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Global Drug Development

Arzerra Injection for Intravenous Infusion/Ofatumumab
(Genetical Recombination)

Final Report

Study Results
Drug Use Investigation for
Arzerra Injection for Intravenous Infusion
(Chronic Lymphocytic Leukemia, COMB157A1401)

REDACTED STUDY REPORT

Author	[redacted], Trial Management

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PASS information

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Version identifier of the final study report	Version 1.0
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Active substance	Ofatumumab (Genetical Recombination)
Medicinal product	[1] Arzerra Injection for Intravenous Infusion 100 mg [2] Arzerra Injection for Intravenous Infusion 1,000 mg
Approval number	[1] 22500AMX00879000 [2] 22500AMX00880000
Procedure number	Not applicable (procedure number is not assigned in Japan)
Marketing authorization holder	Novartis Pharma K.K.
Joint PASS	No
Research question and objectives	The safety and efficacy of Arzerra Injection for Intravenous Infusion under the conditions of actual use after marketing will be investigated in patients with relapsed or refractory CD20-positive chronic lymphocytic leukemia.
Country of study	Japan
Main Author	[redacted], Trial Management

Marketing authorization holder

Marketing authorization holder	Novartis Pharma K.K. 1-23-1 Toranomon, Minato-ku, Tokyo
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History of amendment of this document

Not applicable

1 Abstract

Title	Drug Use Investigation for Arzerra Injection for Intravenous Infusion (Chronic Lymphocytic Leukemia, COMB157A1401)
Version and date	Version 1.0, prepared on 14 June 2022
Name and affiliation of main author	[redacted], Trial Management
Keywords	Japan, ofatumumab, relapsed or refractory CD20-positive chronic lymphocytic leukemia, non-interventional study, post marketing surveillance
Rationale and background	Arzerra Injection for Intravenous Infusion (hereinafter referred to as Arzerra) was approved on 25 March 2013 for the indication of relapsed or refractory CD20-positive chronic lymphocytic leukemia. Because of the very limited number of patients enrolled in the clinical trials of Arzerra in Japan, a drug use investigation (hereinafter referred to as the study) covering all patients receiving Arzerra was started in May 2013 in order to collect as much information as possible on the efficacy and safety in Japanese patients until data from a certain number of patients after marketing are accumulated.
Research question and objectives	The safety and efficacy of Arzerra will be investigated under the conditions of actual use after marketing to identify the status of occurrence of adverse drug reactions and factors affecting the safety and efficacy of Arzerra.
Study design	This study is a multicenter observational study (drug use investigation) without any control group conducted in accordance with GPSP Ordinance and the study protocol.
Study requirements	Not applicable
Study population	All patients who received Arzerra
Main study items	Site/patient information, patient characteristics, prior treatment, status at the first dose, status at each dose, concomitant medications, concomitant therapies, outcome, discontinuation/completion of Arzerra, efficacy, priority study items, and adverse events
Results	[Outline of the study] • This study was started on 24 May 2013, and 347 patients were enrolled by 05 April 2022. • The safety analysis set consisted of 302 patients, and the efficacy analysis set consisted of 298 patients. • Among the 302 patients in the safety analysis set, there were more men (62.25%, 188 patients) than women (37.75%, 114 patients). Patients aged ≥65 years accounted for 74.83% (226 patients). No patients aged <15 years were reported. • In the safety analysis set (302 patients), the total number of doses of Arzerra was 11 to 12 in approximately 50% of patients. The dose of the first dose was 300 mg in many patients, and the mean doses per 1 dose of the second to eighth doses and the ninth and subsequent doses were both 2,000 mg. Patients received Arzerra according to the dosage and administration described in the package insert.

[Safety]

- Among the 302 patients in the safety analysis set, the incidence of adverse drug reactions was 67.55% (204 patients). Common adverse drug reactions (≥5.00%) that occurred were rash in 16.56% (50 patients), pyrexia in 15.56% (47 patients), chills and urticaria in 8.94% (27 patients) each, neutrophil count decreased in 6.29% (19 patients), and dyspnoea in 5.96% (18 patients). The incidence of adverse drug reactions in this study was similar to the results of clinical studies, with similar types of common adverse drug reactions.
- The occurrence of adverse drug reactions specified as priority study items was confirmed, but there were no items to particularly note.
- Rash and pyrexia were also observed as common adverse drug reactions in patients with special characteristics (elderly, hepatic dysfunction, and renal dysfunction). No adverse drug reactions specific to these patients were observed.
- There were no new notable adverse drug reactions in this study compared to the clinical studies, and there were no new safety concerns requiring precautions.

[Efficacy]

- The response rate (CR + PR) in this study was 48.7% (145/298 patients).
- The response rate was low in patients with hepatic dysfunction among patients with special characteristics, but no new concerns were observed also in patients with other special characteristics (elderly and patients with renal dysfunction), showing a certain level of efficacy.
- Although it is impossible to make a definitive comparison because the patient characteristics are different between the clinical studies and this study, a certain response under the conditions of actual use was shown.

Conclusion	Based on the results of this study, no new concerns about the safety or efficacy of Arzerra under the conditions of actual use or issues to be particularly addressed were identified.
Marketing authorization holder	Novartis Pharma K.K.

2 List of abbreviations

Abbreviation	Unabbreviated expression
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
CTCAE	Common terminology criteria for adverse event
ECOG	Eastern cooperative oncology group
GPSP	Good post-marketing study practice
HBc	Hepatitis B core
HBs	Hepatitis B surface antigen
HBV	Hepatitis B virus
MedDRA/J	Medical dictionary for regulatory activities/Japanese version
NE	Not evaluable
PASS	Post-authorization safety studies
PD	Progressive disease
PR	Partial response
PS	Performance status
PT	Preferred term
SD	Stable disease
SOC	System organ class

3 Marketing authorization holder

Novartis Pharma K.K.

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4 Contractors and scope of outsourced operations

A list of contractors and the scope of operations related to the study is shown in Table 4-1.

Table 4-1 Contractors and scope of operations

Item	Contractor
[1] Name of contractor	[redacted] Japan KK
Scope of outsourced operations	Patient registration, self-inspection, and other associated operations
[2] Name of contractor	[redacted]
Scope of outsourced operations	Data entry of case report forms, data clarification, statistical analysis, self-inspection, and other associated operations

5 Milestones

Study milestones are shown in Table 5-1.

Table 5-1 Study milestones

Event name	Planned or actual date
Start of study	24 May 2013
Start of data collection (FPFV)	30 July 2013
End of registration period (LPFV)	23 December 2019
End of observation of the last patient (LPLV)	05 September 2020
End of study (database lock)	05 April 2022
Approval of the final report on the results of post marketing surveillance	30 June 2022

6 Rationale and background

Ofatumumab (genetical recombination) (hereinafter referred to as ofatumumab) is a novel human IgG1κ monoclonal antibody that was discovered by Genmab (Denmark) and specifically recognizes the CD20 epitope. Ofatumumab specifically recognizes an epitope different from that recognized by rituximab (genetical recombination) that is localized in the extracellular loops of large and small size on the CD20 molecule expressed on the surface of B-lymphocytes. Ofatumumab is characterized by high-affinity binding to the CD20 epitope and a slow dissociation rate after binding.

Ofatumumab is considered to exert its antitumor effect by inducing complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity *in vitro* (Cheson 2010). Overseas, clinical studies were conducted in patients with chronic lymphocytic leukemia

(CLL) refractory to fludarabine and alemtuzumab (genetical recombination) or fludarabine-refractory CLL who were inappropriate for alemtuzumab treatment due to bulky lymphadenopathy, and the efficacy and safety in patients with fludarabine- and alemtuzumab-refractory CLL were demonstrated; therefore, marketing approval for the indication of fludarabine- and alemtuzumab-refractory CLL was obtained in the US in October 2009 and in Europe in April 2010.

In Japan, a phase I study in patients with relapsed or refractory CLL was started in September 2008, and favorable tolerability was confirmed. Subsequently, a phase I/II study was conducted in Japanese patients with CLL, and tolerability and efficacy were confirmed. An application for orphan drug designation was also submitted, which was granted in September 2011. An application for approval for the indication of "previously treated CLL" was submitted in April 2012 and approved in March 2013.

Because of the very limited number of patients enrolled in the clinical trials of Arzerra in Japan, an all-case surveillance covering all patients receiving Arzerra was required as a condition for approval until data from a certain number of patients are accumulated after marketing. A drug use investigation in all patients with relapsed or refractory CD20-positive CLL was started in May 2013.

Arzerra was transferred from GlaxoSmithKline K.K. to Novartis Pharma K.K. on 02 November 2015; thus, the study was also transferred to Novartis Pharma K.K. on the same day and conducted by Novartis Pharma K.K.

[Conditions for approval]

The number of patients enrolled in the clinical trials of Arzerra in Japan was quite limited. Therefore, until data from a certain number of patients after marketing are accumulated, a drug use investigation covering all patients receiving Arzerra should be conducted to identify demographic information on patients using Arzerra. In addition, the safety and efficacy of Arzerra should be collected as early as possible, to take necessary measures for the proper use of Arzerra.

7 Research question and objectives

The safety and efficacy of Arzerra will be investigated under the conditions of actual use after marketing to identify the status of occurrence of adverse drug reactions and factors affecting the safety and efficacy of Arzerra.

8 Amendments and updates to the protocol

Amendments and updates to the protocol are shown in Table 8-1.

Table 8-1 Amendments and updates to the protocol

Number	Date	Section of protocol	Amendment or update	Reason
1.00	28 March 2013	-	-	-
1.10	31 October 2014	Overall	Addition of contractor, organizational structure, and correction of errors	Due to addition of contractor, change of organizational structure, and correction of errors
1.20	19 March 2015	Section 11	Addition of contractor	For outsourcing to Novartis Pharma K.K.
2.00	12 August 2015	Section 12	Consistency of description with the package insert	For modifications associated with the amendment of the package insert
2.01	30 October 2015	Overall	Description adjustment, change of protocol number, change of contractor, and specification of the definition of study completion	For changes associated with transfer from GlaxoSmithKline K.K. to Novartis Pharma K.K.
2.02	29 February 2016	Section 8	Addition of description of adverse event reporting	For changes associated with the provisions of Novartis Pharma K.K.
2.03	27 December 2017	Section 10	Change of organizational structure	Due to organizational changes
2.04	15 February 2018	Section 5	Change of the method for confirmation of all-case registration	Due to a change in the method for confirmation of all-case registration
2.05	26 October 2018	Section 7	Addition of drug product lot number to adverse event items	Changes in study items
2.10	17 December 2019	Section 10	Change of organizational structure	Due to organizational changes
2.20	26 March 2020	Cover Section 6	Change of organizational structure Change of the scheduled study period	Due to organizational changes For switching to registration only

9 Research methods

9.1 Study design

9.1.1 Overview of study design

This was a multicenter observational study (drug use investigation) without any control group conducted in accordance with GPSP Ordinance. The target sample size was set to be 300 patients with relapsed or refractory CLL, and the data set for the observation items after administration of Arzerra under the conditions of actual use were obtained. A central registration system was adopted for patient enrollment.

9.1.2 Research methods

9.1.2.1 Confirmation of survey implementation requirements at study sites and request for cooperation with all-case surveillance

The sponsor explained to the investigators that their cooperation in this study was essential when using Arzerra and requested their written consent to cooperate in this study.

9.1.2.2 Contract

The sponsor concluded a contract for this study with the head of a medical institution where Arzerra was adopted and delivered (medical institutions wishing to receive Arzerra) or the head of a local government (no contract with an individual).

The study was to be started after the start date of contract for the study, but patients who started to receive Arzerra before the start date of contract with sites were also included in the study.

9.1.2.3 Explanation of the study and provision of study materials

After concluding the contract, the sponsor explained the objectives and protocol of the study to investigators and subinvestigators using the implementation guideline, and provided them with study materials.

9.1.2.4 Registration of patients

The investigator or subinvestigator was to enter necessary information in the registration form for all patients to be treated with Arzerra and fax the registration form to the registration center promptly.

Patients who started receiving Arzerra after marketing but before conclusion of the contract, as well as those who continue to receive Arzerra started at another medical institution or department were also to be enrolled in the study.

9.1.2.5 Preparation of case report forms

The investigator or subinvestigator was to record case information on all registered patients subject to case report form collection (including those who discontinued or dropped out) in the case report form. Each time new information on registered patients was obtained, the

investigator or subinvestigator was to promptly record it in the case report form. If any adverse event occurred, the investigator or subinvestigator was to promptly notify the sponsor.

The investigator or subinvestigator was to record the information in the case report form and submit it to the sponsor promptly.

9.1.2.6 Confirmation of case report form contents

The sponsor checked the contents of the case report form prepared by the investigator or subinvestigator and queried the investigator or subinvestigator as necessary. The investigator or subinvestigator responded to the queries and corrected the case report form as necessary.

9.1.2.7 Confirmation of all-case registration

After conclusion of the study contract, the sponsor was to confirm that all patients were registered at least once every 6 months by performing sequential monitoring (visits, telephone, and email) at the medical institutions. In addition, the sponsor was to periodically check the status of prescription with the pharmacy department. The sponsor was to confirm the presence or absence of unregistered patients based on this information, and if there was any unregistered patient, the sponsor was to request the investigator or subinvestigator to register the relevant patient with the prescription. The sponsor was to record all registration status in the monitoring report.

9.1.2.8 Materials used

Protocol summary, patient registration form, and case report form

9.1.3 Observation period

The standard observation period for each patient was from the start of treatment with Arzerra to 3 months after completion of the treatment (up to 9 months from the start day of treatment with Arzerra).

[Rationale]

Since the duration of treatment with Arzerra is approximately 6 months and most of the adverse events observed in the phase II study occurred within 9 months after the start of treatment, the standard observation period was set at completion of treatment + 3 months and the maximum observation period was set at 9 months after the start of treatment with Arzerra.

9.1.4 Definition of end of study

The end of the study is defined as the date of database lock.

9.2 Study requirements

Not applicable

9.3 Study population

All patients who received Arzerra for the indication of relapsed or refractory CD20-positive chronic lymphocytic leukemia after the start of the study (24 May 2013).

All patients who received Arzerra were to be included in the study by considering patients who started to receive Arzerra before conclusion of the contract for the study as study patients as well and allowing them to be registered after conclusion of the contract.

9.4 Variables

9.4.1 Site and patient information

The investigator or subinvestigator was to record the following information concerning study sites and patients in the case report form.

Names of the institution, department, and investigators, identification number, year and monthof birth (or age at the start of treatment), gender, start day of treatment with Arzerra, previous treatment with Arzerra at other institutions

9.4.2 Patient characteristics

The investigator or subinvestigator was to record the following information on demographic and disease characteristics at the start of treatment with Arzerra in the case report form.

Hospitalization status, reason for Arzerra use, pregnancy status, appreciable constitutional/hypersensitive predispositions, past medical history, complications, HBV infection, date of diagnosis of CLL

9.4.3 Prior medications

The investigator or subinvestigator was to investigate the use of prior medications at the start of treatment with Arzerra and record the following items in the case report form.

Antineoplastic pharmacotherapy: Presence or absence, drug name, time of discontinuation, route of administration

Hematopoietic stem cell transplantation: Presence or absence, transplantation category, date of transplantation

9.4.4 Administration status of Arzerra

The investigator or subinvestigator was to investigate the administration status of Arzerra and record the following items in the case report form.

9.4.4.1 Conditions at the first administration

Disease stage (Rai stage, Binet stage) at the first administration, ECOG PS, chromosomal aberration, number of lines of Arzerra treatment, and prior anti-CD20 antibody therapy.

9.4.4.2 Conditions at each administration (1st to 12th administrations)

Date, premedication, total dose of Arzerra, infusion rate, etc. of Arzerra, use of in-line filter, infusion reactions (event name, intervention, onset time, medication status at the time of onset, outcome, outcome date, significance ,seriousness, reason for judging as serious, grade, relationship to Arzerra, factors suspected of being associated with the event other than Arzerra, treatment status of Arzerra after onset of the event)

9.4.4.3 Discontinuation or completion of treatment with Arzerra

Date of decision, reason

9.4.5 Concomitant medications

The investigator or subinvestigator was to investigate the use status of concomitant medications during treatment with Arzerra and record the following items in the case report form.

Presence or absence of concomitant medications, drug name, daily dose, dosage unit, duration of treatment, reason for use

9.4.6 Concomitant therapies

The investigator or subinvestigator was to investigate the status of concomitant therapies during treatment with Arzerra and record the following items in the case report form.

Presence or absence of concomitant therapies, details, reason, duration

9.4.7 Efficacy

The investigator or subinvestigator was to record the following information during treatment with Arzerra.

Assessment of response ("complete response [CR]," "partial response [PR]," "stable disease [SD]," "progressive disease [PD]," and "not evaluable [NE]"] in reference to the response criteria (modified NCI-WG response criteria [Cheson, Blood 1996])

9.4.8 Pregnancy

The investigator or subinvestigator was to investigate the presence or absence of pregnancy during the observation period and record it in the case report form.

Pregnancy

9.4.9 Adverse events

The investigator or subinvestigator was to record the following items concerning adverse events.

Presence or absence, adverse event term, onset date, outcome of adverse event, outcome date, significance, seriousness, reason for judging as serious, grade, relationship to Arzerra, factors suspected of being associated with adverse event other than Arzerra, formulation lot number, treatment status of Arzerra after onset of adverse event

Adverse events of priority study items

The following events were selected as the priority study items of this study.

The investigator or subinvestigator investigated the priority study items and recorded them in the case report form.

[Priority study items]

Status of occurrence of infusion reactions, infections, tumour lysis syndrome, hematotoxicity, intestinal obstruction, skin disorder, cardiac disorder, blood pressure decreased, hepatic dysfunction/jaundice, renal disorder, and interstitial lung disease

9.4.9.1 Definitions

9.4.9.1.1 Adverse events

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

In this study, events entered in the adverse event column of the case report form were handled as adverse events.

9.4.9.1.2 Serious adverse events

Adverse events for which "serious" was selected in the seriousness field of the case report form were regarded as serious adverse events, and adverse events for which seriousness was not entered but the details of seriousness were selected were also regarded as serious adverse events.

Events for which the outcome was "fatal" although “seriousness in the case report form was not entered and the details of seriousness were not entered” were also regarded as serious adverse events.

The seriousness was handled as "unknown" for other events for which "seriousness in the case report form was not entered and the details of seriousness were not entered."

9.4.9.1.3 Adverse drug reactions

Adverse events for which the causal relationship with Arzerra could not be ruled out based on the description in the case report form were regarded as adverse drug reactions. Any adverse event for which a causal relationship was not entered was considered as an "adverse event for which a causal relationship with Arzerra could not be ruled out" and regarded as an adverse drug reaction.

9.5 Items related to data

9.5.1 Data sources

In this study, case report form data recorded by the investigator or subinvestigator based on usual medical records at the study site were collected.

9.5.2 Data used for statistical analysis

In this study, only data obtained from case report forms were used for statistical analysis.

9.5.3 Coding

Concomitant medications and prior medications were coded using Iyakuhinmei Data File (22 April 2021). Past medical history, complications, and adverse events were coded using MedDRA/J version 24.0.

9.5.4 Data collection schedule

This study was non-interventional and did not specify a treatment plan, diagnostic/therapeutic procedures, or visit schedule. The investigator or subinvestigator was to provide routine medical care according to the package insert. The sponsor collected necessary data from data obtained from routine medical practice. The investigator or subinvestigator was to record information at each visit as much as possible.

9.6 Study size

300 patients (as patients included in the analysis) (planned number of sites, 200 sites)

[Rationale]

The incidences of the priority study items are considered to be roughly ≥1%. Therefore, to allow the detection of at least one case of each event with a probability of at least 95%, the number of patients to be analyzed was set at 300.

From the aspect of identification of the conditions of actual use, patients who received Arzerra, regardless of the number of doses, and from whom safety information was obtained, were analyzed in this investigation. The necessity of switching to a patient registration system not requiring the completion of case report forms was to be judged in consultation with the Pharmaceuticals and Medical Devices Agency, after confirming that the target information can be collected based on the registration status, CRF collection status, and other information before the number of patients registered reaches the planned sample size.

9.7 Data management

9.7.1 Data collection and entry

The investigator or subinvestigator was to enter necessary information specified in the protocol in the case report form as appropriate. The investigator or subinvestigator was to enter information in the case report form promptly each time new information was obtained, and submit the case report form to the sponsor promptly after completion or discontinuation of the observation period. The target patients for case report form entry were to be identified when the switch to registration only was made, and only registration was to be continued for the subsequent patients treated with Arzerra. The case report form was not to be completed for patients who were only registered unless otherwise instructed by the sponsor.

9.7.2 Systems used for data collection and management

The systems used for data collection and management were defined separately in the operating procedures.

9.8 Bias

No special measures to eliminate bias were taken in this study.

9.9 Data transformation

Not applicable

9.10 Statistical analysis

Details of the statistical analysis are described in "Statistical Analysis Plan for Drug Use Investigation for Arzerra Injection for Intravenous Infusion 100 mg/1,000 mg, Version 5."

9.10.1 Definitions of analysis sets

9.10.1.1 Patients with confirmed registration

Patients with confirmed registration were defined as patients who received the registration form and became eligible.

9.10.1.2 Patients with locked case report forms

Patients with locked case report forms were defined as those whose case report forms had been locked.

9.10.1.3 Safety analysis set

The safety analysis set consisted of patients with locked case report forms who did not meet any of the following conditions for exclusion from the safety analysis.

- Beyond contract period
- Arzerra not administered
- Off-label use
- Patients whose registration had not been determined
- Multiple registrations
- Patients with a history of Arzerra use
- No sign or seal of physician
- Presence or absence of adverse events unknown/not described

9.10.1.4 Efficacy analysis set

The efficacy analysis population consisted of patients in the safety analysis set who did not meet the following condition for exclusion from the efficacy analysis.

- No response assessment

9.10.2 Handling of patient data

9.10.2.1 Handling of deviated data

There were no deviated data to investigate.

9.10.2.2 Handling of missing data

Missing data were not imputed in this study.

9.10.3 Analysis methods

9.10.3.1 Patient composition

In the patients with confirmed registration, the number of patients with confirmed registration, the number of patients whose case report forms were not collected and the breakdown of reasons for not collecting the case report forms, the number of patients with locked case report forms, the number of patients in the safety and efficacy analysis sets, and the number of patients excluded from the analysis and the breakdown of reasons for exclusion were tabulated. In addition, a list of reasons for exclusion of patients excluded from the safety and efficacy analyses was prepared.

9.10.3.2 Status of discontinuation of the study

In the safety analysis set, the number and proportion of discontinued patients were calculated by reason for discontinuation.

9.10.3.3 Administration status of Arzerra

In the safety analysis set, the proportion or summary statistics were calculated for the administration status of Arzerra (dose and treatment duration).

9.10.3.4 Demographic and other characteristics

For demographic and other baseline characteristics (including disease characteristics), frequencies and proportions were calculated for categorical data and summary statistics were calculated for continuous data in the safety analysis set.

9.10.4 Safety endpoints and examination and analysis methods

Unless otherwise specified, safety analyses were performed in the safety analysis set.

9.10.4.1 Definitions related to adverse events

Based on the definitions in Section 9.4.9.1, adverse event data in analyses were handled as follows.

Adverse events

In this study, events listed in the adverse event column of the case report form were regarded as adverse events.

Adverse drug reactions

Among adverse events, those for which the causal relationship with Arzerra could not be ruled out by the investigator or subinvestigator and those whose causal relationship was not entered were regarded as adverse drug reactions.

Serious adverse events

Adverse events for which there was a description indicating that the event was serious and those with a fatal outcome were regarded as serious adverse events.

For events for which seriousness and details of seriousness were not entered in the case report form and the outcome was other than death, seriousness was handled as "unknown."

Priority study items

Priority study items of this study and their definitions are shown in Table 9-1. Events other than infusion reactions are defined by system organ classes (SOCs) or preferred terms (PTs).

Table 9-1 Priority study items and definitions

Priority study item	Definition
Infusion reaction	Events that were determined by the investigator or subinvestigator to have occurred after the start of infusion on the day of infusion of Arzerra and that led to temporary infusion interruption, prolongation of the infusion time, or discontinuation of infusion.
Infections	Infections (SOC)
Tumour lysis syndrome	Tumour lysis syndrome, tumour necrosis, haemorrhagic tumor necrosis (PT)
Hematotoxicity	Agranulocytosis, anaemia, anaemia macrocytic, anaemia neonatal, aplasia pure red cell, aplastic anaemia, aspiration bone marrow abnormal, basophil count decreased, biopsy bone marrow abnormal, differential white blood cell count abnormal, eosinopenia, eosinophil count decreased, erythroid maturation arrest, erythropenia, febrile neutropenia, full blood count abnormal, full blood count decreased, granulocyte count decreased, granulocytes abnormal, granulocytopenia, granulocytopenia neonatal, haematocrit decreased, haemoglobin abnormal, haemoglobin decreased, hypoplastic anaemia, leukopenia, lymphocyte count abnormal, lymphocyte count decreased, lymphocytopenia neonatal, lymphopenia, megakaryocytes abnormal, megakaryocytes decreased, microcytic anaemia, monocyte count decreased, monocytopenia, myelodysplastic syndrome, myelofibrosis, myeloid maturation arrest, myeloid metaplasia, neutropenia, neutropenia neonatal, neutrophil count decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, pancytopenia, plasma cells absent, platelet count abnormal, platelet count decreased, platelet disorder, platelet maturation arrest, platelet production decreased, red blood cell count abnormal, red blood cell count decreased, reticulocyte count abnormal, reticulocyte count decreased, reticulocytopenia, thrombocytopenia, thrombocytopenia neonatal, white blood cell count abnormal, white blood cell count decreased, neutropenic sepsis, haematocrit abnormal, erythropoiesis abnormal, panmyelopathy, granulocytes maturation arrest, leukopenia neonatal, myeloblast count decreased, metamyelocyte count decreased, myelocyte count decreased, promyelocyte count decreased, B-lymphocyte count decreased, T-lymphocyte count decreased, idiopathic neutropenia, bone marrow toxicity, basophil percentage decreased, eosinophil percentage decreased, neutrophil percentage decreased, myeloblast percentage decreased, myelocyte percentage decreased, monocyte percentage decreased, lymphocyte percentage decreased, congenital aplastic anaemia, cyclic neutropenia, leukoerythroblastic anaemia, febrile bone marrow aplasia, scan bone marrow abnormal, B-lymphocyte abnormalities, T-lymphocyte count abnormal, bone marrow

Priority study item	Definition
	myelogram abnormal, band neutrophil count decreased, erythroblast count decreased, erythroblast count abnormal, monoblast count decreased, plasmablast count decreased, bone marrow necrosis, bicytopenia, band neutrophil percentage decreased, platelet toxicity, neutropenic infection, reticulocyte percentage decreased, proerythroblast count abnormal, proerythroblast count decreased, basophil count abnormal, eosinophil count abnormal, haematotoxicity, monocyte count abnormal, neutrophil count abnormal, white blood cell disorder, blood disorder, bone marrow disorder, plasma cell disorder, lymphocyte percentage abnormal, blood count abnormal, plateletcrit decreased, plateletcrit abnormal, bone marrow failure, cytopenia, radiation leukopenia, myelodysplastic syndrome transformation, pure white cell aplasia, autoimmune aplastic anaemia, white blood cell analysis abnormal, bone marrow infiltration, basophilopenia, acquired amegakaryocytic thrombocytopenia, primary myelofibrosis, foetal anaemia, gelatinous transformation of the bone marrow, B-lymphocyte count abnormal, mononuclear cell count decreased (PT)
Intestinal obstruction	Duodenal obstruction, gallstone ileus, gastrointestinal stenosis, ileal stenosis, ileus, intestinal obstruction, intestinal stenosis, jejunal stenosis, rectal stenosis, small intestinal obstruction, duodenal stenosis, distal intestinal obstruction syndrome, gastrointestinal obstruction, large intestinal obstruction, small intestinal stenosis, large intestinal stenosis (PT)
Skin disorder	Skin disorders (SOC)
Cardiac disorder	Cardiac disorders (SOC)
Blood pressure decreased	Altered state of consciousness, blood pressure abnormal, blood pressure ambulatory abnormal, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic abnormal, blood pressure diastolic decreased, blood pressure fluctuation, blood pressure immeasurable, blood pressure systolic abnormal, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, depressed level of consciousness, dizziness, dizziness exertional, dizziness postural, hypotension, labile blood pressure, loss of consciousness, mean arterial pressure decreased, orthostatic hypotension, presyncope, syncope, neonatal hypotension, consciousness fluctuating, blood pressure inadequately controlled, blood pressure orthostatic abnormal, blood pressure orthostatic decreased, procedural hypotension, diastolic hypotension, Schellong test, tilt table test positive, CT hypotension complex, post procedural hypotension (PT)
Hepatic dysfunction/jaundice	5'nucleotidase increased, abnormal faeces, acute fatty liver of pregnancy, acute hepatic failure, alanine aminotransferase abnormal, alanine aminotransferase increased, alcoholic liver disease, ammonia abnormal, ammonia increased, ascites, aspartate aminotransferase abnormal, aspartate aminotransferase increased, asterixis, autoimmune hepatitis, benign hepatic neoplasm, bile duct adenocarcinoma, bile duct adenosquamous carcinoma, bile duct cancer, bile duct cancer recurrent, bile duct squamous cell carcinoma, bile duct stone, biliary cirrhosis, biliary colic, biliary fibrosis, biliary fistula, biliary neoplasm, bilirubin conjugated increased, bilirubinuria, biopsy liver abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, blood cholinesterase abnormal, blood cholinesterase decreased, blood fibrinogen abnormal, blood fibrinogen decreased, blood thrombin abnormal, blood thrombin decreased, blood thromboplastin abnormal, blood thromboplastin decreased, bromosulphthalein test abnormal, cholangioadenoma, cholangiocarcinoma, cholangiogram abnormal, cholangiolitis, cholangitis, cholangitis acute, cholangitis sclerosing, cholecystectomy, cholecystitis,

Priority study item	Definition
	cholecystitis acute, cholecystitis chronic, cholecystogram intravenous abnormal, cholecystostomy, choledochal cyst, choledochotomy, cholelithiasis, cholelithiasis obstructive, cholestasis, chronic hepatitis, chronic hepatitis B, chronic hepatitis C, cirrhosis alcoholic, coagulation factor decreased, coagulation factor IX level decreased, coagulation factor V level decreased, coagulation factor VII level decreased, coagulation factor X level decreased, coma hepatic, complications of transplanted liver, congenital absence of bile ducts, congenital hepatitis B infection, cytomegalovirus hepatitis, dilatation intrahepatic duct congenital, endoscopic retrograde cholangiopancreatography abnormal, endoscopy biliary tract abnormal, faeces pale, fatty liver alcoholic, gallbladder cancer, gallbladder cancer recurrent, gallbladder cholesterolosis, gallbladder disorder, gallbladder fistula, gallbladder obstruction, gallbladder oedema, gallbladder injury, gallstone ileus, gamma-glutamyltransferase abnormal, gamma-glutamyltransferase increased, glycogen storage disease type I, granulomatous liver disease, haemangioma of liver, hepaplastin abnormal, hepaplastin decreased, hepatic adenoma, hepatic atrophy, hepatic cirrhosis, hepatic cyst, hepatic echinococciasis, hepatic encephalopathy, hepatic failure, hepatic fibrosis, hepatic function abnormal, hepatic necrosis, hepatic neoplasm, hepatic pain, hepatic steatosis, hepatitis, hepatitis A, hepatitis A antibody abnormal, hepatitis A antibody positive, hepatitis acute, hepatitis alcoholic, hepatitis B, hepatitis B antibody abnormal, hepatitis B antibody positive, hepatitis B surface antigen positive, hepatitis C, hepatitis C antibody positive, hepatitis C RNA positive, hepatitis cholestatic, hepatitis chronic active, hepatitis chronic persistent, hepatitis D, hepatitis E, hepatitis F, hepatitis fulminant, hepatitis G, hepatitis H, hepatitis infectious mononucleosis, hepatitis mumps, hepatitis neonatal, hepatitis non-A non-B, hepatitis non-A non-B non-C, hepatitis post transfusion, hepatitis syphilitic, hepatitis toxic, hepatitis toxoplasmal, hepatitis viral, hepato-lenticular degeneration, hepatoblastoma recurrent, hepatocellular damage neonatal, hepatocellular injury, hepatomegaly, hepatorenal failure, hepatorenal syndrome, hepatosplenomegaly, hepatosplenomegaly neonatal, hepatotoxicity, hyperammonaemia, hyperbilirubinaemia, hyperbilirubinaemia neonatal, hyperplastic cholecystopathy, hypoalbuminaemia, hypocoagulable state, hypoprothrombinaemia, icterus index increased, international normalised ratio abnormal, international normalised ratio increased, ischaemic hepatitis, jaundice, jaundice cholestatic, jaundice extrahepatic obstructive, jaundice hepatocellular, jaundice neonatal, Kayser-Fleischer ring, kernicterus, leucine aminopeptidase increased, liver abscess, liver disorder, liver function test abnormal, liver tenderness, liver transplant, liver transplant rejection, lupoid hepatic cirrhosis, malformation biliary, malignant neoplasm of ampulla of Vater, mixed hepatocellular cholangiocarcinoma, oesophageal varices haemorrhage, perforation bile duct, porphyria acute, porphyria non-acute, portal hypertension, portal pyaemia, portal shunt, protein C decreased, prothrombin level abnormal, prothrombin level decreased, prothrombin time abnormal, prothrombin time prolonged, prothrombin time ratio increased, Reye's syndrome, schistosomiasis liver, spider naevus, splenorenal shunt, ultrasound liver abnormal, viral hepatitis carrier, Weil's disease, yellow skin, Zieve syndrome, retinol binding protein decreased, cholaemia, biliary adenoma, polycystic liver disease, cholestasis of pregnancy, choledochoenterostomy, glutamate dehydrogenase increased, antithrombin III decreased, oedema due to hepatic disease, cholecystocholangitis, hepatic candidiasis, gallbladder polyp, neonatal hepatomegaly, urine bilirubin increased, liver carcinoma ruptured, portal hypertensive gastropathy, porcelain gallbladder, duodenal varices, gastric

Priority study item	Definition
	varices, radiation hepatitis, gallbladder empyema, nodular regenerative hyperplasia, protein S decreased, hypofibrinogenaemia, congenital hepatomegaly, thrombin time abnormal, guanase increased, bile duct stenosis, bile duct stenosis traumatic, bile output decreased, bile output abnormal, thrombin time prolonged, hepatosplenic candidiasis, liver and pancreas transplant rejection, metastases to gallbladder, hepatic cyst infection, protein S abnormal, bile duct stent insertion, hypercholia, gallbladder abscess, hepatopulmonary syndrome, renal and liver transplant, focal nodular hyperplasia, hepatitis B core antigen positive, hepatitis B e antigen positive, pancreatobiliary sphincterotomy, biliary sphincterotomy, dilatation intrahepatic duct acquired, biliary cyst, liver induration, foetor hepaticus, peritoneovenous shunt, accessory liver lobe, choledochectomy, choledochostomy, cholelithotomy, non-alcoholic steatohepatitis, glycogen storage disease type VI, hepatocellular foamy cell syndrome, glycogen storage disease type IV, glycogen storage disease type III, cholecystogram oral abnormal, cholangiectasis acquired, cerebrohepatorenal syndrome, Gianotti-Crosti syndrome, alagille syndrome, hepatic cyst ruptured, perihepatic discomfort, vanishing bile duct syndrome, hepatic haemangioma rupture, transaminases increased, hepatic cancer metastatic, biliary cancer metastatic, varices oesophageal, bile duct obstruction, biliary anastomosis, benign biliary neoplasm, hepatic infection, hepatobiliary infection, neonatal cholestasis, biliary dyskinesia, congenital hepatic fibrosis, X-ray hepatobiliary abnormal, emphysematous cholecystitis, adenoviral hepatitis, subacute hepatic failure, hydrocholecystis, hepatic mass, biliary dilatation, biliary tract dilation procedure, post cholecystectomy syndrome, gallbladder palpable, gastric varices haemorrhage, chronic hepatic failure, post procedural bile leak, choledocholithotomy, biliary sepsis, ultrasound biliary tract abnormal, hereditary haemochromatosis, hepatitis E antibody positive, gallbladder mucocoele, hepatitis E antibody abnormal, ocular icterus, gallbladder cancer stage II, gallbladder cancer stage III, gallbladder cancer stage IV, gallbladder adenocarcinoma, biopsy bile duct abnormal, biliary fistula repair, gallbladder fistula repair, hepatitis D antigen positive, biliary ischaemia, blood bilirubin abnormal, hypothrombinaemia, hypothromboplastinaemia, bile output increased, hepatitis A antigen positive, hepatitis B reactivation, HBV-DNA polymerase increased, bile duct necrosis, haemobilia, biloma, acute hepatitis B, gallbladder cancer stage 0, gallbladder cancer stage I, hepatic cancer stage I, hepatic cancer stage II, hepatic cancer stage III, hepatic cancer stage IV, bile duct cancer stage I, bile duct cancer stage II, bile duct cancer stage III, bile duct cancer stage IV, bile duct cancer stage 0, gallbladder necrosis, hepatitis D antibody positive, hepatitis D RNA positive, blood alkaline phosphatase increased, blood alkaline phosphatase abnormal, bile culture positive, galactose elimination capacity test abnormal, galactose elimination capacity test decreased, haemorrhagic ascites, hepatitis B DNA assay positive, hepatitis E antigen positive, hepatic enzyme decreased, hepatic enzyme increased, biliary tract disorder, bilirubin excretion disorder, congenital hepatobiliary anomaly, gallbladder anomaly congenital, hepatobiliary neoplasm, biliary tract infection, biliary tract operation, cholangitis chronic, coagulation factor IX level abnormal, coagulation factor V level abnormal, coagulation factor VII level abnormal, coagulation factor X level abnormal, prothrombin time ratio abnormal, liver scan abnormal, gallbladder operation, hepatectomy, hepatic lesion, hepatobiliary disease, hepatoblastoma, liver operation, metastases to biliary tract, cholecystitis infective, hepatic enzyme abnormal, transaminases abnormal, gallbladder enlargement, biliary abscess, biliary anastomosis

