

Original Article

Safety and pharmacokinetics of polatuzumab vedotin in Japanese patients with relapsed/refractory B-cell non-Hodgkin lymphoma: a phase 1 dose-escalation study

Tomohiro Kinoshita^{1,*}, Kiyohiko Hatake², Kazuhito Yamamoto¹, Yusuke Higuchi¹, Satsuki Murakami¹, Yasuhito Terui², Masahiro Yokoyama², Dai Maruyama³, Shinichi Makita³, Yukari Hida⁴, Tomohisa Saito^{4,5}, and Kensei Tobinai³

¹Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Japan, ²Department of Hematology Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, ³Department of Hematology, National Cancer Center Hospital, Tokyo, Japan, ⁴Clinical Science & Strategy Department, Chugai Pharmaceutical Co., Ltd., and Tokyo, Japan, and ⁵Clinical Pharmacology Department, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

*For reprints and all correspondence: Tomohiro Kinoshita, MD, PhD, Japanese Red Cross Aichi Blood Center, 539-3, Minamiyamaguchi-cho, Seto, Aichi 489-8555, Japan. E-mail: kinoshita@med.nagoya-u.ac.jp

Received 18 February 2020; Editorial Decision 8 August 2020; Accepted 20 August 2020

Abstract

Objective: A phase 1 dose-escalation study of polatuzumab vedotin (pola) was conducted to assess safety, pharmacokinetics and preliminary antitumor activity of pola in Japanese patients with relapsed/refractory B-cell non-Hodgkin lymphoma.

Methods: Patients received pola (1.0 or 1.8 mg/kg) intravenously every 21 days until disease progression or intolerance. Intra-patient dose escalation was prohibited. Tolerability was determined by the standard 3 + 3 rule. Blood sampling was performed to characterize pharmacokinetics. Antitumor activity was evaluated through computed tomography and bone marrow sampling.

Results: Four patients received pola 1.0 mg/kg; three received 1.8 mg/kg. Patients had follicular lymphoma ($n = 4$) or diffuse large B-cell lymphoma ($n = 3$), median age of 62 years, received a median of 3 prior therapies; six were female. Pola was well tolerated in both cohorts, with no dose-limiting toxicities observed. The most common adverse event was peripheral sensory neuropathy ($n = 4$). Grade 3 adverse events were cholecystitis and neutrophil count decreased (one each; both 1.0 mg/kg), and syncope and cataract (one each; both 1.8 mg/kg). The plasma half-life of antibody-conjugate monomethyl auristatin E was 4.43–7.98 days, and systemic exposure of unconjugated monomethyl auristatin E was limited in both cohorts. Four patients achieved objective responses (three complete, one partial) without disease progression during the study.

Conclusions: This phase 1 dose-escalation study demonstrated that pola has an acceptable safety profile and offers encouraging antitumor activity to Japanese patients with relapsed/refractory B-cell non-Hodgkin lymphoma. Pola 1.8 mg/kg, the recommended phase 2 dose, was tolerable in Japanese patients.

Key words: polatuzumab vedotin, phase 1 clinical trial, pharmacokinetics, B-cell lymphoma

Introduction

In patients with B-cell non-Hodgkin lymphoma (NHL), relapsed/refractory disease remains a major cause of morbidity and mortality, despite improved clinical outcomes with rituximab and chemotherapy regimens (1). With standard therapy, including rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), approximately one-third of diffuse large B-cell lymphoma (DLBCL) patients will eventually develop relapsed/refractory disease (2). Salvage chemotherapy followed by autologous stem cell transplantation is the standard second-line treatment for relapsed/refractory DLBCL (3). However, 3-year progression-free survival rates for DLBCL patients receiving the widely used regimens R-ICE (rituximab plus ifosfamide, carboplatin and etoposide) and R-DHAP (rituximab plus high-dose cytosine arabinoside, cisplatin and dexamethasone) are only 31 and 42%, respectively (4).

In this context, antibody–drug conjugates (ADCs) have been increasingly investigated as an alternative approach for relapsed/refractory B-cell NHL. ADCs are tripartite molecules consisting of a targeted monoclonal antibody, a covalent linker and a cytotoxic payload (5). ADCs use an antibody-mediated method of delivering cytotoxic drugs to tumors in a targeted manner. Therefore, ADCs can improve efficacy by increasing the accumulation of cytotoxic drugs within or near the tumor site and minimize toxicity by reducing systemic effects (6).

Polatuzumab vedotin (pola) is a CD79b-targeted antibody-drug conjugate delivering monomethyl auristatin E (MMAE), a microtubule inhibitor (7). CD79b is a component of the B-cell receptor and is found to be expressed in nearly all major subtypes of B-cell NHL (8,9). Pola bound to CD79b on B cells is rapidly internalized and its linker cleaved; the released MMAE inhibits cell division and induces cell apoptosis (10). Numerous studies have explored pola-based immunochemotherapy in relapsed/refractory B-cell NHL patients (11–18). In a phase 1 study conducted in the USA, Canada, France and the Netherlands, pola showed encouraging clinical activity as a single agent, with a generally acceptable safety profile in patients with relapsed/refractory B-cell NHL (18). Here, we report the results of a phase 1 dose-escalation study, the aims of which were to assess the safety, PK and antitumor activity of pola monotherapy in Japanese patients with relapsed/refractory B-cell NHL.

