Title: Special Drug Use Surveillance of Adcetris IV Infusion (All-Case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

NCT Number: NCT02139592

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Note; This document was translated into English as the language on original version was Japanese.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Adcetris IV Infusion

(All-Case Surveillance)

“Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma”

Version number	**5**
Date of creation	**June 2, 2017**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

There is limited safety information on Adcetris IV Infusion 50 mg (hereinafter referred to as Adcetris) collected from Japanese patients in Japanese phase 1/2 studies. It is important to promptly collect post-marketing safety information and provide it to healthcare providers. It was also deemed that additional surveillance was required to determine the occurrence of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders in patients using Adcetris in Japan as post-marketing safety specifications.

Thus, an all-case surveillance in all patients receiving treatment with Adcetris will be initiated as an additional pharmacovigilance activity for Adcetris when the drug is launched.

This surveillance study will be conducted in compliance with the GPSP Ordinance and other related regulatory requirements.

2.0 Purpose

The purpose of this study is to evaluate the safety of Adcetris in patients with relapsed/refractoryCD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma in the routine clinical setting, as well as to collect efficacy information for reference.

3.0 Estimated Enrollment and Its Rationale

3.1 Estimated enrollment

140 patients (with relapsed/refractory CD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma)

3.2 Rationale

It is expected that the detailed evaluation of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders will help better understand the safety profile of Adcetris in the routine clinical setting, which will lead to the assessment of the risk-benefit balance of the drug.

The frequencies of peripheral nerve disorders, infections, neutropenia (≥Grade 3), infusion reaction, and pulmonary disorder in non-Japanese phase 2 studies (pooled study data from a study in patients with Hodgkin's lymphoma [SG035-0003, 102 patients] and a study in patients with systemic anaplastic large cell lymphoma [SG035-0004, 58 patients]) were 56%, 61%, 20%, 11%, and 6%, respectively.

Observation of infusion reactions with the lowest frequency of ≥10 patients, aside from pulmonary disorders, with a probability of 95% would require 140 patients, which was therefore determined to be the estimated enrollment. It is estimated that when the number of patients enrolled reaches 140 patients, ≥4 patients have adverse events of pulmonary disorder with a probability of 95%.

4.0 Eligible Patients

All patients receiving treatment with Adcetris

5.0 Dosage Regimen

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (recombinant) infused intravenously once every three weeks. The dose should be adjusted depending on the patient's condition.

See the "PRECAUTIONS" section of the package insert.

6.0 Expected Study Institutions by Department

The study will be conducted at all institutions using Adcetris (e.g., department of hematology) (approximately 100 study institutions are expected to participate in the study).

7.0 Methods

7.1 Observation period

From the start of treatment with Adcetris until the completion of 16 cycles [3 weeks per cycle]

* Rationale for the selection of the observation period

The assessment of the treatment cycle with the initial onset of adverse events in a clinical study [SGN35-006, the extended treatment group] evaluating the safety of Adcetris after Cycle 17 showed a tendency that most adverse events occurred before Cycle 16. In addition, the types and severities did not differ between adverse events occurring after Cycle 17 and those occurring before Cycle 16. This suggested that the safety profile of Adcetris would be generally determined before Cycle 16. Therefore, the observation period was defined as the period from the start of treatment with Adcetris until the completion of 16 cycles.

7.2 Request for participation in this study and contract with each study institution

Paper-based case report forms will be used. To ask each study institution to participate in the study, the representative of Takeda Pharmaceutical Company Limited (representative of Takeda) will confirm before supply of Adcetris and the start of the study that each study institution meets all requirements for study institutions and investigators specified below, and have a written contract with the study institution after prior explanation of the study provided before supply of Adcetris.

(1) Requirements for each study institution and investigator

1) Requirements for each study institution

[1] Is able to cooperate with this all-case surveillance and have a contract with the sponsor.

[2] Is able to provide specialized treatment for hematopoietic tumors.

[3] Is able to provide emergency treatment if required (including a case where such a treatment can be provided in conjunction with another institution

).

* When emergency treatment is provided in conjunction with another institution, information on Adcetris safety measures and treatment of adverse drug reactions should be shared between the institution and the other institution to build a coalition.

2) Requirements for each investigator

[1] Has adequate knowledge and experience regarding the treatment of hematopoietic tumors, or is under the direction of a healthcare professional having such knowledge and experience.

[2] Is able to cooperate with this all-case surveillance.

(2) Prior explanation of the study to be provided before supply of Adcetris and the request for participation in this study

Using "Request for Participation in the Special Drug Use Surveillance," "Study Outline," "Patient Enrollment Form (sample)," "Case Report Form Parts 1 and 2 (sample)," "Precautions for Use/Instruction Manual," and "Proper Usage Guide," the representative of Takeda will explain the purpose and methods (e.g., all-case surveillance) of this survey study and information regarding the proper use of Adcetris to the investigator and ask him/her to participate in the all-case surveillance.

The representative of Takeda will also confirm with the investigator that the institution and the investigator meet all requirements.

(3) Request for participation in this study and contract with each study institution

The representative of Takeda will have a written contract with the study institution after obtaining their agreement to participate in this study Takeda Pharmaceutical Company Limited will inform the outsourced Adcetris supplier that the contract is concluded and Adcetris should be supplied to the study institution. The representative of Takeda will deliver patient enrollment forms to the investigator.

7.3 Method of patient enrollment

The central enrollment method via FAX will be used. For each patient scheduled to receive treatment with Adcetris after the date of the start of the term of the contract with the study institution, the investigator will complete patient enrollment by submitting the Patient Enrollment Form with information required for patient enrollment filled in (see Section 9.1) via FAX to the Central Enrollment Center (see Section 12.3) until noon of the day before the date of the expected initial dose of Adcetris.

The Central Enrollment Center will review the Patient Enrollment Form and send the Enrollment Completion Notice to the investigator via FAX. After receiving the Enrollment Completion Notice, the investigator will initiate treatment with Adcetris.

The Case Report Form consists of Parts 1 and 2 per patient.

The representative of Takeda will deliver Case Report Form Part 1, which is issued after enrollment confirmation by the Central Enrollment Center, to the investigator. Case Report Form Part 2 is issued after Takeda Pharmaceutical receives Case Report Form Part 1.

7.4 Completion and submission of the case report form

For all patients requiring the completion of the case report form, the investigator will complete the case report form during the period from the start of treatment with Adcetris until the end of Cycle 4 and within 1 month after the end of Cycle 16, and submit it to the representative of Takeda.

If treatment with Adcetris is discontinued for any reason before the end of the observation period, the investigator will complete the case report form within 1 month after the completion of required observation submit it to the representative of Takeda. If treatment with Adcetris is discontinued due to any adverse event, however, the investigator will continue to observe the patient after treatment discontinuation until the adverse event resolves or improves wherever possible, and then complete the case report form and submit it to the representative of Takeda.

7.5 Confirmation of all-case surveillance

After the completion of the study, the principal investigator will confirm that case report forms of all patients treated with Adcetris have been submitted, and sign or fill in his/her name with seal on All-Case Surveillance Confirmation Form and submit it to the representative of Takeda.

8.0 Estimated Study Period

Study period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Patient enrollment period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

The expected number of enrolled patients (140) was achieved. Therefore, the study will move to the period only requiring patient enrollment (not requiring the completion and submission of case report forms).

After moving to the period only requiring patient enrollment, it may be required to complete and submit case report forms upon request by the regulatory authority.

9.0 Outcome Measures

The investigator will record data listed below in both Patient Enrollment and Case Report Forms. Study schedule is provided in in Appendix 1.

9.1 Data to be recorded in Patient Enrollment Form

1) Outcome measures

Name of the institution, name of the investigator completing Patient Enrollment Form, expected date of the start of treatment with Adcetris, patient identification number, patient initial, sex, date of birth, diagnosis, performance status, CD30, past history of severe hypersensitivity to any ingredient of Adcetris, expected concomitant use of other antineoplastic drugs, and presence/absence of infections, peripheral nerve disorders, hepatic disorders, severe renal disorders, or pregnancy/breast-feeding

2) When to collect outcome measure data

At the time of patient enrollment

9.2 Data to be recorded in Case Report Form

9.2.1 Cover sheet of Case Report Form

Date of the finial completion of Case Report Form and name of the investigator completing Case Report Form

9.2.2 Patient demographics and baseline characteristics

1) Outcome measures

Date of diagnosis of Hodgkin's or anaplastic large cell lymphoma, site of involvement, ALK (in patients with anaplastic large cell lymphoma), clinical stage, presence/absence of B symptoms, ECOG Performance Status, therapeutic category, (presence/absence and detail of) hypersensitivity disposition, viral test results, past history of and concurrent pulmonary disorders, past history of and concurrent malignant tumours, (presence/absence and detail of) concurrent illnesses [other than pulmonary disorders and malignant tumours], (presence/absence and detail of) past history[other than pulmonary disorders and malignant tumours], height, weight, smoking history, and (presence/absence and detail of) prior treatment for Hodgkin's lymphoma or anaplastic large cell lymphoma (including drug therapy, radiotherapy, and hematopoietic stem cell transplantation)

2) When to collect outcome measure data

At the start of treatment with Adcetris

9.2.3 Treatment given

1) Outcome measures

Treatment with Adcetris and premedication to prevent infusion reaction (dose, date of premedication, and reasons for premedication to prevent infusion reaction and its discontinuation), (use or non-use, type, and date of) post-baseline hematopoietic stem cell transplantation, (presence/absence, name, and duration of) drugs other than Adcetris used for the treatment of the primary disease, and (presence/absence, name, and duration of) drugs used for the prevention of infection

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4 Tests and assessments

9.2.4.1 Laboratory tests

1) Outcome measures

Red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, total bilirubin, AST, ALT, LDH, BUN, and serum creatinine

2) When to collect outcome measure data

At each test time point during the period from the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4.2 Best response

1) Outcome measures

The best response (CR, CRu [for patients with no PET scan data], PR, SD, or PD) will be assessed based on CT and PET scans of the neck, chest, abdomen, and pelvis according to the best response assessment criteria (see Appendix).

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.3 Date of the final observation

1) Outcome measures

Date of the final observation

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.4 Other assessments

1) Outcome measures

Pregnancy during the observation period (for females only)

If pregnancy is detected during the observation period, it should be reported to the representative of Takeda immediately.

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.5 Adverse events

1) Outcome measures

Presence/absence of adverse events (see Table 1), adverse event terms, date of onset, CTCAE grade (the worst one), seriousness and its reason (see Table 2), (presence/absence and detail of) action taken to Adcetris, (presence/absence and detail of) intervention for adverse events, date of outcome, outcome, causal relationship with Adcetris* (see Table 3), and changes in laboratory test values associated with adverse events over time
If the outcome is "not recovered/not resolved" or "unknown," and the causal relationship with Adcetris is considered unevaluable, the event should be followed wherever possible.

* If the event is considered not related to Adcetris, its rationale should be collected. If the causal relationship with Adcetris is considered unevaluable, its reason should be collected.

Note) Points to consider regarding adverse events

Worsening of the primary disease should not be regarded as an adverse event. However, abnormal worsening of the primary disease (e.g., worsening beyond the expected natural course of the disease) should be regarded as an adverse event.

Disease progression should be regarded as worsening of the primary disease rather than an adverse event. However, clinical or laboratory progression of an existing cancer (including new metastasis) that meets any of the criteria for the seriousness of adverse events (see Table 2) should be considered a serious adverse event.

2) Adverse events of particular interest

The events listed below are events of particular interest; detailed information on these events should be collected wherever possible it they are observed:

- Peripheral nerve disorders
- Infections
- Neutropenia
- Infusion reactions
- Pulmonary disorders

* Rationale for the selection of adverse events of particular interest

Of important identified risks listed in Risk Management Plan, those listed above were selected as adverse events of particular interest based on the following rationales:

a) Peripheral nerve disorders

Peripheral nerve disorders are frequently observed after treatment with Adcetris. If the event of peripheral nerve disorder becomes severe, it is difficult to continue treatment with Adcetris. It is important to control the onset of the event to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption). Therefore, the profile of peripheral nerve disorders in Japanese patients as an adverse event of particular interest will be determined (i.e., information useful for continuation of treatment with Adcetris, including risk factors, commonly reported time to onset, outcomes, and the status of treatment with Adcetris, will be collected).

b) Infections

It is expected that Adcetris is used in patients who are immunocompromised due to prior treatment or the prior disease or those who are complicated with infection, and the incidence of infections is likely to be high. Therefore, the profile of infections in Japanese patients as an adverse event of particular interest (i.e., the incidence and temporal relationship with the onset of neutropenia/lymphopenia) will be determined.

c) Neutropenia

It is expected that Adcetris is used in patients with decreased neutrophil count due to prior treatment, which may increase the risk of infection and result in a high incidence of infection/severe infection. It is important to control the neutrophil count to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption) in terms of the prevention of infection. Therefore, the profile of neutropenia in Japanese patients as an adverse event of particular interest will be determined (i.e., the status of treatment with Adcetris and neutrophil count control will be assessed and information useful for continuation of treatment with Adcetris will be collected).

d) Infusion reactions

Infusion reactions are characteristic of monoclonal antibody preparations, the profile of infusion reactions in Japanese patients as an adverse event of particular interest (including the status of premedication and the percentage of patients using premedication to prevent infusion reactions [use/non-use of premedication to prevent infusion reactions]) will be determined.

e) Pulmonary disorders

The occurrence of pulmonary disorders in Japanese patients receiving monotherapy with Adcetris as an adverse event of particular interest will be determined.

3) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

Table 1 Definition of an Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a patient linked in time with the use of a pharmaceutical/ medicinal product and which does not necessarily have to have a causal relationship with this treatment or may or may not be considered related to the product.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Adverse events also include:
•Symptoms observed in an infant breast-fed by a mother receiving treatment with Adcetris.

Table 2 Criteria for the Seriousness of Adverse Events

An adverse event meeting any of the following criteria will be considered serious:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is a medically important condition due to any of the above 1 to 5, including those listed in "Takeda Medically Significant AE List."

<u>Takeda Medically Significant AE List</u>

•Acute respiratory failure/acute respiratory distress syndrome (ARDS)	•Anaphylactic shock
•Torsade de pointes/ventricular fibrillation/ventricular tachycardia	•Acute kidney failure
•Malignant hypertension	•Pulmonary hypertension
•Convulsive seizure (including convulsion and epilepsy)	•Pulmonary fibrosis (including interstitial pneumonia)
•Agranulocytosis	•Neuroleptic malignant syndrome/malignant hyperthermia
•Aplastic anemia	•Spontaneous abortion/stillbirth and fetal death
•Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)	•(Suspected) transmission of infection via a drug
•Hepatic necrosis	•(Suspected) endotoxic shock
•Acute hepatic failure	

Table 3 Criteria for the Assessment of Causal Relationship between Adverse Events and Adcetris

Causality	Assessment criterion
Related	There is a temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation). Or, there are other contributing factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies, but it is also likely that the event is attributable to Adcetris.
Not related	There is no temporal relationship between the event and Adcetris. Or, it is very likely that the event is attributable to other factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies.
Indeterminate	There is limited information required for the assessment of causal relationship, such as temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation), the primary disease, concurrent illnesses, and concomitant medications/therapies.

