Review Report

August 3, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination) (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	January 31, 2018
Dosage Form/Strength	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination)
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage.
Items Warranting Special Mention	Orphan drug (Drug Designation No. 267 of 2012 [*24 yaku*]; PSEHB/PED Notification No. 0319-1 dated March 19, 2012, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of previously untreated CD30-positive Hodgkin's lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of bone marrow depression (neutropenia and febrile neutropenia) should be further investigated via post-marketing surveillance.

Indications	The following ~~relapsed or refractory~~ CD30-positive diseases: Hodgkin's lymphoma <u>Relapsed or refractory</u> anaplastic large-cell lymphoma

(Underline denotes addition; strikethrough denotes deletion.)

Dosage and Administration

1. Previously untreated CD30-positive Hodgkin's lymphoma

In combination with doxorubicin hydrochloride, vinblastine sulfate and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

2. Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma

The usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

(Underline denotes additions.)

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

June 28, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	January 31, 2018
Dosage Form/Strength	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination)
Proposed Indications	The following ~~relapsed or refractory~~ CD30-positive diseases: Hodgkin's lymphoma Relapsed or refractory anaplastic large-cell lymphoma (Underline denotes additions; strikethrough denotes deletions)
Proposed Dosage and Administration	1. Previously untreated CD30-positive Hodgkin's lymphoma In combination with doxorubicin, vinblastine, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered once daily as an intravenous infusion on Day 1 and Day 15, followed by a 13-day recovery period from Day 16 through Day 28. This 4-week cycle is repeated. The dose may be reduced as necessary according to the patient's condition. 2. Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma The usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as necessary according to the patient's condition. (Underline denotes addition.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Overview of the product submitted for approval

CD30 is a type I transmembrane protein belonging to the tumor necrosis factor receptor superfamily. CD30 is expressed on Reed-Sternberg cells of Hodgkin's lymphoma (HL) and T cells inducing other T-cell lymphoproliferative diseases.

Brentuximab Vedotin (Genetical Recombination) (referred to as brentuximab vedotin) is an antibody-drug conjugate discovered by Seattle Genetics, Inc. (US). Brentuximab vedotin is composed of a chimeric monoclonal antibody, which has variable regions derived from a mouse anti-human CD30 antibody and constant regions derived from a human immunoglobulin G1 (IgG1), and monomethyl auristatin E (MMAE), a tubulin polymerization inhibitor, which is covalently bound to the antibody via a linker containing a maleimide, caproyl spacer, valine, citrulline, and *p*-aminobenzyloxy carbonyl group. After binding to CD30 on the cell surface, brentuximab vedotin is internalized via CD30 in the form of an antibody-drug conjugate. Within the cell, MMAE, which is released by proteolytic cleavage, inhibits tumor proliferation by inducing cell cycle arrest and apoptosis.

In Japan, brentuximab vedotin was approved in January 2014 for the indication, "the following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma."

1.2 Development history etc.

Outside Japan, a phase I study (Study SGN35-009) was initiated by Seattle Genetics, Inc. (US) in patients with previously untreated HL in January 2010 as part of the clinical development process of brentuximab vedotin for the treatment of previously untreated HL. Then, a global phase III study (Study C25003) was initiated in November 2012 by Millennium Pharmaceuticals, Inc. (US) in patients with previously untreated classical Hodgkin's lymphoma (cHL).

In the US, an application for approval of brentuximab vedotin was filed in November 2017 for the treatment of previously untreated HL based on the pivotal clinical study results obtained from Study C25003. In March 2018, brentuximab vedotin was approved for the following indication: "ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III or IV cHL, in combination with chemotherapy." In the EU, an application for approval of brentuximab vedotin was filed in November 2017 for the treatment of previously untreated HL based on the pivotal clinical study results obtained from Study C25003, and is currently under review.

As of May 2018, brentuximab vedotin has been approved in 1 country for the treatment of previously untreated HL.

In Japan, enrollment of patients in Study C25003 by the applicant started in [redacted] 20[redacted].

Based on the pivotal study results obtained from Study C25003, the applicant filed an application for partial change for addition to indications and dosage and administration of brentuximab vedotin for the treatment of previously untreated HL.

Brentuximab vedotin was designated as an orphan drug in March 2012 with the proposed indications of "CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma" (Drug Designation No. 267 [*24 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the current application was filed for a new indication and new dosage, "data relating to quality" were not submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The current application was filed for a new indication and new dosage. No new test results were submitted because "data relating to non-clinical pharmacological studies" had already been evaluated for the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The current application was filed for a new indication and new dosage. No new test results were submitted because "data relating to non-clinical pharmacokinetic studies" had already been evaluated for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because this application was filed for a new indication and new dosage, "data relating to toxicity studies" were not submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

6.1.1.1 Assay method for anti-brentuximab vedotin antibody

Anti-brentuximab vedotin antibodies in human serum were detected by electrochemiluminescence (ECL) using immobilized-streptavidin, biotin-labeled brentuximab vedotin, and ruthenium-labeled brentuximab vedotin (sensitivity, 23.573 ng/mL).

Enzyme-linked immunosorbent assay (ELISA) was performed to detect anti-brentuximab vedotin neutralizing antibodies in human serum using brentuximab vedotin, immobilized anti-MMAE antibodies, biotin-labeled soluble CD30 and horseradish peroxidase (HRP)-labeled streptavidin (sensitivity, 375 ng/mL).

The applicant's explanation about the effect of brentuximab vedotin in the sample on measurements of anti-brentuximab vedotin antibodies:

In the above method, the upper limit of brentuximab vedotin concentration in a sample that does not affect anti-brentuximab vedotin antibody measurements was 25 μg/mL. In Study C25003, the above-mentioned assay method was used, and the serum concentrations of brentuximab vedotin were <25 μg/mL in all samples collected at anti-brentuximab vedotin antibody measurement except for 1 sample.[1)] This suggests that anti-brentuximab vedotin antibodies in samples obtained from Study C25003 were measurable in general without the being affected by brentuximab vedotin.

6.2 Clinical pharmacology

The pharmacokinetics (PK) of brentuximab vedotin in patients with cancer was evaluated for use in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

6.2.1 Global phase III study (CTD 5.3.5.1-1, Study C25003 [ongoing since November 2012, data cut-off on April 20, 2017])

An open-label, randomized, comparative study was conducted in 1334 patients (720 of which were included in the PK analysis) with previously untreated advanced stage cHL to compare the efficacy and safety of brentuximab vedotin + AVD with that of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). In the brentuximab vedotin + AVD group, on Days 1 and 15 of each 28-day cycle, brentuximab vedotin 1.2 mg/kg was intravenously administered over 30 minutes to 1 hour in combination with intravenous doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. In the ABVD group, on Days 1 and 15 of each 28-day cycle, doxorubicin 25 mg/m^2, bleomycin 10 units/m^2 (U/m^2), vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 were intravenously administered. In the brentuximab vedotin + AVD group, serum concentrations of brentuximab vedotin, total antibody (MMAE-conjugated and free anti-human CD30 monoclonal antibodies), and plasma MMAE concentrations were studied. Further, plasma concentrations of doxorubicin, vinblastine, and dacarbazine in 118 subjects (59 subjects/group) were also studied.

The PK parameters of brentuximab vedotin, total antibody, and MMAE on Day 1 of Cycles 1 and 3 are presented in Tables 1 and 2. Because the PK parameters of brentuximab vedotin and MMAE on Day 1 of Cycle 1 were similar to those after the administration of brentuximab vedotin 1.2 mg/kg alone (see Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated on November 8, 2013), the applicant explained that the administration of AVD is not likely to affect the PK of brentuximab vedotin and MMAE.

Table 1. PK parameters of brentuximab vedotin and total antibody

Measured	Day	n	C_{max} (μg/mL)	AUC_{14day} (μg·day/mL)	AUC_{∞} (μg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
Brentuximab vedotin	1	55	22.9 (28.1)	43.2 (28.9)	46.0 (25.4)*1	3.70 (19.8)*1	1.68 (28.4)*1	8.96 (29.4)*1
	57	52	23.6 (27.8)	56.1 (23.8)*2	–	5.00 (16.9)*3	1.37 (28.2)*2	9.96 (27.7)*4
Total antibody	1	55	22.6 (23.6)	80.7 (25.3)	89.9 (27.6)*5	4.30 (18.0)*5	–	–
	57	52	26.4 (22.5)	112 (21.9)*4	–	5.35 (20.7)*6	–	–

Geometric mean (coefficient of variation %); –, not calculated; *1, n = 53; *2, n = 50; *3, n = 44; *4, n = 49; *5, n = 51; *6, n = 47

[1)] One subject had a serum brentuximab vedotin concentration of 26.7 μg/mL before dosing on Day 1 of Cycle 2.

Table 2. PK parameters of MMAE

Day	n	C_{max} (ng/mL)	t_{max} [*1] (day)	AUC_{14day} (ng·day/mL)	AUC_{∞} (ng·day/mL)	$t_{1/2}$ (day)
1	59	3.20 (73.6)	1.86 (0.828, 6.94)	18.8 (74.9)	20.1 (75.8)[*2]	3.11 (35.0)[*3]
57	56	1.36 (51.7)	1.88 (0.188, 7.01)	9.46 (50.3)[*4]	–	3.92 (21.9)[*5]

Geometric mean (coefficient of variation %); –, not calculated; *1, median value (range); *2, n = 49; *3, n = 51; *4, n = 54; *5, n = 44

Table 3 shows the PK parameters of doxorubicin, vinblastine, and dacarbazine on Day 1 of Cycle 1.

Table 3. PK parameters of doxorubicin, vinblastine, and dacarbazine

Measured	Treatment group	n	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)
Doxorubicin	Brentuximab vedotin + AVD group	57	695 (78.2)	521 (78.3)[*1]
	ABVD group	56	725 (93.5)	538 (50.1)[*2]
Vinblastine	Brentuximab vedotin + AVD group	55	189 (113)	211 (54.0)[*3]
	ABVD group	56	182 (140)	188 (50.7)[*4]
Dacarbazine	Brentuximab vedotin + AVD group	57	6520 (50.0)	16,400 (61.7)[*4]
	ABVD group	54	7310 (84.4)	14,900 (51.9)[*3]

Geometric mean (coefficient of variation %); *1, n = 56; *2, n = 53; *3, n = 52; *4, n = 54

The applicant's explanation about the effects of brentuximab vedotin and MMAE on the PK of doxorubicin, vinblastine, and dacarbazine based on the above results:

Based on the following observations, brentuximab vedotin and MMAE are unlikely to affect the PK of doxorubicin, vinblastine, and dacarbazine:

- All the exposure levels to doxorubicin, vinblastine, and dacarbazine were similar between the brentuximab vedotin + AVD group and the ABVD group.
- The following facts indicate that bleomycin is unlikely to affect the PK of doxorubicin, vinblastine, or dacarbazine in the ABVD group:
  - Doxorubicin is a substrate for carbonyl reductases, microsomal glycosidases, and adenosine triphosphate (ATP) binding cassette (ABC) transporters (*Drug Metab Dispos*. 1976;4:79-87, *Expert Opin Drug Metab Toxicol*. 2011;7:1201-10), whereas dacarbazine is a substrate for cytochrome P450 (CYP)1A1 and CYP1A2 (*Clin Cancer Res*. 1999;5:2192-7). There have been no reports on pharmacokinetic drug-drug interactions of bleomycin mediated by these enzymes or transporters.
  - Vinblastine is a substrate for CYP3A (*Cancer Res.* 1993;53:5121-6). Bleomycin did not exhibit an inhibitory action against CYP3A *in vitro* (*Int J Clin Pharmacol Ther*. 2001;39:517-28).

6.2.2 Relationship between exposure and efficacy or safety

Based on the results from Study C25003, a relationship between exposure to brentuximab vedotin (time-averaged area under the curve [AUC/time]) and efficacy or safety and a relationship between exposure to MMAE (AUC/time) and safety were investigated. For both brentuximab vedotin and MMAE, AUC/time estimated by a population pharmacokinetic (PPK) analysis[2)] was used in the investigation.

[2)] The PPK analysis was conducted using a nonlinear mixed-effect model (software, NONMEM Version 7.3) based on the PK data of brentuximab vedotin and MMAE obtained from Study C25003 (661 subjects; 15,637 time points for brentuximab vedotin, and 15,656 time points for MMAE).

6.2.2.1 Relationship between exposure and efficacy

A relationship between exposure to brentuximab vedotin (AUC/time)[3)] and modified progression free survival (mPFS) was investigated using Cox proportional hazards regression analysis. The results showed no significant correlation between brentuximab vedotin AUC/time and mPFS.