Patients and methods

Study design

This open-label, multicenter, dose-escalation phase 1 study was conducted in Japanese patients with relapsed/refractory B-cell NHL. The primary objectives were to assess the safety and PK of pola, while a key secondary objective was to evaluate the antitumor activity of pola. Although three dose levels (1.0, 1.8 and 2.4 mg/kg) of pola were initially planned, the highest dose in this study was reduced from 2.4 to 1.8 mg/kg and two dose levels (1.0 and 1.8 mg/kg) of pola were set due to the concerns raised in a previous study about the increased number of grade ≥ 2 peripheral neuropathy events at higher doses (19,20).

There were two dose cohorts (pola 1.0 mg/kg; pola 1.8 mg/kg), with each patient participating in only one of the dose cohorts (three to six patients). Pola was administered intravenously at 1.0 or 1.8 mg/kg every 21 days until disease progression or unacceptable toxicity, or patient or physician decision. The criteria for dose reduction and treatment discontinuation are shown in [Supplementary Table S1](#).

Patient eligibility

Patients were eligible for enrollment if they were 20–74 years old and had histologically confirmed relapsed/refractory B-cell NHL, for which there was no standard therapy available. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 or 1, one or more measurable lesions [in two dimensions by computed tomography (CT) scan with longest diameter > 1.5 cm], a life expectancy of ≥ 12 weeks after enrollment and no history of allogeneic stem cell transplantation. Eligibility criteria also included adequate renal, liver and bone marrow function, defined as hemoglobin ≥ 9 g/dl, neutrophil count $\geq 1500/\mu\text{l}$ and platelet count $\geq 75\,000/\mu\text{l}$, aspartate aminotransferase and alanine aminotransferase ≤ 2.5 of upper limit of normal (ULN), total bilirubin ≤ 1.5 of ULN and serum creatinine ≤ 1.5 of ULN. A washout period was required to eliminate effects from prior therapies (blood transfusion or hematopoietic growth factors, ≥ 2 weeks; surgery, chemotherapy, radiotherapy, monoclonal antibodies and ADC, or other investigational products, ≥ 4 weeks; radioimmunotherapy, autologous hematopoietic stem cell transplantation, ≥ 12 weeks). Patients with chronic lymphocytic leukemia diagnosed according to the National Cancer Institute Working Group diagnostic criteria were excluded. The full exclusion criteria for this study are provided in the [Supplementary Methods](#).

The protocol was approved by applicable ethics committees and institutional review boards, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before the start of the study. The study was registered with clinicaltrials.jp, trial identifier: JapicCTI-142580 (JO29138).

Dose escalation

The dose escalation followed the standard 3 + 3 design. Three patients were evaluated at the first dose level, and in the absence of dose-limiting toxicities (DLTs), three additional patients were enrolled at the next dose level. If one of the initial three patients experienced a DLT, three patients were added at the same dose level. If two or more patients experienced a DLT, no new patients were enrolled in the cohort and the dose was not escalated.

A DLT was defined as any grade ≥ 3 AE related to pola during the first cycle, with the exception of the following: grade 3 or 4 lymphocyte count decreased and white blood cell count decreased; grade 3 or 4 neutrophil count decreased that resolves or improves to grade ≤ 2 by the scheduled infusion date of the next cycle; grade 3 or 4 platelet count decreased that resolves or improves to grade ≤ 2 by the scheduled infusion date of the next cycle in the absence of bleeding and without requiring platelet transfusion; grade 3 infusion reaction that resolves or improves to grade ≤ 1 within 24 hours with supportive care and other measures; grade 3 nausea or vomiting that can be managed with supportive care; and transient asymptomatic laboratory abnormalities associated with antitumor effect of pola that resolve or improve to grade ≤ 2 within 1 week. The severity of AEs was graded according to Common Terminology Criteria for Adverse Events, v4.03. The maximum tolerated dose was defined as the highest dose level at which $< 33\%$ of patients evaluated for DLT will experience DLTs.

Evaluation of patients. Safety evaluations were based on the incidence and severity of AEs, DLTs at each dose level and changes in clinical laboratory test results over time. AEs were monitored and recorded continuously during the study. Laboratory evaluations including hematology and blood chemistry were evaluated at screening, on days 1, 2, 8 and 15 of cycle 1; on days 1, 8 and 15 of cycles 2–4;

on days 1 and 15 of cycles 5–8 and day 1 of each cycle thereafter, and at the final evaluation (28 days after last dosing).