10.0 Data to Be Analyzed and Methods of Analysis

10.1 Patient disposition

Data to be analyzed includes the number of enrolled patients, the number of patients whose case report forms are available, and the number of patients included in and excluded from the safety/efficacy analysis set and reasons for inclusion/exclusion.

10.2 Patient demographics and baseline characteristics

Data to be analyzed includes sex, age, disease duration, site of involvement, and clinical stage.

10.3 Treatment given

Data to be analyzed includes the status of treatment with Adcetris and concomitant medications.

10.4 Safety

The measures specified below will be analyzed using the safety analysis set. Adverse events will be coded using MedDRA/J and summarized using (Preferred Terms [PTs]) and System Organ Classes [SOCs]).

10.4.1 Occurrence of adverse events

The frequency of adverse events observed during the observation period will be analyzed by type, time of onset, seriousness, and Adcetris.

10.4.2 Factors that may affect the safety of Adcetris

The frequency of adverse events observed during the observation period will be analyzed by patient background factors (sex, age, presence/absence of concurrent renal disorders, and presence/absence of concurrent hepatic disorders) and treatment given (the status of treatment with Adcetris and concomitant medications).

10.4.3 Changes in laboratory test data over time

Summary statistics of laboratory test values at baseline and post-baseline will be calculated.

10.5 Efficacy

The measures specified below will be analyzed using the efficacy analysis set.

10.5.1 Best response

The best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed.

10.5.2 Overall survival

The time to death (regardless of the cause of death) will be analyzed using the "final observation date" in specified in Section 9.2.4.3 as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field specified in Section 9.2.5 as the date of death

10.6 Interim analyses

For patients whose case report forms are collected through November 30, 2014 with evaluable safety evaluation, analyses similar to the ones described in Sections 10.1 to 10.4 will be performed to evaluate and analyze safety information obtained in this study at an early stage and publish them as appropriate.

11.0 Posting of Information Regarding This Study

Prior to the start of the study, Takeda Pharmaceutical Company Limited will register information regarding this study to the public website specified below.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- ClinicalTrials.gov (a clinical trial registration system provided by the National Institutes of Health)

12.0 Organizational Structure

12.1 Person responsible for administration

PPD, Takeda Pharmaceutical Company Limited

12.2 Proper Use Committee

The committee will provide advice on the protocol, data analysis, publication of study results, promotion of the proper use of Adcetris, and safety measures.

PPD

(Listed in the order of the Japanese syllabary)

12.3 Central Enrollment Center

PPD

13.0 Contract Research Organization

PPD

14.0 Other Important Information

14.1 Protocol amendment

During the study, the sponsor will monitor the occurrence of adverse drug reactions and serious adverse drug reactions that cannot be predicted by the progress of the study and precautions for use, the presence/absence of an increase in the frequency of specific adverse drug reactions, and the appropriateness of outcome measures, and review and amend this protocol as appropriate. If the approval of partial changes to “Dosage and Administration” or “Indication” is obtained during the study, the sponsor will consider the necessity of amendment of this protocol as appropriate, and amend the protocol as appropriate.

14.2 Measures to be taken in response to issues/questions

If any safety and/or efficacy issue is detected, the sponsor will examine data closely and consider what measures should be taken.

Appendix 1 Study Schedule

Procedure \ Time point		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Patient enrollment	Date of the expected initial dose of Adcetris	○				
	Patient identification number	○				
	Patient initial	○				
	Sex	○				
	Date of birth	○				
	Diagnosis	○				
	Performance status	○				
	CD30	○				
	Past history of severe hypersensitivity to any ingredient of Adcetris	○				
	Expected concomitant use of other antineoplastic drugs	○				
	Presence/absence of infections	○				
	Presence/absence of peripheral nerve disorders	○				
	Presence/absence of hepatic disorders	○				
	Presence/absence of severe renal disorders	○				
	Presence/absence of pregnancy/breast-feeding	○				
Patient demographics and baseline characteristics	Date of diagnosis of Hodgkin or anaplastic large-cell lymphoma		○			
	Site of involvement		○			
	ALK (in patients with anaplastic large cell lymphoma)		○			
	Clinical stage		○			
	Presence/absence of B symptoms		○			
	ECOG Performance Status		○			
	Therapeutic category		○			
	Hypersensitivity disposition		○			
	Viral test results		○			
	Past history of and concurrent pulmonary disorders		○			
	Past history of and concurrent malignant tumours		○			
	Concurrent illness (other than pulmonary disorders and malignant tumours)		○			
	Past history (other than pulmonary disorders and malignant tumours)		○			
	Height and weight		○			
	Smoking history		○			
	Prior treatment for Hodgkin's or anaplastic large cell lymphoma		○			

	Procedure \ Time point	Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Treatment given	Treatment with Adcetris		○	○		
	Post-baseline hematopoietic stem cell transplantation		←○→			○
	Drug(s) other than Adcetris used for the treatment of the primary disease		←○→			○
	Drug(s) used for the prevention of infection		←○→			○
Tests and assessments	Laboratory tests (red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, and liver and kidney function tests)		←○→			○
	Best response				○	○
	Date of the final observation				○	○
	Presence/absence of pregnancy (for females only)		←○→			○
	Adverse events		←○→			○

○ : Data collected

←○→ Data collected throughout the period

Appendix 2 Best Response Assessment Criteria (Revised Response Criteria for Malignant Lymphoma*)

* Extracted from "General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, March 2000 [First Edition])

For patients with PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma The patient is PET negative. If the patient is PET negative, any residual tumor on CT does not matter. 1)-2Variably FDG-avid lymphoma The patient did not undergo PET before treatment. If the patient was negative before treatment, the patient must meet all the following criteria: [1] All nodal target lesions are normal. [2] All extranodal target lesions have resolved. [3] All nodal non-target lesions are normal. [4] The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. [5] All extranodal non-target lesions have resolved. 2) A patient with bone marrow infiltration at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as "negative" because bone marrow test is not required. 3) The patient has no new lesion.
PR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma If the patient had one or more PET positive lesions, or was PET negative AND had bone marrow infiltration at baseline, the patient must be positive for bone marrow infiltration at the time of restaging (or have not undergone testing). 1)-2Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 3) All nodal non-target lesions are normal or free from enlargement. 4) All extranodal non-target lesions have resolved or free from enlargement. 5) Bone marrow infiltration does not matter. Testing is not required. 6) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR but meets any of the criteria 1 and 2 to 6 and 7 listed below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR, the patient will be assessed as having a relapsed disease (RD): 1)-1 Routinely FDG-avid lymphoma The patient has one or more PET positive lesions. 1)-2 Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 3) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long

	diameter) or re-enlargement. 4) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 5) The long diameter of the nodal target lesion which was once normalized and assessed as CR exceeded 1.5 cm. The extranodal target lesion which once resolved reappeared. 6) The patient has a new lesion. 7) The patient became positive after being once negative for bone marrow infiltration.

For patients with no PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. 5) All extranodal non-target lesions have resolved. 6) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 7) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 8) A patient with bone marrow infiltration or indeterminate at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 9) The patient has no new lesion.
CRu	The patient had bone marrow infiltration or was indeterminate at baseline AND meets all the following criteria: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) All extranodal non-target lesions have resolved. 5) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 6) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 7) The patient is indeterminate for bone marrow infiltration. 8) The patient has no new lesion. OR 1) The patient has a 75% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal. 3) All extranodal non-target lesions have resolved. 4) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 5) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 6) The patient has no bone marrow infiltration or indeterminate.

	7) The patient has no new lesion.
PR	The patient meets all the above criteria for CRu except for criterion 6. A patient with bone marrow infiltration or indeterminate at baseline must be positive for bone marrow infiltration at the time of restaging. Or, the patient meets all the following criteria: 1) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal or free from enlargement. 3) All extranodal non-target lesions have resolved or free from enlargement. 4) Enlarged liver, spleen, and kidneys have resolved or are free from progression. 5) All tumor-related symptom (fever and night sweat) have resolved. AND abnormal tumor-related laboratory test results (tumor-related increase in LDH) became normal. 6) Bone marrow infiltration does not matter. Testing is not required. 7) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR or CRu but meets any of the criteria below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR or CRu, the patient will be assessed as having a relapsed disease (RD): 1) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 2) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 3) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 4) The extranodal target lesion which once resolved and was assesses as CR or CRu reappeared. 5) Obvious progression or recurrence of enlarged liver, spleen, or kidney. 6) Obvious progression or recurrence of tumor-related subjective and objective symptoms (fever and night sweat) or abnormal tumor-related laboratory test results (tumor-related increase in LDH). 7) The patient became positive after being once negative for bone marrow infiltration. 8) The patient has a new lesion.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Adcetris IV Infusion

(All-Case Surveillance)

“Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma”

Version number	**4**
Date of creation	**September 6, 2016**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

There is limited safety information on Adcetris IV Infusion 50 mg (hereinafter referred to as Adcetris) collected from Japanese patients in Japanese phase 1/2 studies. It is important to promptly collect post-marketing safety information and provide it to healthcare providers. It was also deemed that additional surveillance was required to determine the occurrence of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders in patients using Adcetris in Japan as post-marketing safety specifications.

Thus, an all-case surveillance in all patients receiving treatment with Adcetris will be initiated as an additional pharmacovigilance activity for Adcetris when the drug is launched.

This surveillance study will be conducted in compliance with the GPSP Ordinance and other related regulatory requirements.

2.0 Purpose

The purpose of this study is to evaluate the safety of Adcetris in patients with relapsed/refractoryCD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma in the routine clinical setting, as well as to collect efficacy information for reference.

3.0 Estimated Enrollment and Its Rationale

3.1 Estimated enrollment

140 patients (with relapsed/refractory CD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma)

3.2 Rationale

It is expected that the detailed evaluation of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders will help better understand the safety profile of Adcetris in the routine clinical setting, which will lead to the assessment of the risk-benefit balance of the drug.

The frequencies of peripheral nerve disorders, infections, neutropenia (≥Grade 3), infusion reaction, and pulmonary disorder in non-Japanese phase 2 studies (pooled study data from a study in patients with Hodgkin's lymphoma [SG035-0003, 102 patients] and a study in patients with systemic anaplastic large cell lymphoma [SG035-0004, 58 patients]) were 56%, 61%, 20%, 11%, and 6%, respectively.

Observation of infusion reactions with the lowest frequency of ≥10 patients, aside from pulmonary disorders, with a probability of 95% would require 140 patients, which was therefore determined to be the estimated enrollment. It is estimated that when the number of patients enrolled reaches 140 patients, ≥4 patients have adverse events of pulmonary disorder with a probability of 95%.

4.0 Eligible Patients

All patients receiving treatment with Adcetris

5.0 Dosage Regimen

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (recombinant) infused intravenously once every three weeks. The dose should be adjusted depending on the patient's condition.

See the "PRECAUTIONS" section of the package insert.

6.0 Expected Study Institutions by Department

The study will be conducted at all institutions using Adcetris (e.g., department of hematology) (approximately 100 study institutions are expected to participate in the study).

7.0 Methods

7.1 Observation period

From the start of treatment with Adcetris until the completion of 16 cycles [3 weeks per cycle]

* Rationale for the selection of the observation period

The assessment of the treatment cycle with the initial onset of adverse events in a clinical study [SGN35-006, the extended treatment group] evaluating the safety of Adcetris after Cycle 17 showed a tendency that most adverse events occurred before Cycle 16. In addition, the types and severities did not differ between adverse events occurring after Cycle 17 and those occurring before Cycle 16. This suggested that the safety profile of Adcetris would be generally determined before Cycle 16. Therefore, the observation period was defined as the period from the start of treatment with Adcetris until the completion of 16 cycles.

7.2 Request for participation in this study and contract with each study institution

Paper-based case report forms will be used. To ask each study institution to participate in the study, the representative of Takeda Pharmaceutical Company Limited (representative of Takeda) will confirm before supply of Adcetris and the start of the study that each study institution meets all requirements for study institutions and investigators specified below, and have a written contract with the study institution after prior explanation of the study provided before supply of Adcetris.

(1) Requirements for each study institution and investigator

1) Requirements for each study institution

[1] Is able to cooperate with this all-case surveillance and have a contract with the sponsor.

[2] Is able to provide specialized treatment for hematopoietic tumors.

[3] Is able to provide emergency treatment if required (including a case where such a treatment can be provided in conjunction with another institution

).

* When emergency treatment is provided in conjunction with another institution, information on Adcetris safety measures and treatment of adverse drug reactions should be shared between the institution and the other institution to build a coalition.

2) Requirements for each investigator

[1] Has adequate knowledge and experience regarding the treatment of hematopoietic tumors, or is under the direction of a healthcare professional having such knowledge and experience.

[2] Is able to cooperate with this all-case surveillance.

(2) Prior explanation of the study to be provided before supply of Adcetris and the request for participation in this study

Using "Request for Participation in the Special Drug Use Surveillance," "Study Outline," "Patient Enrollment Form (sample)," "Case Report Form Parts 1 and 2 (sample)," "Precautions for Use/Instruction Manual," and "Proper Usage Guide," the representative of Takeda will explain the purpose and methods (e.g., all-case surveillance) of this survey study and information regarding the proper use of Adcetris to the investigator and ask him/her to participate in the all-case surveillance.

The representative of Takeda will also confirm with the investigator that the institution and the investigator meet all requirements.

(3) Request for participation in this study and contract with each study institution

The representative of Takeda will have a written contract with the study institution after obtaining their agreement to participate in this study Takeda Pharmaceutical Company Limited will inform the outsourced Adcetris supplier that the contract is concluded and Adcetris should be supplied to the study institution. The representative of Takeda will deliver patient enrollment forms to the investigator.

7.3 Method of patient enrollment

The central enrollment method via FAX will be used. For each patient scheduled to receive treatment with Adcetris after the date of the start of the term of the contract with the study institution, the investigator will complete patient enrollment by submitting the Patient Enrollment Form with information required for patient enrollment filled in (see Section 9.1) via FAX to the Central Enrollment Center (see Section 12.3) until noon of the day before the date of the expected initial dose of Adcetris.

The Central Enrollment Center will review the Patient Enrollment Form and send the Enrollment Completion Notice to the investigator via FAX. After receiving the Enrollment Completion Notice, the investigator will initiate treatment with Adcetris.

The Case Report Form consists of Parts 1 and 2 per patient.

The representative of Takeda will deliver Case Report Form Part 1, which is issued after enrollment confirmation by the Central Enrollment Center, to the investigator. Case Report Form Part 2 is issued after Takeda Pharmaceutical receives Case Report Form Part 1.

7.4 Completion and submission of the case report form

For all patients requiring the completion of the case report form, the investigator will complete the case report form during the period from the start of treatment with Adcetris until the end of Cycle 4 and within 1 month after the end of Cycle 16, and submit it to the representative of Takeda.

If treatment with Adcetris is discontinued for any reason before the end of the observation period, the investigator will complete the case report form within 1 month after the completion of required observation submit it to the representative of Takeda. If treatment with Adcetris is discontinued due to any adverse event, however, the investigator will continue to observe the patient after treatment discontinuation until the adverse event resolves or improves wherever possible, and then complete the case report form and submit it to the representative of Takeda.