6.2.2.2 Relationship between exposure and safety

The relationships between exposures to brentuximab vedotin and MMAE (AUC/time)[4)] and febrile neutropenia, Grade ≥2 neuropathy peripheral, and Grade ≥4 neutropenia, and Grade ≥3 adverse events were investigated by a logistic regression analysis. The incidences of febrile neutropenia and Grade ≥2 neuropathy peripheral increased with increasing brentuximab vedotin AUC/time, while the incidences of febrile neutropenia, Grade ≥4 neutropenia, and Grade ≥3 adverse events increased with increasing MMAE AUC/time. In contrast, no significant correlation was observed between brentuximab vedotin AUC/time and the incidence of Grade ≥4 neutropenia or Grade ≥3 adverse events, and between MMAE AUC/time and the incidence of Grade ≥2 neuropathy peripheral.

6.2.3 Difference in PK between Japanese and non-Japanese patients

The applicant's explanation:

The results from Study C25003 showed that there were no marked differences between Japanese and non-Japanese patients in terms of the PK parameters of brentuximab vedotin, total antibody, or MMAE (Table 4). There are no marked differences in the PK parameters of brentuximab vedotin, total antibody, and MMAE between Japanese and non-Japanese patients.

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3) The AUC values were averaged over the periods from the start to the end of brentuximab vedotin treatment, disease progression, or discontinuation.

4) For patients who did not experience the relevant events, the AUC value was averaged over the brentuximab vedotin treatment period. For patients who experienced the relevant events, the AUC value was averaged over time to the first episode of the event (the highest Grade event for Grade ≥2 neuropathy peripheral and Grade ≥3 adverse events).

Table 4. PK parameters of brentuximab vedotin, total antibody, or MMAE in Japanese and non-Japanese patients

Measured	Day	Japanese				Non-Japanese			
		n	C_{max} (μg/mL[*1])	AUC_{14day} (μg·day/mL[*2])	$t_{1/2}$ (day)	n	C_{max} (μg/mL[*1])	AUC_{14day} (μg·day/mL[*2])	$t_{1/2}$ (day)
Brentuximab vedotin	1	4	30.6 (18.7)	48.0 (24.9)	3.75 (18.3)	51	22.4 (27.9)	42.9 (29.4)	3.70 (20.1)[*6]
	57	3	21.7 (24.0)	53.5 (24.2)	4.54 (10.7)	49	23.7 (28.0)	56.3 (24.0)[*3]	5.03 (17.0v[*7]
Total antibody	1	4	27.8 (11.3)	84.3 (36.8)	4.32 (12.1)	51	22.3 (23.9)	80.4 (24.5)	4.30 (18.5)[*3]
	57	3	25.4 (29.8)	108 (29.8)	5.14 (18.2)	49	26.4 (22.4)	112.5 (21.8)[*4]	5.37 (21.0)[*8]
MMAE	1	4	3.19 (83.4)	22.6 (79.7)	3.73 (57.0)	55	3.20 (73.7)	18.5 (75.1)	3.06 (31.2)[*3]
	57	3	0.852 (53.2)	6.70 (68.2)	4.17 (13.9)	53	1.39 (51.0)	9.65 (49.7)[*5]	3.90 (22.5)[*7]

Geometric mean (coefficient of variation %); *1, ng/mL for MMAE; *2, ng·day/mL for MMAE; *3, n = 47; *4, n = 46; *5, n = 51; *6, n = 49; *7, n = 41; *8, n = 44

6.2.4 Effects of anti-brentuximab vedotin antibodies on the PK of brentuximab vedotin

The production of anti-brentuximab vedotin antibodies was investigated in Study C25003. Of 632 patients who were tested, 109 patients (17.2%) were positive for anti-brentuximab vedotin antibodies. Of these, 12 patients were positive for neutralizing antibodies.[5)]

The applicant's explanation:

Based on the results from Study C25003 including the following outcomes, anti-brentuximab vedotin antibodies are not considered to have marked impact on the PK of brentuximab vedotin.

- At the time of anti-brentuximab vedotin antibody measurement, no marked differences in serum brentuximab vedotin concentrations were observed between the anti-brentuximab vedotin antibody-positive and -negative patients (Table 5).
- At the time of neutralizing antibody measurement,[6)] the serum brentuximab vedotin concentrations in neutralizing antibody-positive patients (7 patients) ranged from 0 to 1.0 μg/mL (median, 0.04 μg/mL), which are within the range of concentrations in neutralizing antibody-negative patients (57 patients), from 0 to 1.8 μg/mL (median, 0.63 μg/mL).

Table 5. Serum brentuximab vedotin concentrations in anti-brentuximab vedotin antibody-positive and -negative patients (μg/mL)

Measurement time point	n	Anti-brentuximab vedotin antibody-positive patient	n	Anti-brentuximab vedotin antibody-negative patient
Before treatment on Day 1 of Cycle 2	65	0.56 (0, 1.8)	529	0.80 (0, 26.7)
Before treatment on Day 1 of Cycle 6	19	1.50 (0.5, 2.2)	506	1.20 (0, 2.9)

Median (range)

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology of brentuximab vedotin is acceptable.

5) Of the 12 neutralizing antibody-positive patients in Study C25003, 10 patients achieved complete remission (CR).

6) The measurement was performed before the treatment on Day 1 of Cycle 2. One of the patients who were positive for anti-brentuximab vedotin antibody at the time point did not undergo neutralizing antibody measurement. Before the treatment on Day 1 of Cycle 6, no patients tested positive for neutralizing antibodies.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from 1 foreign phase I study and 1 global phase III study (Table 6).

Table 6. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Patient population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Global	C25003	III	Patients with previously untreated advanced stage*1 cHL	1334 (a) 664 (b) 670	(a) or (b) was intravenously administered on Days 1 and 15 of each 28-day cycle (up to Cycle 6): (a) Brentuximab vedotin 1.2 mg/kg + AVD (b) ABVD	Efficacy Safety PK
	Foreign	SGN35-009	I	Patients with previously untreated*2 HL	51 (a) 25 (b) 26	(a) or (b) was intravenously administered on Days 1 and 15 of each 28-day cycle (up to Cycle 6): (a) Brentuximab vedotin 0.6, 0.9, or 1.2 mg/kg + ABVD (b) Brentuximab vedotin 1.2 mg/kg + AVD	Safety PK

*1, Stage III or IV; *2, stage IIA (only patients with bulky lesions), stage IIB, stage III, or stage IV

Individual clinical studies are summarized in the following sections.

Major adverse events other than deaths reported in each clinical study are described in Section "7.2 Adverse events and other findings from the clinical studies," and results relating to PK data in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1-1, Study C25003 [ongoing since November 2012, data cut-off on April 20, 2017])

An open-label, randomized, comparative study was conducted in patients with previously untreated advanced stage[7)] cHL (target sample size, 1240 subjects) at 218 study centers in 21 countries or regions including Japan to compare the efficacy and safety of brentuximab vedotin + AVD with the efficacy and safety of ABVD.

In the study, subjects in the brentuximab vedotin + AVD group received brentuximab vedotin 1.2 mg/kg intravenously in combination with intravenous doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 on Days 1 and 15 of each 28-day cycle. Subjects in the ABVD group received doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 intravenously on Days 1 and 15 of each 28-day cycle. In both groups, subjects underwent a positron emission tomography (PET) scan in Cycle 2.[8)] Subjects with the centralized Deauville score for the PET of 5 (*Leuk Lymphoma.* 2010;51:2171-80) were allowed to switch to another alternative therapy[9)] from the assigned treatment by the investigator at the

7) Patients with stage III or IV in the Ann Arbor staging classification system were eligible for enrollment.

8) Subjects were to have a PET scan on Day 25 ± 1 in Cycle 2.

9) The treatment options were defined as chemotherapy or radiation therapy selected by the investigator, and no specific details of treatment were provided.

beginning of the study. Treatment was repeated up to Cycle 6[10] unless another alternative therapy was selected, disease progression occurred, or the discontinuation criterion was met.

All 1334 subjects enrolled in the study and randomized (664 subjects in the brentuximab vedotin + AVD group and 670 subjects in the ABVD group) were defined as the intent to treat (ITT) population and subjected to the efficacy analysis. Also, 1321 subjects in the ITT population who received the study drugs (662 subjects in the brentuximab vedotin + AVD group, and 659 subjects in the ABVD group) were subjected to the safety analysis.

Table 7 summarizes the results of the primary efficacy endpoint, which is mPFS[11] as determined by central review according to the International Working Group (IWG) criteria (*J Clin Oncol.* 2007;25:579-86). Figure 1 shows the Kaplan-Meier curves of mPFS, demonstrating that the brentuximab vedotin + AVD group was superior to the ABVD group.

Table 7. Analytical results of mPFS (ITT population, central review, data cut-off on April 20, 2017)

	Brentuximab vedotin + AVD	ABVD
Number of subjects	664	670
Number of events (%)	117 (17.6)	146 (21.8)
Median [95% confidence interval (CI)] (months)	Not estimable (NE) [48.2, NE]	NE [NE, NE]
Hazard ratio*1 [95%CI]	0.770 [0.603, 0.983]	
P-value (two-sided)*2	0.035	

*1, Calculated using stratified Cox proportional hazard model with risk factor (0-1, 2-3, or 4-7) developed by the International Prognostic Factors Project (IPFP) and region of enrollment (North America, South America, Asia, or Europe) as stratification factors; *2, stratified log-rank test (stratification factors similar to those used for the Cox proportional hazard model), two-sided significance level, 0.05

[10] For patients experiencing a change(s) in treatment, the study was continued until the completion of 1 alternative therapy.

[11] The events of mPFS were defined as (1) disease progression or death due to any cause, (2) implementation of subsequent therapy (chemotherapy or radiation therapy) because CR was not achieved in the assessment at the end of the front-line treatment [See Section 7.R.2.2].

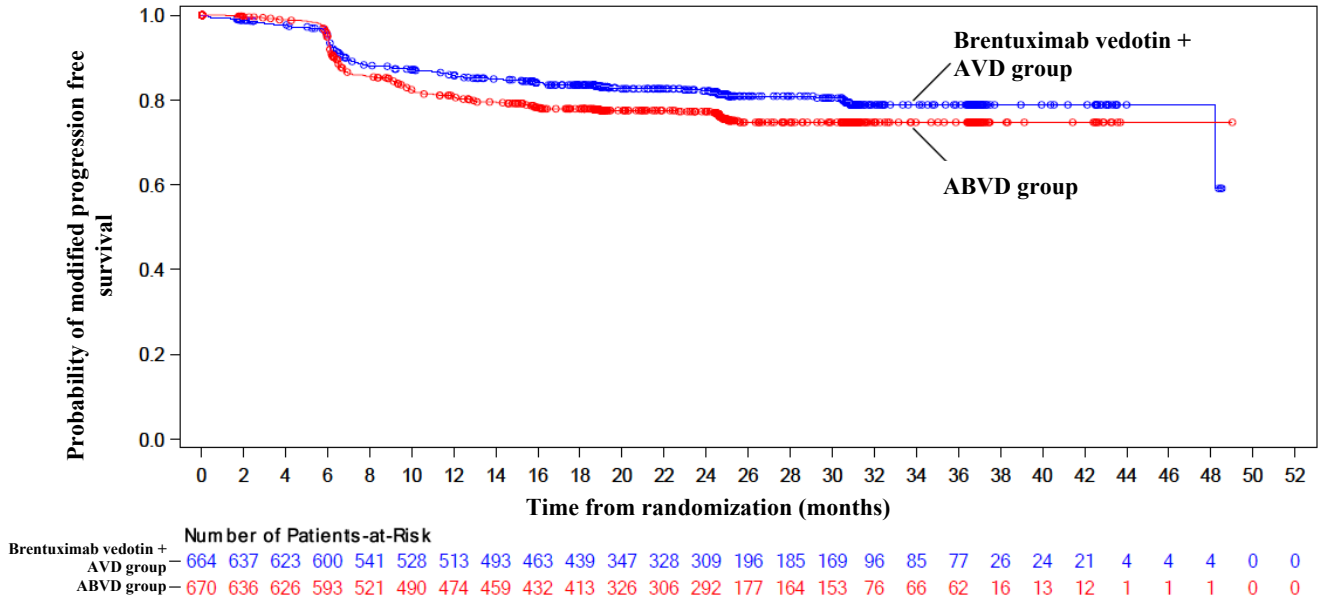

Figure 1. Kaplan-Meier curve of mPFS (ITT population, central review, data cut-off on April 20, 2017)

The safety analysis revealed that, during the treatment period of the study drug or within 30 days of the end of treatment, deaths occurred in 9 of 662 subjects (1.4%) in the brentuximab vedotin + AVD group and 12 of 659 subjects (1.8%) in the ABVD group. The causes of death were myocardial infarction (2 subjects), cardio-respiratory arrest, histiocytosis haematophagic, respiratory failure, multiple organ dysfunction syndrome, neutropenic sepsis, septic shock, and death (unknown cause) (1 subject each) in the brentuximab vedotin + AVD group; pneumonia (3 subjects), cardiac arrest (2 subjects), pneumocystis jirovecii pneumonia, pulmonary toxicity, cardiopulmonary failure, cerebrovascular accident, pneumonitis, respiratory disorder, and death (unknown cause) (1 subject each) in the ABVD group. A causal relationship to the study drug could not be ruled out for myocardial infarction, cardio-respiratory arrest, histiocytosis haematophagic, respiratory failure, multiple organ dysfunction syndrome, neutropenic sepsis, septic shock, and death (unknown cause)[12] (1 subject each) in the brentuximab vedotin + AVD group; pneumonia (2 subjects), cardiac arrest, pneumocystis jirovecii pneumonia, pulmonary toxicity, pneumonitis, and respiratory disorder (1 subject each) in the ABVD group.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase I study (CTD 5.3.5.2-1, Study SGN35-009 [January 2010 to September 2012])

An open-label, uncontrolled study was conducted in patients with previously untreated advanced stage[13] HL (target sample size, 50-70 subjects) at 4 study centers outside Japan to investigate the safety and other aspects of brentuximab vedotin in combination with ABVD or AVD.