Priority study item	Definition
	complication, bile duct pressure increased, cryptogenic cirrhosis, hepatic amoebiasis, asymptomatic viral hepatitis, cholestatic pruritus, total bile acids increased, hepatic infiltration eosinophilic, graft versus host disease in liver, mitochondrial aspartate aminotransferase increased, portal vein pressure increased, acute hepatitis C, hepatic infection bacterial, hepatic infection helminthic, hepatic infection fungal, hepatic calcification, pneumobilia, hepatobiliary scan abnormal, hepatic sequestration, acute graft versus host disease in liver, sphincter of Oddi dysfunction, hepatic encephalopathy prophylaxis, mixed liver injury, molar ratio of total branched-chain amino acid to tyrosine, gallbladder cancer metastatic, pseudocholelithiasis, Lemmel's syndrome, AIDS cholangiopathy, liver injury, portopulmonary hypertension, portal vein flow decreased, retrograde portal vein flow, hepatic hydrothorax, ampulla of Vater stenosis, hepatic angiosarcoma, herpes simplex hepatitis, cholecystoenterostomy, bilirubin conjugated abnormal, lupus hepatitis, haemorrhagic hepatic cyst, splenic varices, cholestatic liver injury, hypertransaminasaemia, Child-Pugh-Turcotte score increased, cystic fibrosis hepatic disease, biliary polyp, hepatic vascular resistance increased, acquired protein S deficiency, hepatitis C RNA increased, hepatitis B DNA increased, bacterascites, splenic varices haemorrhage, liver sarcoidosis, periportal oedema, cholelithiasis migration, portal hypertensive enteropathy, anorectal varices, anorectal varices haemorrhage, hepatic artery flow decreased, peritoneal fluid protein increased, peritoneal fluid protein decreased, peritoneal fluid protein abnormal, small-for-size liver syndrome, hepatolithectomy, bile duct stent removal, hepatitis A virus test positive, hepatitis B virus test positive, hepatitis C virus test positive, hepatitis E virus test positive, Urobilinogen urine increased, urobilinogen urine decreased, hepatitis D virus test positive, acute yellow liver atrophy, Reynold's syndrome, biliary cast syndrome, allergic hepatitis, withdrawal hepatitis, diabetic hepatopathy, hepatitis B core antibody positive, hepatitis B surface antibody positive, hepatitis B e antibody positive, Intestinal varices, deficiency of bile secretion, biloma rupture, chronic graft versus host disease in liver, drug-induced liver injury, varicose veins of abdominal wall, gallbladder varices, limy bile syndrome, intrahepatic portal hepatic venous fistula, hepatitis viral test positive, gallbladder adenosquamous carcinoma, gallbladder squamous cell carcinoma, hepatic cancer, hepatic cancer recurrent, hepatocellular carcinoma, gallbladder neoplasm, hepatobiliary cancer, hepatobiliary cancer in situ, portal vein dilatation, peripancreatic varices, gallbladder papilloma, cholangiostomy, tumour of ampulla of Vater, portal vein cavernous transformation, hepatic fibrosis marker abnormal, biliary ascites, parenteral nutrition associated liver disease, liver iron concentration abnormal, liver iron concentration increased, hepatic fibrosis marker increased, gallbladder volvulus, acquired antithrombin III deficiency, biliary hamartoma, portal fibrosis, hyperfibrinolysis, liver ablation, stomal varices, perinatal HBV infection, portal tract inflammation, cholangitis infective, radiotherapy to gallbladder, liver palpable, progressive familial intrahepatic cholestasis, sustained viral response, minimal hepatic encephalopathy, computerised tomogram liver, gastric variceal injection, gastric variceal ligation, spontaneous intrahepatic portosystemic venous shunt, gallbladder adenoma, hepatic hypertrophy, steatohepatitis, portal venous system anomaly, liver dialysis, ampullary polyp, Child-Pugh-Turcotte score abnormal, benign neoplasm of ampulla of Vater, hepatitis C core antibody positive, hepatic gas gangrene, hepatic steato-fibrosis, non-cirrhotic portal hypertension, splenorenal shunt procedure, model for end stage liver disease score abnormal, model for end stage liver disease score increased, malignant neoplasm papilla of Vater, acute

Priority study item	Definition
	on chronic liver failure, bilirubin urine present, portal shunt procedure, hepatosplenic abscess, anti factor X activity abnormal, anti factor X activity increased, anti factor X activity decreased, liver function test decreased, liver function test increased, biliary dyspepsia, cholangiosarcoma, benign hepatobiliary neoplasm, intestinal varices haemorrhage, gallbladder fibrosis, biopsy gallbladder abnormal, cholelithotripsy, computerised tomogram liver abnormal, white nipple sign, immune-mediated hepatitis, portal hypertensive colopathy, hepatic hamartoma, hepatic lymphocytic infiltration, hepatobiliary cyst, biliary-vascular fistula, biliary-bronchial fistula, primary biliary cholangitis, alloimmune hepatitis, regenerative siderotic hepatic nodule, glycocholic acid increased, acquired hepatocerebral degeneration, gallbladder hyperfunction, gallbladder hypofunction, gallbladder rupture, malignant biliary obstruction, haemorrhagic cholecystitis, nonalcoholic fatty liver disease, cholangiojejunostomy, magnetic resonance proton density fat fraction measurement, increased liver stiffness, multivisceral transplantation, cardiohepatic syndrome, recurrent pyogenic cholangitis, magnetic resonance imaging liver abnormal, splenic artery embolisation, congestive hepatopathy (PT)
Renal disorder	Albuminuria, albumin urine present, anuria, azotaemia, biopsy kidney abnormal, blood bicarbonate abnormal, blood bicarbonate decreased, blood calcium abnormal, blood calcium decreased, blood creatinine abnormal, blood creatinine increased, blood parathyroid hormone abnormal, blood parathyroid hormone increased, blood potassium abnormal, blood potassium increased, blood sodium abnormal, blood sodium decreased, blood urea abnormal, blood urea increased, bone cyst, coma uraemic, creatinine renal clearance decreased, diabetic end stage renal disease, encephalopathy, glomerular filtration rate abnormal, glomerular filtration rate decreased, glomerulonephritis, glomerulonephritis chronic, glomerulonephritis membranoproliferative, glomerulonephritis membranous, glomerulonephritis minimal lesion, glomerulonephritis proliferative, glomerulonephritis rapidly progressive, Goodpasture's syndrome, haemodialysis, haemolytic uraemic syndrome, hepatorenal failure, hypercalcaemic nephropathy, hyperkalaemia, hyperparathyroidism, hyperparathyroidism secondary, hyperphosphataemia, hypervolaemia, hypoalbuminaemia, hypocalcaemia, hyponatraemia, IgA nephropathy, intercapillary glomerulosclerosis, inulin renal clearance decreased, kidney fibrosis, kidney small, lupus nephritis, metabolic acidosis, microalbuminuria, nephritis, nephropathy, nephropathy toxic, nephrosclerosis, nephrotic syndrome, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, oliguria, osteomalacia, pericarditis, pericarditis uraemic, peritoneal dialysis, proteinuria, red blood cells urine positive, renal amyloidosis, renal atrophy, renal failure, renal failure neonatal, renal papillary necrosis, renal rickets, renal transplant, renal tubular atrophy, renal tubular disorder, renal tubular necrosis, secondary hypertension, ultrasound kidney abnormal, uraemic acidosis, uraemic encephalopathy, uraemic neuropathy, urate nephropathy, urea renal clearance decreased, white blood cells urine positive, tubulointerstitial nephritis, oedema due to renal disease, renal impairment neonatal, neonatal anuria, calcification of muscle, blood phosphorus increased, renal tubular dysfunction, blood erythropoietin abnormal, blood urea nitrogen/creatinine ratio increased, leukocyturia, parathyroid gland enlargement, calciphylaxis, vascular calcification, glomerulonephropathy, renal and pancreas transplant, renal and liver transplant, haemofiltration, protein urine present, urine protein/creatinine ratio increased, urine protein/creatinine ratio abnormal, urine albumin/creatinine ratio

Priority study item	Definition
	increased, urine albumin/creatinine ratio abnormal, artificial kidney device user, blood erythropoietin decreased, blood 1,25-dihydroxycholecalciferol decreased, blood phosphorus abnormal, diffuse mesangial sclerosis, creatinine urine decreased, hypertensive nephropathy, uraemia odour, nephrogenic anaemia, eosinophils urine present, dialysis device insertion, dialysis disequilibrium syndrome, haemodialysis-induced symptom, peritoneal fluid analysis abnormal, urine output decreased, uraemic pruritus, dialysis, renal function test abnormal, diabetic nephropathy, glomerulosclerosis, renal impairment, pigment nephropathy, high turnover osteopathy, haemorrhagic diathesis, hypercreatininaemia, low turnover osteopathy, chronic allograft nephropathy, uraemic gastropathy, dialysis amyloidosis, chronic kidney disease, polyomavirus-associated nephropathy, reflux nephropathy, nephritic syndrome, continuous haemodiafiltration, mesangioproliferative glomerulonephritis, peritoneal cloudy effluent, peritoneal effluent leukocyte count increased, peritoneal effluent erythrocyte count increased, bloody peritoneal effluent, nephrogenic systemic fibrosis, urinary casts present, peritoneal dialysis complication, focal segmental glomerulosclerosis, uridrosis, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, creatinine renal clearance abnormal, hepatitis virus-associated nephropathy, extensive interdialytic weight gain, effective peritoneal surface area increased, peritoneal fluid protein increased, peritoneal fluid protein abnormal, kidney injury molecule-1, acute kidney injury, ischaemic nephropathy, ultrafiltration failure, peritoneal effluent abnormal, acute phosphate nephropathy, peritoneal permeability increased, haemodialysis complication, HIV associated nephropathy, acquired cystic kidney disease, creatinine urine abnormal, crystal nephropathy, dialysis related complication, prerenal failure, peritoneal equilibration test abnormal, aluminium overload, intradialytic parenteral nutrition, renal replacement therapy, haemorrhagic fever with renal syndrome, fractional excretion of sodium, paraneoplastic nephrotic syndrome, potassium wasting nephropathy, dialysis membrane reaction, paraneoplastic glomerulonephritis, autoimmune nephritis, inadequate haemodialysis, IgM nephropathy, end stage renal disease, hyponatriuria, C3 glomerulopathy, obstructive nephropathy, uraemic myopathy, chronic kidney disease-mineral and bone disorder, destructive spondyloarthropathy, renal tubular injury, foetal renal impairment, C1q nephropathy, metabolic nephropathy, subacute kidney injury, peritoneal dialysate leakage, acquired perforating dermatosis, increased intraperitoneal volume (PT)

Priority study item	Definition
Interstitial lung disease	Acute respiratory distress syndrome, alveolar proteinosis, alveolitis, biopsy lung abnormal, bronchiolitis, complications of transplanted lung, eosinophilia myalgia syndrome, eosinophilic pneumonia, Goodpasture's syndrome, idiopathic pulmonary fibrosis, interstitial lung disease, lung infiltration, obliterative bronchiolitis, pneumonitis, pneumonitis chemical, polyarteritis nodosa, progressive massive fibrosis, pulmonary alveolar haemorrhage, pulmonary eosinophilia, pulmonary fibrosis, pulmonary granuloma, pulmonary haemosiderosis, pulmonary sarcoidosis, pulmonary vasculitis, radiation alveolitis, radiation fibrosis - lung, radiation pneumonitis, rheumatoid lung, sarcoidosis, systemic sclerosis pulmonary, restrictive pulmonary disease, lymphangioleiomyomatosis, alveolitis necrotising, toxic oil syndrome, lung transplant rejection, transfusion-related acute lung injury, eosinophilic pneumonia acute, eosinophilic pneumonia chronic, lung induration, lupus pneumonitis, pulmonary necrosis, diffuse alveolar damage, pulmonary radiation injury, pulmonary toxicity, idiopathic pneumonia syndrome, acute interstitial pneumonitis, organising pneumonia, pulmonary renal syndrome, antisynthetase syndrome, granulomatous pneumonitis, acute lung injury, Langerhans' cell histiocytosis, necrotising bronchiolitis, granulomatosis with polyangiitis, alveolar lung disease, allergic eosinophilia, airway remodelling, combined pulmonary fibrosis and emphysema, eosinophilic granulomatosis with polyangiitis, idiopathic interstitial pneumonia, cystic lung disease, small airways disease, autoimmune lung disease, hypersensitivity pneumonitis, immune-mediated pneumonitis (PT)

MedDRA version 23.0 was used.

9.10.4.2 Adverse events

For the safety evaluation, the observation period was defined as the safety analysis period, and all adverse events that occurred during this period were included in the tabulation. In patients who discontinued treatment with Arzerra during the observation period, the period from the day of last dose of Arzerra to +3 months (follow-up period) was regarded as the safety analysis period and adverse events were tabulated.

The total number of patients with adverse events represents the number of patients with at least one adverse event. Unless otherwise specified, adverse events were tabulated by system organ class (SOC) and preferred term (PT). A patient who developed the same adverse event more than once was counted as 1 patient for each PT. A patient with multiple adverse events in the same SOC was counted as 1 patient in the total of SOCs.

Adverse events excluded from analysis were listed separately.

Analyses performed for adverse events were as follows:

- Number of patients with adverse events and the incidence (by SOC and PT)
- Number of patients with serious adverse events and the incidence (by SOC and PT)
- Number of patients with adverse events leading to discontinuation of Arzerra and the incidence (by PT)
- Listing of adverse events and listing of adverse events leading to death
- Listing of adverse events excluded from analysis performed in patients with locked case report forms

9.10.4.3 Adverse drug reactions

The following analyses were performed for adverse drug reactions. Similar analyses were performed for serious adverse drug reactions.

- Number of patients with adverse drug reactions and the incidence (by SOC and PT)
- Number of patients with adverse drug reactions leading to discontinuation of Arzerra and the incidence (by PT)
- Number of patients with adverse drug reactions (by total number of doses, SOC, and PT)
- For specific factors such as patient characteristics, the number of patients with adverse drug reactions and the incidence, and odds ratios (ORs) of adverse drug reactions between the categories and their two-sided 95% confidence intervals (CIs) were calculated for each category of the factors. The following factors were used in the analyses:
  - Gender (male and female)
  - Age (<15 years, ≥15 to <65 years, and ≥65 years)
  - Age (15 years) (<15 years and ≥15 years)
  - Age (18 years) (<18 years and ≥18 years)
  - Age (65 years) (<65 years and ≥65 years)
  - Hospitalization status
  - Disease duration (<1 year, ≥1 to <3 years, ≥3 to <6 years, ≥6 to <11 years, and ≥11 years)
  - Presence or absence of pregnancy
  - Presence or absence of noteworthy constitution/predisposition to hypersensitivity
  - Presence or absence of past medical history (hepatic dysfunction, cardiac dysfunction, renal dysfunction, and pulmonary dysfunction)
  - Presence or absence of complication (hepatic dysfunction, cardiac dysfunction, renal dysfunction, and pulmonary dysfunction)
  - Presence or absence of HBV infection
  - Presence or absence of prior treatment (antineoplastic drugs and hematopoietic stem cell transplantation)
  - Disease stage (Rai stage and Binet stage)
  - ECOG PS (0,1,2,3,4)
  - Number of lines of Arzerra treatment (first-line, second-line, and third-line)
  - Presence or absence of prior anti-CD20 antibody therapy
  - Presence or absence of concomitant medications (treatment of primary disease and prevention of infection)
  - Presence or absence of concomitant therapies

9.10.4.4 Priority study items

Events falling under each priority study item were defined by PTs, and the number and proportion of patients with events were tabulated by event of each priority study item and by PT based on the definition. If the same event of each priority study item occurred more than

once in the same patient, the patient was counted as 1 patient in the number of patients with the event of each priority study item. If the same PT occurred more than once in the same patient, the patient was counted as 1 patient in the number of patients with the PT.

9.10.5 Efficacy endpoints and examination and analysis methods

9.10.5.1 Efficacy endpoints

- Best response based on modified NCI-WG response criteria (Cheson, Blood 1996)

The best response was classified into 4 categories, "CR," "PR," "SD," and "PD," and patients with "CR" and "PR" were evaluated as responders.

- Factors that may affect efficacy

9.10.5.2 Efficacy analysis methods

- Best response

With patients with a best response of "PR" or "CR" as responders, the numbers and proportions of responders and non-responders were calculated.

- The response rate was tabulated and tested by patient characteristic.

9.10.6 Examination of subgroups and interactions

The number of patients with adverse drug reactions and the incidence were calculated for children, elderly patients, pregnant women, patients complicated with renal dysfunction, and patients complicated with hepatic dysfunction. In addition, the number of patients with adverse drug reactions and the number and proportion of responders were calculated for each of the following patient factors and compared between the factors.

[Patient factors]

Gender, age (children [<15 years], adults [≥15 to <65 years], and elderly [≥65 years]), hospitalization status, disease duration, pregnancy, noteworthy constitution/predisposition to hypersensitivity, presence/absence of past medical history, past medical history (hepatic dysfunction, cardiac dysfunction, renal dysfunction, and pulmonary dysfunction), presence/absence of complications, complications (hepatic dysfunction, cardiac dysfunction, renal dysfunction, and pulmonary dysfunction), presence/absence of HBV infection, presence/absence of prior treatment, prior treatment (antineoplastic drugs and hematopoietic stem cell transplantation), disease stage (Rai stage and Binet stage), ECOG PS, number of lines of Arzerra treatment, prior anti-CD20 antibody therapy, presence/absence of concomitant medications, concomitant medications (treatment of primary disease and prevention of infection), concomitant therapies

9.10.7 Sensitivity analyses

No sensitivity analysis was performed for this study.

9.10.8 Amendments to the statistical analysis plan described in the protocol and reasons for the changes

The reasons for amendments of the protocol of this study are shown in Table 8-1. There was no change to the statistical analysis methods that required a change to the protocol.

9.11 Quality control

In order to assure the quality of data related to this study, data quality control, quality control of statistical analysis results, and quality control by self-inspection were performed. The methods and procedures are described below.

9.11.1 Data quality control

The sponsor performed detailed examination of the contents recorded in case report forms according to the predetermined procedure. If there were any inadequacies or inconsistencies that met the criteria for detailed examination, the investigator or subinvestigator was inquired about the data.

9.11.2 Quality control of statistical analysis results

For quality control of statistical analysis results, the sponsor prepared a statistical analysis result validation plan.

The sponsor reviewed the contents of the statistical analysis result validation report based on the statistical analysis result validation plan and confirmed that the contents and operating procedures of the validation based on the statistical analysis result validation plan were complied with.

9.11.3 Self-inspection and quality control of this report

The sponsor implements quality control based on periodic process checks for procedures related to report preparation.

In addition, the sponsor performed a quality check for validity and accuracy and confirmed that this report was prepared based on the analysis results.

10 Results

Based on the data obtained from the start of the study (24 May 2013) to the end of the study (database lock date, 05 April 2022), the study results are described in detail. Since no new case report form data were obtained after the cut-off date of 25 October 2021, analytical tabulation results using the data cut off on 25 October 2021 are shown for results other than those in Table 10-1 and Figure 10-1.

10.1 Number of study patients and sites

By 05 April 2022, 347 patients were registered from 190 sites, and the case report forms for 323 of the registered patients were locked. The mean number of registered patients per site was 1.8, with a maximum of 9 and a minimum of 1.

Table 10-1 Number of sites and patients registered for the study

Number of registered patients per site	Maximum	9	patients
	Minimum	1	patients
	Mean	1.8	patients

Source:Table 01

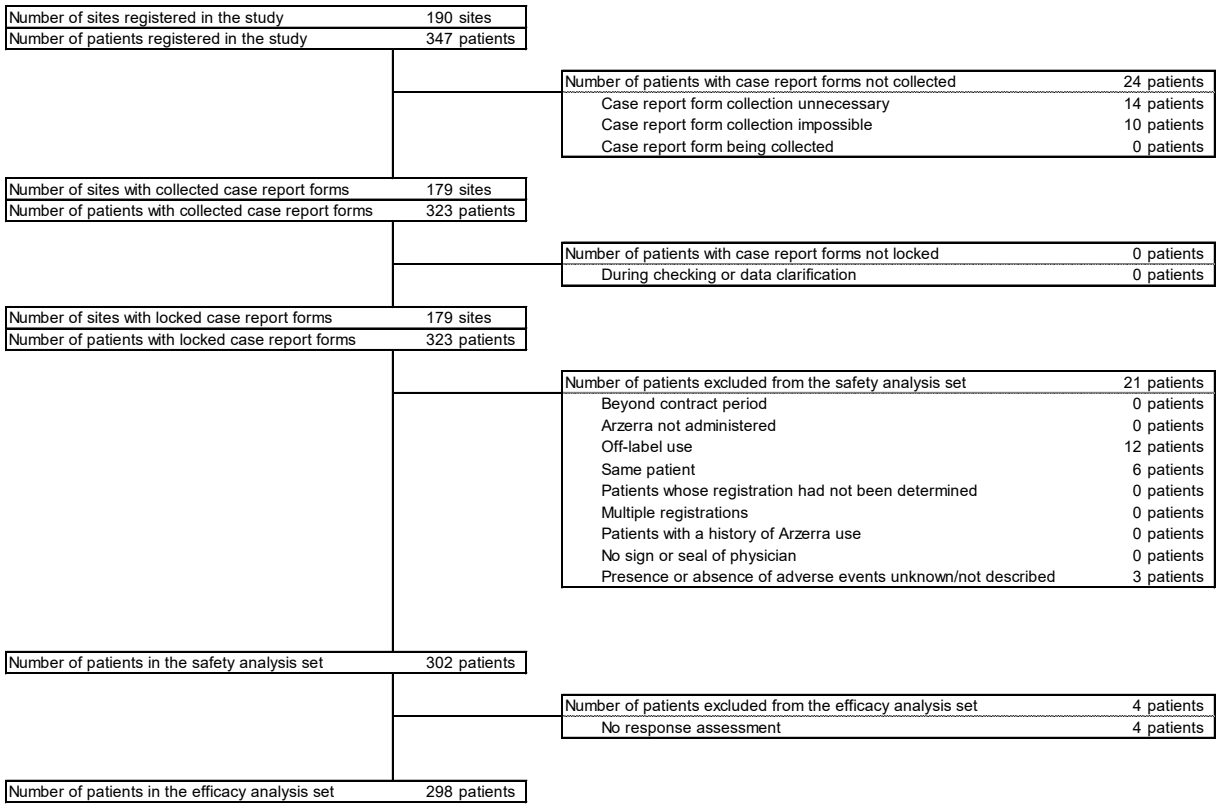
10.2 Patient composition

The patient composition is shown in Figure 10-1.

After excluding 24 patients whose case report forms had not been collected from the patients whose registration was determined, 323 patients had locked case report forms. After excluding 12 patients with off-label use (use for diseases other than chronic lymphocytic leukemia), 6 identical patients, and 3 patients with the presence or absence of adverse events unknown/not described from the 323 patients with locked case report forms, the safety analysis set consisted of 302 patients.

Of the 302 patients in the safety analysis set, 298 patients were included in the efficacy analysis set after excluding 4 patients with no response assessment.

Figure 10-1 Patient composition



Source:Figure_01

10.3 Patient characteristics

Demographic and disease characteristics of 302 patients in the safety analysis set and 298 patients in the efficacy analysis set are shown in Table 10-2.

Among the 302 patients in the safety analysis set, there were more men (62.25%, 188 patients) than women (37.75%, 114 patients). Patients aged ≥65 years accounted for 74.83% (226 patients). No patients aged <15 years were reported.

The proportions of patients complicated with hepatic dysfunction, cardiac dysfunction, renal dysfunction, and pulmonary dysfunction were 9.27% (28 patients), 7.62% (23 patients), 11.59% (35 patients), and 0.99% (3 patients), respectively.

The disease stage (Rai stage) was 0, 1, 2, 3, and 4 in 5.30% (16 patients), 11.92% (36 patients), 13.58% (41 patients), 14.90% (45 patients), and 50.33% (152 patients), respectively. More than 60% of the patients were classified into a high-risk group (Rai stages 3 and 4). The disease stage (Binet stage) was stage A in 7.95% (24 patients), stage B in 23.84% (72 patients), and stage C in 65.23% (197 patients).

The distribution of patient characteristics in the 298 patients in the efficacy analysis set was similar to that in the safety analysis set.

Table 10-2 Demographic and disease characteristics (safety analysis set and efficacy analysis set)

Patient factor		Safety analysis set		Efficacy analysis set	
		Number of patients	(%)	Number of patients	(%)
Total		302	--	298	--
Gender	Male	188	(62.25)	184	(61.74)
	Female	114	(37.75)	114	(38.26)
	Unknown	0	(0.00)	0	(0.00)
Age	<15 years	0	(0.00)	0	(0.00)
Minimum = 44	≥15 to <65 years	73	(24.17)	72	(24.16)
Maximum = 91	≥65 years	226	(74.83)	223	(74.83)
	Unknown	3	(0.99)	3	(1.01)
Age (15 years)	<15 years	0	(0.00)	0	(0.00)
	≥15 years	299	(99.01)	295	(98.99)
	Unknown or not entered	3	(0.99)	3	(1.01)
Age (18 years)	<18 years	0	(0.00)	0	(0.00)
	≥18 years	299	(99.01)	295	(98.99)
	Unknown or not entered	3	(0.99)	3	(1.01)
Age (65 years)	<65 years	73	(24.17)	72	(24.16)
	≥ 65 years	226	(74.83)	223	(74.83)
	Unknown or not entered	3	(0.99)	3	(1.01)
Hospitalization status	Inpatient	270	(89.40)	266	(89.26)
	Outpatient	30	(9.93)	30	(10.07)
	Unknown	2	(0.66)	2	(0.67)
Reason for use (overlapping)	Chronic lymphocytic leukemia	302	(100.00)	298	(100.00)
	Other	2	(0.66)	2	(0.67)
	Unknown	0	(0.00)	0	(0.00)
Disease duration	<1 year	42	(13.91)	42	(14.09)
	≥1 to <3 years	56	(18.54)	55	(18.46)
	≥3 to <6 years	71	(23.51)	71	(23.83)
	≥6 to <11 years	73	(24.17)	72	(24.16)
	≥11 years	37	(12.25)	36	(12.08)
	Unknown	23	(7.62)	22	(7.38)
Pregnancy	No	114	(100.00)	114	(100.00)
	Yes	0	(0.00)	0	(0.00)
	Unknown	0	(0.00)	0	(0.00)

Patient factor		Safety analysis set		Efficacy analysis set	
		Number of patients	(%)	Number of patients	(%)
Noteworthy constitution/predisposition to hypersensitivity	No	264	(87.42)	260	(87.25)
	Yes (overlapping)	38	(12.58)	38	(12.75)
	Drug	27	(8.94)	27	(9.06)
	Food	8	(2.65)	8	(2.68)
	Other	7	(2.32)	7	(2.35)
	Unknown	0	(0.00)	0	(0.00)
Past medical history	No	186	(61.59)	184	(61.74)
	Yes	116	(38.41)	114	(38.26)
	Unknown	0	(0.00)	0	(0.00)
Past medical history (hepatic dysfunction)	No	297	(98.34)	294	(98.66)
	Yes	5	(1.66)	4	(1.34)
	Unknown	0	(0.00)	0	(0.00)
Past medical history (cardiac dysfunction)	No	289	(95.70)	286	(95.97)
	Yes	13	(4.30)	12	(4.03)
	Unknown	0	(0.00)	0	(0.00)
Past medical history (renal dysfunction)	No	294	(97.35)	290	(97.32)
	Yes	8	(2.65)	8	(2.68)
	Unknown	0	(0.00)	0	(0.00)
Past medical history (pulmonary dysfunction)	No	301	(99.67)	297	(99.66)
	Yes	1	(0.33)	1	(0.34)
	Unknown	0	(0.00)	0	(0.00)
Past medical history (other)	No	200	(66.23)	198	(66.44)
	Yes	102	(33.77)	100	(33.56)
	Unknown	0	(0.00)	0	(0.00)
Complication	No	135	(44.70)	131	(43.96)
	Yes	167	(55.30)	167	(56.04)
	Unknown	0	(0.00)	0	(0.00)
Complication (hepatic dysfunction)	No	274	(90.73)	270	(90.60)
	Yes	28	(9.27)	28	(9.40)
	Unknown	0	(0.00)	0	(0.00)
Complication (cardiac dysfunction)	No	279	(92.38)	275	(92.28)
	Yes	23	(7.62)	23	(7.72)
	Unknown	0	(0.00)	0	(0.00)
Complication (renal dysfunction)	No	267	(88.41)	263	(88.26)
	Yes	35	(11.59)	35	(11.74)
	Unknown	0	(0.00)	0	(0.00)
Complication (pulmonary dysfunction)	No	299	(99.01)	295	(98.99)
	Yes	3	(0.99)	3	(1.01)
	Unknown	0	(0.00)	0	(0.00)

Patient factor		Safety analysis set		Efficacy analysis set	
		Number of patients	(%)	Number of patients	(%)
Complication (other)	No	168	(55.63)	164	(55.03)
	Yes	134	(44.37)	134	(44.97)
	Unknown	0	(0.00)	0	(0.00)
HBV infection	No	37	(12.25)	36	(12.08)
	Yes	81	(26.82)	79	(26.51)
	Unknown	184	(60.93)	183	(61.41)
HBV infection (HBs antigen)	Positive	22	(7.28)	21	(7.05)
	Negative	272	(90.07)	270	(90.60)
	Not measured	8	(2.65)	7	(2.35)
HBV infection (HBs antibody)	Positive	46	(15.23)	45	(15.10)
	Negative	222	(73.51)	220	(73.83)
	Not measured	34	(11.26)	33	(11.07)
HBV infection (HBc antibody)	Positive	58	(19.21)	56	(18.79)
	Negative	209	(69.21)	208	(69.80)
	Not measured	35	(11.59)	34	(11.41)
HBV infection (HBV DNA)	Not less than detection sensitivity	14	(4.64)	14	(4.70)
	Less than detection sensitivity	102	(33.77)	99	(33.22)
	Not measured	186	(61.59)	185	(62.08)
Prior treatment	No	122	(40.40)	120	(40.27)
	Yes	180	(59.60)	178	(59.73)
	Unknown	0	(0.00)	0	(0.00)
Prior treatment (antineoplastic drugs)	No	126	(41.72)	124	(41.61)
	Yes	176	(58.28)	174	(58.39)
	Unknown	0	(0.00)	0	(0.00)
Prior treatment (hematopoietic stem cell transplantation)	No	296	(98.01)	292	(97.99)
	Yes	6	(1.99)	6	(2.01)
	Unknown	0	(0.00)	0	(0.00)
Disease stage (Rai stage)	0	16	(5.30)	16	(5.37)
	1	36	(11.92)	35	(11.74)
	2	41	(13.58)	41	(13.76)
	3	45	(14.90)	44	(14.77)
	4	152	(50.33)	150	(50.34)
	Unknown	12	(3.97)	12	(4.03)
Disease stage (Binet stage)	A	24	(7.95)	23	(7.72)
	B	72	(23.84)	72	(24.16)
	C	197	(65.23)	194	(65.10)
	Unknown	9	(2.98)	9	(3.02)

Patient factor		Safety analysis set		Efficacy analysis set	
		Number of patients	(%)	Number of patients	(%)
ECOG PS	0	129	(42.72)	129	(43.29)
	1	111	(36.75)	109	(36.58)
	2	36	(11.92)	34	(11.41)
	3	20	(6.62)	20	(6.71)
	4	6	(1.99)	6	(2.01)
	Unknown	0	(0.00)	0	(0.00)
Chromosomal aberration (overlapping)	Normal karyotype	110	(36.42)	110	(36.91)
	17p deletion	17	(5.63)	17	(5.70)
	11q deletion	14	(4.64)	14	(4.70)
	Other	86	(28.48)	85	(28.52)
	Unknown	82	(27.15)	79	(26.51)
Number of lines of Arzerra treatment	First-line	16	(5.30)	15	(5.03)
	Second-line	119	(39.40)	117	(39.26)
	Third-line	105	(34.77)	104	(34.90)
	Other	0	(0.00)	0	(0.00)
	Unknown	62	(20.53)	62	(20.81)
Prior anti-CD20 antibody therapy	No	126	(41.72)	124	(41.61)
	Yes	171	(56.62)	169	(56.71)
	Unknown	5	(1.66)	5	(1.68)
Concomitant medications	No	77	(25.50)	75	(25.17)
	Yes	225	(74.50)	223	(74.83)
	Unknown	0	(0.00)	0	(0.00)
Concomitant medication (treatment of primary disease)	No	186	(61.59)	184	(61.74)
	Yes	39	(12.91)	39	(13.09)
	Unknown	77	(25.50)	75	(25.17)
Concomitant medication (treatment of infection)	No	167	(55.30)	165	(55.37)
	Yes	58	(19.21)	58	(19.46)
	Unknown	77	(25.50)	75	(25.17)
Concomitant medication (prevention of infection)	No	22	(7.28)	22	(7.38)
	Yes	203	(67.22)	201	(67.45)
	Unknown	77	(25.50)	75	(25.17)
Concomitant therapies	No	296	(98.01)	292	(97.99)
	Yes	6	(1.99)	6	(2.01)
	Unknown	0	(0.00)	0	(0.00)

Source:Table 02_01

* Past medical history and complications of “hepatic dysfunction,”“ cardiac dysfunction,” “renal dysfunction,” and“ pulmonary dysfunction” were not those described in the case report forms but were those identified using the MedDRA PT code list prepared by NPKK.

10.4 Administration status of Arzerra

The administration status of Arzerra in the safety analysis set and the efficacy analysis set are shown in Table 10-3.

Of the 302 patients in the safety analysis set, approximately 50% received 11 to 12 doses of Arzerra, and approximately 50% received a total of >18,300 to ≤22,300 mg. In many patients, the initial dose was 300 mg, and the mean doses per 1 dose of the second to eighth doses and the ninth and subsequent doses were both 2,000 mg. Patients received Arzerra according to the dosage and administration described in the package insert. The number of doses administered exceeded the approved 12 doses (≥13 doses were administered) in 2 patients.

The administration status of Arzerra in the 298 patients in the efficacy analysis set showed a similar tendency to that in the safety analysis set.

[Dosage and administration of the package insert (Version 6)]

The usual adult dosage for intravenous drip infusion of ofatumumab (genetical recombination) is 300 mg for the initial dose and 2,000 mg for the second and subsequent doses once weekly, and the administration should be repeated until the eighth dose. From 4 to 5 weeks after the eighth dose, 2,000 mg of the drug should be administered by intravenous drip infusion once every 4 weeks, and the administration should be repeated until the 12th dose.

Table 10-3 Administration status (safety analysis set and efficacy analysis set)

Administration status of Arzerra		Safety analysis set		Efficacy analysis set	
		Number of patients	(%)	Number of patients	(%)
Total		302	--	298	--
Total dose	≤300 mg	15	(4.97)	13	(4.36)
	300< to ≤2,300 mg	16	(5.30)	15	(5.03)
	2,300< to ≤6,300 mg	27	(8.94)	26	(8.72)
	6,300< to ≤10,300 mg	20	(6.62)	20	(6.71)
	10,300< to ≤14,300 mg	41	(13.58)	41	(13.76)
	14,300< to ≤18,300 mg	33	(10.93)	33	(11.07)
	18,300< to ≤22,300 mg	148	(49.01)	148	(49.66)
	>22,300 mg	2	(0.66)	2	(0.67)
	Unknown	0	(0.00)	0	(0.00)

Administration status of Arzerra			Safety analysis set		Efficacy analysis set	
			Number of patients	(%)	Number of patients	(%)
Total number of doses	1 dose		14	(4.64)	12	(4.03)
	2 doses		16	(5.30)	15	(5.03)
	≥3 to ≤4 doses		27	(8.94)	26	(8.72)
	≥5 to ≤6 doses		20	(6.62)	20	(6.71)
	≥7 to ≤8 doses		41	(13.58)	41	(13.76)
	≥9 to ≤10 doses		33	(10.93)	33	(11.07)
	≥11 to ≤12 doses		149	(49.34)	149	(50.00)
	≥13 doses		2	(0.66)	2	(0.67)
	Unknown		0	(0.00)	0	(0.00)
Observation period	<12 weeks		0	(0.00)	0	(0.00)
	≥12 to <16 weeks		33	(10.93)	30	(10.07)
	≥16 to <20 weeks		34	(11.26)	33	(11.07)
	≥20 to <36 weeks		80	(26.49)	80	(26.85)
	≥36 weeks		153	(50.66)	153	(51.34)
	Unknown		2	(0.66)	2	(0.67)
Number of doses × mean dose per administration	Initial dose	<300 mg	4	(1.32)	3	(1.01)
		300 mg	297	(98.34)	294	(98.66)
		>300 mg	1	(0.33)	1	(0.34)
	Second to eighth doses	<2000 mg	14	(4.64)	14	(4.70)
		2000 mg	274	(90.73)	272	(91.28)
		>2000 mg	0	(0.00)	0	(0.00)
	Ninth and subsequent doses	<2000 mg	5	(1.66)	5	(1.68)
		2000 mg	180	(59.60)	180	(60.40)
		>2000 mg	0	(0.00)	0	(0.00)

Source:Table 02_03

10.4.1 Discontinuations and dropouts

The number of patients who discontinued/dropped out in the safety analysis set and the reasons are shown in Table 10-4.

Among the 302 patients in the safety analysis set, 149 patients (49.34%) completed the treatment as planned.

The most common reason for discontinuation/dropout was “inadequate response” in 45 patients (14.90%), followed by “occurrence of adverse events” in 33 patients (10.93%) and “worsening of primary disease” in 28 patients (9.27%).