Antitumor activity was evaluated every 4 cycles by investigators in accordance with Revised Response Criteria for Malignant Lymphoma (21). CT scans were performed at screening and every 4 cycles from day 1 of cycle 4 until the final evaluation. Bone marrow was sampled at screening and during the study, in order to confirm a complete response (CR) in patients with bone-marrow involvement at baseline, or if clinically indicated.

Leukocyte phenotyping using flow cytometry was conducted at screening, on day 1 of cycle 1 and every 4 cycles from day 1 of cycle 4 until the final evaluation, to determine changes in the number of peripheral blood B cells (CD19+), T cells (CD3+, CD4+ and CD8+) and natural killer (NK) cells (CD16+/CD56+).

Pharmacokinetic analysis

Blood samples for PK analyses were collected pre-dosing, at 30 minutes and 4 hours after the first dose of pola, and on days 2, 4/5, 8, 11 and 15 of cycle 1; pre-dosing and at 30 minutes and 4 hours after dosing on day 1 of cycle 2 and pre-dosing and 30 minutes after dosing on day 1 of cycles 3–8 and cycle 12 and every 4 cycles thereafter, on day 8 and 15 of cycles 2–4 and on day 15 of cycle 8. Final sampling occurred 28 days after the last dosing of pola. The PK profile of pola was characterized by analyzing serum total antibody (including conjugated and unconjugated antibody) by a validated enzyme-linked immunosorbent assay and by analyzing plasma antibody-conjugated MMAE (acMMAE) and unconjugated MMAE by validated liquid chromatography–tandem mass spectrometry. The calculated PK parameters were the maximum plasma or serum concentration (C_{max}), time to reach maximum drug concentration (t_{max}), plasma or serum terminal phase half-life ($t_{1/2}$), area under the concentration–time curve from zero to infinity (AUC_{inf}), clearance (CL) and volume of distribution at steady state (V_{ss}).

Statistics

The number of patients in each proposed cohort was based on the standard 3 + 3 design for dose-escalation studies. A total of 6–12 patients were planned to assess the safety and tolerability of pola, depending on observed toxicities. Descriptive statistics were used for the evaluation of safety, PK and antitumor activity. Patients were considered evaluable for safety and antitumor activity if they received at least one dose of pola. PK analyses were performed in patients who received at least one dose of pola and had data for serum total antibody, acMMAE and unconjugated MMAE. Statistical analyses were carried out with SAS v9.2. Non-compartmental analysis for PK parameters was performed with Phoenix WinNonlin v6.4.

Results

Patients

Seven patients were enrolled (1.0 mg/kg cohort, $n = 4$; 1.8 mg/kg cohort, $n = 3$). All seven patients enrolled in the study were treated with pola, and all seven patients were included in the intent to treat (ITT) and safety analysis populations. Per protocol, a further patient was enrolled to receive pola 1.0 mg/kg to keep the number of PK evaluation population as planned in 1.0 mg/kg because there were defective PK samples in cycle 1 of one of three patients who had been enrolled in 1.0 mg/kg. The PK sampling from this patient in cycle 1 was enough to conduct PK evaluation. Yet, since this patient in 1.0 mg/kg discontinued treatment due to disease progression during

the DLT evaluation period, the patient was excluded from the DLT evaluation population.

All four patients enrolled to receive 1.0 mg/kg pola were included in the ITT, safety and PK analysis populations.

Patient demographics and baseline characteristics are shown in Table 1. Patients had a median age of 62 years (range, 42–67 years), and the majority were female ($n = 6$). There were four patients with follicular lymphoma (FL) and three patients with DLBCL. Median number of prior therapies was 3 (range, 1–5).

Safety

All patients were eligible for the safety analysis. There were no dose reductions due to AEs, and the maximum tolerated dose was not reached (no DLTs). One patient in the 1.8 mg/kg cohort discontinued the study due to left ventricular dysfunction, which was considered not related to pola. Five patients experienced dose delays due to AEs (1.0 mg/kg cohort, $n = 3$; 1.8 mg/kg cohort, $n = 2$). These AEs included peripheral sensory neuropathy ($n = 3$), malaise ($n = 2$), bronchitis ($n = 2$), influenza ($n = 1$), infectious enteritis ($n = 1$), nausea ($n = 1$), vomiting ($n = 1$), cholecystitis ($n = 1$), sinus tachycardia ($n = 1$), decreased appetite ($n = 1$) and neutrophil count decreased ($n = 1$).

A summary of treatment-emergent AEs (TEAE) occurring in two or more patients by dose cohort is shown in Table 2. The frequently reported AEs were peripheral sensory neuropathy ($n = 4$), abdominal discomfort ($n = 3$), malaise ($n = 3$) and influenza ($n = 3$); all were grade 1–2. Grade 3 AEs were cholecystitis ($n = 1$) and neutrophil count decreased ($n = 1$) in the 1.0 mg/kg cohort, and were syncope ($n = 1$) and cataract ($n = 1$) in the 1.8 mg/kg cohort. The single case of neutrophil count decreased was attributed to pola. Cholecystitis occurred on day 1416; it was not related to pola but related to a gallstone. This resulted in treatment discontinuation because patient could not resume treatment within the allowance window in the protocol; the patient recovered on day 1428. Syncope occurred on day 650 and resolved on the same day. It was not related to pola. This event did not result in a dose reduction nor treatment discontinuation. The serious AEs were cholecystitis (1.0 mg/kg cohort, $n = 1$) and cataract (1.8 mg/kg cohort, $n = 1$). No deaths were reported in either cohort.

