), white blood cell count decreased (23%), thrombocytopenia/platelet count decreased/neutrophil count decreased (20% each), and febrile neutropenia (11%). Grade 1-2 peripheral neuropathy (PN; sensory and/or motor) was reported in 14% of patients; there were no ≥grade 3 PN events. This study (JapicCTI-184048) demonstrated the efficacy and safety of pola + BR in Japanese patients with R/R DLBCL who were ineligible for ASCT.

KEYWORDS

bendamustine, diffuse large B-cell lymphoma, polatuzumab vedotin, relapsed/refractory (R/R), rituximab

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an orphan disease (prevalence 1-5 per 10 000 people per annum).[1] It is the most frequently diagnosed subtype of B-cell non-Hodgkin's lymphoma (NHL) accounting for 30%-40% of adult NHL cases.[2-4] It is curable in many cases, with approximately 60%-70%[5] achieving and maintaining remission following first-line treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Nevertheless, 30%-40% of patients will relapse and be refractory to first-line treatment.[6] Patients with relapsed/refractory (R/R) DLBCL who are not eligible for transplant have limited treatment options and a poor prognosis with a median overall survival (OS) of approximately 6 months.[7] Among salvage therapies for transplant-ineligible patients with R/R DLBCL, the bendamustine and rituximab (BR) regimen is active and is associated with manageable hematologic toxicity.[8,9] However, there is still a high unmet need for patients with R/R DLBCL, as there is no standard

treatment for transplant-ineligible patients with R/R DLBCL regardless of line of therapy.[2,10]

Polatuzumab vedotin (pola) is a first-in-class CD79b-targeted antibody-drug conjugate that preferentially delivers a potent antimitotic agent (monomethyl auristatin E, MMAE) to B cells and results in the killing of malignant B cells.[11-14] CD79b is a cell surface antigen expressed exclusively on all mature B cells except plasma cells; it is expressed in almost all B-cell lymphomas.[12] CD79b is an ideal target for the delivery of a cytotoxic drug, as antibodies that are bound to CD79b rapidly migrate into cells.[15,16]

Commonly used chemotherapy regimens for transplant-ineligible R/R DLBCL contain platinum-based agents which have overlapping neurotoxicity and hematologic toxicity with pola. The BR regimen is considered to be a more rational combination partner for pola, as it avoids these overlapping toxicities and there is evidence supporting its use in this setting.[8,9] The phase 1b/2 trial GO29365 (NCT02257567) included a randomized comparison between pola administered with BR (pola + BR) and BR alone in patients with R/R

DLBCL.[11] Pola received regulatory approvals in the United States and the European Union based on the results of the phase 1b/2 trial. However, at the time the phase 2 trial in Japan began in 2018, further validation of the efficacy and safety of pola + BR in R/R DLBCL was required, as data were available from less than only 50 patients in the GO29365 study.

The safety and pharmacokinetics of pola monotherapy in Japanese patients were assessed in a phase 1 dose-escalation study.[17] Pola 1.8 mg/kg was considered tolerable in Japanese patients.

Here, we report the results of the phase 2 trial (P-DRIVE, JO40762; JapicCTI-184048) to evaluate the efficacy, safety and pharmacokinetic (PK) profile of pola + BR in Japanese patients with R/R DLBCL who were ineligible for autologous stem cell transplant (ASCT).

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a multicenter, single-arm, open-label, phase 2 trial (P-DRIVE) of pola + BR in Japanese patients with R/R DLBCL.

Patients received pola 1.8 mg/kg intravenously (IV) on day 2 of cycle 1 and day 1 of subsequent cycles; bendamustine 90 mg/m^2 IV on days 2 and 3 of cycle 1 and then days 1 and 2 of subsequent cycles; rituximab 375 mg/m^2 IV on day 1 of each cycle. Three weeks of treatment was regarded as one cycle, and patients received up to six cycles of treatment. All patients received prophylactic granulocyte colony-stimulating factor (G-CSF), including peg G-CSF. The G-CSF dose and form was selected at the discretion of the principal/subinvestigator. Given the risk of infections associated with bendamustine, antiviral medication (for herpes simplex virus and varicella-zoster virus) and antipneumocystis prophylaxis were required at the initiation of study treatment and continued for at least 6 months after the completion of study treatment. If an adverse reaction occurred, interruption, discontinuation, or reduction of the dose was performed in accordance with the protocol criteria. Full details are available in the protocol (Appendix S1).

