

Phase I / II study of brentuximab vedotin in Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma

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Key words

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Brentuximab vedotin is an antibody–drug conjugate that selectively delivers the antimicrotubule agent monomethyl auristatin E into CD30-expressing cells. To assess its safety, pharmacokinetics, and efficacy in Japanese patients with refractory or relapsed CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma, we carried out a phase I/II study. Brentuximab vedotin was given i.v. on day 1 of each 21-day cycle up to 16 cycles. In the phase I part of a dose-escalation design, three patients per cohort were treated at doses of 1.2 and 1.8 mg/kg. In the phase II part, a dose of 1.8 mg/kg was given to 14 patients (nine with Hodgkin's lymphoma and five with systemic anaplastic large-cell lymphoma). The median number of treatment cycles was 16 (range, 4–16). In the phase I part, no dose-limiting toxicity event was observed. In the total population, common adverse events included lymphopenia (80%), neutropenia (65%), leukopenia (65%), and peripheral sensory neuropathy (60%). Grade 3/4 adverse events in more than two patients were lymphopenia (50%) and neutropenia (15%). The pharmacokinetic profile was similar to that observed in the previous studies in the USA. In the phase II part, six patients (67%) with Hodgkin's lymphoma achieved an objective response with 56% of complete response rate, and five patients (100%) with systemic anaplastic large-cell lymphoma achieved an objective response with 80% of complete response rate. These results show that brentuximab vedotin has an acceptable safety profile and promising antitumor activity in the Japanese population. This trial was registered in JAPIC Clinical Trials Information (JapicCTI-111650).

Brentuximab vedotin (also known as SGN-35) is an ADC linking the antimicrotubule agent MMAE to the CD30-specific mAb cAC10, created by Seattle Genetics (Bothell, WA, USA). CD30 is a member of the tumor necrosis factor receptor superfamily. It is expressed on the surface of Reed–Sternberg cells in HL and ALCL cells, whereas its expression on normal cells is restricted.^(1,2) The antitumor activity of brentuximab vedotin is derived by binding the ADC to CD30-expressing cells, followed by internalization of the ADC–CD30 complex, and release of MMAE through proteolytic cleavage. Thereafter, MMAE binds to tubulin and disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.⁽³⁾

In a phase I study of brentuximab vedotin in the USA, the maximum tolerated dose was determined to be 1.8 mg/kg, given every 3 weeks. In this dosage regimen, half of patients with relapsed or refractory CD30-positive lymphomas achieved an OR.⁽⁴⁾ In two pivotal phase II studies carried out in North

America and Europe, brentuximab vedotin showed a high ORR including CR and acceptable safety profiles in patients with relapsed or refractory HL and sALCL.^(5,6) On the basis of these findings, it was approved in August 2011 by the US Food and Drug Administration for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in those ineligible for ASCT, and for the treatment of patients with sALCL after failure of at least one multi-agent chemotherapy regimen.

We report here the results of a phase I/II study, which was carried out to assess the safety, pharmacokinetics, immunogenicity, and efficacy of brentuximab vedotin in Japanese patients with relapsed or refractory CD30-positive HL and sALCL.

Material and Methods

Study design and patients. We carried out this multicenter, open-label study from October 2011 to May 2013 at five

institutions in Japan. The primary objective was tolerability and safety for phase I, and efficacy and safety for phase II. In addition, the efficacy of brentuximab vedotin including ORR determined by the Independent Review Facility was evaluated in phase II. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical practice. Its protocol was reviewed and approved by the institutional review board of each participating center. All patients gave written informed consent.

Patients aged at least 20 years were eligible for the study if they had histologically confirmed CD30-positive HL or sALCL that was refractory to or relapsed after standard chemotherapy. We included HL patients who were ineligible for ASCT considering the results of safety and efficacy observed in the US study.⁽⁴⁾ CD30-positive disease was confirmed by immunohistochemistry or flow cytometry. Other inclusion criteria were: fluorodeoxyglucose-avid disease by PET and measurable disease of at least 1.5 cm in diameter by CT; Eastern Cooperative Oncology Group performance status of 0–1; and life expectancy of at least 3 months. Patients were also required to have adequate hematologic, renal, and hepatic function defined as follows: absolute neutrophil count $\geq 1500/\mu\text{L}$; platelet count $\geq 75\,000/\mu\text{L}$; serum bilirubin $\leq 1.5 \times \text{ULN}$; serum creatinine $\leq 1.5 \times \text{ULN}$; aspartate aminotransferase $\leq 2.5 \times \text{ULN}$; and alanine aminotransferase $\leq 2.5 \times \text{ULN}$.