Patients with more than one reason for discontinuation/dropout were counted multiple times.

Table 10-4 Discontinuations and dropouts (safety analysis set)

		Safety analysis set	
		Number of patients	(%)
Total		302	--
Reasons for discontinuation/completion of Arzerra (overlapping)	Completed as planned	149	(49.34)
	Patient death*	14	(4.64)
	Occurrence of adverse events	33	(10.93)
	Inadequate response	45	(14.90)
	Worsening of primary disease	28	(9.27)
	Other	25	(8.28)
	Unknown	0	(0.00)

Source:Table 02_02

* "Patient death" in the 14 patients was the reason at the time of discontinuation of Arzerra, and these patients do not include those who died of other factors.

10.5 Safety

10.5.1 Occurrence of adverse events

The occurrence of adverse events in the safety analysis set is shown in Table 10-5.

Among the 302 patients in the safety analysis set, the incidence of adverse events was 79.14% (239 patients).

Common adverse events (≥10.00%) were pyrexia in 17.22% (52 patients), rash in 16.89% (51 patients), and chronic lymphocytic leukaemia (worsening) in 11.26% (34 patients).

Table 10-5 Occurrence of adverse events (by SOC and PT) (safety analysis set)

SOC	PT	Number of patients	Proportion (%)
Total		239	79.14
Skin and subcutaneous tissue disorders		104	34.44
	Rash	51	16.89
	Urticaria	27	8.94
	Erythema	10	3.31
	Pruritus	10	3.31
	Hyperhidrosis	7	2.32
	Rash pruritic	4	1.32
	Cold sweat	2	0.66
	Drug eruption	1	0.33
	Eczema	1	0.33
	Papule	1	0.33
	Rash macular	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Rash maculo-papular	1	0.33
	Skin disorder	1	0.33
	Toxic skin eruption	1	0.33
General disorders and administration site conditions		82	27.15
	Pyrexia	52	17.22
	Chills	27	8.94
	Chest discomfort	5	1.66
	Oedema	5	1.66
	Chest pain	3	0.99
	Fatigue	3	0.99
	Feeling hot	2	0.66
	Malaise	2	0.66
	Oedema peripheral	2	0.66
	Death	1	0.33
	Face oedema	1	0.33
	Feeling abnormal	1	0.33
	Feeling cold	1	0.33
	Mass	1	0.33
	Oedema mucosal	1	0.33
	Pain	1	0.33
	General physical health deterioration	1	0.33
	Non-cardiac chest pain	1	0.33
Investigations		60	19.87
	Neutrophil count decreased	23	7.62
	White blood cell count decreased	15	4.97
	Blood pressure decreased	12	3.97
	Platelet count decreased	9	2.98
	Oxygen saturation decreased	7	2.32
	Alanine aminotransferase increased	3	0.99
	Blood alkaline phosphatase increased	3	0.99
	Aspartate aminotransferase increased	2	0.66
	Blood lactate dehydrogenase increased	2	0.66
	Blood pressure increased	2	0.66
	Gamma-glutamyltransferase increased	2	0.66
	Haemoglobin decreased	2	0.66
	Weight increased	2	0.66
	Blood bilirubin increased	1	0.33
	Blood creatinine increased	1	0.33
	C-reactive protein increased	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Lymphocyte count decreased	1	0.33
	Lymphocyte count increased	1	0.33
Infections and infestations		53	17.55
	Pneumonia	15	4.97
	Bronchitis	7	2.32
	Herpes zoster	7	2.32
	Sepsis	5	1.66
	Infection	4	1.32
	Nasopharyngitis	4	1.32
	Hepatitis B	2	0.66
	Urinary tract infection	2	0.66
	Adenoviral conjunctivitis	1	0.33
	Appendicitis	1	0.33
	Bronchiolitis	1	0.33
	Cellulitis	1	0.33
	Influenza	1	0.33
	Oral candidiasis	1	0.33
	Otitis media	1	0.33
	Periodontitis	1	0.33
	Pharyngitis	1	0.33
	Progressive multifocal leukoencephalopathy	1	0.33
	Pyelonephritis	1	0.33
	Subcutaneous abscess	1	0.33
	Varicella	1	0.33
	Clostridium colitis	1	0.33
	Sinusitis fungal	1	0.33
	Hepatitis B reactivation	1	0.33
	Pneumonia bacterial	1	0.33
	Oral herpes	1	0.33
	Candida infection	1	0.33
	Aspergillus infection	1	0.33
Respiratory, thoracic and mediastinal disorders		50	16.56
	Dyspnoea	19	6.29
	Cough	8	2.65
	Oropharyngeal discomfort	7	2.32
	Hypoxia	4	1.32
	Throat irritation	4	1.32
	Laryngeal discomfort	3	0.99

SOC	PT	Number of patients	Proportion (%)
	Nasal congestion	2	0.66
	Pharyngeal oedema	2	0.66
	Pleural effusion	2	0.66
	Productive cough	2	0.66
	Sneezing	2	0.66
	Wheezing	2	0.66
	Acute respiratory distress syndrome	1	0.33
	Asphyxia	1	0.33
	Aspiration	1	0.33
	Bronchiectasis	1	0.33
	Chronic obstructive pulmonary disease	1	0.33
	Dysphonia	1	0.33
	Hiccups	1	0.33
	Laryngeal oedema	1	0.33
	Oropharyngeal swelling	1	0.33
	Respiratory failure	1	0.33
	Rhinorrhoea	1	0.33
	Upper respiratory tract inflammation	1	0.33
	Pulmonary mass	1	0.33
	Larynx irritation	1	0.33
	Oropharyngeal pain	1	0.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		36	11.92
	Chronic lymphocytic leukemia	34	11.26
	Gastric cancer	1	0.33
	Richter's syndrome	1	0.33
Gastrointestinal disorders		32	10.60
	Nausea	10	3.31
	Vomiting	6	1.99
	Diarrhoea	3	0.99
	Enterocolitis	3	0.99
	Abdominal discomfort	2	0.66
	Constipation	2	0.66
	Oral discomfort	2	0.66
	Hypoaesthesia oral	2	0.66
	Abdominal pain lower	1	0.33
	Ascites	1	0.33
	Dry mouth	1	0.33
	Gastrointestinal haemorrhage	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Gingival bleeding	1	0.33
	Rectal haemorrhage	1	0.33
	Stomatitis	1	0.33
	Large intestinal obstruction	1	0.33
Blood and lymphatic system disorders		26	8.61
	Anaemia	14	4.64
	Febrile neutropenia	5	1.66
	Thrombocytopenia	3	0.99
	Disseminated intravascular coagulation	2	0.66
	Neutropenia	2	0.66
	Hematotoxicity	2	0.66
	Lymph node pain	1	0.33
	Lymphadenopathy	1	0.33
Nervous system disorders		19	6.29
	Headache	4	1.32
	Hypoaesthesia	3	0.99
	Neuropathy peripheral	3	0.99
	Head discomfort	2	0.66
	Peripheral sensory neuropathy	2	0.66
	Somnolence	2	0.66
	Cerebral infarction	1	0.33
	Dizziness	1	0.33
	Haemorrhagic cerebral infarction	1	0.33
	Syncope	1	0.33
	Tremor	1	0.33
	Facial nerve disorder	1	0.33
Hepatobiliary disorders		13	4.30
	Hepatic function abnormal	6	1.99
	Liver disorder	3	0.99
	Jaundice	2	0.66
	Bile duct stone	1	0.33
	Cholangitis	1	0.33
	Cholecystitis	1	0.33
	Cholecystitis acute	1	0.33
	Cholelithiasis	1	0.33
	Hepatic failure	1	0.33
	Hyperbilirubinaemia	1	0.33

SOC	PT	Number of patients	Proportion (%)
Metabolism and nutrition disorders		12	3.97
	Tumour lysis syndrome	5	1.66
	Hypokalaemia	3	0.99
	Decreased appetite	2	0.66
	Hypercalcaemia	1	0.33
	Hyperkalaemia	1	0.33
	Hyperphosphataemia	1	0.33
	Hyperuricaemia	1	0.33
	Hypoalbuminaemia	1	0.33
	Hyponatraemia	1	0.33
Vascular disorders		12	3.97
	Flushing	5	1.66
	Hypotension	4	1.32
	Hot flush	2	0.66
	Hypertension	1	0.33
	Haemorrhage	1	0.33
Cardiac disorders		9	2.98
	Arrhythmia	2	0.66
	Bradycardia	2	0.66
	Atrial fibrillation	1	0.33
	Atrioventricular block second degree	1	0.33
	Cardiac failure	1	0.33
	Cardiac failure chronic	1	0.33
	Myocarditis	1	0.33
Musculoskeletal and connective tissue disorders		8	2.65
	Back pain	4	1.32
	Arthralgia	1	0.33
	Muscular weakness	1	0.33
	Neck pain	1	0.33
	Systemic lupus erythematosus	1	0.33
	Limb discomfort	1	0.33
Renal and urinary disorders		6	1.99
	Renal impairment	4	1.32
	Urinary retention	2	0.66
Eye disorders		5	1.66
	Eyelid oedema	4	1.32
	Conjunctival hyperaemia	1	0.33

SOC	PT	Number of patients	Proportion (%)
Immune system disorders		4	1.32
	Anaphylactoid reaction	2	0.66
	Hypersensitivity	1	0.33
	Immunodeficiency	1	0.33
Injury, poisoning and procedural complications		3	0.99
	Subdural haematoma	2	0.66
	Fall	1	0.33
	Spinal compression fracture	1	0.33
Endocrine disorders		1	0.33
	Silent thyroiditis	1	0.33
Ear and labyrinth disorders		1	0.33
	Deafness	1	0.33
	Ear discomfort	1	0.33
Reproductive system and breast disorders		1	0.33
	Menopausal symptoms	1	0.33

Source:Table 12_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.2 Occurrence of serious adverse events

The occurrence of serious adverse events in the safety analysis set is shown in Table 10-6.

Among the 302 patients in the safety analysis set, the incidence of serious adverse events was 26.82% (81 patients).

Common serious adverse events (≥3.00%) were chronic lymphocytic leukaemia (worsening) in 8.94% (27 patients) and pneumonia in 3.97% (12 patients).

Table 10-6 Occurrence of serious adverse events (by SOC and PT) (safety analysis set)

SOC	PT	Number of patients	Proportion (%)
Total		81	26.82
Infections and infestations		33	10.93
	Pneumonia	12	3.97
	Sepsis	5	1.66
	Herpes zoster	4	1.32
	Infection	3	0.99
	Hepatitis B	2	0.66
	Appendicitis	1	0.33
	Bronchitis	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Influenza	1	0.33
	Progressive multifocal leukoencephalopathy	1	0.33
	Pyelonephritis	1	0.33
	Urinary tract infection	1	0.33
	Sinusitis fungal	1	0.33
	Pneumonia bacterial	1	0.33
	Oral herpes	1	0.33
	Candida infection	1	0.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		28	9.27
	Chronic lymphocytic leukemia	27	8.94
	Gastric cancer	1	0.33
Investigations		17	5.63
	Neutrophil count decreased	6	1.99
	White blood cell count decreased	5	1.66
	Blood lactate dehydrogenase increased	2	0.66
	Blood pressure decreased	2	0.66
	Alanine aminotransferase increased	1	0.33
	Aspartate aminotransferase increased	1	0.33
	Blood bilirubin increased	1	0.33
	Blood creatinine increased	1	0.33
	Lymphocyte count increased	1	0.33
	Oxygen saturation decreased	1	0.33
	Platelet count decreased	1	0.33
	Blood alkaline phosphatase increased	1	0.33
Blood and lymphatic system disorders		8	2.65
	Anaemia	3	0.99
	Febrile neutropenia	3	0.99
	Disseminated intravascular coagulation	1	0.33
	Thrombocytopenia	1	0.33
	Hematotoxicity	1	0.33
Hepatobiliary disorders		8	2.65
	Hepatic function abnormal	4	1.32
	Jaundice	2	0.66
	Bile duct stone	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Cholangitis	1	0.33
	Cholecystitis acute	1	0.33
	Hepatic failure	1	0.33
	Hyperbilirubinaemia	1	0.33
	Liver disorder	1	0.33
Respiratory, thoracic and mediastinal disorders		7	2.32
	Dyspnoea	2	0.66
	Acute respiratory distress syndrome	1	0.33
	Asphyxia	1	0.33
	Aspiration	1	0.33
	Laryngeal oedema	1	0.33
	Pleural effusion	1	0.33
	Respiratory failure	1	0.33
	Pulmonary mass	1	0.33
General disorders and administration site conditions		7	2.32
	Pyrexia	4	1.32
	Chills	1	0.33
	Death	1	0.33
	Oedema mucosal	1	0.33
	General physical health deterioration	1	0.33
Cardiac disorders		4	1.32
	Arrhythmia	1	0.33
	Atrial fibrillation	1	0.33
	Cardiac failure chronic	1	0.33
	Myocarditis	1	0.33
Metabolism and nutrition disorders		3	0.99
	Tumour lysis syndrome	2	0.66
	Hypercalcaemia	1	0.33
	Hyperkalaemia	1	0.33
	Hyperphosphataemia	1	0.33
Gastrointestinal disorders		3	0.99
	Enterocolitis	1	0.33
	Vomiting	1	0.33
	Large intestinal obstruction	1	0.33
Skin and subcutaneous tissue disorders		3	0.99
	Rash	2	0.66

SOC	PT	Number of patients	Proportion (%)
	Urticaria	1	0.33
Nervous system disorders		2	0.66
	Haemorrhagic cerebral infarction	1	0.33
	Syncope	1	0.33
Immune system disorders		1	0.33
	Immunodeficiency	1	0.33
Vascular disorders		1	0.33
	Haemorrhage	1	0.33
Renal and urinary disorders		1	0.33
	Renal impairment	1	0.33
Injury, poisoning and procedural complications		1	0.33
	Fall	1	0.33
	Subdural haematoma	1	0.33

Source:Table 12_03

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.3 Occurrence of adverse drug reactions

The occurrence of adverse drug reactions in the safety analysis set is shown in Table 10-7.

Among the 302 patients in the safety analysis set, the incidence of adverse drug reactions was 67.55% (204 patients).

Common adverse drug reactions (≥5.00%) were rash in 16.56% (50 patients), pyrexia in 15.56% (47 patients), chills and urticaria in 8.94% (27 patients) each, neutrophil count decreased in 6.29% (19 patients), and dyspnoea in 5.96% (18 patients). The outcome was resolved or resolving in nearly 90%, but there were 6 deaths (analysis results, Table 12_05).

The occurrence of adverse drug reactions in the 302 patients in the safety analysis set is shown by number of doses in Table 10-8.

Among the 204 patients with adverse drug reactions, the incidence of adverse drug reactions by number of doses was highest at 79.90% (163 patients) after 1st dose, followed by 33.33% (68 patients) after 2nd doses and 12.75% (26 patients) after 3rd to 4th doses. The incidence of adverse drug reactions by number of doses thereafter ranged from 3.43% to 10.29%. The incidence of adverse drug reactions after the completion of Arzerra treatment was 15.69% (32 patients). The occurrence of adverse drug reactions by number of doses showed no increasing trend in the incidence with increasing number of doses of Arzerra. The number of doses administered exceeded the approved 12 doses (≥13 doses were administered) in 2 patients, in whom no adverse drug reactions were observed.

Table 10-7 Occurrence of adverse drug reactions (by SOC and PT) (safety analysis set)

SOC	PT	Number of patients	Proportion (%)
Total		204	67.55
Skin and subcutaneous tissue disorders		104	34.44
	Rash	50	16.56
	Urticaria	27	8.94
	Pruritus	10	3.31
	Erythema	9	2.98
	Hyperhidrosis	7	2.32
	Rash pruritic	4	1.32
	Cold sweat	2	0.66
	Eczema	1	0.33
	Rash macular	1	0.33
	Rash maculo-papular	1	0.33
	Skin disorder	1	0.33
	Toxic skin eruption	1	0.33
General disorders and administration site conditions		74	24.50
	Pyrexia	47	15.56
	Chills	27	8.94
	Chest discomfort	5	1.66
	Oedema	4	1.32
	Chest pain	2	0.66
	Fatigue	2	0.66
	Feeling hot	2	0.66
	Face oedema	1	0.33
	Feeling abnormal	1	0.33
	Feeling cold	1	0.33
	Malaise	1	0.33
	Oedema mucosal	1	0.33
	Oedema peripheral	1	0.33
	Pain	1	0.33
	Non-cardiac chest pain	1	0.33
Investigations		51	16.89
	Neutrophil count decreased	19	6.29
	White blood cell count decreased	14	4.64
	Blood pressure decreased	10	3.31
	Platelet count decreased	8	2.65
	Oxygen saturation decreased	7	2.32

SOC	PT	Number of patients	Proportion (%)
	Alanine aminotransferase increased	2	0.66
	Blood pressure increased	2	0.66
	Gamma-glutamyltransferase increased	2	0.66
	Weight increased	2	0.66
	Aspartate aminotransferase increased	1	0.33
	Blood creatinine increased	1	0.33
	C-reactive protein increased	1	0.33
	Haemoglobin decreased	1	0.33
	Lymphocyte count decreased	1	0.33
Respiratory, thoracic and mediastinal disorders		45	14.90
	Dyspnoea	18	5.96
	Cough	8	2.65
	Oropharyngeal discomfort	7	2.32
	Hypoxia	4	1.32
	Throat irritation	4	1.32
	Laryngeal discomfort	3	0.99
	Nasal congestion	2	0.66
	Pharyngeal oedema	2	0.66
	Productive cough	2	0.66
	Sneezing	2	0.66
	Acute respiratory distress syndrome	1	0.33
	Dysphonia	1	0.33
	Hiccups	1	0.33
	Laryngeal oedema	1	0.33
	Oropharyngeal swelling	1	0.33
	Pleural effusion	1	0.33
	Respiratory failure	1	0.33
	Rhinorrhoea	1	0.33
	Wheezing	1	0.33
	Upper respiratory tract inflammation	1	0.33
	Larynx irritation	1	0.33
	Oropharyngeal pain	1	0.33
Infections and infestations		31	10.26
	Pneumonia	9	2.98
	Herpes zoster	5	1.66
	Infection	3	0.99
	Sepsis	2	0.66
	Urinary tract infection	2	0.66
	Bronchitis	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Cellulitis	1	0.33
	Hepatitis B	1	0.33
	Influenza	1	0.33
	Nasopharyngitis	1	0.33
	Oral candidiasis	1	0.33
	Otitis media	1	0.33
	Periodontitis	1	0.33
	Progressive multifocal leukoencephalopathy	1	0.33
	Pyelonephritis	1	0.33
	Subcutaneous abscess	1	0.33
	Hepatitis B reactivation	1	0.33
	Oral herpes	1	0.33
	Candida infection	1	0.33
Gastrointestinal disorders		22	7.28
	Nausea	9	2.98
	Vomiting	5	1.66
	Abdominal discomfort	2	0.66
	Diarrhoea	2	0.66
	Oral discomfort	2	0.66
	Hypoaesthesia oral	2	0.66
	Abdominal pain lower	1	0.33
	Constipation	1	0.33
	Dry mouth	1	0.33
	Enterocolitis	1	0.33
	Rectal haemorrhage	1	0.33
Blood and lymphatic system disorders		20	6.62
	Anaemia	8	2.65
	Febrile neutropenia	4	1.32
	Disseminated intravascular coagulation	2	0.66
	Neutropenia	2	0.66
	Thrombocytopenia	2	0.66
	Hematotoxicity	2	0.66
	Lymph node pain	1	0.33
	Lymphadenopathy	1	0.33
Nervous system disorders		15	4.97
	Headache	4	1.32
	Head discomfort	2	0.66
	Hypoaesthesia	2	0.66

SOC	PT	Number of patients	Proportion (%)
	Neuropathy peripheral	2	0.66
	Peripheral sensory neuropathy	2	0.66
	Dizziness	1	0.33
	Haemorrhagic cerebral infarction	1	0.33
	Somnolence	1	0.33
	Syncope	1	0.33
	Tremor	1	0.33
	Facial nerve disorder	1	0.33
Vascular disorders		10	3.31
	Flushing	5	1.66
	Hypotension	4	1.32
	Hot flush	2	0.66
Cardiac disorders		8	2.65
	Arrhythmia	2	0.66
	Bradycardia	2	0.66
	Atrioventricular block second degree	1	0.33
	Cardiac failure	1	0.33
	Cardiac failure chronic	1	0.33
	Myocarditis	1	0.33
Metabolism and nutrition disorders		7	2.32
	Tumour lysis syndrome	5	1.66
	Hyperkalaemia	1	0.33
	Hyperphosphataemia	1	0.33
	Hyperuricaemia	1	0.33
Eye disorders		5	1.66
	Eyelid oedema	4	1.32
	Conjunctival hyperaemia	1	0.33
Hepatobiliary disorders		5	1.66
	Hepatic function abnormal	3	0.99
	Cholangitis	1	0.33
	Cholecystitis acute	1	0.33
	Liver disorder	1	0.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		4	1.32
	Chronic lymphocytic leukemia	4	1.32
Musculoskeletal and connective tissue disorders		4	1.32
	Back pain	2	0.66
	Arthralgia	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Neck pain	1	0.33
	Limb discomfort	1	0.33
Immune system disorders		3	0.99
	Anaphylactoid reaction	2	0.66
	Hypersensitivity	1	0.33
Renal and urinary disorders		2	0.66
	Renal impairment	2	0.66
Ear and labyrinth disorders		1	0.33
	Deafness	1	0.33
	Ear discomfort	1	0.33
Reproductive system and breast disorders		1	0.33
	Menopausal symptoms	1	0.33

Source:Table 12_02

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-8 Occurrence of adverse drug reactions by number of doses (safety analysis population)

Number of patients (%)

Type of adverse drug reaction SOC PT	1 dose	2 doses	≥3 to ≤4 doses	≥5 to ≤6 doses	≥7 to ≤8 doses	≥9 to ≤10 doses	≥11 to ≤12 doses	≥13 doses	After the completion of Arzerra treatment	Unknown or not entered	Total
Infections and infestations	3 (1.00)	3 (1.05)	2 (0.74)	5 (2.06)	6 (2.68)	2 (1.09)	1 (0.67)	0 (0.00)	13 (4.33)	1 (50.00)	36 (11.92)
Bronchitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.67)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Cellulitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Hepatitis B	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Herpes zoster	0 (0.00)	1 (0.35)	1 (0.37)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.67)	0 (0.00)	5 (1.66)
Infection	2 (0.67)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	3 (0.99)
Influenza	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Nasopharyngitis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.41)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.66)
Oral candidiasis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Otitis media	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Periodontitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Pneumonia	1 (0.33)	1 (0.35)	0 (0.00)	2 (0.82)	1 (0.45)	1 (0.55)	0 (0.00)	0 (0.00)	3 (1.00)	1 (50.00)	10 (3.31)
Progressive multifocal leukoencephalopathy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Pyelonephritis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Sepsis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	2 (0.66)
Subcutaneous abscess	0 (0.00)	0 (0.00)	1 (0.37)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Urinary tract infection	0 (0.00)	1 (0.35)	0 (0.00)	1 (0.41)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.66)
Hepatitis B reactivation	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.41)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Oral herpes	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.55)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Candida infection	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.33)	0	(0.00)	4	(1.32)
Chronic lymphocytic leukemia	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.33)	0	(0.00)	4	(1.32)
Blood and lymphatic system disorders	8	(2.67)	1	(0.35)	3	(1.11)	1	(0.41)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	6	(2.00)	0	(0.00)	20	(6.62)
Anaemia	2	(0.67)	1	(0.35)	2	(0.74)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	8	(2.65)
Disseminated intravascular coagulation	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	2	(0.66)
Febrile neutropenia	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	4	(1.32)
Lymph node pain	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Lymphadenopathy	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Neutropenia	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	2	(0.66)
Thrombocytopenia	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hematotoxicity	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Immune system disorders	1	(0.33)	2	(0.70)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Anaphylactoid reaction	1	(0.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hypersensitivity	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	4	(1.33)	2	(0.70)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	8	(2.65)
Hyperkalaemia	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Hyperphosphataemia	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Hyperuricaemia	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Tumour lysis syndrome	4	(1.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	6	(1.99)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Nervous system disorders	8	(2.67)	2	(0.70)	2	(0.74)	2	(0.82)	1	(0.45)	1	(0.55)	1	(0.67)	0	(0.00)	1	(0.33)	1	(50.00)	19	(6.29)
Dizziness	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Haemorrhagic cerebral infarction	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Head discomfort	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Headache	4	(1.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	6	(1.99)
Hypoaesthesia	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(50.00)	2	(0.66)
Neuropathy peripheral	1	(0.33)	0	(0.00)	0	(0.00)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Peripheral sensory neuropathy	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Somnolence	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Syncope	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Tremor	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Facial nerve disorder	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Eye disorders	3	(1.00)	1	(0.35)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	6	(1.99)
Eyelid oedema	3	(1.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	5	(1.66)
Conjunctival hyperaemia	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Deafness	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Ear discomfort	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Cardiac disorders	4	(1.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	2	(0.67)	0	(0.00)	8	(2.65)
Arrhythmia	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Bradycardia	2	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Cardiac failure	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)

Type of adverse drug reaction SOC PT	1 dose	2 doses	≥3 to ≤4 doses	≥5 to ≤6 doses	≥7 to ≤8 doses	≥9 to ≤10 doses	≥11 to ≤12 doses	≥13 doses	After the completion of Arzerra treatment	Unknown or not entered	Total
Cardiac failure chronic	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Myocarditis	1 (0.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Vascular disorders	4 (1.33)	5 (1.75)	0 (0.00)	1 (0.41)	0 (0.00)	1 (0.55)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	12 (3.97)
Flushing	2 (0.67)	2 (0.70)	0 (0.00)	1 (0.41)	0 (0.00)	1 (0.55)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (1.99)
Hypotension	1 (0.33)	3 (1.05)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (1.32)
Hot flush	1 (0.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	2 (0.66)
Respiratory, thoracic and mediastinal disorders	28 (9.33)	23 (8.04)	6 (2.22)	2 (0.82)	3 (1.34)	6 (3.28)	3 (2.00)	0 (0.00)	4 (1.33)	0 (0.00)	75 (24.83)
Acute respiratory distress syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Cough	4 (1.33)	5 (1.75)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	10 (3.31)
Dysphonia	0 (0.00)	0 (0.00)	1 (0.37)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Dyspnoea	12 (4.00)	7 (2.45)	1 (0.37)	1 (0.41)	0 (0.00)	4 (2.19)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	26 (8.61)
Hiccups	0 (0.00)	0 (0.00)	1 (0.37)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Hypoxia	4 (1.33)	3 (1.05)	1 (0.37)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	8 (2.65)
Laryngeal oedema	1 (0.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Nasal congestion	2 (0.67)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.99)
Oropharyngeal swelling	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.67)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Pharyngeal oedema	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.66)
Pleural effusion	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Productive cough	0 (0.00)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.67)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.66)
Respiratory failure	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)	0 (0.00)	1 (0.33)
Rhinorrhoea	0 (0.00)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Sneezing	1 (0.33)	1 (0.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.66)
Throat irritation	0 (0.00)	2 (0.70)	3 (1.11)	2 (0.82)	2 (0.89)	2 (1.09)	2 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	13 (4.30)
Wheezing	1 (0.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)
Upper respiratory tract inflammation	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.33)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Laryngeal discomfort	2	(0.67)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Larynx irritation	1	(0.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Oropharyngeal discomfort	4	(1.33)	4	(1.40)	0	(0.00)	0	(0.00)	0	(0.00)	2	(1.09)	2	(1.33)	0	(0.00)	0	(0.00)	0	(0.00)	12	(3.97)
Oropharyngeal pain	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	10	(3.33)	8	(2.80)	2	(0.74)	0	(0.00)	1	(0.45)	1	(0.55)	1	(0.67)	0	(0.00)	3	(1.00)	1	(50.00)	27	(8.94)
Abdominal discomfort	0	(0.00)	1	(0.35)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Abdominal pain lower	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Constipation	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Diarrhoea	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	2	(0.66)
Dry mouth	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Nausea	5	(1.67)	5	(1.75)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	10	(3.31)
Oral discomfort	1	(0.33)	1	(0.35)	0	(0.00)	0	(0.00)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Rectal haemorrhage	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Vomiting	3	(1.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	5	(1.66)
Hypoaesthesia oral	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(50.00)	2	(0.66)
Hepatobiliary disorders	2	(0.67)	0	(0.00)	1	(0.37)	0	(0.00)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	5	(1.66)
Cholangitis	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Cholecystitis acute	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Hepatic function abnormal	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Liver disorder	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	93	(31.00)	13	(4.55)	4	(1.48)	3	(1.23)	0	(0.00)	3	(1.64)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	117	(8.74)
Cold sweat	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Eczema	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Erythema	6	(2.00)	4	(1.40)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	12	(3.97)
Hyperhidrosis	6	(2.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	7	(2.32)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Pruritus	9	(3.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	10	(3.31)
Rash	46	(15.33)	5	(1.75)	1	(0.37)	2	(0.82)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	54	(17.88)
Rash macular	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Rash maculo-papular	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Rash pruritic	3	(1.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Skin disorder	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Urticaria	27	(9.00)	2	(0.70)	0	(0.00)	0	(0.00)	0	(0.00)	3	(1.64)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	32	(10.60)
Toxic skin eruption	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(0.33)	2	(0.70)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Arthralgia	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Back pain	1	(0.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Neck pain	0	(0.00)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Limb discomfort	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Renal and urinary disorders	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	2	(0.66)
Renal impairment	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Menopausal symptoms	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	59	(19.67)	24	(8.39)	5	(1.85)	3	(1.23)	1	(0.45)	7	(3.83)	1	(0.67)	0	(0.00)	2	(0.67)	0	(0.00)	102	(33.77)
Chest discomfort	3	(1.00)	2	(0.70)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	5	(1.66)
Chest pain	2	(0.67)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Chills	24	(8.00)	3	(1.05)	3	(1.11)	0	(0.00)	0	(0.00)	4	(2.19)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	35	(11.59)
Face oedema	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	1	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Fatigue	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Feeling abnormal	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Feeling cold	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Feeling hot	0	(0.00)	2	(0.70)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Malaise	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oedema	3	(1.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Oedema mucosal	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oedema peripheral	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Pain	1	(0.33)	1	(0.35)	1	(0.37)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Pyrexia	39	(13.00)	12	(4.20)	2	(0.74)	2	(0.82)	1	(0.45)	2	(1.09)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	59	(19.54)
Non-cardiac chest pain	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Investigations	26	(8.67)	9	(3.15)	5	(1.85)	6	(2.47)	4	(1.79)	6	(3.28)	0	(0.00)	0	(0.00)	9	(3.00)	1	(50.00)	66	(21.85)
Alanine aminotransferase increased	2	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Blood creatinine increased	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Blood pressure decreased	8	(2.67)	2	(0.70)	0	(0.00)	1	(0.41)	1	(0.45)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	12	(3.97)
Blood pressure increased	2	(0.67)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
C-reactive protein increased	1	(0.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Gamma-glutamyltransferase increased	1	(0.33)	0	(0.00)	1	(0.37)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Haemoglobin decreased	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)	0	(0.00)	1	(0.33)
Lymphocyte count decreased	0	(0.00)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)

Type of adverse drug reaction SOC PT	1 dose		2 doses		≥3 to ≤4 doses		≥5 to ≤6 doses		≥7 to ≤8 doses		≥9 to ≤10 doses		≥11 to ≤12 doses		≥13 doses		After the completion of Arzerra treatment		Unknown or not entered		Total	
Neutrophil count decreased	5	(1.67)	3	(1.05)	3	(1.11)	4	(1.65)	3	(1.34)	2	(1.09)	0	(0.00)	0	(0.00)	5	(1.67)	1	(50.00)	26	(8.61)
Oxygen saturation decreased	5	(1.67)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	7	(2.32)
Platelet count decreased	4	(1.33)	0	(0.00)	1	(0.37)	1	(0.41)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	8	(2.65)
Weight increased	1	(0.33)	1	(0.35)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
White blood cell count decreased	2	(0.67)	2	(0.70)	4	(1.48)	1	(0.41)	0	(0.00)	3	(1.64)	0	(0.00)	0	(0.00)	2	(0.67)	0	(0.00)	14	(4.64)
Number of patients with events	163	(79.90)	68	(33.33)	26	(12.75)	18	(8.82)	16	(7.84)	21	(10.29)	7	(3.43)	0	(0.00)	32	(15.69)	2	(0.98)	204	
Cumulative number of patients with events	163	(79.90)	175	(85.78)	179	(87.75)	185	(90.69)	187	(91.67)	191	(93.63)	191	(93.63)	191	(93.63)	202	(99.02)	204	(100.00)	204	
Cumulative number of patients	300		286		270		243		224		183		150		2		300		2		302	

Source:Table 04

* The denominator for calculation of (%) of SOC and PT rows was the cumulative number of patients in each period.

* The sum of adverse drug reactions descr bed in the [Adverse events] page of the case report form and adverse drug reactions described in the infusion reaction column of the [Status at each dose] page

10.5.4 Serious adverse drug reactions

The occurrence of serious adverse drug reactions in the safety analysis set is shown in Table 10-9.

Among the 302 patients in the safety analysis set, the incidence of serious adverse drug reactions was 13.91% (42 patients).

Common serious adverse drug reactions (≥1.00%) were pneumonia in 1.99% (6 patients), neutrophil count decreased in 1.66% (5 patients), and white blood cell count decreased in 1.32% (4 patients). The outcomes of pneumonia were resolved or resolving in 3 patients and fatal in 3 patients. The outcomes of neutrophil count decreased were resolved or resolving in 4 patients and not resolved in 1 patient. The outcomes of white blood cell count decreased were resolving in 1 patient and not resolved in 3 patients (analysis results, Listing 03_01).

Table 10-9 Occurrence of serious adverse drug reactions (by SOC and PT) (safety analysis set)

SOC	PT	Number of patients	Proportion (%)
Total		42	13.91
Infections and infestations		19	6.29
	Pneumonia	6	1.99
	Herpes zoster	3	0.99
	Infection	2	0.66
	Sepsis	2	0.66
	Bronchitis	1	0.33
	Hepatitis B	1	0.33
	Influenza	1	0.33
	Progressive multifocal leukoencephalopathy	1	0.33
	Pyelonephritis	1	0.33
	Urinary tract infection	1	0.33
	Oral herpes	1	0.33
	Candida infection	1	0.33
Investigations		10	3.31
	Neutrophil count decreased	5	1.66
	White blood cell count decreased	4	1.32
	Blood creatinine increased	1	0.33
	Oxygen saturation decreased	1	0.33
Respiratory, thoracic and mediastinal disorders		5	1.66
	Dyspnoea	2	0.66
	Acute respiratory distress syndrome	1	0.33

SOC	PT	Number of patients	Proportion (%)
	Laryngeal oedema	1	0.33
	Pleural effusion	1	0.33
	Respiratory failure	1	0.33
Blood and lymphatic system disorders		4	1.32
	Febrile neutropenia	2	0.66
	Disseminated intravascular coagulation	1	0.33
	Hematotoxicity	1	0.33
Metabolism and nutrition disorders		3	0.99
	Tumour lysis syndrome	2	0.66
	Hyperkalaemia	1	0.33
	Hyperphosphataemia	1	0.33
Cardiac disorders		3	0.99
	Arrhythmia	1	0.33
	Cardiac failure chronic	1	0.33
	Myocarditis	1	0.33
Hepatobiliary disorders		3	0.99
	Hepatic function abnormal	2	0.66
	Cholangitis	1	0.33
	Cholecystitis acute	1	0.33
Skin and subcutaneous tissue disorders		3	0.99
	Rash	2	0.66
	Urticaria	1	0.33
General disorders and administration site conditions		3	0.99
	Pyrexia	2	0.66
	Chills	1	0.33
	Oedema mucosal	1	0.33
Nervous system disorders		2	0.66
	Haemorrhagic cerebral infarction	1	0.33
	Syncope	1	0.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1	0.33
	Chronic lymphocytic leukemia	1	0.33

Source:Table 12_04

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.5 Adverse events leading to treatment discontinuation

The occurrence of adverse events leading to treatment discontinuation is shown in Table 10-10.

Among the 302 patients in the safety analysis set, the incidence of adverse events leading to treatment discontinuation was 24.83% (75 patients). Common adverse events leading to treatment discontinuation (≥1.00%) were chronic lymphocytic leukaemia (worsening) in 9.93% (30 patients), neutrophil count decreased in 1.99% (6 patients), pneumonia in 1.66% (5 patients), and vomiting in 1.32% (4 patients).