Eligible patients were aged ≥20 years with histologically confirmed CD20-positive DLBCL. Pathological diagnoses of DLBCL were performed at the study sites based on local classification, for example WHO 2016 classification[18]; central pathological review was not done. Patients had received ≥1 prior lines of therapy, had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2, at least one lesion measurable by computed tomography (CT) scan with a transverse diameter >1.5 cm, a life expectancy of ≥24 weeks, grade ≤1 peripheral neuropathy (PN), and were ineligible for ASCT as assessed by the investigator (INV) or experienced treatment failure with prior ASCT. Refractory status was defined as (a) a best response to the last prior therapy that was not a complete response (CR) or partial response (PR), or (b) the duration between the last treatment day of the last prior therapy and

progressive disease (PD) or the first treatment day in this study was less than 6 months. Full details of the patient inclusion/exclusion criteria are available in the study protocol (Appendix S1).

All patients provided written informed consent before participation in the trial. The trial was approved by the institutional review board at each participating site and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. The study was designed and sponsored by Chugai Pharmaceutical Co., Ltd.

2.2 | Procedures

2.2.1 | Assessments

Positron emission tomography–computed tomography (PET-CT) scans were performed at baseline, after three cycles, and at the end of the treatment (EOT; 6-8 weeks after last dose of study treatment). In addition, a CT scan was repeated every 3 months for 2 years or until disease progression or relapse. A further PET scan was optional.

Adverse events (AEs) were defined by National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). All AEs, including serious AEs (SAEs), were reported from cycle 1 day 1 until 90 days after the last dose of study drug, regardless of relationship to treatment. All related SAEs and all AEs of special interest (AESI) were reported indefinitely. Evaluations throughout this study included AEs according to system organ class (SOC)-preferred term, vital signs, and hematological and biochemical laboratory tests.

The PK profile of pola when used in combination with BR was assessed. Blood samples for PK analyses were collected on: cycle 1 day 1 prior to infusion and at 30 minutes after the end of infusion (first dose of pola), and on days 8 and 15; cycle 2 day 1 prior to infusion; cycle 4 day 1 prior to infusion and 30 minutes after the end of infusion; and 30 days after the last dose of pola. The PK parameters of pola analytes (total antibody, antibody-conjugated MMAE [acMMAE], and unconjugated MMAE) were measured using validated methods.[19-21] Serum/plasma concentrations and PK parameters, including area under the curve (AUC), maximum concentration (C_{max}), time to achieve C_{max} (T_{max}), and half-life ($t_{1/2}$), were assessed.

Immunogenicity analyses were performed on patients in whom ≥1 antidrug antibody (ADA) assessments had been performed before and after study treatment. Cell of origin (COO; activated B cell [ABC]; germinal center B cell [GCB]) was determined centrally by Covance, and the data were analyzed by NanoString. c-MYC and BCL-2 expression were assessed by immunohistochemical staining in the central laboratory at Roche Tissue Diagnostics (Ventana). The cutoffs for positivity of c-MYC and BCL-2 by immunohistochemistry were ≥40% and 2+ or 3+, respectively.[11] CD79b expression was assessed by immunohistochemical staining by HistoGeneX. The range of expression of CD79b 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. 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.[11]

2.2.2 | Endpoints

The primary end point was INV-assessed complete response rate (CRR) to pola + BR, as measured by [^{18}F] fluorodeoxyglucose PET-CT using modified Lugano Response Criteria[22] at EOT (6-8 weeks after the last dose of study treatment). If PET-CT imaging was not performed, the response was considered to be missing or unevaluable, and the patient was treated as a nonresponder. The response evaluation was performed only by the INVs and was not done centrally.

Secondary end points included INV-assessed overall response rate (ORR) at EOT, best overall response (BOR), duration of response (DOR), progression-free survival (PFS), event-free survival (EFS), OS, safety, pharmacokinetics, and immunogenicity. Exploratory end points included biomarker evaluation of efficacy by COO and double-expressor status.

2.3 | Statistical analyses

Efficacy was assessed in the intention-to-treat (ITT) population, which included all enrolled patients. Safety was assessed in the as-treated population, which included all enrolled patients who received at least one dose of the treatment.

The CRR was calculated as the percentage of patients with CR, with confidence intervals (CIs) estimated by the Clopper-Pearson exact method.[23]

As predefined in the protocol, if the lower limit of 95% CI for CRR exceeded 17.5%, which is the CRR of the BR arm from the GO29365 trial,[11] then it would be considered that pola + BR would have demonstrated clinically significant efficacy. Sample size was based on the expected CRR at 40.0% (pola + BR arm in the GO29365 study[11]) and threshold CRR at 17.5% (BR arm in the GO29365 study[11]). To detect an improvement in CRR using Clopper-Pearson's test at a two-sided significance level of 0.05, 35 patients were required to achieve an 80% overall power.