Patients were excluded if they had a current diagnosis of primary cutaneous ALCL (those who had transformed to sALCL were eligible), cerebral/meningeal infiltration, or signs or symptoms suggestive of progressive multifocal leukoencephalopathy. Patients were also excluded if they had undergone ASCT within 12 weeks or allogeneic stem-cell transplantation previously. Pregnant women, breastfeeding women, or patients who did not use adequate contraceptive precautions were also excluded.

Study treatment. Brentuximab vedotin was given i.v. on day 1 of each 21-day cycle. During phase I of the study, three patients were initially treated with a dose of 1.2 mg/kg (Cohort 1). This starting dose was determined on the basis of the previous study results.⁽⁴⁾ If no patient had a DLT in Cohort 1, an escalated dose of 1.8 mg/kg was given to three patients (Cohort 2). If at least one patient experienced a DLT in each dose cohort, the cohort was to be expanded to six patients. During phase II, all patients were treated with a dose of 1.8 mg/kg. At cycles 1 and 2 in phase I, brentuximab vedotin was given over 120 (± 15) min. At other cycles including those in phase II, it was to be given over 30 min. In both parts, patients received 8–16 cycles of treatment if they wished to continue the treatment and had neither unacceptable toxicity nor disease progression.

Dose-limiting toxicity was defined as any treatment-related toxicity that met the following criteria during the 21 days of cycle 1: grade 4 neutropenia lasting more than 7 days; grade 3 febrile neutropenia requiring treatment with antibiotics; grade 4 febrile neutropenia; grade 4 thrombocytopenia; or grade 3 or higher non-hematologic toxicity (except for grade 3 fatigue, grade 3/4 nausea or vomiting lasting less than 24 h, grade 3 non-hematologic laboratory abnormalities resolving to grade 1 or baseline within 14 days, and grade 3/4 allergic reaction or hypersensitivity).

If treatment-related toxicity occurred, the dose could be reduced by one-third according to the type and severity of the toxicity. Study treatment was terminated if the patient required further dose reduction. If additional time was required for

treatment-related toxicity to resolve, the starting day of the subsequent cycle could be delayed for up to 3 weeks (i.e., 6 weeks after the last dosing).

Patients who had been receiving corticosteroids for >1 month before enrolment were permitted to receive corticosteroids (equivalent to prednisolone 10 mg/day or less) concomitantly. Intermittent use of corticosteroids for treating hypersensitivity was also allowed. Patients who had treatment-related neutropenia could receive prophylaxis with granulocyte colony-stimulating factor at the subsequent cycles. If patients experienced infusion-related reactions, premedication with acetaminophen and diphenhydramine was allowed at the subsequent cycles.

Study assessments. In phase I, patients were hospitalized during the first cycle of treatment. In phase II, they were hospitalized until day 2 of the first cycle. Adverse events were monitored throughout the study, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Laboratory variables, vital signs, and 12-lead electrocardiograms were measured or obtained periodically.

Tumor response was assessed by CT or PET, and the best clinical response was determined by the Independent Review Facility according to the Revised Response Criteria for Malignant Lymphoma.⁽⁷⁾ Computed tomography scans of the neck, chest, abdomen, and pelvis were obtained at baseline and days 15–21 of cycles 2, 4, 7, 10, 13, and 16; PET scans were obtained at baseline and days 15–21 of cycles 4 and 7.

In the phase I part, serum samples for PK analysis of brentuximab vedotin were collected on the following time points at cycles 1 and 2: within 2 h before starting infusion; and 0.17, 2, 4, 24, 72, 168, and 336 h after completing infusion. Plasma samples for PK analysis of MMAE were also collected on the above time points and 8, 48, 96, and 240 h after completing infusion at cycle 1. Serum and plasma concentrations of brentuximab vedotin and MMAE were assessed with the use of a validated ELISA and HPLC with tandem-mass spectrometry, respectively.^(4,8) The PK parameters of both analytes were estimated by non-compartmental methods with Phoenix WinNonlin software version 6.2 (Pharsight, Mountain View, CA, USA).