Pharmacokinetics

The selected Cycle 1 PK parameters for acMMAE, total antibody and unconjugated MMAE are shown in Table 3. Both acMMAE and unconjugated MMAE displayed increases in plasma exposure at 1.8 mg/kg compared with 1.0 mg/kg (Fig. 1). Plasma exposure to unconjugated MMAE was lower than that of acMMAE (Fig. 1). As shown in Table 3, unconjugated MMAE C_{max} was 0.46 and 0.27% of acMMAE, unconjugated MMAE exposure (AUC_{inf}) was ~1.56 and 0.79% of acMMAE and the mean $t_{1/2}$ for acMMAE was 4.43 and 7.98 days in the 1.0 and 1.8 mg/kg cohorts, respectively. The mean $t_{1/2}$ for acMMAE and total antibody were similar between the two dose cohorts, with V_{ss} for both mostly limited to plasma volume. PK profiles of plasma acMMAE and unconjugated MMAE showed no significant differences relative to the absence or presence of peripheral sensory neuropathy (Supplementary Fig. S1).

Antitumor activity

All seven patients were evaluable for efficacy. Based on investigator assessment, four of the seven patients (57%) achieved an objective

Table 1. Patient demographics and baseline characteristics

Characteristics	Pola dose		Total (<i>n</i> = 7)
	1.0 mg/kg (<i>n</i> = 4)	1.8 mg/kg (<i>n</i> = 3)	
Sex, <i>n</i>			
Male	1	0	1
Female	3	3	6
Median age, years (range)	64.5 (62–67)	45.0 (42–62)	62.0 (42–67)
ECOG performance status, <i>n</i>			
0	3	3	6
1	1	0	1
Histological subtype, <i>n</i>			
FL	3	1	4
DLBCL	1	2	3
Ann Arbor stage, <i>n</i>			
I/II	1	1	2
III/IV	3	2	5
Median number of prior therapies (range)	2.5 (2–3)	5.0 (1–5)	3.0 (1–5)
Prior therapy, <i>n</i>			
R-based chemotherapy	4	3	7
Other chemotherapy	0	1	1

Pola, polatuzumab vedotin; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; R, rituximab.

Table 2. All-grade TEAEs occurring in two or more patients

TEAEs, <i>n</i> (%)	Pola dose		Total (<i>n</i> = 7)
	1.0 mg/kg (<i>n</i> = 4)	1.8 mg/kg (<i>n</i> = 3)	
Peripheral sensory neuropathy	2 (50)	2 (67)	4 (57)
Abdominal discomfort	2 (50)	1 (33)	3 (43)
Malaise	2 (50)	1 (33)	3 (43)
Influenza	2 (50)	1 (33)	3 (43)
Diarrhea	1 (25)	1 (33)	2 (29)
Constipation	1 (25)	1 (33)	2 (29)
Liver disorder	1 (25)	1 (33)	2 (29)
Bronchitis	1 (25)	1 (33)	2 (29)
Back pain	1 (25)	1 (33)	2 (29)
Nasopharyngitis	2 (50)	0 (0)	2 (29)

TEAEs, treatment-emergent adverse events; Pola, polatuzumab vedotin.

response, including three CRs and one partial response (PR) (Fig. 2). In the 1.0 mg/kg cohort, two patients achieved CR. One of them achieved initially PR on day 581 and achieved a 100% decrease in tumor lesions on day 805, which was maintained until study discontinuation (day 1477). The other patient achieved PR on day 140 and CR on day 552, which was maintained until study discontinuation (day 664). In the 1.8 mg/kg cohort, two patients showed a 100% decrease in tumor lesions. One of them achieved CR on day 328 and continued treatment on the data cut-off date (last tumor evaluation before the data cut-off: day 1559). The response of the other patient was assessed as PR instead of CR because bone marrow infiltration was not evaluated (this patient achieved a 100% decrease in tumor lesions on day 149). Patients with responses were all on study drug for >18 months, with a minimum number of treatment cycles of 27.

Flow cytometry analysis confirmed that peripheral blood B cells (CD19+) were depleted in most patients before and after the administration of pola. There were no significant changes in the

number of peripheral blood T cells (CD3+ CD4/CD8+) or NK cells (CD16 + CD56+). Among all seven patients who expressed CD79b, six highly expressed CD79b as determined by immunohistochemistry (data not shown).