As secondary analyses, summary statistics of efficacy parameters, ORR at EOT, BOR, and best CRR based on PET-CT only or CT only using the Modified Lugano Response Criteria were analyzed with the same methodology as the primary endpoint. The Kaplan-Meier method was used to estimate PFS and OS. If analytically possible, median would be estimated, along with the corresponding 95% CIs using the method of Brookmeyer and Crowley.

Summaries of safety evaluations and AEs were collected. PK parameters, including the time course of mean concentrations of the individual drugs (pola, bendamustine, and rituximab), and the number and percentage of ADA-positive and ADA-negative patients were also summarized.
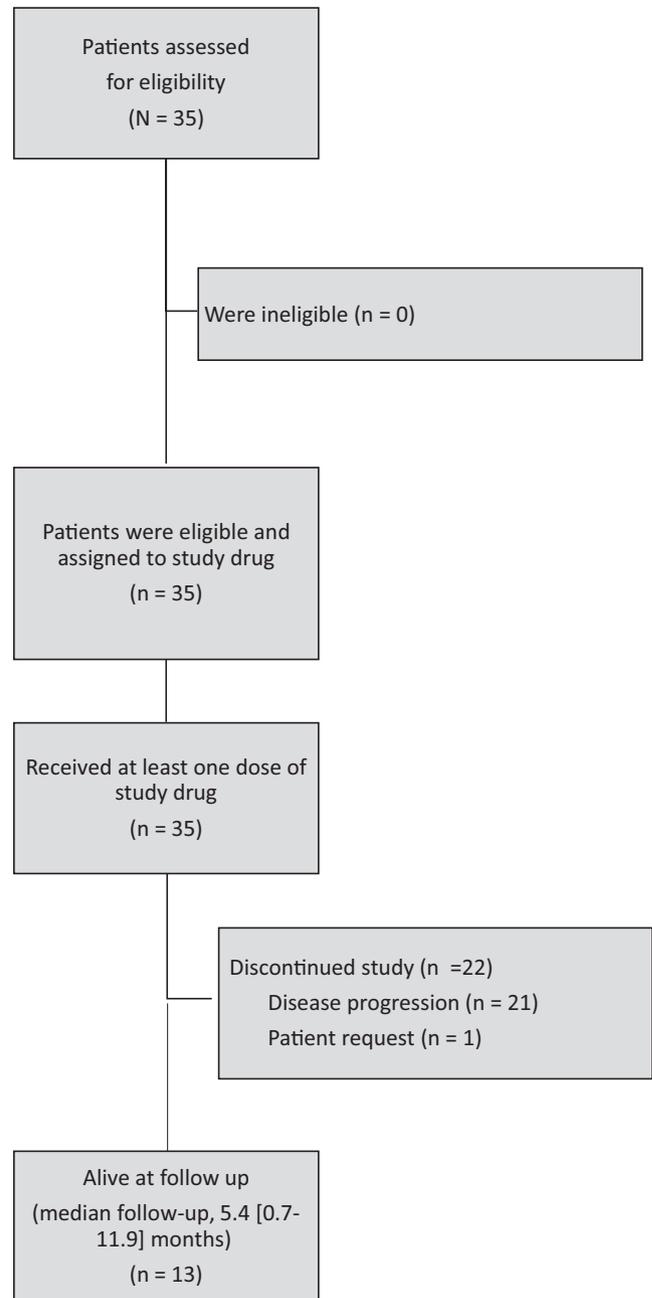

FIGURE 1 Patient disposition

3 | RESULTS

Between October 19, 2018 and July 23, 2019, 35 patients were enrolled (Figure 1). Baseline patient demographics and clinical characteristics are shown in Table 1. Median age was 71 (range 46-86) years. The number of patients who were refractory to last prior antilymphoma therapy was 23 (66%). The median number of prior lines of therapy was 2 (range 1-7), and 23 (66%) patients had received more than two prior lines of therapy. At enrollment, 24 (69%) patients were Ann Arbor stage III-IV and 18 (51%) patients had International Prognostic Index (IPI) score of 3-5. The reasons for ineligibility for ASCT were age (n = 23), insufficient response to salvage therapy (n = 7), patient refused transplant (n = 5), and