During phase I and II, serum samples were collected before infusion at cycle 1 and the following cycles, in order to assess immunogenicity to brentuximab vedotin using a validated electrochemiluminescence assay.⁽⁸⁾

Statistical considerations. In phase I, a sample size of three patients for each dose cohort was determined according to the Japanese guideline for clinical evaluation of anticancer drugs.⁽⁹⁾ In phase II, a sample size of 11 patients was determined to confirm that the true ORR would be greater than the threshold rate of 20%. In this study, we expected that the ORRs in patients with HL and sALCL would be 75% and 86%, respectively, on the basis of the previous study results.^(5,6)

In the efficacy analysis, the rates of tumor response and their exact two-sided 95% CIs were calculated. Furthermore, the median and two-sided 95% CIs for duration of objective response and PFS were estimated by the Kaplan–Meier method. The duration of response was defined as the time from start of the first documentation of tumor response (CR or PR) to the first documentation of tumor response or to death due to any cause, whichever comes first. Progression-free survival was also defined as the time from start of study treatment to

first documentation of tumor progression or to death due to any cause, whichever comes first. All descriptive statistics and CIs were calculated with the use of SAS System version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients. A total of 20 patients (three for each dose cohort of phase I; and 14 for the phase II part) were enrolled into the study. All patients had measurable disease and received the study treatment. They were included in the safety and efficacy analyses. At the time of data cut-off (May 24, 2013), one patient in the phase II part was still receiving the study treatment. The remaining patients had completed the study treatment.

Table 1 shows the demographic and baseline characteristics of the enrolled patients. In the total population, the median age was 41 years (range, 22–88 years). Five of six patients had HL during phase I, whereas nine had HL and five had sALCL in phase II. In the total population, the median number of prior chemotherapies was three (range, 1–11). Eight of 14 patients (57%) with HL had undergone ASCT before the study treatment. Three of six patients with sALCL had diseases progressing from primary cutaneous ALCL. All of the six patients with sALCL had anaplastic lymphoma kinase-negative disease except for one patient. No patient with sALCL had received prior stem-cell transplantation.

Tolerability and safety. At the time of data cut-off, three patients in phase I of the study and eight in phase II completed the maximum number of treatment cycles. One patient in the phase II part was still receiving the study treatment. The other eight patients discontinued the treatment for the following reasons: disease progression (five patients), AE (one patient), consent withdrawal (one patient), and other reason (one patient was withdrawn to receive transplantation). Table 2 summarizes the extent of exposure to brentuximab vedotin. In the total population, the median number of treatment cycles was 16 (range, 4–16), and the median relative dose intensity was 98.1% (range, 80.3–100.6%).

Throughout the study, brentuximab vedotin was well tolerated. In phase I, no DLT was observed during the assessment period, and one patient discontinued the treatment because of an AE (grade 2 peripheral sensory neuropathy). This patient was included in Cohort 2 and had the event after receiving 11 cycles of treatment. The patient's symptoms improved after treatment discontinuation. In phase II, one patient received a reduced dose because of grade 2 peripheral sensory neuropathy.

Table 3 shows AEs that occurred in at least 20% of patients. In the total population, the most common AEs were lymphopenia (80%), neutropenia (65%), leukopenia (65%), and peripheral sensory neuropathy (60%). The majority of grade 3 or higher AEs were laboratory abnormalities including lymphopenia (50%), neutropenia (15%), and leukopenia (10%). Other

Table 1. Baseline characteristics of Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL) enrolled in this phase I/II study of brentuximab vedotin

