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.

Statistical Analysis Plan

ADCETRIS IV Infusion − Special Drug Use Surveillance (All-case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

PPD

Takeda Pharmaceutical Company Limited

PPD

3rd version: Prepared on January 27, 2017

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1.0 Definition of Analysis Sets and Terms and Handling of Test/Measurement Data

1.1 Analysis sets

1.1.1 Safety analysis set

In this survey, the safety analysis set is defined as patients treated with Adcetris IV Infusion with no major protocol violation and evaluable for safety.

1.1.2 Efficacy analysis set

In this survey, the efficacy analysis set is defined as patients treated with Adcetris IV Infusion with no major protocol violation and evaluable for efficacy.

Definition

Term	Definition
This/the product	Refers to Adcetris for intravenous drip infusion in this Statistical Analysis Plan.
SOC	MedDRA/J System Organ Class
HLGT	MedDRA/J High Level Group Term
PT	MedDRA/J Preferred Term
LLT	MedDRA/J Lowest Level Term
Patients registered	Patients whose registration has been approved
Patients whose case report forms are available	Patients whose case report forms have been collected
Patients whose case report forms are not available	Patients registered but whose case report form have not been collected
Fixed patients	Patients whose case report forms are available, with the date of case report form completion entered in the PMS system
Non-fixed patients	Patients whose case report forms are available, with the date of case report form completion not entered in the PMS system
Safety analysis set	Fixed patients included in the safety analysis set
Safety analysis set (Hodgkin's lymphoma)	Patients included in the safety analysis set whose diagnosis is Hodgkin's lymphoma
Safety analysis set (anaplastic large-cell lymphoma)	Patients included in the safety analysis set whose diagnosis is anaplastic large-cell lymphoma
Patients excluded from the safety analysis set	Fixed patients excluded from the safety analysis set
Efficacy analysis set	Patients included in the safety analysis set who are also included in the efficacy analysis set
Patients excluded from the efficacy analysis set	Patients included in the safety analysis set who are excluded from the efficacy analysis set
Patients completing treatment	Patients completing 16 cycles of treatment with Adcetris
Patients discontinuing treatment	Patients not completing 16 cycles of treatment with Adcetris

Term	Definition
Adverse drug reactions, etc.	Refers to “adverse drug reactions and infections.” Adverse events not considered “not related” to Adcetris by the investigator. In this Statistical Analysis Plan, the term “adverse drug reactions and infections” is used in titles and the term “adverse drug reactions, etc.” is used in text and tables.
Serious adverse events	Adverse events considered “serious” by the investigator. Events listed in the MedDRA Coding List in the Takeda Medically Significant AE List should be regarded as serious even if they are considered “non-serious” by the investigator.
Number of patients with adverse events/adverse drug reactions	Number of patients experiencing adverse events or adverse drug reactions, etc.
Number of adverse events/adverse drug reactions	Number of adverse events or adverse drug reactions, etc., observed
Percentage of patients with adverse events/adverse drug reactions	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients excluded from the safety analysis set) × 100.
Percentage of adverse events/adverse drug reactions observed	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula:(number of adverse events/adverse drug reactions observed) / (number of patients excluded from the safety analysis set) × 100.
Time of onset	Is calculated using the following formula: date of onset of adverse events (or adverse drug reactions, etc.) − date of the initial dose of Adcetris + 1. If the day, month, and year of onset of adverse events (or adverse drug reactions, etc.) are unknown, the time of onset should be handled as missing, and the category for the time of onset should be “unknown.”
Time to the worst grade	Is calculated using the following formula: date of the worst CTCAE grade – date of the initial dose of Adcetris + 1.

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>If the day, month, and year of the worst CTCAE grade are unknown, the date of the worst CTCAE grade should be handled as missing, and the category for the date of the worst CTCAE grade should be “unknown.”</td></tr>
<tr><td>Patients with concurrent hepatic disorder</td><td>Patients having a concurrent illness that falls under the category of Standardized MedDRA Query (SMQ) Code 20000005 (SMQ Hepatic disorders [Scope: Narrow])</td></tr>
<tr><td>Grade of hepatic disorder</td><td>The ALT or AST level at baseline with the highest grade will be used to determine the grade of hepatic disorder. The grades of ALT and AST levels will be determined according to the following tables, and the grade should be “unknown” if either the ALT or AST level is missing:
ALT
<table>
<tr><td></td><td>Male</td><td>Female</td></tr>
<tr><td>None</td><td>≤42 IU/L</td><td>≤23 IU/L</td></tr>
<tr><td>Grade 1</td><td>>42 to ≤126 IU/L</td><td>>23 to ≤69 IU/L</td></tr>
<tr><td>Grade 2</td><td>>126 to ≤210 IU/L</td><td>>69 to ≤115 IU/L</td></tr>
<tr><td>≥Grade 3</td><td>>210 IU/L</td><td>>115 IU/L</td></tr>
</table>
AST
<table>
<tr><td></td><td></td></tr>
<tr><td>None</td><td>≤30 IU/L</td></tr>
<tr><td>Grade 1</td><td>>30 to ≤90 IU/L</td></tr>
<tr><td>Grade 2</td><td>>90 to ≤150 IU/L</td></tr>
<tr><td>≥Grade 3</td><td>>150 IU/L</td></tr>
</table></td></tr>
<tr><td>Patients with concurrent renal disorder</td><td>Patients having a concurrent illness that falls under the category of Takeda MedDRA Query (TMQ) (Renal disease)</td></tr>
<tr><td>Grade of renal disorder</td><td>The serum creatinine level at baseline will be classified as shown in the table below. If the serum creatinine level at baseline is missing, the grade of renal disorder should be “unknown:”
Serum creatinine
<table>
<tr><td></td><td>Male</td><td>Female</td></tr>
<tr><td>None</td><td>≤1.07 mg/dL</td><td>≤0.79 mg/dL</td></tr>
<tr><td>Grade 1</td><td>>1.07 to ≤1.605 mg/dL</td><td>>0.79 to ≤1.185 mg/dL</td></tr>
<tr><td>Grade 2</td><td>>1.605 to ≤3.21 mg/dL</td><td>>1.185 to ≤2.37 mg/dL</td></tr>
<tr><td>≥Grade 3</td><td>>3.21 mg/dL</td><td>>2.37 mg/dL</td></tr>
</table></td></tr>
<tr><td>Patients with a past history of pulmonary disorder</td><td>Patients with a past history that falls under the category of Appendix “Definition of Pulmonary Disorders”
(If “No concurrent illness existed at the initiation of treatment with Adcetris” is selected in the field of “Past history/concurrent illness of pulmonary disorders” in the case report form, the pulmonary disorder</td></tr>
</table>

Term	Definition
	should be regarded as a past history.)
Patients with concurrent pulmonary disorder	Patients with a concurrent illness that falls under the category of Appendix "Definition of Pulmonary Disorders" (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of pulmonary disorders" in the case report form, the pulmonary disorder should be regarded as a concurrent illness.)
Patients with a past history of malignant tumour	Patients with a past history that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "No concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be regarded as a past history.)
Patients with concurrent malignant tumour	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be as a concurrent illness.)
Patients with concurrent diabetes mellitus	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000041 (SMQ Hyperglycaemia/new onset diabetes mellitus [Scope: Narrow])
Patients with hypertension	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000147 (SMQ Hypertension [Scope: Narrow])
Patients with concurrent dyslipidaemia	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000026 (SMQ Dyslipidaemia [Scope: Narrow])
Patients with concurrent hyperuricaemia	Patients with a concurrent illness that falls under the category of MedDRA PT Code 10020903 (Hyperuricaemia)
Patients with concurrent infection	Patients with a concurrent illness that falls under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with concurrent peripheral neuropathy	Patients with a concurrent illness that falls under the category of SMQ Code 20000034 (SMQ Peripheral neuropathy [Scope: Narrow])
Patients with other concurrent illnesses	Patients with any concurrent illness other than those listed above
Antibiotics/synthetic antibacterial agents	Drugs with the first three digits of YJ Code being either one of 611 to 616, 619, or 624 that are entered in the field of "Drugs used for the prevention of infection" (If more than one antibiotics/synthetic antibacterial agents are used in the same patient, it will be counted as one patient.)
Antifungals	Drugs with the first three digits of YJ Code being 617 or the first seven

Term	Definition
	digits being 6290002 or 6290004 that are entered in the field of "Drugs used for the prevention of infection" (If more than one antifungals are used in the same patient, it will be counted as one patient.)
Antivirals	Drugs with the first three digits of YJ Code being 625 that are entered in the field of "Drugs used for the prevention of infection" (If more than one antivirals are used in the same patient, it will be counted as one patient.)
Trimethoprim-sulfamethoxazole combinations	Drugs with YJ Code being 62901000 that are entered in the field of "Drugs used for the prevention of infection" (If more than one trimethoprim-sulfamethoxazole combinations are used in the same patient, it will be counted as one patient.)
Other prophylactics against infections	Any drug entered in the field of "Drugs used for the prevention of infection" other than prophylactics against infections listed above (If more than one other prophylactics against infections are used in the same patient, it will be counted as one patient.)
Peripheral sensory neuropathy (as an adverse event)	Adverse events with "Sensory neuropathy" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034620 should be assigned regardless of data entered in "Symptoms" in the field.
Peripheral motor neuropathy (as an adverse event)	Adverse events with "Motor neuropathy" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034580 should be assigned regardless of data entered in "Symptoms" in the field.
Peripheral neuropathy (as an adverse event)	Adverse events with "Other" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10029331 should be assigned, regardless of data entered in "Symptoms" in the field.
Pulmonary disorders (as adverse events)	Adverse events that fall under the category of Appendix "Definition of Pulmonary Disorders"
Infusion reaction (as an adverse event)	MedDRA PT Code 10051792 (Infusion related reaction) will be assigned, regardless of symptoms entered in the field of "Adverse events: [4] Infusion reaction."
Patients with the onset of infection	Patients with adverse drug reactions that fall under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with the onset of bacterial infection	Patients with adverse drug reactions that fall under the category of MedDRA HLGT Code 10004018 (Bacterial infection), 10008555 (Chlamydial infection), 10028474 (Mycoplasma infection) or 10039135 (Rickettsia infection)
Patients with the onset of fungal infection	Patients with adverse drug reactions that fall under the category of MedDRA HLGT Code 10017528 (Fungal infection)

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>Patients with the onset of viral infection</td><td>Patients with adverse drug reactions that fall under the category of MedDRA HLGT Code 10047438 (Viral infection)</td></tr>
<tr><td>Age</td><td>If the month and day of the initial dose of Adcetris is < the month and day of birth, the patient’s age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth − 1.
If the month and day of the initial dose of Adcetris is ≥ the month and day of birth, the patient’s age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth.
If the month and day of birth are unknown, they should be “January 1,” and if the day of birth is unknown, it should the first day of the month.
If the day, month, and year of birth are unknown but the patient’s age is known, the patient’s age should be used as it is.</td></tr>
<tr><td>BMI</td><td>BMI should be calculated using the following formula: Weight (kg)/(0.0001 × height (cm) × height (cm). The obtained value should be rounded off to one decimal place.</td></tr>
<tr><td>Disease duration</td><td>The disease duration should be calculated using the following formula: [“Date of the initial dose of Adcetris” − “date of diagnosis of Hodgkin’s or anaplastic large-cell lymphoma” +1]/365.25.
The day of diagnosis should be the first day of the month provided. If the month of diagnosis is unknown, the date of diagnosis should be “January 1st” of the year provided.</td></tr>
<tr><td>Mean dose of Adcetris</td><td>Is calculated as the total value of each dose of Adcetris given at each treatment cycle divided by the number of cycles.</td></tr>
<tr><td>Dose of Adcetris per 3 weeks</td><td>Is calculated using the following formula: Total “dose of Adcetris”/([“date of the last dose of Adcetris” − “date of the initial dose of Adcetris” + 21)/21].
If only 1 cycle of treatment is given, the “date of the last dose of Adcetris” and the “date of the initial dose of Adcetris” should be regarded as the same.</td></tr>
<tr><td>Degree of decreased neutrophil count at baseline</td><td>The neutrophil count at baseline will be classified as shown in the table below. If the neutrophil count at baseline is missing, the degree of the neutrophil count at baseline should be handled as missing:
<table>
<tr><td>No decrease</td><td>≥2,000 /mm^3</td></tr>
<tr><td>Grade 1</td><td>≥1,500 to <2,000 /mm^3</td></tr>
<tr><td>Grade 2</td><td>≥1,000 to <1,500 /mm^3</td></tr>
<tr><td>Grade 3</td><td>≥500 to <1,000 /mm^3</td></tr>
<tr><td>Grade 4</td><td><500 /mm^3</td></tr>
</table></td></tr>
<tr><td>Days from the month of the completion of the final regimen</td><td>Is calculated using the following formula: date of the initial dose of Adcetris – date of the completion of the final regimen of prior drug</td></tr>
</table>

Term	Definition
of prior drug therapy to the date of 1 cycle of treatment with Adcetris	therapy + 1. If the month of "the completion of the final regimen of prior drug therapy" is missing, the date of the completion of the final regimen of prior drug therapy should be handled as missing.
Days from the month of the completion of the most recent prior radiotherapy to the date of 1 cycle of treatment with Adcetris	Is calculated using the following formula: date of the initial dose of Adcetris – date of the completion of the most recent prior radiotherapy + 1. If the month of "the completion of the most recent prior radiotherapy" is missing, the date of the completion of the most recent prior radiotherapy should be handled as missing.
Days from the date of the last dose of Adcetris to hematopoietic stem cell transplantation (autologous) (Post-baseline hematopoietic stem cell transplantation: autologous)	For patients with post-baseline hematopoietic stem cell transplantation (autologous), this data item will be calculated using the following formula: date of post-baseline hematopoietic stem cell transplantation (autologous) − date of the last dose of Adcetris + 1. If the date of post-baseline hematopoietic stem cell transplantation (autologous) is missing, this data item should be handled as missing. For patients with no post-baseline hematopoietic stem cell transplantation (autologous), this data item should be handled as missing.
Duration of treatment with Adcetris prior to hematopoietic stem cell transplantation (autologous) (Post-baseline hematopoietic stem cell transplantation: autologous)	For patients with post-baseline hematopoietic stem cell transplantation (autologous), this data item will be calculated using the following formula: date of the last dose of Adcetris − date of the initial dose of Adcetris + 1. If the date of post-baseline hematopoietic stem cell transplantation (autologous) is missing, this data item should be handled as missing. For patients with no post-baseline hematopoietic stem cell transplantation (autologous), this data item should be handled as missing.
Days from the date of the last dose of Adcetris to hematopoietic stem cell transplantation (homologous) (Post-baseline hematopoietic stem cell transplantation: homologous)	For patients with post-baseline hematopoietic stem cell transplantation (homologous), this data item will be calculated using the following formula: date of hematopoietic stem cell transplantation (homologous) − date of the last dose of Adcetris + 1. If the date of post-baseline hematopoietic stem cell transplantation (homologous) is missing, this data item should be handled as missing. For patients with no post-baseline hematopoietic stem cell transplantation (homologous), this data item should be handled as missing.
Duration of treatment with Adcetris prior to hematopoietic stem cell transplantation (homologous) (Post-baseline hematopoietic stem cell transplantation:	For patients with post-baseline hematopoietic stem cell transplantation (homologous), this data item will be calculated using the following formula: date of the last dose of Adcetris − date of the initial dose of Adcetris + 1. If the date of post-baseline hematopoietic stem cell transplantation (homologous) is missing, this data item should be handled as missing.

Term	Definition
homologous)	For patients with no post-baseline hematopoietic stem cell transplantation (homologous), this data item should be handled as missing.
Date of the final observation	“Date of the final observation” in the case report form If not provided, the most recent date entered in the case report form should be used.
Summary statistics	Number of patients, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.
Overall survival	Time to the date of death from any cause after the date of the initial dose of Adcetris. Surviving patients will be censored on the date of survival confirmation. The date of outcome of an adverse event with “Died/fetal” recorded in the Outcome field will be used as the date of death, and the final observation date will be used as the date of survival confirmation. The overall survival (date of death or survival confirmation) = date of death or survival confirmation − date of the initial dose of Adcetris+1
1 year	One year is defined as 365.25 days.
1 month	One month is defined as 30.4375 days.

1.2 Display digits

Term	Definition
Percentage (%)	Percentage of patients with or percentage of adverse events or adverse drug reactions, etc.: The obtained value should be rounded off to two decimal places. Other: The obtained value should be rounded off to one decimal place.
Summary statistics	Mean, median, 25th percentile and 75th percentile: The raw data should be rounded off to one decimal place. Standard deviation: The raw data should be rounded off to two decimal places. Minimum and maximum: The same display digit as the one used for the corresponding data will be used.
P value	The obtained value should be rounded down to three decimal places. If the value is less than 0.001 after rounding down to three decimal places, it should be displayed as "p<0.001."

1.3 Level of significance and confidence coefficient

Level of significance: Two-sided 5%

Confidence coefficient: Two-sided 95%

1.4 Handling of test data

Test data will be handled according to the criteria shown below. If there are multiple data for the same criterion, the one with the test date being closest to the date of protocol-specified assessment should be used. If there is no difference in the number of days from the date of protocol-specified assessment, the later value should be used.

The number of days after the date of the initial dose of Adcetris is defined as 1 for the date of the initial dose of Adcetris and 0 for the day before the date of the initial dose of Adcetris.