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[12] A female subject aged 21 years received study drug treatment on Days 1 and 15 of Cycle 1. The subject developed Grade 4 neutropenic sepsis on Day 22 of Cycle 1, and died on the next day.

[13] Patients with stage IIA (only patients with bulky lesions), IIB, III, or IV in the Ann Arbor staging classification system were eligible for enrollment.

In the brentuximab vedotin + ABVD group, on Days 1 and 15 of each 28-day cycle, brentuximab vedotin 0.6, 0.9, or 1.2 mg/kg was intravenously administered in combination with intravenous doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. In the brentuximab vedotin + AVD group, on Days 1 and 15 of each 28-day cycle, brentuximab vedotin 1.2 mg/kg was intravenously administered in combination with intravenous doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. In both groups, treatment cycles were repeated up to Cycle 6 unless disease progression or discontinuation criterion met.

All 51 subjects[14)] enrolled in the study (25 subjects in the brentuximab vedotin + ABVD group [6, 13, and 6 subjects in the brentuximab vedotin 0.6, 0.9, and 1.2 mg/kg groups, respectively] and 26 subjects in the brentuximab vedotin + AVD group) received brentuximab vedotin and were included in the safety analysis set and the dose limiting toxicity (DLT) analysis set.

In Cycle 1, which was defined as the DLT assessment period, no DLT was observed.

The safety analysis revealed no deaths during the treatment period with the study drug or within 30 days after the end of treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Review policy

PMDA concluded that the most important clinical study for evaluating the efficacy and safety of brentuximab vedotin was the global phase III study (Study C25003) conducted in patients with previously untreated advanced stage cHL and decided the evaluation be focused on Study C25003. Further, PMDA decided to assess the efficacy of brentuximab vedotin in Japanese patients from the standpoint of consistency between the entire study population and Japanese subpopulation in Study C25003 based on "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), "Basic principles on Global Clinical Trials (Reference Cases)" (Administrative Notice, dated September 5, 2012), etc.

7.R.2 Efficacy

Based on the following reviews, PMDA concluded that the efficacy of brentuximab vedotin in patients with previously untreated advanced stage cHL has been demonstrated.

7.R.2.1 Rationale for the selection of the control group

The applicant's rationale for the selection of control group in Study C25003:

In 20[redacted] around the time Study C25003 was in its planning phase, ABVD was one of the standard therapy recommended for patients who meet the inclusion criteria of Study C25003 in the guidelines such as "National

[14)] When the study was initially planned, the target sample size for the brentuximab vedotin + ABVD group was specified as 6 subjects, to be assigned to each dose level of brentuximab vedotin. However, because of concerns over the risk for pulmonary toxicity associated with brentuximab vedotin + ABVD, the protocol was revised as of [redacted], 20[redacted] so that the target sample size for the brentuximab vedotin + ABVD group at 0.9 mg/kg was changed (to 12 subjects from 6 subjects) and a new cohort was added to evaluate brentuximab vedotin + AVD.

Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (v.2.2012): Hodgkin Lymphoma" (NCCN Guidelines). Therefore ABVD was selected as the control in Study C25003.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint

The applicant's explanation about the primary endpoint of Study C25003:

A proportion of patients with previously untreated cHL achieve remission after chemotherapy (e.g., *J Clin Oncol.* 2011;29:4215-6). Therefore, it is important in the treatment of these patients to achieve CR after a certain period of chemotherapy such as ABVD and maintain it. If chemotherapy of a certain period fails to achieve CR, another chemotherapy or radiation therapy will follow.

Based on the above, in Study C25003, the study drug treatment (brentuximab vedotin + AVD or ABVD) from the start through Cycle 6[10)] was defined as the frontline therapy. Events that represented mPFS, the primary endpoint of the study, were defined as "disease progression," "deaths from any cause," and "the implementation of subsequent therapies (chemotherapies or radiation therapies) due to failure to achieve CR at the end of frontline therapy."[15)] The specifically defined mPFS events would enable to assess the achievement of CR after frontline therapy and the maintenance of CR appropriately. Furthermore, extension of mPFS is clinically significant. Therefore, mPFS is the appropriate endpoint for the efficacy of brentuximab vedotin in patients with previously untreated cHL

In the frontline therapy of Study C25003, if the PET scan after the completion of study drug treatment (brentuximab vedotin + AVD or ABVD) in Cycle 2 resulted in a Deauville score of 5, subjects were allowed to choose an alternative therapy at the discretion of the investigator (Figure 2). However, to thoroughly evaluate the efficacy of the frontline therapy, therapy switch for any reasons other than disease progression was not regarded as mPFS events or censoring.

[15)] The onset date of an mPFS event was defined as the date of the first PET scan after the completion of frontline therapy that failed to show CR and resulted in a Deauville score of ≥3.

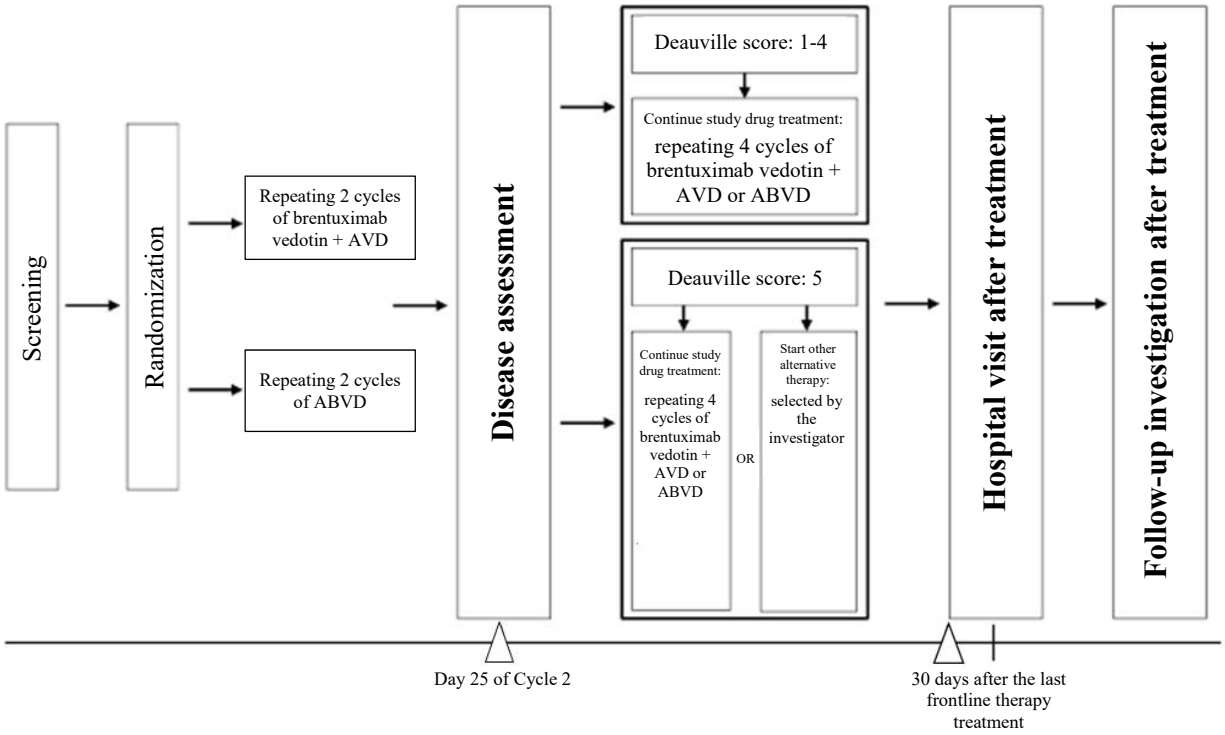

Figure 2. Outline of Study C25003

PMDA's view:

Given that the goal of treatment in patients with previously untreated advanced stage cHL is cure, overall survival (OS) should have been chosen as the primary endpoint to evaluate the efficacy of brentuximab vedotin. Nevertheless, the applicant's view on the clinical significance of mPFS extension following frontline therapy defined in Study C25003 is acceptable to some extent. Therefore, the efficacy evaluation should primarily focus on the results of centrally reviewed mPFS, the primary endpoint of Study C25003, while keeping attention to OS results as well. Furthermore, in Study C25003, (a) switching to an alternative therapy was allowed for patients meeting certain requirements during the frontline therapy period, and there were patients who underwent a therapy switch; (b) whether CR had been achieved was not known in some patients at the end of the frontline therapy period. Therefore, it was decided to assess the effects of (a) and (b) on the efficacy evaluation of brentuximab vedotin.

7.R.2.3 Results of efficacy evaluation

The superiority of the brentuximab vedotin + AVD group over the ABVD group was verified in centrally-reviewed mPFS, the primary endpoint for Study C25003 [See Section 7.1.1].

In Study C25003, (a) switching to an alternative therapy was allowed for patients who met prescribed conditions during the frontline therapy period, and there were patients who underwent a therapy switch and (b) whether CR had been achieved was not known in some patients at the end of the frontline therapy period. PMDA therefore asked the applicant to explain the effects of these factors on the efficacy evaluation of brentuximab vedotin.

The applicant's explanation:
(a) A total of 21 subjects in the brentuximab vedotin + AVD group and 30 subjects in the ABVD group had a Deauville score of 5 on PET scan in Cycle 2. Of these, 1 subject in the brentuximab vedotin + AVD group and 2 subjects[16)] in the ABVD group underwent a therapy switch. (b) One subject in the brentuximab vedotin + AVD group and 3 subjects in the ABVD group had unknown CR status at the end of the frontline therapy period and received subsequent therapies.

The primary endpoint of Study C25003, mPFS, was analyzed based on the following cases of (i) and (ii). Given that the results from these analyses (Table 8) were similar to those of the main analysis, it is unlikely that the factors (a) or (b) above affect the efficacy evaluation of brentuximab vedotin.

(i) A therapy switch to an alternative therapy based on a Deauville score of 5 on PET scan in Cycle 2 was regarded as an event.

(ii) A subsequent therapy given to patients with unknown CR status at the end of the frontline therapy period was regarded as an event.

Table 8. Analytical results of mPFS with different event definitions (ITT population, central review, data cut-off on April 20, 2017)

	Analysis (i)		Analysis (ii)	
	Brentuximab vedotin + AVD	ABVD	Brentuximab vedotin + AVD	ABVD
Number of subjects	664	670	664	670
Number of events (%)	117 (17.6)	146 (21.8)	118 (17.8)	149 (22.2)
Median [95%CI] (months)	NE [48.2, NE]	NE [NE, NE]	NE [48.2, NE]	NE [NE, NE]
Hazard ratio *1[95%CI]	0.770 [0.604, 0.983]		0.760 [0.596, 0.968]	
P-value (two-sided)*2	0.035		0.026	

*1, Calculated using stratified Cox proportional hazard model with risk factor (0-1, 2-3, or 4-7) developed by the IPFP, and registration region (North America, South America, Asia, or Europe) as stratification factors; *2, stratified log-rank test (stratification factors similar to those used for the Cox proportional hazard model)

The secondary endpoint of Study C25003 was interim OS analysis results (data cut-off on April 20, 2017). The results are summarized in Table 9, and the Kaplan-Meier curves are shown in Figure 3. In Study C25003, tests for OS were to be performed in a hierarchical manner when a statistically significant difference was identified in the primary endpoint. However, the interim OS analysis revealed no statistically significant difference.