7.5 Confirmation of all-case surveillance

After the completion of the study, the principal investigator will confirm that case report forms of all patients treated with Adcetris have been submitted, and sign or fill in his/her name with seal on All-Case Surveillance Confirmation Form and submit it to the representative of Takeda.

8.0 Estimated Study Period

Study period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Patient enrollment period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

The expected number of enrolled patients (140) was achieved. Therefore, the study will move to the period only requiring patient enrollment (not requiring the completion and submission of case report forms).

After moving to the period only requiring patient enrollment, it may be required to complete and submit case report forms upon request by the regulatory authority.

9.0 Outcome Measures

The investigator will record data listed below in both Patient Enrollment and Case Report Forms. Study schedule is provided in in Appendix 1.

9.1 Data to be recorded in Patient Enrollment Form

1) Outcome measures

Name of the institution, name of the investigator completing Patient Enrollment Form, expected date of the start of treatment with Adcetris, patient identification number, patient initial, sex, date of birth, diagnosis, performance status, CD30, past history of severe hypersensitivity to any ingredient of Adcetris, expected concomitant use of other antineoplastic drugs, and presence/absence of infections, peripheral nerve disorders, hepatic disorders, severe renal disorders, or pregnancy/breast-feeding

2) When to collect outcome measure data

At the time of patient enrollment

9.2 Data to be recorded in Case Report Form

9.2.1 Cover sheet of Case Report Form

Date of the finial completion of Case Report Form and name of the investigator completing Case Report Form

9.2.2 Patient demographics and baseline characteristics

1) Outcome measures

Date of diagnosis of Hodgkin's or anaplastic large cell lymphoma, site of involvement, ALK (in patients with anaplastic large cell lymphoma), clinical stage, presence/absence of B symptoms, ECOG Performance Status, therapeutic category, (presence/absence and detail of) hypersensitivity disposition, viral test results, past history of and concurrent pulmonary disorders, past history of and concurrent malignant tumours, (presence/absence and detail of) concurrent illnesses [other than pulmonary disorders and malignant tumours], (presence/absence and detail of) past history[other than pulmonary disorders and malignant tumours], height, weight, smoking history, and (presence/absence and detail of) prior treatment for Hodgkin's lymphoma or anaplastic large cell lymphoma (including drug therapy, radiotherapy, and hematopoietic stem cell transplantation)

2) When to collect outcome measure data

At the start of treatment with Adcetris

9.2.3 Treatment given

1) Outcome measures

Treatment with Adcetris and premedication to prevent infusion reaction (dose, date of premedication, and reasons for premedication to prevent infusion reaction and its discontinuation), (use or non-use, type, and date of) post-baseline hematopoietic stem cell transplantation, (presence/absence, name, and duration of) drugs other than Adcetris used for the treatment of the primary disease, and (presence/absence, name, and duration of) drugs used for the prevention of infection

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4 Tests and assessments

9.2.4.1 Laboratory tests

1) Outcome measures

Red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, total bilirubin, AST, ALT, LDH, BUN, and serum creatinine

2) When to collect outcome measure data

At each test time point during the period from the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4.2 Best response

1) Outcome measures

The best response (CR, CRu [for patients with no PET scan data], PR, SD, or PD) will be assessed based on CT and PET scans of the neck, chest, abdomen, and pelvis according to the best response assessment criteria (see Appendix).

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.3 Date of the final observation

1) Outcome measures

Date of the final observation

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.4 Other assessments

1) Outcome measures

Pregnancy during the observation period (for females only)

If pregnancy is detected during the observation period, it should be reported to the representative of Takeda immediately.

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.5 Adverse events

1) Outcome measures

Presence/absence of adverse events (see Table 1), adverse event terms, date of onset, CTCAE grade (the worst one), seriousness and its reason (see Table 2), (presence/absence and detail of) action taken to Adcetris, (presence/absence and detail of) intervention for adverse events, date of outcome, outcome, causal relationship with Adcetris* (see Table 3), and changes in laboratory test values associated with adverse events over time
If the outcome is "not recovered/not resolved" or "unknown," and the causal relationship with Adcetris is considered unevaluable, the event should be followed wherever possible.

* If the event is considered not related to Adcetris, its rationale should be collected. If the causal relationship with Adcetris is considered unevaluable, its reason should be collected.

Note) Points to consider regarding adverse events

Worsening of the primary disease should not be regarded as an adverse event. However, abnormal worsening of the primary disease (e.g., worsening beyond the expected natural course of the disease) should be regarded as an adverse event.

Disease progression should be regarded as worsening of the primary disease rather than an adverse event. However, clinical or laboratory progression of an existing cancer (including new metastasis) that meets any of the criteria for the seriousness of adverse events (see Table 2) should be considered a serious adverse event.

2) Adverse events of particular interest

The events listed below are events of particular interest; detailed information on these events should be collected wherever possible it they are observed:

- Peripheral nerve disorders
- Infections
- Neutropenia
- Infusion reactions
- Pulmonary disorders

* Rationale for the selection of adverse events of particular interest

Of important identified risks listed in Risk Management Plan, those listed above were selected as adverse events of particular interest based on the following rationales:

a) Peripheral nerve disorders

Peripheral nerve disorders are frequently observed after treatment with Adcetris. If the event of peripheral nerve disorder becomes severe, it is difficult to continue treatment with Adcetris. It is important to control the onset of the event to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption). Therefore, the profile of peripheral nerve disorders in Japanese patients as an adverse event of particular interest will be determined (i.e., information useful for continuation of treatment with Adcetris, including risk factors, commonly reported time to onset, outcomes, and the status of treatment with Adcetris, will be collected).

b) Infections

It is expected that Adcetris is used in patients who are immunocompromised due to prior treatment or the prior disease or those who are complicated with infection, and the incidence of infections is likely to be high. Therefore, the profile of infections in Japanese patients as an adverse event of particular interest (i.e., the incidence and temporal relationship with the onset of neutropenia/lymphopenia) will be determined.

c) Neutropenia

It is expected that Adcetris is used in patients with decreased neutrophil count due to prior treatment, which may increase the risk of infection and result in a high incidence of infection/severe infection. It is important to control the neutrophil count to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption) in terms of the prevention of infection. Therefore, the profile of neutropenia in Japanese patients as an adverse event of particular interest will be determined (i.e., the status of treatment with Adcetris and neutrophil count control will be assessed and information useful for continuation of treatment with Adcetris will be collected).

d) Infusion reactions

Infusion reactions are characteristic of monoclonal antibody preparations, the profile of infusion reactions in Japanese patients as an adverse event of particular interest (including the status of premedication and the percentage of patients using premedication to prevent infusion reactions [use/non-use of premedication to prevent infusion reactions]) will be determined.

e) Pulmonary disorders

The occurrence of pulmonary disorders in Japanese patients receiving monotherapy with Adcetris as an adverse event of particular interest will be determined.

3) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

Table 1 Definition of an Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a patient linked in time with the use of a pharmaceutical/ medicinal product and which does not necessarily have to have a causal relationship with this treatment or may or may not be considered related to the product.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Adverse events also include:
• Symptoms observed in an infant breast-fed by a mother receiving treatment with Adcetris.

Table 2 Criteria for the Seriousness of Adverse Events

An adverse event meeting any of the following criteria will be considered serious:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is a medically important condition due to any of the above 1 to 5, including those listed in "Takeda Medically Significant AE List."

Takeda Medically Significant AE List

- Acute respiratory failure/acute respiratory distress syndrome (ARDS)
- Torsade de pointes/ventricular fibrillation/ventricular tachycardia
- Malignant hypertension
- Convulsive seizure (including convulsion and epilepsy)
- Agranulocytosis
- Aplastic anemia
- Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)
- Hepatic necrosis
- Acute hepatic failure
- Anaphylactic shock
- Acute kidney failure
- Pulmonary hypertension
- Pulmonary fibrosis (including interstitial pneumonia)
- Neuroleptic malignant syndrome/malignant hyperthermia
- Spontaneous abortion/stillbirth and fetal death
- (Suspected) transmission of infection via a drug
- (Suspected) endotoxic shock

Table 3 Criteria for the Assessment of Causal Relationship between Adverse Events and Adcetris

Causality	Assessment criterion
Related	There is a temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation). Or, there are other contributing factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies, but it is also likely that the event is attributable to Adcetris.
Not related	There is no temporal relationship between the event and Adcetris. Or, it is very likely that the event is attributable to other factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies.
Indeterminate	There is limited information required for the assessment of causal relationship, such as temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation), the primary disease, concurrent illnesses, and concomitant medications/therapies.

10.0 Data to Be Analyzed and Methods of Analysis

10.1 Patient disposition

Data to be analyzed includes the number of enrolled patients, the number of patients whose case report forms are available, and the number of patients included in and excluded from the safety/efficacy analysis set and reasons for inclusion/exclusion.

10.2 Patient demographics and baseline characteristics

Data to be analyzed includes sex, age, disease duration, site of involvement, and clinical stage.

10.3 Treatment given

Data to be analyzed includes the status of treatment with Adcetris and concomitant medications.

10.4 Safety

The measures specified below will be analyzed using the safety analysis set. Adverse events will be coded using MedDRA/J and summarized using (Preferred Terms [PTs]) and System Organ Classes [SOCs]).

10.4.1 Occurrence of adverse events

The frequency of adverse events observed during the observation period will be analyzed by type, time of onset, seriousness, and Adcetris.

10.4.2 Factors that may affect the safety of Adcetris

The frequency of adverse events observed during the observation period will be analyzed by patient background factors (sex, age, presence/absence of concurrent renal disorders, and presence/absence of concurrent hepatic disorders) and treatment given (the status of treatment with Adcetris and concomitant medications).

10.4.3 Changes in laboratory test data over time

Summary statistics of laboratory test values at baseline and post-baseline will be calculated.

10.5 Efficacy

The measures specified below will be analyzed using the efficacy analysis set.

10.5.1 Best response

The best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed.

10.5.2 Overall survival

The time to death (regardless of the cause of death) will be analyzed using the "final observation date" in specified in Section 9.2.4.3 as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field specified in Section 9.2.5 as the date of death

10.6 Interim analyses

For patients whose case report forms are collected through November 30, 2014 with evaluable safety evaluation, analyses similar to the ones described in Sections 10.1 to 10.4 will be performed to evaluate and analyze safety information obtained in this study at an early stage and publish them as appropriate.

11.0 Posting of Information Regarding This Study

Prior to the start of the study, Takeda Pharmaceutical Company Limited will register information regarding this study to the public website specified below.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- ClinicalTrials.gov (a clinical trial registration system provided by the National Institutes of Health)

12.0 Organizational Structure

12.1 Person responsible for administration

PPD, Takeda Pharmaceutical Company Limited

12.2 Proper Use Committee

The committee will provide advice on the protocol, data analysis, publication of study results, promotion of the proper use of Adcetris, and safety measures.

PPD

(Listed in the order of the Japanese syllabary)

12.3 Central Enrollment Center

PPD

13.0 Contract Research Organization

PPD

14.0 Other Important Information

14.1 Protocol amendment

During the study, the sponsor will monitor the occurrence of adverse drug reactions and serious adverse drug reactions that cannot be predicted by the progress of the study and precautions for use, the presence/absence of an increase in the frequency of specific adverse drug reactions, and the appropriateness of outcome measures, and review and amend this protocol as appropriate. If the approval of partial changes to “Dosage and Administration” or “Indication” is obtained during the study, the sponsor will consider the necessity of amendment of this protocol as appropriate, and amend the protocol as appropriate.

14.2 Measures to be taken in response to issues/questions

If any safety and/or efficacy issue is detected, the sponsor will examine data closely and consider what measures should be taken.

Appendix 1 Study Schedule

Procedure \ Time point		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Patient enrollment	Date of the expected initial dose of Adcetris	○				
	Patient identification number	○				
	Patient initial	○				
	Sex	○				
	Date of birth	○				
	Diagnosis	○				
	Performance status	○				
	CD30	○				
	Past history of severe hypersensitivity to any ingredient of Adcetris	○				
	Expected concomitant use of other antineoplastic drugs	○				
	Presence/absence of infections	○				
	Presence/absence of peripheral nerve disorders	○				
	Presence/absence of hepatic disorders	○				
	Presence/absence of severe renal disorders	○				
	Presence/absence of pregnancy/breast-feeding	○				
Patient demographics and baseline characteristics	Date of diagnosis of Hodgkin or anaplastic large-cell lymphoma		○			
	Site of involvement		○			
	ALK (in patients with anaplastic large cell lymphoma)		○			
	Clinical stage		○			
	Presence/absence of B symptoms		○			
	ECOG Performance Status		○			
	Therapeutic category		○			
	Hypersensitivity disposition		○			
	Viral test results		○			
	Past history of and concurrent pulmonary disorders		○			
	Past history of and concurrent malignant tumours		○			
	Concurrent illness (other than pulmonary disorders and malignant tumours)		○			
	Past history (other than pulmonary disorders and malignant tumours)		○			
	Height and weight		○			
	Smoking history		○			
	Prior treatment for Hodgkin's or anaplastic large cell lymphoma		○			

	Procedure \ Time point	Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Treatment given	Treatment with Adcetris		○	○		
	Post-baseline hematopoietic stem cell transplantation		←○→			○
	Drug(s) other than Adcetris used for the treatment of the primary disease		←○→			○
	Drug(s) used for the prevention of infection		←○→			○
Tests and assessments	Laboratory tests (red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, and liver and kidney function tests)		←○→			○
	Best response				○	○
	Date of the final observation				○	○
	Presence/absence of pregnancy (for females only)		←○→			○
	Adverse events		←○→			○

○ : Data collected

←○→: Data collected throughout the period

Appendix 2 Best Response Assessment Criteria (Revised Response Criteria for Malignant Lymphoma*)

* Extracted from "General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, March 2000 [First Edition])

For patients with PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma The patient is PET negative. If the patient is PET negative, any residual tumor on CT does not matter. 1)-2Variably FDG-avid lymphoma The patient did not undergo PET before treatment. If the patient was negative before treatment, the patient must meet all the following criteria: [1] All nodal target lesions are normal. [2] All extranodal target lesions have resolved. [3] All nodal non-target lesions are normal. [4] The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. [5] All extranodal non-target lesions have resolved. 2) A patient with bone marrow infiltration at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as "negative" because bone marrow test is not required. 3) The patient has no new lesion.
PR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma If the patient had one or more PET positive lesions, or was PET negative AND had bone marrow infiltration at baseline, the patient must be positive for bone marrow infiltration at the time of restaging (or have not undergone testing). 1)-2Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 3) All nodal non-target lesions are normal or free from enlargement. 4) All extranodal non-target lesions have resolved or free from enlargement. 5) Bone marrow infiltration does not matter. Testing is not required. 6) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR but meets any of the criteria 1 and 2 to 6 and 7 listed below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR, the patient will be assessed as having a relapsed disease (RD): 1)-1 Routinely FDG-avid lymphoma The patient has one or more PET positive lesions. 1)-2 Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 3) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long

	diameter) or re-enlargement. 4) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 5) The long diameter of the nodal target lesion which was once normalized and assessed as CR exceeded 1.5 cm. The extranodal target lesion which once resolved reappeared. 6) The patient has a new lesion. 7) The patient became positive after being once negative for bone marrow infiltration.