Discussion

The present phase 1 study was designed to assess pola as a single agent in Japanese patients with relapsed/refractory B-cell NHL. Overall, pola showed an acceptable tolerability profile at both the 1.0 and 1.8 mg/kg doses; no DLTs were observed. This is in line with previous studies of pola in non-Japanese patients (NCT01290549) (18). Pola has demonstrated generally acceptable tolerability in patients with B-cell NHL both as monotherapy and when used in combination with chemoimmunotherapy (11–18). In particular, the safety profiles of single-agent pola shown in the current study are comparable with those from a phase 1 study conducted in non-Japanese

Table 3. Selected cycle 1 pharmacokinetic parameters for polatuzumab vedotin: acMMAE, total antibody and unconjugated MMAE

PK parameter	acMMAE		Total antibody		Unconjugated MMAE	
	1.0 mg/kg	1.8 mg/kg	1.0 mg/kg	1.8 mg/kg	1.0 mg/kg	1.8 mg/kg
C_{max} , ng/ml	315 (28.7)	613 (67.2)	19600 (4310)	47400 (8960)	1.46 (0.260)	1.67 (0.471)
AUC_{inf} , day \times ng/ml	823 (177)	2250 (274)	85300 (30500)	336000 (44200)	12.8 (2.47)	17.7 (3.18)
$t_{1/2}$, days	4.43 (0.979)	7.98 (1.21)	5.77 (2.13)	10.8 (1.01)	3.68 (0.355)	4.65 (0.762)
V_{ss} , ml/kg	64.3 (21.6)	91.7 (9.98)	61.9 (18.3)	70.5 (7.34)	–	–
CL, ml/day/kg	22.2 (4.24)	14.4 (1.84)	12.7 (4.08)	5.41 (0.747)	–	–
t_{max} , days	0.135 (0.0845)	0.137 (0.0818)	0.0868 (0.00318)	0.137 (0.0818)	3.28 (0.485)	4.30 (1.45)

The PK parameters are expressed as mean (SD). The PK parameters were calculated based on data collected from cycle 1 to cycle 2 pre-infusion. The number of patients for each assessment was three except for $t_{1/2}$, for which the number of patients was four (1.0 mg/kg dose cohort). acMMAE, plasma antibody-conjugated monomethyl auristatin E; MMAE, monomethyl auristatin E; PK, pharmacokinetics; C_{max} , maximum plasma or serum concentration; AUC_{inf} , area under the concentration–time curve from zero to infinity; $t_{1/2}$, plasma or serum terminal phase half-life; V_{ss} , volume of distribution at steady state; CL, clearance; t_{max} , time to reach maximum drug concentration; SD, standard deviation

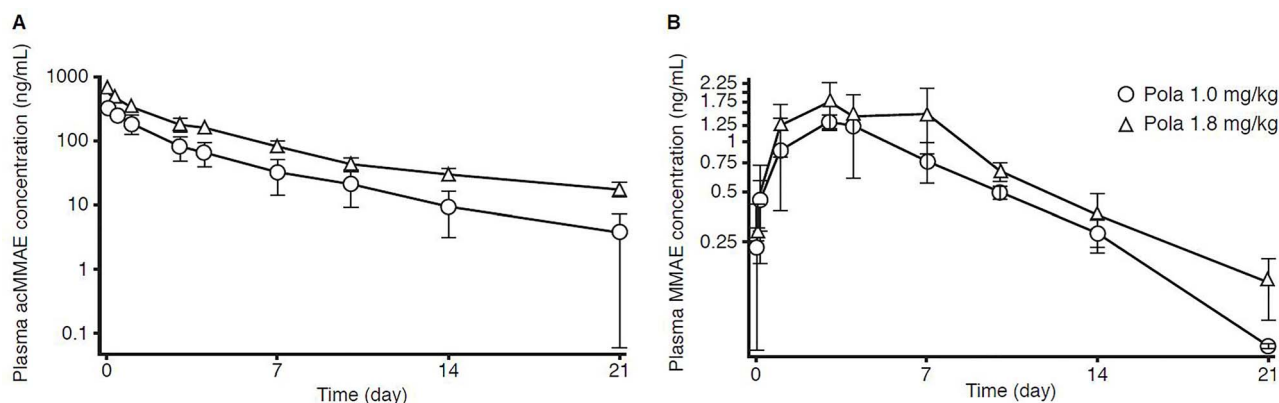


Figure 1. Plasma concentration–time curves of (A) acMMAE and (B) unconjugated MMAE following intravenous administration of polatuzumab vedotin 1.0 or 1.8 mg/kg. Curves shown are semi-log plots. Error bars represent standard deviation. acMMAE, plasma antibody-conjugated monomethyl auristatin E; MMAE, monomethyl auristatin E; Pola, polatuzumab vedotin.

patients (18). In non-Japanese NHL patients, TEAEs except for neutropenia were generally grade 1–2 in severity with pola 0.1–2.4 mg/kg. Among NHL patients who received pola 1.8 mg/kg, the grade 3–4 TEAEs were neutropenia (50%) and thrombocytopenia (33%), and diarrhea, peripheral sensory neuropathy, fatigue, anemia, pain in extremity and hyperglycemia (17% each). In NHL patients who received pola <1.8 mg/kg, grade 3–4 TEAEs were neutropenia (29%), fatigue (12%), peripheral sensory neuropathy, decreased appetite, pain in extremity and hyperglycemia (6% each). Notably, in the current study, the only grade 3 AEs experienced were cholecystitis and neutrophil count decreased (1.0 mg/kg cohort, one case each), and syncope and cataract (1.8 mg/kg cohort, one case each). All grade 3 AEs were considered not related to pola, except for the single case of neutrophil count decreased in the 1.0 mg/kg cohort.