16) Excluding 1 subject who underwent a therapy switch following an mPFS event diagnosed (disease progression).

Table 9. Analysis results of OS (ITT population, central review, data cut-off on April 20, 2017)

	Brentuximab vedotin + AVD	ABVD
Number of subjects	664	670
Death (%)	28 (4.2)	39 (5.8)
Median [95%CI] (months)	NE [NE, NE]	NE [NE, NE]
Hazard ratio*1 [95%CI]	0.728 [0.448, 1.184]	
P-value (two-sided)*2	0.199	

*1, Calculated using stratified Cox proportional hazard model with risk factor (0-1, 2-3, or 4-7) developed by the IPFP, and enrollment region (North America, South America, Asia, or Europe) as stratification factors; *2, stratified log-rank test (stratification factors similar to those used for the Cox proportional hazard model), two-sided significance level, 0.0075

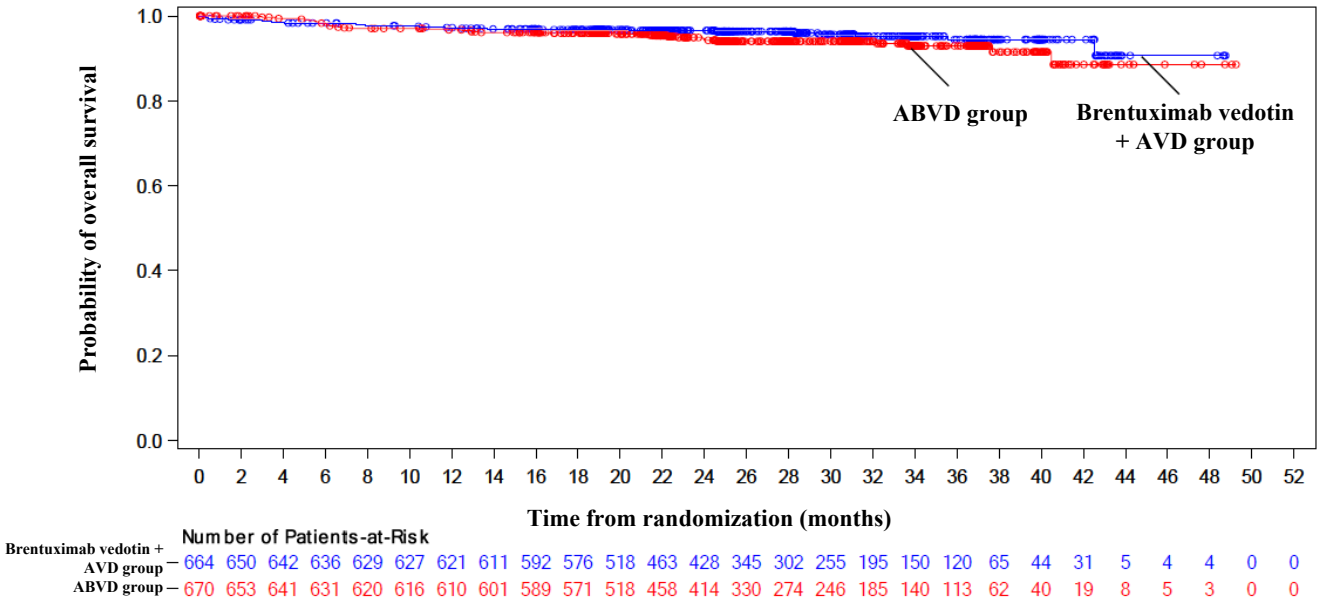

Figure 3. Kaplan-Meier curve of OS (ITT population, central review, data cut-off on April 20, 2017)

The sub-group analysis results in Japanese patients for centrally reviewed mPFS, the primary endpoint of Study C25003, are summarized in Table 10, and the Kaplan-Meier curves are shown in Figure 4.

Table 10. Analytical results of mPFS in Japanese patients (ITT population, central review, data cut-off on April 20, 2017)

	Brentuximab vedotin + AVD	ABVD
Number of subjects	10	13
Number of events (%)	2 (20.0)	3 (23.1)
Median [95%CI] (months)	NE [2.7, NE]	NE [6.8, NE]
Hazard ratio*1 [95%CI]	0.903 [0.150, 5.417]	
P-value (two-sided)*2	0.911	

*1, Calculated using non-stratified Cox proportional hazard model; *2, non-stratified log-rank test

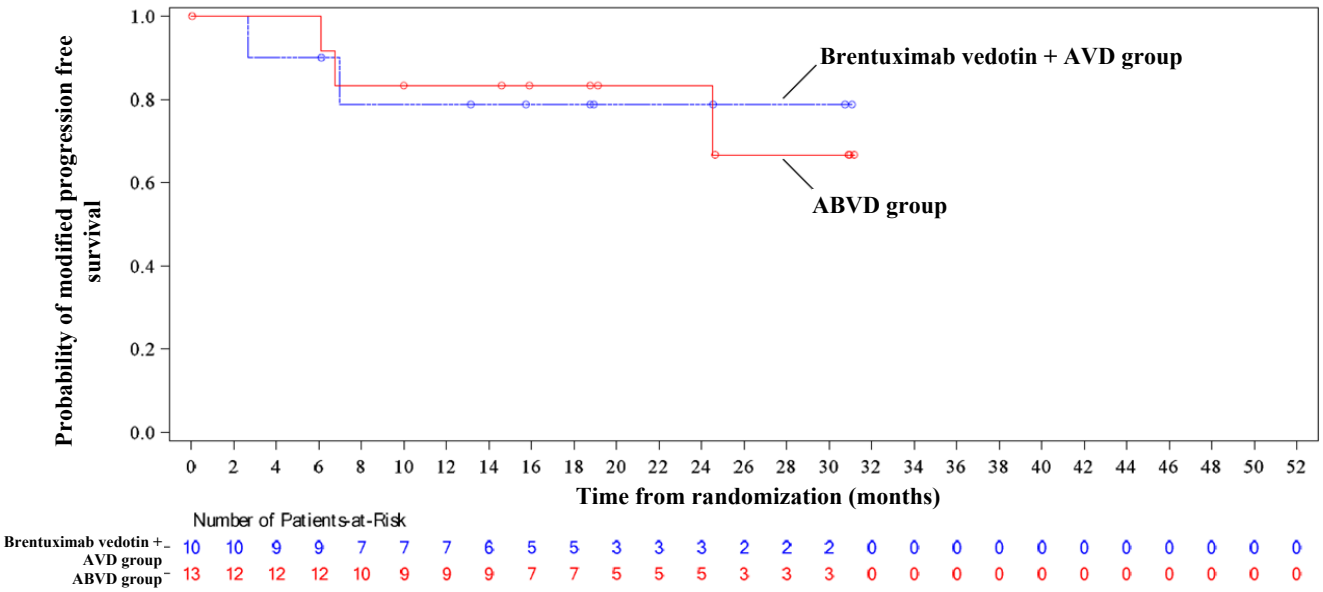

Figure 4. Kaplan-Meier curve of mPFS in Japanese patients (ITT population, central review, data cut-off on April 20, 2017)

PMDA's view:

The following observations indicate that the efficacy of brentuximab vedotin was demonstrated in patients with previously untreated cHL enrolled in Study C25003.

- The results of Study C25003 demonstrated the superiority of the brentuximab vedotin + AVD group over the ABVD group in the primary endpoint, i.e., centrally reviewed mPFS according to IWG criteria. Furthermore, the results of the above sensitivity analysis based on different mPFS event definitions did not differ markedly from the primary endpoint analysis results.
- There was no marked trend towards decreasing OS, the secondary endpoint for Study C25003, in the brentuximab vedotin + AVD group as compared to the ABVD group.
- In Study C25003, the limited number of Japanese patients precluded rigorous evaluation. However, no clear inconsistency was seen between the Japanese sub-group and the entire study population in the mPFS results.

7.R.3 Safety [See Section "7.2 Adverse events and other findings observed in clinical studies" for adverse events]

Based on the discussions in the following sections, PMDA recognized that treatment with brentuximab vedotin in patients with previously untreated cHL requires particular attention to adverse events (infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome, lung disorders, pancreatitis acute, and hepatic dysfunction), which had already been identified during the review for the approved indications. (For details, see Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated on November 8, 2013). PMDA concluded that caution should be exercised against these adverse events in the use of brentuximab vedotin for previously untreated cHL as with for the approved indication.

PMDA concluded that brentuximab vedotin treatment, although requires due vigilance for these adverse events, is tolerable in patients with previously untreated cHL as well when appropriate follow-up, i.e., monitoring and managing of adverse events, dose delay of brentuximab vedotin, etc., is performed by physicians with sufficient knowledge and experience in the treatment of haematopoietic malignancies.

7.R.3.1 Safety profile of brentuximab vedotin

The applicant's explanation about the safety profile of brentuximab vedotin:

Table 11 summarizes the safety data from Study C25003.

Table 11. Summary of safety data (Study C25003)

	Number of subjects (%)	
	Brentuximab vedotin + AVD 662 subjects	ABVD 659 subjects
All adverse events	653 (98.6)	646 (98.0)
Grade ≥3 adverse events	549 (82.9)	434 (65.9)
Adverse events resulting in death	9 (1.4)	13 (2.0)
Serious adverse events	284 (42.9)	178 (27.0)
Adverse events leading to treatment discontinuation of the study drug(s)*1	88 (13.3)	105 (15.9)
Adverse events leading to treatment discontinuation of brentuximab vedotin*2	67 (10.1)	–
Adverse events leading to dose delay of the study drug(s)*1	44 (6.6)	32 (4.9)
Adverse events leading to dose delay of brentuximab vedotin*2	40 (6.0)	–
Adverse events leading to dose reduction of the study drug(s)*1	191 (28.9)	65 (9.9)
Adverse events leading to dose reduction of brentuximab vedotin*2	166 (25.1)	–

*1, Treatment discontinuation, dose delay, or dose reduction of at least one of the following drugs: brentuximab vedotin, doxorubicin, bleomycin, vinblastine, or dacarbazine; *2, specific names of adverse events leading to treatment discontinuation, dose delay, or dose reduction of brentuximab vedotin were not collected.

In Study C25003, adverse events that occurred at a ≥10% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group were neutropenia (382 subjects [57.7%] in the brentuximab vedotin + AVD group and 295 subjects [44.8%] in the ABVD group), peripheral sensory neuropathy (189 subjects [28.5%] and 111 subjects [16.8%]), neuropathy peripheral (174 subjects [26.3%] and 85 subjects [12.9%]), weight decreased (148 subjects [22.4%] and 40 subjects [6.1%]), abdominal pain (142 subjects [21.5%] and 65 subjects [9.9%]), anaemia (140 subjects [21.1%] and 67 subjects [10.2%]), and febrile neutropenia (128 subjects [19.3%] and 52 subjects [7.9%]). Grade ≥3 adverse events that occurred at a ≥3% incidence in the brentuximab vedotin + AVD group than in the ABVD group were neutropenia (357 subjects [53.9%] and 260 subjects [39.5%]), febrile neutropenia (128 subjects [19.3%] and 52 subjects [7.9%]), anaemia (54 subjects [8.2%] and 25 subjects [3.8%]), peripheral sensory neuropathy (31 subjects [4.7%] and 3 subjects [0.5%]), neuropathy peripheral (27 subjects [4.1%] and 6 subjects [0.9%]), and alanine aminotransferase (ALT) increased (22 subjects [3.3%] and 1 subject [0.2%]). Serious adverse events that occurred at a ≥2% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group by were febrile neutropenia (114 subjects [17.2%] and 43 subjects [6.5%]), pyrexia (44 subjects [6.6%] and 28 subjects [4.2%]), and neutropenia (19 subjects [2.9%] and 4 subjects [0.6%]). Adverse events leading to discontinuation of the study drug(s) with a ≥2% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group were peripheral

sensory neuropathy (23 subjects [3.5%] and 6 subjects [0.9%]). Adverse events leading to dose delay of the study drug(s) with a ≥2% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group were peripheral sensory neuropathy (19 subjects [2.9%] and 5 subjects [0.8%]) and neuropathy peripheral (16 subjects [2.4%] and 1 subject [0.2%]). Adverse events leading to dose reduction of the study drug(s) with a ≥2% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group were peripheral sensory neuropathy (55 subjects [8.3%] and 16 subjects [2.4%]), neuropathy peripheral (57 subjects [8.6%] and 10 subjects [1.5%]), peripheral motor neuropathy (16 subjects [2.4%] and 1 subject [0.2%]), and weight decreased (15 subjects [2.3%] and 1 subject [0.2%]). There were no adverse events leading to death with a ≥1% higher incidence in the brentuximab vedotin + AVD group than in the ABVD group.