Time point for testing	Date of protocol-specified assessment	Acceptable time window
At the initial dose of Adcetris	Date of the initial dose of Adcetris	−15 days to the d ate of the initial dose of Adcetris
After 1 cycle	• If Cycle 2 is initiated: Date of Cycle 2 • If Cycle 2 is not initiated: 21 days after the date of the initial dose of Adcetris s	• If Cycle 2 is initiated: Date of Cycle 2 • If Cycle 2 is not initiated: 21 days after the date of the initial dose of Adcetris

Time point for testing	Date of protocol-specified assessment	Acceptable time window
After 2 cycles	• If Cycle 3 is initiated: Date of Cycle 3 • If Cycle 3 is not initiated: 21 days after the date of Cycle 2	• If Cycle 3 is initiated: From the day after the date of Cycle 2 to the day of Cycle 3 • If Cycle 3 is not initiated: From the day after the date of Cycle 2 to 21 days after the date of Cycle 2
After 3 cycles	• If Cycle 4 is initiated: Date of Cycle 4 • If Cycle 4 is not initiated: 21 days after the date of Cycle 3	• If Cycle 4 is initiated: From the day after the date of Cycle 3 to the day of Cycle 4 • If Cycle 4 is not initiated: From the day after the date of Cycle 3 to 21 days after the date of Cycle 3
After 4 cycles	• If Cycle 5 is initiated: Date of Cycle 5 • If Cycle 5 is not initiated: 21 days after the date of Cycle 4	• If Cycle 5 is initiated: From the day after the date of Cycle 4 to the day of Cycle 5 • If Cycle 5 is not initiated: From the day after the date of Cycle 4 to 21 days after the date of Cycle 4
After 5 cycles	• If Cycle 6 is initiated: Date of Cycle 6 • If Cycle 6 is not initiated: 21 days after the date of Cycle 5	• If Cycle 6 is initiated: From the day after the date of Cycle 5 to the day of Cycle 6 • If Cycle 6 is not initiated: From the day after the date of Cycle 5 to 21 days after the date of Cycle 5
After 6 cycles	• If Cycle 7 is initiated: Date of Cycle 7 • If Cycle 7 is not initiated: 21 days after the date of Cycle 6	• If Cycle 7 is initiated: From the day after the date of Cycle 6 to the day of Cycle 7 • If Cycle 7 is not initiated: From the day after the date of Cycle 6 to 21 days after the date of Cycle 6
After 7 cycles	• If Cycle 8 is initiated: Date of Cycle 8 • If Cycle 8 is not initiated: 21 days after the date of Cycle 7	• If Cycle 8 is initiated: From the day after the date of Cycle 7 to the day of Cycle 8 • If Cycle 8 is not initiated: From the day after the date of Cycle 7 to 21 days after the date of Cycle 7

Time point for testing	Date of protocol-specified assessment	Acceptable time window
After 8 cycles	• If Cycle 9 is initiated: Date of Cycle 9 • If Cycle 9 is not initiated: 21 days after the date of Cycle 8	• If Cycle 9 is initiated: From the day after the date of Cycle 8 to the day of Cycle 9 • If Cycle 9 is not initiated: From the day after the date of Cycle 8 to 21 days after the date of Cycle 8
After 9 cycles	• If Cycle 10 is initiated: Date of Cycle 10 • If Cycle 10 is not initiated: 21 days after the date of Cycle 9	• If Cycle 10 is initiated: From the day after the date of Cycle 9 to the day of Cycle 10 • If Cycle 10 is not initiated: From the day after the date of Cycle 9 to 21 days after the date of Cycle 9
After 10 cycles	• If Cycle 11 is initiated: Date of Cycle 11 • If Cycle 11 is not initiated: 21 days after the date of Cycle 10	• If Cycle 11 is initiated: From the day after the date of Cycle 10 to the day of Cycle 11 • If Cycle 11 is not initiated: From the day after the date of Cycle 10 to 21 days after the date of Cycle 10
After 11 cycles	• If Cycle 12 is initiated: Date of Cycle 12 • If Cycle 12 is not initiated: 21 days after the date of Cycle 11	• If Cycle 12 is initiated: From the day after the date of Cycle 11 to the day of Cycle 12 • If Cycle 12 is not initiated: From the day after the date of Cycle 11 to 21 days after the date of Cycle 11
After 12 cycles	• If Cycle 13 is initiated: Date of Cycle 13 • If Cycle 13 is not initiated: 21 days after the date of Cycle 12	• If Cycle 13 is initiated: From the day after the date of Cycle 12 to the day of Cycle 13 • If Cycle 13 is not initiated: From the day after the date of Cycle 12 to 21 days after the date of Cycle 12
After 13 cycles	• If Cycle 14 is initiated: Date of Cycle 14 • If Cycle 14 is not initiated: 21 days after the date of Cycle 13	• If Cycle 14 is initiated: From the day after the date of Cycle 13 to the day of Cycle 14 • If Cycle 14 is not initiated: From the day after the date of Cycle 13 to 21 days after the date of Cycle 13

Time point for testing	Date of protocol-specified assessment	Acceptable time window
After 14 cycles	• If Cycle 15 is initiated: Date of Cycle 15 • If Cycle 15 is not initiated: 21 days after the date of Cycle 14	• If Cycle 15 is initiated: From the day after the date of Cycle 14 to the day of Cycle 15 • If Cycle 15 is not initiated: From the day after the date of Cycle 14 to 21 days after the date of Cycle 14
After 15 cycles	• If Cycle 16 is initiated: Date of Cycle 16 • If Cycle 16 is not initiated: 21 days after the date of Cycle 15	• If Cycle 16 is initiated: From the day after the date of Cycle 15 to the day of Cycle 16 • If Cycle 16 is not initiated: From the day after the date of Cycle 15 to 21 days after the date of Cycle 15

1.5 Handling of missing data

- As a general rule, missing data will not be imputed.
- In the analysis of the frequency qualitative variables, missing data will be handles as “unknown.” In the analysis of summary statistics of quantitative variables, missing data will be excluded.

1.6 Others

- In the analysis for the preparation of documents for the Final Survey Report (final analysis), MedDRA version 19.1 will be used for adverse events, concurrent illness, and past history.
- If a patient has multiple data for a single laboratory test and date of testing, the mean value will be calculated for the analysis of laboratory test results.
- If the date of diagnostic imaging for the assessment of the best response is missing, it will be handled as missing.

2.0 Patient Disposition (Patient Disposition Diagram)

(1) Analysis set to be used

Patients registered

(2) Data to be analyzed

Data to be analyzed includes the numbers of patients registered, institutions with patients registered, patients whose case report forms are available/not available, fixed/non-fixed patients, patients included in/excluded from the safety analysis set, and patients included in/excluded from the efficacy analysis set.

For the number of institutions with patients registered, the same institutions with different departments should not be counted more than once.

For patients whose case report forms are not available, the number of patients by reason for unavailability will be calculated. The reason for unavailability should be transfer or health problems of the investigator or other.

For patients included in safety evaluation, the number of patients by primary disease (Hodgkin's or anaplastic large-cell lymphoma or other) and the overall number of patients will be calculated. For patients included in efficacy evaluation, the number of patients by primary disease (Hodgkin's or anaplastic large-cell lymphoma) and the overall number of patients will be calculated.

For patients excluded from the safety/efficacy analysis set, the number of patients by reason for exclusion will be calculated, and a patient list will be generated.

The selection of patients to be included in safety evaluation and those who are to be included in efficacy evaluation will be made as shown below:

Criterion	Safety evaluation	Efficacy evaluation
Adcetris has never been administered [found afterwards]	×	×
No data for safety evaluation (data to determine the presence or absence of adverse events) are available	×	×
Non-primary disease	○	×

○: Included, ×: Excluded

(3) Figure/table number

Figure 2.0 and Table2.0

3.0 Patient Demographics and Baseline Characteristics

3.1 Patient Demographics and Baseline Characteristics

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the categories below, and the frequency will be calculated. In addition, summary statistics of continuous variable will be calculated:

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 39 years, 40 to 64 years, 65 to 74 years, or ≥75 years
	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
Diagnosis	Hodgkin's or anaplastic large-cell lymphoma or other
Status	Relapsed/refractory, or new-onset
CD30	Positive, negative, or not measured
Site(s) of involvement	Lymph node, spleen, liver, lung, bone, central nerve, bone marrow, skin, and/or other
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Therapeutic category	Outpatient, inpatient, or unkown
Hypersensitivity disposition	Absent, present, or unknown
Specific hypersensitivity disposition(s)	Medications, food allergy, and/or other
HCV antibody	Negative, positive, or unknown
HBs antigen	Negative, positive, or unknown
HBs antibody	Negative, positive, or unknown
HBV DNA	Negative, positive, or unknown
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present

Data item	Category
Past history of malignant tumours	Absent or present
Concurrent malignant tumours	Absent or present
Past history (other than pulmonary disorders and malignant tumours)	Absent, present, or unknown
Concurrent illness (other than pulmonary disorders and malignant tumours)	Absent or present
Specific concurrent illness(es) (other than pulmonary disorders and malignant tumours)	Diabetes mellitus, hypertension, dyslipidaemia, hyperuricaemia, hepatic disease(s), renal disease(s), infections, peripheral nerve disorders, and/or other
Past history (other than pulmonary disorders and malignant tumours)	Absent, present, or unknown
Concurrent hepatic disorders	Absent or present
Grade of hepatic disorder (Grade based on AST and ALT levels)	None, Grade 1, Grade 2, ≥Grade 3, or unknown
Concurrent renal disorders	Absent or present
Grade of renal disorder (Grade based on serum creatinine)	None, Grade 1, Grade 2, ≥Grade 3, or unknown
Concurrent peripheral neuropathy	None, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, or ≥70 kg
BMI	<18.5 kg/m^2, <18.5 to 25 kg/m^2, <25 to 30 kg/m^2, or ≥30 kg/m^2
Smoking history	Never, current, past, or unknown

Data item	Category
Prior drug therapy	Absent or present
Prior drug therapy regimen(s)	ABVD, CHOP, and/or other (If more than one drug therapies in the same regimen is used in the same patient, it will be counted as one patient.)
Number of prior drug therapy regimens	-
Days from the month of the completion of the final regimen of prior drug therapy to the date of 1 cycle of treatment with Adcetris (Prior drug therapy: Yes)	-
Prior radiotherapy	Absent or present
Days from the month of the completion of the most recent prior radiotherapy to the date of 1 cycle of treatment with Adcetris (Prior radiotherapy: yes)	-
Prior hematopoietic stem cell transplantation	Absent, present (autologous), present (homologous), present (autologous and homologous), or unknown
Other prior therapies	Absent, present, or unknown
Pregnancy during the observation period (for females only)	Absent or present

(3) Figure/table number

Tables 3-1 to 3.1-3

3.2 Prior drug therapy (details)

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's

lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For prior drug therapy, patients will be stratified into the categories below, and the frequency will be calculated. The percentage of prior drug therapy will be calculated using the number of patients with prior drug therapy as the denominator. In addition, specific prior drug therapies and their percentages will be presented in a pie chart:

Data item	Category
Specific prior drug therapy(ies)	ABVD, CHOP, BEACOPP, C-MOPP, CHASE, CHOEP, DeVIC, EPOCH, ESHAP, GCD, GDP, GEM, ICE, THP-COP, or other (If more than one drug therapies in the same regimen is used in the same patient, it will be counted as one patient.) Prior drug therapies should be listed in descending order of the number of patients. However, “Other” should be listed lastly.

(3) Figure/table number

Tables 3.2-1 to 3.2-3 and Figures 3.2-1 to 3.2-3

4.0 Treatment Given

4.1 Treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories below, and the frequency will be calculated. In addition, summary statistics of continuous variable will be calculated:

Data item	Category
Initial dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Mean dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Duration of treatment with Adcetris	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or ≥17 cycles
Reason(s) for discontinuation of Adcetris	Treatment goal achieved, adverse event(s), lost to follow-up, transfer to another hospital, pregnancy, inadequate response, and/or other
Post-baseline hematopoietic stem cell transplantation	Absent, present, or unknown
Type of post-baseline hematopoietic stem cell transplantation	Autologous or homologous
Days from the date of the last dose of Adcetris to hematopoietic stem cell transplantation (autologous) (Post-baseline hematopoietic stem cell transplantation: autologous)	-
Duration of treatment with Adcetris prior to	-

hematopoietic stem cell transplantation (autologous) (Post-baseline hematopoietic stem cell transplantation: autologous)	
Days from the date of the last dose of Adcetris to hematopoietic stem cell transplantation (homologous) (Post-baseline hematopoietic stem cell transplantation: homologous)	-
Duration of treatment with Adcetris prior to hematopoietic stem cell transplantation (homologous) (Post-baseline hematopoietic stem cell transplantation: homologous)	-
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present
Drug(s) used for the prevention of infection	Absent or present
Specific drug(s) used for the prevention of infection	Antibiotics/synthetic antibacterial agents, antifungals, antivirals, trimethoprim-sulfamethoxazole combinations, and/or other prophylactics against infections

(3) Figure/table number

Tables 4.1-1 to 4.1-3

4.2 Premedication to prevent infusion reaction

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each cycle, patients will be stratified into the following categories, and the frequency will be calculated:

Data item	Category
Premedication to prevent infusion reaction	Absent, present, or unknown
Specific premedication(s) used to prevent infusion reaction	Acetaminophen, antihistamines, and/or corticosteroids
Specific premedication(s) used to prevent infusion reaction (in each patient)	Acetaminophen, antihistamines, corticosteroids, acetaminophen + antihistamines, acetaminophen + corticosteroids, antihistamines + corticosteroids, or acetaminophen + antihistamines + corticosteroids

(3) Figure/table number

Tables 4.2-1 to 4.2-3

4.3 Patient demographics and baseline characteristics by initial dose of Adcetris

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the frequency will be calculated by initial dose of Adcetris (<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg):

Data item	Category
Age	<18 years, 18 to 39 years, 40 to 64 years, 65 to 74 years, or ≥75 years
ECOG Performance Status	0, 1, 2, 3, or 4
Concurrent hepatic disorders	Absent or present
Grade of hepatic disorder (Grade based on AST	None, Grade 1, Grade 2, ≥Grade 3, or unknown

Data item	Category
and ALT levels)	
Concurrent renal disorders	Absent or present
Grade of renal disorder (Grade based on serum creatinine)	None, Grade 1, Grade 2, ≥Grade 3, or unknown
Concurrent infection	Absent or present
Concurrent peripheral nerve disorder	None, Grade 1, Grade 2, Grade 3, Grade 4, or unknown

(3) Figure/table number

Tables 4.3-1 to 4.3-3

5.0 Safety Analysis

5.1 Occurrences of adverse events and adverse drug reactions/infections

5.1.1 Occurrence of adverse events

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

For data entered in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form, MedDRA PT Code for peripheral sensory neuropathy, peripheral motor neuropathy, or peripheral neuropathy should be assigned, regardless of data entered in "Symptoms" field (see Section 1.2, the same applies hereinafter).

MedDRA PT Code for "Infusion related reaction" should be assigned to the field of "Adverse events: [4] Infusion reaction" in the case report form, regardless of data entered in "Symptoms" field (see Section 1.2, the same applies hereinafter).

Neutrophil count decreased (PT Code 10029366) will be replaced by Neutropenia (PT Code 10029354), Lymphocyte count decreased (PT Code 10025256) by Lymphopenia (PT Code 10025327), White blood cell count decreased (PT Code 10047942) by Leukopenia (PT Code 10024384), and Platelet count decreased (PT Code 10035528) by Thrombocytopenia (PT Code 10043554) (the same applies hereinafter).

Data item	Data to be analyzed
Number of patients with adverse events	Number of patients experiencing adverse events
Number of adverse events	Number of adverse events observed. If the same patient has multiple occurrences of the same adverse event (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse events	Is calculated using the following formula: number of patients with adverse events/number of patients included in the safety analysis set × 100.
Type of adverse events	The incidence of adverse events will be calculated by SOC and PT. For SOC, the number and percentage of patients with adverse events will be calculated. For PT, the number and percentage of adverse events will be calculated. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same adverse event (PT), the event will be counted once per patient.

(3) Figure/table number

Tables 5.1-1 to 5.1.1-3

5.1.2 Occurrence of adverse drug reactions/infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with adverse drug reactions, etc.	Number of patients experiencing adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse drug reactions, etc.	Is calculated using the following formula: number of patients with adverse drug reactions, etc./number of patients included in the safety analysis set × 100.
Type of adverse drug reactions, etc.	The incidence of adverse drug reactions, etc., will be calculated by SOC and PT. For SOC, the number and percentage of patients with adverse drug reactions, etc., will be calculated. For PT, the number and percentage of adverse drug reactions, etc., will be calculated. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction will be counted once per patient.

(3) Figure/table number

Tables 5.1-2 to 5.1.2-3

5.2 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrences of adverse events and adverse drug reactions/infections by outcome

5.2.1 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse events by outcome

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, unknown, or not provided

The type of adverse events will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events by SOC/PT
Number of adverse events, etc.	Number of adverse events observed by SOC/PT If the same patient has multiple occurrences of the same adverse event (PT), all these occurrences will be counted (i.e., the overlap should be reflected).
Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and outcome	The number of adverse events will be calculated by SOC and PT. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same adverse event (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these events will be counted once for each category). If the same patient has multiple occurrences of the same adverse event classified into the same category, all these occurrences will be counted (i.e., the overlap should be reflected).

(3) Figure/table number

Tables 5.2.1-1 to 5.2.1-3

5.2.2 Occurrence of adverse events by CTCAE Grade (the worst one)

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse events will be analyzed as follows:

Data item	Data to be analyzed
Type of adverse events	The incidence of adverse events for each CTCAE grade (the worst one) will be calculated by SOC and PT. For SOC, the number and percentage of patients with adverse events will be calculated. For PT, the number and percentage of adverse events will be calculated. SOCs will be presented in the internationally

	agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are “Investigations,” and in ascending order of PT code otherwise. The CTCAE grade (the worst one) is higher in the order of ≥Grade 3, ≤Grade 2, and unknown. If the same patient has multiple occurrences of the same adverse event (PT), the event with the highest CTCAE grade will be counted once per patient.

