Clinical Study Protocol

NCT Number: NCT04213209

Title: Specified drug use Surveillance for ADCETRIS Intravenous Infusion 50 mg "Relapsed or refractory CD30 positive peripheral T-cell lymphoma and Hodgkin lymphoma (pediatric only)"

Study Number: C25021

Document Version and Date: Version 7.0 / 12-Sep-2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

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

Special drug use Surveillance protocol

Specified drug use Surveillance for ADCETRIS Intravenous Infusion 50 mg "Relapsed or refractory CD30 positive peripheral T-cell lymphoma and Hodgkin lymphoma (pediatric only)"

Investigation sponsor	**Takeda Pharmaceutical Co., Ltd.**
Protocol number	**C25021**
Version Number	**Version 7.0**
Date of preparation	**Sep.12, 2023**

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1.0 BACKGROUND OF IMPLEMENTATION

ADCETRIS® intravenous injection 50mg (drug) has been confirmed to be safe and effective in the post-marketing period for indications of relapsed or refractory CD30 positive Hodgkin Lymphoma (hereafter HL) or undifferentiated large-cell Lymphoma (hereafter ALCL) in adults. On the other hand, there is little information on the safety of this product in Japanese patients with relapsed or refractory peripheral T-cell lymphomas (PTCL) who are CD30 positive other than ALCL. There are also limited data available from clinical studies in pediatric patients with relapsed or refractory CD30 positive PTCL or HL-HL. Therefore, the safety of drug should be confirmed in adult patients with relapsed or refractory CD30 positive PTCL (excluding ALCL) and pediatric patients with relapsed or refractory CD30 positive PTCL or HL in routine clinical practice after obtaining approvals for the indication of CD30 positive PTCL in drug, and the safety should be appropriately communicated to healthcare professionals. This survey was therefore planned.

This survey will be conducted in compliance with GPSP ordinances and other relevant regulatory requirements.

2.0 OBJECTIVE

To evaluate the safety of the safety parameters included in this survey in adult patients with relapsed or refractory CD30 positive PTCL (excluding ALCL) and pediatric patients with relapsed or refractory CD30 positive PTCL or HL in routine clinical practice.

The following items are examined.

・ Peripheral neuropathy: Confirmation of the status of onset (incidence, seriousness, time of onset, etc.), drug dose-adjustment status, and effects of background factors

・ Myelosuppression (neutropenia): Confirmation of the occurrence of myelosuppression (incidence, seriousness, time of onset, etc.), drug dose-adjustment status, and effects of background factors

・ Lung disorders: Confirmation of the effects of the event (incidence, seriousness, time of onset, etc.) and patient demographic factors

3.0 SAFETY SPECIFICATION

Peripheral neuropathy, myelosuppression (neutropenia), pulmonary disorder

4.0 SCHEDULED SAMPLE SIZE AND BASIS FOR SETTING

4.1 PLANNED SAMPLE SIZE

Adults (18 years of age or older at the start of treatment):

80 patients with relapsed or refractory CD30 positive PTCL (excluding ALCL)

(as a safety analysis set)

Children (aged <18 years at the start of treatment):

Six patients with relapsed or refractory CD30 positive PTCL or HL

(as a safety analysis set)

4.2 RATIONALE FOR SAMPLE SIZE

Among the events specified as safety specifications in this survey (peripheral neuropathy, myelosuppression (neutropenia), and pulmonary disorder), the most frequently reported adverse event in the special drug use surveillance in patients with relapsed or refractory CD30 positive HL and ALCL was febrile neutropenia (3.87%). Therefore, since 76 cases are required to observe this event in at least 1 case with a probability of 95% or more, the number of subjects collected in the adult survey was set at 80 cases. The number of cases of recurrent or refractory HL patient and PTCL patient of the child was estimated to be about 10 cases per year, and the planned number of cases of the child was set to 6 in consideration of investigation period, expected prescription of Adcetris, etc..