Adverse events leading to treatment discontinuation of the study drug(s) with a ≥2% higher incidence in the ABVD group than in the brentuximab vedotin + AVD group were dyspnoea (2 subjects [0.3%] in the brentuximab vedotin + AVD group, and 25 subjects [3.8%] in the ABVD group). In the ABVD group, there were no adverse events with a ≥10% higher incidence, Grade ≥3 adverse events with a ≥3% higher incidence, adverse events leading to death with a ≥1% higher incidence, serious adverse events with a ≥2% higher incidence, or adverse events leading to dose delay or dose reduction of the study drug(s) with a ≥2% higher incidence than in the brentuximab vedotin + AVD group.

The applicant's explanation about the differences in the safety profiles of brentuximab vedotin between patients with previously untreated cHL and patients with relapsed or refractory CD30-positive HL, the approved indication:
The occurrence of adverse events in the brentuximab vedotin + AVD group of Study C25003 conducted in patients with previously untreated cHL was compared against that in a foreign phase II study (Study SG035-0003)[17] conducted in patients with relapsed or refractory CD30-positive HL.

Safety data from the brentuximab vedotin + AVD group of Study C25003 and Study SG035-0003 are summarized in Table 12.

[17] Brentuximab vedotin was administered alone intravenously at 1.8 mg/kg every 3 weeks.

Table 12. Summary of safety data from the brentuximab vedotin group of Study C25003 and Study SG035-0003

	Number of subjects (%)	
	Study C25003 Brentuximab vedotin + AVD 662 subjects	Study SG035-0003 (Brentuximab vedotin monotherapy) 102 subjects
All adverse events	653 (98.6)	100 (98.0)
Grade ≥3 adverse events	549 (82.9)	56 (54.9)
Adverse events leading to death	9 (1.4)	0
Serious adverse events	284 (42.9)	24 (23.5)
Adverse events leading to treatment discontinuation of brentuximab vedotin *	67 (10.1)	19 (18.6)

* In Study C25003, adverse events leading to discontinuation of brentuximab vedotin were not collected by event term.

Adverse events that occurred at a ≥30% higher incidence in the brentuximab vedotin + AVD group of Study C25003 than in Study SG035-0003[18)] were neutropenia (382 subjects [57.7%] in Study C25003 and 22 subjects [21.6%] in Study SG035-0003). Grade ≥3 adverse events that occurred at a ≥5% higher incidence in the brentuximab vedotin + AVD group of Study C25003 than in Study SG035-0003 were neutropenia (357 subjects [53.9%] and 20 subjects [19.6%]), febrile neutropenia (128 subjects [19.3%] and 0 subjects), and neutrophil count decreased (83 subjects [12.5%] and 0 subjects). Serious adverse events that occurred at a ≥2% higher incidence in the brentuximab vedotin + AVD group of Study C25003 than in Study SG035-0003 were febrile neutropenia (114 subjects [17.2%] and 0 subjects), pyrexia (44 subjects [6.6%] and 2 subjects [2.0%]), neutropenia (19 subjects [2.9%] and 0 subjects), and sepsis (14 subjects [2.1%] and 0 subjects). Results obtained from post-marketing surveillance (covering all patients) conducted in patients with relapsed or refractory CD30-positive HL or anaplastic large cell lymphoma (ALCL), the approved indications, have so far suggested no events requiring additional caution.

The applicant's explanation about the differences in the safety of the brentuximab vedotin + AVD group between the Japanese and non-Japanese populations:
The safety data from the brentuximab vedotin + AVD group of Study C25003 in Japanese and non-Japanese patients are summarized in Table 13.

[18)] Adverse event data from Study SG035-0003 were collected using MedDRA/J ver.13.0.

Table 13. Summary of safety data between the Japanese and non-Japanese (Study C25003)

	Number of subjects (%)			
	Brentuximab vedotin + AVD		ABVD	
	Japanese 10 subjects	Non-Japanese 652 subjects	Japanese 13 subjects	Non-Japanese 646 subjects
All adverse events	10 (100)	643 (98.6)	13 (100)	633 (98.0)
Grade ≥3 adverse events	7 (70.0)	542 (83.1)	9 (69.2)	425 (65.8)
Adverse events leading to death	0	9 (1.4)	0	13 (2.0)
Serious adverse events	4 (40.0)	280 (42.9)	3 (23.1)	175 (27.1)
Adverse events leading to treatment discontinuation of the study drug(s)*1	2 (20.0)	86 (13.2)	1 (7.7)	104 (16.1)
Adverse events leading to treatment discontinuation of brentuximab vedotin *2	1 (10.0)	66 (10.1)	–	–
Adverse events leading to dose delay of the study drug(s)*1	0	44 (6.7)	0	32 (5.0)
Adverse events leading to dose delay of brentuximab vedotin*2	0	40 (6.1)	–	–
Adverse events leading to dose reduction of the study drug(s)*1	3 (30.0)	188 (28.8)	1 (7.7)	64 (9.9)
Adverse events leading to dose reduction of brentuximab vedotin*2	2 (20.0)	164 (25.2)	–	–

*1, Treatment discontinuation, dose delay, or dose reduction of at least one of the following drugs: brentuximab vedotin, doxorubicin, bleomycin, vinblastine, or dacarbazine; *2, specific names of adverse events leading to treatment discontinuation, dose delay, or dose reduction of brentuximab vedotin were not collected.

In the brentuximab vedotin + AVD group of Study C25003, adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥20% were peripheral sensory neuropathy (10 Japanese subjects [100%] and 179 non-Japanese subjects [27.5%]), constipation (7 subjects [70.0%] and 272 subjects [41.7%]), alopecia (7 subjects [70.0%] and 166 subjects [25.5%]), decreased appetite (6 subjects [60.0%] and 112 subjects [17.2%]), insomnia (5 subjects [50.0%] and 121 subjects [18.6%]), upper respiratory tract infection (4 subjects [40.0%] and 66 subjects [10.1%]), hepatic function abnormal (3 subjects [30.0%] and 2 subjects [0.3%]), vascular pain (3 subjects [30.0%] and 1 subject [0.2%]), and vasculitis (2 subjects [20.0%] and 0 subjects). Grade ≥3 adverse events that occurred at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were febrile neutropenia (3 subjects [30.0%] and 125 subjects [19.2%]) and leukopenia (2 subjects [20.0%] and 23 subjects [3.5%]). Serious adverse events that occurred at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were pancreatitis acute (1 subject [10.0%] and 0 subjects) and rash maculo-papular (1 subject [10.0%] and 0 subjects). Adverse events leading to treatment discontinuation of the study drug(s) with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was pancreatitis acute (1 subject [10.0%] and 0 subjects). Adverse events leading to dose reduction of the study drug(s) with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were nausea (2 subjects [20.0%] and 0 subjects), decreased appetite (1 subject [10.0%] and 0 subjects), and vomiting (1 subject [10.0%] and 0 subjects). There were no adverse events leading to death with a ≥10% higher incidence in Japanese patients or those leading to dose delay of the study drug(s) with a ≥10% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

Adverse events requiring vigilance in the use of brentuximab vedotin + AVD are those showing a gap in their incidences between the brentuximab vedotin + AVD group and the ABVD group in Study C25003 and those

with a higher incidence in the brentuximab vedotin + AVD group of Study C25003 than in Study SG035-0003 (brentuximab vedotin monotherapy). It is difficult to make a conclusion on difference in the safety of brentuximab vedotin + AVD treatment between Japanese and non-Japanese patients based on the results from Study C25003 with extremely limited number of Japanese subjects. Vigilance is required for adverse events that occurred more frequently in Japanese patients than in non-Japanese patients. However, all the above-mentioned events are known adverse events of brentuximab vedotin, and PMDA concluded that brentuximab vedotin + AVD is tolerable in patients with previously untreated cHL as well when appropriate follow-up, i.e., monitoring and managing of adverse events, dose delay of brentuximab vedotin, etc., is performed by physicians with sufficient knowledge and experience in the treatment of haematopoietic malignancies.

In the following subsections, PMDA's review focuses on neutropenia and febrile neutropenia, which were serious adverse events occurring more frequently in the brentuximab vedotin + AVD group than in the ABVD group of Study C25003.

7.R.3.2 Neutropenia and febrile neutropenia

The applicant's explanation about the occurrence of neutropenia and febrile neutropenia following the administration of brentuximab vedotin + AVD:

Preferred terms (PTs) falling under a MedDRA Standardized MedDRA Query (SMQ) (MedDRA/J ver.19.0) of "Haematopoietic leukopenia" (narrow) were retrieved as neutropenia- and febrile neutropenia-related adverse events.

Table 14 shows the incidences of neutropenia- and febrile neutropenia-related adverse events in Study C25003.

Table 14. The incidences of neutropenia- and febrile neutropenia-related adverse events (Study C25003)

MedDRA PT (MedDRA/J ver.19.0)	Number of subjects (%)			
	Brentuximab vedotin + AVD 662 subjects		ABVD 659 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia- and febrile neutropenia-related adverse events	501 (75.7)	476 (71.9)	392 (59.5)	347 (52.7)
Neutropenia	382 (57.7)	357 (53.9)	295 (44.8)	260 (39.5)
Febrile neutropenia	128 (19.3)	128 (19.3)	52 (7.9)	52 (7.9)
Neutrophil count decreased	86 (13.0)	83 (12.5)	79 (12.0)	67 (10.2)
White blood cell count decreased	46 (6.9)	26 (3.9)	34 (5.2)	18 (2.7)
Leukopenia	42 (6.3)	25 (3.8)	37 (5.6)	18 (2.7)
Lymphocyte count decreased	15 (2.3)	6 (0.9)	11 (1.7)	4 (0.6)
Neutropenic sepsis	8 (1.2)	8 (1.2)	2 (0.3)	2 (0.3)
Agranulocytosis	3 (0.5)	3 (0.5)	1 (0.2)	1 (0.2)
Granulocyte count decreased	2 (0.3)	2 (0.3)	1 (0.2)	0
Lymphopenia	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)

After the number of patients enrolled reached 70% of the planned sample size of Study C25003, the incidence of febrile neutropenia was higher in the brentuximab vedotin + AVD group than in the ABVD group. Accordingly, the independent data monitoring committee recommended to perform primary prophylaxis with granulocyte colony stimulating factor (G-CSF) for patients in the brentuximab vedotin + AVD group from

Cycle 1. The incidences of neutropenia- and febrile neutropenia-related adverse events with or without G-CSF primary prophylaxis are shown in Table 15.

Table 15. The incidences of neutropenia-and febrile neutropenia-related adverse events with or without G-CSF primary prophylaxis (all Grades, Study C25003)

MedDRA PT (MedDRA/J ver.19.0)	Number of subjects (%)			
	Brentuximab vedotin + AVD 662 subjects		ABVD 659 subjects	
	Without G-CSF 579 subjects	With G-CSF 83 subjects	Without G-CSF 616 subjects	With G-CSF 43 subjects
Neutropenia-and febrile neutropenia-related adverse events	464 (80.1)	37 (44.6)	379 (61.5)	13 (30.2)
Neutropenia	357 (61.7)	25 (30.1)	286 (46.4)	9 (20.9)
Febrile neutropenia	119 (20.6)	9 (10.8)	49 (8.0)	3 (7.0)
Neutrophil count decreased	81 (14.0)	5 (6.0)	79 (12.8)	0
White blood cell count decreased	40 (6.9)	6 (7.2)	34 (5.5)	0
Leukopenia	40 (6.9)	2 (2.4)	34 (5.5)	3 (7.0)
Lymphocyte count decreased	12 (2.1)	3 (3.6)	11 (1.8)	0
Neutropenic sepsis	7 (1.2)	1 (1.2)	2 (0.3)	0
Granulocyte count decreased	2 (0.3)	0	1 (0.2)	0
Lymphopenia	2 (0.3)	0	1 (0.2)	0
Agranulocytosis	1 (0.2)	2 (2.4)	1 (0.2)	0

A neutropenia-and febrile neutropenia-related adverse event resulted in death in 1 subject who did not receive G-CSF primary prophylaxis (0.2%; neutropenic sepsis) in the brentuximab vedotin + AVD group of Study C25003. A causal relationship to the study drug could not be ruled out for the event. Serious neutropenia-and febrile neutropenia-related adverse events occurred in 125 subjects who did not receive G-CSF primary prophylaxis (21.6%; febrile neutropenia [105 subjects], neutropenia [19 subjects], neutropenic sepsis [7 subjects], and neutrophil count decreased [3 subjects]), and 10 subjects with G-CSF primary prophylaxis (12.0%; febrile neutropenia [9 subjects] and neutropenic sepsis [1 subject]). A causal relationship to the study drug could not be ruled out in 123 subjects who did not receive G-CSF primary prophylaxis (21.2%; febrile neutropenia [102 subjects], neutropenia [19 subjects], neutropenic sepsis [7 subjects], and neutrophil count decreased [3 subjects]) and in 9 subjects with G-CSF primary prophylaxis (10.8%; febrile neutropenia [8 subjects] and neutropenic sepsis [1 subject]). Neutropenia-and febrile neutropenia-related adverse events leading to treatment discontinuation occurred in 11 subjects who did not receive G-CSF primary prophylaxis (1.9%; febrile neutropenia [8 subjects] and neutropenia [3 subjects]) and 1 subject with G-CSF primary prophylaxis (1.2%; febrile neutropenia). Neutropenia-and febrile neutropenia-related adverse events leading to dose delay of the study drug(s) occurred in 2 subjects who did not receive G-CSF primary prophylaxis (0.3%; febrile neutropenia and neutropenia [1 subject each]) and did not occur in subjects with G-CSF primary prophylaxis. Neutropenia-and febrile neutropenia-related adverse events leading to dose reduction of the study drug(s) occurred in 22 subjects who did not receive G-CSF primary prophylaxis (3.8%; neutropenia [10 subjects], febrile neutropenia [8 subjects], neutrophil count decreased [3 subjects], white blood cell count decreased [2 subjects], and granulocyte count decreased [1 subject]) and 1 subject with G-CSF primary prophylaxis (1.2%; neutropenia).