TABLE 1 Patient demographic and clinical characteristics at baseline (safety-evaluable population)

Variable	Pola + BR N = 35
Sex, n (%)	
Male	22 (62.9)
Female	13 (37.1)
Median, y (range)	71 (46-86)
Age group, n (%)	
<65 y	10 (28.6)
≥65 y	25 (71.4)
Lines of prior therapy, n (%)	
1	12 (34.3)
2	8 (22.9)
≥3	15 (42.9)
Baseline ECOG PS, n (%)	
0	23 (65.7)
1	9 (25.7)
2	3 (8.6)
Ann Arbor stage at enrollment, n (%)	
Stage I	4 (11.4)
Stage II	7 (20.0)
Stage III	7 (20.0)
Stage IV	17 (48.6)
IPI at enrollment, n (%)	
1	3 (8.6)
2	14 (40.0)
3	10 (28.6)
4	7 (20.0)
5	1 (2.9)
Duration of response to last therapy, n (%)	
≤12 mo	26 (74.3)
>12 mo	9 (25.7)
Prior autologous stem cell transplantation, n (%)	
Yes	4 (11.4)
No	31 (88.6)
Prior anti-CD20 agents, n (%)	
Yes	34 (97.1)
No	1 (2.9)
Refractory to last prior antilymphoma therapy, n (%)	
Yes	23 (65.7)
No	12 (34.3)
Cell of origin, n (%)[a]	
ABC	13 (40.6)
GCB	14 (43.8)
Unclassified	5 (15.6)
BCL-2, n (%)[b]	

(Continues)

TABLE 1 (Continued)

Variable	Pola + BR N = 35
Negative	11 (32.4)
Positive	23 (67.6)
c-MYC, n (%)[c]	
Negative	6 (18.2)
Positive	27 (81.8)

Abbreviations: ABC, activated B cell; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, international prognostic index.

[a]n = 32.
[b]n = 34.
[c]n = 33.

failure of prior autologous hematopoietic transplant (n = 3). One patient had a prior autologous hematopoietic transplant at the age of 67 years; however, as this patient was 83 years old, age was selected by the INV as the reason for ASCT-ineligibility. The median duration of follow-up was 5.4 months (range 0.7-11.9), and patients received a median of five treatment cycles (range 1-6), with 14 (40%) patients completing all six cycles of treatment. Twenty-one patients discontinued any study drug due to PD (n = 12), AEs (n = 7), and noncompliance with the administration of study drugs (n = 2).

3.1 | Efficacy

The data cutoff for the primary analysis was on December 24, 2019. By modified Lugano response criteria based on PET-CT, 12 patients (34.3%, 95% CI 19.1-52.2) achieved CR (Table 2), and the primary endpoint was met. Seven of 12 patients who achieved CR completed six cycles of treatment. Fifteen patients (42.9%, 95% CI 26.3-60.7) achieved an overall response (12 patients CR; 3 patients PR). At a median follow-up of 5.4 months, median DOR, PFS, and EFS were 6.6 months, 5.2 months, and 5.1 months, respectively (Table 2; Figure 2). Twenty-three patients (65.7%) were alive, and median OS was not reached (95% CI 8.4-not evaluable [NE]).

3.2 | Adverse events

All patients had at least one AE, and the total number of events was 392 (Table S1). Thirty-one patients (89%) experienced grade 3-4 AEs, and 12 patients (34%) experienced serious AEs. There were no fatal AEs. Grade 3-4 anemia was reported in 13 patients (37%), grade 3-4 neutropenia in 11 patients (31%), grade 3-4 white blood cell count decrease in eight patients (23%), and grade 3-4 thrombocytopenia, platelet count decrease, and neutrophil count decrease in seven patients (20%, each) (Table 3). Thirty-one patients (88.6%) experienced grade 3-4 lymphocyte count decrease (laboratory test

TABLE 2 Summary of efficacy outcomes (ITT population)