5.0 PATIENTS TO BE SURVEYED

The study is conducted in adult patients with PTCL (excluding ALCL) and pediatric patients with PTCL or HL. However, the following inclusion criteria and exclusion criteria shall not be met.

Refer to the package insert.

5.1 SELECTION CRITERIA

Patients are eligible for the study if they meet the following criteria:

① Patients with relapsed or refractory disease

② CD30 positive patients

③ Patients who receive drug after obtaining approval for the indication of PTCL

5.2 EXCLUSION CRITERIA

Patients who meet the following criteria are not eligible.

① Patients with a history of severe hypersensitivity to any ingredient of the product

② Patients receiving bleomycin hydrochloride

6.0 DOSAGE AND ADMINISTRATION

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

For details, refer to the package insert.

7.0 NUMBER OF MEDICAL INSTITUTIONS BY PLANNED CLINICAL DEPARTMENT

About 80 medical institutions, including hematology and pediatrics, and about 6 medical institutions

8.0 METHODS

8.1 OBSERVATION PERIOD

12 months from the initiation of drug treatment (until that time for discontinued or dropout patients)

Note) For patients who started Adcetris on or after July 1, 2022, the observation period will be until June 30, 2023.

* Rationale for observation period

A review of the first infusion cycles of AEs in adult subjects with relapsed or refractory CD30 positive HL and sALCL in foreign phase 2 studies (SG035-0003 and SG035-0004 studies) showed that many AEs tended to occur by 16 cycles. In a special drug use surveillance in patients with relapsed or refractory CD30 positive HL and ALCL, 98.2% (660/672) of patients experienced adverse reactions by 336 days after the initiation of treatment. Based on the above, it was considered that the incidence of events that were included in the safety specification in this survey could be generally observed within 12 months from the start of administration.

8.2 REQUEST AND CONTRACT FOR MEDICAL INSTITUTIONS

The person in charge of Takeda Pharmaceutical Co., Ltd. (hereinafter referred to as the person in charge of Takeda) will request this investigation on the premise that a written agreement with the participating medical organization will be concluded.

(1) Request for cooperation in this study

Using the Request for Cooperation in Special drug use surveillance, Outline of Implementation, Registration Form for Patients (Sample), and Questionnaire (Sample), the person in charge of Takeda explained the objectives, content, investigation methods, and drug information on proper use of the survey to the physician-in-charge, and obtained approval from the physician-in-charge for cooperation in the survey.

(2) Contract for investigation

The person in charge of Takeda makes a written contract with the medical institution immediately after the approval of the physician-in-charge of the investigation, and brings the "Patient Registration Form" to the physician-in-charge of the investigation.

8.3 PATIENT'S CONSENT

Prior to enrolling patients, the physician-in-charge shall explain the content of the consent/information document to the patient (or legally acceptable representative) and obtain

the patient's (or legally acceptable representative) oral or written consent to provide information for the survey.

When obtaining written informed consent, the patient (or legally acceptable representative) shall sign and date the informed consent form. The investigator shall retain the original of the signed consent form.

The informed consent form states that the patient can discontinue participation in the survey without disadvantage of treatment, without explaining the details of the information provision, the handling of the patient's personal information and personal medical information in this survey, and the patient's reason at any time.

Give the identification number to the patient from whom the consent was obtained.

8.4 HOW TO ENROLL PATIENTS

This is carried out by "central registration system" by mail.

The person * designated by the investigator or the investigator shall mail the "Patient Registration Form" to the central registration center basically 30 days after the starting day of administration of drug (the starting day of administration is defined as "day 0" and the day after the starting day of administration is defined as "day 1"). Patients who were started on or after the date of approval for the indication of CD30 positive PTCL in drug may be retrospectively enrolled even if the treatment was started prior to the conclusion of the contract.