(3) Figure/table number

Tables 5.2.2-1 to 5.2.2-3

5.2.3 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse drug reactions/infections by outcome

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, unknown, or not provided

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse drug reactions, etc., by SOC/PT If the same patient has multiple occurrences of the same adverse drug reactions, etc. (PT), all these occurrences will be counted (i.e., the overlap should be reflected).
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed by SOC/PT
Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and outcome	The number of adverse drug reactions, etc., will be calculated by SOC and PT. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be

	calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these adverse drug reactions will be counted once for each category). If the same patient has multiple occurrences of the same adverse drug reaction, etc., classified into the same category, all these occurrences will be counted (i.e., the overlap should be reflected).

(3) Figure/table number

Tables 5.2.3-1 to 5.2.3-3

5.2.4 Occurrence of adverse drug reactions/infections by CTCAE Grade (the worst one)

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Type of adverse drug reactions, etc.	The incidence of adverse drug reactions, etc., for each CTCAE grade (the worst one) will be calculated by SOC and PT. For SOC, the number and percentage of patients with drug reactions, etc., will be calculated. For PT, the number and percentage of drug reactions, etc., will be calculated. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. The CTCAE grade (the worst one) is higher in the order of ≥Grade 3, ≤Grade 2, and unknown. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction with the highest CTCAE grade will be counted once per patient.

(3) Figure/table number

Tables 5.2.4-1 to 5.2.4-3

5.3 Percentage of patients with adverse drug reactions/infections by patient demographics and baseline characteristics and treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the percentage of patients with adverse drug reactions, etc. (with point estimate and 95% confidence interval) will be determined.

For categories associated and not associated with ranking, Fisher's exact and Mann-Whitney U tests, respectively, will be used. If there is a category of "unknown," it will be excluded to perform

the Mann-Whitney U test.

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present
Past history of malignant tumours	Absent or present
Concurrent malignant tumours	Absent or present
Concurrent hepatic disorders	Absent or present
Grade of hepatic disorder (Grade based on AST and ALT levels)	None, Grade 1, Grade 2, ≥Grade 3, or unknown
Concurrent renal disorders	Absent or present
Grade of renal disorder (Grade based on serum creatinine)	None, Grade 1, Grade 2, ≥Grade 3, or unknown
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, or ≥70 kg
BMI	<18.5 kg/m^2, <18.5 to 25 kg/m^2, <25 to 30 kg/m^2, or ≥30 kg/m^2
Smoking history	Never, current, past, or unknown
Prior drug therapy	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), present (homologous), present (autologous and homologous), or unknown
Initial dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg

Data item	Category
Mean dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present

(3) Figure/table number

Tables 5.3-1 to 5.3-3

5.4 Occurrence of adverse drug reactions/infections by age group

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The similar calculation as the one described in Section 5.1.2, will be performed by age group (<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years).

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.4-1 to 5.4-3

5.5 Occurrence of adverse drug reactions/infections by presence or absence and grade of concurrent hepatic disorder

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The similar calculation as the one described in Section 5.1.2, will be performed by presence or absence and grade of concurrent hepatic disorder.

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.5-1 to 5.5-3

5.6 Occurrence of adverse drug reactions/infections by presence or absence and grade of concurrent renal disorder

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The similar calculation as the one described in Section 5.1.2, will be performed by presence or absence and grade of concurrent renal disorder

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.6-1 to 5.6-3

5.7 Occurrence of serious adverse events

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with serious adverse events	Number of patients experiencing serious adverse events
Number of serious adverse events	Number of serious adverse events observed If the same patient has multiple occurrences of the same serious adverse event (PT), the total number of occurrences will be calculated.
Percentage of patients with serious adverse events	Is calculated using the following formula: number of patients with serious adverse events/number of patients included in the safety analysis set × 100.
Type of serious adverse events	The incidence of serious adverse events will be calculated by SOC and PT. For SOC, the number and percentage of patients with serious adverse events will be calculated. For PT, the number and percentage of serious adverse events will be calculated SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same serious adverse event (PT), the event will be counted once per patient. For serious adverse events considered not related to Adcetris, the number of these events will be presented in ( ).

(3) Figure/table number

Tables 5.7-1 to 5.7-3

5.8 Change in test data over time

5.8.1 Change in laboratory test results over time

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Summary statistics of 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 will be calculated at each test time point [at baseline, after 1 cycle, ... and after 15 cycles]. In addition, box plots of hemoglobin level, neutrophil count, lymphocyte count, and platelet count will be generated at each test time point.

(3) Figure/table number

Tables 5.8.1-1 to 5.8.1-3 and Figures 5.8.1-1 to 5.8.1-3

5.9 Analysis of items of particular interest

5.9.1 Occurrence of the adverse drug reaction of peripheral nerve disorder and infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The incidence of peripheral nerve disorders considered related to Adcetris will be calculated for each CTCAE grade (the worst one) by symptom of peripheral nerve disorder (peripheral sensory neuropathy, peripheral motor neuropathy, or peripheral neuropathy) and PT (see Section 1.2 for the definition of symptoms of peripheral nerve disorders). For symptoms of peripheral nerve disorders, the number and percentage of patients with peripheral nerve disorder will be calculated. For PT, the number and percentage of peripheral nerve disorder will be calculated. PTs will be presented in ascending order of PT code.

The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of the same symptom of peripheral nerve disorder or the same PT, the symptom of peripheral nerve disorder or PT with the highest CTCAE grade (the worst one) will be counted for the respective category once per patient:

Data item	Category
CTCAE Grade (the worst one) for peripheral nerve disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.1-1 to 5.9.1-3

5.9.2 Occurrence of peripheral nerve disorders considered related to Adcetris by patient demographics and baseline characteristics and treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item of patient demographics and baseline characteristics and treatment given, patients will be stratified into the categories below, and the incidence of peripheral nerve disorders considered related to Adcetris will be calculated by CTCAE Grade (the worst one). The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the peripheral nerve disorder with the highest CTCAE grade will be counted once for the category:

Data item	Category
CTCAE Grade (the worst one) of peripheral nerve disorder	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Items and categories of patient demographics and baseline characteristics and treatment given

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
ECOG Performance Status	0, 1, 2, 3, or 4
Concurrent peripheral nerve disorders	None, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, or ≥70 kg
Prior ABVD or CHOP	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), present (homologous), present (autologous and homologous), or unknown
Initial dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Mean dose of Adcetris	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.2 mg/kg, 1.2 mg/kg, >1.2 mg/kg to <1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Concurrent diabetes mellitus	Absent or present

(3) Figure/table number

Tables 5.9.2-1 to 5.9.2-3

5.9.3 Treatment with Adcetris at the onset of peripheral nerve disorders considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience peripheral nerve disorders considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of peripheral nerve disorders considered related to Adcetris, patients will be stratified into the categories below, and the incidence of peripheral nerve disorders will be calculated. If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category). The percentage of peripheral nerve disorders for each category will be calculated using the number of peripheral nerve disorders for each CTCAE grade (the worst one) as the denominator.

For each data item, missing data will be handled as "not provided."

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation, or not provided

(3) Figure/table number

Tables 5.9.3-1 to 5.9.3-3

5.9.4 Outcome of peripheral nerve disorders (≥CTCAE Grade 3) considered related to Adcetris by action taken with Adcetris

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma) who experience peripheral nerve disorder (≥CTCAE Grade 3) considered related to Adcetris

(2) Data to be analyzed

For peripheral nerve disorders considered related to Adcetris, patients will be stratified into the categories below for each outcome and the incidence of these peripheral nerve disorders will be calculated. If the same patient has multiple occurrences of peripheral nerve disorder, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category).

For each data item, missing data will be handled as "not provided." The percentage of peripheral nerve disorders for each category will be calculated using the total number of peripheral nerve

disorders for each category as the denominator:

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation, or not provided

(3) Figure/table number

Tables 5.9.4-1 to 5.9.4-3

5.9.5 Occurrence of infections considered related to Adcetris by presence or absence of drugs used for the prevention of infection

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Patients will be stratified into the categories below and the incidence of infections considered related to Adcetris for each CTCAE grade (the worst one) will be calculated by presence or absence of drugs used for the prevention of infection, using Mann-Whitney U test. The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of the same infection, the occurrence with the highest CTCAE grade will be counted once for the category.

Similar analyses will be performed by use or non-use of antibiotics/synthetic antibacterial agents or trimethoprim-sulfamethoxazole combinations and by use or non-use of trimethoprim-sulfamethoxazole combinations for bacterial infection, by use or non-use of antifungals for fungal infection, and by use or non-use of antivirals for viral infection.

For patients included in safety evaluation who use antivirals for the prevention of viral infection but experience viral infection, a list of the following items will be generated: patient number, viral infection (name of the infection), age, sex, diagnosis, past history of hematopoietic stem cell transplantation (autologous or homologous), and drugs used for the prevention of infection (antivirals). If the same patient has multiple viral infections, all these viral infections will be counted.

Data item	Category
CTCAE Grade (the worst one) of infections	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.5-1 to 5.9.5-3 and 5.9.5-4

5.9.6 Occurrence of infections considered related to Adcetris by presence or absence of prior hematopoietic stem cell transplantation

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The incidence of infections considered related to Adcetris for each CTCAE grade (the worst one) will be calculated by presence or absence of prior hematopoietic stem cell transplantation (absent, present [autologous], present [homologous], present [autologous and homologous], or unknown) using Kruskal-Wallis test. The grade category of "unknown" will be excluded from the test.

The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple infections, the one with the highest CTCAE grade (the worst one) will be counted once for the category (the worst one).

Similary analyses will be performed for bacterial, fungal, and viral infections.

Data item	Category
CTCAE Grade (the worst one) of infection	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.6-1 to 5.9.6-3

5.9.7 Occurrence of neutropenia considered related to Adcetris by patient demographics and baseline characteristics

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item of patient demographics and baseline characteristics, patients will be stratified into the categories below, and the incidence of neutropenia considered related to Adcetris will be calculated by CTCAE Grade (the worst one). The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of neutropenia, the event with the highest CTCAE grade will be counted once.

Data item	Category
CTCAE Grade (the worst one) of neutropenia	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Items and categories of patient demographics and baseline characteristics

Data item	Category
Prior hematopoietic stem cell transplantation	Absent, present (autologous), present (homologous), present (autologous and homologous), or unknown

Degree of decreased neutrophil count at baseline	No decrease, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Drugs used for the prevention of infection	Absent or present
Specific drug(s) used for the prevention of infection	Antibiotics/synthetic antibacterial agents, antifungals, antivirals, trimethoprim-sulfamethoxazole combinations, or other

(3) Figure/table number

Tables 5.9.7-1 to 5.9.7-3

5.9.8 Treatment with Adcetris at the onset of neutropenia considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of neutropenia considered related to Adcetris, patients will be stratified into the categories below, and the incidence of events of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category). The percentage of neutropenia for each category will be calculated using the number of neutropenia for each CTCAE grade (the worst one) as the denominator.

For each data item, missing data will be handled as "not provided."

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation or not provided

(3) Figure/table number

Tables 5.9.8-1 to 5.9.8-3

5.9.9 Outcome of neutropenia considered related to Adcetris by action taken with Adcetris

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For neutropenia considered related to Adcetris, patients will be stratified into the categories below for each outcome and the incidence of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of neutropenia requiring dose reduction and one episode of neutropenia leading to treatment discontinuation, these episodes of neutropenia will be counted once for each category). The percentage of neutropenia for each category will be calculated using the total number of neutropenia for each category as the denominator.

For each data item, missing data will be handled as "not provided."

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation, or not provided

(3) Figure/table number

Tables 5.9.9-1 to 5.9.9-3

5.9.10 Occurrence of infusion reaction considered related to Adcetris

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The incidence of infusion reaction considered related to Adcetris for each CTCAE grade (the worst one) will be calculated by infusion reaction and PT (see Section 1.2 for the definition of infusion reaction). For infusion reactions, the number and percentage of patients with infusion reaction will be calculated. For PT, the number and percentage of infusion reactions will be calculated. PTs will be presented in ascending order or PT Code.

The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of infusion reaction or there are multiple occurrences of the same PT, the highest CTCAE grade (the worst one) for the patient or PT will be counted once for the category:

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.10-1 to 5.9.10-3

5.9.11 Occurrence of the new onset of infusion reaction observed within 2 days after treatment with Adcetris and considered related to Adcetris (time of the new onset)

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The incidence of the new onset of infusion reaction observed within 2 days after treatment with Adcetris and considered related to Adcetris will be calculated by time of onset. In addition, similar calculation will be performed by use or non-use of premedication to prevent infusion reaction. See the table below for the categories of time of onset:

Data item	Category
Time of onset	During infusion of Adcetris, after the completion of infusion of Adcetris (≤1 hour, >1 hour to ≤12 hours, >12 hours to ≤24 hours, >24 hours), or unknown

(3) Figure/table number

Tables 5.9.11-1 to 5.9.11-3

5.9.12 Occurrence of infusion reaction observed within 2 days after treatment with Adcetris and considered related to Adcetris by use or non-use of premedication to prevent infusion reaction

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The total number of doses of Adcetris[*1] will be calculated by use or non-use of premedication to prevent infusion reaction (absent, present, or unknown). In addition, the incidence of infusion reaction observed within 2 days of the most recent treatment with Adcetris (i.e., observed on the day of treatment or on the day after treatment with Adcetris) and considered related to Adcetris will be calculated for each CTCAE grade (the worst one). The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurences of infusion reaction during the same period, the one with the highest CTCAE grade (the worst one) will be counted once[*2].

The percentage of infusion reaction by use or non-use of premedication to prevent infusion reaction will be calculated using the total number of doses of Adcetris for each of these categories (i.e., use or non-use) as the denominator.

*1: The total number of doses of Adcetris by use or non-use of premedication to prevent infusion reaction refers to the total doses per patient calculated by use or non-use of premedication. For example, if one patient receives 8 doses of Adcetris with premedication and 8 doses of Adcetris

without premedication, and another patient receives 10 doses of Adcetris with premedication and 6 doses of Adcetris without premedication, the total number of doses of Adcetris will be 18 (8 + 10) for the use of premedication and 14 (8 + 6) for the non-use of premedication.

*2: For example, if the date the most recent treatment with Adcetris is January 1, 2016 and "Grade 2" infusion reaction is observed on January 1, 2016, and "Grade 3" infusion reaction on January 2, 2016, these two episodes of infusion reaction will be counted as one episode of "Grade 3" infusion reaction.

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.12-1 to 5.9.12-3

5.9.13 Occurrence of adverse drug reactions of pulmonary disorder and infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The incidence of pulmonary disorders considered related to Adcetris for each CTCAE grade (the worst one) will be calculated by pulmonary disorder and PT. PTs and PT Codes will be presented in ascending order.

In addition, the incidence of pulmonary disorders considered related to Adcetris for each CTCAE grade (the worst one) will be calculated by patient demographics and baseline characteristics.

The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of pulmonary disorders or there are multiple occurrences of the same PT, the highest CTCAE grade (the worst one) for the patient or PT will be counted once for the category:

Data item	Category
CTCAE Grade (the worst one) for pulmonary disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Items and categories of patient demographics and baseline characteristics

Data item	Category
History of or concurrent pulmonary disorder	Absent or present
Smoking history	Non-smoker or smoker * Patients other than those who have never smoked will be classified into "smoker."
Prior radiotherapy	Absent or present

(3) Figure/table number

Tables 5.9.13-1 to 5.9.13-4

5.10 analysis setanalysis setanalysis setList of actions taken with Adcetris in patients experiencing peripheral nerve disorders considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set analysis setanalysis setwho experience peripheral nerve disorders considered related to Adcetris

(2) Data to be analyzed

(3) For each patient, a list of the following data items: patient number, diagnosis, action taken or not taken with Adcetris, reason for action taken, date of dosing and dose for each cycle, date of onset of peripheral nerve disorder, CTCAE grade (the worst one), outcome, and the date of outcome. If the

same patient has multiple occurrences of peripheral nerve disorder, all these occurrences will be counted. Figure/table number

Table 5.10

5.11 List of actions taken with Adcetris in patients experiencing neutropenia considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set analysis setanalysis setwho experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each patient, a list of the following data items: patient number, diagnosis, action taken or not taken with Adcetris, reason for action taken, date of dosing and dose for each cycle, date of onset of neutropenia, intervention provided for neutropenia, specific intervention (e.g., name of drugs/therapies) outcome, and the date of outcome. If the same patient has multiple occurrences of neutropenia, all these occurrences will be counted.

(3) Figure/table number

Table 5.11

6.0 Efficacy Analysis

6.1 Best response

(1) Analysis set to be used

Patients included in efficacy evaluation who complete best response assessmentanalysis set

(2) Data to be analyzed

The frequency of the best response after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed in patients Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma. In addition, the point estimate of the response rate (CR + Cru + PR) with two-sided 95% confidence interval will be calculated, and a bar chart of the percentage of each category will be generated. Similar analyses will be performed by presence or absence of PET assessment, and a bar chart will be generated. For the handling of best response assessment data, see Section 1.7.

(3) Figure/table number

Table 6.1 and Figure 6.1

6.2 Days to the best response

(1) Analysis set to be used

Patients included in efficacy evaluation who complete best response assessmentanalysis set

(2) Data to be analyzed

The frequency of days to the best response (1 to 21 days, 22 to 42 days, 43 to 63 days, [segmented similarly using a 21-day time window thereafter], 316 to 336 days, or ≥337 days) in patients with Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma will be analyzed and summary statistics will be calculated. For the handling of best response assessment data, see Section 1.7. Figure/table number

Table 6.2 and Figure 6.2

6.3 Overall survival

(3) Analysis sets to be used

Patients included in efficacy evaluation

(4) Data to be analyzed

The 1-year survivals with two-sided 95% confidence intervals in patients will be calculated using the Kaplan-Meier method, and a Kaplan-Meier plot will be generated for Hodgkin's lymphoma and patients and anaplastic large-cell lymphoma respectively.