In the present study, four of seven patients experienced grade 1–2 peripheral sensory neuropathy, which is a common AE with pola and consistent with the mechanism of action of MMAE (22,23). A patient who had peripheral sensory neuropathy at baseline deteriorated to

Grade 2 on day 98 and resolved at the time of study discontinuation (day 109). Grade 1 peripheral sensory neuropathy occurred in 3 patients and continued until the study discontinuation or last observation before the data cut-off date (onset to last observation: day 26–1477, 147–664 and 168–1559). In the phase 1 study of pola monotherapy in non-Japanese patients, among the six NHL patients who received pola at a dose of 1.8 mg/kg, peripheral sensory neuropathy was one of the main TEAEs (grade 1–2, 50%; grade 3, 17%) (18). In studies of pola in combination with other therapies, peripheral neuropathy has also been frequently reported (incidence 36–44%) (14–17). Previously, an exposure-response analysis of pola data by logistic regression suggested that pola-induced peripheral neuropathy increased with conjugate (i.e. acMMAE) exposure and treatment duration (19). It has therefore been suggested that a treatment duration of six to eight cycles and doses of 1.8 mg/kg every 21 days might offer better tolerability and reduce the risk of developing peripheral neuropathy. Preliminary data in patients with FL suggest that by reducing doses of pola from 2.4 to 1.8 mg/kg, consistent improvements in safety will be observed (in particular,

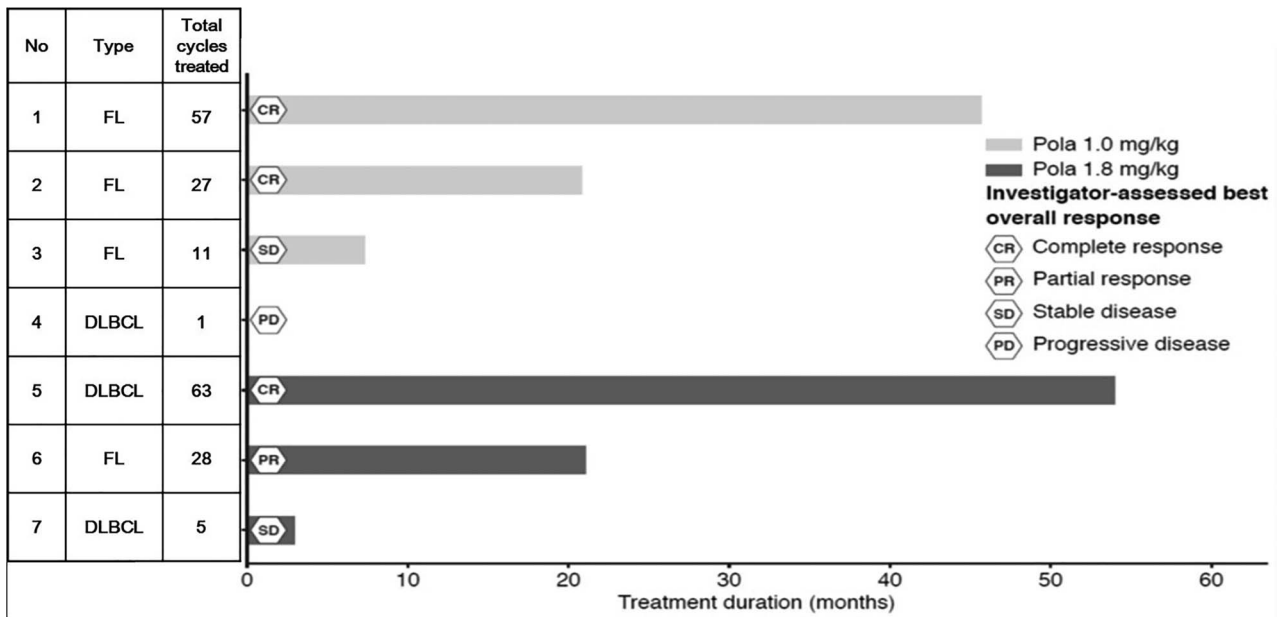


Figure 2. Polatuzumab vedotin treatment duration by histology and investigator-assessed best overall response. The patient who achieved a PR in the 1.8 mg/kg cohort showed a 100% decrease in tumor lesions by computed tomography, but the response was judged a PR because bone marrow infiltration was not evaluated. FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