* The term "person designated by the investigator" is defined as a person who belongs to the medical institution concerned (including a person who has concluded a contract with the medical institution such as the dispatched CRC) and who, after being designated by the investigator in advance, performs the duties related to the investigation based on the instructions of the investigator. When a person designated by a physician in charge of the investigation performs duties such as patient registration, the physician who is responsible for the investigation (one person for each investigation site or clinical department at the time of the contract) shall prepare a record of the designation and date of designation (irrespective of the form), sign or subscribe and seal the record, and submit the record to the person in charge of Takeda.

8.5 PREPARATION AND SUBMISSION OF SURVEY FORMS

Collect information using paper questionnaires.

For all enrolled cases, the investigator or a person designated by the physician-in-charge shall promptly prepare a questionnaire after completion of the observation period for each case, sign or seal the questionnaire, and submit the questionnaire to Takeda Pharmaceutical Co., Ltd.

If drug treatment is discontinued or dropped out during the observation period for any reason, the investigator or a person designated by the investigator shall promptly prepare a questionnaire and submit it to Takeda Pharmaceutical Co., Ltd. after completion of the

required observation period. However, for cases in which administration of drug is discontinued or dropped out due to the onset of adverse events, the investigator will continue observation after discontinuing administration until the adverse event recovers or resolves as much as possible, and the investigator or the person designated by the investigator will prepare a questionnaire and submit it to Takeda Pharmaceutical Co., Ltd.

9.0 DURATION OF THE PROJECT

Survey period: from the date of approval for the indication of CD30 positive PTCL in ADCETRIS to September 30, 2023

Patient registration period: NOTE) from the date of approval for the indication of CD30 positive PTCL in ADCETRIS to June 30, 2023

Survey Completion date (Estimated completion date of Statistical Analysis): planed as Decmber 31, 2023

NOTE) Patient enrollment will not be accepted after July 1, 2023 even if the administration of drug was started by June 30, 2023.

If the enrolled subjects will reach the planned number of adult or pediatric subjects (80 adult subjects and 6 pediatric subjects in the safety analysis set) before June 30, 2023, the enrollment reception for adult or pediatric subjects will be completed before the patient enrollment period. If the patient enrollment period is shortened, the investigation period will be changed according to the shortened period.

10.0 EXAMINATIONS AND OBSERVATIONS

A person designated by the physician-in-charge of the survey or the physician-in-charge of the survey writes the following items in the patient registration sheet and the survey form.

10.1 PATIENT ENROLLMENT

1) Investigation items

Date of commencement (planned) of administration of ADCETRIS, patient identification number, sex, age, inclusion criteria, exclusion criteria, and presence or absence of consent

2) Time of investigation

At the time of patient registration

10.2 PATIENT CHARACTERISTICS

1) Investigation items

Diagnosis of PTCL or HL; diagnosis name; PTCL type; lesion site; clinical stage (Ann Arbor or Murphy classification); recurrent or refractory disease category; presence or

absence of B symptoms; ECOG Performance Status; treatment category; complications (presence or absence and detail); medical history (presence or absence and detail); smoking history, height, body weight; and presence or absence of pregnancy or lactation (females only)

2) Time of investigation

Initiation of drug treatment

10.3 Treatment of PTCL or HL prior to initiation of drug treatment

1) Investigation items

Number of regimens, pharmacotherapy (presence/absence and details), presence/absence of radiotherapy, hematopoietic stem-cell transplantation (presence/absence and details), date of completion of treatment immediately before administration of ADCETRIS

2) Time of investigation

Initiation of drug treatment

10.4 Treatment

1) Investigation items

ADCETRIS status, reason for discontinuation or termination of ADCETRIS, concomitant medication status (presence/absence, drug name, duration, and objective of administration), radiotherapy status (presence/absence and detail)

2) Time of investigation

Between the initiation of ADCETRIS treatment and Month 12 (until the time of discontinuation/dropout)

10.5 Beneficial against colorectal

1) Test item

PTCL other than adult T-cell leukaemia/lymphoma (ATLL) or HL: Best Response will be determined by CR, CRu (if PET was not measured), PR, SD, or PD according to the results of CT and PET of the neck, chest, abdomen, and pelvis, and according to the antitumor response criteria.