Response	Pola + BR (N = 35)
Response at EOT based on PET-CT (Lugano)	
Responders	15 (42.9)
Nonresponders	20 (57.1)
95% CI for response rates	26.3-60.7
Complete response	
n (%)	12 (34.3)
95% CI	19.1-52.2
Partial response	
n (%)	3 (8.6)
Stable disease	
n (%)	1 (2.9)
Progressive disease	
n (%)	8 (22.9)
Missing or NE[a]	
n (%)	11 (31.4)
Best overall response based on PET-CT (Lugano)	
Responders	25 (71.4)
Nonresponders	10 (28.6)
95% CI for response rates	53.7-85.4
Complete response	
n (%)	15 (42.9)
95% CI	26.3-60.7
Partial response	
n (%)	10 (28.6)
Stable disease	
n (%)	1 (2.9)
Progressive disease	
n (%)	2 (5.7)
Missing or NE[a]	
n (%)	7 (20.0)
Median duration of response, months (95% CI)	
Based on PET-CT	6.6 (3.9-NE)
Median progression-free survival, months (95% CI)	
Based on PET-CT or CT[b]	5.2 (3.6-NE)
Median event-free survival, months (95% CI)	
Based on PET-CT or CT[b]	5.1 (3.6-6.3)
Median overall survival, months (95% CI)	NE (8.4-NE)

Abbreviations: CI, confidence interval; CT, computed tomography; EOT, end of the treatment; ITT, intention-to-treat; MRI, magnetic resonance imaging; NE, not evaluable; PET-CT, positron emission tomography–computed tomography; pola + BR, polatuzumab vedotin +bendamustine + rituximab.

[a]Reasons for missing or unevaluable response: CT or MRI performed without PET at EOT (n = 11) and at the best response (n = 7).

[b]Tumor assessment results were based on PET-CT results if they were valid, or CT results if the PET-CT results were not valid.
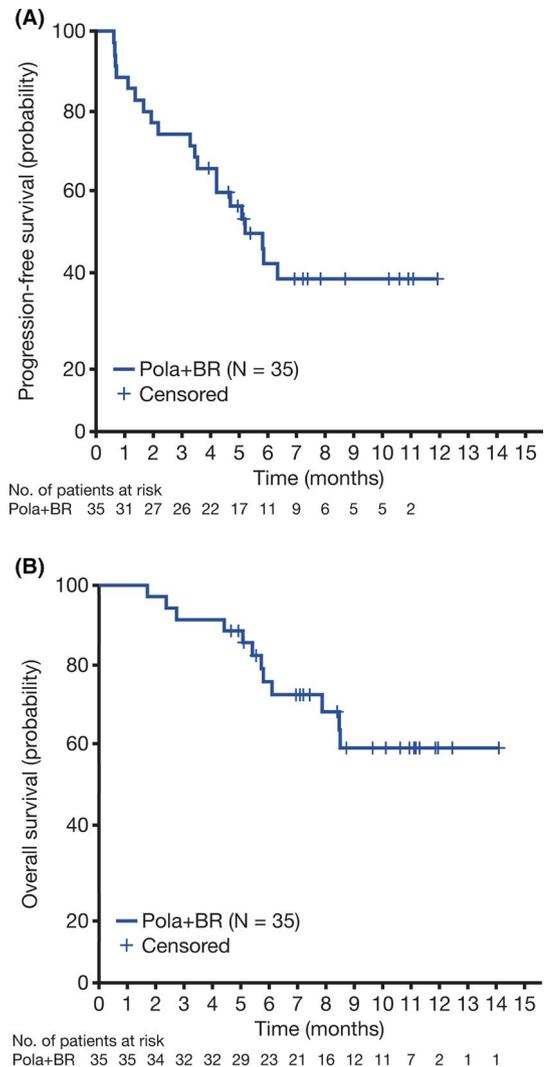

FIGURE 2 Progression-free survival and overall survival (ITT population): A, Progression-free survival by investigator based on PET-CT or CT. B, Overall survival. ITT, intention-to-treat; OS, overall survival; PET-CT, positron emission tomography–computed tomography; pola + BR, polatuzumab vedotin + bendamustine + rituximab; PFS, progression-free survival

result). Twenty-eight patients (80.0%) experienced nonsevere decreased immunoglobulin (laboratory test result).

Serious AEs occurring in >5% of patients were acute renal dysfunction and febrile neutropenia (6% each). These events were considered unrelated to the study treatment; they occurred during receipt of new antilymphoma treatment after completion of the pola + BR regimen. Five patients experienced PN (sensory or motor; grade 2 [two patients] and grade 1 [three patients]).