The applicant's explanation about preventive measures for neutropenia-and febrile neutropenia-related adverse events following the treatment with brentuximab vedotin + AVD:
Japanese clinical practice guidelines recommend primary prophylaxis with G-CSF when the incidence of febrile neutropenia in patients treated with a chemotherapy regimen is ≥20% (e.g., *Guidelines for proper use of the G-CSF*, 2013 edition, edited by Japan Society of Clinical Oncology, published by Kanehara & Co., Ltd.;2013). In the brentuximab vedotin + AVD group of Study C25003, the incidence of febrile neutropenia in patients who did not receive G-CSF primary prophylaxis was 20.6%. Therefore, G-CSF primary prophylaxis is recommended when administering brentuximab vedotin + AVD in accordance with the clinical practice guidelines.

PMDA's view:
The incidences of Grade ≥3 or serious neutropenia and febrile neutropenia were higher with brentuximab vedotin + AVD than with brentuximab vedotin alone. Therefore, data on the occurrence of neutropenia and febrile neutropenia in the brentuximab vedotin + AVD group of Study C25003 should be shown in the package insert, and healthcare professionals should be appropriately advised to consider the use of G-CSF as primary prophylaxis when treating patients with brentuximab vedotin + AVD by referring to the latest clinical guidelines, etc.

7.R.4 Clinical positioning and indications

The proposed indications for brentuximab vedotin are "The following CD30-positive diseases: Hodgkin's lymphoma, relapsed or refractory anaplastic large-cell lymphoma," which were modified from the approved indications, i.e., "the following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma." The following statements were presented in the "Precautions for Indications" section as they are for the approved indications:

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in CD30 antigen-positive patients confirmed by immunohistochemistry, etc. The positivity of CD30 should be verified by a pathologist or at a laboratory with sufficient experience.

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and in the following subsections, PMDA concluded that the proposed indications and precautions for indications are appropriately defined.

7.R.4.1 Clinical positioning and indications of brentuximab vedotin + AVD treatment

Descriptions of treatment with brentuximab vedotin + AVD in patients with previously untreated cHL in clinical practice guidelines and major textbooks in clinical oncology and hematology published in and outside Japan are as follows.

Clinical practice guidelines

- NCCN Guidelines (v.3.2018): Brentuximab vedotin + AVD is recommended for patients with previously untreated, stage III or IV cHL based on the Ann Arbor staging system (Category 2A[19)] in patients with IPFP risk factors ≥4, or patients in whom bleomycin is contraindicated, and with no neuropathy; Category 2B[20)] in other patients).

The applicant's explanation about the clinical positioning and indications of brentuximab vedotin in patients with previously untreated CD30-positive HL:
The results of Study C25003 conducted in patients with previously untreated advanced stage (Stage III or IV based on the Ann Arbor staging system) cHL demonstrated that brentuximab vedotin + AVD is clinically beneficial [See Sections 7.R.2 and 7.R.3]. Therefore, treatment with brentuximab vedotin + AVD can be recognized as a treatment option for these patients.

Study SGN35-009 demonstrated CR in 6 of 7 patients in a local or regional stage (Stage IIA [only patients with bulky lesions] or Stage IIB, according to the Ann Arbor staging system). The results suggest that the efficacy of brentuximab vedotin has been demonstrated in cHL patients whose disease is in a local or regional stage). However, patients with localized cHL (Stage I or II based on the Ann Arbor staging system) were excluded from Study C25003, and thus it is not known whether treatment with brentuximab vedotin + AVD is clinically beneficial in this patient population. Therefore, brentuximab vedotin + AVD is not recommended in patients with localized cHL.

Furthermore, only patients with histologic type of cHL were eligible for Study C25003, and patients with nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), a non-cHL type of the disease, were excluded. However, given that the majority of cHL patients are CD30-positive while majority of NLPHL patients are CD30- negative (*WHO Classification of Tumours of haematopoietic an Lymphoid Tissues*, Revised 4th Edition, International Agency for Research on Cancer;2017), the histologic type of CD30-positive HL is largely consistent with that of cHL. In addition, 99.5% (1020 of 1025) of subjects (527 of 528 in the brentuximab vedotin + AVD group and 493 of 497 in the ABVD group) in whom CD30 expression was tested[21)] were positive for CD30[22)] in Study C25003, the indications of brentuximab vedotin need not be limited to cHL.

Accordingly, the indications of brentuximab vedotin were defined as "The following CD30-positive diseases: Hodgkin's lymphoma, relapsed or refractory anaplastic large-cell lymphoma" along with the histologic type and disease stages of eligible patients for Study C25003 noted in the "CLINICAL STUDIES" section and the cautionary statements shown below, which have been also presented for the approved indications, in the "Precautions for Indications" section of the package insert.

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19) Based upon lower level evidence, there is uniform NCCN consensus that intervention is appropriate.
20) Based upon lower level evidence, there is NCCN consensus that intervention is appropriate.
21) Approximately 20% of patients in the brentuximab vedotin + AVD group and 26% of patients in the ABVD group failed to obtain a CD30 result, primarily due to inadequate specimens or poor handling of specimens.
22) Specimen were determined to be CD30-positive based on immunohistochemistry-detected CD30 in ≥20% of evaluable lymphocytes.

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in patients who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

PMDA's view:
Based on the applicant's explanation and a premise that brentuximab vedotin is used by physicians with sufficient knowledge and experience in the treatment of haematopoietic malignancies, the "Indication" and "Precautions for Indications" sections should be described as per the applicant's proposal.

7.R.5 Dosage and administration

The proposed dosage and administration of brentuximab vedotin for the treatment of previously untreated CD30-positive HL was "In combination with doxorubicin, vinblastine, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered once daily as an intravenous infusion on Days 1 and 15, followed by a 13-day recovery period from Day 16 through Day 28. This 4-week cycle is repeated. The dose may be reduced as appropriate according to the patient's condition." Further, in the "Precautions for Dosage and Administration" section, the following information was added to the existing statements for the approved indications.

- As a rule, the administration of brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine should be repeated for 6 cycles. The efficacy and safety of treatment exceeding 6 cycles have not been established.
- The efficacy and safety of concomitant use of brentuximab vedotin with antineoplastic drugs other than doxorubicin, vinblastine, dacarbazine, and brentuximab vedotin monotherapy have not been established.
- Treating physicians should administer brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine based on full understanding of "CLINICAL STUDIES" section. The package inserts of the concomitant agents must be read thoroughly.
- Guidelines for dose modification following an adverse drug reaction of brentuximab vedotin

Based on the discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety," as well as in the sections below, PMDA concluded that the dosage and administration and precautions for dosage and administration of brentuximab vedotin should be defined as follows.

Dosage and Administration

- In combination with doxorubicin hydrochloride, vinblastine sulfate and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

Precautions for Dosage and Administration

- The preparation of injectable solution and infusion duration.
- The administration of brentuximab vedotin to patients with hepatic impairment and patients with severe renal impairment.
- If an adverse drug reaction has occurred after administration of brentuximab vedotin, patients should have dose delay, dose reduction, or treatment discontinuation by referring to the following guidelines.

Peripheral neuropathy

Grade*	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Continue dosing at a reduced dose of 0.9 mg/kg.
Grade 3 (interfering with activities of daily living)	Hold dosing until it improves to Grade ≤2. After recovery, resume treatment at a reduced dose of 0.9 mg/kg. Consider dose reduction of a neurotoxic concomitant drug, if any, referring to the package insert.
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

* Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0

Neutropenia

Grade*	Measures
Grade 1 (< LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)	Continue dosing at the same dose regimen.
Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)	Hold dosing until it improves to Grade ≤2 or baseline. After recovery, resume treatment at the same dose regimen.

*, Based on NCI-CTCAE v3.0

7.R.5.1 Dosage and administration of brentuximab vedotin

The applicant's rationale for the proposed dosage and administration of brentuximab vedotin:

In the foreign phase I study (Study SGN35-009) in patients with previously untreated HL, pulmonary toxicity-related adverse events for which a causal relationship to the study drug could not be ruled out occurred in 11 of 25 subjects (pulmonary toxicity [9 subjects], and interstitial lung disease and pneumonitis [1 subject each]) in the brentuximab vedotin + ABVD group (brentuximab vedotin at 0.6, 0.9, or 1.2 mg/kg). In contrast, pulmonary toxicity-related adverse events did not occur in the brentuximab vedotin + AVD group, demonstrating that brentuximab vedotin 1.2 mg/kg used with AVD was tolerable. Therefore, the dosage regimen of brentuximab vedotin for Study C25003 was specified as brentuximab vedotin 1.2 mg/kg intravenously administered once daily on Days 1 and 15 of each 28-day cycle in combination with AVD.

The results of Study C25003 demonstrated that brentuximab vedotin + AVD is clinically beneficial in patients with previously untreated cHL [See Sections 7.R.2 and 7.R.3]. Therefore, the proposed dosage and administration of brentuximab vedotin were specified based on the dosage regimen of the study.

PMDA accepted the applicant's explanation.

7.R.5.2 Number of treatment cycles (number of doses) of brentuximab vedotin

The applicant's explanation about the number of treatment cycles of brentuximab vedotin:

In the primary therapy of advanced stage cHL, whether a patient is transferred to follow-up period or switched to a subsequent therapy is often determined after the completion of Cycle 6 based on an efficacy assessment. Therefore, in Study C25003, the brentuximab vedotin + AVD regimen was continued up to 6 cycles unless disease progression or discontinuation criterion met. Based on the clinical benefits of the brentuximab vedotin + AVD regimen demonstrated by Study C25003 and the completion of the 6-cycle regimen by 593 of 662 subjects (89.6%), the administration of brentuximab vedotin + AVD for 6 cycles is recommended for patients who has no difficulty receiving it. The "Precautions for Dosage and Administration" section will mention that brentuximab vedotin + AVD should be administered for 6 cycles as a rule. No clinical study data are available on the efficacy and safety of the brentuximab vedotin + AVD regimen in >6 cycles. Nevertheless, (1) there are no data suggestive of safety concerns with >6 cycle-treatment and (2) the Japanese clinical practice guidelines (*Clinical Practice Guidelines for Hematopoietic Tumor*, 2013 edition, the Japanese Society of Hematology, Kanehara & Co., Ltd.;2013) recommend 6- to 8-cycle ABVD therapy. Limiting the number of treatment cycles is therefore considered not necessary.

PMDA's view:

Because of the lack of clinical study data on the brentuximab vedotin + AVD regimen repeated for >6 cycles in patients with previously untreated advanced stage cHL, the efficacy and safety of the regimen are unknown. Treatment with brentuximab vedotin + AVD for >6 cycles is thus not recommended at present. Due to the possibility that brentuximab vedotin + AVD be administered at 2-week intervals, the number of doses of brentuximab vedotin should be limited to no more than 12 times in the "Dosage and Administration" section.

7.R.5.3 Concomitant use of brentuximab vedotin with antineoplastic drugs and brentuximab vedotin monotherapy

The applicant's explanation:

No clinical study results have been obtained regarding the concomitant use of brentuximab vedotin with antineoplastic drugs other than AVD, or brentuximab vedotin monotherapy in patients with previously untreated CD30-positive HL. The following cautionary statement will be presented in the "Precautions for Dosage and Administration" section.