ATLL: Best Response is assessed by CR, PR, SD, PD, or NE according to response criteria.

Childhood PTCL or HL: To determine Best Response according to the Japanese Childhood Leukemic Lymphoma Study Group (JPLSG) edition of Childhood PTCL or the Antitumor Efficacy Criteria for Childhood HL.

2) Time of investigation

Between the initiation of ADCETRIS treatment and Month 12 (after discontinuation/dropout at that time)
(However, until before the start of the next treatment)

10.6 LAST DAY OF OBSERVATION

1) Investigation items
Last day of observation
(the closest examination date to the date when the questionnaire was completed)
2) Time of investigation
12 months after commencement of administration (after discontinuation/dropout at that time)

10.7 OTHER OBSERVATIONS

1) Observation items
Presence or absence of pregnancy during the observation period (only in women), withdrawal of consent (only in patients who withdrew consent)
2) Time of investigation
Between the initiation of ADCETRIS treatment and Month 12 (until the time of discontinuation/dropout)

10.8 ADVERSE EVENTS

Peripheral neuropathy, myelosuppression (neutropenia), pulmonary disorder, adverse events leading to discontinuation of ADCETRIS, and serious adverse events that fall under the Safety Specification will be collected regardless of the CTCAE Grade. All other events are subject to CTCAE Grade3 or higher.

1) Investigation items
AEs, names of adverse events, categories of adverse events (peripheral neuropathy), symptoms (peripheral neuropathy), onset date, CTCAE Grade*(worst-case and worst-case onset date), seriousness and serious reason, changes in drug dosage and administration (presence or absence and details), other actions for the event (presence or absence and details), date of outcome assessment, outcome, causal relationship with ADCETRIS **, and changes in laboratory values (neutrophil count, etc.) related to the adverse events included in the Safety Specification
If the outcome is judged to be unresolved or unknown, follow-up will be conducted whenever possible.

*Evaluate according to the "National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5. 0)". In addition, when the standard values of laboratory values peculiar to children are required at the time of Grade evaluation, refer to Vol. 112, No. 7, 1117-1132 of the

Journal of the Japanese Society of Pediatrics (2008).

** If ADCETRIS is assessed to be not related, the rationale for assessment should be collected.

2) Safety specification

The following events will be regarded as safety specification, and at the time of occurrence, detailed information will be collected whenever possible.

・ Peripheral neuropathy, myelosuppression (neutropenia), pulmonary disorder

* Rationale for safety specification

The special drug use surveillance (all-case survey) in adults with relapsed or refractory CD30 positive HL and ALCL patients was conducted with peripheral neuropathy, infections, neutropenia, infusion reaction, and pulmonary disorder as priority survey items. The incidence of adverse drug reactions etc. obtained in the all-case survey did not exceed the expected range based on the information up to the time of approval. However, the incidence of adverse drug reactions in peripheral neuropathy and neutropenia was high (44.26% and 34.51%, respectively). The incidence of pulmonary disorder was 0.6% in foreign clinical studies and 4.58% in all-case surveys, while these were not observed in Japanese clinical studies. Therefore, the incidence and seriousness of peripheral neuropathy, myelosuppression (neutropenia), and pulmonary disorder in Japanese patients including pediatric patients should be checked after the indication of CD30 positive PTCL has been approved. Therefore, these events were included in the safety specification.

3) Time of investigation

Between the initiation of ADCETRIS treatment and Month 12 (until the time of discontinuation/dropout)

11.0 ANALYSIS ITEMS AND METHODS

11.1 ITEMS RELATED TO CASE COMPOSITION

The number of patients enrolled, the number of patients collected in the questionnaire, the number of patients evaluable for safety and efficacy, the number of patients excluded from evaluation, and the reason for exclusion will be tabulated.

11.2 PATIENT CHARACTERISTICS

Patient characteristics such as sex, age, diagnosis, disease duration, lesion site, disease type, and clinical stage will be tabulated.