Characteristics	Phase I		Phase II		Phase I/II Total n = 20
	1.2 mg/kg n = 3	1.8 mg/kg n = 3	HL n = 9	sALCL n = 5	
Age, years					
Median (range)	41 (41–50)	42 (31–79)	32 (22–88)	44 (37–66)	41 (22–88)
Sex, n (%)					
Male	1 (33)	1 (33)	4 (44)	5 (100)	11 (55)
Female	2 (67)	2 (67)	5 (56)	0 (0)	9 (45)
ECOG PS, n (%)					
0	2 (67)	2 (67)	7 (78)	0 (0)	11 (55)
1	1 (33)	1 (33)	2 (22)	5 (100)	9 (45)
Disease type, n (%)					
HL	2 (67)	3 (100)	9 (100)	0 (0)	14 (70)
NS	2 (67)	2 (67)	8 (89)	–	12 (60)
MC	0 (0)	1 (33)	0 (0)	–	1 (5)
Not classifiable	0 (0)	0 (0)	1 (11)†	–	1 (5)
ALCL	1 (33)	0 (0)	0 (0)	5 (100)	6 (30)
ALK positive	1 (33)	–	–	0 (0)	1 (5)
ALK negative	0 (0)	–	–	5 (100)	5 (25)
Stage at study entry, n (%)					
I	0 (0)	0 (0)	2 (22)	1 (20)	3 (15)
II	0 (0)	0 (0)	3 (33)	1 (20)	4 (20)
III	1 (33)	1 (33)	3 (33)	0 (0)	5 (25)
IV	2 (67)	2 (67)	1 (11)	3 (60)	8 (40)
No. of prior chemotherapies					
Median (range)	5 (3–9)	5 (1–11)	3 (1–5)	3 (1–6)	3 (1–11)
Prior ASCT, n (%)					
Yes	2 (67)	2 (67)	4 (44)	0 (0)	8 (40)

–, Not applicable; ALK, anaplastic lymphoma kinase; ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mixed cellularity; NS, nodular sclerosis. †One of the HL patients in phase II of the study was not classifiable but was confirmed as having histologically CD-30-positive HL.

Table 2. Exposure of Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma to brentuximab vedotin

Exposure	Phase I		Phase II	Phase I/II
	1.2 mg/kg <i>n</i> = 3	1.8 mg/kg <i>n</i> = 3	Total <i>n</i> = 14	Total <i>n</i> = 20
No. of treatment cycles				
Median (range)	16 (16)	11 (4–15)	16 (6–16)	16 (4–16)
Duration of treatment, weeks				
Median (range)	48 (48–49)	34 (12–46)	48 (19–59)	48 (12–59)
No. of treated cycles, <i>n</i> (%)				
≥1 cycle	3 (100)	3 (100)	14 (100)	20 (100)
≥5 cycles	3 (100)	2 (67)	14 (100)	19 (95)
≥9 cycles	3 (100)	2 (67)	11 (79)	16 (80)
≥13 cycles	3 (100)	1 (33)	9 (64)	13 (65)
Any dose reduction, <i>n</i> (%)	0 (0)	0 (0)	1 (7)	1 (5)
Adverse event, <i>n</i> (%)	0 (0)	0 (0)	1 (7)	1 (5)
Relative dose intensity†, %				
Median (range)	99.4 (97.4–99.4)	98.3 (96.9–100.0)	95.7 (80.3–100.6)	98.1 (80.3–100.6)

†Relative dose intensity = [(Dose Intensity)/(Total dose expected per initial dose/3)] × 100.

than these events, two patients (10%) experienced grade 3 hypophosphatemia. Lymphopenia was generally transient and did not require treatment discontinuation or dose reduction.

Grade 1 or 2 peripheral sensory neuropathy occurred in 12 patients. Of these, one patient also experienced peripheral motor neuropathy at the 16th cycle. Seven patients had peripheral neuropathy by the fourth cycle. The median time to onset

of peripheral neuropathy was 11.3 (range, 0.3–48.9) weeks among the patients experiencing the event. Peripheral neuropathy resolved in one patient but had not resolved in the others as of the data cut-off date.

Serious AEs were reported in five patients. In the phase I part, grade 2 aseptic meningitis occurred in one patient receiving 1.2 mg/kg brentuximab vedotin. This patient also had grade 3 disseminated herpes zoster and grade 4 MDS during the follow-up period after the study treatment. In phase II, one patient each experienced grade 2 pneumocystis jiroveci pneumonia, grade 3 hypersensitivity, grade 3 cellulitis, and grade 3 pneumonia. These events did not lead to treatment discontinuation or dose reduction.

Efficacy. Table 4 summarizes the tumor response. In phase I, two patients (67%) for each dose cohort achieved an OR. In the phase II part, six patients (67%) with HL and five (100%) with sALCL achieved an OR. The median PFS was 11.1 months for patients with HL and 10.8 months for those with sALCL.