Precautions for Dosage and Administration

- The efficacy and safety of concomitant use of brentuximab vedotin with antineoplastic drugs other than doxorubicin, vinblastine, and dacarbazine and brentuximab vedotin monotherapy have not been established.

PMDA's view:

The efficacy and safety of brentuximab vedotin used with antineoplastic drugs other than AVD or brentuximab vedotin alone in patients with previously untreated CD30-positive HL are unknown. These treatments are thus not recommended in patients with previously untreated CD30-positive HL at present. The "Dosage and

administration" section should state clearly that brentuximab vedotin must be used in combination with doxorubicin, vinblastine, and dacarbazine. Where the concomitant drugs are specifically mentioned, there will be little need for the above cautionary statement to be presented in the "Precautions for Dosage and Administration" section as suggested by the applicant.

7.R.5.4 Dose modification of brentuximab vedotin

PMDA asked the applicant to give an explanation about dose modification of brentuximab vedotin.

The applicant's explanation:

In Study C25003, brentuximab vedotin was well tolerated when the recommended guidelines for treatment discontinuation, dose delay, and reduction were followed. The "Precautions for Dosage and Administration" section presents dose modification criteria for brentuximab vedotin based on the criteria used in Study C25003 with the following changes:

- In Study C25003, dose delay was recommended for all study drugs following Grade 3 or 4 non-hematological toxicity events other than peripheral neuropathy, until recovery to Grade ≤2 or baseline. However, they were not recognized as compulsory criteria, and dose modification would be feasible at the discretion of the treating physician following the onset of event depending on the patient's condition. Accordingly, dose modification criteria following Grade 3 or 4 non-hematological toxicity events other than peripheral neuropathy were not considered necessary. In Study C25003, Grade 3 or 4 non-hematological toxicity events other than peripheral neuropathy led to dose delay of brentuximab vedotin + AVD in 4 patients (constipation, device related infection, pneumonitis, and rash macular [1 patient each]), and actions other than dose delay of brentuximab vedotin were taken for many patients (dose postponement in 107 subjects and dose reduction in 22 subjects).
- In Study C25003, there were no recommended dose modification criteria for Grade 3 or 4 hematotoxicity, and each study center was required to cope with the event by following its own policy. However, neutropenia led to dose modification in a number of subjects [See Section 7.R.3.2] in Study C25003. Therefore, the dose modification criteria of brentuximab vedotin following neutropenia were defined as per the relevant criteria for the approved indications.

PMDA's view:

The applicant's explanation was largely acceptable. Healthcare professionals should be appropriately provided with written materials, etc. detailing dose modification of brentuximab vedotin following the onset of Grade 3 or 4 non-hematological events other than peripheral neuropathy which was used in Study C25003.

7.R.6 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance in patients with previously untreated CD30-positive HL receiving brentuximab vedotin to investigate the safety, etc. of the product in the post-marketing clinical setting.

Based on the occurrence of adverse events in Study C25003, bone marrow depression (neutropenia and febrile neutropenia) was selected as the safety specification for the survey.

The planned sample size is 100, according to the incidence of febrile neutropenia in Study C25003.

The observation period begins at the start of treatment with brentuximab vedotin and ends at the completion of Cycle 6.

PMDA's view:
There are limited safety data of Japanese patients treated with brentuximab vedotin + AVD. The results of Study C25003 and a foreign phase II study (Study SG035-003) in patients with relapsed or refractory CD30-positive HL revealed that febrile neutropenia occurred more frequently in patients with previously untreated CD30-positive HL receiving brentuximab vedotin + AVD than in those receiving brentuximab vedotin alone. The occurrence of febrile neutropenia (including severity, measures, and outcome) need to be further investigated in actual clinical use. The survey therefore should aim to investigate the occurrence of bone marrow depression (neutropenia and febrile neutropenia) as the applicant proposed.

The planned sample size and the duration of the observation period planned by the applicant are acceptable.

7.R.7 Development for pediatric use

PMDA asked the applicant about the progress in the development of brentuximab vedotin for children with previously untreated HL.
The applicant's explanation:
A global phase II study of brentuximab vedotin + AVD in children with previously untreated CD30-positive HL is ongoing, and the results will be available in [redacted] 20[redacted]. The discussion will begin as soon as the study results are available on a partial change application for an additional dosage regimen for pediatric patients with previously untreated CD30-positive HL in Japan.

PMDA accepted the applicant's explanation.

7.2 Adverse events and other findings observed in clinical studies

The following sections describe major adverse events included in the results of clinical studies submitted for safety evaluation, except the results for death, which are described in Section "7.1 Evaluation data."

7.2.1 Global phase III study (Study C25003)

Adverse events occurred in 653 of 662 subjects (98.6%) in the brentuximab vedotin + AVD group and 646 of 659 subjects (98.0%) in the ABVD group. A causal relationship between the study drug(s) and events could not be ruled out in 641 of 662 subjects (96.8%) in the brentuximab vedotin + AVD group and 617 of 659 subjects (93.6%) in the ABVD group. Adverse events that occurred at an incidence of ≥20% in either group are presented in Table 16.

Table 16. Adverse events that occurred at an incidence of ≥20% in either group

System organ class (SOC) PT (MedDRA/J ver.19.0)	Number of subjects (%)			
	Brentuximab vedotin + AVD 662 subjects		ABVD 659 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	653 (98.6)	549 (82.9)	646 (98.0)	434 (65.9)
Gastrointestinal disorders				
Nausea	348 (52.6)	20 (3.0)	371 (56.3)	7 (1.1)
Constipation	279 (42.1)	11 (1.7)	241 (36.6)	4 (0.6)
Vomiting	216 (32.6)	23 (3.5)	183 (27.8)	9 (1.4)
Diarrhoea	181 (27.3)	19 (2.9)	121 (18.4)	5 (0.8)
Stomatitis	138 (20.8)	10 (1.5)	104 (15.8)	3 (0.5)
Abdominal pain	142 (21.5)	21 (3.2)	65 (9.9)	4 (0.6)
Nervous system disorders				
Peripheral sensory neuropathy	189 (28.5)	31 (4.7)	111 (16.8)	3 (0.5)
Neuropathy peripheral	174 (26.3)	27 (4.1)	85 (12.9)	6 (0.9)
Blood and lymphatic system disorders				
Neutropenia	382 (57.7)	357 (53.9)	295 (44.8)	260 (39.5)
Anaemia	140 (21.1)	54 (8.2)	67 (10.2)	25 (3.8)
General disorders and administration site conditions				
Fatigue	211 (31.9)	19 (2.9)	211 (32.0)	7 (1.1)
Pyrexia	179 (27.0)	19 (2.9)	147 (22.3)	13 (2.0)
Skin and subcutaneous tissue disorders				
Alopecia	173 (26.1)	1 (0.2)	146 (22.2)	0
Investigations				
Weight decreased	148 (22.4)	6 (0.9)	40 (6.1)	1 (0.2)

Serious adverse events occurred in 284 of 662 subjects (42.9%) in the brentuximab vedotin + AVD group and 178 of 659 subjects (27.0%) in the ABVD group. Serious adverse events that occurred in ≥10 subjects in the brentuximab vedotin + AVD group were febrile neutropenia (114 subjects; 17.2%), pyrexia (44 subjects; 6.6%), neutropenia (19 subjects; 2.9%), pneumonia (18 subjects; 2.7%), abdominal pain (14 subjects; 2.1%), sepsis (14 subjects; 2.1%), constipation (11 subjects; 1.7%), diarrhoea (11 subjects; 1.7%), pulmonary embolism (11 subjects; 1.7%), vomiting (11 subjects; 1.7%), and dehydration (10 subjects; 1.5%); and those in the ABVD group were febrile neutropenia (43 subjects; 6.5%), pyrexia (28 subjects; 4.2%), pneumonia (15 subjects; 2.3%), and pneumonitis (12 subjects; 1.8%). A causal relationship to the study drug(s) could not be ruled out for febrile neutropenia (110 subjects), pyrexia (39 subjects), neutropenia (19 subjects), pneumonia (14 subjects), sepsis (13 subjects), abdominal pain (11 subjects), constipation (10 subjects), vomiting (10 subjects), diarrhoea (9 subjects), dehydration (6 subjects), and pulmonary embolism (5 subjects) in the brentuximab vedotin + AVD group; and febrile neutropenia (38 subjects), pyrexia (21 subjects), pneumonitis (10 subjects), and pneumonia (9 subjects) in the ABVD group.

Adverse events led to discontinuation of the study drug(s) in 88 of 662 subjects (13.3%) in the brentuximab vedotin + AVD group and 105 of 659 subjects (15.9%) in the ABVD group. Adverse events leading to discontinuation of the study drug(s) in ≥10 subjects in the brentuximab vedotin + AVD group were peripheral sensory neuropathy (23 subjects, 3.5%), neuropathy peripheral (16 subjects, 2.4%), and peripheral motor neuropathy (10 subjects, 1.5%); and those in the ABVD group were dyspnoea (25 subjects, 3.8%), pulmonary toxicity (12 subjects, 1.8%), cough (12 subjects, 1.8%), and carbon monoxide diffusing capacity decreased (10

subjects, 1.5%). A causal relationship to the study drug(s) could not be ruled out for peripheral sensory neuropathy (23 subjects), neuropathy peripheral (14 subjects), and peripheral motor neuropathy (10 subjects) in the brentuximab vedotin + AVD group; and dyspnoea (25 subjects), pulmonary toxicity (11 subjects), cough (11 subjects), and carbon monoxide diffusing capacity decreased (8 subjects) in the ABVD group.

7.2.2 Foreign phase I study (Study SGN35-009)

Adverse events occurred in 24 of 25 subjects (96.0%) in the brentuximab vedotin + ABVD group and 26 of 26 subjects (100%) in the brentuximab vedotin + AVD group. A causal relationship between brentuximab vedotin and events could not be ruled out in 22 of 25 subjects (88.0%) in the brentuximab vedotin + ABVD group, and 26 of 26 subjects (100%) in the brentuximab vedotin + AVD group. Adverse events that occurred at an incidence of ≥30% in either group are presented in Table 17.

Table 17. Adverse events that occurred at an incidence of ≥30% in either group

SOC PT (MedDRA/J ver.15.1)	Number of subjects (%)			
	Brentuximab vedotin + ABVD 25 subjects		Brentuximab vedotin + AVD 26 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	24 (96.0)	22 (88.0)	26 (100)	21 (80.8)
Gastrointestinal disorders				
Nausea	18 (72.0)	0	22 (84.6)	0
Vomiting	15 (60.0)	0	11 (42.3)	0
Constipation	12 (48.0)	0	9 (34.6)	0
Diarrhoea	6 (24.0)	0	11 (42.3)	0
Blood and lymphatic system disorders				
Neutropenia	20 (80.0)	20 (80.0)	20 (76.9)	20 (76.9)
General disorders and administration site conditions				
Pyrexia	14 (56.0)	1 (4.0)	3 (11.5)	0
Fatigue	11 (44.0)	1 (4.0)	13 (50.0)	1 (3.8)
Chills	11 (44.0)	0	2 (7.7)	0
Investigations				
Weight decreased	8 (32.0)	0	5 (19.2)	0
Musculoskeletal and connective tissue disorders				
Bone pain	5 (20.0)	0	10 (38.5)	0
Nervous system disorders				
Peripheral sensory neuropathy	18 (72.0)	0	19 (73.1)	1 (3.8)
Headache	9 (36.0)	0	4 (15.4)	0
Psychiatric disorders				
Insomnia	7 (28.0)	0	10 (38.5)	0
Respiratory, thoracic and mediastinal disorders				
Pulmonary toxicity	9 (36.0)	6 (24.0)	0	0
Cough	9 (36.0)	1 (4.0)	3 (11.5)	0
Pulmonary toxicity	8 (32.0)	3 (12.0)	6 (23.1)	1 (3.8)
Skin and subcutaneous tissue disorders				
Alopecia	9 (36.0)	0	9 (34.6)	0

Serious adverse events occurred in 14 of 25 subjects (56.0%) in the brentuximab vedotin + ABVD group and 7 of 26 subjects (26.9%) in the brentuximab vedotin + AVD group. Serious adverse events that occurred in ≥2 subjects in the brentuximab vedotin + ABVD group were pulmonary toxicity (6 subjects; 24.0%), febrile neutropenia (4 subjects; 16.0%), pyrexia (3 subjects; 12.0%), dyspnoea (2 subjects; 8.0%); and those in the

brentuximab vedotin + AVD group were febrile neutropenia (2 subjects; 7.7%). A causal relationship to brentuximab vedotin could not be ruled out for all these events.