(5) Figure/table number

Table 6.3 and Figure 6.3

Appendix: Definition of Pulmonary Disorders (MedDRA Preferred Terms)

- Acute interstitial pneumonitis (10066728)
- Acute lung injury (10069351)
- Acute respiratory distress syndrome (10001052)
- Acute respiratory failure (10001053)
- Alveolar proteinosis (10001881)
- Alveolitis (10001889)
- Alveolitis allergic (10001890)
- Systemic sclerosis pulmonary (10042954)
- Alveolitis necrotising (10050343)
- Bronchiolitis (10006448)
- Diffuse alveolar damage (10060902)
- Eosinophilic pneumonia (10014962)
- Eosinophilic pneumonia acute (10052832)
- Eosinophilic pneumonia chronic (10052833)
- Hypoxia (10021143)
- Idiopathic pneumonia syndrome (10063725)
- Idiopathic pulmonary fibrosis (10021240)
- Interstitial lung disease (10022611)
- Lung disorder (10025082)
- Lung infiltration (10025102)
- Necrotising bronchiolitis (10070831)
- Obliterative bronchiolitis (10029888)
- Organising pneumonia (10067472)
- Pneumonitis (10035742)
- Pneumonitis chemical (10035745)
- Progressive massive fibrosis (10036805)
- Pulmonary alveolar haemorrhage (10037313)
- Pulmonary eosinophilia (10037382)
- Pulmonary fibrosis (10037383)
- Pulmonary granuloma (10037391)
- Pulmonary haemosiderosis (10037396)
- Pulmonary necrosis (10058824)
- Pulmonary oedema (10037423)
- Pulmonary radiation injury (10061473)
- Pulmonary sarcoidosis (10037430)
- Pulmonary toxicity (10061924)
- Pulmonary vasculitis (10037457)
- Radiation alveolitis (10037754)
- Radiation fibrosis – lung (10037758)
- Radiation pneumonitis (10037765)
- Respiratory arrest (10038669)
- Respiratory distress (10038687)
- Respiratory failure (10038695)
- Sarcoidosis (10039486)

The above definition is consistent with the one used in clinical studies of Adcetris.

Statistical Analysis Plan

ADCETRIS IV Infusion − Special Drug Use Surveillance (All-case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

PPD

Takeda Pharmaceutical Company Limited

PPD

Statistical Analysis Agent

PPD

2nd version: Prepared on September 25, 2015

Table of Contents

1.0 Definition of Terms and Handling of Test/Measurement Data

1.1 Definition

Term	Definition
This/the product	Refers to Adcetris for intravenous drip infusion in this Statistical Analysis Plan.
SOC	MedDRA/J System Organ Class
HLGT	MedDRA/J High Level Group Term
PT	MedDRA/J Preferred Term
LLT	MedDRA/J Lowest Level Term
Patients registered	Patients whose registration has been approved
Patients whose case report forms are available	Patients whose case report forms have been collected
Patients whose case report forms are not available	Patients registered but whose case report form have not been collected
Fixed patients	Patients whose case report forms are available, with the date of case report form completion entered in the PMS system
Non-fixed patients	Patients whose case report forms are available, with the date of case report form completion not entered in the PMS system
Safety analysis set	Fixed patients included in the safety analysis set
Safety analysis set (Hodgkin's lymphoma)	Patients included in the safety analysis set whose diagnosis is Hodgkin's lymphoma
Safety analysis set (anaplastic large-cell lymphoma)	Patients included in the safety analysis set whose diagnosis is anaplastic large-cell lymphoma
Patients excluded from the safety analysis set	Fixed patients excluded from the safety analysis set
Efficacy analysis set	Patients included in the safety analysis set who are also included in the efficacy analysis set
Patients excluded from the efficacy analysis set	Patients included in the safety analysis set who are excluded from the efficacy analysis set
Patients completing treatment	Patients completing 16 cycles of treatment with Adcetris
Patients discontinuing treatment	Patients not completing 16 cycles of treatment with Adcetris
Adverse events, etc.	Refers to "adverse events and infections." In this Statistical Analysis Plan, the term "adverse events and infections" is used in titles and the term "adverse events, etc." is used in text and tables.
Adverse drug reactions, etc.	Refers to "adverse drug reactions and infections." Adverse events, etc., not considered "not related" to Adcetris by the investigator.

Term	Definition
	In this Statistical Analysis Plan, the term “adverse drug reactions and infections” is used in titles and the term “adverse drug reactions, etc.” is used in text and tables.
Serious adverse events, etc.	Refers to “serious adverse events and infections.” Adverse events considered “serious” by the investigator. Events listed in the MedDRA Coding List in the Takeda Medically Significant AE List should be regarded as serious even if they are considered “non-serious” by the investigator. In this Statistical Analysis Plan, the term “serious adverse events and infections” is used in titles and the term “serious adverse events, etc.” is used in text and tables.
Number of patients with adverse events/adverse drug reactions	Number of patients experiencing adverse events, etc., or adverse drug reactions, etc.
Number of adverse events/adverse drug reactions	Number of adverse events, etc., or adverse drug reactions, etc., observed
Percentage of patients with adverse events/adverse drug reactions	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients excluded from the safety analysis set) × 100.
Percentage of adverse events/adverse drug reactions observed	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients excluded from the safety analysis set) × 100.
Time of onset	Is calculated using the following formula: date of onset of adverse events, etc. (or adverse drug reactions, etc.) − date of the initial dose of Adcetris + 1. If the day and month of onset of adverse events, etc. (or adverse drug reactions, etc.) are unknown, the date of onset should be “January 1.” However, if the year of the initial dose of Adcetris is the year of onset of adverse events, etc. (or adverse drug reactions, etc.), the date of onset

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>should be the day and month of the initial dose of Adcetris.
If the day of onset of adverse events, etc. (or adverse drug reactions, etc.) is unknown, the date of onset should be the first day of the month. However, if the year and month of the initial dose of Adcetris is the year and month of onset of adverse events, etc. (or adverse drug reactions, etc.), the date of the initial dose of Adcetris should be the date of onset.</td></tr>
<tr><td>Patients with concurrent hepatic disorder</td><td>Patients having a concurrent illness that falls under the category of Standardized MedDRA Query (SMQ) Code 20000005 (SMQ Hepatic disorders [Scope: Narrow])</td></tr>
<tr><td>Grade of hepatic disorder</td><td>The ALT or AST level at baseline with the highest CTCAE grade will be used to determine the grade of hepatic disorder. The grades of ALT and AST levels will be determined according to the following tables:
<table>
<tr><td>ALT</td><td>Male</td><td>Female</td></tr>
<tr><td>None</td><td>≤42 IU/L</td><td>≤23 IU/L</td></tr>
<tr><td>Grade 1</td><td>>42 to 126 IU/L</td><td>>23 to 69 IU/L</td></tr>
<tr><td>Grade 2</td><td>>126 to 210 IU/L</td><td>>69 to 115 IU/L</td></tr>
<tr><td>≥Grade 3</td><td>>210 IU/L</td><td>>115 IU/L</td></tr>
</table>
<table>
<tr><td>AST</td><td></td></tr>
<tr><td>None</td><td>≤30 IU/L</td></tr>
<tr><td>Grade 1</td><td>>30 to 90 IU/L</td></tr>
<tr><td>Grade 2</td><td>>90 to 150 IU/L</td></tr>
<tr><td>≥Grade 3</td><td>>150 IU/L</td></tr>
</table></td></tr>
<tr><td>Patients with concurrent renal disorder</td><td>Patients having a concurrent illness that falls under the category of Takeda MedDRA Query (TMQ) (Renal disease)</td></tr>
<tr><td>Grade of renal disorder: None</td><td>The serum creatinine level at baseline is:
≤1.07 mg/dL for males
≤0.79 mg/dL for females</td></tr>
<tr><td>Grade of renal disorder: 1</td><td>The serum creatinine level at baseline is:
>1.07 to 1.605 mg/dL for males
>0.79 to 1.185 mg/dL for females</td></tr>
<tr><td>Grade of renal disorder: 2</td><td>The serum creatinine level at baseline is:
>1.605 to 3.21 mg/dL for males
>1.185 to 2.37 mg/dL for females</td></tr>
<tr><td>Grade of renal disorder: ≥3</td><td>The serum creatinine level at baseline is:
>3.21 mg/dL for males
>2.37 mg/dL for females</td></tr>
<tr><td>Patients with a past history of</td><td>Patients with a past history that falls under the category of Appendix</td></tr>
</table>

Term	Definition
pulmonary disorder	"Definition of Pulmonary Disorders" (If "No concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of pulmonary disorders" in the case report form, the pulmonary disorder should be regarded as a past history.)
Patients with concurrent pulmonary disorder	Patients with a concurrent illness that falls under the category of Appendix "Definition of Pulmonary Disorders" (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of pulmonary disorders" in the case report form, the pulmonary disorder should be regarded as a concurrent illness.)
Patients with a past history of malignant tumour	Patients with a past history that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "No concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be regarded as a past history.)
Patients with concurrent malignant tumour	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be as a concurrent illness.)
Patients with concurrent diabetes mellitus	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000041 (SMQ Hyperglycaemia/new onset diabetes mellitus [Scope: Narrow])
Patients with hypertension	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000147 (SMQ Hypertension [Scope: Narrow])
Patients with concurrent dyslipidaemia	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000026 (SMQ Dyslipidaemia [Scope: Narrow])
Patients with concurrent hyperuricaemia	Patients with a concurrent illness that falls under the category of MedDRA PT Code 10020903 (Hyperuricaemia)
Patients with concurrent infection	Patients with a concurrent illness that falls under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with concurrent peripheral neuropathy	Patients with a concurrent illness that falls under the category of SMQ Code 20000034 (SMQ Peripheral neuropathy [Scope: Narrow])
Patients with other concurrent illnesses	Patients with any concurrent illness other than those listed above
Antibiotics/synthetic	Prophylactics against infections that fall under the category of those with

Term	Definition
antibacterial agents	the first three digits of YJ Code being 611 to 616 or 619 (If more than one antibiotics/synthetic antibacterial agents are used in the same patient, it will be counted as one patient.)
Antifungals	Prophylactics against infections that fall under the category of those with the first three digits of YJ Code being 617 (If more than one antifungals are used in the same patient, it will be counted as one patient.)
Antivirals	Prophylactics against infections that fall under the category of those with the first three digits of YJ Code being 625 (If more than one antivirals are used in the same patient, it will be counted as one patient.)
Trimethoprim-sulfamethoxazole combinations	Prophylactics against infections that fall under the category of those with YJ Code being 629010007 to 9
Other prophylactics against infections	Any drug entered in the field of "Drugs used for the prevention of infection" other than prophylactics against infections listed above (If more than one other prophylactics against infections are used in the same patient, it will be counted as one patient.)
Peripheral sensory neuropathy (as an adverse event)	Adverse events with "Sensory neuropathy" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034620 should be assigned regardless of data entered in "Symptoms" in the field.
Peripheral motor neuropathy (as an adverse event)	Adverse events with "Motor neuropathy" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034580 should be assigned regardless of data entered in "Symptoms" in the field.
Peripheral neuropathy (as an adverse event)	Adverse events with "Other" entered in the "Category of peripheral nerve disorders" in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10029331 should be assigned, regardless of data entered in "Symptoms" in the field.
Pulmonary disorders (as adverse events)	Adverse events that fall under the category of Appendix "Definition of Pulmonary Disorders"
Infusion reaction	Adverse events entered in the field of "Adverse events: [4] Infusion reaction," regardless of data entered in "Symptoms" in the field.
Patients with the onset of infection	Patients with adverse drug reactions that fall under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with the onset of bacterial infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10004018 (Bacterial infection), 10008555 (Chlamydial infection), 10028474 (Mycoplasma infection) or 10039135 (Rickettsia infection)
Patients with the onset of fungal infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10017528 (Fungal infection)

Term	Definition
Patients with the onset of viral infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10047438 (Viral infection)
Age	If the month and day of the initial dose of Adcetris is < the month and day of birth, the patient's age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth − 1. If the month and day of the initial dose of Adcetris is ≥ the month and day of birth, the patient's age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth. If the month and day of birth are unknown, they should be "January 1," and if the day of birth is unknown, it should the first day of the month.
BMI	BMI should be calculated using the following formula: Weight (kg)/(0.0001 × height (cm) × height (cm). The obtained value should be rounded off to one decimal place.
Disease duration	The disease duration should be calculated using the following formula: ["Date of the initial dose of Adcetris" − "date of diagnosis of Hodgkin's or anaplastic large-cell lymphoma" +1]/365.25. The day of diagnosis should be the first day of the month provided. If the month of diagnosis is unknown, the date of diagnosis should be "January 1st" of the year provided.
Mean dose of Adcetris	Is calculated as the total value of each dose of Adcetris given at each treatment cycle divided by the number of cycles.
Dose of Adcetris per 3 weeks	Is calculated using the following formula: Total "dose of Adcetris"/(["date of the last dose of Adcetris" − "date of the initial dose of Adcetris" + 21)/21]. If only 1 cycle of treatment is given, the "date of the last dose of Adcetris" and the "date of the initial dose of Adcetris" should be regarded as the same.
Degree of decreased neutrophil count at baseline: No decrease	Neutrophil count at baseline ≥2,000 /mm^3
Degree of decreased neutrophil count at baseline: Grade 1	Neutrophil count at baseline <2,000 to 1,500 /mm^3
Degree of decreased neutrophil count at baseline: Grade 2	Neutrophil count at baseline <1,500 to 1,000 /mm^3
Degree of decreased neutrophil count at baseline: Grade 3	Neutrophil count at baseline <1,000 to 500 /mm^3
Degree of decreased neutrophil count at baseline: Grade 4	Neutrophil count at baseline <500 /mm^3
Date of the final observation	"Date of the final observation" in the case report form If not provided, the most recent date entered in the case report form should

Term	Definition
	be used.
Summary statistics	Includes mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

1.2 Display digits

Term	Definition
Percentage (%)	Percentage of patients with or percentage of adverse events, etc., or adverse drug reactions, etc.: The obtained value should be rounded off to two decimal places. Other: The obtained value should be rounded off to one decimal place.
Summary statistics (mean and standard deviation)	Mean: The raw data should be rounded off to one decimal place. Standard deviation: The raw data should be rounded off to two decimal places.
P value	The obtained value should be rounded down to three decimal places. If the value is less than 0.001 after rounding down to three decimal places, it should be displayed as "p<0.001."

1.3 Level of significance

Two-sided 5%

1.4 Handling of test data

Test data will be handled according to the criteria shown below. If there are multiple data for the same criterion, the one with the test date being closest to the date of protocol-specified assessment should be used. If there is no difference in the number of days from the date of protocol-specified assessment, the later value should be used. For the final assessment, *however, the most recently measured value (including the one measured during the off-treatment period) after the date of the initial dose of Adcetris should be used. Values measured after 30 days after the last dose of Adcetris should not be used.

The number of days after the date of the initial dose of Adcetris is defined as 1 for the date of the initial dose of Adcetris and 0 for the day before the date of the initial dose of Adcetris.

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

Time point for testing	Acceptable time window	Date of protocol-specified assessment
At the initial dose of Adcetris	−21 to 1 days	Date of the initial dose of Adcetris
After 1 cycle	2 to 31 days	Date of the initial dose of Adcetris + 21
After 2 cycles	32 to 52 days	Date of the initial dose of Adcetris + 42
After 3 cycles	53 to 73 days	Date of the initial dose of Adcetris + 63
After 4 cycles	74 to 94 days	Date of the initial dose of Adcetris + 84
After 5 cycles	95 to 115 days	Date of the initial dose of Adcetris + 105
After 6 cycles	116 to 136 days	Date of the initial dose of Adcetris + 126
After 7 cycles	137 to 157 days	Date of the initial dose of Adcetris + 147

Time point for testing	Acceptable time window	Date of protocol-specified assessment
After 8 cycles	158 to 178 days	Date of the initial dose of Adcetris + 168
After 9 cycles	179 to 199 days	Date of the initial dose of Adcetris + 189
After 10 cycles	200 to 220 days	Date of the initial dose of Adcetris + 210
After 11 cycles	221 to 241 days	Date of the initial dose of Adcetris + 231
After 12 cycles	242 to 262 days	Date of the initial dose of Adcetris + 252
After 13 cycles	263 to 283 days	Date of the initial dose of Adcetris + 273
After 14 cycles	284 to 304 days	Date of the initial dose of Adcetris + 294
After 15 cycles	305 to 325 days	Date of the initial dose of Adcetris + 315
After 16 cycles	326 to 346 days	Date of the initial dose of Adcetris + 336

2.0 Patient Disposition (Patient Disposition Diagram)

(1) Analysis set to be used

Patients registered to this specified drug-use survey

(2) Data to be analyzed

Data to be analyzed includes the numbers of patients registered, institutions with patients registered, patients whose case report forms are available/not available, fixed/non-fixed patients, patients included in/excluded from the safety analysis set, and patients included in/excluded from the efficacy analysis set.

For the number of institutions with patients registered, the same institutions with different departments should not be counted more than once.

For patients whose case report forms are not available, the number of patients by reason for unavailability and the total number of patients will be calculated.

For patients excluded from the safety/efficacy analysis set, the number of patients by reason for exclusion and the total number of patients will be calculated.