For patients with no PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. 5) All extranodal non-target lesions have resolved. 6) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 7) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 8) A patient with bone marrow infiltration or indeterminate at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 9) The patient has no new lesion.
CRu	The patient had bone marrow infiltration or was indeterminate at baseline AND meets all the following criteria: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) All extranodal non-target lesions have resolved. 5) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 6) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 7) The patient is indeterminate for bone marrow infiltration. 8) The patient has no new lesion. OR 1) The patient has a 75% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal. 3) All extranodal non-target lesions have resolved. 4) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 5) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 6) The patient has no bone marrow infiltration or indeterminate.

	7) The patient has no new lesion.
PR	The patient meets all the above criteria for CRu except for criterion 6. A patient with bone marrow infiltration or indeterminate at baseline must be positive for bone marrow infiltration at the time of restaging. Or, the patient meets all the following criteria: 1) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal or free from enlargement. 3) All extranodal non-target lesions have resolved or free from enlargement. 4) Enlarged liver, spleen, and kidneys have resolved or are free from progression. 5) All tumor-related symptom (fever and night sweat) have resolved. AND abnormal tumor-related laboratory test results (tumor-related increase in LDH) became normal. 6) Bone marrow infiltration does not matter. Testing is not required. 7) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR or CRu but meets any of the criteria below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR or CRu, the patient will be assessed as having a relapsed disease (RD): 1) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 2) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 3) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 4) The extranodal target lesion which once resolved and was assesses as CR or CRu reappeared. 5) Obvious progression or recurrence of enlarged liver, spleen, or kidney. 6) Obvious progression or recurrence of tumor-related subjective and objective symptoms (fever and night sweat) or abnormal tumor-related laboratory test results (tumor-related increase in LDH). 7) The patient became positive after being once negative for bone marrow infiltration. 8) The patient has a new lesion.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Adcetris IV Infusion

(All-Case Surveillance)

“Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma”

Version number	**3**
Date of creation	**April 1, 2015**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

There is limited safety information on Adcetris IV Infusion 50 mg (hereinafter referred to as Adcetris) collected from Japanese patients in Japanese phase 1/2 studies. It is important to promptly collect post-marketing safety information and provide it to healthcare providers. It was also deemed that additional surveillance was required to determine the occurrence of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders in patients using Adcetris in Japan as post-marketing safety specifications.

Thus, an all-case surveillance in all patients receiving treatment with Adcetris will be initiated as an additional pharmacovigilance activity for Adcetris when the drug is launched.

This surveillance study will be conducted in compliance with the GPSP Ordinance and other related regulatory requirements.

2.0 Purpose

The purpose of this study is to evaluate the safety of Adcetris in patients with relapsed/refractoryCD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma in the routine clinical setting, as well as to collect efficacy information for reference.

3.0 Estimated Enrollment and Its Rationale

3.1 Estimated enrollment

140 patients (with relapsed/refractory CD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma)

3.2 Rationale

It is expected that the detailed evaluation of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders will help better understand the safety profile of Adcetris in the routine clinical setting, which will lead to the assessment of the risk-benefit balance of the drug.

The frequencies of peripheral nerve disorders, infections, neutropenia (≥Grade 3), infusion reaction, and pulmonary disorder in non-Japanese phase 2 studies (pooled study data from a study in patients with Hodgkin's lymphoma [SG035-0003, 102 patients] and a study in patients with systemic anaplastic large cell lymphoma [SG035-0004, 58 patients]) were 56%, 61%, 20%, 11%, and 6%, respectively.

Observation of infusion reactions with the lowest frequency of ≥10 patients, aside from pulmonary disorders, with a probability of 95% would require 140 patients, which was therefore determined to be the estimated enrollment. It is estimated that when the number of patients enrolled reaches 140 patients, ≥4 patients have adverse events of pulmonary disorder with a probability of 95%.

4.0 Eligible Patients

All patients receiving treatment with Adcetris

5.0 Dosage Regimen

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (recombinant) infused intravenously once every three weeks. The dose should be adjusted depending on the patient's condition.

See the "PRECAUTIONS" section of the package insert.

6.0 Expected Study Institutions by Department

The study will be conducted at all institutions using Adcetris (e.g., department of hematology) (approximately 100 study institutions are expected to participate in the study).

7.0 Methods

7.1 Observation period

From the start of treatment with Adcetris until the completion of 16 cycles [3 weeks per cycle]

* Rationale for the selection of the observation period

The assessment of the treatment cycle with the initial onset of adverse events in a clinical study [SGN35-006, the extended treatment group] evaluating the safety of Adcetris after Cycle 17 showed a tendency that most adverse events occurred before Cycle 16. In addition, the types and severities did not differ between adverse events occurring after Cycle 17 and those occurring before Cycle 16. This suggested that the safety profile of Adcetris would be generally determined before Cycle 16. Therefore, the observation period was defined as the period from the start of treatment with Adcetris until the completion of 16 cycles.

7.2 Request for participation in this study and contract with each study institution

Paper-based case report forms will be used. To ask each study institution to participate in the study, the representative of Takeda Pharmaceutical Company Limited (representative of Takeda) will confirm before supply of Adcetris and the start of the study that each study institution meets all requirements for study institutions and investigators specified below, and have a written contract with the study institution after prior explanation of the study provided before supply of Adcetris.

(1) Requirements for each study institution and investigator

1) Requirements for each study institution

[1] Is able to cooperate with this all-case surveillance and have a contract with the sponsor.

[2] Is able to provide specialized treatment for hematopoietic tumors.

[3] Is able to provide emergency treatment if required (including a case where such a treatment can be provided in conjunction with another institution

).

* When emergency treatment is provided in conjunction with another institution, information on Adcetris safety measures and treatment of adverse drug reactions should be shared between the institution and the other institution to build a coalition.

2) Requirements for each investigator

[1] Has adequate knowledge and experience regarding the treatment of hematopoietic tumors, or is under the direction of a healthcare professional having such knowledge and experience.

[2] Is able to cooperate with this all-case surveillance.

(2) Prior explanation of the study to be provided before supply of Adcetris and the request for participation in this study

Using "Request for Participation in the Special Drug Use Surveillance," "Study Outline," "Patient Enrollment Form (sample)," "Case Report Form Parts 1 and 2 (sample)," "Precautions for Use/Instruction Manual," and "Proper Usage Guide," the representative of Takeda will explain the purpose and methods (e.g., all-case surveillance) of this survey study and information regarding the proper use of Adcetris to the investigator and ask him/her to participate in the all-case surveillance.

The representative of Takeda will also confirm with the investigator that the institution and the investigator meet all requirements.

(3) Request for participation in this study and contract with each study institution

The representative of Takeda will have a written contract with the study institution after obtaining their agreement to participate in this study Takeda Pharmaceutical Company Limited will inform the outsourced Adcetris supplier that the contract is concluded and Adcetris should be supplied to the study institution. The representative of Takeda will deliver patient enrollment forms to the investigator.

7.3 Method of patient enrollment

The central enrollment method via FAX will be used. For each patient scheduled to receive treatment with Adcetris after the date of the start of the term of the contract with the study institution, the investigator will complete patient enrollment by submitting the Patient Enrollment Form with information required for patient enrollment filled in (see Section 9.1) via FAX to the Central Enrollment Center (see Section 12.3) until noon of the day before the date of the expected initial dose of Adcetris.

The Central Enrollment Center will review the Patient Enrollment Form and send the Enrollment Completion Notice to the investigator via FAX. After receiving the Enrollment Completion Notice, the investigator will initiate treatment with Adcetris.

The Case Report Form consists of Parts 1 and 2 per patient.

The representative of Takeda will deliver Case Report Form Part 1, which is issued after enrollment confirmation by the Central Enrollment Center, to the investigator. Case Report Form Part 2 is issued after the completion of follow-up on Case Report Form Part 1.

7.4 Completion and submission of the case report form

For all patients requiring the completion of the case report form, the investigator will complete the case report form during the period from the start of treatment with Adcetris until the end of Cycle 4 and within 1 month after the end of Cycle 16, and submit it to the representative of Takeda.

If treatment with Adcetris is discontinued for any reason before the end of the observation period, the investigator will complete the case report form within 1 month after the completion of required observation submit it to the representative of Takeda. If treatment with Adcetris is discontinued due to any adverse event, however, the investigator will continue to observe the patient after treatment discontinuation until the adverse event resolves or improves wherever possible, and then complete the case report form and submit it to the representative of Takeda.

7.5 Confirmation of all-case surveillance

After the completion of the study, the principal investigator will confirm that case report forms of all patients treated with Adcetris have been submitted, and sign or fill in his/her name with seal on All-Case Surveillance Confirmation Form and submit it to the representative of Takeda.

8.0 Estimated Study Period

Study period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Patient enrollment period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

The expected number of enrolled patients (140) was achieved. Therefore, the study will move to the period only requiring patient enrollment (not requiring the completion and submission of case report forms).

After moving to the period only requiring patient enrollment, it may be required to complete and submit case report forms upon request by the regulatory authority.

9.0 Outcome Measures

The investigator will record data listed below in both Patient Enrollment and Case Report Forms. Study schedule is provided in in Appendix 1.

9.1 Data to be recorded in Patient Enrollment Form

1) Outcome measures

Name of the institution, name of the investigator completing Patient Enrollment Form, expected date of the start of treatment with Adcetris, patient identification number, patient initial, sex, date of birth, diagnosis, performance status, CD30, past history of severe hypersensitivity to any ingredient of Adcetris, expected concomitant use of other antineoplastic drugs, and presence/absence of infections, peripheral nerve disorders, hepatic disorders, severe renal disorders, or pregnancy/breast-feeding

2) When to collect outcome measure data

At the time of patient enrollment

9.2 Data to be recorded in Case Report Form

9.2.1 Cover sheet of Case Report Form

Date of the finial completion of Case Report Form and name of the investigator completing Case Report Form

9.2.2 Patient demographics and baseline characteristics

1) Outcome measures

Date of diagnosis of Hodgkin's or anaplastic large cell lymphoma, site of involvement, ALK (in patients with anaplastic large cell lymphoma), clinical stage, presence/absence of B symptoms, ECOG Performance Status, therapeutic category, (presence/absence and detail of) hypersensitivity disposition, viral test results, past history of and concurrent pulmonary disorders, past history of and concurrent malignant tumours, (presence/absence and detail of) concurrent illnesses [other than pulmonary disorders and malignant tumours], (presence/absence and detail of) past history[other than pulmonary disorders and malignant tumours], height, weight, smoking history, and (presence/absence and detail of) prior treatment for Hodgkin's lymphoma or anaplastic large cell lymphoma (including drug therapy, radiotherapy, and hematopoietic stem cell transplantation)

2) When to collect outcome measure data

At the start of treatment with Adcetris

9.2.3 Treatment given

1) Outcome measures

Treatment with Adcetris and premedication to prevent infusion reaction (dose, date of premedication, and reasons for premedication to prevent infusion reaction and its discontinuation), (use or non-use, type, and date of) post-baseline hematopoietic stem cell transplantation, (presence/absence, name, and duration of) drugs other than Adcetris used for the treatment of the primary disease, and (presence/absence, name, and duration of) drugs used for the prevention of infection

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4 Tests and assessments

9.2.4.1 Laboratory tests

1) Outcome measures

Red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, total bilirubin, AST, ALT, LDH, BUN, and serum creatinine

2) When to collect outcome measure data

At each test time point during the period from the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4.2 Best response

1) Outcome measures

The best response (CR, CRu [for patients with no PET scan data], PR, SD, or PD) will be assessed based on CT and PET scans of the neck, chest, abdomen, and pelvis according to the best response assessment criteria (see Appendix).

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.3 Date of the final observation

1) Outcome measures

Date of the final observation

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.4 Other assessments

1) Outcome measures

Pregnancy during the observation period (for females only)

If pregnancy is detected during the observation period, it should be reported to the representative of Takeda immediately.

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.5 Adverse events

1) Outcome measures

Presence/absence of adverse events (see Table 1), adverse event terms, date of onset, CTCAE grade (the worst one), seriousness and its reason (see Table 2), (presence/absence and detail of) action taken to Adcetris, (presence/absence and detail of) intervention for adverse events, date of outcome, outcome, causal relationship with Adcetris* (see Table 3), and changes in laboratory test values associated with adverse events over time
If the outcome is "not recovered/not resolved" or "unknown," and the causal relationship with Adcetris is considered unevaluable, the event should be followed wherever possible.

* If the event is considered not related to Adcetris, its rationale should be collected. If the causal relationship with Adcetris is considered unevaluable, its reason should be collected.

Note) Points to consider regarding adverse events

Worsening of the primary disease should not be regarded as an adverse event. However, abnormal worsening of the primary disease (e.g., worsening beyond the expected natural course of the disease) should be regarded as an adverse event.

Disease progression should be regarded as worsening of the primary disease rather than an adverse event. However, clinical or laboratory progression of an existing cancer (including new metastasis) that meets any of the criteria for the seriousness of adverse events (see Table 2) should be considered a serious adverse event.

2) Adverse events of particular interest

The events listed below are events of particular interest; detailed information on these events should be collected wherever possible it they are observed:

- Peripheral nerve disorders
- Infections
- Neutropenia
- Infusion reactions
- Pulmonary disorders

* Rationale for the selection of adverse events of particular interest

Of important identified risks listed in Risk Management Plan, those listed above were selected as adverse events of particular interest based on the following rationales:

a) Peripheral nerve disorders

Peripheral nerve disorders are frequently observed after treatment with Adcetris. If the event of peripheral nerve disorder becomes severe, it is difficult to continue treatment with Adcetris. It is important to control the onset of the event to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption). Therefore, the profile of peripheral nerve disorders in Japanese patients as an adverse event of particular interest will be determined (i.e., information useful for continuation of treatment with Adcetris, including risk factors, commonly reported time to onset, outcomes, and the status of treatment with Adcetris, will be collected).

b) Infections

It is expected that Adcetris is used in patients who are immunocompromised due to prior treatment or the prior disease or those who are complicated with infection, and the incidence of infections is likely to be high. Therefore, the profile of infections in Japanese patients as an adverse event of particular interest (i.e., the incidence and temporal relationship with the onset of neutropenia/lymphopenia) will be determined.

c) Neutropenia

It is expected that Adcetris is used in patients with decreased neutrophil count due to prior treatment, which may increase the risk of infection and result in a high incidence of infection/severe infection. It is important to control the neutrophil count to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption) in terms of the prevention of infection. Therefore, the profile of neutropenia in Japanese patients as an adverse event of particular interest will be determined (i.e., the status of treatment with Adcetris and neutrophil count control will be assessed and information useful for continuation of treatment with Adcetris will be collected).

d) Infusion reactions

Infusion reactions are characteristic of monoclonal antibody preparations, the profile of infusion reactions in Japanese patients as an adverse event of particular interest (including the status of premedication and the percentage of patients using premedication to prevent infusion reactions [use/non-use of premedication to prevent infusion reactions]) will be determined.

e) Pulmonary disorders

The occurrence of pulmonary disorders in Japanese patients receiving monotherapy with Adcetris as an adverse event of particular interest will be determined.

3) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

Table 1 Definition of an Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a patient linked in time with the use of a pharmaceutical/ medicinal product and which does not necessarily have to have a causal relationship with this treatment or may or may not be considered related to the product.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Adverse events also include:
• Symptoms observed in an infant breast-fed by a mother receiving treatment with Adcetris.

Table 2 Criteria for the Seriousness of Adverse Events

An adverse event meeting any of the following criteria will be considered serious:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is a medically important condition due to any of the above 1 to 5, including those listed in "Takeda Medically Significant AE List."

Takeda Medically Significant AE List

• Acute respiratory failure/acute respiratory distress syndrome (ARDS)	• Anaphylactic shock
• Torsade de pointes/ventricular fibrillation/ventricular tachycardia	• Acute kidney failure
• Malignant hypertension	• Pulmonary hypertension
• Convulsive seizure (including convulsion and epilepsy)	• Pulmonary fibrosis (including interstitial pneumonia)
• Agranulocytosis	• Neuroleptic malignant syndrome/malignant hyperthermia
• Aplastic anemia	• Spontaneous abortion/stillbirth and fetal death
• Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)	• (Suspected) transmission of infection via a drug
• Hepatic necrosis	• (Suspected) endotoxic shock
• Acute hepatic failure	

Table 3 Criteria for the Assessment of Causal Relationship between Adverse Events and Adcetris

Causality	Assessment criterion
Related	There is a temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation). Or, there are other contributing factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies, but it is also likely that the event is attributable to Adcetris.
Not related	There is no temporal relationship between the event and Adcetris. Or, it is very likely that the event is attributable to other factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies.
Indeterminate	There is limited information required for the assessment of causal relationship, such as temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation), the primary disease, concurrent illnesses, and concomitant medications/therapies.

10.0 Data to Be Analyzed and Methods of Analysis

10.1 Patient disposition

Data to be analyzed includes the number of enrolled patients, the number of patients whose case report forms are available, and the number of patients included in and excluded from the safety/efficacy analysis set and reasons for inclusion/exclusion.

10.2 Patient demographics and baseline characteristics

Data to be analyzed includes sex, age, disease duration, site of involvement, and clinical stage.

10.3 Treatment given

Data to be analyzed includes the status of treatment with Adcetris and concomitant medications.

10.4 Safety

The measures specified below will be analyzed using the safety analysis set. Adverse events will be coded using MedDRA/J and summarized using (Preferred Terms [PTs]) and System Organ Classes [SOCs]).

10.4.1 Occurrence of adverse events

The frequency of adverse events observed during the observation period will be analyzed by type, time of onset, seriousness, and Adcetris.

10.4.2 Factors that may affect the safety of Adcetris

The frequency of adverse events observed during the observation period will be analyzed by patient background factors (sex, age, presence/absence of concurrent renal disorders, and presence/absence of concurrent hepatic disorders) and treatment given (the status of treatment with Adcetris and concomitant medications).

10.4.3 Changes in laboratory test data over time

Summary statistics of laboratory test values at baseline and post-baseline will be calculated.

10.5 Efficacy

The measures specified below will be analyzed using the efficacy analysis set.

10.5.1 Best response

The best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed.

10.5.2 Overall survival

The time to death (regardless of the cause of death) will be analyzed using the "final observation date" in specified in Section 9.2.4.3 as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field specified in Section 9.2.5 as the date of death

10.6 Interim analyses

For patients whose case report forms are collected through November 30, 2014 with evaluable safety evaluation, analyses similar to the ones described in Sections 10.1 to 10.4 will be performed to evaluate and analyze safety information obtained in this study at an early stage and publish them as appropriate.

11.0 Posting of Information Regarding This Study

Prior to the start of the study, Takeda Pharmaceutical Company Limited will register information regarding this study to the public website specified below.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- ClinicalTrials.gov (a clinical trial registration system provided by the National Institutes of Health)

12.0 Organizational Structure

12.1 Person responsible for administration

PPD, Takeda Pharmaceutical Company Limited

12.2 Proper Use Committee

The committee will provide advice on the protocol, data analysis, publication of study results, promotion of the proper use of Adcetris, and safety measures.

(Listed in the order of the Japanese syllabary)

12.3 Central Enrollment Center

13.0 Contract Research Organization

14.0 Other Important Information

14.1 Protocol amendment

During the study, the sponsor will monitor the occurrence of adverse drug reactions and serious adverse drug reactions that cannot be predicted by the progress of the study and precautions for use, the presence/absence of an increase in the frequency of specific adverse drug reactions, and the appropriateness of outcome measures, and review and amend this protocol as appropriate. If the approval of partial changes to “Dosage and Administration” or “Indication” is obtained during the study, the sponsor will consider the necessity of amendment of this protocol as appropriate, and amend the protocol as appropriate.

14.2 Measures to be taken in response to issues/questions

If any safety and/or efficacy issue is detected, the sponsor will examine data closely and consider what measures should be taken.

Appendix 1 Study Schedule

Time point / Procedure		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Patient enrollment	Date of the expected initial dose of Adcetris	○				
	Patient identification number	○				
	Patient initial	○				
	Sex	○				
	Date of birth	○				
	Diagnosis	○				
	Performance status	○				
	CD30	○				
	Past history of severe hypersensitivity to any ingredient of Adcetris	○				
	Expected concomitant use of other antineoplastic drugs	○				
	Presence/absence of infections	○				
	Presence/absence of peripheral nerve disorders	○				
	Presence/absence of hepatic disorders	○				
	Presence/absence of severe renal disorders	○				
	Presence/absence of pregnancy/breast-feeding	○				
Patient demographics and baseline characteristics	Date of diagnosis of Hodgkin or anaplastic large-cell lymphoma		○			
	Site of involvement		○			
	ALK (in patients with anaplastic large cell lymphoma)		○			
	Clinical stage		○			
	Presence/absence of B symptoms		○			
	ECOG Performance Status		○			
	Therapeutic category		○			
	Hypersensitivity disposition		○			
	Viral test results		○			
	Past history of and concurrent pulmonary disorders		○			
	Past history of and concurrent malignant tumours		○			
	Concurrent illness (other than pulmonary disorders and malignant tumours)		○			
	Past history (other than pulmonary disorders and malignant tumours)		○			
	Height and weight		○			
	Smoking history		○			
	Prior treatment for Hodgkin's or anaplastic large cell lymphoma		○			

	Procedure \ Time point	Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Treatment given	Treatment with Adcetris		○	○		
	Post-baseline hematopoietic stem cell transplantation		←○→			○
	Drug(s) other than Adcetris used for the treatment of the primary disease		←○→			○
	Drug(s) used for the prevention of infection		←○→			○
Tests and assessments	Laboratory tests (red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, and liver and kidney function tests)		←○→			○
	Best response				○	○
	Date of the final observation				○	○
	Presence/absence of pregnancy (for females only)		←○→			○
	Adverse events		←○→			○

○ : Data collected

←○→: Data collected throughout the period

Appendix 2 Best Response Assessment Criteria (Revised Response Criteria for Malignant Lymphoma*)

* Extracted from "General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, March 2000 [First Edition])

For patients with PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma The patient is PET negative. If the patient is PET negative, any residual tumor on CT does not matter. 1)-2Variably FDG-avid lymphoma The patient did not undergo PET before treatment. If the patient was negative before treatment, the patient must meet all the following criteria: [1] All nodal target lesions are normal. [2] All extranodal target lesions have resolved. [3] All nodal non-target lesions are normal. [4] The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. [5] All extranodal non-target lesions have resolved. 2) A patient with bone marrow infiltration at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as "negative" because bone marrow test is not required. 3) The patient has no new lesion.
PR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma If the patient had one or more PET positive lesions, or was PET negative AND had bone marrow infiltration at baseline, the patient must be positive for bone marrow infiltration at the time of restaging (or have not undergone testing). 1)-2Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 3) All nodal non-target lesions are normal or free from enlargement. 4) All extranodal non-target lesions have resolved or free from enlargement. 5) Bone marrow infiltration does not matter. Testing is not required. 6) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR but meets any of the criteria 1 and 2 to 6 and 7 listed below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR, the patient will be assessed as having a relapsed disease (RD): 1)-1 Routinely FDG-avid lymphoma The patient has one or more PET positive lesions. 1)-2 Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 3) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long

	diameter) or re-enlargement. 4) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 5) The long diameter of the nodal target lesion which was once normalized and assessed as CR exceeded 1.5 cm. The extranodal target lesion which once resolved reappeared. 6) The patient has a new lesion. 7) The patient became positive after being once negative for bone marrow infiltration.

For patients with no PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. 5) All extranodal non-target lesions have resolved. 6) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 7) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 8) A patient with bone marrow infiltration or indeterminate at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 9) The patient has no new lesion.
CRu	The patient had bone marrow infiltration or was indeterminate at baseline AND meets all the following criteria: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) All extranodal non-target lesions have resolved. 5) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 6) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 7) The patient is indeterminate for bone marrow infiltration. 8) The patient has no new lesion. OR 1) The patient has a 75% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal. 3) All extranodal non-target lesions have resolved. 4) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 5) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 6) The patient has no bone marrow infiltration or indeterminate.

	7) The patient has no new lesion.
PR	The patient meets all the above criteria for CRu except for criterion 6. A patient with bone marrow infiltration or indeterminate at baseline must be positive for bone marrow infiltration at the time of restaging. Or, the patient meets all the following criteria: 1) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal or free from enlargement. 3) All extranodal non-target lesions have resolved or free from enlargement. 4) Enlarged liver, spleen, and kidneys have resolved or are free from progression. 5) All tumor-related symptom (fever and night sweat) have resolved. AND abnormal tumor-related laboratory test results (tumor-related increase in LDH) became normal. 6) Bone marrow infiltration does not matter. Testing is not required. 7) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR or CRu but meets any of the criteria below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR or CRu, the patient will be assessed as having a relapsed disease (RD): 1) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 2) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 3) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 4) The extranodal target lesion which once resolved and was assesses as CR or CRu reappeared. 5) Obvious progression or recurrence of enlarged liver, spleen, or kidney. 6) Obvious progression or recurrence of tumor-related subjective and objective symptoms (fever and night sweat) or abnormal tumor-related laboratory test results (tumor-related increase in LDH). 7) The patient became positive after being once negative for bone marrow infiltration. 8) The patient has a new lesion.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Adcetris IV Infusion

(All-Case Surveillance)

“Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma”

Version number	**2**
Date of creation	**August 25, 2014**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

There is limited safety information on Adcetris IV Infusion 50 mg (hereinafter referred to as Adcetris) collected from Japanese patients in Japanese phase 1/2 studies. It is important to promptly collect post-marketing safety information and provide it to healthcare providers. It was also deemed that additional surveillance was required to determine the occurrence of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders in patients using Adcetris in Japan as post-marketing safety specifications.

Thus, an all-case surveillance in all patients receiving treatment with Adcetris will be initiated as an additional pharmacovigilance activity for Adcetris when the drug is launched.

This surveillance study will be conducted in compliance with the GPSP Ordinance and other related regulatory requirements.

2.0 Purpose

The purpose of this study is to evaluate the safety of Adcetris in patients with relapsed/refractoryCD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma in the routine clinical setting, as well as to collect efficacy information for reference.

3.0 Estimated Enrollment and Its Rationale

3.1 Estimated enrollment

140 patients (with relapsed/refractory CD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma)

3.2 Rationale

It is expected that the detailed evaluation of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders will help better understand the safety profile of Adcetris in the routine clinical setting, which will lead to the assessment of the risk-benefit balance of the drug.

The frequencies of peripheral nerve disorders, infections, neutropenia (≥Grade 3), infusion reaction, and pulmonary disorder in non-Japanese phase 2 studies (pooled study data from a study in patients with Hodgkin's lymphoma [SG035-0003, 102 patients] and a study in patients with systemic anaplastic large cell lymphoma [SG035-0004, 58 patients]) were 56%, 61%, 20%, 11%, and 6%, respectively.

Observation of infusion reactions with the lowest frequency of ≥10 patients, aside from pulmonary disorders, with a probability of 95% would require 140 patients, which was therefore determined to be the estimated enrollment. It is estimated that when the number of patients enrolled reaches 140 patients, ≥4 patients have adverse events of pulmonary disorder with a probability of 95%.

4.0 Eligible Patients

All patients receiving treatment with Adcetris

5.0 Dosage Regimen

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (recombinant) infused intravenously once every three weeks. The dose should be adjusted depending on the patient's condition.

See the "PRECAUTIONS" section of the package insert.

6.0 Expected Study Institutions by Department

The study will be conducted at all institutions using Adcetris (e.g., department of hematology) (approximately 100 study institutions are expected to participate in the study).

7.0 Methods

7.1 Observation period

From the start of treatment with Adcetris until the completion of 16 cycles [3 weeks per cycle]

* Rationale for the selection of the observation period

The assessment of the treatment cycle with the initial onset of adverse events in a clinical study [SGN35-006, the extended treatment group] evaluating the safety of Adcetris after Cycle 17 showed a tendency that most adverse events occurred before Cycle 16. In addition, the types and severities did not differ between adverse events occurring after Cycle 17 and those occurring before Cycle 16. This suggested that the safety profile of Adcetris would be generally determined before Cycle 16. Therefore, the observation period was defined as the period from the start of treatment with Adcetris until the completion of 16 cycles.

7.2 Request for participation in this study and contract with each study institution

Paper-based case report forms will be used. To ask each study institution to participate in the study, the medical representative of Takeda Pharmaceutical Company Limited (Takeda MR) will confirm before supply of Adcetris and the start of the study that each study institution meets all requirements for study institutions and investigators specified below, and have a written contract with the study institution after prior explanation of the study provided before supply of Adcetris.

(1) Requirements for each study institution and investigator

1) Requirements for each study institution

[1] Is able to cooperate with this all-case surveillance and have a contract with the sponsor.

[2] Is able to provide specialized treatment for hematopoietic tumors.

[3] Is able to provide emergency treatment if required (including a case where such a treatment can be provided in conjunction with another institution

).

* When emergency treatment is provided in conjunction with another institution, information on Adcetris safety measures and treatment of adverse drug reactions should be shared between the institution and the other institution to build a coalition.

2) Requirements for each investigator

[1] Has adequate knowledge and experience regarding the treatment of hematopoietic tumors, or is under the direction of a healthcare professional having such knowledge and experience.

[2] Is able to cooperate with this all-case surveillance.

(2) Prior explanation of the study to be provided before supply of Adcetris and the request for participation in this study

Using "Request for Participation in the Special Drug Use Surveillance," "Study Outline," "Patient Enrollment Form (sample)," "Case Report Form Parts 1 and 2 (sample)," "Precautions for Use/Instruction Manual," and "Proper Usage Guide," the Takeda MR will explain the purpose and methods (e.g., all-case surveillance) of this survey study and information regarding the proper use of Adcetris to the investigator and ask him/her to participate in the all-case surveillance.

The Takeda MR will also confirm with the investigator that the institution and the investigator meet all requirements.