a reduction in the incidence of peripheral neuropathy) without impairing efficacy (20). Furthermore, data showed that incidence of peripheral neuropathy was lower with both the 1.8 and 2.4 mg doses during the first eight cycles than at completion of pola treatment (median of 9.5 cycles: 1.8 mg/kg and 10 cycles: 2.4 mg/kg). In the present study, patients with antitumor responses were on treatment for a median follow-up period of at least 18 months. The peripheral sensory neuropathy events observed were mostly grade 1, which can be managed by dosing schedule modification, and none led to discontinuation of treatment. This suggests that pola might be safely administered at 1.0 or 1.8 mg/kg over a longer treatment period. Our results found no clinically relevant impact of plasma acMMAE exposure on the occurrence of peripheral sensory neuropathy. However, as the sample size of this phase 1 study was small and the dose range was limited (1.0 or 1.8 mg/kg), further studies are needed to clarify whether greater acMMAE exposure and longer treatment duration may increase the likelihood of pola-related peripheral neuropathy in Japanese patients.

PK profile of pola was characterized by analysis of acMMAE, total antibody and unconjugated MMAE in the phase 1 study in non-Japanese B-cell NHL patients. Exposures for the key analyte acMMAE in Japanese patients and non-Japanese patients were similar. Unconjugated MMAE exposure to the analytes was slightly lower and total antibody exposure to the analytes was slightly higher in Japanese patients (18).

Responses were demonstrated in one DLBCL and three FL patients. The objective response rate of 57% (four of seven) observed in this study was in line with that reported in the phase 1 study in non-Japanese B-cell NHL patients treated with single-agent pola 2.4 mg/kg (51%; 23 of 45) (18).

Clinical development of pola has mainly focused on pola-based combinations with conventional cytotoxic chemotherapy or immunotherapy (11–17). For patients with relapsed/refractory DLBCL, pola in combination with bendamustine plus rituximab

was approved by the US FDA to treat those who have received at least two prior therapies (7), and was also granted conditional approval by the European Medicines Agency to treat patients with stem cell transplant-ineligible relapsed/refractory DLBCL (24). In front-line treatment of DLBCL, pola is currently being evaluated as a replacement for vincristine within the standard R-CHOP regimen (NCT03274492) (25).

In conclusion, this phase 1 dose-escalation study demonstrated that pola has an acceptable safety profile and offers encouraging antitumor activity to Japanese patients with relapsed/refractory B-cell NHL. Peripheral sensory neuropathy was mostly grade 1 and manageable, and pola 1.8 mg/kg was tolerable as the recommended phase 2 dose. The safety and efficacy of pola monotherapy in Japanese patients with B-cell NHL were comparable with those previously seen in non-Japanese patients. Exposures for the key analyte acMMAE in Japanese patients and non-Japanese patients were similar. This phase 1 dose-escalation study supports further clinical development of pola, as a single agent or in combination with other antitumor agents, for use in Japanese patients with B-cell NHL.

Supplementary Material

Supplementary material can be found at *Japanese Journal of Clinical Oncology* online.

Data availability statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). For further details on Chugai's Data Sharing Policy and how to request access to related clinical study

documents, see here (www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html).

Acknowledgments

Editorial assistance for this manuscript was provided by Ashfield Healthcare Communications and MIMS and was funded by Chugai Pharmaceutical, Co., Ltd.

Funding

This work was supported by Chugai Pharmaceutical, Co., Ltd (Tokyo, Japan).

Conflict of interest statement

Tomohiro Kinoshita has received research support from Chugai, MSD, Eisai, Solasia, Ono and Takeda and has received honoraria from Takeda.

Kiyohiko Hatake has received honoraria from Takeda, Celgene, Daiich-Sankyo and Eisai; fees for promotional materials from Takeda and Celgene and scholarship donations from Eisai, Mochida and Kyowa Kirin.

Kazuhito Yamamoto has had an advisory role in AbbVie, AstraZeneca, Celgene, Chugai, Daiichi Sankyo, Eisai, HUYA, Meiji Seika Pharma, MSD, Mundipharma, Ono, Otsuka, Stemline Therapeutics and Takeda; has received honoraria from AbbVie, Bristol-Myers Squibb, Celgene, Chugai, Eisai, HUYA, Janssen, Kyowa Kirin, Meiji Seika Pharma, Mochida, MSD, Mundipharma, Nippon Shinyaku, Novartis, Ono, Otsuka, Pfizer, Sanofi, Sumitomo Dainippon and Takeda; has received fees for promotional materials from Chugai, CLS Behring, Eisai, Kyowa Kirin, Pfizer and Zenyaku; and has received research support from AbbVie, ARIAD Pharmaceuticals, Astra-Zeneca, Bayer, Celgene, Chugai, Eisai, Gilead Sciences, Incyte, MSD, Mundipharma, Nippon Shinyaku, Novartis, Ono, Solasia Pharma, Symbio, Takeda and Zenyaku.

Yusuke Higuchi declares no conflicts of interest.

Satsuki Murakami declares no conflicts of interest.