Table 10-10 Occurrence of adverse events leading to treatment discontinuation (by PT) (safety analysis set)

Adverse event term (PT)	Number of patients (%)	
Total	75	(24.83)
Chronic lymphocytic leukemia	30	(9.93)
Neutrophil count decreased	6	(1.99)
Pneumonia	5	(1.66)
Vomiting	4	(1.32)
Pyrexia	3	(0.99)
Rash	3	(0.99)
Sepsis	3	(0.99)
Anaemia	2	(0.66)
Blood lactate dehydrogenase increased	2	(0.66)
Blood pressure decreased	2	(0.66)
Hepatic function abnormal	2	(0.66)
Herpes zoster	2	(0.66)
Jaundice	2	(0.66)
Pleural effusion	2	(0.66)
Respiratory failure	2	(0.66)
Subdural haematoma	2	(0.66)
Renal impairment	2	(0.66)
Acute respiratory distress syndrome	1	(0.33)
Arrhythmia	1	(0.33)
Asphyxia	1	(0.33)
Aspiration	1	(0.33)
Atrial fibrillation	1	(0.33)
Back pain	1	(0.33)
Blood creatinine increased	1	(0.33)
Bronchiectasis	1	(0.33)
Bronchiolitis	1	(0.33)
Cardiac failure chronic	1	(0.33)
Cellulitis	1	(0.33)
Cerebral infarction	1	(0.33)
Cholangitis	1	(0.33)

Adverse event term (PT)	Number of patients (%)	
Cholecystitis acute	1	(0.33)
Cough	1	(0.33)
Death	1	(0.33)
Diarrhoea	1	(0.33)
Disseminated intravascular coagulation	1	(0.33)
Dyspnoea	1	(0.33)
Face oedema	1	(0.33)
Fall	1	(0.33)
Fatigue	1	(0.33)
Febrile neutropenia	1	(0.33)
Gastrointestinal haemorrhage	1	(0.33)
Haemoglobin decreased	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.33)
Hepatic failure	1	(0.33)
Hepatitis B	1	(0.33)
Hyperhidrosis	1	(0.33)
Hyperkalaemia	1	(0.33)
Hyperphosphataemia	1	(0.33)
Hypoaesthesia	1	(0.33)
Infection	1	(0.33)
Influenza	1	(0.33)
Liver disorder	1	(0.33)
Lymphocyte count increased	1	(0.33)
Nausea	1	(0.33)
Neutropenia	1	(0.33)
Oxygen saturation decreased	1	(0.33)
Platelet count decreased	1	(0.33)
Progressive multifocal leukoencephalopathy	1	(0.33)
Pyelonephritis	1	(0.33)
Syncope	1	(0.33)
Systemic lupus erythematosus	1	(0.33)
Urticaria	1	(0.33)
White blood cell count decreased	1	(0.33)
Haemorrhage	1	(0.33)
Richter's syndrome	1	(0.33)
Decreased appetite	1	(0.33)
Large intestinal obstruction	1	(0.33)
Oral herpes	1	(0.33)

Source:Table 12_06

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

(Tabulated by MedDRA Ver. 24.0)

10.5.6 Adverse drug reactions leading to treatment discontinuation

The occurrence of adverse drug reactions leading to treatment discontinuation is shown in Table 10-11.

Among the 302 patients in the safety analysis set, the incidence of adverse drug reactions leading to treatment discontinuation was 11.59% (35 patients). Common adverse drug reactions leading to treatment discontinuation (≥1.00%) were neutrophil count decreased in 1.66% (5 patients) and chronic lymphocytic leukaemia (worsening) in 1.32% (4 patients).

Table 10-11 Occurrence of adverse drug reactions leading to treatment discontinuation (by PT) (safety analysis set)

Adverse drug reaction term (PT)	Number of patients (%)	
Total	35	(11.59)
Neutrophil count decreased	5	(1.66)
Chronic lymphocytic leukemia	4	(1.32)
Pneumonia	3	(0.99)
Rash	3	(0.99)
Vomiting	3	(0.99)
Pyrexia	2	(0.66)
Acute respiratory distress syndrome	1	(0.33)
Anaemia	1	(0.33)
Arrhythmia	1	(0.33)
Blood creatinine increased	1	(0.33)
Cardiac failure chronic	1	(0.33)
Cellulitis	1	(0.33)
Cholangitis	1	(0.33)
Cholecystitis acute	1	(0.33)
Cough	1	(0.33)
Diarrhoea	1	(0.33)
Disseminated intravascular coagulation	1	(0.33)
Dyspnoea	1	(0.33)
Face oedema	1	(0.33)
Fatigue	1	(0.33)
Febrile neutropenia	1	(0.33)
Haemoglobin decreased	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.33)
Hepatic function abnormal	1	(0.33)
Hepatitis B	1	(0.33)
Herpes zoster	1	(0.33)
Hyperhidrosis	1	(0.33)
Hyperkalaemia	1	(0.33)
Hyperphosphataemia	1	(0.33)
Infection	1	(0.33)
Influenza	1	(0.33)

Adverse drug reaction term (PT)	Number of patients (%)	
Nausea	1	(0.33)
Neutropenia	1	(0.33)
Oxygen saturation decreased	1	(0.33)
Platelet count decreased	1	(0.33)
Pleural effusion	1	(0.33)
Progressive multifocal leukoencephalopathy	1	(0.33)
Pyelonephritis	1	(0.33)
Respiratory failure	1	(0.33)
Sepsis	1	(0.33)
Syncope	1	(0.33)
Urticaria	1	(0.33)
White blood cell count decreased	1	(0.33)
Renal impairment	1	(0.33)
Oral herpes	1	(0.33)

Source:Table 12_06_02

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

(Tabulated by MedDRA Ver. 24.0)

10.5.7 Deaths

A list of deaths is provided in Table 10-12.

Among the 302 patients in the safety analysis set, 32 patients had adverse events leading to death during the observation period. Among the reported adverse events, deaths due to worsening of primary disease (chronic lymphocytic leukemia) were reported in 18 patients, and adverse events leading to death other than worsening of primary disease were pneumonia in 6 patients, and general physical health deterioration, hepatic function abnormal, hyperbilirubinaemia, fall, subdural haematoma, blood creatinine increased, hyperphosphataemia, arrhythmia, hyperkalaemia, pyelonephritis, hepatic failure, liver disorder, death, blood pressure decreased, sepsis, acute respiratory distress syndrome, haemorrhage, asphyxia, aspiration, and large intestinal obstruction in 1 patient each. Of these, the following events occurred in the same patient: pneumonia and general physical health deterioration; hepatic function abnormal and hyperbilirubinaemia; fall and subdural haematoma; blood creatinine increased, hyperphosphataemia, arrhythmia, and hyperkalaemia; hepatic failure and liver disorder; acute respiratory distress syndrome and pneumonia; and asphyxia and aspiration.

Six of the deaths were due to adverse events for which a causal relationship with Arzerra could not be ruled out. These events included pneumonia in 3 patients and blood creatinine increased, hyperphosphataemia, arrhythmia, hyperkalaemia, pyelonephritis, sepsis, and acute respiratory distress syndrome in 1 patient each.

Table 10-12 List of deaths (safety analysis set)

No	Gender	Age	Verbatim term	PT	Number of days to onset	Outcome	Number of days to outcome	Relationship with Arzerra
1	[redacted]			Chronic lymphocytic leukemia	27	Death	1	Not related
2				Chronic lymphocytic leukemia	20	Death	1	Not related
3				Chronic lymphocytic leukemia	19	Death	9	Not related
4				Pneumonia	113	Death	53	Not related
				General physical health deterioration	115	Death	51	Not related
5				Chronic lymphocytic leukemia	75	Death	64	Not related
6				Pneumonia	10	Death	12	Not related
7				Hepatic function abnormal	19	Death	9	Not related
				Hyperbilirubinaemia	26	Death	2	Not related
8				Chronic lymphocytic leukemia	100	Death	41	Not related
9				Fall	83	Death	1	Not related
				Subdural haematoma	83	Death	1	Not related
10				Chronic lymphocytic leukemia	1	Death	7	Not related
11				Blood creatinine increased	180	Death	9	Related
				Hyperphosphataemia	180	Death	9	Related
				Arrhythmia	188	Death	1	Related
				Chronic lymphocytic leukemia	188	Death	1	Not related
				Hyperkalaemia	188	Death	1	Related
12				Pyelonephritis	95	Death	68	
13				Pneumonia	35	Death	13	Related
14				Hepatic failure	23	Death	23	Not related
				Liver disorder	23	Death	23	Not related
15				Death	36	Death	31	Not related
16				Chronic lymphocytic leukemia	11	Death	8	Not related
17				Chronic lymphocytic leukemia	11	Death	1	Not related
18				Chronic lymphocytic leukemia	15	Death	51	Not related

No	Gender	Age	Verbatim term	PT	Number of days to onset	Outcome	Number of days to outcome	Relationship with Arzerra
19	[redacted]			Blood pressure decreased	5	Death	3	Not related
				Chronic lymphocytic leukemia	7	Death	1	Not related
20				Sepsis	54	Death	2	Related
21				Acute respiratory distress syndrome	3	Death	6	Related
				Pneumonia	3	Death	6	Related
22				Chronic lymphocytic leukemia	200	Death	48	Not related
23				Pneumonia	58	Death	9	Related
24				Chronic lymphocytic leukemia	141	Death	1	Not related
25				Haemorrhage	15	Death	25	Not related
26				Asphyxia	2	Death	1	Not related
				Aspiration	2	Death	1	Not related
27				Pneumonia	12	Death	7	Not related
28				Chronic lymphocytic leukemia	95	Death	1	Not related
29				Chronic lymphocytic leukemia	17	Death	40	Not related
30				Chronic lymphocytic leukemia	23	Death	53	Not related
31				Chronic lymphocytic leukemia	32	Death	1	Not related
32				Chronic lymphocytic leukemia	1	Death	21	Not related
				Large intestinal obstruction	11	Death	11	Not related

Source:Listing 03_05

* The output is the sum of events described in the [Adverse events] page of the case report form and events described in the Infusion Reaction column of the [Status at each dose] page.

10.5.8 Priority study items

10.5.8.1 Occurrence of infusion reactions

The occurrence of infusion reactions is shown in Table 10-13.

Among the 302 patients in the safety analysis set, the incidence of adverse events related to infusion reactions was 50.99% (154 patients). A causal relationship with Arzerra could not be ruled out for all events. Common infusion reactions (≥5.00%) were rash in 14.90% (45 patients), pyrexia in 13.91% (42 patients), chills in 8.94% (27 patients), urticaria in 8.61% (26 patients), and dyspnoea in 5.63% (17 patients). All these events occurred after the first or second dose in many of the patients. The outcomes were not resolved for oral discomfort, feeling abnormal, and somnolence in 1 patient each, and resolved or resolving for the other events except for pyrexia and bradycardia in 1 patient each, whose outcomes were unknown (analysis results, Table 06). Grade ≥3 infusion reactions were rash and urticaria in 1.99% (6 patients) each, dyspnoea in 1.32% (4 patients), pyrexia, hypotension, and hypoxia in 0.66% (2 patients) each, and chills, cough, oxygen saturation decreased, hyperhidrosis, blood pressure increased, larynx irritation, feeling cold, oedema mucosal, and syncope in 0.33% (1 patient) each (analysis results, Table 06).

The status at each dose is shown in Table 10-14.

Among the 302 patients in the safety analysis set, premedication to alleviate infusion reactions was performed in at least 99% of the patients at all doses, showing that premedication was performed at most doses.

The infusion rate of Arzerra was "as specified in precautions concerning dosage and administration" in 64.24% (194/302 patients) at the first dose, 82.99% (239/288 patients) at the second dose, and ≥93% at the third and subsequent doses. The proportion of patients who needed "deceleration or readministration after interruption" was 34.11% (103/302 patients) at the first dose and 16.32% (47/288 patients) at the second dose. Many patients were treated as specified in the package insert, including those who required deceleration or readministration after interruption. The most frequently reported events of rash, pyrexia, chills, urticaria, and dyspnoea are detailed below.

Table 10-13 Occurrence of infusion reactions (by PT) (safety analysis set)

	Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion
Number of patients in the safety analysis set	302	100.00	302	100.00	288	100.00	272	100.00	263	100.00	245	100.00	232	100.00	225	100.00	218	100.00	185	100.00	166	100.00	152	100.00	144	100.00
Rash	45	14.90	44	14.57	5	1.74	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pyrexia	42	13.91	38	12.58	11	3.82	1	0.37	1	0.38	0	0.00	1	0.43	1	0.44	0	0.00	1	0.54	0	0.00	0	0.00	0	0.00
Chills	27	8.94	23	7.62	3	1.04	2	0.74	2	0.76	0	0.00	0	0.00	0	0.00	0	0.00	2	1.08	2	1.20	0	0.00	0	0.00
Urticaria	26	8.61	25	8.28	2	0.69	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.54	2	1.20	0	0.00	0	0.00
Dyspnoea	17	5.63	12	3.97	7	2.43	1	0.37	0	0.00	1	0.41	0	0.00	0	0.00	0	0.00	1	0.54	3	1.81	0	0.00	0	0.00
Pruritus	9	2.98	8	2.65	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Erythema	8	2.65	4	1.32	4	1.39	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.66	0	0.00
Blood pressure decreased	8	2.65	6	1.99	1	0.35	0	0.00	0	0.00	0	0.00	1	0.43	1	0.44	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cough	7	2.32	4	1.32	4	1.39	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nausea	7	2.32	4	1.32	3	1.04	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxygen saturation decreased	7	2.32	5	1.66	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.54	0	0.00	0	0.00	0	0.00
Oropharyngeal discomfort	6	1.99	4	1.32	3	1.04	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.54	1	0.60	1	0.66	1	0.69
Hyperhidrosis	6	1.99	5	1.66	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.60	0	0.00	0	0.00
Chest discomfort	5	1.66	3	0.99	2	0.69	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Flushing	4	1.32	1	0.33	2	0.69	0	0.00	0	0.00	0	0.00	1	0.43	0	0.00	0	0.00	0	0.00	1	0.60	0	0.00	0	0.00
Headache	4	1.32	3	0.99	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.60	0	0.00	0	0.00

	Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion
Eyelid oedema	4	1.32	3	0.99	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.66	0	0.00
Hypotension	4	1.32	1	0.33	3	1.04	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rash pruritic	4	1.32	3	0.99	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Throat irritation	3	0.99	0	0.00	2	0.69	1	0.37	1	0.38	1	0.41	1	0.43	1	0.44	1	0.46	1	0.54	1	0.60	1	0.66	1	0.69
Hypoxia	3	0.99	3	0.99	3	1.04	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Vomiting	3	0.99	2	0.66	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Laryngeal discomfort	3	0.99	2	0.66	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oral discomfort	2	0.66	1	0.33	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	1	0.44	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Abdominal discomfort	2	0.66	0	0.00	1	0.35	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Anaphylactoid reaction	2	0.66	1	0.33	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blood pressure increased	2	0.66	2	0.66	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Bradycardia	2	0.66	2	0.66	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cold sweat	2	0.66	1	0.33	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Feeling hot	2	0.66	0	0.00	2	0.69	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Head discomfort	2	0.66	1	0.33	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pharyngeal oedema	2	0.66	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	1.08	0	0.00	0	0.00	0	0.00
Productive cough	2	0.66	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.66	0	0.00
Sneezing	2	0.66	1	0.33	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hot flush	2	0.66	1	0.33	0	0.00	0	0.00	1	0.38	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pain	1	0.33	1	0.33	1	0.35	0	0.00	1	0.38	0	0.00	1	0.43	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Chest pain	1	0.33	1	0.33	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

	Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion
Face oedema	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.60	1	0.66	0	0.00
Larynx irritation	1	0.33	1	0.33	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Abdominal pain lower	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arrhythmia	1	0.33	0	0.00	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Arthralgia	1	0.33	0	0.00	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Back pain	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dry mouth	1	0.33	0	0.00	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dysphonia	1	0.33	0	0.00	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eczema	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatigue	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Feeling abnormal	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Feeling cold	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypersensitivity	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Laryngeal oedema	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Malaise	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Menopausal symptoms	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Nasal congestion	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neck pain	1	0.33	0	0.00	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oedema	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oedema mucosal	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oropharyngeal swelling	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.66	0	0.00

	Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion	Number of patients	Proportion
Rash macular	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rhinorrhoea	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Somnolence	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Syncope	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tremor	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Wheezing	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Conjunctival hyperaemia	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hypoaesthesia oral	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Facial nerve disorder	1	0.33	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Non-cardiac chest pain	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oropharyngeal pain	1	0.33	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Source:Table 06

Table 10-14 Status at each dose (safety analysis population)

		Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
		Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)
Number of pa ients in the safety analysis set		302	100.00	302	100.00	288	100.00	272	100.00	263	100.00	245	100.00	232	100.00	225	100.00	218	100.00	185	100.00	166	100.00	152	100.00	144	100.00
Premedication	Yes	302	100.00	302	100.00	288	100.00	272	100.00	263	100.00	243	99.18	231	99.57	224	99.56	217	99.54	184	99.46	165	99.40	151	99.34	143	99.31
	No	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.82	1	0.43	1	0.44	1	0.46	1	0.54	1	0.60	1	0.66	1	0.69
Adrenocortical hormone preparation	Yes	295	97.68	294	97.35	279	96.88	247	90.81	233	88.59	212	86.53	201	86.64	190	84.44	181	83.03	156	84.32	139	83.73	129	84.87	121	84.03
	No	7	2.32	8	2.65	9	3.13	25	9.19	30	11.41	33	13.47	31	13.36	35	15.56	37	16.97	29	15.68	27	16.27	23	15.13	23	15.97
	Prednisolone	203	67.22	197	65.23	187	64.93	159	58.46	150	57.03	132	53.88	127	54.74	118	52.44	115	52.75	100	54.05	88	53.01	82	53.95	78	54.17
	Other medications	109	36.09	97	32.12	94	32.64	89	32.72	84	31.94	80	32.65	74	31.90	72	32.00	66	30.28	56	30.27	51	30.72	47	30.92	43	29.86
Antipyretic analgesic	Yes	294	97.35	292	96.69	278	96.53	264	97.06	254	96.58	235	95.92	222	95.69	216	96.00	209	95.87	179	96.76	161	96.99	147	96.71	139	96.53
	No	8	2.65	10	3.31	10	3.47	8	2.94	9	3.42	10	4.08	10	4.31	9	4.00	9	4.13	6	3.24	5	3.01	5	3.29	5	3.47
	Acetaminophen	238	78.81	232	76.82	223	77.43	211	77.57	204	77.57	189	77.14	177	76.29	172	76.44	165	75.69	140	75.68	126	75.90	114	75.00	108	75.00
	Other medications	66	21.85	60	19.87	55	19.10	53	19.49	50	19.01	46	18.78	45	19.40	44	19.56	44	20.18	39	21.08	35	21.08	33	21.71	31	21.53
Antihistamine	Yes	297	98.34	296	98.01	282	97.92	265	97.43	256	97.34	237	96.73	226	97.41	219	97.33	212	97.25	180	97.30	162	97.59	148	97.37	140	97.22
	No	5	1.66	6	1.99	6	2.08	7	2.57	7	2.66	8	3.27	6	2.59	6	2.67	6	2.75	5	2.70	4	2.41	4	2.63	4	2.78
Total dose of Arzerra	Mean	1794.1		302.9		1948.7		1964.7		1970.7		1982.0		1991.4		1995.6		1995.4		1983.9		1994.0		1988.0		1993.1	
	Median	2000.0		300.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0		2000.0	
	Maximum	2000		2000		2000		2000		2000		2000		2000		2000		2000		2000		2000		2000		2000	
	Minimum	30		60		75		300		300		1000		1000		1000		1000		30		1000		1000		1000	
Infusion rate of Arzerra	As specified in precautions concerning dosage and administration	288	95.36	194	64.24	239	82.99	256	94.12	252	95.82	234	95.51	222	95.69	216	96.00	212	97.25	175	94.59	156	93.98	145	95.39	138	95.83
	Deceleration or readministration after interruption	116	38.41	103	34.11	47	16.32	16	5.88	11	4.18	10	4.08	9	3.88	8	3.56	5	2.29	8	4.32	9	5.42	5	3.29	5	3.47
	Discontinua ion	8	2.65	5	1.66	2	0.69	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.54	0	0.00	1	0.66	0	0.00
	Unknown	1	0.33	0	0.00	0	0.00	0	0.00	0	0.00	1	0.41	1	0.43	1	0.44	1	0.46	1	0.54	1	0.60	1	0.66	1	0.69

		Overall		1st dose		2nd dose		3rd dose		4th dose		5th dose		6th dose		7th dose		8th dose		9th dose		10th dose		11th dose		12th dose	
		Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)	Number of patients	Proportion (%)
Number of pa ients in the safety analysis set		302	100.00	302	100.00	288	100.00	272	100.00	263	100.00	245	100.00	232	100.00	225	100.00	218	100.00	185	100.00	166	100.00	152	100.00	144	100.00
Infusion reaction	Related	154	50.99	143	47.35	54	18.75	9	3.31	4	1.52	2	0.82	4	1.72	3	1.33	1	0.46	6	3.24	8	4.82	4	2.63	2	1.39
	Infections	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Tumour lysis syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Hematotoxicity	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Intestinal obstruction	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Skin disorder	93	30.79	87	28.81	13	4.51	2	0.74	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.54	3	1.81	1	0.66	0	0.00
	Cardiac disorder	3	0.99	2	0.66	0	0.00	1	0.37	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Blood pressure decreased	13	4.30	8	2.65	4	1.39	0	0.00	0	0.00	0	0.00	1	0.43	1	0.44	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Hepatic dysfunction/jaundice	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Renal disorder	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	Interstitial lung disease	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Presence/absence of IR × presence/ absence of in-line filter	No × No	97	32.12	99	32.78	150	52.08	167	61.40	165	62.74	156	63.67	142	61.21	138	61.33	133	61.01	110	59.46	94	56.63	93	61.18	89	61.81
	No × Yes	61	20.20	60	19.87	84	29.17	96	35.29	94	35.74	87	35.51	86	37.07	84	37.33	84	38.53	69	37.30	64	38.55	55	36.18	53	36.81
	Yes × No	104	34.44	96	31.79	36	12.50	7	2.57	3	1.14	2	0.82	3	1.29	2	0.89	1	0.46	3	1.62	7	4.22	3	1.97	1	0.69
	Yes × Yes	50	16.56	47	15.56	18	6.25	2	0.74	1	0.38	0	0.00	1	0.43	1	0.44	0	0.00	3	1.62	1	0.60	1	0.66	1	0.69

Source:Table 08

* Multiple doses of premedication were allowed.

10.5.8.1.1 Rash

Amon the 302 patients in the safety analysis set, adverse events of rash were observed in 14.90% (45 patients). The outcomes were resolved in 41 patients and resolving in 4 patients. Grade ≥3 rash was reported in 1.99% (6 patients).

Rash occurred in 44 patients after the first dose and 5 patients after the second dose (including patients with multiple occurrences). Rash did not occur after the third to 12th doses. Rash tended to occur early in treatment.

10.5.8.1.2 Pyrexia

Among the 302 patients in the safety analysis set, adverse events of pyrexia were observed in 13.91% (42 patients). The outcomes were resolved in 39 patients and resolving in 2 patients. Grade ≥3 pyrexia was observed in 0.66% (2 patients).

Pyrexia occurred in 38 patients after the first dose, 11 patients after the second dose, and 1 patient each after the third, fourth, sixth, seventh, and ninth doses (including patients with multiple occurrences). Pyrexia tended to occur early in treatment in many patients.

10.5.8.1.3 Chills

Among the 302 patients in the safety analysis set, adverse events of chills were observed in 8.94% (27 patients). The outcomes were resolved in 25 patients and resolving in 2 patients. Grade ≥3 chills was observed in 0.33% (1 patient). Chills occurred in 23 patients after the first dose, 3 patients after the second dose, and 2 patients each after the third, fourth, ninth, and 10th doses (including patients with multiple occurrences). Chills tended to occur early in treatment in many patients.

10.5.8.1.4 Urticaria

Among the 302 patients in the safety analysis set, adverse events of urticaria were observed in 8.61% (26 patients). The outcomes were resolved in 22 patients and resolving in 4 patients. Grade ≥3 urticaria was observed in 1.99% (6 patients). Urticaria occurred in 25 patients after the first dose, 2 patients each after the second and 10th doses, and 1 patient after the ninth dose (including patients with multiple occurrences). Urticaria tended to occur early in treatment in many patients.

10.5.8.1.5 Dyspnoea

Among the 302 patients in the safety analysis set, adverse events of dyspnoea were observed in 5.63% (17 patients). The outcomes were resolved in 15 patients and resolving in 2 patients. Grade ≥3 dyspnoea was reported in 1.32% (4 patients). Dyspnoea occurred in 12 patients after the first dose, 7 patients after the second dose, 3 patients after the 10th dose, and 1 patient each after the third, fifth, and ninth doses (including patients with multiple occurrences). Dyspnoea tended to occur early in treatment in many patients.

10.5.8.2 Occurrence of infections

The occurrence of infections and their outcomes and grades are shown in Table 10-15 and Table 10-16, respectively.

Among the 302 patients in the safety analysis set, adverse events related to infections were observed in 17.55% (53 patients). Grade ≥3 infections were observed in 9.27% (28 patients). Common adverse events were pneumonia in 4.97% (15 patients), bronchitis and herpes zoster in 2.32% (7 patients) each, and sepsis in 1.66% (5 patients).

The mean total number of doses up to the time of onset (initial onset) was 5.4. The outcomes were resolved in 18 patients, resolving in 12 patients, not resolved in 11 patients, sequelae in 1 patient, and fatal in 10 patients. In 5 of the deaths, a causal relationship with Arzerra could not be ruled out.

As for the administration status of Arzerra after the onset of adverse events, 30 patients continued administration, showing that more than half of the patients continued administration.

The occurrence of infections is shown by presence or absence of prophylactic drugs for infections in Table 10-17.

The proportion of patients with infections was 18.23% (37/203 patients) in 203 patients with prophylactic drugs, 45.45% (10/22 patients) in 22 patients without prophylactic drugs, and 7.79% (6/77 patients) in 77 patients in whom the presence or absence of prophylactic drug administration was unknown, indicating that the proportion of patients with adverse events related to infections was higher in patients without prophylactic drugs.

Table 10-15 Occurrence of infections (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Infections	53	17.55	33	10.93	28	9.27
Adenoviral conjunctivitis	1	0.33	0	0.00	0	0.00
Appendicitis	1	0.33	1	0.33	1	0.33
Bronchiolitis	1	0.33	0	0.00	0	0.00
Bronchitis	7	2.32	1	0.33	1	0.33
Cellulitis	1	0.33	0	0.00	0	0.00
Hepatitis B	2	0.66	2	0.66	2	0.66
Herpes zoster	7	2.32	4	1.32	2	0.66
Infection	4	1.32	3	0.99	1	0.33
Influenza	1	0.33	1	0.33	1	0.33
Nasopharyngitis	4	1.32	0	0.00	0	0.00
Oral candidiasis	1	0.33	0	0.00	0	0.00
Otitis media	1	0.33	0	0.00	0	0.00

Priority study item		All		Serious		Grade ≥3	
		Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
	Periodontitis	1	0.33	0	0.00	0	0.00
	Pharyngitis	1	0.33	0	0.00	0	0.00
	Pneumonia	15	4.97	12	3.97	10	3.31
	Progressive multifocal leukoencephalopathy	1	0.33	1	0.33	1	0.33
	Pyelonephritis	1	0.33	1	0.33	1	0.33
	Sepsis	5	1.66	5	1.66	5	1.66
	Subcutaneous abscess	1	0.33	0	0.00	0	0.00
	Urinary tract infection	2	0.66	1	0.33	2	0.66
	Varicella	1	0.33	0	0.00	0	0.00
	Clostridium colitis	1	0.33	0	0.00	0	0.00
	Sinusitis fungal	1	0.33	1	0.33	0	0.00
	Hepatitis B reactivation	1	0.33	0	0.00	0	0.00
	Pneumonia bacterial	1	0.33	1	0.33	1	0.33
	Oral herpes	1	0.33	1	0.33	1	0.33
	Candida infection	1	0.33	1	0.33	1	0.33
	Aspergillus infection	1	0.33	0	0.00	0	0.00

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-16 Outcome and grade of infections (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Infections			53	17.55
	Total number of doses up to the onset (initial onset)	Median	5.0	
		Mean	5.4	
		Maximum	12	
		Minimum	1	
	Time of onset (total number of doses)	Median	6.0	
		Mean	5.9	
		Maximum	12	
		Minimum	1	
	Outcome	Resolved	18	5.96
		Resolving	12	3.97
		Not resolved	11	3.64
		Sequelae	1	0.33
		Death	10	3.31
		Unknown	1	0.33
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	3	0.99
		2	17	5.63
		3	15	4.97
		4	2	0.66
		5	11	3.64
		Unknown/other	5	1.66
	Administration status of Arzerra after the onset of the event	Discontinuation	18	5.96
		Interrupted	8	2.65
		Dose reduced	1	0.33
		Continued	30	9.93
		Unknown/other	6	1.99

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-17 Occurrence of infections by infection prophylaxis (safety analysis set)

		Number of patients	Number of patients with events	Proportion (%)
Prophylactic drug	Yes	203	37	(18.23)
	No	22	10	(45.45)
	Unknown	77	6	(7.79)

Source:Table 07

10.5.8.3 Occurrence of tumour lysis syndrome

The occurrence of tumour lysis syndrome and its outcome and grade are shown in Table 10-18 and Table 10-19, respectively.

Among the 302 patients in the safety analysis set, adverse events of tumour lysis syndrome were observed in 1.66% (5 patients). Grade ≥3 tumour lysis syndrome was observed in 0.99% (3 patients).

The time of onset (initial onset) was after the first dose in all 5 patients. The outcomes were resolved in all patients.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 4 patients and interrupted in 2 patients.

Table 10-18 Occurrence of tumour lysis syndrome (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Tumour lysis syndrome	5	1.66	2	0.66	3	0.99
Tumour lysis syndrome	5	1.66	2	0.66	3	0.99

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-19 Outcome and grade of tumour lysis syndrome (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Tumour lysis syndrome			5	1.66
	Total number of doses up to the onset (initial onset)	Median	1.0	
		Mean	1.0	
		Maximum	1	
		Minimum	1	
	Time of onset (total number of doses)	Median	1.0	
		Mean	1.2	
		Maximum	2	
		Minimum	1	

			Number of patients	Proportion
	Outcome	Resolved	5	1.66
		Resolving	0	0.00
		Not resolved	0	0.00
		Sequelae	0	0.00
		Death	0	0.00
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	1	0.33
		2	1	0.33
		3	3	0.99
		4	0	0.00
		5	0	0.00
		Unknown/other	0	0.00
	Administration status of Arzerra after the onset of the event	Discontinuation	0	0.00
		Interrupted	2	0.66
		Dose reduced	0	0.00
		Continued	4	1.32
		Unknown/other	0	0.00

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.4 Occurrence of hematotoxicity

The occurrence of hematotoxicity and its outcome and grade are shown in Table 10-20 and Table 10-21, respectively.

Among the 302 patients in the safety analysis set, adverse events related to hematotoxicity were observed in 16.23% (49 patients). Grade ≥3 hematotoxicity was observed in 12.58% (38 patients). Common adverse events (top 3) were neutrophil count decreased in 7.62% (23 patients), white blood cell count decreased in 4.97% (15 patients), and anaemia in 4.64% (14 patients).

The mean total number of doses up to the time of onset (initial onset) was 3.6. The outcomes were resolved in 25 patients, resolving in 13 patients, and not resolved in 11 patients.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 34 patients, interrupted in 7 patients, and discontinued in 11 patients, showing that many patients continued administration.

Table 10-20 Occurrence of hematotoxicity (safety analysis population)

Priority study item		All		Serious		Grade ≥3	
		Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Hematotoxicity		49	16.23	15	4.97	38	12.58
	Anaemia	14	4.64	3	0.99	12	3.97
	Febrile neutropenia	5	1.66	3	0.99	4	1.32
	Haemoglobin decreased	2	0.66	0	0.00	2	0.66
	Lymphocyte count decreased	1	0.33	0	0.00	1	0.33
	Neutropenia	2	0.66	0	0.00	1	0.33
	Neutrophil count decreased	23	7.62	6	1.99	19	6.29
	Platelet count decreased	9	2.98	1	0.33	8	2.65
	Thrombocyto-penia	3	0.99	1	0.33	3	0.99
	White blood cell count decreased	15	4.97	5	1.66	9	2.98
	Hematotoxicity	2	0.66	1	0.33	2	0.66

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-21 Outcome and grade of hematotoxicity (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Hematotoxicity			49	16.23
	Total number of doses up to the onset (initial onset)	Median	2.0	
		Mean	3.6	
		Maximum	10	
		Minimum	1	

			Number of patients	Proportion
	Time of onset (total number of doses)	Median	3.0	
		Mean	3.7	
		Maximum	12	
		Minimum	1	
	Outcome	Resolved	25	8.28
		Resolving	13	4.30
		Not resolved	11	3.64
		Sequelae	0	0.00
		Death	0	0.00
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	2	0.66
		2	8	2.65
		3	18	5.96
		4	20	6.62
		5	0	0.00
		Unknown/other	1	0.33
	Administration status of Arzerra after the onset of the event	Discontinuation	11	3.64
		Interrupted	7	2.32
		Dose reduced	0	0.00
		Continued	34	11.26
		Unknown/other	1	0.33

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.5 Occurrence of intestinal obstruction

The occurrence of intestinal obstruction and its outcome and grade are shown in Table 10-22 and Table 10-23, respectively.

Among the 302 patients in the safety analysis set, adverse events related to intestinal obstruction were observed in 0.33% (1 patient). The adverse event was large intestinal obstruction, which was Grade 3. The total number of doses administered up to the time of onset (initial onset) was 2. Arzerra was discontinued after the onset of the adverse event. The outcome was fatal. A causal relationship with Arzerra was ruled out.

Table 10-22 Occurrence of intestinal obstruction (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Intestinal obstruction	1	0.33	1	0.33	1	0.33
Large intestinal obstruction	1	0.33	1	0.33	1	0.33

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-23 Outcome and grade of intestinal obstruction (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Intestinal obstruction			1	0.33
	Total number of doses up to the onset (initial onset)	Median	2.0	
		Mean	2.0	
		Maximum	2	
		Minimum	2	
	Time of onset (total number of doses)	Median	2.0	
		Mean	2.0	
		Maximum	2	
		Minimum	2	
	Outcome	Resolved	0	0.00
		Resolving	0	0.00
		Not resolved	0	0.00
		Sequelae	0	0.00
		Death	1	0.33
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	0	0.00
		2	0	0.00
		3	1	0.33
		4	0	0.00
		5	0	0.00
		Unknown/other	0	0.00

			Number of patients	Proportion
	Administration status of Arzerra after the onset of the event	Discontinuation	1	0.33
		Interrupted	0	0.00
		Dose reduced	0	0.00
		Continued	0	0.00
		Unknown/other	0	0.00

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.6 Occurrence of skin disorder

The occurrence of skin disorder and its outcome and grade are shown in Table 10-24 and Table 10-25, respectively.

Among the 302 patients in the safety analysis set, adverse events related to skin disorder were observed in 34.44% (104 patients). Grade ≥3 skin disorder was observed in 4.64% (14 patients). Common adverse events (top 3) were rash in 16.89% (51 patients), urticaria in 8.94% (27 patients), and erythema and pruritus in 3.31% (10 patients) each.

The mean total number of doses up to the time of onset (initial onset) was 1.3. The outcome was resolved or resolving in all patients.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 84 patients, interrupted in 10 patients, and discontinued and dose reduced in 5 patients each, showing that many patients continued administration.

Table 10-24 Occurrence of skin disorder (safety analysis set)

Priority study item		All		Serious		Grade ≥3	
		Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Skin disorder		104	34.44	3	0.99	14	4.64
	Cold sweat	2	0.66	0	0.00	0	0.00
	Drug eruption	1	0.33	0	0.00	0	0.00
	Eczema	1	0.33	0	0.00	0	0.00
	Erythema	10	3.31	0	0.00	0	0.00
	Hyperhidrosis	7	2.32	0	0.00	1	0.33
	Papule	1	0.33	0	0.00	0	0.00
	Pruritus	10	3.31	0	0.00	0	0.00
	Rash	51	16.89	2	0.66	7	2.32
	Rash macular	1	0.33	0	0.00	0	0.00
	Rash maculo-papular	1	0.33	0	0.00	0	0.00

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Rash pruritic	4	1.32	0	0.00	0	0.00
Skin disorder	1	0.33	0	0.00	0	0.00
Urticaria	27	8.94	1	0.33	7	2.32
Toxic skin eruption	1	0.33	0	0.00	0	0.00

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-25 Outcome and grade of skin disorder (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Skin disorder			104	34.44
	Total number of doses up to the onset (initial onset)	Median	1.0	
		Mean	1.3	
		Maximum	6	
		Minimum	1	
	Time of onset (total number of doses)	Median	1.0	
		Mean	1.8	
		Maximum	11	
		Minimum	1	
	Outcome	Resolved	87	28.81
		Resolving	17	5.63
		Not resolved	0	0.00
		Sequelae	0	0.00
		Death	0	0.00
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	31	10.26
		2	57	18.87
		3	13	4.30
		4	1	0.33
		5	0	0.00
		Unknown/other	2	0.66

			Number of patients	Proportion
	Administration status of Arzerra after the onset of the event	Discontinuation	5	1.66
		Interrupted	10	3.31
		Dose reduced	5	1.66
		Continued	84	27.81
		Unknown/other	1	0.33

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.7 Occurrence of cardiac disorder

The occurrence of cardiac disorder and its outcome and grade are shown in Table 10-26 and Table 10-27, respectively.

Among the 302 patients in the safety analysis set, adverse events related to cardiac disorder were observed in 2.65% (8 patients). Grade ≥3 cardiac disorder was observed in 0.33% (1 patient). Adverse events reported were arrhythmia and bradycardia in 0.65% (2 patients) each, and atrial fibrillation, atrioventricular block second degree, cardiac failure, and myocarditis in 0.33% (1 patient) each.

The mean total number of doses up to the time of onset (initial onset) was 4.4. The outcomes were resolved in 6 patients and fatal in 1 patient. A causal relationship with Arzerra could not be ruled out for the patient who died. The patient had cardiac dysfunction as a complication.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 4 patients, interrupted in 1 patient, and discontinued in 2 patients.

Table 10-26 Occurrence of cardiac disorder (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Cardiac disorder	8	2.65	3	0.99	1	0.33
Arrhythmia	2	0.66	1	0.33	1	0.33
Atrial fibrillation	1	0.33	1	0.33	0	0.00
Atrioventricular block second degree	1	0.33	0	0.00	0	0.00
Bradycardia	2	0.66	0	0.00	0	0.00
Cardiac failure	1	0.33	0	0.00	0	0.00
Myocarditis	1	0.33	1	0.33	0	0.00

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-27 Outcome and grade of cardiac disorder (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Cardiac disorder			8	2.65
	Total number of doses up to the onset (initial onset)	Median	2.0	
		Mean	4.4	
		Maximum	11	
		Minimum	1	
	Time of onset (total number of doses)	Median	3.0	
		Mean	5.0	
		Maximum	11	
		Minimum	1	
	Outcome	Resolved	6	1.99
		Resolving	0	0.00
		Not resolved	0	0.00
		Sequelae	0	0.00
		Death	1	0.33
		Unknown	1	0.33
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	2	0.66
		2	2	0.66
		3	0	0.00
		4	0	0.00
		5	1	0.33
		Unknown/other	3	0.99
	Administration status of Arzerra after the onset of the event	Discontinuation	2	0.66
		Interrupted	1	0.33
		Dose reduced	0	0.00
		Continued	4	1.32
		Unknown/other	2	0.66

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.8 Occurrence of blood pressure decreased

The occurrence of blood pressure decreased and its outcome and grade are shown in Table 10-28 and Table 10-29, respectively.