(3) Request for participation in this study and contract with each study institution

The Takeda MR will have a written contract with the study institution after obtaining their agreement to participate in this study Takeda Pharmaceutical Company Limited will inform the outsourced Adcetris supplier that the contract is concluded and Adcetris should be supplied to the study institution. The Takeda MR will deliver patient enrollment forms to the investigator.

7.3 Method of patient enrollment

The central enrollment method via FAX will be used. For each patient scheduled to receive treatment with Adcetris after the date of the start of the term of the contract with the study institution, the investigator will complete patient enrollment by submitting the Patient Enrollment Form with information required for patient enrollment filled in (see Section 9.1) via FAX to the Central Enrollment Center (see Section 12.3) until noon of the day before the date of the expected initial dose of Adcetris.

The Central Enrollment Center will review the Patient Enrollment Form and send the Enrollment Completion Notice to the investigator via FAX. After receiving the Enrollment Completion Notice, the investigator will initiate treatment with Adcetris.

The Case Report Form consists of Parts 1 and 2 per patient.

The Takeda MR will deliver Case Report Form Part 1, which is issued after enrollment confirmation by the Central Enrollment Center, to the investigator. Case Report Form Part 2 is issued after the completion of follow-up on Case Report Form Part 1.

7.4 Completion and submission of the case report form

For all patients requiring the completion of the case report form, the investigator will complete the case report form during the period from the start of treatment with Adcetris until the end of Cycle 4 and within 1 month after the end of Cycle 16, and submit it to the Takeda MR.

If treatment with Adcetris is discontinued for any reason before the end of the observation period, the investigator will complete the case report form within 1 month after the completion of required observation submit it to the Takeda MR. If treatment with Adcetris is discontinued due to any adverse event, however, the investigator will continue to observe the patient after treatment discontinuation until the adverse event resolves or improves wherever possible, and then complete the case report form and submit it to the Takeda MR.

7.5 Confirmation of all-case surveillance

After the completion of the study, the principal investigator will confirm that case report forms of all patients treated with Adcetris have been submitted, and sign or fill in his/her name with seal on All-Case Surveillance Confirmation Form and submit it to the Takeda MR.

8.0 Estimated Study Period

Study period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Patient enrollment period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

The expected number of enrolled patients (140) was achieved. Therefore, the study will move to the period only requiring patient enrollment (not requiring the completion and submission of case report forms).

After moving to the period only requiring patient enrollment, it may be required to complete and submit case report forms upon request by the regulatory authority.

9.0 Outcome Measures

The investigator will record data listed below in both Patient Enrollment and Case Report Forms. Study schedule is provided in in Appendix 1.

9.1 Data to be recorded in Patient Enrollment Form

1) Outcome measures

Name of the institution, name of the investigator completing Patient Enrollment Form,

expected date of the start of treatment with Adcetris, patient identification number, patient initial, sex, date of birth, diagnosis, performance status, CD30, past history of severe hypersensitivity to any ingredient of Adcetris, expected concomitant use of other antineoplastic drugs, and presence/absence of infections, peripheral nerve disorders, hepatic disorders, severe renal disorders, or pregnancy/breast-feeding

2) When to collect outcome measure data

At the time of patient enrollment

9.2 Data to be recorded in Case Report Form

9.2.1 Cover sheet of Case Report Form

Date of the finial completion of Case Report Form and name of the investigator completing Case Report Form

9.2.2 Patient demographics and baseline characteristics

1) Outcome measures

Date of diagnosis of Hodgkin's or anaplastic large cell lymphoma, site of involvement, ALK (in patients with anaplastic large cell lymphoma), clinical stage, presence/absence of B symptoms, ECOG Performance Status, therapeutic category, (presence/absence and detail of) hypersensitivity disposition, viral test results, past history of and concurrent pulmonary disorders, past history of and concurrent malignant tumours, (presence/absence and detail of) concurrent illnesses [other than pulmonary disorders and malignant tumours], (presence/absence and detail of) past history[other than pulmonary disorders and malignant tumours], height, weight, smoking history, and (presence/absence and detail of) prior treatment for Hodgkin's lymphoma or anaplastic large cell lymphoma (including drug therapy, radiotherapy, and hematopoietic stem cell transplantation)

2) When to collect outcome measure data

At the start of treatment with Adcetris

9.2.3 Treatment given

1) Outcome measures

Treatment with Adcetris and premedication to prevent infusion reaction (dose, date of premedication, and reasons for premedication to prevent infusion reaction and its discontinuation), (use or non-use, type, and date of) post-baseline hematopoietic stem cell transplantation, (presence/absence, name, and duration of) drugs other than Adcetris used for the treatment of the primary disease, and (presence/absence, name, and duration of) drugs used for the prevention of infection

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4 Tests and assessments

9.2.4.1 Laboratory tests

1) Outcome measures

Red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, total bilirubin, AST, ALT, LDH, BUN, and serum creatinine

2) When to collect outcome measure data

At each test time point during the period from the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4.2 Best response

1) Outcome measures

The best response (CR, CRu [for patients with no PET scan data], PR, SD, or PD) will be assessed based on CT and PET scans of the neck, chest, abdomen, and pelvis according to the best response assessment criteria (see Appendix).

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.3 Date of the final observation

1) Outcome measures

Date of the final observation

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.4 Other assessments

1) Outcome measures

Pregnancy during the observation period (for females only)

If pregnancy is detected during the observation period, it should be reported to the Takeda MR immediately.

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.5 Adverse events

1) Outcome measures

Presence/absence of adverse events (see Table 1), adverse event terms, date of onset, CTCAE grade (the worst one), seriousness and its reason (see Table 2), (presence/absence and detail of) action taken to Adcetris, (presence/absence and detail of) intervention for

adverse events, date of outcome, outcome, causal relationship with Adcetris* (see Table 3), and changes in laboratory test values associated with adverse events over time
If the outcome is "not recovered/not resolved" or "unknown," and the causal relationship with Adcetris is considered unevaluable, the event should be followed wherever possible.

* If the event is considered not related to Adcetris, its rationale should be collected. If the causal relationship with Adcetris is considered unevaluable, its reason should be collected.

Note) Points to consider regarding adverse events

Worsening of the primary disease should not be regarded as an adverse event. However, abnormal worsening of the primary disease (e.g., worsening beyond the expected natural course of the disease) should be regarded as an adverse event.

Disease progression should be regarded as worsening of the primary disease rather than an adverse event. However, clinical or laboratory progression of an existing cancer (including new metastasis) that meets any of the criteria for the seriousness of adverse events (see Table 2) should be considered a serious adverse event.

2) Adverse events of particular interest

The events listed below are events of particular interest; detailed information on these events should be collected wherever possible it they are observed:

- Peripheral nerve disorders
- Infections
- Neutropenia
- Infusion reactions
- Pulmonary disorders

* Rationale for the selection of adverse events of particular interest

Of important identified risks listed in Risk Management Plan, those listed above were selected as adverse events of particular interest based on the following rationales:

a) Peripheral nerve disorders

Peripheral nerve disorders are frequently observed after treatment with Adcetris. If the event of peripheral nerve disorder becomes severe, it is difficult to continue treatment with Adcetris. It is important to control the onset of the event to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption). Therefore, the profile of peripheral nerve disorders in Japanese patients as an adverse event of particular interest will be determined (i.e., information useful for continuation of treatment with Adcetris, including risk factors, commonly reported time to onset, outcomes, and the status of treatment with Adcetris, will be collected).

b) Infections

It is expected that Adcetris is used in patients who are immunocompromised due to prior treatment or the prior disease or those who are complicated with infection, and the incidence of infections is likely to be high. Therefore, the profile of infections in Japanese

patients as an adverse event of particular interest (i.e., the incidence and temporal relationship with the onset of neutropenia/lymphopenia) will be determined.

c) Neutropenia

It is expected that Adcetris is used in patients with decreased neutrophil count due to prior treatment, which may increase the risk of infection and result in a high incidence of infection/severe infection. It is important to control the neutrophil count to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption) in terms of the prevention of infection. Therefore, the profile of neutropenia in Japanese patients as an adverse event of particular interest will be determined (i.e., the status of treatment with Adcetris and neutrophil count control will be assessed and information useful for continuation of treatment with Adcetris will be collected).

d) Infusion reactions

Infusion reactions are characteristic of monoclonal antibody preparations, the profile of infusion reactions in Japanese patients as an adverse event of particular interest (including the status of premedication and the percentage of patients using premedication to prevent infusion reactions [use/non-use of premedication to prevent infusion reactions]) will be determined.

e) Pulmonary disorders

The occurrence of pulmonary disorders in Japanese patients receiving monotherapy with Adcetris as an adverse event of particular interest will be determined.

3) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

Table 1 Definition of an Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a patient linked in time with the use of a pharmaceutical/ medicinal product and which does not necessarily have to have a causal relationship with this treatment or may or may not be considered related to the product.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Adverse events also include:

・Symptoms observed in an infant breast-fed by a mother receiving treatment with Adcetris.

Table 2 Criteria for the Seriousness of Adverse Events

An adverse event meeting any of the following criteria will be considered serious:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is a medically important condition due to any of the above 1 to 5, including those listed in "Takeda Medically Significant AE List."

Takeda Medically Significant AE List

•Acute respiratory failure/acute respiratory distress syndrome (ARDS)	•Anaphylactic shock
•Torsade de pointes/ventricular fibrillation/ventricular tachycardia	•Acute kidney failure
•Malignant hypertension	•Pulmonary hypertension
•Convulsive seizure (including convulsion and epilepsy)	•Pulmonary fibrosis (including interstitial pneumonia)
•Agranulocytosis	•Neuroleptic malignant syndrome/malignant hyperthermia
•Aplastic anemia	•Spontaneous abortion/stillbirth and fetal death
•Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)	•(Suspected) transmission of infection via a drug
•Hepatic necrosis	•(Suspected) endotoxic shock or
•Acute hepatic failure	

Table 3 Criteria for the Assessment of Causal Relationship between Adverse Events and Adcetris

Causality	Assessment criterion
Related	There is a temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation). Or, there are other contributing factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies, but it is also likely that the event is attributable to Adcetris.
Not related	There is no temporal relationship between the event and Adcetris. Or, it is very likely that the event is attributable to other factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies.
Indeterminate	There is limited information required for the assessment of causal relationship, such as temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation), the primary disease, concurrent illnesses, and concomitant medications/therapies.

10.0 Data to Be Analyzed and Methods of Analysis

10.1 Patient disposition

Data to be analyzed includes the number of enrolled patients, the number of patients whose case report forms are available, and the number of patients included in and excluded from the safety/efficacy analysis set and reasons for inclusion/exclusion.

10.2 Patient demographics and baseline characteristics

Data to be analyzed includes sex, age, disease duration, site of involvement, and clinical stage.

10.3 Treatment given

Data to be analyzed includes the status of treatment with Adcetris and concomitant medications.

10.4 Safety

The measures specified below will be analyzed using the safety analysis set. Adverse events will be coded using MedDRA/J and summarized using (Preferred Terms [PTs]) and System Organ Classes [SOCs]).

10.4.1 Occurrence of adverse events

The frequency of adverse events observed during the observation period will be analyzed by type, time of onset, seriousness, and Adcetris.

10.4.2 Factors that may affect the safety of Adcetris

The frequency of adverse events observed during the observation period will be analyzed by patient background factors (sex, age, presence/absence of concurrent renal disorders, and presence/absence of concurrent hepatic disorders) and treatment given (the status of treatment with Adcetris and concomitant medications).

10.4.3 Changes in laboratory test data over time

Summary statistics of laboratory test values at baseline and post-baseline will be calculated.

10.5 Efficacy

The measures specified below will be analyzed using the efficacy analysis set.

10.5.1 Best response

The best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed.

10.5.2 Overall survival

The time to death (regardless of the cause of death) will be analyzed using the "final observation date" in specified in Section 9.2.4.3 as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field specified in Section 9.2.5 as the date of death

10.6 Interim analyses

For patients whose case report forms are collected through November 30, 2014 with evaluable safety evaluation, analyses similar to the ones described in Sections 10.1 to 10.4 will be performed to evaluate and analyze safety information obtained in this study at an early stage and publish them as appropriate.

11.0 Posting of Information Regarding This Study

Prior to the start of the study, Takeda Pharmaceutical Company Limited will register information regarding this study to the public website specified below.

- Japan Pharmaceutical Information Center-Clinical Trials Information
- ClinicalTrials.gov (a clinical trial registration system provided by the National Institutes of Health)

12.0 Organizational Structure

12.1 Person responsible for administration

PPD

Takeda Pharmaceutical Company Limited

12.2 Proper Use Committee

The committee will provide advice on the protocol, data analysis, publication of study results, promotion of the proper use of Adcetris, and safety measures.

PPD

(Listed in the order of the Japanese syllabary)

12.3 Central Enrollment Center

PPD

13.0 Contract Research Organization

PPD

14.0 Other Important Information

14.1 Protocol amendment

During the study, the sponsor will monitor the occurrence of adverse drug reactions and serious adverse drug reactions that cannot be predicted by the progress of the study and precautions for use, the presence/absence of an increase in the frequency of specific adverse drug reactions, and the appropriateness of outcome measures, and review and amend this protocol as appropriate. If the approval of partial changes to “Dosage and Administration” or “Indication” is obtained during the study, the sponsor will consider the necessity of amendment of this protocol as appropriate, and amend the protocol as appropriate.

14.2 Measures to be taken in response to issues/questions

If any safety and/or efficacy issue is detected, the sponsor will examine data closely and consider what measures should be taken.