It will be determined as follows whether patients meeting the following criteria should be included or excluded:

Criterion	Registration	Safety evaluation	Efficacy evaluation
Duplicate registration (of the same patient) [found afterwards]	×	×	×
Non-primary disease	○	○	×
Adcetris has never been administered [found afterwards]	×	×	×
No definite safety evaluation results are available	○	×	×
No definite efficacy evaluation results are available	○	○	×
No case report form is available	○	×	×

○: Included, ×: Excluded

(3) Figure/table number

Figure 2.0 and Table2.0

3.0 Patient Demographics and Baseline Characteristics

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Sex	Male or female
Age	Summary statistics
	<18 years, 18 to 39 years, 40 to 64 years, 65 to 74 years, or ≥75 years
	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
Diagnosis	Hodgkin's or anaplastic large-cell lymphoma or other
Status	Relapsed/refractory, or new-onset
CD30	Positive, negative, or not measured
Site(s) of involvement	Lymph node, spleen, liver, lung, bone, central nerve, bone marrow, skin, and/or other
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Therapeutic category	Outpatient or inpatient
Hypersensitivity disposition	Absent, present, or unknown
Specific hypersensitivity disposition(s)	Medications, food allergy, and/or other
HCV antibody	Negative, positive, or unknown
HBs antigen	Negative, positive, or unknown
HBs antibody	Negative, positive, or unknown
HBV DNA	Negative, positive, or unknown
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present

Data item	Category
Past history of malignant tumours	Absent or present
Concurrent malignant tumours	Absent or present
Past history (other than pulmonary disorders and malignant tumours)	Absent, present, or unknown
Concurrent illness (other than pulmonary disorders and malignant tumours)	Absent or present
Specific concurrent illness(es) (other than pulmonary disorders and malignant tumours)	Diabetes mellitus, hypertension, dyslipidaemia, hyperuricaemia, hepatic disease(s), renal disease(s), infections, peripheral nerve disorders, and/or other
Concurrent renal disorders	Absent or present
Grade of hepatic disorder (CTCAE grade based on AST and ALT levels)	None, Grade 1, Grade 2, or ≥Grade 3
Concurrent renal disorders	Absent or present
Grade of renal disorder (CTCAE grade based on serum creatinine)	None, Grade 1, Grade 2, or ≥Grade 3
Weight	Summary statistics
	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
BMI	Summary statistics
	<18.5 kg/m^2, <18.5 to 25 kg/m^2, <25 to 30 kg/m^2, ≥30 kg/m^2, or unknown
Smoking history	Never, current, past, or unknown
Prior drug therapy	Absent or present

Data item	Category
Prior drug therapy regimen(s)	ABVD, CHOP, and/or other (If more than one drug therapies in the same category is used in the same patient, it will be counted as one patient.)
Number of prior drug therapy regimens	Summary statistics
Days from the month of the completion of the final regimen of prior drug therapy to the date of 1 cycle of treatment with Adcetris (Prior drug therapy: Yes)	Summary statistics
Prior radiotherapy	Absent or present
Days from the month of the completion of the most recent prior radiotherapy to the date of 1 cycle of treatment with Adcetris (Prior radiotherapy: yes)	Summary statistics
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Other prior therapies	Absent or present
Pregnancy during the observation period (for females only)	Absent or present

(3) Figure/table number

Tables 3.0-1 to 3.0-3

4.0 Treatment Given

4.1 Treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Duration of treatment with Adcetris	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 cycles
Reason(s) for discontinuation of Adcetris	Treatment goal achieved, adverse event(s), lost to follow-up, transfer to another hospital, pregnancy, inadequate response, and/or other
Post-baseline hematopoietic stem cell transplantation	Absent or present
Type of post-baseline hematopoietic stem cell transplantation	Autologous or homologous
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present
Drug(s) used for the prevention of infection	Absent or present
Specific drug(s) used for the prevention of infection	Antibiotics/synthetic antibacterial agents, antifungals, antivirals, trimethoprim-sulfamethoxazole combinations, and/or other prophylactics against infections

(3) Figure/table number

Tables 4.1-1 to 4.1-3

4.2 Premedication to prevent infusion reaction

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each cycle, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Premedication to prevent infusion reaction	Absent or present
Specific premedication(s) used to prevent infusion reaction	Acetaminophen, antihistamines, and/or corticosteroids

(3) Figure/table number

Tables 4.2-1 to 4.2-3

5.0 Safety Analysis

5.1 Occurrences of adverse events/infections and adverse drug reactions/infections

5.1.1 Occurrence of adverse events/infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

For data entered in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form, MedDRA PT Code for peripheral sensory neuropathy, peripheral motor neuropathy, or peripheral neuropathy should be assigned, regardless of the LLT code entered in "Symptoms" field (see Section 1.1 ,the same applies hereinafter).

Neutrophil count decreased (PT Code 10029366) will be replaced by Neutropenia (PT Code 10029354), Lymphocyte count decreased (PT Code 10025256) by Lymphopenia (PT Code 10025327), White blood cell count decreased (PT Code 10047942) by Leukopenia (PT Code 10024384), and Platelet count decreased (PT Code 10035528) by Thrombocytopenia (PT Code 10043554) (the same applies hereinafter).

Data item	Data to be analyzed
Number of patients with adverse events, etc.	Number of patients experiencing adverse events, etc.
Number of adverse events, etc.	Number of adverse events, etc., observed If the same patient has multiple occurrences of the same adverse event, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse events, etc.	Is calculated using the following formula: number of patients with adverse events, etc./number of patients included in the safety analysis set × 100.
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with adverse events, etc., will be presented in the internationally agreed order. For PT, the number and percentage of adverse events, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the event will be counted once per patient.

(3) Figure/table number

Tables 5.1-1 to 5.1.1-3

5.1.2 Occurrence of adverse drug reactions/infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with adverse drug reactions, etc.	Number of patients experiencing adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse drug reactions, etc.	Is calculated using the following formula: number of patients with adverse drug reactions, etc./number of patients included in the safety analysis set × 100.
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with adverse drug reactions, etc., will be presented in the internationally agreed order. For PT, the number and percentage of adverse drug reactions, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction will be counted once per patient.

(3) Figure/table number

Tables 5.1-2 to 5.1.2-3

5.2 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrences of adverse events/infections and adverse drug reactions/infections by outcome

5.2.1 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse events/infections by outcome

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events, etc., will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, or ≥337 days
	1 to 7 days, 8 to 14 days, 15 to 21 days, (segmented similarly using a 7-day time window thereafter), 330 to 336 days, or ≥337 days
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, or ≥337 days
	1 to 7 days, 8 to 14 days, 15 to 21 days, (segmented similarly using a 7-day time window thereafter), 330 to 336 days, or ≥337 days
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, or unknown

The type of adverse events, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events, etc., by SOC/PT
Number of adverse events, etc.	Number of adverse events, etc., observed by SOC/PT
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these events will be counted once for each category).

(3) Figure/table number

Tables 5.2.1-1 to 5.2.1-3

5.2.2 Occurrence of adverse events/infections by CTCAE Grade (the worst one)

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events, etc., will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse events, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events, etc., by SOC/PT
Number of adverse events, etc.	Number of adverse events, etc., observed by SOC/PT
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed

	order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the event with the worst CTCAE grade will be counted once.

(3) Figure/table number

Tables 5.2.2-1 to 5.2.2-3

5.2.3 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse drug reactions/infections by outcome

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, or ≥337 days
	1 to 7 days, 8 to 14 days, 15 to 21 days, (segmented similarly using a 7-day time window thereafter), 330 to 336 days, or ≥337 days
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, or ≥337 days
	1 to 7 days, 8 to 14 days, 15 to 21 days, (segmented similarly using a 7-day time window thereafter), 330 to 336 days, or ≥337 days
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, or unknown

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse drug reactions, etc., by SOC/PT
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed by SOC/PT
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be

	further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these adverse drug reactions will be counted once for each category).

(3) Figure/table number

Tables 5.2.3-1 to 5.2.3-3

5.2.4 Occurrence of adverse drug reactions/infections by CTCAE Grade (the worst one)

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse drug reactions, etc., by SOC/PT
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed by SOC/PT
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction with the worst CTCAE grade will be counted once.

(3) Figure/table number

Tables 5.2.4-1 to 5.2.4-3

5.3 Percentage of patients with adverse drug reactions/infections by patient demographics and baseline characteristics and treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the percentage of patients with adverse drug reactions, etc. (with point estimate and 95% confidence interval) will be determined.

For categories associated and not associated with ranking, Fisher's exact and Mann-Whitney U tests, respectively, will be used.

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present
Past history of malignant tumours	Absent or present
Concurrent malignant tumours	Absent or present
Concurrent hepatic disorders	Absent or present
Grade of hepatic disorder (CTCAE grade based on AST and ALT levels)	None, Grade 1, Grade 2, or ≥Grade 3
Concurrent renal disorders	Absent or present
Grade of renal disorder (CTCAE grade based on serum creatinine)	None, Grade 1, Grade 2, or ≥Grade 3
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
BMI	<18.5 kg/m^2, <18.5 to 25 kg/m^2, <25 to 30 kg/m^2, ≥30 kg/m^2, or unknown
Smoking history	Never, current, past, or unknown
Prior drug therapy	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg

Data item	Category
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present

(3) Figure/table number

Tables 5.3-1 to 5.3-3

5.4 Occurrence of adverse drug reactions/infections by age group

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by age group (<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years).

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.4-1 to 5.4-3

5.5 Occurrence of adverse drug reactions/infections by presence or absence of concurrent hepatic disorder

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by presence or absence of concurrent hepatic disorder.

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.5-1 to 5.5-3

5.6 Occurrence of adverse drug reactions/infections by presence or absence of concurrent renal disorder

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by presence or absence of concurrent renal disorder.

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Tables 5.6-1 to 5.6-3

5.7 List of the occurrence of serious adverse events/infections

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with serious adverse events, etc.	Number of patients experiencing serious adverse events, etc.
Number of serious adverse events, etc.	Number of serious adverse events, etc., observed If the same patient has multiple occurrences of the same serious adverse event, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with serious adverse events, etc.	Is calculated using the following formula: number of patients with serious adverse events, etc./number of patients included in the safety analysis set × 100.
Type of serious adverse events	Serious adverse events, etc., will first be classified by SOC, within each of which serious adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with serious adverse events, etc., will be presented in the internationally agreed order. For PT, the number and percentage of serious adverse events, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same serious adverse event, etc. (PT), the event will be counted once per patient. For serious adverse events, etc., considered not related to Adcetris, the number of these events will be presented in [ ].

(3) Figure/table number

Tables 5.7-1 to 5.7-3

5.8 Change in test data over time

5.8.1 Laboratory tests

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Summary statistics of 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 will be calculated at each test time point [at baseline, after 1 cycle, ... and after 16 cycles].

(3) Figure/table number

Tables 5.8.1-1 to 5.8.1-3

5.9 Analysis of items of particular interest

5.9.1 Occurrence of peripheral nerve disorder

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of peripheral nerve disorders will be calculated:

Data item	Category
CTCAE Grade (the worst one) for peripheral nerve disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Symptoms of peripheral nerve disorders will be analyzed as follows:

Data item	Data to be analyzed
Symptoms of peripheral nerve disorders	Peripheral nerve disorders will first be classified into peripheral sensory, peripheral motor, and peripheral neuropathies listed in Section 1.1, and symptoms associated with these peripheral nerve disorders will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Tables 5.9.1-1 to 5.9.1-3

5.9.2 Occurrence of peripheral nerve disorders by patient demographics and baseline characteristics and treatment given

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the categories below, and the incidence of peripheral nerve disorders will be calculated by CTCAE Grade (the worst one). If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the peripheral nerve disorder with the worst CTCAE grade will be counted once.

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
ECOG Performance Status	0, 1, 2, 3, or 4
Grade of concurrent peripheral nerve disorders	None, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
Prior ABVD or CHOP	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or >1.8 mg/kg
Concurrent diabetes mellitus	Absent or present

(3) Figure/table number

Tables 5.9.2-1 to 5.9.2-3

5.9.3 Treatment with Adcetris at the onset of peripheral nerve disorders

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience peripheral nerve disorders considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of peripheral nerve disorders, patients will be stratified into the categories below, and the number of peripheral nerve disorders will be calculated. If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category).

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), or treatment discontinuation

(3) Figure/table number

Tables 5.9.3-1 to 5.9.3-3

5.9.4 Occurrence of infections by presence or absence of drugs used for the prevention of infection

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Patients will be stratified into the categories below and the number of patients with infection considered related to Adcetris will be calculated by presence or absence of drugs used for the prevention of infection using Mann-Whitney U test. If the same patient has multiple occurrences of the same infection, the occurrence with the worst CTCAE grade will be counted once.

Similarly, the number of patients with the onset of bacterial infection will be calculated by the use or non-use of antibiotics/synthetic antibacterial agents or trimethoprim-sulfamethoxazole combinations, the number of patients with the onset of fungal infection will be calculated by the use or non-use of antifungals, and the number of patients with the onset of viral infection will be calculated by the use or non-use of antivirals.

Data item	Category
CTCAE Grade (the worst one) of infections	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.4-1 to 5.9.4-3

5.9.5 Occurrence of neutropenia by patient demographics and baseline characteristics

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the categories below, and the incidence of neutropenia considered related to Adcetris will be calculated by CTCAE Grade (the worst one). If the same patient has multiple occurrences of neutropenia, the event with the worst CTCAE grade will be counted once.

Data item	Category
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Degree of decreased neutrophil count at baseline	No decrease, Grade 1, Grade 2, Grade 3, Grade 4, or unknown

(3) Figure/table number

Tables 5.9.5-1 to 5.9.5-3

5.9.6 Treatment with Adcetris at the onset of neutropenia

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of neutropenia, patients will be stratified into the categories below, and the number of events of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category).

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), or treatment discontinuation

(3) Figure/table number

Tables 5.9.6-1 to 5.9.6-3

5.9.7 Occurrence of infusion reaction

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of infusion reaction considered related to Adcetris will be calculated:

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Infusion reaction will be analyzed as follows:

Data item	Data to be analyzed
Symptoms of infusion reaction	Infusion reaction and its symptoms will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Tables 5.9.7-1 to 5.9.7-3

5.9.8 Occurrence of infusion reaction by the use or non-use of premedication to prevent infusion reaction

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Patients will be stratified into the following categories and the number of events of infusion reaction considered related to Adcetris will be calculated by the use or non-use of premedication to prevent infusion reaction (for example, if a patient receives no premedication and experiences "Grade 2" infusion reaction during Cycle 1 and receives premedication and experiences no infusion reaction during Cycle 2, these events of infusion reaction will be counted once for each category).

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.9.8-1 to 5.9.8-3

5.9.9 Occurrence of pulmonary disorders

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of events of pulmonary disorder considered related to Adcetris will be calculated:

Data item	Category
CTCAE Grade (the worst one) for pulmonary disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Diagnoses or symptoms of pulmonary disorder will be analyzed as follows:

Data item	Data to be analyzed
Diagnosis or symptom of pulmonary disorder	Pulmonary disorders and their diagnoses or symptoms will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Tables 5.9.9-1 to 5.9.9-3

5.10 Occurrence of infections by presence or absence of hematopoietic stem cell transplantation

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

Patients will be stratified into the categories below and the number of patients with infection considered related to Adcetris will be calculated by presence or absence of prior hematopoietic stem cell transplantation (Absent, present [autologous], or present [homologous]) using Mann-Whitney U test. If the same patient has multiple occurrences of the same infection, the occurrence with the worst CTCAE grade will be counted once.

Data item	Category
CTCAE Grade (the worst one) of infections	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Tables 5.10-1 to 5.10-3

5.11 List of actions taken with Adcetris in patients experiencing peripheral nerve disorders

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience peripheral nerve disorders considered related to Adcetris

(2) Data to be analyzed

For each patient, actions taken or not taken with Adcetris, specific action(s) taken, date of dosing and dose for each cycle, date of onset of peripheral nerve disorders, outcome, and date of outcome will be presented. If the same patient has multiple occurrences of peripheral nerve disorder, all the occurrences will be counted.

(3) Figure/table number

Tables 5.11-1 to 5.11-3

5.12 List of actions taken with Adcetris in patients experiencing neutropenia

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each patient, actions taken or not taken with Adcetris, specific action(s) taken, date of dosing and dose for each cycle, date of onset of neutropenia, outcome, and date of outcome will be presented. If the same patient has multiple occurrences of neutropenia, all the occurrences will be counted.

(3) Figure/table number

Tables 5.12-1 to 5.12-3

6.0 Efficacy Analysis

6.1 Best response

(1) Analysis set to be used

Efficacy analysis set

(2) Data to be analyzed

The best responses after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed in patients Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma.

(3) Figure/table number

Table 6.1

6.2 Overall survival

(1) Analysis set to be used

Efficacy analysis set

(2) Data to be analyzed

The survivals from the date of the initial dose of Adcetris in patients Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma will be calculated, using the final observation date as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field as the date of death.

Kaplan-Meier curves of the survival will also be constructed (i.e., a table of the numbers of adverse events, etc., and adverse drug reactions, etc., printed out by SAS will be attached).

(3) Figure/table number

Table 6.2 and Figure 6.2

Appendix: Definition of Pulmonary Disorders (MedDRA Preferred Terms)

- Acute interstitial pneumonitis (10066728)
- Acute lung injury (10069351)
- Acute respiratory distress syndrome (10001052)
- Acute respiratory failure (10001053)
- Alveolar proteinosis (10001881)
- Alveolitis (10001889)
- Alveolitis allergic (10001890)
- Systemic sclerosis pulmonary (10042954)
- Alveolitis necrotising (10050343)
- Bronchiolitis (10006448)
- Diffuse alveolar damage (10060902)
- Eosinophilic pneumonia (10014962)
- Eosinophilic pneumonia acute (10052832)
- Eosinophilic pneumonia chronic (10052833)
- Hypoxia (10021143)
- Idiopathic pneumonia syndrome (10063725)
- Idiopathic pulmonary fibrosis (10021240)
- Interstitial lung disease (10022611)
- Lung disorder (10025082)
- Lung infiltration (10025102)
- Necrotising bronchiolitis (10070831)
- Obliterative bronchiolitis (10029888)
- Organising pneumonia (10067472)
- Pneumonitis (10035742)
- Pneumonitis chemical (10035745)
- Progressive massive fibrosis (10036805)
- Pulmonary alveolar haemorrhage (10037313)
- Pulmonary eosinophilia (10037382)
- Pulmonary fibrosis (10037383)
- Pulmonary granuloma (10037391)
- Pulmonary haemosiderosis (10037396)
- Pulmonary necrosis (10058824)
- Pulmonary oedema (10037423)
- Pulmonary radiation injury (10061473)
- Pulmonary sarcoidosis (10037430)
- Pulmonary toxicity (10061924)
- Pulmonary vasculitis (10037457)
- Radiation alveolitis (10037754)
- Radiation fibrosis – lung (10037758)
- Radiation pneumonitis (10037765)
- Respiratory arrest (10038669)
- Respiratory distress (10038687)
- Respiratory failure (10038695)
- Sarcoidosis (10039486)

The above definition is consistent with the one used in clinical studies of Adcetris.