Yasuhito Terui has received honoraria from Chugai, Celgene, Bristol-Myers Squibb, Novartis and Janssen and has received research support from BMS.

Masahiro Yokoyama has been a medical advisor for Chugai.

Dai Maruyama has received honoraria from Mundipharma, Celgene, Janssen, Takeda, Eisai, Ono and Chugai and has received research support from Merck, Mundipharma, Janssen, Takeda, Eisai, Chugai, Ono, Celgene, AbbVie, MSD, Astellas, Amgen, Otsuka, Novartis, Pfizer, Bayer, Zenyaku, Solasia, AstraZeneca, Kyowa Kirin, Sanofi, Bristol-Myers Squibb, Daiichi Sankyo, Symbio, IQVIA and CMIC.

Shinichi Makita has received honoraria from Takeda and Novartis.

Yukari Hida is an employee of Chugai Pharmaceutical Co., Ltd.

Tomohisa Saito is an employee of Chugai Pharmaceutical Co., Ltd.

Kensei Tobinai has had an advisory role in Celgene, Zenyaku Kogyo, HUYA, Daiichi Sankyo, Takeda, Mundipharma and Ono; has received honoraria from Zenyaku Kogyo, Eisai, Takeda, Mundipharma, HUYA, Kyowa Hakko Kirin, Celgene, Chugai, Ono, Yakult, Daiichi Sankyo, Bristol-Myers Squibb, Meiji Seika Kaisha, Solasia and Verastem and has received research support from Chugai,

Kyowa Hakko Kirin, Ono, Celgene, Janssen, Eisai, Mundipharma, Takeda and AbbVie.

References

- Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program* 2011;2011:498–505.
- Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* 2005;23:5027–33.
- NCCN® Guidelines Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. 2020 (3 February 2020, date last accessed).
- 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* 2010;28:4184–90.
- Herrera AF, Molina A. Investigational antibody-drug conjugates for treatment of B-lineage malignancies. *Clin Lymphoma Myeloma Leuk* 2018;18:452–68.e4.
- Wolska-Washer A, Robak P, Smolewski P, Robak T. Emerging antibody-drug conjugates for treating lymphoid malignancies. *Expert Opin Emerg Drugs* 2017;22:259–73.
- Genentech Inc. Polivy™ (Polatuzumab vedotin-piiq) for injection, for intravenous use: US prescribing information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761121s000lbl.pdf. (5 September 2019, date last accessed).
- 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* 2009;114:2721–9.
- Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. *Blood* 2007;110:616–23.
- Deeks ED. Polatuzumab vedotin: first global approval. *Drugs* 2019;79:1467–75.
- Morschhauser F, Flinn I, Advani RH, et al. Updated results of a phase II randomized study (ROMULUS) of polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed/refractory non-Hodgkin lymphoma. *Blood* 2014;124:4457.
- Matasar M, Herrera AF, Kamdar M, et al. Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory FL or DLBCL: updated results of a phase 1b/2 study. *Hematol Oncol* 2017;35:271–2.
- Phillips T, Brunvand M, Chen A, et al. Polatuzumab vedotin combined with obinutuzumab for patients with relapsed or refractory non-Hodgkin lymphoma: preliminary safety and clinical activity of a phase 1b/II study. *Blood* 2016;128:622.
- Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 2020;38:155–65.
- Tilly H, Sharman J, Bartlett N, et al. Pola-R-CHP: polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, prednisone for patients with previously untreated diffuse large B-cell lymphoma. *Hematol Oncol* 2017;35:90–1.
- 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* 2019;6:e254–65.
- Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. *Lancet Oncol* 2019;20:998–1010.
- Palanca-Wessels MC, 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* 2015;16:704–15.
- Lu D, Gillespie WR, Girish S, et al. Time-to-event analysis of polatuzumab vedotin-induced peripheral neuropathy to assist in the comparison

- of clinical dosing regimens. *CPT Pharmacometrics Syst Pharmacol* 2017;6:401–8.
20. Advani RH, Flinn I, Sharman JP, et al. Two doses of polatuzumab vedotin (PoV, anti-CD79b antibody-drug conjugate) in patients (pts) with relapsed/refractory (RR) follicular lymphoma (FL): durable responses at lower dose level. *J Clin Oncol* 2015;33:8503.
 21. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–86.
 22. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010;363:1812–21.
 23. Advani HJ, Lebovic D, Chen A, et al. Phase I study of the anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res* 2017;23:1167–76.
 24. Roche Registration GmbH. Polivy 140 mg powder for concentrate for solution for infusion: summary of product characteristics. 2020. <https://www.ema.europa.eu/en/medicines/human/EPAR/polivy#product-information-section>. (3 February 2020, date last accessed).
 25. Tilly H, Flowers C, Friedberg JW, et al. POLARIX: a phase 3 study of polatuzumab vedotin (pola) plus R-CHP versus R-CHOP in patients (pts) with untreated DLBCL. *J Clin Oncol* 2019;37:TPS7571.