Appendix 1 Study Schedule

Procedure \ Time point		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Patient enrollment	Date of the expected initial dose of Adcetris	○				
	Patient identification number	○				
	Patient initial	○				
	Sex	○				
	Date of birth	○				
	Diagnosis	○				
	Performance status	○				
	CD30	○				
	Past history of severe hypersensitivity to any ingredient of Adcetris	○				
	Expected concomitant use of other antineoplastic drugs	○				
	Presence/absence of infections	○				
	Presence/absence of peripheral nerve disorders	○				
	Presence/absence of hepatic disorders	○				
	Presence/absence of severe renal disorders	○				
	Presence/absence of pregnancy/breast-feeding	○				
Patient demographics and baseline characteristics	Date of diagnosis of Hodgkin or anaplastic large-cell lymphoma		○			
	Site of involvement		○			
	ALK (in patients with anaplastic large cell lymphoma)		○			
	Clinical stage		○			
	Presence/absence of B symptoms		○			
	ECOG Performance Status		○			
	Therapeutic category		○			
	Hypersensitivity disposition		○			
	Viral test results		○			
	Past history of and concurrent pulmonary disorders		○			
	Past history of and concurrent malignant tumours		○			
	Concurrent illness (other than pulmonary disorders and malignant tumours)		○			
	Past history (other than pulmonary disorders and malignant tumours)		○			
	Height and weight		○			
	Smoking history		○			
	Prior treatment for Hodgkin's or anaplastic large cell lymphoma		○			

Procedure \ Time point		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Treatment given	Treatment with Adcetris		○	○		
	Post-baseline hematopoietic stem cell transplantation		←○→			○
	Drug(s) other than Adcetris used for the treatment of the primary disease		←○→			○
	Drug(s) used for the prevention of infection		←○→			○
Tests and assessments	Laboratory tests (red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, and liver and kidney function tests)		←○→			○
	Best response				○	○
	Date of the final observation				○	○
	Presence/absence of pregnancy (for females only)		←○→			○
	Adverse events		←○→			○

○ : Data collected

←○→: Data collected throughout the period

Appendix 2 Best Response Assessment Criteria (Revised Response Criteria for Malignant Lymphoma*)

* Extracted from "General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, March 2000 [First Edition])

For patients with PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma The patient is PET negative. If the patient is PET negative, any residual tumor on CT does not matter. 1)-2Variably FDG-avid lymphoma The patient did not undergo PET before treatment. If the patient was negative before treatment, the patient must meet all the following criteria: [1] All nodal target lesions are normal. [2] All extranodal target lesions have resolved. [3] All nodal non-target lesions are normal. [4] The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. [5] All extranodal non-target lesions have resolved. 2) A patient with bone marrow infiltration at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 3) The patient has no new lesion.
PR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma If the patient had one or more PET positive lesions, or was PET negative AND had bone marrow infiltration at baseline, the patient must be positive for bone marrow infiltration at the time of restaging (or have not undergone testing). 1)-2Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 3) All nodal non-target lesions are normal or free from enlargement. 4) All extranodal non-target lesions have resolved or free from enlargement. 5) Bone marrow infiltration does not matter. Testing is not required. 6) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR but meets any of the criteria 1 and 2 to 6 and 7 listed below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR, the patient will be assessed as having a relapsed disease (RD): 1)-1 Routinely FDG-avid lymphoma The patient has one or more PET positive lesions. 1)-2 Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 3) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 4) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 5) The long diameter of the nodal target lesion which was once normalized and assessed as CR exceeded 1.5

	cm. The extranodal target lesion which once resolved reappeared. 6) The patient has a new lesion. 7) The patient became positive after being once negative for bone marrow infiltration.

For patients with no PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. 5) All extranodal non-target lesions have resolved. 6) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 7) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 8) A patient with bone marrow infiltration or indeterminate at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 9) The patient has no new lesion.
CRu	The patient had bone marrow infiltration or was indeterminate at baseline AND meets all the following criteria: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) All extranodal non-target lesions have resolved. 5) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 6) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 7) The patient is indeterminate for bone marrow infiltration. 8) The patient has no new lesion. OR 1) The patient has a 75% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal. 3) All extranodal non-target lesions have resolved. 4) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 5) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 6) The patient has no bone marrow infiltration or indeterminate. 7) The patient has no new lesion.
PR	The patient meets all the above criteria for CRu except for criterion 6. A patient with bone marrow infiltration or indeterminate at baseline must be positive for bone marrow infiltration at the time of restaging. Or, the patient meets all the following criteria:

	1) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal or free from enlargement. 3) All extranodal non-target lesions have resolved or free from enlargement. 4) Enlarged liver, spleen, and kidneys have resolved or are free from progression. 5) All tumor-related symptom (fever and night sweat) have resolved. AND abnormal tumor-related laboratory test results (tumor-related increase in LDH) became normal. 6) Bone marrow infiltration does not matter. Testing is not required. 7) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR or CRu but meets any of the criteria below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR or CRu, the patient will be assessed as having a relapsed disease (RD): 1) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 2) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 3) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 4) The extranodal target lesion which once resolved and was assesses as CR or CRu reappeared. 5) Obvious progression or recurrence of enlarged liver, spleen, or kidney. 6) Obvious progression or recurrence of tumor-related subjective and objective symptoms (fever and night sweat) or abnormal tumor-related laboratory test results (tumor-related increase in LDH). 7) The patient became positive after being once negative for bone marrow infiltration. 8) The patient has a new lesion.

Special Drug Use Surveillance Protocol

Special Drug Use Surveillance of Adcetris IV Infusion

(All-Case Surveillance)

“Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma”

Version number	**Initial**
Date of creation	**January 17, 2014**
Sponsor	**Takeda Pharmaceutical Company Limited**

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1.0 Background

There is limited safety information on Adcetris IV Infusion 50 mg (hereinafter referred to as Adcetris) collected from Japanese patients in Japanese phase 1/2 studies. It is important to promptly collect post-marketing safety information and provide it to healthcare providers. It was also deemed that additional surveillance was required to determine the occurrence of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders in patients using Adcetris in Japan as post-marketing safety specifications.

Thus, an all-case surveillance in all patients receiving treatment with Adcetris will be initiated as an additional pharmacovigilance activity for Adcetris when the drug is launched.

This surveillance study will be conducted in compliance with the GPSP Ordinance and other related regulatory requirements.

2.0 Purpose

The purpose of this study is to evaluate the safety of Adcetris in patients with relapsed/refractoryCD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma in the routine clinical setting, as well as to collect efficacy information for reference.

3.0 Estimated Enrollment and Its Rationale

3.1 Estimated enrollment

140 patients (with relapsed/refractory CD30+ Hodgkin's lymphoma or anaplastic large cell lymphoma)

3.2 Rationale

It is expected that the detailed evaluation of peripheral nerve disorders, infections, neutropenia, infusion reactions, and pulmonary disorders will help better understand the safety profile of Adcetris in the routine clinical setting, which will lead to the assessment of the risk-benefit balance of the drug.

The frequencies of peripheral nerve disorders, infections, neutropenia (≥Grade 3), infusion reaction, and pulmonary disorder in non-Japanese phase 2 studies (pooled study data from a study in patients with Hodgkin's lymphoma [SG035-0003, 102 patients] and a study in patients with systemic anaplastic large cell lymphoma [SG035-0004, 58 patients]) were 56%, 61%, 20%, 11%, and 6%, respectively.

Observation of infusion reactions with the lowest frequency of ≥10 patients, aside from pulmonary disorders, with a probability of 95% would require 140 patients, which was therefore determined to be the estimated enrollment. It is estimated that when the number of patients enrolled reaches 140 patients, ≥4 patients have adverse events of pulmonary disorder with a probability of 95%.

4.0 Eligible Patients

All patients receiving treatment with Adcetris

5.0 Dosage Regimen

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (recombinant) infused intravenously once every three weeks. The dose should be adjusted depending on the patient's condition.

See the "PRECAUTIONS" section of the package insert.

6.0 Expected Study Institutions by Department

The study will be conducted at all institutions using Adcetris (e.g., department of hematology) (approximately 100 study institutions are expected to participate in the study).

7.0 Methods

7.1 Observation period

From the start of treatment with Adcetris until the completion of 16 cycles [3 weeks per cycle]

* Rationale for the selection of the observation period

The assessment of the treatment cycle with the initial onset of adverse events in a clinical study [SGN35-006, the extended treatment group] evaluating the safety of Adcetris after Cycle 17 showed a tendency that most adverse events occurred before Cycle 16. In addition, the types and severities did not differ between adverse events occurring after Cycle 17 and those occurring before Cycle 16. This suggested that the safety profile of Adcetris would be generally determined before Cycle 16. Therefore, the observation period was defined as the period from the start of treatment with Adcetris until the completion of 16 cycles.

7.2 Request for participation in this study and contract with each study institution

Paper-based case report forms will be used. To ask each study institution to participate in the study, the medical representative of Takeda Pharmaceutical Company Limited (Takeda MR) will confirm before supply of Adcetris and the start of the study that each study institution meets all requirements for study institutions and investigators specified below, and have a written contract with the study institution after prior explanation of the study provided before supply of Adcetris.

(1) Requirements for each study institution and investigator

1) Requirements for each study institution

[1] Is able to cooperate with this all-case surveillance and have a contract with the sponsor.

[2] Is able to provide specialized treatment for hematopoietic tumors.

[3] Is able to provide emergency treatment if required (including a case where such a treatment can be provided in conjunction with another institution

).

* When emergency treatment is provided in conjunction with another institution, information on Adcetris safety measures and treatment of adverse drug reactions should be shared between the institution and the other institution to build a coalition.

2) Requirements for each investigator

[1] Has adequate knowledge and experience regarding the treatment of hematopoietic tumors, or is under the direction of a healthcare professional having such knowledge and experience.

[2] Is able to cooperate with this all-case surveillance.

(2) Prior explanation of the study to be provided before supply of Adcetris and the request for participation in this study

Using "Request for Participation in the Special Drug Use Surveillance," "Study Outline," "Patient Enrollment Form (sample)," "Case Report Form Parts 1 and 2 (sample)," "Precautions for Use/Instruction Manual," and "Proper Usage Guide," the Takeda MR will explain the purpose and methods (e.g., all-case surveillance) of this survey study and information regarding the proper use of Adcetris to the investigator and ask him/her to participate in the all-case surveillance.

The Takeda MR will also confirm with the investigator that the institution and the investigator meet all requirements.

(3) Request for participation in this study and contract with each study institution

The Takeda MR will have a written contract with the study institution after obtaining their agreement to participate in this study Takeda Pharmaceutical Company Limited will inform the outsourced Adcetris supplier that the contract is concluded and Adcetris should be supplied to the study institution. The Takeda MR will deliver patient enrollment forms to the investigator.

7.3 Method of patient enrollment

The central enrollment method via FAX will be used. For each patient scheduled to receive treatment with Adcetris after the date of the start of the term of the contract with the study institution, the investigator will complete patient enrollment by submitting the Patient Enrollment Form with information required for patient enrollment filled in (see Section 9.1) via FAX to the Central Enrollment Center (see Section 12.3) until noon of the day before the date of the expected initial dose of Adcetris.

The Central Enrollment Center will review the Patient Enrollment Form and send the Enrollment Completion Notice to the investigator via FAX. After receiving the Enrollment Completion Notice, the investigator will initiate treatment with Adcetris.

The Case Report Form consists of Parts 1 and 2 per patient.
The Takeda MR will deliver Case Report Form Part 1, which is issued after enrollment confirmation by the Central Enrollment Center, to the investigator. Case Report Form Part 2 is issued after the completion of follow-up on Case Report Form Part 1.

7.4 Completion and submission of the case report form

For all patients requiring the completion of the case report form, the investigator will complete the case report form during the period from the start of treatment with Adcetris until the end of Cycle 4 and within 1 month after the end of Cycle 16, and submit it to the Takeda MR.
If treatment with Adcetris is discontinued for any reason before the end of the observation period, the investigator will complete the case report form within 1 month after the completion of required observation submit it to the Takeda MR. If treatment with Adcetris is discontinued due to any adverse event, however, the investigator will continue to observe the patient after treatment discontinuation until the adverse event resolves or improves wherever possible, and then complete the case report form and submit it to the Takeda MR.

7.5 Confirmation of all-case surveillance

After the completion of the study, the principal investigator will confirm that case report forms of all patients treated with Adcetris have been submitted, and sign or fill in his/her name with seal on All-Case Surveillance Confirmation Form and submit it to the Takeda MR.

8.0 Estimated Study Period

Study period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Patient enrollment period: Starts on the day of the launch of Adcetris (April, 2014) and ends once the all-case surveillance is no longer a condition for approval of the product.

Once it is predicted exactly when the estimated number of enrolled patients will be achieved, the sponsor will discuss with Pharmaceuticals and Medical Devices Agency to determine when to move to the period only requiring patient enrollment (not requiring the completion and submission of case report forms) from the period requiring the completion and submission of case report forms, after confirming that required data will be available based on enrollment status and the progress of the collection of case report forms.
It is expected that the number of enrolled patients will reach 140 in September 2015.

* Rationale for the expectation

It was expected that the estimated number of enrolled patients (140) would be achieved in September 2015 (1 year and 6 months after the expected date of launch) based on the estimated number of patients treated with Adcetris during the post-marketing period

(approximately 100 person/years).

9.0 Outcome Measures

The investigator will record data listed below in both Patient Enrollment and Case Report Forms. Study schedule is provided in in Appendix 1.

9.1 Data to be recorded in Patient Enrollment Form

1) Outcome measures

Name of the institution, name of the investigator completing Patient Enrollment Form, expected date of the start of treatment with Adcetris, patient identification number, patient initial, sex, date of birth, diagnosis, performance status, CD30, past history of severe hypersensitivity to any ingredient of Adcetris, expected concomitant use of other antineoplastic drugs, and presence/absence of infections, peripheral nerve disorders, hepatic disorders, severe renal disorders, or pregnancy/breast-feeding

2) When to collect outcome measure data

At the time of patient enrollment

9.2 Data to be recorded in Case Report Form

9.2.1 Cover sheet of Case Report Form

Date of the finial completion of Case Report Form and name of the investigator completing Case Report Form

9.2.2 Patient demographics and baseline characteristics

1) Outcome measures

Date of diagnosis of Hodgkin's or anaplastic large cell lymphoma, site of involvement, ALK (in patients with anaplastic large cell lymphoma), clinical stage, presence/absence of B symptoms, ECOG Performance Status, therapeutic category, (presence/absence and detail of) hypersensitivity disposition, viral test results, past history of and concurrent pulmonary disorders, past history of and concurrent malignant tumours, (presence/absence and detail of) concurrent illnesses [other than pulmonary disorders and malignant tumours], (presence/absence and detail of) past history[other than pulmonary disorders and malignant tumours], height, weight, smoking history, and (presence/absence and detail of) prior treatment for Hodgkin's lymphoma or anaplastic large cell lymphoma (including drug therapy, radiotherapy, and hematopoietic stem cell transplantation)

2) When to collect outcome measure data

At the start of treatment with Adcetris

9.2.3 Treatment given

1) Outcome measures

Treatment with Adcetris and premedication to prevent infusion reaction (dose, date of premedication, and reasons for premedication to prevent infusion reaction and its

discontinuation), (use or non-use, type, and date of) post-baseline hematopoietic stem cell transplantation, (presence/absence, name, and duration of) drugs other than Adcetris used for the treatment of the primary disease, and (presence/absence, name, and duration of) drugs used for the prevention of infection

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4 Tests and assessments

9.2.4.1 Laboratory tests

1) Outcome measures

Red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, total bilirubin, AST, ALT, LDH, BUN, and serum creatinine

2) When to collect outcome measure data

At each test time point during the period from the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.4.2 Best response

1) Outcome measures

The best response (CR, CRu [for patients with no PET scan data], PR, SD, or PD) will be assessed based on CT and PET scans of the neck, chest, abdomen, and pelvis according to the best response assessment criteria (see Appendix).

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.3 Date of the final observation

1) Outcome measures

Date of the final observation

2) When to collect outcome measure data

After 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris)

9.2.4.4 Other assessments

1) Outcome measures

Pregnancy during the observation period (for females only)

If pregnancy is detected during the observation period, it should be reported to the Takeda MR immediately.

2) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

9.2.5 Adverse events

1) Outcome measures

Presence/absence of adverse events (see Table 1), adverse event terms, date of onset, CTCAE grade (the worst one), seriousness and its reason (see Table 2), (presence/absence and detail of) action taken to Adcetris, (presence/absence and detail of) intervention for adverse events, date of outcome, outcome, causal relationship with Adcetris* (see Table 3), and changes in laboratory test values associated with adverse events over time

If the outcome is "not recovered/not resolved" or "unknown," and the causal relationship with Adcetris is considered unevaluable, the event should be followed wherever possible.

* If the event is considered not related to Adcetris, its rationale should be collected. If the causal relationship with Adcetris is considered unevaluable, its reason should be collected.