Figure 1 shows the maximum tumor reduction in individual patients in phase II. Five patients (56%) with HL and four (80%) with sALCL had a best response of CR. In this part, five patients with HL had not previously undergone ASCT. Of these, four patients (80%) achieved an OR, including two CRs. Furthermore, three patients had primary cutaneous ALCL that had transformed to sALCL, and they all had a CR.

Pharmacokinetics and immunogenicity. Serum concentration–time profiles and PK parameters of brentuximab vedotin assessed in the phase I part are shown in Figure 2 and Table 5, respectively. The serum concentration gradually declined after the completion of each infusion. The mean terminal-phase half-life ranged from 5 to 7 days. At both dose levels, the mean values of AUC and C_{max} were similar between days 1 (first infusion) and 21 (second infusion). Furthermore, the mean AUC and C_{max} increased in a dose-related manner. Minor MMAE was determined in plasma samples. Plasma concentrations of MMAE reached C_{max} until approximately 4 days after the infusion and then declined with the mean half-life of approximately 4 days at 1.8 mg/kg. The mean C_{max} and AUC accounted for 0.0036 µg/mL and

Table 3. Common adverse events experienced by at least 20% of patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma treated with brentuximab vedotin

Events	Phase I/II	
	Total <i>n</i> = 20 <i>n</i> (%)	Grade 3/4
Lymphopenia	16 (80)	10 (50)
Neutropenia	13 (65)	3 (15)
Leukopenia	13 (65)	2 (10)
Peripheral sensory neuropathy	12 (60)	0 (0)
Anemia	7 (35)	1 (5)
Nasopharyngitis	7 (35)	0 (0)
Fatigue	6 (30)	0 (0)
Rash	6 (30)	0 (0)
Nausea	5 (25)	1 (5)
ALT increased	5 (25)	0 (0)
AST increased	5 (25)	0 (0)
Blood LDH increased	5 (25)	0 (0)
Diarrhea	5 (25)	0 (0)
Decreased appetite	4 (20)	1 (5)
Upper respiratory tract infection	4 (20)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 14.1. Grades were based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. A patient counts once for each preferred-term.

Table 4. Tumor response in patients with relapsed or refractory CD30-positive Hodgkin's lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL) treated with brentuximab vedotin, according to the Independent Review Facility

Responses	Phase I		Phase II	
	1.2 mg/kg n = 3	1.8 mg/kg n = 3	HL n = 9	sALCL n = 5
Best overall response, n (%)				
CR	0 (0)	1 (33)	5 (56)	4 (80)
PR	2 (67)	1 (33)	1 (11)	1 (20)
SD	1 (33)	1 (33)	3 (33)	0 (0)
PD	0 (0)	0 (0)	0 (0)	0 (0)
ORR, % (95% CI)	67 (9–99)	67 (9–99)	67 (30–93)	100 (55–100)
CR rate, % (95% CI)	0 (0–63)	33 (1–91)	56 (21–86)	80 (28–100)
Median time to OR, months	2.7	2.6	2.7	1.2
Median duration of OR, months	12.1	NE	NE	9.7
Median PFS, months	14.1	NE	11.1	10.8

CI, confidence interval; NE, not evaluable; OR, objective response; PD, progressive disease; PFS, progression-free survival; SD, stable disease. Tumor response was assessed by computed tomography or PET, and the best clinical response was determined by the Independent Review Facility according to the Revised Response Criteria for Malignant Lymphoma. Objective overall response (ORR) includes complete response (CR) and partial response (PR).

0.023 day/ $\mu\text{g}/\text{mL}$ on cycle 1 and 0.0019 $\mu\text{g}/\text{mL}$ and 0.016 day/ $\mu\text{g}/\text{mL}$ on cycle 2, respectively.

In 16 patients with negative for antitherapeutic antibodies at baseline, nine patients remained negative during the treatment, five developed transiently positive (positive in one or two post-baseline samples), and two developed persistently positive (positive in more than two post-baseline samples).