Statistical Analysis Plan

ADCETRIS IV Infusion − Special Drug Use Surveillance (All-case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

PPD

Takeda Pharmaceutical Company Limited

PPD

Statistical Analysis Agent

PPD

Initial version: Prepared on October 7, 2014

Table of Contents

1.0 Definition of Terms and Handling of Test/Measurement Data

1.1 Definition

Term	Definition
This/the product	Refers to Adcetris for intravenous drip infusion in this Statistical Analysis Plan.
SOC	MedDRA/J System Organ Class
HLGT	MedDRA/J High Level Group Term
PT	MedDRA/J Preferred Term
LLT	MedDRA/J Lowest Level Term
Patients registered	Patients whose registration has been approved
Patients whose case report forms are available	Patients whose case report forms have been collected
Patients whose case report forms are not available	Patients registered but whose case report form have not been collected
Fixed patients	Patients whose case report forms are available, with the date of case report form completion entered in the PMS system
Non-fixed patients	Patients whose case report forms are available, with the date of case report form completion not entered in the PMS system
Safety analysis set	Fixed patients included in the safety analysis set
Patients excluded from the safety analysis set	Fixed patients excluded from the safety analysis set
Efficacy analysis set	Patients included in the safety analysis set who are also included in the efficacy analysis set
Patients excluded from the efficacy analysis set	Patients included in the safety analysis set who are excluded from the efficacy analysis set
Patients completing treatment	Patients completing 16 cycles of treatment with Adcetris
Patients discontinuing treatment	Patients not completing 16 cycles of treatment with Adcetris
Adverse events, etc.	Refers to “adverse events and infections.” In this Statistical Analysis Plan, the term “adverse events and infections” is used in titles and the term “adverse events, etc.” is used in text and tables.
Adverse drug reactions, etc.	Refers to “adverse drug reactions and infections.” Adverse events, etc., not considered “not related” to Adcetris by the investigator. In this Statistical Analysis Plan, the term “adverse drug reactions and infections” is used in titles and the term “adverse drug reactions, etc.” is used in text and tables.
Serious adverse events, etc.	Refers to “serious adverse events and infections.”

Term	Definition
	Adverse events considered “serious” by the investigator. Events listed in the MedDRA Coding List in the Takeda Medically Significant AE List should be regarded as serious even if they are considered “non-serious” by the investigator. In this Statistical Analysis Plan, the term “serious adverse events and infections” is used in titles and the term “serious adverse events, etc.” is used in text and tables.
Number of patients with adverse events/adverse drug reactions	Number of patients experiencing adverse events, etc., or adverse drug reactions, etc.
Number of adverse events/adverse drug reactions	Number of adverse events, etc., or adverse drug reactions, etc., observed
Percentage of patients with adverse events/adverse drug reactions	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients excluded from the safety analysis set) × 100.
Percentage of adverse events/adverse drug reactions observed	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients excluded from the safety analysis set) × 100.
Time of onset	Is calculated using the following formula: date of onset of adverse events, etc. (or adverse drug reactions, etc.) − date of the initial dose of Adcetris + 1. If the day and month of onset of adverse events, etc. (or adverse drug reactions, etc.) are unknown, the date of onset should be “January 1.” However, if the year of the initial dose of Adcetris is the year of onset of adverse events, etc. (or adverse drug reactions, etc.), the date of onset should be the day and month of the initial dose of Adcetris. If the day of onset of adverse events, etc. (or adverse drug reactions, etc.) is unknown, the date of onset should be the first day of the month. However, if the year and month of the initial dose of Adcetris is the year

Term	Definition
	and month of onset of adverse events, etc. (or adverse drug reactions, etc.), the date of the initial dose of Adcetris should be the date of onset.
Patients with concurrent hepatic disorder	Patients having a concurrent illness that falls under the category of Standardized MedDRA Query (SMQ) Code 20000005 (SMQ Hepatic disorders [Scope: Narrow])
Patients with concurrent renal disorder	Patients having a concurrent illness that falls under the category of Takeda MedDRA Query (TMQ) (Renal disorders)
Patients with a past history of pulmonary disorder	Patients with a past history that falls under the category of Appendix "Definition of Pulmonary Disorders" (If "No concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of pulmonary disorders" in the case report form, the pulmonary disorder should be regarded as a past history.)
Patients with concurrent pulmonary disorder	Patients with a concurrent illness that falls under the category of Appendix "Definition of Pulmonary Disorders" (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of pulmonary disorders" in the case report form, the pulmonary disorder should be regarded as a concurrent illness.)
Patients with a past history of malignant tumour	Patients with a past history that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "No concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be regarded as a past history.)
Patients with concurrent malignant tumour	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000194 (SMQ Malignant tumours [Scope: Narrow]) (If "A concurrent illness existed at the initiation of treatment with Adcetris" is selected in the field of "Past history/concurrent illness of malignant tumours" in the case report form, the pulmonary disorder should be as a concurrent illness.)
Patients with concurrent diabetes mellitus	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000041 (SMQ Hyperglycaemia/new onset diabetes mellitus [Scope: Narrow])
Patients with hypertension	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000147 (SMQ Hypertension [Scope: Narrow])
Patients with concurrent dyslipidaemia	Patients with a concurrent illness that falls under the category of MedDRA SMQ Code 20000026 (SMQ Dyslipidaemia [Scope: Narrow])
Patients with concurrent	Patients with a concurrent illness that falls under the category of MedDRA

Term	Definition
hyperuricaemia	PT Code 10020903 (Hyperuricaemia)
Patients with concurrent infection	Patients with a concurrent illness that falls under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with concurrent peripheral neuropathy	Patients with a concurrent illness that falls under the category of SMQ Code 20000034 (SMQ Peripheral neuropathy [Scope: Narrow])
Patients with other concurrent illnesses	Patients with any concurrent illness other than those listed above
Antibiotics/synthetic antibacterial agents	Prophylactics against infections that fall under the category of those with the first three digits of YJ Code being 611 to 616 or 619 (If more than one antibiotics/synthetic antibacterial agents are used in the same patient, it will be counted as one patient.)
Antifungals	Prophylactics against infections that fall under the category of those with the first three digits of YJ Code being 617 (If more than one antifungals are used in the same patient, it will be counted as one patient.)
Antivirals	Prophylactics against infections that fall under the category of those with the first three digits of YJ Code being 625 (If more than one antivirals are used in the same patient, it will be counted as one patient.)
Trimethoprim-sulfamethoxazole combinations	Prophylactics against infections that fall under the category of those with YJ Code being 629010007 to 9
Other prophylactics against infections	Any drug entered in the field of “Drugs used for the prevention of infection” other than prophylactics against infections listed above (If more than one other prophylactics against infections are used in the same patient, it will be counted as one patient.)
Peripheral sensory neuropathy (as an adverse event)	Adverse events with “Sensory neuropathy” entered in the “Category of peripheral nerve disorders” in the field of “Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034620 should be assigned regardless of data entered in “Symptoms” in the field.
Peripheral motor neuropathy (as an adverse event)	Adverse events with “Motor neuropathy” entered in the “Category of peripheral nerve disorders” in the field of “Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10034580 should be assigned regardless of data entered in “Symptoms” in the field.
Peripheral neuropathy (as an adverse event)	Adverse events with “Other” entered in the “Category of peripheral nerve disorders” in the field of “Adverse events: [1] Peripheral nerve disorders] in the case report form. MedDRA PT Code 10029331 should be assigned, regardless of data entered in “Symptoms” in the field.
Pulmonary disorders (as adverse events)	Adverse events that fall under the category of Appendix “Definition of Pulmonary Disorders”
Infusion reaction	Adverse events entered in the field of “Adverse events: [4] Infusion reaction,” regardless of data entered in “Symptoms” in the field.

Term	Definition
Patients with the onset of infection	Patients with adverse drug reactions that fall under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Patients with the onset of bacterial infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10004018 (Bacterial infection), 10008555 (Chlamydial infection), 10028474 (Mycoplasma infection) or 10039135 (Rickettsia infection)
Patients with the onset of fungal infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10017528 (Fungal infection)
Patients with the onset of viral infection	Patients with adverse drug reactions that fall under the category of MedDRA HGLT Code 10047438 (Viral infection)
Age	If the month and day of the initial dose of Adcetris is < the month and day of birth, the patient's age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth − 1. If the month and day of the initial dose of Adcetris is ≥ the month and day of birth, the patient's age will be calculated using the following formula: Year of the initial dose of Adcetris − year of birth. If the month and day of birth are unknown, they should be "January 1," and if the day of birth is unknown, it should the first day of the month.
BMI	BMI should be calculated using the following formula: Weight (kg) / (0.0001 × height (cm) × height (cm). The obtained value should be rounded off to one decimal place.
Disease duration	The disease duration should be calculated using the following formula: ["Date of the initial dose of Adcetris" − "date of diagnosis of Hodgkin's or anaplastic large-cell lymphoma" +1] / 365.25. The day of diagnosis should be the first day of the month provided. If the month of diagnosis is unknown, the date of diagnosis should be "January 1st" of the year provided.
Mean dose of Adcetris	Is calculated as the total value of each dose of Adcetris given at each treatment cycle divided by the number of cycles.
Dose of Adcetris per 3 weeks	Is calculated using the following formula: Total "dose of Adcetris" / (["date of the last dose of Adcetris" − "date of the initial dose of Adcetris" + 21)/21]. If only 1 cycle of treatment is given, the "date of the last dose of Adcetris" and the "date of the initial dose of Adcetris" should be regarded as the same.
Degree of decreased neutrophil count at baseline: No decrease	Neutrophil count at baseline ≥2,000 /mm^3
Degree of decreased neutrophil count at baseline: Grade 1	Neutrophil count at baseline <2,000 to 1,500 /mm^3

Term	Definition
Degree of decreased neutrophil count at baseline: Grade 2	Neutrophil count at baseline <1,500 to 1,000 /mm^3
Degree of decreased neutrophil count at baseline: Grade 3	Neutrophil count at baseline <1,000 to 500 /mm^3
Degree of decreased neutrophil count at baseline: Grade 4	Neutrophil count at baseline <500 /mm^3
Date of the final observation	"Date of the final observation" in the case report form If not provided, the most recent date entered in the case report form should be used.
Summary statistics	Includes mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

1.2 Display digits

Term	Definition
Percentage (%)	Percentage of patients with or percentage of adverse events, etc., or adverse drug reactions, etc.: The obtained value should be rounded off to two decimal places. Other: The obtained value should be rounded off to one decimal place.
Summary statistics (mean and standard deviation)	Mean: The raw data should be rounded off to one decimal place. Standard deviation: The raw data should be rounded off to two decimal places.
P value	The obtained value should be rounded down to three decimal places. If the value is less than 0.001 after rounding down to three decimal places, it should be displayed as "p<0.001."

1.3 Level of significance

Two-sided 5%

1.4 Handling of test data

Test data will be handled according to the criteria shown below. If there are multiple data for the same criterion, the one with the test date being closest to the date of protocol-specified assessment should be used. If there is no difference in the number of days from the date of protocol-specified assessment, the later value should be used. For the final assessment, *however, the most recently measured value (including the one measured during the off-treatment period) after the date of the initial dose of Adcetris should be used. Values measured after 30 days after the last dose of Adcetris should not be used.

The number of days after the date of the initial dose of Adcetris is defined as 1 for the date of the initial dose of Adcetris and 0 for the day before the date of the initial dose of Adcetris.

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

Time point for testing	Acceptable time window	Date of protocol-specified assessment
At the initial dose of Adcetris	−21 to 1 days	Date of the initial dose of Adcetris
After 1 cycle	2 to 31 days	Date of the initial dose of Adcetris + 21
After 2 cycles	32 to 52 days	Date of the initial dose of Adcetris + 42
After 3 cycles	53 to 73 days	Date of the initial dose of Adcetris + 63
After 4 cycles	74 to 94 days	Date of the initial dose of Adcetris + 84
After 5 cycles	95 to 115 days	Date of the initial dose of Adcetris + 105
After 6 cycles	116 to 136 days	Date of the initial dose of Adcetris + 126
After 7 cycles	137 to 157 days	Date of the initial dose of Adcetris + 147

Time point for testing	Acceptable time window	Date of protocol-specified assessment
After 8 cycles	158 to 178 days	Date of the initial dose of Adcetris + 168
After 9 cycles	179 to 199 days	Date of the initial dose of Adcetris + 189
After 10 cycles	200 to 220 days	Date of the initial dose of Adcetris + 210
After 11 cycles	221 to 241 days	Date of the initial dose of Adcetris + 231
After 12 cycles	242 to 262 days	Date of the initial dose of Adcetris + 252
After 13 cycles	263 to 283 days	Date of the initial dose of Adcetris + 273
After 14 cycles	284 to 304 days	Date of the initial dose of Adcetris + 294
After 15 cycles	305 to 325 days	Date of the initial dose of Adcetris + 315
After 16 cycles	326 to 346 days	Date of the initial dose of Adcetris + 336

2.0 Patient Disposition (Patient Disposition Diagram)

(1) Analysis set to be used

Patients registered to this specified drug-use survey

(2) Data to be analyzed

Data to be analyzed includes the numbers of patients registered, institutions with patients registered, patients whose case report forms are available/not available, fixed/non-fixed patients, patients included in/excluded from the safety analysis set, and patients included in/excluded from the efficacy analysis set.

For the number of institutions with patients registered, the same institutions with different departments should not be counted more than once.

For patients whose case report forms are not available, the number of patients by reason for unavailability and the total number of patients will be calculated.

For patients excluded from the safety/efficacy analysis set, the number of patients by reason for exclusion and the total number of patients will be calculated.

It will be determined as follows whether patients meeting the following criteria should be included or excluded:

Criterion	Registration	Safety evaluation	Efficacy evaluation
Duplicate registration (of the same patient) [found afterwards]	○	×	×
Non-primary disease	○	○	×
Adcetris has never been administered [found afterwards]	○	×	×
No definite safety evaluation results are available	○	×	×
No definite efficacy evaluation results are available	○	○	×
No case report form is available	○	×	×

○: Included, ×: Excluded

(3) Figure/table number

Figure 2.0-1 and Table2.0-1

3.0 Patient Demographics and Baseline Characteristics

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Sex	Male or female
Age	Summary statistics
	<18 years, 18 to 39 years, 40 to 64 years, 65 to 74 years, or ≥75 years
	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
Diagnosis	Hodgkin's or anaplastic large-cell lymphoma or other
Status	Relapsed/refractory, or new-onset
CD30	Positive, negative, or not measured
Site(s) of involvement	Lymph node, spleen, liver, lung, bone, central nerve, bone marrow, skin, and/or other
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Therapeutic category	Outpatient or inpatient
Hypersensitivity disposition	Absent, present, or unknown
Specific hypersensitivity disposition(s)	Medications, food allergy, and/or other
HCV antibody	Negative, positive, or unknown
HBs antigen	Negative, positive, or unknown
HBs antibody	Negative, positive, or unknown
HBV DNA	Negative, positive, or unknown
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present
Past history of	Absent or present

Data item	Category
malignant tumours	
Concurrent malignant tumours	Absent or present
Concurrent illness (other than pulmonary disorders and malignant tumours)	Absent or present
Specific concurrent illness(es) (other than pulmonary disorders and malignant tumours)	Diabetes mellitus, hypertension, dyslipidaemia, hyperuricaemia, hepatic disease(s), renal disease(s), infections, peripheral nerve disorders, and/or other
Past history (other than pulmonary disorders and malignant tumours)	Absent, present, or unknown
Weight	Summary statistics
	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
BMI	Summary statistics
	<18.5, <18.5 to 25, <25 to 30, ≥30, or unknown
Smoking history	Never, current, past, or unknown
Prior drug therapy	Absent or present
Prior drug therapy regimen(s)	ABVD, CHOP, and/or other (If more than one drug therapies in the same category is used in the same patient, it will be counted as one patient.)
Number of prior drug therapy regimens	Summary statistics
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Other prior therapies	Absent or present
Pregnancy during the observation period (for females only)	Absent or present

(3) Figure/table number

Table 3.0-1

4.0 Treatment Given

4.1 Treatment given

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Duration of treatment with Adcetris	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 cycles
Reason(s) for discontinuation of Adcetris	Treatment goal achieved, adverse event(s), lost to follow-up, transfer to another hospital, pregnancy, inadequate response, and/or other
Post-baseline hematopoietic stem cell transplantation	Absent or present
Type of post-baseline hematopoietic stem cell transplantation	Autologous or homologous
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present
Drug(s) used for the prevention of infection	Absent or present
Specific drug(s) used for the prevention of infection	Antibiotics/synthetic antibacterial agents, antifungals, antivirals, trimethoprim-sulfamethoxazole combinations, and/or other prophylactics against infections

(3) Figure/table number

Table 4.1-1

4.2 Premedication to prevent infusion reaction

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each cycle, patients will be stratified into the following categories, and the number and frequency of patients will be calculated:

Data item	Category
Premedication to prevent infusion reaction	Absent or present
Specific premedication(s) used to prevent infusion reaction	Acetaminophen, antihistamines, and/or corticosteroids

(3) Figure/table number

Table 4.2-1

5.0 Safety Analysis

5.1 Occurrences of adverse events/infections and adverse drug reactions/infections

5.1.1 Occurrence of adverse events/infections

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Data listed below will be analyzed.

For data entered in the field of "Adverse events: [1] Peripheral nerve disorders] in the case report form, MedDRA PT Code for peripheral sensory neuropathy, peripheral motor neuropathy, or peripheral neuropathy should be assigned, regardless of the LLT code entered in "Symptoms" field (see Section 1.1 "Definition;" the same applies hereinafter).