11.3 TREATMENT

The status of administration of ADCETRIS, etc. will be tabulated.

11.4 SAFETY ISSUES

The following tabulation will be conducted for patients evaluated for safety. Adverse events will be read using MedDRA/J and summarised by preferred term (Preferred Term; PT) and system organ class (System Organ Class; SOC).

11.4.1 Incidence of adverse events

The frequency of adverse events that occurred during the run-in period will be tabulated by time of onset, severity (CTCAE Grade) seriousness, and causality to ADCETRIS.

11.4.2 Factors that may affect safety

The incidence of adverse drug reactions that occurred during the observation period will be tabulated by stratification of patient background factors (e.g., gender).

11.5 ITEMS RELATED TO EFFICACY

The following tabulation is performed on the efficacy evaluation population.

11.5.1 Antitumor effects (Best Response)

The antitumor effects (Best Response) at 12 months after the initiation of ADCETRIS treatment will be tabulated.

11.5.2 Overall survival

The time to death (regardless of cause of death) will be tabulated using the date of confirmation of survival as the "last observation day" in Section 10.6 and the date of death as the "outcome assessment" in the "Outcome" section in the "Adverse Events" section in Section 10.8.

12.0 REGISTRATION OF SURVEY INFORMATION

Prior to the commencement of this survey, information from this survey will be registered on the following public websites.

- Clinical trial information, Japan Pharmaceutical Information Center:
  Japan Pharmaceutical Information Center-Clinical Trials Information
- National Institutes of Health registry: ClinicalTrials.gov

13.0 ORGANIZATIONAL STRUCTURE

13.1 MANAGEMENT REPRESENTATIVE

Takeda Pharmaceutical Co., Ltd.

[redacted]

13.2 MEDICAL ADVISOR

[redacted]

(Unordered)

14.0 CONTRACT RESEARCH ORGANIZATION

(1) [redacted]

Assignment:Registration center, data management operations, storage of records, medical writing, and support operations related to post-marketing surveys

(2) [redacted]

Assignment: Statistical analysis

(3) [redacted]

Assignment: Monitoring

15.0 ADDITIONAL ACTIONS THAT MAY BE TAKEN BASED ON THE RESULTS OF THE INVESTIGATION

See Draft Risk Management Plan 2. Summary of Pharmacovigilance Plan

16.0 IMPLEMENTATION STATUS OF THE INVESTIGATION, TIME OF MILESTONE ASSESSMENT OR REPORTING

See Draft Risk Management Plan 2. Summary of Pharmacovigilance Plan

17.0 OTHER REQUIRED ITEMS.

17.1 PROTOCOL AMENDMENT

During the study period, the status of progress, the occurrence of unexpected adverse

reactions/serious adverse reactions based on the precautions, the presence or absence of an increase in the incidence of specific adverse reactions, and the appropriateness of investigation items will be ascertained. If necessary, this protocol will be reviewed and revised. If approval for partial changes in dosage and administration or indications is received during the study period, the necessity of revision of this protocol should be considered as necessary, and the protocol should be revised as necessary.

17.2 MEASURES TO BE TAKEN IN THE EVENT THAT PROBLEMS OR QUESTIONS ARE IDENTIFIED

If any problems with safety or efficacy are found, data should be carefully reviewed and actions taken.

Document History

Version	Date	Comments
original version	2020/1/29	New document
2nd version	2021/1/15	To add “14.0 Contract Research Organization” and other minor changes
3rd version	2021/3/31	To extend the patient registration period and survey period
4th version	2022/4/4	To define the end of the observation period for patients who started ADCETRIS after July 1, 2022, and to extend the overall registration period
5th version	2022/5/11	To add minor changes in “13.0 Organizational Structure”
6th version	2023/4/6	To add minor changes in “15.0 Contract Research Organization”
7th version	2023/9/12	To add the survey completion date (completion date of statistical analysis) in “9.0 Duration of the Project”