Twenty patients experienced AEs that led to dose modification or interruption of any treatments (Table S1). Seven patients had AEs which led to the withdrawal of any treatments (Table S1). The incidence rate of related AEs that led to dose modification or interruption of any study drug was 57.1% (20/35 subjects). AEs with an incidence rate of 5% or more, that led to dose modification or interruption of any study drug, were platelet count decreased (11.4%); neutrophil count decreased (8.6%); and aspartate aminotransferase

TABLE 3 Adverse events by highest NCI CTCAE grade (safety-evaluable population)

| Adverse event | Pola + BR (N = 35) | |
	All grades, N (%)	Grades 3-4, N (%)
Any event	35 (100)	31 (89)
Gastrointestinal disorders		
Overall	26 (74.3)	0
Constipation	13 (37.1)	0
Nausea	12 (34.3)	0
Diarrhea	9 (25.7)	0
Blood and lymphatic system disorders		
Overall	26 (74.3)	25 (71.4)
Anemia	16 (45.7)	13 (37.1)
Neutropenia	12 (34.3)	11 (31.4)
Thrombocytopenia	9 (25.7)	7 (20.0)
General disorders and administration site conditions		
Overall	23 (65.7)	2 (5.7)[a]
Fever	12 (34.3)	0
Fatigue	8 (22.9)	0
Skin and subcutaneous tissue disorders		
Overall	19 (54.3)	2 (5.7)[a]
Investigations		
Overall	19 (54.3)	16 (45.7)
Platelet count decrease	9 (25.7)	7 (20.0)
Neutrophil count decrease	8 (22.9)	7 (20.0)
White blood cell count decrease	8 (22.9)	8 (22.9)
Metabolism and nutrition disorders		
Overall	18 (51.4)	5 (14.3)
Loss of appetite	8 (22.9)	1 (2.9)
Infections and infestations		
Overall	14 (40.0)	6 (17.1)
Respiratory, thoracic, and mediastinal disorders		
Overall	12 (34.3)	1 (2.9)[a]
Nervous system disorders		
Overall	8 (22.9)	0

Note: All-grade adverse events (AEs) occurred in ≥20% of patients and grade 3-4 AEs in ≥10% of patients. All counts represent subjects; percentages are based on total number of subjects (N = 35). AEs were coded using MedDRA version 21.0. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term. For the system organ class (SOC) overall row counts, a patient contributes only once with the AE occurring with the greatest intensity within the SOC.

Abbreviations: NCI CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; pola + BR, polatuzumab vedotin + bendamustine + rituximab.

[a]Grade 3 only.

increase, neutropenia, decreased appetite, and rash (5.7% each). These events were considered to be related to the study treatment.

Two patients discontinued any treatment due to neutropenia (grade 4), and one patient each due to gamma-glutamyltransferase increase (grade 2), thrombocytopenia (grade 4), platelet count decrease (grade 4), and drug hypersensitivity (grade 3). One patient also discontinued treatment due to experiencing both fatigue (grade 3) and PN (both motor and sensory; each grade 2).

3.3 | Immunogenicity and pharmacokinetics

All patients with available samples after treatment administration (34 out of 35) were negative for ADAs to pola.

PK parameters of serum total antibody, plasma acMMAE, and plasma-unconjugated MMAE are summarized in Table 4. For total antibody, mean C_{max} was 29.4 µg/mL, mean AUC_{inf} concentration was 256 µg-d/mL, and mean $t_{1/2}$ was 9.58 days. For plasma acMMAE, mean C_{max} was 533 ng/mL, mean AUC_{inf} was 2510 ng-d/mL, and mean $t_{1/2}$ was 6.06 days. For plasma-unconjugated MMAE, C_{max} was 2.19 ng/mL.

The T_{max} for total antibody and acMMAE occurred at 30 minutes after the end of first infusion, and the C_{max} of total antibody and acMMAE were 29.4 µg/mL and 533 ng/mL each and then decreased to 3.47 µg/mL for total antibody and 15 ng/mL for acMMAE on average at day 20 (Figure S1). The T_{max} for unconjugated MMAE occurred at 6 days after the end of first infusion; the C_{max} of unconjugated MMAE was 2.19 ng/mL and then decreased to 0.197 ng/mL for unconjugated MMAE at day 20.

3.4 | Biomarker analysis

COO distribution was ABC, 40.6% (13/32 patients); GCB, 43.8% (14/32 patients); and unclassifiable 15.6% (5/32 patients; Table 1). CRR was lower in the GCB subgroups (7.1%; 1/14 patients) compared with ABC (46.2%; 6/13 patients). Double-expressor lymphoma (DEL) status was assessed in 35 patient samples; 48.6% were identified as DEL. CRR was comparable between DEL (35.3%) and non-DEL (33.3%) patients. No clear relationship was observed between levels of CD79b expression at baseline and clinical outcomes (Table S3).