Adverse events led to discontinuation of brentuximab vedotin in 6 of 25 subjects (24.0%) in the brentuximab vedotin + ABVD group and 3 of 26 subjects (11.5%) in the brentuximab vedotin + AVD group. These adverse events were peripheral sensory neuropathy (3 subjects; 12.0%), dyspnoea (2 subjects; 8.0%), hyponatraemia (1 subject; 4.0%), in the brentuximab vedotin + ABVD group and peripheral sensory neuropathy (2 subjects; 7.7%), peripheral motor neuropathy (1 subject; 3.8%) in the brentuximab vedotin + AVD group. A causal relationship to brentuximab vedotin could not be ruled out for all these events.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that brentuximab vedotin has efficacy in the treatment of previously untreated CD30-positive HL, and that brentuximab vedotin has acceptable safety in view of its benefits. Brentuximab vedotin is clinically significant because it offers a new treatment option for patients with previously untreated CD30-positive HL. The indications, dosage and administration, and other aspects of brentuximab vedotin should be further evaluated.

PMDA has concluded that brentuximab vedotin may be approved if brentuximab vedotin is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 3, 2018

Product Submitted for Approval

Brand Name	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	January 31, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As reviewed in Section "7.R.2 Efficacy" of Review Report (1), in the global phase III study (Study C25003) conducted in patients with previously untreated advanced stage cHL, brentuximab vedotin + AVD was superior to the control (ABVD) in the primary endpoint of centrally reviewed mPFS. Accordingly, PMDA concluded that the efficacy of brentuximab vedotin has been demonstrated in patients with previously untreated advanced stage cHL

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors:

- In Study C25003, the incidence of neutropenia was higher in the brentuximab vedotin + AVD group than in the ABVD group [See Section 7.R.3.2 of Review Report (1)], suggesting that hematopoietic stem cells may be suppressed by brentuximab vedotin + AVD. Therefore, it is encouraged to investigate the impact of brentuximab vedotin + AVD on the efficiency in the collection of hematopoietic stem cells from relapsed patients undergoing high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HDC/ASCT).

Based on the discussion at the Expert Discussion, PMDA asked the applicant to explain the impact of the brentuximab vedotin + AVD in patients with previously untreated cHL on the efficiency in hematopoietic stem cell collection prior to HDC/ASCT.

The applicant's explanation:
The following observations indicate that the brentuximab vedotin + AVD is unlikely to adversely affect the efficiency in hematopoietic stem cell collection from relapsed patients with previously untreated cHL undergoing HDC/ASCT.

- In Study C25003, data on the efficiency in hematopoietic stem cell collection were not obtained from patients who had undergone the procedure after the completion of the front-line therapy. However, 16 subjects in the brentuximab vedotin + AVD group and 17 subjects in the ABVD group underwent HDC/ASCT as the secondary therapy.
- According to a published article, when patients with relapsed or refractory CD30-positive malignant lymphoma underwent HDC/ASCT after salvage chemotherapy including brentuximab vedotin, the salvage chemotherapy did not adversely affect the efficiency in hematopoietic stem cell collection (*Biol Blood Marrow Transplant.* 2015;21:1529-31).

PMDA's view:
At present, lack of clinical study data precludes a definite conclusion on the effect of brentuximab vedotin + AVD on hematopoietic stem cell collection efficiency. Relevant data, for being crucial for the implementation of subsequent therapy, should be further collected from patients with relapsed previously untreated cHL in the post-marketing setting. Available new findings should be communicated to healthcare professionals promptly.

Based on the above, PMDA instructed the applicant to take appropriate measures according to the above advice. The applicant agreed.

1.2 Safety

Based on the discussion in Section "7.R.3 Safety" of Review Report (1), PMDA concluded that treatment with brentuximab vedotin in patients with previously untreated cHL requires vigilance for adverse events, in particular, infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome, lung disorder, pancreatitis acute, and hepatic dysfunction. All these events have previously been identified as attention-requiring adverse events during the review for the approved indication.

PMDA further concluded that brentuximab vedotin treatment, although requires due vigilance for these adverse events, is tolerable in patients with previously untreated cHL as well when appropriate follow-up, i.e., monitoring and managing of adverse events, dose delay of brentuximab vedotin, etc., is performed by physicians with sufficient knowledge and experience in the treatment of haematopoietic malignancies.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indications

Based on the discussion in Section "7.R.4 Clinical positioning and indications" of Review Report (1), PMDA concluded that the indications of brentuximab vedotin should be defined as "The following CD30-positive diseases: Hodgkin's lymphoma, relapsed or refractory anaplastic large-cell lymphoma" as per the applicant's proposal. Further, the "CLINICAL STUDIES" section of the package insert should mention the histologic type and disease stages of eligible patients for Study C25003, and the "Precautions for Indications" section should give the following cautionary statements, which have been also given for the approved indications.

Precautions for Indications

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to define the "Indications" and "Precautions for Indications" as above. The applicant agreed.

1.4 Dosage and administration

Based on the discussion in Section "7.R.5 Dosage and administration" of Review Report (1), PMDA concluded that the dosage regimen of brentuximab vedotin should be defined as "In combination with doxorubicin hydrochloride, vinblastine sulfate, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition," with the following information provided in the "Precautions for Dosage and Administration" section.

Precautions for Dosage and Administration

- The preparation method of injectable solution and infusion duration
- The administration of brentuximab vedotin to patients with hepatic impairment or severe renal impairment.
- Criteria for dose modification following an adverse drug reaction of brentuximab vedotin.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to define dosage and administration and precautions for dosage and administration as above. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance in patients with previously untreated CD30-positive HL who receiving brentuximab vedotin to investigate bone marrow depression (neutropenia and febrile neutropenia) in the post-marketing clinical setting. The target sample size is 100 patients. The observation period begins with the start of treatment with brentuximab vedotin and ends with the completion of Cycle 6.

Based on the discussion in Section "7.R.6 Post-marketing investigations" of Review Report (1), PMDA concluded that the applicant 's decision to conduct post-marketing surveillance aiming to investigate bone marrow depression (neutropenia and febrile neutropenia) is appropriate, and the details of the post-marketing surveillance plan shown above are acceptable.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above discussion, PMDA concluded that the risk management plan (draft) should include the safety specification presented in Table 18 and that the applicant should implement additional pharmacovigilance and risk minimization activities presented in Tables 19 and 20.

Table 18. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Peripheral neuropathy • Infections • Progressive multifocal leukoencephalopathy (PML) • Bone marrow depression • Infusion reaction • Tumour lysis syndrome • Stevens-Johnson syndrome • Pancreatitis acute • Hepatic dysfunction • Lung disorder	• Gastrointestinal disorder • Reproductive toxicity • Depletion of thymic lymphoid tissue • Interactions with CYP3A4 inhibitors	Not applicable
Efficacy specification		
• Not applicable		

No changes in the partial change application

Table 19. Summary of additional pharmacovigilance and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Survey/study on efficacy	Additional risk minimization activities
• Use-results survey in patients with previously untreated CD30-positive HL • Post-marketing clinical study (extension study of Study C25003)	• Not applicable	• Preparation and dissemination of guidance materials for healthcare professionals

Underline denotes planned activities for the new indications to be added

Table 20. Outline of post-marketing surveillance (draft)

Objective	To investigate the occurrence of neutropenia and febrile neutropenia following the administration of brentuximab vedotin + AVD in the post marketing clinical setting
Survey method	Central registration method
Population	Patients with previously untreated CD30-positive HL receiving brentuximab vedotin
Observation period	From the start of treatment with brentuximab vedotin and until 2 weeks after the completion of 12 doses (1 dose every 2 weeks)
Planned sample size	100 patients
Main survey items	Safety specification: bone marrow depression (neutropenia and febrile neutropenia) Other main survey items: patient characteristics (e.g., age, sex, disease stage classification, medical history, and complications), status of treatment with brentuximab vedotin, status of treatment with a concomitant chemotherapy

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and dosage and administration as shown below, with the following conditions. The approval is however predicated on the due provision of appropriate cautions and information through the package insert about the proper use of the product in the post-marketing setting, and on due adherence to the proper use of the product under the supervision of a physician with sufficient knowledge and experience in the treatment of haematopoietic malignancies at medical institutions fully capable of emergency care. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until January 16, 2024).

Indications (Underline denotes additions; strikethrough denotes deletions)

The following ~~relapsed or refractory~~ CD30-positive diseases:

Hodgkin's lymphoma

<u>Relapsed or refractory</u> anaplastic large-cell lymphoma

Dosage and Administration (Underline denotes additions)

1. Previously untreated CD30-positive Hodgkin's lymphoma

In combination with doxorubicin hydrochloride, vinblastine sulfate and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

2. Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma

The usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

1. The product should be administered only to patients considered eligible for brentuximab vedotin therapy under the supervision of a physician with sufficient knowledge and experience in treatment of haematopoietic malignancies at a medical institution well-equipped to cope with emergencies. Consent should be obtained, prior to treatment, from the patient or his/her family member who has been fully informed of the benefits and risks of the therapy.
2. Fungal infection with a fatal outcome after administration of brentuximab vedotin in patients with moderate or severe hepatic impairment has been reported from foreign clinical studies. The use of brentuximab vedotin should be carefully determined in these patients.

Contraindications (No change)

1. Patients with a history of severe hypersensitivity to any ingredients of the product
2. Patients who are receiving bleomycin

Precautions for Indications (No change)

1. Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
2. Brentuximab vedotin should be used in patients who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

Precautions for Dosage and Administration (Underline denotes additions)

1. Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma
   The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established.
2. Preparation of injectable solution and infusion duration:
   Reconstitute the contents of one vial with 10.5 mL of Water for Injection (JP), and dilute a suitable volume with Isotonic Sodium Chloride Solution (JP) or 5% Glucose Injection (JP) to make a 0.4 to 1.2 mg/mL solution. The diluted solution should be intravenously infused over at least 30 minutes.
3. Since blood concentrations of monomethyl auristatin E (MMAE; a component of brentuximab vedotin) increase in patients with hepatic impairment or severe renal impairment, dose reduction should be considered. These patients should be closely monitored and caution should be exercised for occurrence of adverse events.
4. If an adverse drug reaction occurred after administration of brentuximab vedotin, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Peripheral neuropathy
1) Previously untreated CD30-positive Hodgkin's lymphoma

Grade *Note	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Continue dosing at a reduced dose of 0.9 mg/kg.
Grade 3 (interfering with activities of daily living)	Hold dosing until it improves to Grade ≤2. After recovery, resume treatment at a reduced dose of 0.9 mg/kg. Consider dose reduction of a neurotoxic concomitant agent, if any, referring to the package insert.
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

2) Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma

Grade*Note	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Hold dosing until it improves to Grade ≤1 or baseline. After recovery, resume treatment at a reduced dose of 1.2 mg/kg.
Grade 3 (interfering with activities of daily living)	
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

Neutropenia (for all indications)

Grade*Note	Measures
Grade 1 (< LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)	Continue dosing at the same dose regimen.
Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)	Hold dosing until it improves to Grade ≤2 or baseline. After recovery, resume treatment at the same dose regimen.

* Based on NCI-CTCAE v3.0

Appendix

List of Abbreviations

ABC transporter	ATP binding cassette transporter
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
ALCL	Anaplastic large cell lymphoma
ALT	Alanine aminotransferase
ATP	Adenosine triphosphate
AVD	Doxorubicin, vinblastine, and dacarbazine
Bleomycin	Bleomycin hydrochloride
Brentuximab vedotin + ABVD	Brentuximab vedotin used in combination with doxorubicin, bleomycin, vinblastine, and dacarbazine
Brentuximab vedotin + AVD	Brentuximab vedotin used in combination with doxorubicin, vinblastine, and dacarbazine
cHL	Classical Hodgkin's lymphoma
CR	Complete remission
CYP	Cytochrome P450
DLT	Dose limiting toxicity
Doxorubicin	Doxorubicin hydrochloride
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
G-CSF	Granulocyte colony stimulating factor
HDC/ASCT	High-dose chemotherapy with autologous hematopoietic stem cell transplantation
HL	Hodgkin's lymphoma
HRP	Horseradish peroxidase
Ig	Immunoglobulin
IPFP	International Prognostic Factors Project (*N Engl J Med.* 1998;339:1506-14)
ITT	Intent to treat
IWG criteria	International Working Group criteria
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMAE	Monomethyl auristatin E
mPFS	Modified progression free survival
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
OS	Overall survival
PET	Positron emission tomography
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred term
SMQ	Standardized MedDRA query
SOC	System organ class
Total antibody	MMAE-conjugated and free anti-human CD30 monoclonal antibodies
U	Unit
Vinblastine	Vinblastine sulfate