Note) Points to consider regarding adverse events

Worsening of the primary disease should not be regarded as an adverse event. However, abnormal worsening of the primary disease (e.g., worsening beyond the expected natural course of the disease) should be regarded as an adverse event.

Disease progression should be regarded as worsening of the primary disease rather than an adverse event. However, clinical or laboratory progression of an existing cancer (including new metastasis) that meets any of the criteria for the seriousness of adverse events (see Table 2) should be considered a serious adverse event.

2) Adverse events of particular interest

The events listed below are events of particular interest; detailed information on these events should be collected wherever possible it they are observed:

- Peripheral nerve disorders
- Infections
- Neutropenia
- Infusion reactions
- Pulmonary disorders

* Rationale for the selection of adverse events of particular interest

Of important identified risks listed in Risk Management Plan, those listed above were selected as adverse events of particular interest based on the following rationales:

a) Peripheral nerve disorders

Peripheral nerve disorders are frequently observed after treatment with Adcetris. If the event of peripheral nerve disorder becomes severe, it is difficult to continue treatment with Adcetris. It is important to control the onset of the event to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption).

Therefore, the profile of peripheral nerve disorders in Japanese patients as an adverse event of particular interest will be determined (i.e., information useful for continuation of treatment with Adcetris, including risk factors, commonly reported time to onset, outcomes, and the status of treatment with Adcetris, will be collected).

b) Infections

It is expected that Adcetris is used in patients who are immunocompromised due to prior treatment or the prior disease or those who are complicated with infection, and the incidence of infections is likely to be high. Therefore, the profile of infections in Japanese patients as an adverse event of particular interest (i.e., the incidence and temporal relationship with the onset of neutropenia/lymphopenia) will be determined.

c) Neutropenia

It is expected that Adcetris is used in patients with decreased neutrophil count due to prior treatment, which may increase the risk of infection and result in a high incidence of infection/severe infection. It is important to control the neutrophil count to allow for continuation of treatment (including dose reduction and restart of treatment after treatment interruption) in terms of the prevention of infection. Therefore, the profile of neutropenia in Japanese patients as an adverse event of particular interest will be determined (i.e., the status of treatment with Adcetris and neutrophil count control will be assessed and information useful for continuation of treatment with Adcetris will be collected).

d) Infusion reactions

Infusion reactions are characteristic of monoclonal antibody preparations, the profile of infusion reactions in Japanese patients as an adverse event of particular interest (including the status of premedication and the percentage of patients using premedication to prevent infusion reactions [use/non-use of premedication to prevent infusion reactions]) will be determined.

e) Pulmonary disorders

The occurrence of pulmonary disorders in Japanese patients receiving monotherapy with Adcetris as an adverse event of particular interest will be determined.

3) When to collect outcome measure data

From the start of treatment with Adcetris until the completion of 16 cycles (or upon discontinuation of treatment with Adcetris)

Table 1 Definition of an Adverse Event

An adverse event (AE) is any untoward or undesirable medical occurrence in a patient linked in time with the use of a pharmaceutical/ medicinal product and which does not necessarily have to have a causal relationship with this treatment or may or may not be considered related to the product.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.
Adverse events also include:

・Symptoms observed in an infant breast-fed by a mother receiving treatment with Adcetris.

Table 2 Criteria for the Seriousness of Adverse Events

An adverse event meeting any of the following criteria will be considered serious:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is a medically important condition due to any of the above 1 to 5, including those listed in "Takeda Medically Significant AE List."

Takeda Medically Significant AE List

•Acute respiratory failure/acute respiratory distress syndrome (ARDS)	•Anaphylactic shock
•Torsade de pointes/ventricular fibrillation/ventricular tachycardia	•Acute kidney failure
•Malignant hypertension	•Pulmonary hypertension
•Convulsive seizure (including convulsion and epilepsy)	•Pulmonary fibrosis (including interstitial pneumonia)
•Agranulocytosis	•Neuroleptic malignant syndrome/malignant hyperthermia
•Aplastic anemia	•Spontaneous abortion/stillbirth and fetal death
•Toxic epidermal necrolysis/oculomucocutaneous syndrome (Stevens-Johnson syndrome)	•(Suspected) transmission of infection via a drug
•Hepatic necrosis	•(Suspected) endotoxic shock
•Acute hepatic failure	

Table 3 Criteria for the Assessment of Causal Relationship between Adverse Events and Adcetris

Causality	Assessment criterion
Related	There is a temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation). Or, there are other contributing factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies, but it is also likely that the event is attributable to Adcetris.
Not related	There is no temporal relationship between the event and Adcetris. Or, it is very likely that the event is attributable to other factors, such as the primary disease, concurrent illnesses, and concomitant medications/therapies.
Indeterminate	There is limited information required for the assessment of causal relationship, such as temporal relationship between the event and Adcetris (and the clinical course after treatment discontinuation), the primary disease, concurrent illnesses, and concomitant medications/therapies.

10.0 Data to Be Analyzed and Methods of Analysis

10.1 Patient disposition

Data to be analyzed includes the number of enrolled patients, the number of patients whose case report forms are available, and the number of patients included in and excluded from the safety/efficacy analysisset and reasons for inclusion/exclusion.

10.2 Patient demographics and baseline characteristics

Data to be analyzed includes sex, age, disease duration, site of involvement, and clinical stage.

10.3 Treatment given

Data to be analyzed includes the status of treatment with Adcetris and concomitant medications.

10.4 Safety

The measures specified below will be analyzed using the safety analysis set. Adverse events will be coded using MedDRA/J and summarized using (Preferred Terms [PTs]) and System Organ Classes [SOCs]).

10.4.1 Occurrence of adverse events

The frequency of adverse events observed during the observation period will be analyzed by type, time of onset, seriousness, and Adcetris.

10.4.2 Factors that may affect the safety of Adcetris

The frequency of adverse events observed during the observation period will be analyzed by patient background factors (sex, age, presence/absence of concurrent renal disorders, and presence/absence of concurrent hepatic disorders) and treatment given (the status of treatment with Adcetris and concomitant medications).

10.4.3 Changes in laboratory test data over time

Summary statistics of laboratory test values at baseline and post-baseline will be calculated.

10.5 Efficacy

The measures specified below will be analyzed using the efficacy analysis set.

10.5.1 Best response

The best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed.

10.5.2 Overall survival

The time to death (regardless of the cause of death) will be analyzed using the "final observation date" in specified in Section 9.2.4.3 as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field specified in Section 9.2.5 as the date of death

10.6 Interim analyses

For patients whose case report forms are collected through March 31, 2015 with evaluable safety evaluation, analyses similar to the ones described in Sections 10.1 to 10.4 will be performed to evaluate and analyze safety information obtained in this study at an early stage and publish them as appropriate.

11.0 Posting of Information Regarding This Study

Prior to the start of the study, Takeda Pharmaceutical Company Limited will register information regarding this study to Clinical Trials.gov and a public website (JAPIC-CTI*).

*Japan Pharmaceutical Center-Clinical Trials Information

12.0 Organizational Structure

12.1 Person responsible for administration

PPD

Takeda Pharmaceutical Company Limited

12.2 Proper Use Committee

The committee will provide advice on the protocol, data analysis, publication of study results,

promotion of the proper use of Adcetris, and safety measures.

PPD

(Listed in the order of the Japanese syllabary)

12.3 Central Enrollment Center

PPD

13.0 Contract Research Organization

PPD

14.0 Other Important Information

14.1 Protocol amendment

During the study, the sponsor will monitor the occurrence of adverse drug reactions and serious adverse drug reactions that cannot be predicted by the progress of the study and precautions for use, the presence/absence of an increase in the frequency of specific adverse drug reactions, and the appropriateness of outcome measures, and review and amend this protocol as appropriate. If the approval of partial changes to “Dosage and Administration” or “Indication” is obtained during the study, the sponsor will consider the necessity of amendment of this protocol as appropriate, and amend the protocol as appropriate.

14.2 Measures to be taken in response to issues/questions

If any safety and/or efficacy issue is detected, the sponsor will examine data closely and consider what measures should be taken.

Appendix 1 Study Schedule

Procedure \ Time point		Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Patient enrollment	Date of the expected initial dose of Adcetris	○				
	Patient identification number	○				
	Patient initial	○				
	Sex	○				
	Date of birth	○				
	Diagnosis	○				
	Performance status	○				
	CD30	○				
	Past history of severe hypersensitivity to any ingredient of Adcetris	○				
	Expected concomitant use of other antineoplastic drugs	○				
	Presence/absence of infections	○				
	Presence/absence of peripheral nerve disorders	○				
	Presence/absence of hepatic disorders	○				
	Presence/absence of severe renal disorders	○				
	Presence/absence of pregnancy/breast-feeding	○				
Patient demographics and baseline characteristics	Date of diagnosis of Hodgkin or anaplastic large-cell lymphoma		○			
	Site of involvement		○			
	ALK (in patients with anaplastic large cell lymphoma)		○			
	Clinical stage		○			
	Presence/absence of B symptoms		○			
	ECOG Performance Status		○			
	Therapeutic category		○			
	Hypersensitivity disposition		○			
	Viral test results		○			
	Past history of and concurrent pulmonary disorders		○			
	Past history of and concurrent malignant tumours		○			
	Concurrent illness (other than pulmonary disorders and malignant tumours)		○			
	Past history (other than pulmonary disorders and malignant tumours)		○			
	Height and weight		○			
	Smoking history		○			
	Prior treatment for Hodgkin's or anaplastic large cell lymphoma		○			

	Time point / Procedure	Observation period				
		At the time of patient enrollment	At the start of treatment with Adcetris	During treatment	After 16 cycles	Upon discontinuation of treatment
Treatment given	Treatment with Adcetris		○	○		
	Post-baseline hematopoietic stem cell transplantation		← ○ →			○
	Drug(s) other than Adcetris used for the treatment of the primary disease		← ○ →			○
	Drug(s) used for the prevention of infection		← ○ →			○
Tests and assessments	Laboratory tests (red blood cell count, hemoglobin level, white blood cell count, neutrophil count, lymphocyte count, platelet count, and liver and kidney function tests)		← ○ →			○
	Best response				○	○
	Date of the final observation				○	○
	Presence/absence of pregnancy (for females only)		← ○ →			○
	Adverse events		← ○ →			○

○ : Data collected

←○→: Data collected throughout the period

Appendix 2 Best Response Assessment Criteria (Revised Response Criteria for Malignant Lymphoma*)

* Extracted from "General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, March 2000 [First Edition])

For patients with PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma The patient is PET negative. If the patient is PET negative, any residual tumor on CT does not matter. 1)-2Variably FDG-avid lymphoma The patient did not undergo PET before treatment. If the patient was negative before treatment, the patient must meet all the following criteria: [1] All nodal target lesions are normal. [2] All extranodal target lesions have resolved. [3] All nodal non-target lesions are normal. [4] The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. [5] All extranodal non-target lesions have resolved. 2) A patient with bone marrow infiltration at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as "negative" because bone marrow test is not required. 3) The patient has no new lesion.
PR	All the following criteria are met: 1)-1 Routinely FDG-avid lymphoma If the patient had one or more PET positive lesions, or was PET negative AND had bone marrow infiltration at baseline, the patient must be positive for bone marrow infiltration at the time of restaging (or have not undergone testing). 1)-2Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 3) All nodal non-target lesions are normal or free from enlargement. 4) All extranodal non-target lesions have resolved or free from enlargement. 5) Bone marrow infiltration does not matter. Testing is not required. 6) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR but meets any of the criteria 1 and 2 to 6 and 7 listed below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR, the patient will be assessed as having a relapsed disease (RD): 1)-1 Routinely FDG-avid lymphoma The patient has one or more PET positive lesions. 1)-2 Variably FDG-avid lymphoma If the patient did not undergo a PET scan or was PET negative prior to treatment, no PET assessment should be performed. 2) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 3) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long

	diameter) or re-enlargement. 4) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 5) The long diameter of the nodal target lesion which was once normalized and assessed as CR exceeded 1.5 cm. The extranodal target lesion which once resolved reappeared. 6) The patient has a new lesion. 7) The patient became positive after being once negative for bone marrow infiltration.

For patients with no PET scan data available

Assessment	Criteria
CR	All the following criteria are met: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) The image shows the resolution of all nodal lesions in all organs including the spleen and the liver. 5) All extranodal non-target lesions have resolved. 6) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 7) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 8) A patient with bone marrow infiltration or indeterminate at baseline must be negative for bone marrow infiltration. A patient with no bone marrow infiltration at baseline should be regarded as “negative” because bone marrow test is not required. 9) The patient has no new lesion.
CRu	The patient had bone marrow infiltration or was indeterminate at baseline AND meets all the following criteria: 1) All nodal target lesions are normal. 2) All extranodal target lesions have resolved. 3) All nodal non-target lesions are normal. 4) All extranodal non-target lesions have resolved. 5) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 6) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 7) The patient is indeterminate for bone marrow infiltration. 8) The patient has no new lesion. OR 1) The patient has a 75% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal. 3) All extranodal non-target lesions have resolved. 4) There is no enlarged liver, spleen, or kidney (all lesions have resolved). 5) There is no tumor-related symptom (fever and night sweat) (all symptom have resolved) OR no abnormal tumor-related laboratory test results (tumor-related increase in LDH) (normal). 6) The patient has no bone marrow infiltration or indeterminate.

	7) The patient has no new lesion.
PR	The patient meets all the above criteria for CRu except for criterion 6. A patient with bone marrow infiltration or indeterminate at baseline must be positive for bone marrow infiltration at the time of restaging. Or, the patient meets all the following criteria: 1) The patient has a 50% or more decrease (reduction) in the SPD of target lesion from baseline. 2) All nodal non-target lesions are normal or free from enlargement. 3) All extranodal non-target lesions have resolved or free from enlargement. 4) Enlarged liver, spleen, and kidneys have resolved or are free from progression. 5) All tumor-related symptom (fever and night sweat) have resolved. AND abnormal tumor-related laboratory test results (tumor-related increase in LDH) became normal. 6) Bone marrow infiltration does not matter. Testing is not required. 7) The patient has no new lesion.
SD	The patient achieved a response of <PR and >PD.
PD	If the patient is not assessed as achieving CR or CRu but meets any of the criteria below, the patient will be assessed as having progressive disease (PD). If the patient meets any of the criteria listed below after being assessed as achieving CR or CRu, the patient will be assessed as having a relapsed disease (RD): 1) The patient has a 50% or more increase in the SPD of target lesion from the minimum SPD. 2) The patient has an obvious increase in the nodal non-target lesion (a 50% or more increase in the long diameter) or re-enlargement. 3) The patient has an obvious increase in the extranodal non-target lesion (a 50% or more increase in the long diameter) or recurrence. 4) The extranodal target lesion which once resolved and was assesses as CR or CRu reappeared. 5) Obvious progression or recurrence of enlarged liver, spleen, or kidney. 6) Obvious progression or recurrence of tumor-related subjective and objective symptoms (fever and night sweat) or abnormal tumor-related laboratory test results (tumor-related increase in LDH). 7) The patient became positive after being once negative for bone marrow infiltration. 8) The patient has a new lesion.