Among the 302 patients in the safety analysis set, adverse events related to blood pressure decreased were observed in 5.96% (18 patients). Grade ≥3 blood pressure decreased was observed in 1.66% (5 patients). Adverse events reported were blood pressure decreased in

3.97% (12 patients), hypotension in 1.32% (4 patients), and dizziness and syncope in 0.33% (1 subject) each.

The mean total number of doses up to the time of onset (initial onset) was 2.6. The outcomes were resolved in 12 patients, resolving in 4 patients, and not resolved and fatal in 1 patient each. A causal relationship with Arzerra was ruled out for the patient who died.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 9 patients, interrupted in 2 patients, and discontinued and dose reduced in 3 patients each.

Table 10-28 Occurrence of blood pressure decreased (safety analysis set)

Priority study item		All		Serious		Grade ≥3	
		Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Blood pressure decreased		18	5.96	3	0.99	5	1.66
	Blood pressure decreased	12	3.97	2	0.66	2	0.66
	Dizziness	1	0.33	0	0.00	0	0.00
	Hypotension	4	1.32	0	0.00	2	0.66
	Syncope	1	0.33	1	0.33	1	0.33

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-29 Outcome and grade of blood pressure decreased (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Blood pressure decreased			18	5.96
	Total number of doses up to the onset (initial onset)	Median	1.0	
		Mean	2.6	
		Maximum	11	
		Minimum	1	
	Time of onset (total number of doses)	Median	1.0	
		Mean	2.8	
		Maximum	11	
		Minimum	1	

			Number of patients	Proportion
	Outcome	Resolved	12	3.97
		Resolving	4	1.32
		Not resolved	1	0.33
		Sequelae	0	0.00
		Death	1	0.33
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	4	1.32
		2	8	2.65
		3	3	0.99
		4	1	0.33
		5	1	0.33
		Unknown/other	1	0.33
	Administration status of Arzerra after the onset of the event	Discontinuation	3	0.99
		Interrupted	2	0.66
		Dose reduced	3	0.99
		Continued	9	2.98
		Unknown/other	2	0.66

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.9 Occurrence of hepatic dysfunction/jaundice

The occurrence of hepatic dysfunction/jaundice and their outcomes and grades are shown in Table 10-30 and Table 10-31, respectively.

Among the 302 patients in the safety analysis set, adverse events related to hepatic dysfunction/jaundice were observed in 7.28% (22 patients). Grade ≥3 hepatic dysfunction/jaundice were observed in 3.31% (10 patients). Common adverse events (top 3) were hepatic function abnormal in 1.99% (6 patients), alanine aminotransferase increased, liver disorder, and blood alkaline phosphatase increased in 0.99% (3 patients) each, and aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatitis B, and jaundice in 0.66% (2 patients) each.

The mean total number of doses up to the time of onset (initial onset) was 3.4. The outcomes were resolved in 9 patients, resolving in 3 patients, not resolved in 7 patients, and fatal in 2 patients. A causal relationship with Arzerra was ruled out for the 2 patients who died.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 13 patients, interrupted in 2 patients, and discontinued in 6 patients.

Table 10-30 Occurrence of hepatic dysfunction/jaundice (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Hepatic dysfunction/jaundice	22	7.28	10	3.31	10	3.31
Alanine aminotransferase increased	3	0.99	1	0.33	0	0.00
Ascites	1	0.33	0	0.00	0	0.00
Aspartate aminotransferase increased	2	0.66	1	0.33	1	0.33
Bile duct stone	1	0.33	1	0.33	1	0.33
Blood bilirubin increased	1	0.33	1	0.33	0	0.00
Cholangitis	1	0.33	1	0.33	1	0.33
Cholecystitis	1	0.33	0	0.00	0	0.00
Cholecystitis acute	1	0.33	1	0.33	1	0.33
Cholelithiasis	1	0.33	0	0.00	0	0.00
Gamma-glutamyltransferase increased	2	0.66	0	0.00	0	0.00
Hepatic failure	1	0.33	1	0.33	1	0.33
Hepatic function abnormal	6	1.99	4	1.32	4	1.32
Hepatitis B	2	0.66	2	0.66	2	0.66
Hyperbilirubinaemia	1	0.33	1	0.33	1	0.33
Hypoalbuminaemia	1	0.33	0	0.00	0	0.00
Jaundice	2	0.66	2	0.66	2	0.66
Liver disorder	3	0.99	1	0.33	1	0.33
Hepatitis B reactivation	1	0.33	0	0.00	0	0.00
Blood alkaline phosphatase increased	3	0.99	1	0.33	0	0.00

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-31 Outcome and grade of hepatic dysfunction/jaundice (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Hepatic dysfunction/jaundice			22	7.28
	Total number of doses up to the onset (initial onset)	Median	2.5	
		Mean	3.4	
		Maximum	8	
		Minimum	1	
	Time of onset (total number of doses)	Median	4.0	
		Mean	4.0	
		Maximum	8	
		Minimum	1	
	Outcome	Resolved	9	2.98
		Resolving	3	0.99
		Not resolved	7	2.32
		Sequelae	0	0.00
		Death	2	0.66
		Unknown	1	0.33
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	7	2.32
		2	5	1.66
		3	7	2.32
		4	1	0.33
		5	2	0.66
		Unknown/other	0	0.00
	Administration status of Arzerra after the onset of the event	Discontinuation	6	1.99
		Interrupted	2	0.66
		Dose reduced	0	0.00
		Continued	13	4.30
		Unknown/other	1	0.33

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.10Occurrence of renal disorder

The occurrence of renal disorder and its outcome and grade are shown in Table 10-32 and Table 10-33, respectively.

Among the 302 patients in the safety analysis set, adverse events related to renal disorder were observed in 1.99% (6 patients). Grade ≥3 renal disorder was observed in 0.66% (2 patients). Adverse events reported were renal impairment in 1.32% (4 patients), and blood

creatinine increased, hyperkalaemia, hyperphosphataemia, hypoalbuminaemia, and hyponatraemia in 0.33% (1 patient) each.

The mean total number of doses up to the time of onset (initial onset) was 4.8. The outcomes were resolved and resolving in 2 patients each, and not resolved and fatal in 1 patient each. A causal relationship with Arzerra could not be ruled out for the patient who died.

As for the administration status of Arzerra after the onset of adverse events, administration was continued in 3 patients and discontinued in 3 patients.

Table 10-32 Occurrence of renal disorder (safety analysis set)

Priority study item		All		Serious		Grade ≥3	
		Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Renal disorder		6	1.99	2	0.66	2	0.66
	Blood creatinine increased	1	0.33	1	0.33	1	0.33
	Hyperkalaemia	1	0.33	1	0.33	1	0.33
	Hyperphosphataemia	1	0.33	1	0.33	1	0.33
	Hypoalbuminaemia	1	0.33	0	0.00	0	0.00
	Hyponatraemia	1	0.33	0	0.00	0	0.00
	Renal impairment	4	1.32	1	0.33	1	0.33

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-33 Outcome and grade of renal disorder (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Renal disorder			6	1.99
	Total number of doses up to the onset (initial onset)	Median	4.5	
		Mean	4.8	
		Maximum	10	
		Minimum	1	
	Time of onset (total number of doses)	Median	8.0	
		Mean	5.6	
		Maximum	10	
		Minimum	1	

			Number of patients	Proportion
	Outcome	Resolved	2	0.66
		Resolving	2	0.66
		Not resolved	1	0.33
		Sequelae	0	0.00
		Death	1	0.33
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	1	0.33
		2	3	0.99
		3	0	0.00
		4	1	0.33
		5	1	0.33
		Unknown/other	0	0.00
	Administration status of Arzerra after the onset of the event	Discontinuation	3	0.99
		Interrupted	0	0.00
		Dose reduced	0	0.00
		Continued	3	0.99
		Unknown/other	0	0.00

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.8.11 Occurrence of interstitial lung disease

The occurrence of interstitial lung disease and its outcome and grade are shown in Table 10-34 and Table 10-35, respectively.

Among the 302 patients in the safety analysis set, adverse events related to interstitial lung disease were observed in 0.66% (2 patients). Grade ≥3 interstitial lung disease was observed in 0.33% (1 patient). Adverse events reported were acute respiratory distress syndrome and bronchiolitis in 0.33% (1 patient) each.

The mean number of doses up to the time of onset (initial onset) was 4.5. The outcomes were not resolved and fatal in 1 patient each. A causal relationship with Arzerra could not be ruled out for the patient who died. The patient had pulmonary dysfunction as a complication.

As for the administration status of Arzerra after the onset of adverse events, administration was discontinued in 2 patients.

Table 10-34 Occurrence of interstitial lung disease (safety analysis set)

Priority study item	All		Serious		Grade ≥3	
	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)	Number of patients with events	Incidence (%)
Interstitial lung disease	2	0.66	1	0.33	1	0.33
Acute respiratory distress syndrome	1	0.33	1	0.33	1	0.33
Bronchiolitis	1	0.33	0	0.00	0	0.00

Source:Table 13_01

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

Table 10-35 Outcome and grade of interstitial lung disease (safety analysis set)

			Number of patients	Proportion
Number of patients in the safety analysis set			302	100.00
Interstitial lung disease			2	0.66
	Total number of doses up to the onset (initial onset)	Median	4.5	
		Mean	4.5	
		Maximum	8	
		Minimum	1	
	Time of onset (total number of doses)	Median	4.5	
		Mean	4.5	
		Maximum	8	
		Minimum	1	
	Outcome	Resolved	0	0.00
		Resolving	0	0.00
		Not resolved	1	0.33
		Sequelae	0	0.00
		Death	1	0.33
		Unknown	0	0.00
	Grade (CTCAE criteria) * Number of patients and proportion are those for the maximum grade.	1	0	0.00
		2	1	0.33
		3	0	0.00
		4	0	0.00
		5	1	0.33
		Unknown/other	0	0.00

			Number of patients	Proportion
	Administration status of Arzerra after the onset of the event	Discontinuation	2	0.66
		Interrupted	0	0.00
		Dose reduced	0	0.00
		Continued	0	0.00
		Unknown/other	0	0.00

Source:Table 14

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.9 Safety analysis by patient factor

The occurrence of adverse drug reactions by patient factor in the 302 patients in the safety analysis set is shown in Table 10-36.

To examine factors that may affect the safety, odds ratios and their 95% confidence intervals (CIs) were calculated by patient factor defined in Section 9.10.6.

As a result, the 95% CI of the odds ratio did not include 1 for "past medical history (yes)," "prior treatment (yes)," "prior treatment (antineoplastic drugs) (yes)," "ECOG PS (2)," and "concomitant medication (yes)," and the examination result is described in detail below.

Table 10-36 Occurrence of adverse drug reactions by patient factor (safety analysis set)

Patient factor		Number of patients	Adverse drug reactions		Odds ratio (95%CI)		
			Number of patients with events (%)		OR	lower-upper	
Safety analysis set		302	204	(67.55)	--	--	
Gender	Male	188	120	(63.83)	--	--	
	Female	114	84	(73.68)	1.587	(0.951 ,	2.648)
	Unknown	0	0	(-)	--	--	
Age	<15 years	0	0	(-)	-	(- ,	-)
Minimum = 44	≥15 to <65 years	73	51	(69.86)	--	--	
Maximum = 91	≥65 years	226	150	(66.37)	0.851	(0.481 ,	1.507)
	Unknown	3	3	(100.00)	--	--	
Age (15 years)	<15 years	0	0	(-)	--	--	
	≥15 years	299	201	(67.22)	-	(- ,	-)
	Unknown or not entered	3	3	(100.00)	--	--	
Age (18 years)	<18 years	0	0	(-)	--	--	
	≥18 years	299	201	(67.22)	-	(- ,	-)
	Unknown or not entered	3	3	(100.00)	--	--	

Patient factor		Number of patients	Adverse drug reactions		Odds ratio (95%CI)		
			Number of patients with events (%)		OR	lower-upper	
Age (65 years)	<65 years	73	51	(69.86)	--	--	
	≥65 years	226	150	(66.37)	0.851	(0.481 , 1.507)	
	Unknown or not entered	3	3	(100.00)	--	--	
Hospitalization status	Inpatient	270	182	(67.41)	--	--	
	Outpatient	30	20	(66.67)	0.967	(0.434 , 2.153)	
	Unknown	2	2	(100.00)	--	--	
Disease duration	<1 year	42	27	(64.29)	--	--	
	≥1 to <3 years	56	37	(66.07)	1.082	(0.467 , 2.504)	
	≥3 to <6 years	71	50	(70.42)	1.323	(0.588 , 2.977)	
	≥6 to <11 years	73	52	(71.23)	1.376	(0.612 , 3.091)	
	≥11 years	37	26	(70.27)	1.313	(0.510 , 3.383)	
	Unknown	23	12	(52.17)	--	--	
Pregnancy	No	114	84	(73.68)	--	--	
	Yes	0	0	(-)	-	(- , -)	
	Unknown	0	0	(-)	--	--	
Noteworthy constitution/predisposition to hypersensitivity	No	264	176	(66.67)	--	--	
	Yes	38	28	(73.68)	1.400	(0.651 , 3.012)	
	Drug	27	19	(70.37)	--	--	
	Food	8	5	(62.50)	--	--	
	Other	7	7	(100.00)	--	--	
	Unknown	0	0	(-)	--	--	
Past medical history	No	186	113	(60.75)	--	--	
	Yes	116	91	(78.45)	2.352	(1.382 , 4.001)	
	Unknown	0	0	(-)	--	--	
Past medical history (hepatic dysfunction)	No	297	199	(67.00)	--	--	
	Yes	5	5	(100.00)	-	(- , -)	
	Unknown	0	0	(-)	--	--	
Past medical history (cardiac dysfunction)	No	289	193	(66.78)	--	--	
	Yes	13	11	(84.62)	2.736	(0.595 , 12.588)	
	Unknown	0	0	(-)	--	--	
Past medical history (renal dysfunction)	No	294	200	(68.03)	--	--	
	Yes	8	4	(50.00)	0.470	(0.115 , 1.920)	
	Unknown	0	0	(-)	--	--	
Past medical history (pulmonary dysfunction)	No	301	203	(67.44)	--	--	
	Yes	1	1	(100.00)	-	(- , -)	
	Unknown	0	0	(-)	--	--	

Patient factor		Number of patients	Adverse drug reactions		Odds ratio (95%CI)		
			Number of patients with events (%)		OR	lower-upper	
Complication	No	135	90	(66.67)	--	--	
	Yes	167	114	(68.26)	1.075	(0.663 , 1.745)	
	Unknown	0	0	(-)	--	--	
Complication (hepatic dysfunction)	No	274	188	(68.61)	--	--	
	Yes	28	16	(57.14)	0.610	(0.277 , 1.345)	
	Unknown	0	0	(-)	--	--	
Complication (cardiac dysfunction)	No	279	188	(67.38)	--	--	
	Yes	23	16	(69.57)	1.106	(0.440 , 2.784)	
	Unknown	0	0	(-)	--	--	
Complication (renal dysfunction)	No	267	181	(67.79)	--	--	
	Yes	35	23	(65.71)	0.911	(0.433 , 1.916)	
	Unknown	0	0	(-)	--	--	
Complication (pulmonary dysfunction)	No	299	201	(67.22)	--	--	
	Yes	3	3	(100.00)	-	(- , -)	
	Unknown	0	0	(-)	--	--	
HBV infection	No	37	25	(67.57)	--	--	
	Yes	81	50	(61.73)	0.774	(0.341 , 1.760)	
	Unknown	184	129	(70.11)	--	--	
Prior treatment	No	122	91	(74.59)	--	--	
	Yes	180	113	(62.78)	0.575	(0.346 , 0.954)	
	Unknown	0	0	(-)	--	--	
Prior treatment (antineoplastic drugs)	No	126	94	(74.60)	--	--	
	Yes	176	110	(62.50)	0.567	(0.343 , 0.939)	
	Unknown	0	0	(-)	--	--	
Prior treatment (hematopoietic stem cell transplantation)	No	296	200	(67.57)	--	--	
	Yes	6	4	(66.67)	0.960	(0.173 , 5.331)	
	Unknown	0	0	(-)	--	--	
Disease stage (Rai stage)	0	16	11	(68.75)	--	--	
	I	36	27	(75.00)	1.364	(0.372 , 4.997)	
	II	41	29	(70.73)	1.098	(0.314 , 3.846)	
	III	45	30	(66.67)	0.909	(0.267 , 3.096)	
	IV	152	97	(63.82)	0.802	(0.265 , 2.427)	
	Unknown	12	10	(83.33)	--	--	
Disease stage (Binet stage)	A	24	17	(70.83)	--	--	
	B	72	51	(70.83)	1.000	(0.362 , 2.763)	
	C	197	128	(64.97)	0.764	(0.302 , 1.931)	
	Unknown	9	8	(88.89)	--	--	

Patient factor		Number of patients	Adverse drug reactions	Odds ratio (95%CI)	
			Number of patients with events (%)	OR	lower-upper
ECOG PS	0	129	95 (73.64)	--	--
	1	111	76 (68.47)	0.777	(0.444 , 1.361)
	2	36	19 (52.78)	0.400	(0.187 , 0.858)
	3	20	12 (60.00)	0.537	(0.202 , 1.426)
	4	6	2 (33.33)	0.179	(0.031 , 1.022)
	Unknown	0	0 (-)	--	--
Number of lines of Arzerra treatment	First-line	16	14 (87.50)	--	--
	Second-line	119	83 (69.75)	0.329	(0.071 , 1.525)
	Third-line	105	66 (62.86)	0.242	(0.052 , 1.121)
	Other	0	0 (-)	-	(- , -)
	Unknown	62	41 (66.13)	--	--
Prior anti-CD20 antibody therapy	No	126	89 (70.63)	--	--
	Yes	171	111 (64.91)	0.769	(0.469 , 1.262)
	Unknown	5	4 (80.00)	--	--
Concomitant medications	No	77	45 (58.44)	--	--
	Yes	225	159 (70.67)	1.713	(1.002 , 2.929)
	Unknown	0	0 (-)	--	--
Concomitant medication (treatment of primary disease)	No	186	132 (70.97)	--	--
	Yes	39	27 (69.23)	0.920	(0.435 , 1.949)
	Unknown	77	45 (58.44)	--	--
Concomitant medication (prevention of infection)	No	22	14 (63.64)	--	--
	Yes	203	145 (71.43)	1.429	(0.569 , 3.586)
	Unknown	77	45 (58.44)	--	--
Concomitant therapies	No	296	200 (67.57)	--	--
	Yes	6	4 (66.67)	0.960	(0.173 , 5.331)
	Unknown	0	0 (-)	--	--

Source:Table 03

* Past medical history and complications of “hepatic dysfunction,”“ cardiac dysfunction,” “renal dysfunction,” and“ pulmonary dysfunction” were not those described in the case report forms but were those identified using the MedDRA PT code list prepared by NPKK.

10.5.9.1 Past medical history

The occurrence of adverse drug reactions by presence or absence of past medical history is shown in Table 10-37.

Of the 302 patients in the safety analysis set, 116 patients (38.41%) had a past medical history and 186 patients (61.59%) had no past medical history (Table 10-2).

The incidence of adverse drug reactions in the patients with a past medical history was 78.45% (91/116 patients), being higher in the patients with a past medical history than in the patients without a past medical history (60.75% [113/186 patients]) (odds ratio, 2.352). The most common adverse drug reactions in both populations were rash and pyrexia. The common adverse drug reaction observed only in the patients with a past medical history was rash pruritic in 3.45% (4 patients), and other adverse drug reactions were each observed in 1 to 2 patients.

The incidence of serious adverse drug reactions was comparable between patients with and without a past medical history: 13.79% (16/116 patients) and 13.98% (26/186 patients), respectively (analysis results, Table 21_05_02).

The outcomes of serious adverse drug reactions were similar: resolved in 5 patients, resolving in 4 patients, not resolved in 3 patients, with sequelae in 1 patient, and fatal in 2 patients with a past medical history; and resolved in 13 patients, resolving in 6 patients, not resolved in 3 patients, and fatal in 4 patients without a past medical history (analysis results, Table 21_05_03).

There was a difference in the incidence of adverse drug reactions between patients with and without a past medical history, but there was no notable trend in the type, seriousness, and outcome of adverse drug reactions.

Table 10-37 Occurrence of adverse drug reactions by presence or absence of past medical history (safety analysis set)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	18	(9.68)	13	(11.21)	31	(10.26)
Pneumonia	5	(2.69)	4	(3.45)	9	(2.98)
Herpes zoster	3	(1.61)	2	(1.72)	5	(1.66)
Infection	2	(1.08)	1	(0.86)	3	(0.99)
Sepsis	1	(0.54)	1	(0.86)	2	(0.66)
Urinary tract infection	2	(1.08)	0	(0.00)	2	(0.66)
Bronchitis	1	(0.54)	0	(0.00)	1	(0.33)
Cellulitis	1	(0.54)	0	(0.00)	1	(0.33)
Hepatitis B	1	(0.54)	0	(0.00)	1	(0.33)
Influenza	1	(0.54)	0	(0.00)	1	(0.33)
Nasopharyngitis	1	(0.54)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.86)	1	(0.33)
Otitis media	0	(0.00)	1	(0.86)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.86)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.86)	1	(0.33)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Pyelonephritis	1	(0.54)	0	(0.00)	1	(0.33)
Subcutaneous abscess	1	(0.54)	0	(0.00)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.86)	1	(0.33)
Oral herpes	0	(0.00)	1	(0.86)	1	(0.33)
Candida infection	0	(0.00)	1	(0.86)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(1.61)	1	(0.86)	4	(1.32)
Chronic lymphocytic leukemia	3	(1.61)	1	(0.86)	4	(1.32)
Blood and lymphatic system disorders	9	(4.84)	11	(9.48)	20	(6.62)
Anaemia	2	(1.08)	6	(5.17)	8	(2.65)
Febrile neutropenia	2	(1.08)	2	(1.72)	4	(1.32)
Disseminated intravascular coagulation	2	(1.08)	0	(0.00)	2	(0.66)
Neutropenia	1	(0.54)	1	(0.86)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(1.72)	2	(0.66)
Hematotoxicity	1	(0.54)	1	(0.86)	2	(0.66)
Lymph node pain	1	(0.54)	0	(0.00)	1	(0.33)
Lymphadenopathy	0	(0.00)	1	(0.86)	1	(0.33)
Immune system disorders	0	(0.00)	3	(2.59)	3	(0.99)
Anaphylactoid reaction	0	(0.00)	2	(1.72)	2	(0.66)
Hypersensitivity	0	(0.00)	1	(0.86)	1	(0.33)
Metabolism and nutrition disorders	4	(2.15)	3	(2.59)	7	(2.32)
Tumour lysis syndrome	2	(1.08)	3	(2.59)	5	(1.66)
Hyperkalaemia	1	(0.54)	0	(0.00)	1	(0.33)
Hyperphosphataemia	1	(0.54)	0	(0.00)	1	(0.33)
Hyperuricaemia	1	(0.54)	0	(0.00)	1	(0.33)
Nervous system disorders	9	(4.84)	6	(5.17)	15	(4.97)
Headache	2	(1.08)	2	(1.72)	4	(1.32)
Head discomfort	1	(0.54)	1	(0.86)	2	(0.66)
Hypoaesthesia	1	(0.54)	1	(0.86)	2	(0.66)
Neuropathy peripheral	1	(0.54)	1	(0.86)	2	(0.66)
Peripheral sensory neuropathy	2	(1.08)	0	(0.00)	2	(0.66)
Dizziness	0	(0.00)	1	(0.86)	1	(0.33)
Haemorrhagic cerebral infarction	0	(0.00)	1	(0.86)	1	(0.33)
Somnolence	1	(0.54)	0	(0.00)	1	(0.33)
Syncope	1	(0.54)	0	(0.00)	1	(0.33)
Tremor	0	(0.00)	1	(0.86)	1	(0.33)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Facial nerve disorder	1	(0.54)	0	(0.00)	1	(0.33)
Eye disorders	2	(1.08)	3	(2.59)	5	(1.66)
Eyelid oedema	1	(0.54)	3	(2.59)	4	(1.32)
Conjunctival hyperaemia	1	(0.54)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.86)	1	(0.33)
Deafness	0	(0.00)	1	(0.86)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.86)	1	(0.33)
Cardiac disorders	5	(2.69)	3	(2.59)	8	(2.65)
Arrhythmia	2	(1.08)	0	(0.00)	2	(0.66)
Bradycardia	0	(0.00)	2	(1.72)	2	(0.66)
Atrioventricular block second degree	1	(0.54)	0	(0.00)	1	(0.33)
Cardiac failure	0	(0.00)	1	(0.86)	1	(0.33)
Cardiac failure chronic	1	(0.54)	0	(0.00)	1	(0.33)
Myocarditis	1	(0.54)	0	(0.00)	1	(0.33)
Vascular disorders	5	(2.69)	5	(4.31)	10	(3.31)
Flushing	2	(1.08)	3	(2.59)	5	(1.66)
Hypotension	3	(1.61)	1	(0.86)	4	(1.32)
Hot flush	1	(0.54)	1	(0.86)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	28	(15.05)	17	(14.66)	45	(14.90)
Dyspnoea	12	(6.45)	6	(5.17)	18	(5.96)
Cough	4	(2.15)	4	(3.45)	8	(2.65)
Oropharyngeal discomfort	5	(2.69)	2	(1.72)	7	(2.32)
Hypoxia	3	(1.61)	1	(0.86)	4	(1.32)
Throat irritation	2	(1.08)	2	(1.72)	4	(1.32)
Laryngeal discomfort	2	(1.08)	1	(0.86)	3	(0.99)
Nasal congestion	1	(0.54)	1	(0.86)	2	(0.66)
Pharyngeal oedema	1	(0.54)	1	(0.86)	2	(0.66)
Productive cough	0	(0.00)	2	(1.72)	2	(0.66)
Sneezing	2	(1.08)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	1	(0.54)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.86)	1	(0.33)
Hiccups	1	(0.54)	0	(0.00)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.86)	1	(0.33)
Oropharyngeal swelling	1	(0.54)	0	(0.00)	1	(0.33)
Pleural effusion	1	(0.54)	0	(0.00)	1	(0.33)
Respiratory failure	0	(0.00)	1	(0.86)	1	(0.33)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Rhinorrhoea	1	(0.54)	0	(0.00)	1	(0.33)
Wheezing	1	(0.54)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	1	(0.54)	0	(0.00)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.86)	1	(0.33)
Oropharyngeal pain	0	(0.00)	1	(0.86)	1	(0.33)
Gastrointestinal disorders	13	(6.99)	9	(7.76)	22	(7.28)
Nausea	5	(2.69)	4	(3.45)	9	(2.98)
Vomiting	5	(2.69)	0	(0.00)	5	(1.66)
Abdominal discomfort	1	(0.54)	1	(0.86)	2	(0.66)
Diarrhoea	1	(0.54)	1	(0.86)	2	(0.66)
Oral discomfort	2	(1.08)	0	(0.00)	2	(0.66)
Hypoaesthesia oral	1	(0.54)	1	(0.86)	2	(0.66)
Abdominal pain lower	0	(0.00)	1	(0.86)	1	(0.33)
Constipation	0	(0.00)	1	(0.86)	1	(0.33)
Dry mouth	1	(0.54)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.86)	1	(0.33)
Rectal haemorrhage	1	(0.54)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	2	(1.08)	3	(2.59)	5	(1.66)
Hepatic function abnormal	1	(0.54)	2	(1.72)	3	(0.99)
Cholangitis	0	(0.00)	1	(0.86)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.86)	1	(0.33)
Liver disorder	1	(0.54)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	58	(31.18)	46	(39.66)	104	(34.44)
Rash	33	(17.74)	17	(14.66)	50	(16.56)
Urticaria	14	(7.53)	13	(11.21)	27	(8.94)
Pruritus	5	(2.69)	5	(4.31)	10	(3.31)
Erythema	4	(2.15)	5	(4.31)	9	(2.98)
Hyperhidrosis	5	(2.69)	2	(1.72)	7	(2.32)
Rash pruritic	0	(0.00)	4	(3.45)	4	(1.32)
Cold sweat	1	(0.54)	1	(0.86)	2	(0.66)
Eczema	1	(0.54)	0	(0.00)	1	(0.33)
Rash macular	1	(0.54)	0	(0.00)	1	(0.33)
Rash maculo-papular	0	(0.00)	1	(0.86)	1	(0.33)
Skin disorder	1	(0.54)	0	(0.00)	1	(0.33)
Toxic skin eruption	0	(0.00)	1	(0.86)	1	(0.33)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Musculoskeletal and connective tissue disorders	3	(1.61)	1	(0.86)	4	(1.32)
Back pain	2	(1.08)	0	(0.00)	2	(0.66)
Arthralgia	1	(0.54)	0	(0.00)	1	(0.33)
Neck pain	1	(0.54)	0	(0.00)	1	(0.33)
Limb discomfort	0	(0.00)	1	(0.86)	1	(0.33)
Renal and urinary disorders	2	(1.08)	0	(0.00)	2	(0.66)
Renal impairment	2	(1.08)	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	0	(0.00)	1	(0.86)	1	(0.33)
Menopausal symptoms	0	(0.00)	1	(0.86)	1	(0.33)
General disorders and administration site conditions	37	(19.89)	37	(31.90)	74	(24.50)
Pyrexia	23	(12.37)	24	(20.69)	47	(15.56)
Chills	14	(7.53)	13	(11.21)	27	(8.94)
Chest discomfort	1	(0.54)	4	(3.45)	5	(1.66)
Oedema	1	(0.54)	3	(2.59)	4	(1.32)
Chest pain	0	(0.00)	2	(1.72)	2	(0.66)
Fatigue	0	(0.00)	2	(1.72)	2	(0.66)
Feeling hot	1	(0.54)	1	(0.86)	2	(0.66)
Face oedema	1	(0.54)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.54)	0	(0.00)	1	(0.33)
Feeling cold	1	(0.54)	0	(0.00)	1	(0.33)
Malaise	1	(0.54)	0	(0.00)	1	(0.33)
Oedema mucosal	1	(0.54)	0	(0.00)	1	(0.33)
Oedema peripheral	1	(0.54)	0	(0.00)	1	(0.33)
Pain	1	(0.54)	0	(0.00)	1	(0.33)
Non-cardiac chest pain	0	(0.00)	1	(0.86)	1	(0.33)
Investigations	26	(13.98)	25	(21.55)	51	(16.89)
Neutrophil count decreased	10	(5.38)	9	(7.76)	19	(6.29)
White blood cell count decreased	5	(2.69)	9	(7.76)	14	(4.64)
Blood pressure decreased	4	(2.15)	6	(5.17)	10	(3.31)
Platelet count decreased	5	(2.69)	3	(2.59)	8	(2.65)
Oxygen saturation decreased	3	(1.61)	4	(3.45)	7	(2.32)
Alanine aminotransferase increased	1	(0.54)	1	(0.86)	2	(0.66)
Blood pressure increased	0	(0.00)	2	(1.72)	2	(0.66)
Gamma-glutamyltransferase increased	1	(0.54)	1	(0.86)	2	(0.66)
Weight increased	0	(0.00)	2	(1.72)	2	(0.66)

	Past medical history				Total	
	No		Yes			
Number of patients with adverse drug reactions	113		91		204	
Incidence of adverse drug reactions	(60.75)		(78.45)		(67.55)	
Type of adverse drug reaction SOC PT	Incidence (number of patients) (%) of adverse drug reactions by type					
Aspartate aminotransferase increased	1	(0.54)	0	(0.00)	1	(0.33)
Blood creatinine increased	1	(0.54)	0	(0.00)	1	(0.33)
C-reactive protein increased	0	(0.00)	1	(0.86)	1	(0.33)
Haemoglobin decreased	1	(0.54)	0	(0.00)	1	(0.33)
Lymphocyte count decreased	1	(0.54)	0	(0.00)	1	(0.33)

Source:Table 21_05_01

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.

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10.5.9.2 Prior medications

The occurrence of adverse drug reactions by prior treatment is shown in Table 10-38.

Of the 302 patients in the safety analysis set, 180 patients (59.60%) had received prior treatment and 122 patients (40.40%) had received no prior treatment (Table 10-2).

The incidence of adverse drug reactions in the patients with prior treatment was 62.78% (113/180 patients), which was lower than the incidence of adverse drug reactions in the patients without prior treatment (74.59% [91/122 patients]) (odds ratio, 0.575). The most common adverse drug reactions in both populations were rash and pyrexia. The common adverse drug reactions observed only in the patients with prior treatment were hypotension in 2.22% (4 patients) and hepatic function abnormal in 1.67% (3 patients), and other adverse drug reactions were each observed in 1 to 2 patients.

The incidence of serious adverse drug reactions was comparable between patients with and without prior treatment: 15.56% (28/180 patients) and 11.48% (14/122 patients), respectively (analysis results, Table 21_06_02).

The outcomes of serious adverse drug reactions were resolved in 13 patients, resolving in 5 patients, not resolved in 6 patients, with sequelae in 1 patient, and fatal in 3 patients in the presence of prior treatment, and resolved in 5 patients, resolving in 5 patients, and fatal in 3 patients in the absence of prior treatment, showing a similar tendency (analysis results, Table 21_06_03).

There was a difference in the incidence of adverse drug reactions between patients with and without prior treatment, but there was no notable trend in the type, seriousness, and outcome of adverse drug reactions.