Discussion

Despite advances in the chemotherapy regimens, approximately 15–30% of patients with HL experience treatment failure with front-line combination chemotherapy.⁽¹⁰⁾ Although ASCT is a potential curative treatment for younger patients

with HL that has relapsed after front-line chemotherapy, its benefit is limited to a subset of patients.^(11,12) For ALCL, 40–65% of patients relapse after front-line chemotherapy.⁽¹³⁾ These patients have few therapeutic options, and ASCT is effective only in those with chemotherapy-sensitive disease.^(14,15) Under these circumstances, an innovative treatment option has been required.

In North America and Europe, two pivotal phase II studies of brentuximab vedotin in patients with relapsed or refractory HL and sALCL showed high efficacy and acceptable safety profiles.^(5,6) The study we reported here is the first Japanese phase I/II study of brentuximab vedotin in patients with relapsed or refractory HL and sALCL. In the safety assessment, brentuximab vedotin was well tolerated in Japanese patients.

Peripheral sensory neuropathy has been reported as the most clinically meaningful AE of brentuximab vedotin.^(4–6) Because brentuximab vedotin is a conjugate of the antibody and antimicrotubule agent that cause neuropathy, peripheral sensory neuropathy is considered to be derived from its cytotoxic component.⁽¹⁶⁾ Across two pivotal phase II studies carried out in North America and Europe, approximately 55% of patients experienced peripheral neuropathy, and grade 3 events were reported in 10–15% of patients.^(5,6) In our study, 12 of 20 patients (60%) experienced peripheral neuropathy and the events were generally manageable with dose delay or dose reduction. No grade 3 or higher peripheral neuropathy was reported in our study: the limited number of patients might be a reason for this difference. Resolution of the symptoms was not observed in the majority of patients at the end of treatment visit in our study. In the pivotal studies that carried out in North America and Europe, however, neuropathy improved or resolved in approximately 80% of patients with dose delay or dose reduction, or both, and the median time to improvement or resolution was 9.9–13.2 weeks.^(5,6) The difference may be caused by the shorter follow-up for neuropathy events in our study, as compared to those of the previous studies.

Other common AEs were lymphopenia, neutropenia, and leukopenia. These hematologic AEs were transient and resolved without additional treatment. Other AEs were generally mild or moderate in severity, and the incidence of these events was similar to that in the pivotal studies. No unexpected toxicities were reported in our study.

Serious AEs were reported in five patients in our study. Of these, three patients had AEs of interest: disseminated herpes zoster and MDS in one patient; pneumocystis jiroveci pneumonia in one patient; and pneumonia in one patient. In the first patient, herpes zoster and MDS were observed at 3 and

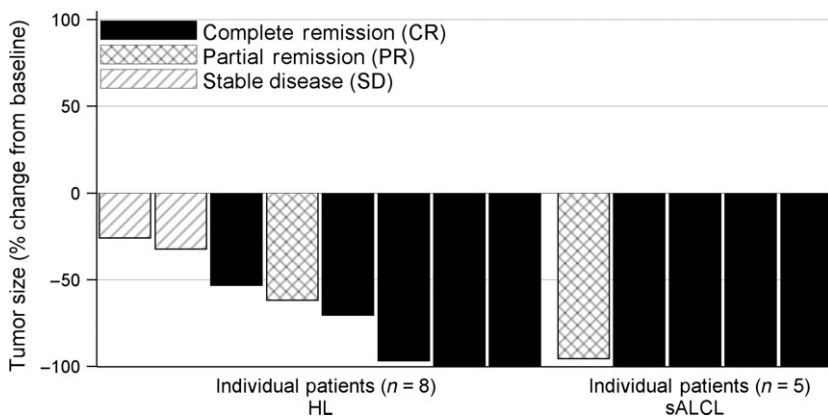


Fig. 1. Maximum percent reduction from baseline by patient per the Independent Review Facility in a phase II study of brentuximab vedotin in Japanese patients with refractory or relapsed CD30-positive Hodgkin's lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL). One patient had no measurable lesions per the Independent Review Facility.