4 | DISCUSSION

Therapeutic options are limited for patients with transplant-ineligible R/R DLBCL, who also have very poor clinical outcomes. In this single-arm, open-label, clinical trial (P-DRIVE) conducted in Japan, pola + BR was effective and had a tolerable safety profile in patients with transplant-ineligible R/R DLBCL.

In P-DRIVE, the BR arm of the GO29365 study was set as a historical control in order to confirm the efficacy of pola + BR. Overall, baseline characteristics in the BR arm of GO29365 and P-DRIVE are

PK parameter	N^a	Missing^b	Mean (SD)	Median (range)
Serum total antibody				
C_{max}, µg/mL	33	0	29.4 (7.34)	28.4 (14.9-46.1)
AUC_{inf}, day*µg/mL	33	5	256 (58.3)	257 (144-395)
$t_{1/2}$ d	33	5	9.58 (1.62)	9.11 (7.12-14.4)
Plasma acMMAE				
C_{max}, ng/mL	33	0	533 (101)	522 (318-717)
AUC_{inf}, day*ng/mL	33	4	2510 (508)	2550 (1040-3420)
$t_{1/2}$, days	33	4	6.06 (0.853)	5.93 (4.59-7.87)
Plasma unconjugated MMAE				
C_{max}, ng/mL	33	0	2.19 (1.48)	1.93 (0.149-7.18)
AUC_{last}, d*ng/mL	33	0	19.1 (11.6)	18.7 (0.0066-53.2)

TABLE 4 Summary of pharmacokinetic parameters for polatuzumab vedotin analytes following first 1.8 mg/kg dose of polatuzumab vedotin on day 1 of cycle 1

Abbreviations: acMMAE, antibody-conjugated monomethyl auristatin E; AUC_{inf}, area under the curve; C_{max}, maximum concentration; MMAE, monomethyl auristatin E; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life.

^{a}The number of patients with available samples for PK analysis.

^{b}The number of patients in whom PK parameters could not be calculated.

very similar. The median age of patients was 71 years in the BR arm of GO29365 versus 71 years in the P-DRIVE study. The proportions of patients with ECOG PS 2 and IPI scores of ≥3 at enrollment were 20.0% and 72.5% in the BR arm of GO29365 and 8.6% and 51.4% in the current study, respectively. The percentages of patients with a DOR to last treatment ≤12 months were 82.5% in the BR arm of GO29365 and 74.3% in P-DRIVE. The median number of lines of prior therapies was two in both the BR arm of GO29365 and the P-DRIVE study. The percentages of refractory patients were 85.0% in the BR arm of GO29365 and 65.7% in the P-DRIVE study. Yet, the percentages of patients completing six cycles of all treatments were 23.1% in the BR arm of GO29365 and 40% in the P-DRIVE study. The efficacy endpoints of CRR and ORR were numerically higher in P-DRIVE (34.3% [95% CI 19.1%-52.2%] and 42.9% [95% CI 26.3%-60.7%], respectively) than by independent review committee (IRC) assessment in the BR arm of GO29365 (17.5% and 17.5%, respectively). The lower limit of the 95% CI for P-DRIVE (19.1%) was higher than that of the BR arm of GO29365 (17.5%), and as such the trial met its primary objective.

Baseline characteristics in the pola + BR arm of GO29365 and P-DRIVE were also very similar in terms of age, sex, ECOG PS, IPI, the number of refractory patients, the number of patients for which the DOR to last treatment was within 12 months, and the median number of lines of prior therapies. The efficacy endpoints of CRR and ORR in P-DRIVE (34.3% [95% CI 19.1%-52.2%] and 42.9% [95% CI 26.3%-60.7%], respectively), were similar to the pola + BR arm of GO29365 by IRC assessment (40.0% [95% CI 24.9%-56.7%] and 45.0% [95% CI 29.3%-61.5%], respectively). As the observational period was short in P-DRIVE compared with the GO29365 study (5.4 vs 27.0 months, respectively), the PFS and OS data from P-DRIVE are immature.