Table 10-38 Occurrence of adverse drug reactions by presence or absence of prior treatment (safety analysis set)

	Prior treatment				Total	

	No		Yes			
Number of patients with adverse drug reactions	91		113		204	
Incidence of adverse drug reactions	(74.59)		(62.78)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	11	(9.02)	20	(11.11)	31	(10.26)
Pneumonia	5	(4.10)	4	(2.22)	9	(2.98)
Herpes zoster	2	(1.64)	3	(1.67)	5	(1.66)
Infection	1	(0.82)	2	(1.11)	3	(0.99)
Sepsis	0	(0.00)	2	(1.11)	2	(0.66)
Urinary tract infection	0	(0.00)	2	(1.11)	2	(0.66)
Bronchitis	0	(0.00)	1	(0.56)	1	(0.33)
Cellulitis	0	(0.00)	1	(0.56)	1	(0.33)
Hepatitis B	0	(0.00)	1	(0.56)	1	(0.33)
Influenza	0	(0.00)	1	(0.56)	1	(0.33)
Nasopharyngitis	1	(0.82)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.56)	1	(0.33)
Otitis media	1	(0.82)	0	(0.00)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.56)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.56)	1	(0.33)
Pyelonephritis	1	(0.82)	0	(0.00)	1	(0.33)
Subcutaneous abscess	0	(0.00)	1	(0.56)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.56)	1	(0.33)
Oral herpes	1	(0.82)	0	(0.00)	1	(0.33)
Candida infection	0	(0.00)	1	(0.56)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.64)	2	(1.11)	4	(1.32)
Chronic lymphocytic leukemia	2	(1.64)	2	(1.11)	4	(1.32)
Blood and lymphatic system disorders	8	(6.56)	12	(6.67)	20	(6.62)
Anaemia	4	(3.28)	4	(2.22)	8	(2.65)
Febrile neutropenia	1	(0.82)	3	(1.67)	4	(1.32)
Disseminated intravascular coagulation	2	(1.64)	0	(0.00)	2	(0.66)
Neutropenia	0	(0.00)	2	(1.11)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(1.11)	2	(0.66)
Hematotoxicity	0	(0.00)	2	(1.11)	2	(0.66)
Lymph node pain	1	(0.82)	0	(0.00)	1	(0.33)
Lymphadenopathy	1	(0.82)	0	(0.00)	1	(0.33)
Immune system disorders	1	(0.82)	2	(1.11)	3	(0.99)
Anaphylactoid reaction	1	(0.82)	1	(0.56)	2	(0.66)
Hypersensitivity	0	(0.00)	1	(0.56)	1	(0.33)
Metabolism and nutrition disorders	3	(2.46)	4	(2.22)	7	(2.32)
Tumour lysis syndrome	3	(2.46)	2	(1.11)	5	(1.66)
Hyperkalaemia	0	(0.00)	1	(0.56)	1	(0.33)

	Prior treatment				Total	
	No		Yes			
Number of patients with adverse drug reactions	91		113		204	
Incidence of adverse drug reactions	(74.59)		(62.78)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Hyperphosphataemia	0	(0.00)	1	(0.56)	1	(0.33)
Hyperuricaemia	0	(0.00)	1	(0.56)	1	(0.33)
Nervous system disorders	8	(6.56)	7	(3.89)	15	(4.97)
Headache	2	(1.64)	2	(1.11)	4	(1.32)
Head discomfort	0	(0.00)	2	(1.11)	2	(0.66)
Hypoaesthesia	1	(0.82)	1	(0.56)	2	(0.66)
Neuropathy peripheral	1	(0.82)	1	(0.56)	2	(0.66)
Peripheral sensory neuropathy	2	(1.64)	0	(0.00)	2	(0.66)
Dizziness	0	(0.00)	1	(0.56)	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.82)	0	(0.00)	1	(0.33)
Somnolence	1	(0.82)	0	(0.00)	1	(0.33)
Syncope	1	(0.82)	0	(0.00)	1	(0.33)
Tremor	1	(0.82)	0	(0.00)	1	(0.33)
Facial nerve disorder	0	(0.00)	1	(0.56)	1	(0.33)
Eye disorders	2	(1.64)	3	(1.67)	5	(1.66)
Eyelid oedema	1	(0.82)	3	(1.67)	4	(1.32)
Conjunctival hyperaemia	1	(0.82)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.56)	1	(0.33)
Deafness	0	(0.00)	1	(0.56)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.56)	1	(0.33)
Cardiac disorders	2	(1.64)	6	(3.33)	8	(2.65)
Arrhythmia	1	(0.82)	1	(0.56)	2	(0.66)
Bradycardia	1	(0.82)	1	(0.56)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	1	(0.56)	1	(0.33)
Cardiac failure	0	(0.00)	1	(0.56)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.56)	1	(0.33)
Myocarditis	0	(0.00)	1	(0.56)	1	(0.33)
Vascular disorders	4	(3.28)	6	(3.33)	10	(3.31)
Flushing	3	(2.46)	2	(1.11)	5	(1.66)
Hypotension	0	(0.00)	4	(2.22)	4	(1.32)
Hot flush	1	(0.82)	1	(0.56)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	17	(13.93)	28	(15.56)	45	(14.90)
Dyspnoea	5	(4.10)	13	(7.22)	18	(5.96)
Cough	2	(1.64)	6	(3.33)	8	(2.65)
Oropharyngeal discomfort	2	(1.64)	5	(2.78)	7	(2.32)
Hypoxia	3	(2.46)	1	(0.56)	4	(1.32)
Throat irritation	1	(0.82)	3	(1.67)	4	(1.32)

	Prior treatment				Total	
	No		Yes			
Number of patients with adverse drug reactions	91		113		204	
Incidence of adverse drug reactions	(74.59)		(62.78)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Laryngeal discomfort	1	(0.82)	2	(1.11)	3	(0.99)
Nasal congestion	0	(0.00)	2	(1.11)	2	(0.66)
Pharyngeal oedema	0	(0.00)	2	(1.11)	2	(0.66)
Productive cough	0	(0.00)	2	(1.11)	2	(0.66)
Sneezing	0	(0.00)	2	(1.11)	2	(0.66)
Acute respiratory distress syndrome	1	(0.82)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.56)	1	(0.33)
Hiccups	0	(0.00)	1	(0.56)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.56)	1	(0.33)
Oropharyngeal swelling	0	(0.00)	1	(0.56)	1	(0.33)
Pleural effusion	0	(0.00)	1	(0.56)	1	(0.33)
Respiratory failure	0	(0.00)	1	(0.56)	1	(0.33)
Rhinorrhoea	0	(0.00)	1	(0.56)	1	(0.33)
Wheezing	1	(0.82)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	1	(0.82)	0	(0.00)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.56)	1	(0.33)
Oropharyngeal pain	1	(0.82)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	13	(10.66)	9	(5.00)	22	(7.28)
Nausea	6	(4.92)	3	(1.67)	9	(2.98)
Vomiting	4	(3.28)	1	(0.56)	5	(1.66)
Abdominal discomfort	0	(0.00)	2	(1.11)	2	(0.66)
Diarrhoea	2	(1.64)	0	(0.00)	2	(0.66)
Oral discomfort	0	(0.00)	2	(1.11)	2	(0.66)
Hypoaesthesia oral	1	(0.82)	1	(0.56)	2	(0.66)
Abdominal pain lower	1	(0.82)	0	(0.00)	1	(0.33)
Constipation	1	(0.82)	0	(0.00)	1	(0.33)
Dry mouth	1	(0.82)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.56)	1	(0.33)
Rectal haemorrhage	0	(0.00)	1	(0.56)	1	(0.33)
Hepatobiliary disorders	1	(0.82)	4	(2.22)	5	(1.66)
Hepatic function abnormal	0	(0.00)	3	(1.67)	3	(0.99)
Cholangitis	0	(0.00)	1	(0.56)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.56)	1	(0.33)
Liver disorder	1	(0.82)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	52	(42.62)	52	(28.89)	104	(34.44)
Rash	25	(20.49)	25	(13.89)	50	(16.56)
Urticaria	12	(9.84)	15	(8.33)	27	(8.94)

	Prior treatment				Total	
	No		Yes			
Number of patients with adverse drug reactions	91		113		204	
Incidence of adverse drug reactions	(74.59)		(62.78)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Pruritus	2	(1.64)	8	(4.44)	10	(3.31)
Erythema	6	(4.92)	3	(1.67)	9	(2.98)
Hyperhidrosis	2	(1.64)	5	(2.78)	7	(2.32)
Rash pruritic	2	(1.64)	2	(1.11)	4	(1.32)
Cold sweat	1	(0.82)	1	(0.56)	2	(0.66)
Eczema	0	(0.00)	1	(0.56)	1	(0.33)
Rash macular	1	(0.82)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(0.82)	0	(0.00)	1	(0.33)
Skin disorder	1	(0.82)	0	(0.00)	1	(0.33)
Toxic skin eruption	1	(0.82)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(0.82)	3	(1.67)	4	(1.32)
Back pain	0	(0.00)	2	(1.11)	2	(0.66)
Arthralgia	0	(0.00)	1	(0.56)	1	(0.33)
Neck pain	0	(0.00)	1	(0.56)	1	(0.33)
Limb discomfort	1	(0.82)	0	(0.00)	1	(0.33)
Renal and urinary disorders	1	(0.82)	1	(0.56)	2	(0.66)
Renal impairment	1	(0.82)	1	(0.56)	2	(0.66)
Reproductive system and breast disorders	0	(0.00)	1	(0.56)	1	(0.33)
Menopausal symptoms	0	(0.00)	1	(0.56)	1	(0.33)
General disorders and administration site conditions	33	(27.05)	41	(22.78)	74	(24.50)
Pyrexia	19	(15.57)	28	(15.56)	47	(15.56)
Chills	11	(9.02)	16	(8.89)	27	(8.94)
Chest discomfort	2	(1.64)	3	(1.67)	5	(1.66)
Oedema	2	(1.64)	2	(1.11)	4	(1.32)
Chest pain	1	(0.82)	1	(0.56)	2	(0.66)
Fatigue	1	(0.82)	1	(0.56)	2	(0.66)
Feeling hot	1	(0.82)	1	(0.56)	2	(0.66)
Face oedema	1	(0.82)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.82)	0	(0.00)	1	(0.33)
Feeling cold	0	(0.00)	1	(0.56)	1	(0.33)
Malaise	0	(0.00)	1	(0.56)	1	(0.33)
Oedema mucosal	1	(0.82)	0	(0.00)	1	(0.33)
Oedema peripheral	1	(0.82)	0	(0.00)	1	(0.33)
Pain	0	(0.00)	1	(0.56)	1	(0.33)
Non-cardiac chest pain	1	(0.82)	0	(0.00)	1	(0.33)

	Prior treatment				Total	
	No		Yes			
Number of patients with adverse drug reactions	91		113		204	
Incidence of adverse drug reactions	(74.59)		(62.78)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Investigations	22	(18.03)	29	(16.11)	51	(16.89)
Neutrophil count decreased	6	(4.92)	13	(7.22)	19	(6.29)
White blood cell count decreased	6	(4.92)	8	(4.44)	14	(4.64)
Blood pressure decreased	7	(5.74)	3	(1.67)	10	(3.31)
Platelet count decreased	3	(2.46)	5	(2.78)	8	(2.65)
Oxygen saturation decreased	2	(1.64)	5	(2.78)	7	(2.32)
Alanine aminotransferase increased	0	(0.00)	2	(1.11)	2	(0.66)
Blood pressure increased	2	(1.64)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	1	(0.82)	1	(0.56)	2	(0.66)
Weight increased	2	(1.64)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	0	(0.00)	1	(0.56)	1	(0.33)
Blood creatinine increased	0	(0.00)	1	(0.56)	1	(0.33)
C-reactive protein increased	0	(0.00)	1	(0.56)	1	(0.33)
Haemoglobin decreased	0	(0.00)	1	(0.56)	1	(0.33)
Lymphocyte count decreased	1	(0.82)	0	(0.00)	1	(0.33)

Source:Table 21_06_01
SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
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10.5.9.3 Prior medications (antineoplastic drugs)

The occurrence of adverse drug reactions by prior treatment (antineoplastic drugs) is shown in Table 10-39.

Of the 302 patients in the safety analysis set, 176 patients (58.28%) had received prior treatment (antineoplastic drugs) and 126 patients (41.72%) had not received prior treatment (antineoplastic drugs) (Table 10-2).

The incidence of adverse drug reactions in the patients with prior treatment (antineoplastic drugs) was 62.50% (110/176 patients), and the incidence of adverse drug reactions was lower in the patients with prior treatment (antineoplastic drugs) than in the patients without prior treatment (antineoplastic drugs) (74.60% [94/126 patients]) (odds ratio, 0.567). The most common adverse drug reactions in both populations were rash and pyrexia. The common adverse drug reaction observed only in the patients with prior treatment (antineoplastic drugs) was hypotension in 2.27% (4 patients), and other adverse drug reactions were each observed in 1 to 2 patients.

The incidence of serious adverse drug reactions was comparable: 14.77% (26/176 patients) in the patients with prior treatment (antineoplastic drugs) and 12.70% (16/126 patients) in the patients without prior treatment (antineoplastic drugs) (analysis results, Table 21_04_02).

The outcomes of serious adverse drug reactions were resolved in 13 patients, resolving in 3 patients, not resolved in 6 patients, with sequelae in 1 patient, and fatal in 3 patients with prior treatment (antineoplastic drugs), and resolved in 5 patients, resolving in 7 patients, and fatal in 3 patients without prior treatment (antineoplastic drugs); there were no major differences between the populations (analysis results, Table 21_04_03).

Although there was a difference in the incidence of adverse drug reactions between patients with and without prior treatment (antineoplastic drugs), there were no notable trends in the type, seriousness, and outcome of adverse drug reactions.

Table 10-39 Occurrence of adverse drug reactions by presence or absence of prior treatment (antineoplastic drugs) (safety analysis set)

	Prior treatment (antineoplastic drugs)				Total	
	No		Yes			
Number of patients with adverse drug reactions	94		110		204	
Incidence of adverse drug reactions	(74.60)		(62.50)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	13	(10.32)	18	(10.23)	31	(10.26)
Pneumonia	6	(4.76)	3	(1.70)	9	(2.98)
Herpes zoster	3	(2.38)	2	(1.14)	5	(1.66)
Infection	1	(0.79)	2	(1.14)	3	(0.99)
Sepsis	0	(0.00)	2	(1.14)	2	(0.66)
Urinary tract infection	0	(0.00)	2	(1.14)	2	(0.66)
Bronchitis	0	(0.00)	1	(0.57)	1	(0.33)
Cellulitis	0	(0.00)	1	(0.57)	1	(0.33)
Hepatitis B	0	(0.00)	1	(0.57)	1	(0.33)
Influenza	0	(0.00)	1	(0.57)	1	(0.33)
Nasopharyngitis	1	(0.79)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.57)	1	(0.33)
Otitis media	1	(0.79)	0	(0.00)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.57)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.57)	1	(0.33)
Pyelonephritis	1	(0.79)	0	(0.00)	1	(0.33)
Subcutaneous abscess	0	(0.00)	1	(0.57)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.57)	1	(0.33)
Oral herpes	1	(0.79)	0	(0.00)	1	(0.33)
Candida infection	0	(0.00)	1	(0.57)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(1.59)	2	(1.14)	4	(1.32)
Chronic lymphocytic leukemia	2	(1.59)	2	(1.14)	4	(1.32)
Blood and lymphatic system disorders	8	(6.35)	12	(6.82)	20	(6.62)
Anaemia	4	(3.17)	4	(2.27)	8	(2.65)
Febrile neutropenia	1	(0.79)	3	(1.70)	4	(1.32)

	Prior treatment (antineoplastic drugs)				Total	
	No		Yes			
Number of patients with adverse drug reactions	94		110		204	
Incidence of adverse drug reactions	(74.60)		(62.50)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Disseminated intravascular coagulation	2	(1.59)	0	(0.00)	2	(0.66)
Neutropenia	0	(0.00)	2	(1.14)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(1.14)	2	(0.66)
Hematotoxicity	0	(0.00)	2	(1.14)	2	(0.66)
Lymph node pain	1	(0.79)	0	(0.00)	1	(0.33)
Lymphadenopathy	1	(0.79)	0	(0.00)	1	(0.33)
Immune system disorders	1	(0.79)	2	(1.14)	3	(0.99)
Anaphylactoid reaction	1	(0.79)	1	(0.57)	2	(0.66)
Hypersensitivity	0	(0.00)	1	(0.57)	1	(0.33)
Metabolism and nutrition disorders	3	(2.38)	4	(2.27)	7	(2.32)
Tumour lysis syndrome	3	(2.38)	2	(1.14)	5	(1.66)
Hyperkalaemia	0	(0.00)	1	(0.57)	1	(0.33)
Hyperphosphataemia	0	(0.00)	1	(0.57)	1	(0.33)
Hyperuricaemia	0	(0.00)	1	(0.57)	1	(0.33)
Nervous system disorders	8	(6.35)	7	(3.98)	15	(4.97)
Headache	2	(1.59)	2	(1.14)	4	(1.32)
Head discomfort	0	(0.00)	2	(1.14)	2	(0.66)
Hypoaesthesia	1	(0.79)	1	(0.57)	2	(0.66)
Neuropathy peripheral	1	(0.79)	1	(0.57)	2	(0.66)
Peripheral sensory neuropathy	2	(1.59)	0	(0.00)	2	(0.66)
Dizziness	0	(0.00)	1	(0.57)	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.79)	0	(0.00)	1	(0.33)
Somnolence	1	(0.79)	0	(0.00)	1	(0.33)
Syncope	1	(0.79)	0	(0.00)	1	(0.33)
Tremor	1	(0.79)	0	(0.00)	1	(0.33)
Facial nerve disorder	0	(0.00)	1	(0.57)	1	(0.33)
Eye disorders	2	(1.59)	3	(1.70)	5	(1.66)
Eyelid oedema	1	(0.79)	3	(1.70)	4	(1.32)
Conjunctival hyperaemia	1	(0.79)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.57)	1	(0.33)
Deafness	0	(0.00)	1	(0.57)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.57)	1	(0.33)
Cardiac disorders	2	(1.59)	6	(3.41)	8	(2.65)
Arrhythmia	1	(0.79)	1	(0.57)	2	(0.66)
Bradycardia	1	(0.79)	1	(0.57)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	1	(0.57)	1	(0.33)

	Prior treatment (antineoplastic drugs)				Total	
	No		Yes			
Number of patients with adverse drug reactions	94		110		204	
Incidence of adverse drug reactions	(74.60)		(62.50)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Cardiac failure	0	(0.00)	1	(0.57)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.57)	1	(0.33)
Myocarditis	0	(0.00)	1	(0.57)	1	(0.33)
Vascular disorders	4	(3.17)	6	(3.41)	10	(3.31)
Flushing	3	(2.38)	2	(1.14)	5	(1.66)
Hypotension	0	(0.00)	4	(2.27)	4	(1.32)
Hot flush	1	(0.79)	1	(0.57)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	18	(14.29)	27	(15.34)	45	(14.90)
Dyspnoea	5	(3.97)	13	(7.39)	18	(5.96)
Cough	3	(2.38)	5	(2.84)	8	(2.65)
Oropharyngeal discomfort	2	(1.59)	5	(2.84)	7	(2.32)
Hypoxia	3	(2.38)	1	(0.57)	4	(1.32)
Throat irritation	1	(0.79)	3	(1.70)	4	(1.32)
Laryngeal discomfort	1	(0.79)	2	(1.14)	3	(0.99)
Nasal congestion	0	(0.00)	2	(1.14)	2	(0.66)
Pharyngeal oedema	0	(0.00)	2	(1.14)	2	(0.66)
Productive cough	0	(0.00)	2	(1.14)	2	(0.66)
Sneezing	0	(0.00)	2	(1.14)	2	(0.66)
Acute respiratory distress syndrome	1	(0.79)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.57)	1	(0.33)
Hiccups	0	(0.00)	1	(0.57)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.57)	1	(0.33)
Oropharyngeal swelling	0	(0.00)	1	(0.57)	1	(0.33)
Pleural effusion	0	(0.00)	1	(0.57)	1	(0.33)
Respiratory failure	0	(0.00)	1	(0.57)	1	(0.33)
Rhinorrhoea	0	(0.00)	1	(0.57)	1	(0.33)
Wheezing	1	(0.79)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	1	(0.79)	0	(0.00)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.57)	1	(0.33)
Oropharyngeal pain	1	(0.79)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	13	(10.32)	9	(5.11)	22	(7.28)
Nausea	6	(4.76)	3	(1.70)	9	(2.98)
Vomiting	4	(3.17)	1	(0.57)	5	(1.66)
Abdominal discomfort	0	(0.00)	2	(1.14)	2	(0.66)
Diarrhoea	2	(1.59)	0	(0.00)	2	(0.66)
Oral discomfort	0	(0.00)	2	(1.14)	2	(0.66)

	Prior treatment (antineoplastic drugs)				Total	
	No		Yes			
Number of patients with adverse drug reactions	94		110		204	
Incidence of adverse drug reactions	(74.60)		(62.50)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Hypoaesthesia oral	1	(0.79)	1	(0.57)	2	(0.66)
Abdominal pain lower	1	(0.79)	0	(0.00)	1	(0.33)
Constipation	1	(0.79)	0	(0.00)	1	(0.33)
Dry mouth	1	(0.79)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.57)	1	(0.33)
Rectal haemorrhage	0	(0.00)	1	(0.57)	1	(0.33)
Hepatobiliary disorders	2	(1.59)	3	(1.70)	5	(1.66)
Hepatic function abnormal	1	(0.79)	2	(1.14)	3	(0.99)
Cholangitis	0	(0.00)	1	(0.57)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.57)	1	(0.33)
Liver disorder	1	(0.79)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	53	(42.06)	51	(28.98)	104	(34.44)
Rash	26	(20.63)	24	(13.64)	50	(16.56)
Urticaria	12	(9.52)	15	(8.52)	27	(8.94)
Pruritus	2	(1.59)	8	(4.55)	10	(3.31)
Erythema	6	(4.76)	3	(1.70)	9	(2.98)
Hyperhidrosis	2	(1.59)	5	(2.84)	7	(2.32)
Rash pruritic	2	(1.59)	2	(1.14)	4	(1.32)
Cold sweat	1	(0.79)	1	(0.57)	2	(0.66)
Eczema	0	(0.00)	1	(0.57)	1	(0.33)
Rash macular	1	(0.79)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(0.79)	0	(0.00)	1	(0.33)
Skin disorder	1	(0.79)	0	(0.00)	1	(0.33)
Toxic skin eruption	1	(0.79)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(0.79)	3	(1.70)	4	(1.32)
Back pain	0	(0.00)	2	(1.14)	2	(0.66)
Arthralgia	0	(0.00)	1	(0.57)	1	(0.33)
Neck pain	0	(0.00)	1	(0.57)	1	(0.33)
Limb discomfort	1	(0.79)	0	(0.00)	1	(0.33)
Renal and urinary disorders	1	(0.79)	1	(0.57)	2	(0.66)
Renal impairment	1	(0.79)	1	(0.57)	2	(0.66)
Reproductive system and breast disorders	0	(0.00)	1	(0.57)	1	(0.33)
Menopausal symptoms	0	(0.00)	1	(0.57)	1	(0.33)
General disorders and administration site conditions	33	(26.19)	41	(23.30)	74	(24.50)
Pyrexia	19	(15.08)	28	(15.91)	47	(15.56)

	Prior treatment (antineoplastic drugs)				Total	
	No		Yes			
Number of patients with adverse drug reactions	94		110		204	
Incidence of adverse drug reactions	(74.60)		(62.50)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Chills	11	(8.73)	16	(9.09)	27	(8.94)
Chest discomfort	2	(1.59)	3	(1.70)	5	(1.66)
Oedema	2	(1.59)	2	(1.14)	4	(1.32)
Chest pain	1	(0.79)	1	(0.57)	2	(0.66)
Fatigue	1	(0.79)	1	(0.57)	2	(0.66)
Feeling hot	1	(0.79)	1	(0.57)	2	(0.66)
Face oedema	1	(0.79)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.79)	0	(0.00)	1	(0.33)
Feeling cold	0	(0.00)	1	(0.57)	1	(0.33)
Malaise	0	(0.00)	1	(0.57)	1	(0.33)
Oedema mucosal	1	(0.79)	0	(0.00)	1	(0.33)
Oedema peripheral	1	(0.79)	0	(0.00)	1	(0.33)
Pain	0	(0.00)	1	(0.57)	1	(0.33)
Non-cardiac chest pain	1	(0.79)	0	(0.00)	1	(0.33)
Investigations	23	(18.25)	28	(15.91)	51	(16.89)
Neutrophil count decreased	7	(5.56)	12	(6.82)	19	(6.29)
White blood cell count decreased	6	(4.76)	8	(4.55)	14	(4.64)
Blood pressure decreased	7	(5.56)	3	(1.70)	10	(3.31)
Platelet count decreased	3	(2.38)	5	(2.84)	8	(2.65)
Oxygen saturation decreased	2	(1.59)	5	(2.84)	7	(2.32)
Alanine aminotransferase increased	0	(0.00)	2	(1.14)	2	(0.66)
Blood pressure increased	2	(1.59)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	1	(0.79)	1	(0.57)	2	(0.66)
Weight increased	2	(1.59)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	0	(0.00)	1	(0.57)	1	(0.33)
Blood creatinine increased	0	(0.00)	1	(0.57)	1	(0.33)
C-reactive protein increased	0	(0.00)	1	(0.57)	1	(0.33)
Haemoglobin decreased	0	(0.00)	1	(0.57)	1	(0.33)
Lymphocyte count decreased	1	(0.79)	0	(0.00)	1	(0.33)

Source:Table 21_04_01
SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
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10.5.9.4 ECOG PS

The occurrence of adverse drug reactions by ECOG PS is shown in Table 10-40.

Of the 302 patients in the safety analysis set, 36 patients (11.92%) had ECOG PS (2) and 129 patients (42.72%) had ECOG PS (0) (Table 10-2).

Common adverse drug reactions were pyrexia and neutrophil count decreased in 11.11% (4 patients) each, and pneumonia, chills, and white blood cell count decreased in 8.33% (3 patients) each in patients with ECOG PS (2), and rash in 21.71% (28 patients), pyrexia in 16.28% (21 patients), urticaria in 10.08% (13 patients), and chills in 6.98% (9 patients) in patients with ECOG PS (0). Adverse drug reactions that occurred only in patients with ECOG PS (2) and ECOG PS (0) were sporadically observed, but these events occurred in 1 or 2 patients, and it was considered that there were no adverse drug reactions that occurred specifically depending on ECOG PS. The incidence of adverse drug reactions in patients with ECOG PS (2) was lower than that in patients with ECOG PS (0), while the incidences of adverse drug reactions in patients with ECOG PS (0) to (4) were 73.64%, 68.47%, 52.78%, 60.00%, and 33.33%, respectively, showing no tendency toward higher incidence in patients with poorer ECOG PS.

The incidence of serious adverse drug reactions was 30.56% (11/36 patients) in patients with ECOG PS (2) and 11.63% (15/129 patients) in patients with ECOG PS (0). While the incidence of serious adverse drug reactions was higher in patients with ECOG PS (2), the incidences of serious adverse drug reactions in patients with ECOG PS (0) to (4) were 11.63%, 10.81%, 30.56%, 15.00%, and 16.67%, respectively (analysis results, Table 21_07_02). The outcomes of serious adverse drug reactions were resolved in 2 patients, resolving and with sequelae in 1 patient each, not resolved in 3 patients, and fatal in 4 patients in patients with ECOG PS (2), while they were resolved in 8 patients, resolving in 5 patients, and fatal in 1 patient in patients with ECOG PS (0) (analysis results, Table 21_07_03).

The incidence of serious adverse drug reactions was higher in patients with ECOG PS (2) than in patients with ECOG PS (0), but the incidence of overall adverse drug reactions was lower in patients with ECOG PS (2), and there was no tendency toward a higher incidence of adverse drug reactions in patients with poor ECOG PS. There was no occurrence specific to the type of adverse drug reactions, and no notable trend was observed.

Table 10-40 Occurrence of adverse drug reactions by ECOG PS (safety analysis set)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Infections and infestations	12	(9.30)	9	(8.11)	7	(19.44)	2	(10.00)	1	(16.67)	31	(10.26)
Pneumonia	3	(2.33)	3	(2.70)	3	(8.33)	0	(0.00)	0	(0.00)	9	(2.98)
Herpes zoster	3	(2.33)	0	(0.00)	0	(0.00)	1	(5.00)	1	(16.67)	5	(1.66)
Infection	0	(0.00)	1	(0.90)	2	(5.56)	0	(0.00)	0	(0.00)	3	(0.99)
Sepsis	0	(0.00)	1	(0.90)	1	(2.78)	0	(0.00)	0	(0.00)	2	(0.66)
Urinary tract infection	0	(0.00)	0	(0.00)	1	(2.78)	1	(5.00)	0	(0.00)	2	(0.66)
Bronchitis	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Cellulitis	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Hepatitis B	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Influenza	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Nasopharyngitis	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Otitis media	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Pyelonephritis	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Subcutaneous abscess	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oral herpes	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Candida infection	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.78)	3	(2.70)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Chronic lymphocytic leukemia	1	(0.78)	3	(2.70)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Blood and lymphatic system disorders	6	(4.65)	11	(9.91)	1	(2.78)	2	(10.00)	0	(0.00)	20	(6.62)
Anaemia	3	(2.33)	4	(3.60)	0	(0.00)	1	(5.00)	0	(0.00)	8	(2.65)
Febrile neutropenia	0	(0.00)	2	(1.80)	0	(0.00)	2	(10.00)	0	(0.00)	4	(1.32)
Disseminated intravascular coagulation	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Neutropenia	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hematotoxicity	1	(0.78)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	2	(0.66)
Lymph node pain	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Lymphadenopathy	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Immune system disorders	3	(2.33)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)
Anaphylactoid reaction	2	(1.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hypersensitivity	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	0	(0.00)	4	(3.60)	2	(5.56)	1	(5.00)	0	(0.00)	7	(2.32)
Tumour lysis syndrome	0	(0.00)	4	(3.60)	1	(2.78)	0	(0.00)	0	(0.00)	5	(1.66)
Hyperkalaemia	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Hyperphosphataemia	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Hyperuricaemia	0	(0.00)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	1	(0.33)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Nervous system disorders	8	(6.20)	6	(5.41)	0	(0.00)	1	(5.00)	0	(0.00)	15	(4.97)
Headache	0	(0.00)	4	(3.60)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Head discomfort	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hypoaesthesia	2	(1.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Neuropathy peripheral	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Peripheral sensory neuropathy	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Dizziness	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Somnolence	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Syncope	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Tremor	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Facial nerve disorder	0	(0.00)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	1	(0.33)
Eye disorders	3	(2.33)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	5	(1.66)
Eyelid oedema	2	(1.55)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Conjunctival hyperaemia	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Deafness	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Cardiac disorders	4	(3.10)	1	(0.90)	2	(5.56)	1	(5.00)	0	(0.00)	8	(2.65)
Arrhythmia	1	(0.78)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	2	(0.66)
Bradycardia	2	(1.55)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	1	(0.33)
Cardiac failure	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Myocarditis	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Vascular disorders	1	(0.78)	5	(4.50)	2	(5.56)	2	(10.00)	0	(0.00)	10	(3.31)
Flushing	1	(0.78)	4	(3.60)	0	(0.00)	0	(0.00)	0	(0.00)	5	(1.66)
Hypotension	0	(0.00)	0	(0.00)	2	(5.56)	2	(10.00)	0	(0.00)	4	(1.32)
Hot flush	0	(0.00)	1	(0.90)	0	(0.00)	1	(5.00)	0	(0.00)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	15	(11.63)	23	(20.72)	4	(11.11)	3	(15.00)	0	(0.00)	45	(14.90)
Dyspnoea	5	(3.88)	8	(7.21)	2	(5.56)	3	(15.00)	0	(0.00)	18	(5.96)
Cough	3	(2.33)	5	(4.50)	0	(0.00)	0	(0.00)	0	(0.00)	8	(2.65)
Oropharyngeal discomfort	2	(1.55)	5	(4.50)	0	(0.00)	0	(0.00)	0	(0.00)	7	(2.32)
Hypoxia	0	(0.00)	3	(2.70)	1	(2.78)	0	(0.00)	0	(0.00)	4	(1.32)
Throat irritation	2	(1.55)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Laryngeal discomfort	1	(0.78)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.99)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Nasal congestion	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Pharyngeal oedema	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Productive cough	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Sneezing	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Hiccups	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Laryngeal oedema	0	(0.00)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	1	(0.33)
Oropharyngeal swelling	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Pleural effusion	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Respiratory failure	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Rhinorrhoea	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Wheezing	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oropharyngeal pain	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	11	(8.53)	8	(7.21)	2	(5.56)	1	(5.00)	0	(0.00)	22	(7.28)
Nausea	4	(3.10)	2	(1.80)	2	(5.56)	1	(5.00)	0	(0.00)	9	(2.98)
Vomiting	3	(2.33)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	5	(1.66)
Abdominal discomfort	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Diarrhoea	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Oral discomfort	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Hypoaesthesia oral	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Abdominal pain lower	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Constipation	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Dry mouth	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Rectal haemorrhage	0	(0.00)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	3	(2.33)	1	(0.90)	0	(0.00)	0	(0.00)	1	(16.67)	5	(1.66)
Hepatic function abnormal	2	(1.55)	0	(0.00)	0	(0.00)	0	(0.00)	1	(16.67)	3	(0.99)
Cholangitis	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Liver disorder	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	56	(43.41)	37	(33.33)	6	(16.67)	4	(20.00)	1	(16.67)	104	(34.44)
Rash	28	(21.71)	18	(16.22)	2	(5.56)	1	(5.00)	1	(16.67)	50	(16.56)
Urticaria	13	(10.08)	10	(9.01)	2	(5.56)	2	(10.00)	0	(0.00)	27	(8.94)
Pruritus	4	(3.10)	5	(4.50)	1	(2.78)	0	(0.00)	0	(0.00)	10	(3.31)
Erythema	4	(3.10)	4	(3.60)	1	(2.78)	0	(0.00)	0	(0.00)	9	(2.98)
Hyperhidrosis	2	(1.55)	2	(1.80)	2	(5.56)	1	(5.00)	0	(0.00)	7	(2.32)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Rash pruritic	3	(2.33)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Cold sweat	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Eczema	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Rash macular	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Skin disorder	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Toxic skin eruption	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(0.78)	2	(1.80)	1	(2.78)	0	(0.00)	0	(0.00)	4	(1.32)
Back pain	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Arthralgia	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Neck pain	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Limb discomfort	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Renal and urinary disorders	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Renal impairment	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Menopausal symptoms	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	29	(22.48)	32	(28.83)	8	(22.22)	5	(25.00)	0	(0.00)	74	(24.50)
Pyrexia	21	(16.28)	18	(16.22)	4	(11.11)	4	(20.00)	0	(0.00)	47	(15.56)
Chills	9	(6.98)	12	(10.81)	3	(8.33)	3	(15.00)	0	(0.00)	27	(8.94)
Chest discomfort	2	(1.55)	2	(1.80)	1	(2.78)	0	(0.00)	0	(0.00)	5	(1.66)
Oedema	1	(0.78)	3	(2.70)	0	(0.00)	0	(0.00)	0	(0.00)	4	(1.32)
Chest pain	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Fatigue	1	(0.78)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	2	(0.66)
Feeling hot	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Face oedema	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Feeling cold	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Malaise	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
Oedema mucosal	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Oedema peripheral	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Pain	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Non-cardiac chest pain	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Investigations	22	(17.05)	16	(14.41)	9	(25.00)	4	(20.00)	0	(0.00)	51	(16.89)
Neutrophil count decreased	7	(5.43)	7	(6.31)	4	(11.11)	1	(5.00)	0	(0.00)	19	(6.29)
White blood cell count decreased	4	(3.10)	5	(4.50)	3	(8.33)	2	(10.00)	0	(0.00)	14	(4.64)

	ECOG PS										Total	
	0		1		2		3		4			
Number of patients with adverse drug reactions	95		76		19		12		2		204	
Incidence of adverse drug reactions	(73.64)		(68.47)		(52.78)		(60.00)		(33.33)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type											
Blood pressure decreased	6	(4.65)	2	(1.80)	2	(5.56)	0	(0.00)	0	(0.00)	10	(3.31)
Platelet count decreased	3	(2.33)	3	(2.70)	0	(0.00)	2	(10.00)	0	(0.00)	8	(2.65)
Oxygen saturation decreased	5	(3.88)	1	(0.90)	1	(2.78)	0	(0.00)	0	(0.00)	7	(2.32)
Alanine aminotransferase increased	0	(0.00)	2	(1.80)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Blood pressure increased	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	1	(0.78)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	2	(0.66)
Weight increased	1	(0.78)	0	(0.00)	0	(0.00)	1	(5.00)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Blood creatinine increased	0	(0.00)	0	(0.00)	1	(2.78)	0	(0.00)	0	(0.00)	1	(0.33)
C-reactive protein increased	1	(0.78)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Haemoglobin decreased	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)
Lymphocyte count decreased	0	(0.00)	1	(0.90)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.33)

Source:Table 21_07_01

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.

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10.5.9.5 Concomitant medications

The occurrence of adverse drug reactions by presence or absence of concomitant medications is shown in Table 10-41.

Of the 302 patients in the safety analysis set, 225 patients (74.50%) had concomitant medications and 77 patients (25.50%) did not have concomitant medications (Table 10-2).

The most common adverse drug reactions in both populations were rash and pyrexia. Common adverse drug reactions (≥5 patients) observed only in patients with concomitant medications were cough and platelet count decreased in 3.56% (8 patients) each and herpes zoster and tumour lysis syndrome in 2.22% (5 patients) each.

The incidence of serious adverse drug reactions was 13.78% (31/225 patients) in patients with concomitant medications and 14.29% (11/77 patients) in patients without concomitant medications, showing comparable values (analysis results, Table 21_08_02).

The outcomes of serious adverse drug reactions were resolved in 13 patients, resolving in 7 patients, not resolved in 6 patients, with sequelae in 1 patient, and fatal in 4 patients in patients with concomitant drugs, and resolved in 5 patients, resolving in 3 patients, and fatal in 2 patients in patients without concomitant medications (analysis results, Table 21_08_03).

Although the incidence of adverse drug reactions was higher in patients concomitantly receiving therapeutic drugs than in those without, the incidence of serious adverse drug reactions was comparable, and there were no notable trends in the type, seriousness, and outcome of adverse drug reactions.