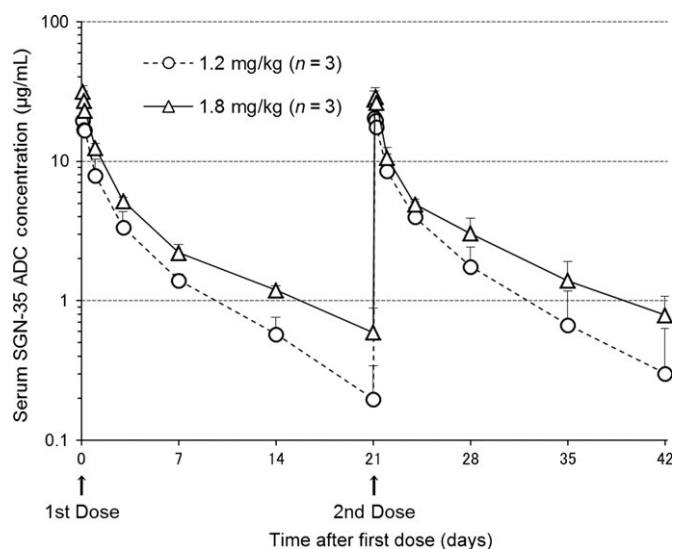


Fig. 2. Pharmacokinetic parameters of brentuximab vedotin (SGN-35), assessed in a phase I study of its safety, pharmacokinetics, and efficacy in Japanese patients with refractory or relapsed CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma. ADC, antibody–drug conjugate.

8 months after the completion of study treatment, respectively. This patient had received several anticancer therapies including ASCT before starting the study treatment. Clinical response was not observed until the onset of disseminated herpes zoster and MDS. The second patient experiencing pneumocystis jiroveci pneumonia had a previous history of ASCT. The pneumonia was asymptomatic and diagnosed at the time of a planned CT examination. The patient was treated with trimethoprim-sulfamethoxazole, and the event resolved after the treatment. This patient completed the maximum treatment cycles with prophylaxis against pneumocystis jiroveci. The third patient had pneumonia with unknown etiology. This infection resolved after treatment with antibiotics, and the patient continued the study treatment. Although it is unclear whether prophylaxis against herpes zoster, pneumocystis jiroveci infection, and other infections is needed, careful monitoring for opportunistic infections will be necessary.

In the PK analysis, the mean AUC and C_{max} of brentuximab vedotin and MMAE at 1.8 mg/kg in our study were similar to those in the previous phase I study carried out in the USA,⁽⁴⁾ suggesting no remarkable ethnic difference in pharmacokinetics. Development of antitherapeutic antibodies after treatment with brentuximab vedotin was observed in seven patients, however, any change in safety and efficacy of brentuximab vedotin after the development was not clearly indicated in the patients.

In the efficacy analysis, more than half of patients had a CR and the median PFS was approximately 11 months. These results are consistent with those from the previous phase II studies. In these previous studies, 34% of patients with HL and 57% of those with sALCL had a CR, and the median PFS was 5.6 and 13.3 months, respectively.^(5,6) Although the sample size of our study was limited, this consistency indicates the efficacy of brentuximab vedotin in the Japanese population. In addition, our results compare favorably with those obtained from the other chemotherapy regimens. In particular, a higher percentage of patients achieved a CR in our study in contrast to the CR rates of 3–19% that were recently reported in other studies.^(17–19)

Table 5. Pharmacokinetic parameters of brentuximab vedotin antibody–drug conjugate, as determined by a phase I study in Japanese patients with refractory or relapsed CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma

Parameters	Phase I	
	1.2 mg/kg <i>n</i> = 3	1.8 mg/kg <i>n</i> = 3
Cycle 1		
AUC_{0-inf} (day* μ g/mL)		
Geo. mean (%CV)	41.96 (31.67)	74.23 (5.70)
C_{max} (μ g/mL)		
Geo. mean (%CV)	18.89 (34.33)	31.47 (9.61)
T_{max} (days)		
Median (range)	0.09 (0.09–0.23)	0.09 (0.09–0.09)
$t_{1/2}$ (days)		
Geo. mean (%CV)	4.94 (41.29)	7.42 (49.29)
Cycle 2		
AUC_{0-21d} (day* μ g/mL)		
Geo. mean (%CV)	44.94 (47.09)	71.42 (12.93)
Geo. mean ratio (90% CI),	1.12 (0.85–1.48)	1.07 (0.84–1.36)
Cycle 2/cycle 1		
C_{max} (μ g/mL)		
Geo. mean (%CV)	20.31 (40.46)	29.60 (12.81)
Geo. mean ratio (90% CI),	1.08 (0.91–1.27)	0.94 (0.75–1.19)
Cycle 2/cycle 1		
T_{max} (days)		
Median (range)	0.09 (0.08–0.17)	0.17 (0.17–0.24)
$t_{1/2}$ (days)		
Geo. mean (%CV)	5.06 (65.27)	7.20 (13.19)