Neutropenia (PT Code 10029354) will be assigned to Neutrophil count decreased (LLT Code 10029366), Lymphopenia (PT Code 10025327) to Lymphocyte count decreased (LLT Code 10025256), Leukopenia (PT Code 10024384) to White blood cell count decreased (LLT Code 10047942), and Thrombocytopenia (PT Code 10043554) to Platelet count decreased (LLT Code 10035528) (the same applies hereinafter).

Data item	Data to be analyzed
Number of patients with adverse events, etc.	Number of patients experiencing adverse events, etc.
Number of adverse events, etc.	Number of adverse events, etc., observed If the same patient has multiple occurrences of the same adverse event, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse events, etc.	Is calculated using the following formula: number of patients with adverse events, etc./number of patients included in the safety analysis set × 100.
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with adverse events, etc., will be presented in the internationally agreed order. For PT, the number and percentage of adverse events, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the event will be counted once per patient.

(3) Figure/table number

Table 5.1-1

5.1.2 Occurrence of adverse drug reactions/infections

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with adverse drug reactions, etc.	Number of patients experiencing adverse drug reactions, etc.
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with adverse drug reactions, etc.	Is calculated using the following formula: number of patients with adverse drug reactions, etc./number of patients included in the safety analysis set × 100.
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with adverse drug reactions, etc., will be presented in the internationally agreed order. For PT, the number and percentage of adverse drug reactions, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction will be counted once per patient.

(3) Figure/table number

Table 5.1-2

5.2 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrences of adverse events/infections and adverse drug reactions/infections by outcome

5.2.1 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse events/infections by outcome

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events, etc., will be analyzed:

Data item	Category

Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, or unknown

The type of adverse events, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events, etc., by SOC/PT
Number of adverse events, etc.	Number of adverse events, etc., observed by SOC/PT
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these events will be counted once for each category).

(3) Figure/table number

Table 5.2-1

5.2.2 Occurrence of adverse events/infections by CTCAE Grade (the worst one)

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events, etc., will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse events, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events, etc., by SOC/PT
Number of adverse events, etc.	Number of adverse events, etc., observed by SOC/PT
Type of adverse events, etc.	Adverse events, etc., will first be classified by SOC, within each of which adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse event, etc. (PT), the event with the worst CTCAE grade will be counted once.

(3) Figure/table number

Table 5.2-2

5.2.3 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrence of adverse drug reactions/infections by outcome

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, or ≥337 days
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, or unknown

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse drug reactions, etc., by SOC/PT
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed by SOC/PT
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these adverse drug reactions will be counted once for each category).

(3) Figure/table number

Table 5.2-3

5.2.4 Occurrence of adverse drug reactions/infections by CTCAE Grade (the worst one)

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse drug reactions, etc., will be analyzed:

Data item	Category
CTCAE Grade (the worst one)	≤Grade 2, ≥Grade 3, or unknown

The type of adverse drug reactions, etc., will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse drug reactions, etc., by SOC/PT
Number of adverse drug reactions, etc.	Number of adverse drug reactions, etc., observed by SOC/PT
Type of adverse drug reactions, etc.	Adverse drug reactions, etc., will first be classified by SOC, within each of which adverse drug reactions, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, data will be presented in the internationally agreed order. For PT, data will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same adverse drug reaction, etc. (PT), the reaction with the worst CTCAE grade will be counted once.

(3) Figure/table number

Table 5.2-4

5.3 Percentage of patients with adverse drug reactions/infections by patient demographics and baseline characteristics and treatment given

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the percentage of patients with adverse drug reactions, etc. (with point estimate and 95% confidence interval) will be determined.

For categories associated and not associated with ranking, Fisher's exact and Mann-Whitney U tests, respectively, will be used.

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
Diagnosis	Hodgkin's or anaplastic large-cell lymphoma or other
ALK (for patients with anaplastic large-cell lymphoma)	Positive, negative, or unknown
Clinical stage	I, II, III, IV, or unknown
B symptoms	Absent or present
ECOG Performance Status	0, 1, 2, 3, or 4
Hypersensitivity disposition	Absent, present, or unknown
Past history of pulmonary disorders	Absent or present
Concurrent pulmonary disorders	Absent or present
Past history of malignant tumours	Absent or present
Concurrent malignant tumours	Absent or present
Concurrent hepatic disorders	Absent or present
Concurrent renal disorders	Absent or present
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
BMI	<18.5, <18.5 to 25, <25 to 30, ≥30, or unknown
Smoking history	Never, current, past, or unknown
Prior drug therapy	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Drug(s) other than Adcetris used for the treatment of the primary disease	Absent or present

(3) Figure/table number

Table 5.3-1

5.4 Occurrence of adverse drug reactions/infections by age group

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by age group (<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years).

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Table 5.4-1

5.5 Occurrence of adverse drug reactions/infections by presence or absence of concurrent hepatic disorder

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by presence or absence of concurrent hepatic disorder.

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Table 5.5-1

5.6 Occurrence of adverse drug reactions/infections by presence or absence of concurrent renal disorder

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

The type of adverse drug reactions, etc., will be analyzed by presence or absence of concurrent renal disorder.

The type of adverse drug reactions, etc., will be analyzed in the same manner as described in Section 5.1.

(3) Figure/table number

Table 5.6-1

5.7 List of the occurrence of serious adverse events/infections

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Data listed below will be analyzed.

Data item	Data to be analyzed
Number of patients with serious adverse events, etc.	Number of patients experiencing serious adverse events, etc.
Number of serious adverse events, etc.	Number of serious adverse events, etc., observed If the same patient has multiple occurrences of the same serious adverse event, etc. (PT), the total number of occurrences will be calculated.
Percentage of patients with serious adverse events, etc.	Is calculated using the following formula: number of patients with serious adverse events, etc./number of patients included in the safety analysis set × 100.
Type of serious adverse events	Serious adverse events, etc., will first be classified by SOC, within each of which serious adverse events, etc., will be further classified by PT. Laboratory test data will first be classified by SOC, and will then be grouped into each HLGT and will be further classified by PT. For SOC, the number and percentage of patients with serious adverse events, etc., will be presented in the internationally agreed order. For PT, the number and percentage of serious adverse events, etc., will be presented in ascending order of PT codes. If the same patient has multiple occurrences of the same serious adverse event, etc. (PT), the event will be counted once per patient. For serious adverse events, etc., considered not related to Adcetris, the number of these events will be presented in [ ].

(3) Figure/table number

Table 5.7-1

5.8 Change in test data over time

5.8.1 Laboratory tests

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Summary statistics of 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 will be calculated at each test time point [at baseline, after 1 cycle, ... and after 16 cycles].

(3) Figure/table number

Table 5.8-1

5.9 Analysis of items of particular interest

5.9.1 Occurrence of peripheral nerve disorder

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of peripheral nerve disorders will be calculated:

Data item	Category
CTCAE Grade (the worst one) for peripheral nerve disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Symptoms of peripheral nerve disorders will be analyzed as follows:

Data item	Data to be analyzed
Symptoms of peripheral nerve disorders	Peripheral nerve disorders will first be classified into peripheral sensory, peripheral motor, and peripheral neuropathies listed in Section 1.1, and symptoms associated with these peripheral nerve disorders will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Table 5.9-1

5.9.2 Occurrence of peripheral nerve disorders by patient demographics and baseline characteristics and treatment given

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the categories below, and the incidence of peripheral nerve disorders will be calculated by CTCAE Grade (the worst one). If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the peripheral nerve disorder with the worst CTCAE grade will be counted once.

Data item	Category
Sex	Male or female
Age	<18 years, 18 to 64 years, 65 to 74 years, or ≥75 years
Disease duration	<1 year, <1 to 3 years, <3 to 5years, ≥5 years, or unknown
ECOG Performance Status	0, 1, 2, 3, or 4
Grade of concurrent peripheral nerve disorders	None, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Weight	<40 kg, <40 to 50 kg, <50 to 60 kg, <60 to 70 kg, ≥70 kg, or not measured
Prior ABVD or CHOP	Absent or present
Prior radiotherapy	Absent or present
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Initial dose of Adcetris	1.8 mg/kg or other
Mean dose of Adcetris	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Dose of Adcetris per 3 weeks	<1.8 mg/kg, 1.8 mg/kg, or ≥1.8 mg/kg
Concurrent diabetes mellitus	Absent or present

(3) Figure/table number

Table 5.9-2

5.9.3 Treatment with Adcetris at the onset of peripheral nerve disorders

(1) Analysis set to be used

Patients included in the safety analysis set who experience peripheral nerve disorders considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of peripheral nerve disorders, patients will be stratified into the categories below, and the number of peripheral nerve disorders will be calculated. If the same patient has multiple occurrences of the same peripheral nerve disorder (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category).

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), or treatment discontinuation

(3) Figure/table number

Table 5.9-3

5.9.4 Occurrence of infections by presence or absence of drugs used for the prevention of infection

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Patients will be stratified into the categories below and the number of patients with infection will be calculated by presence or absence of drugs used for the prevention of infection using Mann-Whitney U test. If the same patient has multiple occurrences of the same infection, the occurrence with the worst CTCAE grade will be counted once.

Similarly, the number of patients with the onset of bacterial infection will be calculated by the use or non-use of antibiotics/synthetic antibacterial agents or trimethoprim-sulfamethoxazole combinations, the number of patients with the onset of fungal infection will be calculated by the use or non-use of antifungals, and the number of patients with the onset of viral infection will be calculated by the use or non-use of antivirals.

Data item	Category
CTCAE Grade (the worst one) of infections	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Table 5.9-4

5.9.5 Occurrence of neutropenia by patient demographics and baseline characteristics

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For each data item, patients will be stratified into the categories below, and the incidence of neutropenia will be calculated by CTCAE Grade (the worst one). If the same patient has multiple occurrences of neutropenia, the event with the worst CTCAE grade will be counted once.

Data item	Category
Prior hematopoietic stem cell transplantation	Absent, present (autologous), or present (homologous)
Degree of decreased neutrophil count at baseline	No decrease, Grade 1, Grade 2, Grade 3, Grade 4, or unknown

(3) Figure/table number

Table 5.9-5

5.9.6 Treatment with Adcetris at the onset of neutropenia

(1) Analysis set to be used

Patients included in the safety analysis set who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of neutropenia, patients will be stratified into the categories below, and the number of events of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category).

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), or treatment discontinuation

(3) Figure/table number

Table 5.9-6

5.9.7 Occurrence of infusion reaction

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of infusion reaction will be calculated:

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Infusion reaction will be analyzed as follows:

Data item	Data to be analyzed
Symptoms of infusion reaction	Infusion reaction and its symptoms will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Table 5.9-7

5.9.8 Occurrence of infusion reaction by the use or non-use of premedication to prevent infusion reaction

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

Patients will be stratified into the following categories and the number of events of infusion reaction considered related to Adcetris will be calculated by the use or non-use of premedication to prevent infusion reaction (for example, if a patient receives no premedication and experiences “Grade 2” infusion reaction during Cycle 1 and receives premedication and experiences no infusion reaction during Cycle 2, these events of infusion reaction will be counted once for each category).

Data item	Category
CTCAE Grade (the worst one) of infusion reaction	None, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

(3) Figure/table number

Table 5.9-8

5.9.9 Occurrence of pulmonary disorders

(1) Analysis set to be used

Safety analysis set

(2) Data to be analyzed

For CTCAE Grade (the worst one), patients will be stratified into the following categories, and the incidence of events of pulmonary disorder will be calculated:

Data item	Category
CTCAE Grade (the worst one) for pulmonary disorders	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Diagnoses or symptoms of pulmonary disorder will be analyzed as follows:

Data item	Data to be analyzed
Diagnosis or symptom of pulmonary disorder	Pulmonary disorders and their diagnoses or symptoms will be analyzed by PT. If the same patient has multiple occurrences of the same symptom (PT), the symptom with the worst CTCAE grade will be counted once.

(3) Figure/table number

Table 5.9-9

6.0 Efficacy Analysis

6.1 Best response

(1) Analysis set to be used

Efficacy analysis set

(2) Data to be analyzed

The best responses after 16 cycles of treatment with Adcetris (or upon discontinuation of treatment with Adcetris) will be analyzed in patients Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma.

(3) Figure/table number

Table 6.1-1

6.2 Overall survival

(1) Analysis set to be used

Efficacy analysis set

(2) Data to be analyzed

The survivals from the date of the initial dose of Adcetris in patients Hodgkin's lymphoma and patients with anaplastic large-cell lymphoma will be calculated, using the final observation date as the date of survival confirmation and the date of outcome of an adverse event with "Died/fetal" recorded in the Outcome field as the date of death.

Kaplan-Meier curves of the survival will also be constructed (i.e., a table of the numbers of adverse events, etc., and adverse drug reactions, etc., printed out by SAS will be attached).

(3) Figure/table number

Table 6.2-1 and Figure 6.2-1

Appendix: Definition of Pulmonary Disorders (MedDRA Preferred Terms)

- Acute interstitial pneumonitis (10066728)
- Acute lung injury (10069351)
- Acute respiratory distress syndrome (10001052)
- Acute respiratory failure (10001053)
- Alveolar proteinosis (10001881)
- Alveolitis (10001889)
- Alveolitis allergic (10001890)
- Systemic sclerosis pulmonary (10042954)
- Alveolitis necrotising (10050343)
- Bronchiolitis (10006448)
- Diffuse alveolar damage (10060902)
- Eosinophilic pneumonia (10014962)
- Eosinophilic pneumonia acute (10052832)
- Eosinophilic pneumonia chronic (10052833)
- Hypoxia (10021143)
- Idiopathic pneumonia syndrome (10063725)
- Idiopathic pulmonary fibrosis (10021240)
- Interstitial lung disease (10022611)
- Lung disorder (10025082)
- Lung infiltration (10025102)
- Necrotising bronchiolitis (10070831)
- Obliterative bronchiolitis (10029888)
- Organising pneumonia (10067472)
- Pneumonitis (10035742)
- Pneumonitis chemical (10035745)
- Progressive massive fibrosis (10036805)
- Pulmonary alveolar haemorrhage (10037313)
- Pulmonary eosinophilia (10037382)
- Pulmonary fibrosis (10037383)
- Pulmonary granuloma (10037391)
- Pulmonary haemosiderosis (10037396)
- Pulmonary necrosis (10058824)
- Pulmonary oedema (10037423)
- Pulmonary radiation injury (10061473)
- Pulmonary sarcoidosis (10037430)
- Pulmonary toxicity (10061924)
- Pulmonary vasculitis (10037457)
- Radiation alveolitis (10037754)
- Radiation fibrosis – lung (10037758)
- Radiation pneumonitis (10037765)
- Respiratory arrest (10038669)
- Respiratory distress (10038687)
- Respiratory failure (10038695)
- Sarcoidosis (10039486)

The above definition is consistent with the one used in clinical studies of Adcetris.

Supplemental Statistical Analysis Plan

ADCETRIS IV Infusion − Special Drug Use Surveillance (All-case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

PPD

Takeda Pharmaceutical Company Limited

PPD

Initial version: Prepared on September 15, 2017

Table of Contents

1.0 Definition of Analysis sets and Terms and Handling of Test/Measurement Data

1.1 Analysis sets

1.1.1 Safety analysis set

In this survey, the safety analysis set is defined as patients treated with Adcetris IV Infusion with no major protocol violation and evaluable for safety. In this Statistical Analysis Plan, the safety analysis set refers to patients included in safety evaluation.

1.2 Definition

Term	Definition
This/the product	Refers to Adcetris for intravenous drip infusion in this Statistical Analysis Plan.
SOC	MedDRA/J System Organ Class
PT	MedDRA/J Preferred Term
Safety analysis set	Fixed patients included in the safety analysis set
Safety analysis set (Hodgkin's lymphoma)	Patients included in the safety analysis set whose diagnosis is Hodgkin's lymphoma
Safety analysis set (anaplastic large-cell lymphoma)	Patients included in the safety analysis set whose diagnosis is anaplastic large-cell lymphoma
Adverse drug reactions, etc.	Refers to "adverse drug reactions and infections." Adverse events not considered "not related" to Adcetris by the investigator. In this Statistical Analysis Plan, the term "adverse drug reactions and infections" is used in titles and the term "adverse drug reactions, etc." is used in text and tables.
Number of patients with adverse events/adverse drug reactions	Number of patients experiencing adverse events or adverse drug reactions, etc.
Number of adverse events/adverse drug reactions	Number of adverse events or adverse drug reactions, etc., observed
Percentage of patients with adverse events/adverse drug reactions	[For safety analysis using patients included in the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of patients with adverse events/adverse drug reactions) / (number of patients excluded from the safety analysis set) × 100.
Percentage of adverse	[For safety analysis using patients included in the safety analysis set]

Term	Definition
events/adverse drug reactions observed	Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients included in the safety analysis set) × 100. [For safety analysis using patients excluded from the safety analysis set] Is calculated using the following formula: (number of adverse events/adverse drug reactions observed) / (number of patients excluded from the safety analysis set) × 100.
Time of onset	Is calculated using the following formula: date of onset of adverse events (or adverse drug reactions, etc.) − date of the initial dose of Adcetris + 1. If the day, month, and year of onset of adverse events (or adverse drug reactions, etc.) are unknown, the time of onset should be handled as missing, and the category for the time of onset should be "unknown."
Time to the worst grade	Is calculated using the following formula: date of the worst CTCAE grade – date of the initial dose of Adcetris + 1. If the day, month, and year of the worst CTCAE grade are unknown, the date of the worst CTCAE grade should be handled as missing, and the category for the date of the worst CTCAE grade should be "unknown."
Infection	A concurrent illness or adverse event that falls under the category of MedDRA SOC Code 10021881 (Infections and infestations)
Grade 3 or 4 decreased neutrophil count	Neutrophil count <1,000/mm^3
Grade 3 or 4 decreased lymphocyte count	Lymphocyte count < 500/mm^3
Neutropenia	An adverse event equivalent to MedDRA PT Codes 10029366 (Neutrophil count decreased) and 10029354 (Neutropenia).
Lymphopenia	An adverse event equivalent to MedDRA PT Codes 10025256 (Lymphocyte count decreased) and 10025327 (Lymphopenia).