Table 10-41 Occurrence of adverse drug reactions by presence or absence of concomitant medications (safety analysis set)

	Concomitant medications				Total	
	No		Yes			
Number of patients with adverse drug reactions	45		159		204	
Incidence of adverse drug reactions	(58.44)		(70.67)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	5	(6.49)	26	(11.56)	31	(10.26)
Pneumonia	1	(1.30)	8	(3.56)	9	(2.98)
Herpes zoster	0	(0.00)	5	(2.22)	5	(1.66)
Infection	0	(0.00)	3	(1.33)	3	(0.99)
Sepsis	0	(0.00)	2	(0.89)	2	(0.66)
Urinary tract infection	0	(0.00)	2	(0.89)	2	(0.66)
Bronchitis	1	(1.30)	0	(0.00)	1	(0.33)
Cellulitis	0	(0.00)	1	(0.44)	1	(0.33)
Hepatitis B	1	(1.30)	0	(0.00)	1	(0.33)
Influenza	1	(1.30)	0	(0.00)	1	(0.33)
Nasopharyngitis	0	(0.00)	1	(0.44)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.44)	1	(0.33)
Otitis media	0	(0.00)	1	(0.44)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.44)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.44)	1	(0.33)
Pyelonephritis	1	(1.30)	0	(0.00)	1	(0.33)
Subcutaneous abscess	0	(0.00)	1	(0.44)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.44)	1	(0.33)
Oral herpes	0	(0.00)	1	(0.44)	1	(0.33)
Candida infection	0	(0.00)	1	(0.44)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.00)	4	(1.78)	4	(1.32)
Chronic lymphocytic leukemia	0	(0.00)	4	(1.78)	4	(1.32)
Blood and lymphatic system disorders	4	(5.19)	16	(7.11)	20	(6.62)
Anaemia	1	(1.30)	7	(3.11)	8	(2.65)

	Concomitant medications				Total	
	No		Yes			
Number of patients with adverse drug reactions	45		159		204	
Incidence of adverse drug reactions	(58.44)		(70.67)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Febrile neutropenia	0	(0.00)	4	(1.78)	4	(1.32)
Disseminated intravascular coagulation	1	(1.30)	1	(0.44)	2	(0.66)
Neutropenia	1	(1.30)	1	(0.44)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(0.89)	2	(0.66)
Hematotoxicity	1	(1.30)	1	(0.44)	2	(0.66)
Lymph node pain	0	(0.00)	1	(0.44)	1	(0.33)
Lymphadenopathy	0	(0.00)	1	(0.44)	1	(0.33)
Immune system disorders	1	(1.30)	2	(0.89)	3	(0.99)
Anaphylactoid reaction	1	(1.30)	1	(0.44)	2	(0.66)
Hypersensitivity	0	(0.00)	1	(0.44)	1	(0.33)
Metabolism and nutrition disorders	0	(0.00)	7	(3.11)	7	(2.32)
Tumour lysis syndrome	0	(0.00)	5	(2.22)	5	(1.66)
Hyperkalaemia	0	(0.00)	1	(0.44)	1	(0.33)
Hyperphosphataemia	0	(0.00)	1	(0.44)	1	(0.33)
Hyperuricaemia	0	(0.00)	1	(0.44)	1	(0.33)
Nervous system disorders	5	(6.49)	10	(4.44)	15	(4.97)
Headache	0	(0.00)	4	(1.78)	4	(1.32)
Head discomfort	1	(1.30)	1	(0.44)	2	(0.66)
Hypoaesthesia	1	(1.30)	1	(0.44)	2	(0.66)
Neuropathy peripheral	0	(0.00)	2	(0.89)	2	(0.66)
Peripheral sensory neuropathy	0	(0.00)	2	(0.89)	2	(0.66)
Dizziness	0	(0.00)	1	(0.44)	1	(0.33)
Haemorrhagic cerebral infarction	1	(1.30)	0	(0.00)	1	(0.33)
Somnolence	1	(1.30)	0	(0.00)	1	(0.33)
Syncope	1	(1.30)	0	(0.00)	1	(0.33)
Tremor	0	(0.00)	1	(0.44)	1	(0.33)
Facial nerve disorder	0	(0.00)	1	(0.44)	1	(0.33)
Eye disorders	1	(1.30)	4	(1.78)	5	(1.66)
Eyelid oedema	1	(1.30)	3	(1.33)	4	(1.32)
Conjunctival hyperaemia	0	(0.00)	1	(0.44)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.44)	1	(0.33)
Deafness	0	(0.00)	1	(0.44)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.44)	1	(0.33)
Cardiac disorders	1	(1.30)	7	(3.11)	8	(2.65)
Arrhythmia	1	(1.30)	1	(0.44)	2	(0.66)

	Concomitant medications				Total	
	No		Yes			
Number of patients with adverse drug reactions	45		159		204	
Incidence of adverse drug reactions	(58.44)		(70.67)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Bradycardia	0	(0.00)	2	(0.89)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	1	(0.44)	1	(0.33)
Cardiac failure	0	(0.00)	1	(0.44)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.44)	1	(0.33)
Myocarditis	0	(0.00)	1	(0.44)	1	(0.33)
Vascular disorders	1	(1.30)	9	(4.00)	10	(3.31)
Flushing	1	(1.30)	4	(1.78)	5	(1.66)
Hypotension	0	(0.00)	4	(1.78)	4	(1.32)
Hot flush	0	(0.00)	2	(0.89)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	7	(9.09)	38	(16.89)	45	(14.90)
Dyspnoea	2	(2.60)	16	(7.11)	18	(5.96)
Cough	0	(0.00)	8	(3.56)	8	(2.65)
Oropharyngeal discomfort	2	(2.60)	5	(2.22)	7	(2.32)
Hypoxia	0	(0.00)	4	(1.78)	4	(1.32)
Throat irritation	0	(0.00)	4	(1.78)	4	(1.32)
Laryngeal discomfort	0	(0.00)	3	(1.33)	3	(0.99)
Nasal congestion	0	(0.00)	2	(0.89)	2	(0.66)
Pharyngeal oedema	0	(0.00)	2	(0.89)	2	(0.66)
Productive cough	0	(0.00)	2	(0.89)	2	(0.66)
Sneezing	0	(0.00)	2	(0.89)	2	(0.66)
Acute respiratory distress syndrome	1	(1.30)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.44)	1	(0.33)
Hiccups	1	(1.30)	0	(0.00)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.44)	1	(0.33)
Oropharyngeal swelling	0	(0.00)	1	(0.44)	1	(0.33)
Pleural effusion	0	(0.00)	1	(0.44)	1	(0.33)
Respiratory failure	0	(0.00)	1	(0.44)	1	(0.33)
Rhinorrhoea	0	(0.00)	1	(0.44)	1	(0.33)
Wheezing	1	(1.30)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	0	(0.00)	1	(0.44)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.44)	1	(0.33)
Oropharyngeal pain	1	(1.30)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	6	(7.79)	16	(7.11)	22	(7.28)
Nausea	1	(1.30)	8	(3.56)	9	(2.98)
Vomiting	3	(3.90)	2	(0.89)	5	(1.66)

	Concomitant medications				Total	
	No		Yes			
Number of patients with adverse drug reactions	45		159		204	
Incidence of adverse drug reactions	(58.44)		(70.67)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Abdominal discomfort	0	(0.00)	2	(0.89)	2	(0.66)
Diarrhoea	0	(0.00)	2	(0.89)	2	(0.66)
Oral discomfort	0	(0.00)	2	(0.89)	2	(0.66)
Hypoaesthesia oral	0	(0.00)	2	(0.89)	2	(0.66)
Abdominal pain lower	1	(1.30)	0	(0.00)	1	(0.33)
Constipation	0	(0.00)	1	(0.44)	1	(0.33)
Dry mouth	1	(1.30)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.44)	1	(0.33)
Rectal haemorrhage	0	(0.00)	1	(0.44)	1	(0.33)
Hepatobiliary disorders	1	(1.30)	4	(1.78)	5	(1.66)
Hepatic function abnormal	1	(1.30)	2	(0.89)	3	(0.99)
Cholangitis	0	(0.00)	1	(0.44)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.44)	1	(0.33)
Liver disorder	0	(0.00)	1	(0.44)	1	(0.33)
Skin and subcutaneous tissue disorders	26	(33.77)	78	(34.67)	104	(34.44)
Rash	9	(11.69)	41	(18.22)	50	(16.56)
Urticaria	8	(10.39)	19	(8.44)	27	(8.94)
Pruritus	3	(3.90)	7	(3.11)	10	(3.31)
Erythema	3	(3.90)	6	(2.67)	9	(2.98)
Hyperhidrosis	1	(1.30)	6	(2.67)	7	(2.32)
Rash pruritic	1	(1.30)	3	(1.33)	4	(1.32)
Cold sweat	0	(0.00)	2	(0.89)	2	(0.66)
Eczema	1	(1.30)	0	(0.00)	1	(0.33)
Rash macular	0	(0.00)	1	(0.44)	1	(0.33)
Rash maculo-papular	0	(0.00)	1	(0.44)	1	(0.33)
Skin disorder	0	(0.00)	1	(0.44)	1	(0.33)
Toxic skin eruption	1	(1.30)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(1.30)	3	(1.33)	4	(1.32)
Back pain	1	(1.30)	1	(0.44)	2	(0.66)
Arthralgia	0	(0.00)	1	(0.44)	1	(0.33)
Neck pain	0	(0.00)	1	(0.44)	1	(0.33)
Limb discomfort	0	(0.00)	1	(0.44)	1	(0.33)
Renal and urinary disorders	1	(1.30)	1	(0.44)	2	(0.66)
Renal impairment	1	(1.30)	1	(0.44)	2	(0.66)

	Concomitant medications				Total	
	No		Yes			
Number of patients with adverse drug reactions	45		159		204	
Incidence of adverse drug reactions	(58.44)		(70.67)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Reproductive system and breast disorders	0	(0.00)	1	(0.44)	1	(0.33)
Menopausal symptoms	0	(0.00)	1	(0.44)	1	(0.33)
General disorders and administration site conditions	14	(18.18)	60	(26.67)	74	(24.50)
Pyrexia	10	(12.99)	37	(16.44)	47	(15.56)
Chills	8	(10.39)	19	(8.44)	27	(8.94)
Chest discomfort	1	(1.30)	4	(1.78)	5	(1.66)
Oedema	0	(0.00)	4	(1.78)	4	(1.32)
Chest pain	0	(0.00)	2	(0.89)	2	(0.66)
Fatigue	0	(0.00)	2	(0.89)	2	(0.66)
Feeling hot	0	(0.00)	2	(0.89)	2	(0.66)
Face oedema	0	(0.00)	1	(0.44)	1	(0.33)
Feeling abnormal	1	(1.30)	0	(0.00)	1	(0.33)
Feeling cold	0	(0.00)	1	(0.44)	1	(0.33)
Malaise	0	(0.00)	1	(0.44)	1	(0.33)
Oedema mucosal	0	(0.00)	1	(0.44)	1	(0.33)
Oedema peripheral	0	(0.00)	1	(0.44)	1	(0.33)
Pain	0	(0.00)	1	(0.44)	1	(0.33)
Non-cardiac chest pain	0	(0.00)	1	(0.44)	1	(0.33)
Investigations	8	(10.39)	43	(19.11)	51	(16.89)
Neutrophil count decreased	5	(6.49)	14	(6.22)	19	(6.29)
White blood cell count decreased	2	(2.60)	12	(5.33)	14	(4.64)
Blood pressure decreased	1	(1.30)	9	(4.00)	10	(3.31)
Platelet count decreased	0	(0.00)	8	(3.56)	8	(2.65)
Oxygen saturation decreased	2	(2.60)	5	(2.22)	7	(2.32)
Alanine aminotransferase increased	0	(0.00)	2	(0.89)	2	(0.66)
Blood pressure increased	1	(1.30)	1	(0.44)	2	(0.66)
Gamma-glutamyltransferase increased	0	(0.00)	2	(0.89)	2	(0.66)
Weight increased	0	(0.00)	2	(0.89)	2	(0.66)
Aspartate aminotransferase increased	0	(0.00)	1	(0.44)	1	(0.33)
Blood creatinine increased	0	(0.00)	1	(0.44)	1	(0.33)
C-reactive protein increased	0	(0.00)	1	(0.44)	1	(0.33)
Haemoglobin decreased	0	(0.00)	1	(0.44)	1	(0.33)
Lymphocyte count decreased	0	(0.00)	1	(0.44)	1	(0.33)

Source:Table 21_08_01

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
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10.5.10 Patients with special background

10.5.10.1 Children (<15 years)

No pediatric use (<15 years) was collected from the 302 patients in the safety analysis set.

10.5.10.2 Elderly (≥65 years)

The occurrence of adverse drug reactions and serious adverse drug reactions in elderly and non-elderly patients are shown in Table 10-42 and Table 10-43, respectively.

Of the 302 patients in the safety analysis set, 226 patients (74.83%) were elderly aged ≥65 years (Table 10-2).

The most common adverse drug reactions in both populations were rash and pyrexia.

The incidence of serious adverse drug reactions was 15.49% (35/226 patients) in the elderly and 9.59% (7/73 patients) in the non-elderly. Common serious adverse drug reactions observed in the elderly were pneumonia in 2.21% (5/226 patients), neutrophil count decreased in 1.77% (4/226 patients), and herpes zoster and white blood cell count decreased in 1.33% (3/226 patients) each. The incidences of serious adverse drug reactions that occurred in non-elderly patients were all 1.37% (1/73 patients), and there was no serious adverse drug reaction that occurred in ≥2 patients.

The incidence of serious adverse drug reactions was higher in the elderly, but there was no notable trend in the type and seriousness of adverse drug reactions. In addition, caution should be exercised because elderly patients generally have reduced physiological function and adverse drug reactions tend to become serious.

Table 10-42 Occurrence of adverse drug reactions in elderly and non-elderly patients (safety analysis set)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Infections and infestations	4	(5.48)	27	(11.95)	0	(0.00)	31	(10.26)
Pneumonia	1	(1.37)	8	(3.54)	0	(0.00)	9	(2.98)
Herpes zoster	0	(0.00)	5	(2.21)	0	(0.00)	5	(1.66)
Infection	1	(1.37)	2	(0.88)	0	(0.00)	3	(0.99)
Sepsis	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Urinary tract infection	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Bronchitis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Cellulitis	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Hepatitis B	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Influenza	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Nasopharyngitis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Otitis media	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Periodontitis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Pyelonephritis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Subcutaneous abscess	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Hepatitis B reactivation	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Oral herpes	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Candida infection	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.37)	3	(1.33)	0	(0.00)	4	(1.32)
Chronic lymphocytic leukemia	1	(1.37)	3	(1.33)	0	(0.00)	4	(1.32)
Blood and lymphatic system disorders	2	(2.74)	18	(7.96)	0	(0.00)	20	(6.62)
Anaemia	1	(1.37)	7	(3.10)	0	(0.00)	8	(2.65)
Febrile neutropenia	0	(0.00)	4	(1.77)	0	(0.00)	4	(1.32)
Disseminated intravascular coagulation	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Neutropenia	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Thrombocytopenia	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Hematotoxicity	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Lymph node pain	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Lymphadenopathy	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Immune system disorders	1	(1.37)	2	(0.88)	0	(0.00)	3	(0.99)
Anaphylactoid reaction	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Hypersensitivity	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	2	(2.74)	5	(2.21)	0	(0.00)	7	(2.32)
Tumour lysis syndrome	1	(1.37)	4	(1.77)	0	(0.00)	5	(1.66)
Hyperkalaemia	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Hyperphosphataemia	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Hyperuricaemia	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Nervous system disorders	6	(8.22)	9	(3.98)	0	(0.00)	15	(4.97)
Headache	2	(2.74)	2	(0.88)	0	(0.00)	4	(1.32)
Head discomfort	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Hypoaesthesia	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Neuropathy peripheral	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Peripheral sensory neuropathy	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Dizziness	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Haemorrhagic cerebral infarction	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Somnolence	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Syncope	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Tremor	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Facial nerve disorder	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Eye disorders	2	(2.74)	3	(1.33)	0	(0.00)	5	(1.66)
Eyelid oedema	2	(2.74)	2	(0.88)	0	(0.00)	4	(1.32)
Conjunctival hyperaemia	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Deafness	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Ear discomfort	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Cardiac disorders	2	(2.74)	6	(2.65)	0	(0.00)	8	(2.65)
Arrhythmia	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Bradycardia	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Atrioventricular block second degree	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Cardiac failure	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Myocarditis	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Vascular disorders	3	(4.11)	7	(3.10)	0	(0.00)	10	(3.31)
Flushing	0	(0.00)	5	(2.21)	0	(0.00)	5	(1.66)
Hypotension	3	(4.11)	1	(0.44)	0	(0.00)	4	(1.32)
Hot flush	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	8	(10.96)	36	(15.93)	1	(33.33)	45	(14.90)
Dyspnoea	2	(2.74)	16	(7.08)	0	(0.00)	18	(5.96)
Cough	2	(2.74)	6	(2.65)	0	(0.00)	8	(2.65)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Oropharyngeal discomfort	1	(1.37)	6	(2.65)	0	(0.00)	7	(2.32)
Hypoxia	1	(1.37)	3	(1.33)	0	(0.00)	4	(1.32)
Throat irritation	0	(0.00)	4	(1.77)	0	(0.00)	4	(1.32)
Laryngeal discomfort	1	(1.37)	2	(0.88)	0	(0.00)	3	(0.99)
Nasal congestion	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Pharyngeal oedema	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Productive cough	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Sneezing	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Dysphonia	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Hiccups	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Oropharyngeal swelling	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Pleural effusion	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Respiratory failure	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Rhinorrhoea	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Wheezing	0	(0.00)	0	(0.00)	1	(33.33)	1	(0.33)
Upper respiratory tract inflammation	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Larynx irritation	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Oropharyngeal pain	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	4	(5.48)	18	(7.96)	0	(0.00)	22	(7.28)
Nausea	3	(4.11)	6	(2.65)	0	(0.00)	9	(2.98)
Vomiting	1	(1.37)	4	(1.77)	0	(0.00)	5	(1.66)
Abdominal discomfort	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Diarrhoea	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Oral discomfort	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Hypoaesthesia oral	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Abdominal pain lower	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Constipation	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Dry mouth	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Enterocolitis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Rectal haemorrhage	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	1	(1.37)	4	(1.77)	0	(0.00)	5	(1.66)
Hepatic function abnormal	0	(0.00)	3	(1.33)	0	(0.00)	3	(0.99)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Cholangitis	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Liver disorder	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	29	(39.73)	73	(32.30)	2	(66.67)	104	(34.44)
Rash	15	(20.55)	35	(15.49)	0	(0.00)	50	(16.56)
Urticaria	5	(6.85)	21	(9.29)	1	(33.33)	27	(8.94)
Pruritus	5	(6.85)	5	(2.21)	0	(0.00)	10	(3.31)
Erythema	1	(1.37)	7	(3.10)	1	(33.33)	9	(2.98)
Hyperhidrosis	2	(2.74)	5	(2.21)	0	(0.00)	7	(2.32)
Rash pruritic	1	(1.37)	3	(1.33)	0	(0.00)	4	(1.32)
Cold sweat	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Eczema	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Rash macular	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Skin disorder	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Toxic skin eruption	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	1	(1.37)	3	(1.33)	0	(0.00)	4	(1.32)
Back pain	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Arthralgia	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Neck pain	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Limb discomfort	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Renal and urinary disorders	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Renal impairment	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Menopausal symptoms	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	23	(31.51)	49	(21.68)	2	(66.67)	74	(24.50)
Pyrexia	16	(21.92)	30	(13.27)	1	(33.33)	47	(15.56)
Chills	9	(12.33)	17	(7.52)	1	(33.33)	27	(8.94)
Chest discomfort	1	(1.37)	4	(1.77)	0	(0.00)	5	(1.66)
Oedema	2	(2.74)	2	(0.88)	0	(0.00)	4	(1.32)
Chest pain	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Fatigue	2	(2.74)	0	(0.00)	0	(0.00)	2	(0.66)

	Age (65 years)						Total	
	<65 years		≥65 years		Unknown or not entered			
Number of patients with adverse drug reactions	51		150		3		204	
Incidence of adverse drug reactions	(69.86)		(66.37)		(100.00)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type							
Feeling hot	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Face oedema	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Feeling abnormal	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Feeling cold	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Malaise	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Oedema mucosal	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Oedema peripheral	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Pain	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Non-cardiac chest pain	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Investigations	14	(19.18)	37	(16.37)	0	(0.00)	51	(16.89)
Neutrophil count decreased	4	(5.48)	15	(6.64)	0	(0.00)	19	(6.29)
White blood cell count decreased	4	(5.48)	10	(4.42)	0	(0.00)	14	(4.64)
Blood pressure decreased	5	(6.85)	5	(2.21)	0	(0.00)	10	(3.31)
Platelet count decreased	4	(5.48)	4	(1.77)	0	(0.00)	8	(2.65)
Oxygen saturation decreased	0	(0.00)	7	(3.10)	0	(0.00)	7	(2.32)
Alanine aminotransferase increased	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Blood pressure increased	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	0	(0.00)	2	(0.88)	0	(0.00)	2	(0.66)
Weight increased	1	(1.37)	1	(0.44)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Blood creatinine increased	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
C-reactive protein increased	0	(0.00)	1	(0.44)	0	(0.00)	1	(0.33)
Haemoglobin decreased	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)
Lymphocyte count decreased	1	(1.37)	0	(0.00)	0	(0.00)	1	(0.33)

Source:Table 21_01_01

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.

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Table 10-43 Occurrence of serious adverse drug reactions in elderly and non-elderly patients (safety analysis set)

	Age (65 years)				Total	
	<65 years		≥65 years			
Number of patients with adverse drug reactions	7		35		42	
Incidence of adverse drug reactions	(9.59)		(15.49)		(13.91)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	2	(2.74)	17	(7.52)	19	(6.29)
Pneumonia	1	(1.37)	5	(2.21)	6	(1.99)
Herpes zoster	0	(0.00)	3	(1.33)	3	(0.99)
Infection	1	(1.37)	1	(0.44)	2	(0.66)
Sepsis	0	(0.00)	2	(0.88)	2	(0.66)
Bronchitis	0	(0.00)	1	(0.44)	1	(0.33)
Hepatitis B	0	(0.00)	1	(0.44)	1	(0.33)
Influenza	0	(0.00)	1	(0.44)	1	(0.33)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.44)	1	(0.33)
Pyelonephritis	0	(0.00)	1	(0.44)	1	(0.33)
Urinary tract infection	0	(0.00)	1	(0.44)	1	(0.33)
Oral herpes	0	(0.00)	1	(0.44)	1	(0.33)
Candida infection	0	(0.00)	1	(0.44)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(1.37)	0	(0.00)	1	(0.33)
Chronic lymphocytic leukemia	1	(1.37)	0	(0.00)	1	(0.33)
Blood and lymphatic system disorders	0	(0.00)	4	(1.77)	4	(1.32)
Febrile neutropenia	0	(0.00)	2	(0.88)	2	(0.66)
Disseminated intravascular coagulation	0	(0.00)	1	(0.44)	1	(0.33)
Hematotoxicity	0	(0.00)	1	(0.44)	1	(0.33)
Metabolism and nutrition disorders	0	(0.00)	3	(1.33)	3	(0.99)
Tumour lysis syndrome	0	(0.00)	2	(0.88)	2	(0.66)
Hyperkalaemia	0	(0.00)	1	(0.44)	1	(0.33)
Hyperphosphataemia	0	(0.00)	1	(0.44)	1	(0.33)
Nervous system disorders	1	(1.37)	1	(0.44)	2	(0.66)
Haemorrhagic cerebral infarction	1	(1.37)	0	(0.00)	1	(0.33)
Syncope	0	(0.00)	1	(0.44)	1	(0.33)
Cardiac disorders	1	(1.37)	2	(0.88)	3	(0.99)
Arrhythmia	0	(0.00)	1	(0.44)	1	(0.33)
Cardiac failure chronic	0	(0.00)	1	(0.44)	1	(0.33)
Myocarditis	1	(1.37)	0	(0.00)	1	(0.33)
Respiratory, thoracic and mediastinal disorders	1	(1.37)	4	(1.77)	5	(1.66)
Dyspnoea	1	(1.37)	1	(0.44)	2	(0.66)
Acute respiratory distress syndrome	0	(0.00)	1	(0.44)	1	(0.33)
Laryngeal oedema	0	(0.00)	1	(0.44)	1	(0.33)

	Age (65 years)		Total
	<65 years	≥65 years	
Number of patients with adverse drug reactions	7	35	42
Incidence of adverse drug reactions	(9.59)	(15.49)	(13.91)
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type		
Pleural effusion	0 (0.00)	1 (0.44)	1 (0.33)
Respiratory failure	0 (0.00)	1 (0.44)	1 (0.33)
Hepatobiliary disorders	0 (0.00)	3 (1.33)	3 (0.99)
Hepatic function abnormal	0 (0.00)	2 (0.88)	2 (0.66)
Cholangitis	0 (0.00)	1 (0.44)	1 (0.33)
Cholecystitis acute	0 (0.00)	1 (0.44)	1 (0.33)
Skin and subcutaneous tissue disorders	0 (0.00)	3 (1.33)	3 (0.99)
Rash	0 (0.00)	2 (0.88)	2 (0.66)
Urticaria	0 (0.00)	1 (0.44)	1 (0.33)
General disorders and administration site conditions	1 (1.37)	2 (0.88)	3 (0.99)
Pyrexia	1 (1.37)	1 (0.44)	2 (0.66)
Chills	0 (0.00)	1 (0.44)	1 (0.33)
Oedema mucosal	0 (0.00)	1 (0.44)	1 (0.33)
Investigations	2 (2.74)	8 (3.54)	10 (3.31)
Neutrophil count decreased	1 (1.37)	4 (1.77)	5 (1.66)
White blood cell count decreased	1 (1.37)	3 (1.33)	4 (1.32)
Blood creatinine increased	0 (0.00)	1 (0.44)	1 (0.33)
Oxygen saturation decreased	0 (0.00)	1 (0.44)	1 (0.33)

Source:Table 21_01_02
SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
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10.5.10.3Pregnant women

No cases of use in pregnant and parturient women were collected.

10.5.10.4Patients complicated with renal dysfunction

The occurrence of adverse drug reactions and serious adverse drug reactions by presence or absence of concurrent renal dysfunction are shown in Table 10-44 and Table 10-45, respectively.

Of the 302 patients in the safety analysis set, 35 patients (11.59%) had concurrent renal dysfunction at the start of treatment (Table 10-2).

The incidence of adverse drug reactions in the patients complicated with renal dysfunction was 65.71% (23/35 patients) while that in the patients not complicated with renal dysfunction was 67.79% (181/267 patients), showing no major difference.

The most common adverse drug reactions in both populations were rash and pyrexia. The adverse drug reactions that occurred only in the patients complicated with renal dysfunction were influenza, oral candidiasis, constipation, and oedema mucosal, but they occurred in 1 patient each and also in the patients not complicated with renal dysfunction, and there were no major differences in the types of adverse drug reactions that occurred between the patients complicated with renal dysfunction and the patients not complicated with renal dysfunction.

The incidence of serious adverse drug reactions was 11.43% (4/35 patients) in the patients complicated with renal dysfunction and 14.23% (38/267 patients) in the patients not complicated with renal dysfunction.

The serious adverse drug reactions in the patients complicated with renal dysfunction were pneumonia in 5.71% (2/35 patients), and influenza, tumour lysis syndrome, rash, and oedema mucosal in 2.86% (1/35 patients) each.

In the results of this study, worsening of renal dysfunction including laboratory abnormalities was not observed in patients complicated with renal dysfunction.

Table 10-44 Occurrence of adverse drug reactions by presence or absence of concurrent renal dysfunction (safety analysis set)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	181		23		204	
Incidence of adverse drug reactions	(67.79)		(65.71)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	27	(10.11)	4	(11.43)	31	(10.26)
Pneumonia	7	(2.62)	2	(5.71)	9	(2.98)
Herpes zoster	5	(1.87)	0	(0.00)	5	(1.66)
Infection	3	(1.12)	0	(0.00)	3	(0.99)
Sepsis	2	(0.75)	0	(0.00)	2	(0.66)
Urinary tract infection	2	(0.75)	0	(0.00)	2	(0.66)
Bronchitis	1	(0.37)	0	(0.00)	1	(0.33)
Cellulitis	1	(0.37)	0	(0.00)	1	(0.33)
Hepatitis B	1	(0.37)	0	(0.00)	1	(0.33)
Influenza	0	(0.00)	1	(2.86)	1	(0.33)
Nasopharyngitis	1	(0.37)	0	(0.00)	1	(0.33)
Oral candidiasis	0	(0.00)	1	(2.86)	1	(0.33)
Otitis media	1	(0.37)	0	(0.00)	1	(0.33)
Periodontitis	1	(0.37)	0	(0.00)	1	(0.33)
Progressive multifocal leukoencephalopathy	1	(0.37)	0	(0.00)	1	(0.33)
Pyelonephritis	1	(0.37)	0	(0.00)	1	(0.33)
Subcutaneous abscess	1	(0.37)	0	(0.00)	1	(0.33)
Hepatitis B reactivation	1	(0.37)	0	(0.00)	1	(0.33)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	181		23		204	
Incidence of adverse drug reactions	(67.79)		(65.71)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Oral herpes	1	(0.37)	0	(0.00)	1	(0.33)
Candida infection	1	(0.37)	0	(0.00)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(1.12)	1	(2.86)	4	(1.32)
Chronic lymphocytic leukemia	3	(1.12)	1	(2.86)	4	(1.32)
Blood and lymphatic system disorders	19	(7.12)	1	(2.86)	20	(6.62)
Anaemia	8	(3.00)	0	(0.00)	8	(2.65)
Febrile neutropenia	3	(1.12)	1	(2.86)	4	(1.32)
Disseminated intravascular coagulation	2	(0.75)	0	(0.00)	2	(0.66)
Neutropenia	2	(0.75)	0	(0.00)	2	(0.66)
Thrombocytopenia	2	(0.75)	0	(0.00)	2	(0.66)
Hematotoxicity	2	(0.75)	0	(0.00)	2	(0.66)
Lymph node pain	1	(0.37)	0	(0.00)	1	(0.33)
Lymphadenopathy	1	(0.37)	0	(0.00)	1	(0.33)
Immune system disorders	3	(1.12)	0	(0.00)	3	(0.99)
Anaphylactoid reaction	2	(0.75)	0	(0.00)	2	(0.66)
Hypersensitivity	1	(0.37)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	5	(1.87)	2	(5.71)	7	(2.32)
Tumour lysis syndrome	3	(1.12)	2	(5.71)	5	(1.66)
Hyperkalaemia	1	(0.37)	0	(0.00)	1	(0.33)
Hyperphosphataemia	1	(0.37)	0	(0.00)	1	(0.33)
Hyperuricaemia	1	(0.37)	0	(0.00)	1	(0.33)
Nervous system disorders	14	(5.24)	1	(2.86)	15	(4.97)
Headache	4	(1.50)	0	(0.00)	4	(1.32)
Head discomfort	2	(0.75)	0	(0.00)	2	(0.66)
Hypoaesthesia	1	(0.37)	1	(2.86)	2	(0.66)
Neuropathy peripheral	2	(0.75)	0	(0.00)	2	(0.66)
Peripheral sensory neuropathy	2	(0.75)	0	(0.00)	2	(0.66)
Dizziness	1	(0.37)	0	(0.00)	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.37)	0	(0.00)	1	(0.33)
Somnolence	1	(0.37)	0	(0.00)	1	(0.33)
Syncope	1	(0.37)	0	(0.00)	1	(0.33)
Tremor	1	(0.37)	0	(0.00)	1	(0.33)
Facial nerve disorder	1	(0.37)	0	(0.00)	1	(0.33)
Eye disorders	5	(1.87)	0	(0.00)	5	(1.66)
Eyelid oedema	4	(1.50)	0	(0.00)	4	(1.32)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	181		23		204	
Incidence of adverse drug reactions	(67.79)		(65.71)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Conjunctival hyperaemia	1	(0.37)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	1	(0.37)	0	(0.00)	1	(0.33)
Deafness	1	(0.37)	0	(0.00)	1	(0.33)
Ear discomfort	1	(0.37)	0	(0.00)	1	(0.33)
Cardiac disorders	8	(3.00)	0	(0.00)	8	(2.65)
Arrhythmia	2	(0.75)	0	(0.00)	2	(0.66)
Bradycardia	2	(0.75)	0	(0.00)	2	(0.66)
Atrioventricular block second degree	1	(0.37)	0	(0.00)	1	(0.33)
Cardiac failure	1	(0.37)	0	(0.00)	1	(0.33)
Cardiac failure chronic	1	(0.37)	0	(0.00)	1	(0.33)
Myocarditis	1	(0.37)	0	(0.00)	1	(0.33)
Vascular disorders	9	(3.37)	1	(2.86)	10	(3.31)
Flushing	4	(1.50)	1	(2.86)	5	(1.66)
Hypotension	4	(1.50)	0	(0.00)	4	(1.32)
Hot flush	2	(0.75)	0	(0.00)	2	(0.66)
Respiratory, thoracic and mediastinal disorders	40	(14.98)	5	(14.29)	45	(14.90)
Dyspnoea	17	(6.37)	1	(2.86)	18	(5.96)
Cough	7	(2.62)	1	(2.86)	8	(2.65)
Oropharyngeal discomfort	7	(2.62)	0	(0.00)	7	(2.32)
Hypoxia	2	(0.75)	2	(5.71)	4	(1.32)
Throat irritation	3	(1.12)	1	(2.86)	4	(1.32)
Laryngeal discomfort	3	(1.12)	0	(0.00)	3	(0.99)
Nasal congestion	2	(0.75)	0	(0.00)	2	(0.66)
Pharyngeal oedema	2	(0.75)	0	(0.00)	2	(0.66)
Productive cough	2	(0.75)	0	(0.00)	2	(0.66)
Sneezing	2	(0.75)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	1	(0.37)	0	(0.00)	1	(0.33)
Dysphonia	1	(0.37)	0	(0.00)	1	(0.33)
Hiccups	1	(0.37)	0	(0.00)	1	(0.33)
Laryngeal oedema	1	(0.37)	0	(0.00)	1	(0.33)
Oropharyngeal swelling	1	(0.37)	0	(0.00)	1	(0.33)
Pleural effusion	1	(0.37)	0	(0.00)	1	(0.33)
Respiratory failure	1	(0.37)	0	(0.00)	1	(0.33)
Rhinorrhoea	1	(0.37)	0	(0.00)	1	(0.33)
Wheezing	1	(0.37)	0	(0.00)	1	(0.33)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	181		23		204	
Incidence of adverse drug reactions	(67.79)		(65.71)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Upper respiratory tract inflammation	1	(0.37)	0	(0.00)	1	(0.33)
Larynx irritation	1	(0.37)	0	(0.00)	1	(0.33)
Oropharyngeal pain	1	(0.37)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	19	(7.12)	3	(8.57)	22	(7.28)
Nausea	8	(3.00)	1	(2.86)	9	(2.98)
Vomiting	5	(1.87)	0	(0.00)	5	(1.66)
Abdominal discomfort	2	(0.75)	0	(0.00)	2	(0.66)
Diarrhoea	1	(0.37)	1	(2.86)	2	(0.66)
Oral discomfort	2	(0.75)	0	(0.00)	2	(0.66)
Hypoaesthesia oral	1	(0.37)	1	(2.86)	2	(0.66)
Abdominal pain lower	1	(0.37)	0	(0.00)	1	(0.33)
Constipation	0	(0.00)	1	(2.86)	1	(0.33)
Dry mouth	1	(0.37)	0	(0.00)	1	(0.33)
Enterocolitis	1	(0.37)	0	(0.00)	1	(0.33)
Rectal haemorrhage	1	(0.37)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	5	(1.87)	0	(0.00)	5	(1.66)
Hepatic function abnormal	3	(1.12)	0	(0.00)	3	(0.99)
Cholangitis	1	(0.37)	0	(0.00)	1	(0.33)
Cholecystitis acute	1	(0.37)	0	(0.00)	1	(0.33)
Liver disorder	1	(0.37)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	92	(34.46)	12	(34.29)	104	(34.44)
Rash	43	(16.10)	7	(20.00)	50	(16.56)
Urticaria	24	(8.99)	3	(8.57)	27	(8.94)
Pruritus	9	(3.37)	1	(2.86)	10	(3.31)
Erythema	9	(3.37)	0	(0.00)	9	(2.98)
Hyperhidrosis	6	(2.25)	1	(2.86)	7	(2.32)
Rash pruritic	3	(1.12)	1	(2.86)	4	(1.32)
Cold sweat	2	(0.75)	0	(0.00)	2	(0.66)
Eczema	1	(0.37)	0	(0.00)	1	(0.33)
Rash macular	1	(0.37)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(0.37)	0	(0.00)	1	(0.33)
Skin disorder	1	(0.37)	0	(0.00)	1	(0.33)
Toxic skin eruption	1	(0.37)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	4	(1.50)	0	(0.00)	4	(1.32)
Back pain	2	(0.75)	0	(0.00)	2	(0.66)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	181		23		204	
Incidence of adverse drug reactions	(67.79)		(65.71)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Arthralgia	1	(0.37)	0	(0.00)	1	(0.33)
Neck pain	1	(0.37)	0	(0.00)	1	(0.33)
Limb discomfort	1	(0.37)	0	(0.00)	1	(0.33)
Renal and urinary disorders	1	(0.37)	1	(2.86)	2	(0.66)
Renal impairment	1	(0.37)	1	(2.86)	2	(0.66)
Reproductive system and breast disorders	1	(0.37)	0	(0.00)	1	(0.33)
Menopausal symptoms	1	(0.37)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	69	(25.84)	5	(14.29)	74	(24.50)
Pyrexia	43	(16.10)	4	(11.43)	47	(15.56)
Chills	27	(10.11)	0	(0.00)	27	(8.94)
Chest discomfort	5	(1.87)	0	(0.00)	5	(1.66)
Oedema	4	(1.50)	0	(0.00)	4	(1.32)
Chest pain	2	(0.75)	0	(0.00)	2	(0.66)
Fatigue	2	(0.75)	0	(0.00)	2	(0.66)
Feeling hot	2	(0.75)	0	(0.00)	2	(0.66)
Face oedema	1	(0.37)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.37)	0	(0.00)	1	(0.33)
Feeling cold	1	(0.37)	0	(0.00)	1	(0.33)
Malaise	1	(0.37)	0	(0.00)	1	(0.33)
Oedema mucosal	0	(0.00)	1	(2.86)	1	(0.33)
Oedema peripheral	1	(0.37)	0	(0.00)	1	(0.33)
Pain	1	(0.37)	0	(0.00)	1	(0.33)
Non-cardiac chest pain	1	(0.37)	0	(0.00)	1	(0.33)
Investigations	47	(17.60)	4	(11.43)	51	(16.89)
Neutrophil count decreased	17	(6.37)	2	(5.71)	19	(6.29)
White blood cell count decreased	13	(4.87)	1	(2.86)	14	(4.64)
Blood pressure decreased	9	(3.37)	1	(2.86)	10	(3.31)
Platelet count decreased	8	(3.00)	0	(0.00)	8	(2.65)
Oxygen saturation decreased	7	(2.62)	0	(0.00)	7	(2.32)
Alanine aminotransferase increased	2	(0.75)	0	(0.00)	2	(0.66)
Blood pressure increased	2	(0.75)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	2	(0.75)	0	(0.00)	2	(0.66)
Weight increased	2	(0.75)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	1	(0.37)	0	(0.00)	1	(0.33)
Blood creatinine increased	1	(0.37)	0	(0.00)	1	(0.33)

	Complication (renal dysfunction)		Total
	No	Yes	
Number of patients with adverse drug reactions	181	23	204
Incidence of adverse drug reactions	(67.79)	(65.71)	(67.55)
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type		
C-reactive protein increased	1 (0.37)	0 (0.00)	1 (0.33)
Haemoglobin decreased	1 (0.37)	0 (0.00)	1 (0.33)
Lymphocyte count decreased	1 (0.37)	0 (0.00)	1 (0.33)

Source:Table 21_03_01
SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
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Table 10-45 Occurrence of serious adverse drug reactions by presence or absence of concurrent renal dysfunction (safety analysis set)

	Complication (renal dysfunction)		Total
	No	Yes	
Number of patients with adverse drug reactions	38	4	42
Incidence of adverse drug reactions	(14.23)	(11.43)	(13.91)
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type		
Infections and infestations	16 (5.99)	3 (8.57)	19 (6.29)
Pneumonia	4 (1.50)	2 (5.71)	6 (1.99)
Herpes zoster	3 (1.12)	0 (0.00)	3 (0.99)
Infection	2 (0.75)	0 (0.00)	2 (0.66)
Sepsis	2 (0.75)	0 (0.00)	2 (0.66)
Bronchitis	1 (0.37)	0 (0.00)	1 (0.33)
Hepatitis B	1 (0.37)	0 (0.00)	1 (0.33)
Influenza	0 (0.00)	1 (2.86)	1 (0.33)
Progressive multifocal leukoencephalopathy	1 (0.37)	0 (0.00)	1 (0.33)
Pyelonephritis	1 (0.37)	0 (0.00)	1 (0.33)
Urinary tract infection	1 (0.37)	0 (0.00)	1 (0.33)
Oral herpes	1 (0.37)	0 (0.00)	1 (0.33)
Candida infection	1 (0.37)	0 (0.00)	1 (0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.37)	0 (0.00)	1 (0.33)
Chronic lymphocytic leukemia	1 (0.37)	0 (0.00)	1 (0.33)
Blood and lymphatic system disorders	4 (1.50)	0 (0.00)	4 (1.32)
Febrile neutropenia	2 (0.75)	0 (0.00)	2 (0.66)
Disseminated intravascular coagulation	1 (0.37)	0 (0.00)	1 (0.33)
Hematotoxicity	1 (0.37)	0 (0.00)	1 (0.33)

	Complication (renal dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	38		4		42	
Incidence of adverse drug reactions	(14.23)		(11.43)		(13.91)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Metabolism and nutrition disorders	2	(0.75)	1	(2.86)	3	(0.99)
Tumour lysis syndrome	1	(0.37)	1	(2.86)	2	(0.66)
Hyperkalaemia	1	(0.37)	0	(0.00)	1	(0.33)
Hyperphosphataemia	1	(0.37)	0	(0.00)	1	(0.33)
Nervous system disorders	2	(0.75)	0	(0.00)	2	(0.66)
Haemorrhagic cerebral infarction	1	(0.37)	0	(0.00)	1	(0.33)
Syncope	1	(0.37)	0	(0.00)	1	(0.33)
Cardiac disorders	3	(1.12)	0	(0.00)	3	(0.99)
Arrhythmia	1	(0.37)	0	(0.00)	1	(0.33)
Cardiac failure chronic	1	(0.37)	0	(0.00)	1	(0.33)
Myocarditis	1	(0.37)	0	(0.00)	1	(0.33)
Respiratory, thoracic and mediastinal disorders	5	(1.87)	0	(0.00)	5	(1.66)
Dyspnoea	2	(0.75)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	1	(0.37)	0	(0.00)	1	(0.33)
Laryngeal oedema	1	(0.37)	0	(0.00)	1	(0.33)
Pleural effusion	1	(0.37)	0	(0.00)	1	(0.33)
Respiratory failure	1	(0.37)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	3	(1.12)	0	(0.00)	3	(0.99)
Hepatic function abnormal	2	(0.75)	0	(0.00)	2	(0.66)
Cholangitis	1	(0.37)	0	(0.00)	1	(0.33)
Cholecystitis acute	1	(0.37)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	2	(0.75)	1	(2.86)	3	(0.99)
Rash	1	(0.37)	1	(2.86)	2	(0.66)
Urticaria	1	(0.37)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	2	(0.75)	1	(2.86)	3	(0.99)
Pyrexia	2	(0.75)	0	(0.00)	2	(0.66)
Chills	1	(0.37)	0	(0.00)	1	(0.33)
Oedema mucosal	0	(0.00)	1	(2.86)	1	(0.33)
Investigations	10	(3.75)	0	(0.00)	10	(3.31)
Neutrophil count decreased	5	(1.87)	0	(0.00)	5	(1.66)
White blood cell count decreased	4	(1.50)	0	(0.00)	4	(1.32)
Blood creatinine increased	1	(0.37)	0	(0.00)	1	(0.33)
Oxygen saturation decreased	1	(0.37)	0	(0.00)	1	(0.33)

Source:Table 21_03_02

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.