AUC_{0-inf} , area under the concentration–time curve from time zero to infinity; AUC_{0-21d} , area under the concentration–time curve for a dosing interval (21 days); CI, confidence interval; CL, systemic clearance; C_{max} , maximum observed concentration after dosing; CV, coefficient of variation; Geo. mean, geometric mean; $t_{1/2}$, terminal elimination half-life; T_{max} , time to maximum concentration; V_{ss} , volume of distribution at steady state.

In summary, our results show that brentuximab vedotin (1.8 mg/kg, administered every 3 weeks) has an acceptable safety profile and promising antitumor activity in Japanese patients with relapsed or refractory CD30-positive HL and sALCL. These results were consistent with those from the preceding foreign studies. No ethnic difference was found. Thus, we concluded that brentuximab vedotin (1.8 mg/kg, administered every 3 weeks) is a beneficial treatment for Japanese patients with relapsed or refractory CD30-positive HL and sALCL. Considering the relatively small number of patients in this study, further investigation to evaluate the exact role of brentuximab vedotin in the treatment of CD30-positive lymphoid malignancies is warranted.

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Abbreviations

ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large-cell lymphoma
ASCT	autologous stem-cell transplantation

AUC	area under serum concentration–time curve
CI	confidence interval
Cmax	maximum observed concentration
CR	complete response
DLT	dose-limiting toxicity
HL	Hodgkin's lymphoma
MDS	myelodysplastic syndrome
MMAE	monomethyl auristatin E
OR	objective response
ORR	objective response rate
PFS	progression-free survival
PK	pharmacokinetic
sALCL	systemic anaplastic large-cell lymphoma
ULN	upper limit of normal

References

- Dürkop H, Latza U, Hummel M, Eitelbach F, Seed B, Stein H. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. *Cell* 1992; **68**: 421–7.
- Falini B, Pileri S, Pizzolo G *et al*. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. *Blood* 1995; **85**: 1–14.
- Doronina SO, Toki BE, Torgov MY *et al*. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. *Nat Biotechnol* 2003; **21**: 778–84.
- 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.
- Younes A, Gopal AK, Smith SE *et al*. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; **30**: 2183–9.
- Pro B, Advani R, Brice P *et al*. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 2012; **30**: 2190–6.
- Cheson BD, Pfistner B, Juweid ME *et al*. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25**: 579–86.
- Fanale MA, Forero-Torres A, Rosenblatt JD *et al*. Phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res* 2012; **18**: 248–55.
- Japanese Ministry of Health, Labour, and Welfare. Revision of guidelines for clinical evaluation methods of anti-cancer drugs in Japan. Issued on November 1, 2005. (Japanese)
- Diehl V, Franklin J, Pfreundschuh M *et al*. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003; **348**: 2386–95.
- Sureda A, Constans M, Iriando A *et al*. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. *Ann Oncol* 2005; **16**: 625–33.
- Majhail NS, Weisdorf DJ, Defor TE *et al*. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biol Blood Marrow Transplant* 2006; **12**: 1065–72.
- Savage KJ, Harris NL, Vose JM *et al*. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood* 2008; **111**: 5496–504.
- Moskowitz CH, Nimer SD, Glassman JR *et al*. The International Prognostic Index predicts for outcome following autologous stem cell transplantation in patients with relapsed and primary refractory intermediate-grade lymphoma. *Bone Marrow Transplant* 1999; **23**: 561–7.
- Shipp MA, Abeloff MD, Antman KH *et al*. International consensus conference on high-dose therapy with hematopoietic stem cell transplantation in aggressive non-Hodgkin's lymphomas: report of the jury. *J Clin Oncol* 1999; **17**: 423–9.
- Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006; **24**: 1633–42.
- Bartlett NL, Niedzwiecki D, Johnson JL *et al*. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007; **18**: 1071–9.
- Fehniger TA, Larson S, Trinkaus K *et al*. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. *Blood* 2011; **118**: 5119–25.
- O'Connor OA, Pro B, Pinter-Brown L *et al*. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 2011; **29**: 1182–9.