AEs were also similar in P-DRIVE and GO29365; no cases of grade 3-4 PN were reported in both studies, and the majority of grade 3-4

AEs were hematologic. The safety findings from P-DRIVE did not show any additional concerns relating to the known safety profile of pola + BR. Seven patients discontinued any treatment due to AEs: two patients due to neutropenia, two due to thrombocytopenia, one patient each due to gamma-glutamyltransferase increase and drug hypersensitivity, and one patient who experienced fatigue and PN (both motor and sensory). After treatment discontinuation, all events of neutropenia, drug hypersensitivity, and fatigue resolved, but the other AEs did not. As pola, bendamustine, and rituximab are known to cause myelosuppression,[24] so blood counts need to be monitored throughout treatment; prophylactic G-CSF administration and a delay, dose reduction, or discontinuation of pola and bendamustine should be considered in accordance with label recommendations.[24]

As PN is recognized as an AESI in MMAE-based antibody-drug conjugates, it was monitored closely in the P-DRIVE study. Five patients experienced low-grade PN (sensory and/or motor; grade 2 in two patients and grade 1 in three patients), and only one patient discontinued pola + BR due to peripheral sensory neuropathy and peripheral motor neuropathy. This is consistent with the results of our phase 1 study in which there was no clinically relevant impact of plasma acMMAE and unconjugated MMAE exposure on the occurrence of peripheral sensory neuropathy.[17]

Serum total antibody, plasma acMMAE, and plasma-unconjugated MMAE concentrations were measured to evaluate the pharmacokinetics of pola in the P-DRIVE study. The PK profile of these analytes was generally consistent with that seen for pola monotherapy in the previous Japanese phase 1 study,[17] and also consistent with the pharmacokinetics for non-Asian patients in an ethnic sensitivity analysis.[25] Based on these cross-study comparisons, bendamustine and rituximab do not appear to have a clinically significant impact on the pharmacokinetics of pola, and there were no clinically meaningful differences in pola pharmacokinetics based on Japanese ethnicity.

An international consensus panel recommended a bendamustine dose of 90-120 mg/m^2 in combination with rituximab for six cycles in R/R DLBCL.[26] In studies that have evaluated BR alone in this patient population, a dose of bendamustine (120 mg/m^2) was generally used; varying levels of efficacy were observed.[8,9] A best CRR of 37% (evaluated by Cheson 2007 criteria) was achieved in a study by Ohmachi et al, which assessed bendamustine 120 mg/m^2 (on day 2 and 3) in combination with rituximab Q3W in ASCT-ineligible patients (ECOG PS of 0-1; ≤3 prior therapies). However, high hematologic toxicity was observed; specifically, neutropenia in 88% of patients (grade 3, 31% and grade 4, 46%) and leukopenia in 83% of patients (grade 3, 63% and grade 4, 10%). In comparison, a CRR of 17.5% at EOT was reported in the randomized BR arm of the GO29365 study (bendamustine dose 90 mg/m^2), and the best CRR by INV was 20.0%.[11] In a more recent study by Kiguchi et al (in patients in Japan who were of a similar age group), a CRR of 47% was seen with BR.[27] By contrast, in a study by Vacirca et al[9] that included patients who were slightly older (median age 74 [range 25-90] years), a CRR of just 15.3% by Cheson 2007 criteria was reported with BR (bendamustine dose of 120 mg/m^2 used in most patients).

In the GO29365 study, the addition of pola to bendamustine 90 mg/m^2 in combination with rituximab improved efficacy versus bendamustine 90 mg/m^2 in combination with rituximab alone.[11] As studies of bendamustine 120 mg/m^2 were conducted in different patient populations using different evaluation methods from GO29365 and P-DRIVE, it is not possible to make direct comparisons. Furthermore, based on the randomized, phase 1/2 GO29365 study, pola + BR is included as one of the preferred regimens for patients with R/R DLBCL who are not candidates for transplant in the National Comprehensive Cancer Network guidelines, while BR is suggested to be useful in certain circumstances.[28]

In the GO29365 study, improved outcomes were observed in patients receiving pola + BR compared with BR in ABC and GCB subgroups of patients and in DEL and non-DEL patients. This suggests that pola + BR benefits all types of patients regardless of COO or DEL status. In the P-DRIVE study, responses were also observed across subgroups, although the numbers of patients were too small to indicate any trends in efficacy in exploratory subgroup analyses. As CD79b is expressed on the B cells of most DLBCL patients, CD79b expression was not set as an inclusion/exclusion criterion in either the GO29365 or P-DRIVE studies. In both studies, the expression level of CD79b was measured exploratively. There was no association between the expression level of CD79b and response at EOT of pola + BR.[11]

In conclusion, the present study met the primary efficacy endpoint of CRR with the pola + BR regimen in Japanese patients with transplant-ineligible R/R DLBCL. Efficacy and safety data were comparable with the results obtained in the previous global randomized phase 2 study (GO29365), confirming the role of the pola + BR regimen in this population. Thus, in this orphan disease, the findings of our study add weight to the previous findings.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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