1.3 Display digits

Term	Definition
Percentage (%)	Percentage of patients with or percentage of adverse events or adverse drug reactions, etc.: The obtained value should be rounded off to two decimal places. Other: The obtained value should be rounded off to one decimal place.

1.4 Handling of test data

Test data will be handled according to the criteria shown below. If there are multiple data for the same criterion, the one with the test date being closest to the date of protocol-specified assessment should be used. If there is no difference in the number of days from the date of protocol-specified assessment, the later value should be used.

The number of days after the date of the initial dose of Adcetris is defined as 1 for the date of the initial dose of Adcetris and 0 for the day before the date of the initial dose of Adcetris.

Time point for testing	Date of protocol-specified assessment	Acceptable time window
At the initial dose of Adcetris	Date of the initial dose of Adcetris	−15 days to the d ate of the initial dose of Adcetris
After 1 cycle	• If Cycle 2 is initiated: Date of Cycle 2 • If Cycle 2 is not initiated: 21 days after the date of the initial dose of Adcetris s	• If Cycle 2 is initiated: Date of Cycle 2 • If Cycle 2 is not initiated: 21 days after the date of the initial dose of Adcetris
After 2 cycles	• If Cycle 3 is initiated: Date of Cycle 3 • If Cycle 3 is not initiated: 21 days after the date of Cycle 2	• If Cycle 3 is initiated: From the day after the date of Cycle 2 to the day of Cycle 3 • If Cycle 3 is not initiated: From the day after the date of Cycle 2 to 21 days after the date of Cycle 2
After 3 cycles	• If Cycle 4 is initiated: Date of Cycle 4 • If Cycle 4 is not initiated: 21 days after the date of Cycle 3	• If Cycle 4 is initiated: From the day after the date of Cycle 3 to the day of Cycle 4 • If Cycle 4 is not initiated: From the day after the date of Cycle 3 to 21 days after the date of Cycle 3

Time point for testing	Date of protocol-specified assessment	Acceptable time window
After 4 cycles	• If Cycle 5 is initiated: Date of Cycle 5 • If Cycle 5 is not initiated: 21 days after the date of Cycle 4	• If Cycle 5 is initiated: From the day after the date of Cycle 4 to the day of Cycle 5 • If Cycle 5 is not initiated: From the day after the date of Cycle 4 to 21 days after the date of Cycle 4
After 5 cycles	• If Cycle 6 is initiated: Date of Cycle 6 • If Cycle 6 is not initiated: 21 days after the date of Cycle 5	• If Cycle 6 is initiated: From the day after the date of Cycle 5 to the day of Cycle 6 • If Cycle 6 is not initiated: From the day after the date of Cycle 5 to 21 days after the date of Cycle 5
After 6 cycles	• If Cycle 7 is initiated: Date of Cycle 7 • If Cycle 7 is not initiated: 21 days after the date of Cycle 6	• If Cycle 7 is initiated: From the day after the date of Cycle 6 to the day of Cycle 7 • If Cycle 7 is not initiated: From the day after the date of Cycle 6 to 21 days after the date of Cycle 6
After 7 cycles	• If Cycle 8 is initiated: Date of Cycle 8 • If Cycle 8 is not initiated: 21 days after the date of Cycle 7	• If Cycle 8 is initiated: From the day after the date of Cycle 7 to the day of Cycle 8 • If Cycle 8 is not initiated: From the day after the date of Cycle 7 to 21 days after the date of Cycle 7
After 8 cycles	• If Cycle 9 is initiated: Date of Cycle 9 • If Cycle 9 is not initiated: 21 days after the date of Cycle 8	• If Cycle 9 is initiated: From the day after the date of Cycle 8 to the day of Cycle 9 • If Cycle 9 is not initiated: From the day after the date of Cycle 8 to 21 days after the date of Cycle 8
After 9 cycles	• If Cycle 10 is initiated: Date of Cycle 10 • If Cycle 10 is not initiated: 21 days after the date of Cycle 9	• If Cycle 10 is initiated: From the day after the date of Cycle 9 to the day of Cycle 10 • If Cycle 10 is not initiated: From the day after the date of Cycle 9 to 21 days after the date of Cycle 9

Time point for testing	Date of protocol-specified assessment	Acceptable time window
After 10 cycles	• If Cycle 11 is initiated: Date of Cycle 11 • If Cycle 11 is not initiated: 21 days after the date of Cycle 10	• If Cycle 11 is initiated: From the day after the date of Cycle 10 to the day of Cycle 11 • If Cycle 11 is not initiated: From the day after the date of Cycle 10 to 21 days after the date of Cycle 10
After 11 cycles	• If Cycle 12 is initiated: Date of Cycle 12 • If Cycle 12 is not initiated: 21 days after the date of Cycle 11	• If Cycle 12 is initiated: From the day after the date of Cycle 11 to the day of Cycle 12 • If Cycle 12 is not initiated: From the day after the date of Cycle 11 to 21 days after the date of Cycle 11
After 12 cycles	• If Cycle 13 is initiated: Date of Cycle 13 • If Cycle 13 is not initiated: 21 days after the date of Cycle 12	• If Cycle 13 is initiated: From the day after the date of Cycle 12 to the day of Cycle 13 • If Cycle 13 is not initiated: From the day after the date of Cycle 12 to 21 days after the date of Cycle 12
After 13 cycles	• If Cycle 14 is initiated: Date of Cycle 14 • If Cycle 14 is not initiated: 21 days after the date of Cycle 13	• If Cycle 14 is initiated: From the day after the date of Cycle 13 to the day of Cycle 14 • If Cycle 14 is not initiated: From the day after the date of Cycle 13 to 21 days after the date of Cycle 13
After 14 cycles	• If Cycle 15 is initiated: Date of Cycle 15 • If Cycle 15 is not initiated: 21 days after the date of Cycle 14	• If Cycle 15 is initiated: From the day after the date of Cycle 14 to the day of Cycle 15 • If Cycle 15 is not initiated: From the day after the date of Cycle 14 to 21 days after the date of Cycle 14
After 15 cycles	• If Cycle 16 is initiated: Date of Cycle 16 • If Cycle 16 is not initiated: 21 days after the date of Cycle 15	• If Cycle 16 is initiated: From the day after the date of Cycle 15 to the day of Cycle 16 • If Cycle 16 is not initiated: From the day after the date of Cycle 15 to 21 days after the date of Cycle 15

1.5 Handling of missing data

- As a general rule, missing data will not be imputed.
- In the analysis of the frequency qualitative variables, missing data will be handles as “unknown.”

1.6 Others

- In the analysis for the preparation of documents for the Final Survey Report, MedDRA version 19.1 will be used for adverse events, concurrent illness, and past history.
- If a patient has multiple data for a single laboratory test and date of testing, the mean value will be calculated for the analysis of laboratory test results.

2.0 Safety Analysis

2.1 Seriousness, CTCAE Grade (the worst one), time of onset, time to the worst grade, and occurrences of adverse drug reactions/infections by outcome

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item, patients will be stratified into the following categories, and the type of adverse events will be analyzed:

Data item	Category
Seriousness	Serious or non-serious
CTCAE Grade (the worst one)	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown
Time of onset	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Time to the worst grade	1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 84 days, 85 to 168 days, 169 to 252 days, 253 to 336 days, ≥337 days, or unknown
	1 to 21 days, 22 to 42 days, 43 to 63 days, (segmented similarly using a 21-day time window thereafter), 316 to 336 days, ≥337 days, or unknown
Outcome	Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, died/fatal, unknown, or not provided

The type of adverse events will be analyzed as follows:

Data item	Data to be analyzed
Number of patients	Number of patients with adverse events by SOC/PT
Number of adverse events, etc.	Number of adverse events observed by SOC/PT If the same patient has multiple occurrences of the same adverse event (PT), all these occurrences will be counted (i.e., the overlap should be reflected).
Seriousness, time of onset, and outcome	The number of adverse events will be calculated by SOC and PT. SOCs will be presented in the internationally agreed order, and PTs will be presented in ascending order of HLGT and PT codes if their SOCs are "Investigations," and in ascending order of PT code otherwise. If the same patient has multiple occurrences of the same adverse

	event (PT), the total number of occurrences will be calculated per category (for example, if the same patient has one episode of serious diarrhea and one episode of non-serious diarrhea, these events will be counted once for each category). If the same patient has multiple occurrences of the same adverse event classified into the same category, all these occurrences will be counted (i.e., the overlap should be reflected).
CTCAE Grade (the worst one) and time to the worst grade	The number of adverse events will be calculated by SOC and PT. The CTCAE grade is higher in the order of Grade 5, 4, 3, 2, 1, and unknown. The event with the highest CTCAE grade (the worst one) and the shortest time to the worst grade will be counted once.

2.2 Analysis of items of particular interest

2.2.1 Treatment-related infections reported within 7 days after the date of the worst grade of Grade 3 or 4 neutropenia or the date of onset of Grade 3 or 4 decreased neutrophil count considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set with confirmed Grade 3 or 4 neutropenia or decreased neutrophil count considered related to Adcetris

(2) Data to be analyzed

The number and percentage of patients experiencing treatment-related infections reported within 7 days after the date of the worst grade of Grade 3 or 4 neutropenia or the date of onset of Grade 3 or 4 decreased neutrophil count considered related to Adcetris will be calculated by infection and PT (for the definition of infection, see Section 1.2). PTs will be presented in ascending order of PT codes.

2.2.2 Treatment-related infections reported within 7 days after the date of the worst grade of Grade 3 or 4 lymphopenia or the date of onset of Grade 3 or 4 decreased lymphocyte count considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set with confirmed Grade 3 or 4 lymphopenia or decreased lymphocyte count considered related to Adcetris

(2) Data to be analyzed

The number and percentage of patients experiencing treatment-related infections reported within 7 days after the date of the worst grade of Grade 3 or 4 lymphopenia or the date of onset of Grade 3 or 4 decreased lymphocyte count considered related to Adcetris will be calculated by infection and PT (for the definition of infection, see Section 1.2). PTs will be presented in ascending order of PT codes.

Supplemental Statistical Analysis Plan 2

Additional Analysis on Neutropenia

ADCETRIS IV Infusion − Special Drug Use Surveillance (All-case Surveillance) "Relapsed or Refractory CD30+ Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma"

PPD

Takeda Pharmaceutical Company Limited

PPD

Initial version: Prepared on November 21, 2017

Table of Contents

1.0 Definition of Analysis sets and Terms and Handling of Test/Measurement Data

1.1 Analysis sets

1.1.1 Safety analysis set

In this survey, the safety analysis set is defined as patients treated with Adcetris IV Infusion with no major protocol violation and evaluable for safety. In this Statistical Analysis Plan, the safety analysis set refers to patients included in safety evaluation.

1.2 Definition

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>This/the product</td><td>Refers to Adcetris for intravenous drip infusion in this Statistical Analysis Plan.</td></tr>
<tr><td>SOC</td><td>MedDRA/J System Organ Class</td></tr>
<tr><td>PT</td><td>MedDRA/J Preferred Term</td></tr>
<tr><td>Safety analysis set</td><td>Fixed patients included in the safety analysis set</td></tr>
<tr><td>Safety analysis set (Hodgkin’s lymphoma)</td><td>Patients included in the safety analysis set whose diagnosis is Hodgkin’s lymphoma</td></tr>
<tr><td>Safety analysis set (anaplastic large-cell lymphoma)</td><td>Patients included in the safety analysis set whose diagnosis is anaplastic large-cell lymphoma</td></tr>
<tr><td>Neutropenia</td><td>Events equivalent to MedDRA PT Codes 10029354 (Neutropenia) and 10016288 (Febrile neutropenia) will be collected and analyzed. Neutrophil count decreased (PT Code 10029366) will be replaced with Neutropenia (PT Code 10029354).</td></tr>
<tr><td>Degree of decreased neutrophil count at baseline</td><td>The neutrophil count at baseline will be classified as shown in the table below. If the neutrophil count at baseline is missing, the degree of decreased neutrophil count should be handled as missing:
<table>
<tr><td>No decrease</td><td>≥2,000 /mm^3</td></tr>
<tr><td>Grade 1</td><td>≥1,500 to <2,000 /mm^3</td></tr>
<tr><td>Grade 2</td><td>≥1,000 to <1,500 /mm^3</td></tr>
<tr><td>Grade 3</td><td>≥500 to <1,000 /mm^3</td></tr>
<tr><td>Grade 4</td><td><500 /mm^3</td></tr>
</table></td></tr>
<tr><td>Antibiotics/synthetic antibacterial agents</td><td>Drugs with the first three digits of YJ Code being either one of 611 to 616, 619, or 624 that are entered in the field of “Drugs used for the prevention of infection” (If more than one antibiotics/synthetic antibacterial agents are used in the same patient, it will be counted as one patient.)</td></tr>
<tr><td>Antifungals</td><td>Drugs with the first three digits of YJ Code being 617 or the first seven digits being 6290002 or 6290004 that are entered in the field of “Drugs used for the prevention of infection” (If more than one antifungals are</td></tr>
</table>

Term	Definition
	used in the same patient, it will be counted as one patient.)
Antivirals	Drugs with the first three digits of YJ Code being 625 that are entered in the field of “Drugs used for the prevention of infection” (If more than one antivirals are used in the same patient, it will be counted as one patient.)
Trimethoprim-sulfamethoxazole combinations	Drugs with YJ Code being 62901000 that are entered in the field of “Drugs used for the prevention of infection” (If more than one trimethoprim-sulfamethoxazole combinations are used in the same patient, it will be counted as one patient.)
Other prophylactics against infections	Any drug entered in the field of “Drugs used for the prevention of infection” other than prophylactics against infections listed above (If more than one other prophylactics against infections are used in the same patient, it will be counted as one patient.)

1.3 Display digits

Term	Definition
Percentage (%)	Percentage of patients with or percentage of adverse events or adverse drug reactions, etc.: The obtained value should be rounded off to two decimal places. Other: The obtained value should be rounded off to one decimal place.

1.4 Handling of missing data

- As a general rule, missing data will not be imputed.
- In the analysis of the frequency qualitative variables, missing data will be handles as “unknown.” In the analysis of summary statistics of quantitative variables, missing data will be excluded.

1.5 Others

- In the analysis for the preparation of documents for the Final Survey Report (final analysis), MedDRA version 19.1 will be used for adverse events, concurrent illness, and past history.

2.0 Safety Analysis

2.1 Analysis of items of particular interest

2.1.1 Occurrence of neutropenia considered related to Adcetris by patient demographics and baseline characteristics

(1) Analysis sets to be used

Safety analysis set, safety analysis set (Hodgkin's lymphoma), and safety analysis set (anaplastic large-cell lymphoma)

(2) Data to be analyzed

For each data item of patient demographics and baseline characteristics, patients will be stratified into the categories below, and the incidence of neutropenia considered related to Adcetris will be calculated by CTCAE Grade (the worst one). The CTCAE grade (the worst one) is higher in the order of Grades 5, 4, 3, 2, 1, and unknown. If the same patient has multiple occurrences of neutropenia, the event with the highest CTCAE grade will be counted once.

Data item	Category
CTCAE Grade (the worst one) of neutropenia	Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or unknown

Items and categories of patient demographics and baseline characteristics

Data item	Category
Prior hematopoietic stem cell transplantation	Absent, present (autologous), present (homologous), present (autologous and homologous), or unknown
Degree of decreased neutrophil count at baseline	No decrease, Grade 1, Grade 2, Grade 3, Grade 4, or unknown
Drugs used for the prevention of infection	Absent or present
Specific drug(s) used for the prevention of infection	Antibiotics/synthetic antibacterial agents, antifungals, antivirals, trimethoprim-sulfamethoxazole combinations, or other

(3) Figure/table number

Tables 2.1.1-1 to 2.1.1-3

2.1.2 Treatment with Adcetris at the onset of neutropenia considered related to Adcetris

(1) Analysis sets to be used

Patients included in the safety analysis set and safety analysis set (Hodgkin's lymphoma) or safety analysis set (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For each CTCAE Grade (the worst one) of neutropenia considered related to Adcetris, patients will be stratified into the categories below, and the incidence of events of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of

peripheral nerve disorder requiring dose reduction and one episode of peripheral nerve disorder leading to treatment discontinuation, these episodes of peripheral nerve disorder will be counted once for each category). The percentage of neutropenia for each category will be calculated using the number of neutropenia for each CTCAE grade (the worst one) as the denominator.

For each data item, missing data will be handled as "not provided."

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation or not provided

(3) Figure/table number

Tables 2.1.2-1 to 2.1.2-3

2.1.3 Outcome of neutropenia considered related to Adcetris by action taken with Adcetris

(1) Analysis sets to be used

Patients included in safety evaluation and patients included in safety evaluation (Hodgkin's lymphoma) or patients included in safety evaluation (anaplastic large-cell lymphoma) who experience neutropenia considered related to Adcetris

(2) Data to be analyzed

For neutropenia considered related to Adcetris, patients will be stratified into the categories below for each outcome and the incidence of neutropenia will be calculated. If the same patient has multiple occurrences of neutropenia, the total number of occurrences will be calculated per category (for example, if the same patient has one episode of neutropenia requiring dose reduction and one episode of neutropenia leading to treatment discontinuation, these episodes of neutropenia will be counted once for each category). The percentage of neutropenia for each category will be calculated using the total number of neutropenia for each category as the denominator.

For each data item, missing data will be handled as "not provided."

Data item	Category
Action taken to Adcetris	No action taken or action taken in response to the event or not provided
Specific action taken to Adcetris	Dose reduction, treatment interruption (treatment delay), treatment discontinuation, or not provided

(3) Figure/table number

Tables 2.1.3-1 to 2.1.3-3