MedDRA/J version 24.0

10.5.10.5Patients complicated with hepatic dysfunction

The occurrence of adverse drug reactions and serious adverse drug reactions by presence or absence of concurrent hepatic dysfunction are shown in Table 10-46 and Table 10-47, respectively.

Of the 302 patients in the safety analysis set, 28 patients (9.27%) had concurrent hepatic dysfunction at the start of treatment (Table 10-2).

The incidence of adverse drug reactions in the patients complicated with hepatic dysfunction was 57.14% (16/28 patients), showing no increase in the incidence of adverse drug reactions in the patients complicated with hepatic dysfunction compared to that in the patients not complicated with hepatic dysfunction (68.61% [188/274 patients]).

Common adverse drug reactions in the patients complicated with hepatic dysfunction were pyrexia in 21.43% (6/28 patients), chills in 17.86% (5/28 patients), and rash, urticaria, pruritus, and white blood cell count decreased in 10.71% (3/28 patients) each. Common adverse drug reactions in the patients not complicated with hepatic dysfunction were rash in 17.15% (47/274 patients), pyrexia in 14.96% (41/274 patients), urticaria in 8.76% (24/274 patients), and chills in 8.03% (22/274 patients). Adverse drug reactions that occurred only in the patients complicated with hepatic dysfunction were constipation, cholangitis, cholecystitis acute, and lymphocyte count decreased, but they occurred in 1 patient each. Other adverse drug reactions were observed in both populations.

The incidence of serious adverse drug reactions was 10.71% (3/28 patients) in the patients complicated with hepatic dysfunction and 14.23% (39/274 patients) in the patients not complicated with hepatic dysfunction.

The serious adverse drug reactions in the patients complicated with hepatic dysfunction were febrile neutropenia, cholangitis, cholecystitis acute, and white blood cell count decreased in 1 patient each.

In the patients complicated with hepatic dysfunction, cholangitis and cholecystitis acute occurred as adverse drug reactions related to hepatic dysfunction in 3.57% (1/28 patients) each. Relapse of hepatitis B or fulminant hepatitis may occur due to the immunosuppressive effect of Arzerra, and therefore more caution should be exercised in patients complicated with hepatic dysfunction. Monitoring of liver function test values and hepatitis viral markers, and hematology should be performed regularly.

To alert healthcare professionals in clinical settings, "Patients infected with hepatitis virus or with such history (Hepatitis may occur due to reactivation of hepatitis B virus.)" has been described in the sections of [Warnings], and [Precautions] "1. Careful Administration," "2. Important Precautions," and "4. Adverse Reactions (1) Clinically Significant Adverse Reactions" of the package insert (Version 6).

Table 10-46 Occurrence of adverse drug reactions by presence or absence of concurrent hepatic dysfunction (safety analysis set)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	188		16		204	
Incidence of adverse drug reactions	(68.61)		(57.14)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	30	(10.95)	1	(3.57)	31	(10.26)
Pneumonia	8	(2.92)	1	(3.57)	9	(2.98)
Herpes zoster	5	(1.82)	0	(0.00)	5	(1.66)
Infection	3	(1.09)	0	(0.00)	3	(0.99)
Sepsis	2	(0.73)	0	(0.00)	2	(0.66)
Urinary tract infection	2	(0.73)	0	(0.00)	2	(0.66)
Bronchitis	1	(0.36)	0	(0.00)	1	(0.33)
Cellulitis	1	(0.36)	0	(0.00)	1	(0.33)
Hepatitis B	1	(0.36)	0	(0.00)	1	(0.33)
Influenza	1	(0.36)	0	(0.00)	1	(0.33)
Nasopharyngitis	1	(0.36)	0	(0.00)	1	(0.33)
Oral candidiasis	1	(0.36)	0	(0.00)	1	(0.33)
Otitis media	1	(0.36)	0	(0.00)	1	(0.33)
Periodontitis	1	(0.36)	0	(0.00)	1	(0.33)
Progressive multifocal leukoencephalopathy	1	(0.36)	0	(0.00)	1	(0.33)
Pyelonephritis	1	(0.36)	0	(0.00)	1	(0.33)
Subcutaneous abscess	1	(0.36)	0	(0.00)	1	(0.33)
Hepatitis B reactivation	1	(0.36)	0	(0.00)	1	(0.33)
Oral herpes	1	(0.36)	0	(0.00)	1	(0.33)
Candida infection	1	(0.36)	0	(0.00)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(1.09)	1	(3.57)	4	(1.32)
Chronic lymphocytic leukemia	3	(1.09)	1	(3.57)	4	(1.32)
Blood and lymphatic system disorders	16	(5.84)	4	(14.29)	20	(6.62)
Anaemia	6	(2.19)	2	(7.14)	8	(2.65)
Febrile neutropenia	2	(0.73)	2	(7.14)	4	(1.32)
Disseminated intravascular coagulation	2	(0.73)	0	(0.00)	2	(0.66)
Neutropenia	1	(0.36)	1	(3.57)	2	(0.66)
Thrombocytopenia	2	(0.73)	0	(0.00)	2	(0.66)
Hematotoxicity	2	(0.73)	0	(0.00)	2	(0.66)
Lymph node pain	1	(0.36)	0	(0.00)	1	(0.33)
Lymphadenopathy	1	(0.36)	0	(0.00)	1	(0.33)
Immune system disorders	3	(1.09)	0	(0.00)	3	(0.99)
Anaphylactoid reaction	2	(0.73)	0	(0.00)	2	(0.66)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	188		16		204	
Incidence of adverse drug reactions	(68.61)		(57.14)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Hypersensitivity	1	(0.36)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	7	(2.55)	0	(0.00)	7	(2.32)
Tumour lysis syndrome	5	(1.82)	0	(0.00)	5	(1.66)
Hyperkalaemia	1	(0.36)	0	(0.00)	1	(0.33)
Hyperphosphataemia	1	(0.36)	0	(0.00)	1	(0.33)
Hyperuricaemia	1	(0.36)	0	(0.00)	1	(0.33)
Nervous system disorders	13	(4.74)	2	(7.14)	15	(4.97)
Headache	3	(1.09)	1	(3.57)	4	(1.32)
Head discomfort	2	(0.73)	0	(0.00)	2	(0.66)
Hypoaesthesia	1	(0.36)	1	(3.57)	2	(0.66)
Neuropathy peripheral	2	(0.73)	0	(0.00)	2	(0.66)
Peripheral sensory neuropathy	2	(0.73)	0	(0.00)	2	(0.66)
Dizziness	1	(0.36)	0	(0.00)	1	(0.33)
Haemorrhagic cerebral infarction	1	(0.36)	0	(0.00)	1	(0.33)
Somnolence	1	(0.36)	0	(0.00)	1	(0.33)
Syncope	1	(0.36)	0	(0.00)	1	(0.33)
Tremor	1	(0.36)	0	(0.00)	1	(0.33)
Facial nerve disorder	1	(0.36)	0	(0.00)	1	(0.33)
Eye disorders	4	(1.46)	1	(3.57)	5	(1.66)
Eyelid oedema	3	(1.09)	1	(3.57)	4	(1.32)
Conjunctival hyperaemia	1	(0.36)	0	(0.00)	1	(0.33)
Ear and labyrinth disorders	1	(0.36)	0	(0.00)	1	(0.33)
Deafness	1	(0.36)	0	(0.00)	1	(0.33)
Ear discomfort	1	(0.36)	0	(0.00)	1	(0.33)
Cardiac disorders	8	(2.92)	0	(0.00)	8	(2.65)
Arrhythmia	2	(0.73)	0	(0.00)	2	(0.66)
Bradycardia	2	(0.73)	0	(0.00)	2	(0.66)
Atrioventricular block second degree	1	(0.36)	0	(0.00)	1	(0.33)
Cardiac failure	1	(0.36)	0	(0.00)	1	(0.33)
Cardiac failure chronic	1	(0.36)	0	(0.00)	1	(0.33)
Myocarditis	1	(0.36)	0	(0.00)	1	(0.33)
Vascular disorders	9	(3.28)	1	(3.57)	10	(3.31)
Flushing	4	(1.46)	1	(3.57)	5	(1.66)
Hypotension	4	(1.46)	0	(0.00)	4	(1.32)
Hot flush	2	(0.73)	0	(0.00)	2	(0.66)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	188		16		204	
Incidence of adverse drug reactions	(68.61)		(57.14)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Respiratory, thoracic and mediastinal disorders	42	(15.33)	3	(10.71)	45	(14.90)
Dyspnoea	18	(6.57)	0	(0.00)	18	(5.96)
Cough	7	(2.55)	1	(3.57)	8	(2.65)
Oropharyngeal discomfort	6	(2.19)	1	(3.57)	7	(2.32)
Hypoxia	4	(1.46)	0	(0.00)	4	(1.32)
Throat irritation	3	(1.09)	1	(3.57)	4	(1.32)
Laryngeal discomfort	3	(1.09)	0	(0.00)	3	(0.99)
Nasal congestion	2	(0.73)	0	(0.00)	2	(0.66)
Pharyngeal oedema	2	(0.73)	0	(0.00)	2	(0.66)
Productive cough	2	(0.73)	0	(0.00)	2	(0.66)
Sneezing	2	(0.73)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	1	(0.36)	0	(0.00)	1	(0.33)
Dysphonia	1	(0.36)	0	(0.00)	1	(0.33)
Hiccups	1	(0.36)	0	(0.00)	1	(0.33)
Laryngeal oedema	1	(0.36)	0	(0.00)	1	(0.33)
Oropharyngeal swelling	1	(0.36)	0	(0.00)	1	(0.33)
Pleural effusion	1	(0.36)	0	(0.00)	1	(0.33)
Respiratory failure	1	(0.36)	0	(0.00)	1	(0.33)
Rhinorrhoea	1	(0.36)	0	(0.00)	1	(0.33)
Wheezing	1	(0.36)	0	(0.00)	1	(0.33)
Upper respiratory tract inflammation	1	(0.36)	0	(0.00)	1	(0.33)
Larynx irritation	1	(0.36)	0	(0.00)	1	(0.33)
Oropharyngeal pain	1	(0.36)	0	(0.00)	1	(0.33)
Gastrointestinal disorders	18	(6.57)	4	(14.29)	22	(7.28)
Nausea	7	(2.55)	2	(7.14)	9	(2.98)
Vomiting	4	(1.46)	1	(3.57)	5	(1.66)
Abdominal discomfort	2	(0.73)	0	(0.00)	2	(0.66)
Diarrhoea	1	(0.36)	1	(3.57)	2	(0.66)
Oral discomfort	2	(0.73)	0	(0.00)	2	(0.66)
Hypoaesthesia oral	1	(0.36)	1	(3.57)	2	(0.66)
Abdominal pain lower	1	(0.36)	0	(0.00)	1	(0.33)
Constipation	0	(0.00)	1	(3.57)	1	(0.33)
Dry mouth	1	(0.36)	0	(0.00)	1	(0.33)
Enterocolitis	1	(0.36)	0	(0.00)	1	(0.33)
Rectal haemorrhage	1	(0.36)	0	(0.00)	1	(0.33)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	188		16		204	
Incidence of adverse drug reactions	(68.61)		(57.14)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Hepatobiliary disorders	4	(1.46)	1	(3.57)	5	(1.66)
Hepatic function abnormal	3	(1.09)	0	(0.00)	3	(0.99)
Cholangitis	0	(0.00)	1	(3.57)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(3.57)	1	(0.33)
Liver disorder	1	(0.36)	0	(0.00)	1	(0.33)
Skin and subcutaneous tissue disorders	95	(34.67)	9	(32.14)	104	(34.44)
Rash	47	(17.15)	3	(10.71)	50	(16.56)
Urticaria	24	(8.76)	3	(10.71)	27	(8.94)
Pruritus	7	(2.55)	3	(10.71)	10	(3.31)
Erythema	8	(2.92)	1	(3.57)	9	(2.98)
Hyperhidrosis	5	(1.82)	2	(7.14)	7	(2.32)
Rash pruritic	4	(1.46)	0	(0.00)	4	(1.32)
Cold sweat	2	(0.73)	0	(0.00)	2	(0.66)
Eczema	1	(0.36)	0	(0.00)	1	(0.33)
Rash macular	1	(0.36)	0	(0.00)	1	(0.33)
Rash maculo-papular	1	(0.36)	0	(0.00)	1	(0.33)
Skin disorder	1	(0.36)	0	(0.00)	1	(0.33)
Toxic skin eruption	1	(0.36)	0	(0.00)	1	(0.33)
Musculoskeletal and connective tissue disorders	4	(1.46)	0	(0.00)	4	(1.32)
Back pain	2	(0.73)	0	(0.00)	2	(0.66)
Arthralgia	1	(0.36)	0	(0.00)	1	(0.33)
Neck pain	1	(0.36)	0	(0.00)	1	(0.33)
Limb discomfort	1	(0.36)	0	(0.00)	1	(0.33)
Renal and urinary disorders	2	(0.73)	0	(0.00)	2	(0.66)
Renal impairment	2	(0.73)	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	1	(0.36)	0	(0.00)	1	(0.33)
Menopausal symptoms	1	(0.36)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	65	(23.72)	9	(32.14)	74	(24.50)
Pyrexia	41	(14.96)	6	(21.43)	47	(15.56)
Chills	22	(8.03)	5	(17.86)	27	(8.94)
Chest discomfort	5	(1.82)	0	(0.00)	5	(1.66)
Oedema	4	(1.46)	0	(0.00)	4	(1.32)
Chest pain	2	(0.73)	0	(0.00)	2	(0.66)
Fatigue	2	(0.73)	0	(0.00)	2	(0.66)
Feeling hot	2	(0.73)	0	(0.00)	2	(0.66)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	188		16		204	
Incidence of adverse drug reactions	(68.61)		(57.14)		(67.55)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Face oedema	1	(0.36)	0	(0.00)	1	(0.33)
Feeling abnormal	1	(0.36)	0	(0.00)	1	(0.33)
Feeling cold	1	(0.36)	0	(0.00)	1	(0.33)
Malaise	1	(0.36)	0	(0.00)	1	(0.33)
Oedema mucosal	1	(0.36)	0	(0.00)	1	(0.33)
Oedema peripheral	1	(0.36)	0	(0.00)	1	(0.33)
Pain	1	(0.36)	0	(0.00)	1	(0.33)
Non-cardiac chest pain	1	(0.36)	0	(0.00)	1	(0.33)
Investigations	47	(17.15)	4	(14.29)	51	(16.89)
Neutrophil count decreased	17	(6.20)	2	(7.14)	19	(6.29)
White blood cell count decreased	11	(4.01)	3	(10.71)	14	(4.64)
Blood pressure decreased	10	(3.65)	0	(0.00)	10	(3.31)
Platelet count decreased	6	(2.19)	2	(7.14)	8	(2.65)
Oxygen saturation decreased	7	(2.55)	0	(0.00)	7	(2.32)
Alanine aminotransferase increased	2	(0.73)	0	(0.00)	2	(0.66)
Blood pressure increased	2	(0.73)	0	(0.00)	2	(0.66)
Gamma-glutamyltransferase increased	2	(0.73)	0	(0.00)	2	(0.66)
Weight increased	2	(0.73)	0	(0.00)	2	(0.66)
Aspartate aminotransferase increased	1	(0.36)	0	(0.00)	1	(0.33)
Blood creatinine increased	1	(0.36)	0	(0.00)	1	(0.33)
C-reactive protein increased	1	(0.36)	0	(0.00)	1	(0.33)
Haemoglobin decreased	1	(0.36)	0	(0.00)	1	(0.33)
Lymphocyte count decreased	0	(0.00)	1	(3.57)	1	(0.33)

Source:Table 21_02_01

SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.

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Table 10-47 Occurrence of serious adverse drug reactions by presence or absence of concurrent hepatic dysfunction (safety analysis set)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	39		3		42	
Incidence of adverse drug reactions	(14.23)		(10.71)		(13.91)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Infections and infestations	19	(6.93)	0	(0.00)	19	(6.29)
Pneumonia	6	(2.19)	0	(0.00)	6	(1.99)
Herpes zoster	3	(1.09)	0	(0.00)	3	(0.99)
Infection	2	(0.73)	0	(0.00)	2	(0.66)
Sepsis	2	(0.73)	0	(0.00)	2	(0.66)
Bronchitis	1	(0.36)	0	(0.00)	1	(0.33)
Hepatitis B	1	(0.36)	0	(0.00)	1	(0.33)
Influenza	1	(0.36)	0	(0.00)	1	(0.33)
Progressive multifocal leukoencephalopathy	1	(0.36)	0	(0.00)	1	(0.33)
Pyelonephritis	1	(0.36)	0	(0.00)	1	(0.33)
Urinary tract infection	1	(0.36)	0	(0.00)	1	(0.33)
Oral herpes	1	(0.36)	0	(0.00)	1	(0.33)
Candida infection	1	(0.36)	0	(0.00)	1	(0.33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.36)	0	(0.00)	1	(0.33)
Chronic lymphocytic leukemia	1	(0.36)	0	(0.00)	1	(0.33)
Blood and lymphatic system disorders	3	(1.09)	1	(3.57)	4	(1.32)
Febrile neutropenia	1	(0.36)	1	(3.57)	2	(0.66)
Disseminated intravascular coagulation	1	(0.36)	0	(0.00)	1	(0.33)
Hematotoxicity	1	(0.36)	0	(0.00)	1	(0.33)
Metabolism and nutrition disorders	3	(1.09)	0	(0.00)	3	(0.99)
Tumour lysis syndrome	2	(0.73)	0	(0.00)	2	(0.66)
Hyperkalaemia	1	(0.36)	0	(0.00)	1	(0.33)
Hyperphosphataemia	1	(0.36)	0	(0.00)	1	(0.33)
Nervous system disorders	2	(0.73)	0	(0.00)	2	(0.66)
Haemorrhagic cerebral infarction	1	(0.36)	0	(0.00)	1	(0.33)
Syncope	1	(0.36)	0	(0.00)	1	(0.33)
Cardiac disorders	3	(1.09)	0	(0.00)	3	(0.99)
Arrhythmia	1	(0.36)	0	(0.00)	1	(0.33)
Cardiac failure chronic	1	(0.36)	0	(0.00)	1	(0.33)
Myocarditis	1	(0.36)	0	(0.00)	1	(0.33)
Respiratory, thoracic and mediastinal disorders	5	(1.82)	0	(0.00)	5	(1.66)
Dyspnoea	2	(0.73)	0	(0.00)	2	(0.66)
Acute respiratory distress syndrome	1	(0.36)	0	(0.00)	1	(0.33)

	Complication (hepatic dysfunction)				Total	
	No		Yes			
Number of patients with adverse drug reactions	39		3		42	
Incidence of adverse drug reactions	(14.23)		(10.71)		(13.91)	
Type of adverse drug reaction	Incidence (number of patients) (%) of adverse drug reactions by type					
Laryngeal oedema	1	(0.36)	0	(0.00)	1	(0.33)
Pleural effusion	1	(0.36)	0	(0.00)	1	(0.33)
Respiratory failure	1	(0.36)	0	(0.00)	1	(0.33)
Hepatobiliary disorders	2	(0.73)	1	(3.57)	3	(0.99)
Hepatic function abnormal	2	(0.73)	0	(0.00)	2	(0.66)
Cholangitis	0	(0.00)	1	(3.57)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(3.57)	1	(0.33)
Skin and subcutaneous tissue disorders	3	(1.09)	0	(0.00)	3	(0.99)
Rash	2	(0.73)	0	(0.00)	2	(0.66)
Urticaria	1	(0.36)	0	(0.00)	1	(0.33)
General disorders and administration site conditions	3	(1.09)	0	(0.00)	3	(0.99)
Pyrexia	2	(0.73)	0	(0.00)	2	(0.66)
Chills	1	(0.36)	0	(0.00)	1	(0.33)
Oedema mucosal	1	(0.36)	0	(0.00)	1	(0.33)
Investigations	9	(3.28)	1	(3.57)	10	(3.31)
Neutrophil count decreased	5	(1.82)	0	(0.00)	5	(1.66)
White blood cell count decreased	3	(1.09)	1	(3.57)	4	(1.32)
Blood creatinine increased	1	(0.36)	0	(0.00)	1	(0.33)
Oxygen saturation decreased	1	(0.36)	0	(0.00)	1	(0.33)

Source:Table 21_02_02
SOC is shown by internationally agreed order, PT is shown in descending order of the number of patients with events → in order of PT code.
MedDRA/J version 24.0

10.5.11 Adverse drug reactions during the follow-up period

Adverse drug reactions during the follow-up period are shown in Table 10-48.

Of the 302 patients in the safety analysis set, 32 patients (10.60%) experienced adverse drug reactions during the post-treatment follow-up period (up to 3 months). The adverse drug reactions were neutrophil count decreased in 1.66% (5 patients), chronic lymphocytic leukaemia (worsening) in 1.32% (4 patients), pneumonia in 0.99% (3 patients), and herpes zoster, anaemia, renal impairment, platelet count decreased, and white blood cell count decreased in 0.66% (2 patients) each, and the other adverse drug reactions were observed in 0.33% (1 patient) each.

Adverse drug reactions that occurred only during the follow-up period were those related to worsening of primary disease, which occurred in 4 patients, while other adverse drug

reactions occurred in 1 to 2 patients. Many adverse drug reactions occurred both during the treatment and follow-up periods, showing no particular tendency.

Table 10-48 Adverse drug reactions during the follow-up period (safety analysis set)

Type of adverse drug reaction	Treatment period (%)		Follow-up period (%)	
Number of patients in the safety analysis set	302			
Number of patients with events	193	(63.91)	32	(10.60)
Infections and infestations	21	(6.95)	13	(4.30)
Bronchitis	1	(0.33)	0	(0.00)
Cellulitis	0	(0.00)	1	(0.33)
Hepatitis B	0	(0.00)	1	(0.33)
Herpes zoster	3	(0.99)	2	(0.66)
Infection	2	(0.66)	1	(0.33)
Influenza	0	(0.00)	1	(0.33)
Nasopharyngitis	1	(0.33)	0	(0.00)
Oral candidiasis	1	(0.33)	0	(0.00)
Otitis media	0	(0.00)	1	(0.33)
Periodontitis	1	(0.33)	0	(0.00)
Pneumonia	7	(2.32)	3	(0.99)
Progressive multifocal leukoencephalopathy	0	(0.00)	1	(0.33)
Pyelonephritis	0	(0.00)	1	(0.33)
Sepsis	1	(0.33)	1	(0.33)
Subcutaneous abscess	1	(0.33)	0	(0.00)
Urinary tract infection	2	(0.66)	0	(0.00)
Hepatitis B reactivation	1	(0.33)	0	(0.00)
Oral herpes	1	(0.33)	0	(0.00)
Candida infection	1	(0.33)	0	(0.00)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.00)	4	(1.32)
Chronic lymphocytic leukemia	0	(0.00)	4	(1.32)
Blood and lymphatic system disorders	14	(4.64)	6	(1.99)
Anaemia	6	(1.99)	2	(0.66)
Disseminated intravascular coagulation	1	(0.33)	1	(0.33)
Febrile neutropenia	3	(0.99)	1	(0.33)
Lymph node pain	1	(0.33)	0	(0.00)
Lymphadenopathy	0	(0.00)	1	(0.33)
Neutropenia	1	(0.33)	1	(0.33)
Thrombocytopenia	2	(0.66)	0	(0.00)
Hematotoxicity	2	(0.66)	0	(0.00)
Immune system disorders	3	(0.99)	0	(0.00)
Anaphylactoid reaction	2	(0.66)	0	(0.00)
Hypersensitivity	1	(0.33)	0	(0.00)

Type of adverse drug reaction	Treatment period (%)		Follow-up period (%)	
Metabolism and nutrition disorders	5	(1.66)	2	(0.66)
Hyperkalaemia	0	(0.00)	1	(0.33)
Hyperphosphataemia	0	(0.00)	1	(0.33)
Hyperuricaemia	1	(0.33)	0	(0.00)
Tumour lysis syndrome	4	(1.32)	1	(0.33)
Nervous system disorders	14	(4.64)	1	(0.33)
Dizziness	1	(0.33)	0	(0.00)
Haemorrhagic cerebral infarction	0	(0.00)	1	(0.33)
Head discomfort	2	(0.66)	0	(0.00)
Headache	4	(1.32)	0	(0.00)
Hypoaesthesia	2	(0.66)	0	(0.00)
Neuropathy peripheral	2	(0.66)	0	(0.00)
Peripheral sensory neuropathy	2	(0.66)	0	(0.00)
Somnolence	1	(0.33)	0	(0.00)
Syncope	1	(0.33)	0	(0.00)
Tremor	1	(0.33)	0	(0.00)
Facial nerve disorder	1	(0.33)	0	(0.00)
Eye disorders	5	(1.66)	0	(0.00)
Eyelid oedema	4	(1.32)	0	(0.00)
Conjunctival hyperaemia	1	(0.33)	0	(0.00)
Ear and labyrinth disorders	1	(0.33)	0	(0.00)
Deafness	1	(0.33)	0	(0.00)
Ear discomfort	1	(0.33)	0	(0.00)
Cardiac disorders	6	(1.99)	2	(0.66)
Arrhythmia	1	(0.33)	1	(0.33)
Atrioventricular block second degree	1	(0.33)	0	(0.00)
Bradycardia	2	(0.66)	0	(0.00)
Cardiac failure	1	(0.33)	0	(0.00)
Cardiac failure chronic	0	(0.00)	1	(0.33)
Myocarditis	1	(0.33)	0	(0.00)
Vascular disorders	10	(3.31)	1	(0.33)
Flushing	5	(1.66)	0	(0.00)
Hypotension	4	(1.32)	0	(0.00)
Hot flush	1	(0.33)	1	(0.33)
Respiratory, thoracic and mediastinal disorders	42	(13.91)	4	(1.32)
Acute respiratory distress syndrome	0	(0.00)	1	(0.33)
Cough	8	(2.65)	0	(0.00)
Dysphonia	1	(0.33)	0	(0.00)
Dyspnoea	17	(5.63)	1	(0.33)
Hiccups	1	(0.33)	0	(0.00)
Hypoxia	4	(1.32)	0	(0.00)
Laryngeal oedema	1	(0.33)	0	(0.00)

Type of adverse drug reaction	Treatment period (%)		Follow-up period (%)	
Nasal congestion	2	(0.66)	0	(0.00)
Oropharyngeal swelling	1	(0.33)	0	(0.00)
Pharyngeal oedema	2	(0.66)	0	(0.00)
Pleural effusion	0	(0.00)	1	(0.33)
Productive cough	2	(0.66)	0	(0.00)
Respiratory failure	0	(0.00)	1	(0.33)
Rhinorrhoea	1	(0.33)	0	(0.00)
Sneezing	2	(0.66)	0	(0.00)
Throat irritation	4	(1.32)	0	(0.00)
Wheezing	1	(0.33)	0	(0.00)
Upper respiratory tract inflammation	1	(0.33)	0	(0.00)
Laryngeal discomfort	3	(0.99)	0	(0.00)
Larynx irritation	1	(0.33)	0	(0.00)
Oropharyngeal discomfort	7	(2.32)	0	(0.00)
Oropharyngeal pain	1	(0.33)	0	(0.00)
Gastrointestinal disorders	20	(6.62)	3	(0.99)
Abdominal discomfort	2	(0.66)	0	(0.00)
Abdominal pain lower	1	(0.33)	0	(0.00)
Constipation	1	(0.33)	0	(0.00)
Diarrhoea	1	(0.33)	1	(0.33)
Dry mouth	1	(0.33)	0	(0.00)
Enterocolitis	1	(0.33)	0	(0.00)
Nausea	9	(2.98)	0	(0.00)
Oral discomfort	2	(0.66)	0	(0.00)
Rectal haemorrhage	0	(0.00)	1	(0.33)
Vomiting	4	(1.32)	1	(0.33)
Hypoaesthesia oral	2	(0.66)	0	(0.00)
Hepatobiliary disorders	4	(1.32)	1	(0.33)
Cholangitis	0	(0.00)	1	(0.33)
Cholecystitis acute	0	(0.00)	1	(0.33)
Hepatic function abnormal	3	(0.99)	0	(0.00)
Liver disorder	1	(0.33)	0	(0.00)
Skin and subcutaneous tissue disorders	104	(34.44)	0	(0.00)
Cold sweat	2	(0.66)	0	(0.00)
Eczema	1	(0.33)	0	(0.00)
Erythema	9	(2.98)	0	(0.00)
Hyperhidrosis	7	(2.32)	0	(0.00)
Pruritus	10	(3.31)	0	(0.00)
Rash	50	(16.56)	0	(0.00)
Rash macular	1	(0.33)	0	(0.00)
Rash maculo-papular	1	(0.33)	0	(0.00)
Rash pruritic	4	(1.32)	0	(0.00)

Type of adverse drug reaction	Treatment period (%)		Follow-up period (%)	
Skin disorder	1	(0.33)	0	(0.00)
Urticaria	27	(8.94)	0	(0.00)
Toxic skin eruption	1	(0.33)	0	(0.00)
Musculoskeletal and connective tissue disorders	4	(1.32)	0	(0.00)
Arthralgia	1	(0.33)	0	(0.00)
Back pain	2	(0.66)	0	(0.00)
Neck pain	1	(0.33)	0	(0.00)
Limb discomfort	1	(0.33)	0	(0.00)
Renal and urinary disorders	0	(0.00)	2	(0.66)
Renal impairment	0	(0.00)	2	(0.66)
Reproductive system and breast disorders	1	(0.33)	0	(0.00)
Menopausal symptoms	1	(0.33)	0	(0.00)
General disorders and administration site conditions	73	(24.17)	2	(0.66)
Chest discomfort	5	(1.66)	0	(0.00)
Chest pain	2	(0.66)	0	(0.00)
Chills	27	(8.94)	1	(0.33)
Face oedema	1	(0.33)	0	(0.00)
Fatigue	2	(0.66)	0	(0.00)
Feeling abnormal	1	(0.33)	0	(0.00)
Feeling cold	1	(0.33)	0	(0.00)
Feeling hot	2	(0.66)	0	(0.00)
Malaise	1	(0.33)	0	(0.00)
Oedema	4	(1.32)	0	(0.00)
Oedema mucosal	1	(0.33)	0	(0.00)
Oedema peripheral	1	(0.33)	0	(0.00)
Pain	1	(0.33)	0	(0.00)
Pyrexia	46	(15.23)	1	(0.33)
Non-cardiac chest pain	1	(0.33)	0	(0.00)
Investigations	44	(14.57)	9	(2.98)
Alanine aminotransferase increased	2	(0.66)	0	(0.00)
Aspartate aminotransferase increased	1	(0.33)	0	(0.00)
Blood creatinine increased	0	(0.00)	1	(0.33)
Blood pressure decreased	10	(3.31)	0	(0.00)
Blood pressure increased	2	(0.66)	0	(0.00)
C-reactive protein increased	1	(0.33)	0	(0.00)
Gamma-glutamyltransferase increased	2	(0.66)	0	(0.00)
Haemoglobin decreased	0	(0.00)	1	(0.33)
Lymphocyte count decreased	1	(0.33)	0	(0.00)
Neutrophil count decreased	16	(5.30)	5	(1.66)
Oxygen saturation decreased	7	(2.32)	0	(0.00)
Platelet count decreased	6	(1.99)	2	(0.66)
Weight increased	2	(0.66)	0	(0.00)

Type of adverse drug reaction	Treatment period (%)		Follow-up period (%)	
White blood cell count decreased	12	(3.97)	2	(0.66)

Source:Table 12_7

* The sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

(Tabulated by MedDRA/J Ver. 24.0)

10.5.12 Adverse events excluded from analysis

10.5.12.1 List of adverse events in patients excluded from the safety analysis set

Adverse events observed in patients excluded from the safety analysis set are listed in Table 10-49.

Table 10-49 List of adverse events in patients excluded from the safety analysis set

No	Gender	Age	PT	Outcome	Seriousness	Relationship with Arzerra
1	[redacted]	[redacted]	Neutrophil count decreased	Resolved	Non-serious	Related
			White blood cell count decreased	Resolved	Non-serious	Related
			Richter's syndrome	Death	Serious	Not related
2			Pyrexia	Resolving	Non-serious	Not related
3			Pruritus	Resolving	Non-serious	Not related
			Inflammation	Resolving	Non-serious	Not related
4			Pruritus	Resolved	Non-serious	Related
			Pyrexia	Resolved	Non-serious	Related
			Pyrexia	Resolved	Non-serious	Related
			Anaemia	Resolved	Non-serious	Related
5			Hepatic function abnormal	Not resolved	Serious	Not related
6			Hypoxia	Resolved	Non-serious	Related
			Urticaria	Resolved	Non-serious	Related
			Infection	Resolving	Non-serious	Related
7			Rash	Resolved	Non-serious	Related
			Septic shock	Resolving	Serious	Not related
8			Hairy cell leukaemia	Not resolved	Non-serious	Not related
			Death	Death	Serious	Not related
9			Pneumonia	Death	Serious	
10			Oropharyngeal discomfort	Resolved	Non-serious	Related
11			Oropharyngeal discomfort	Resolving	Non-serious	Related

Source:Listing 03_06

* The output is the sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.5.12.2List of adverse events outside the safety analysis period

A list of adverse events that occurred outside of the safety analysis period is provided in Table 10-50.

As adverse events outside the safety analysis period, chronic lymphocytic leukaemia (worsening) was reported in 6 patients. Adverse events other than worsening of primary disease were pancreatic carcinoma, pneumonia, aortic aneurysm, blood pressure increased, Richter's syndrome, death, therapeutic product effect incomplete, and thrombocytopenia in 1 patient each.

Table 10-50 List of adverse events outside the safety analysis period (patients with locked case report forms)

No	Gender	Age	PT	Number of days to onset	Outcome	Seriousness	Relation-ship with Arzerra	Factors suspected of being associated with the event other than Arzerra
1	[redacted]		Pancreatic carcinoma	437	Death	Serious	Not related	No
2			Chronic lymphocytic leukemia	174	Death	Serious	Not related	Yes
3			Pneumonia	388	Death	Serious	Not related	Yes
4			Aortic aneurysm	309	Resolved	Non-serious	Not related	Yes
5			Chronic lymphocytic leukemia	744	Resolving	Non-serious	Not related	
6			Chronic lymphocytic leukemia	536	Death	Serious	Not related	Yes
7			Blood pressure increased	294	Resolved	Non-serious	Related	No
8			Richter's syndrome	260	Death	Serious	Not related	Yes
9			Chronic lymphocytic leukemia	771	Death	Serious	Not related	Yes
10			Death	195	Death	Serious	Not related	Yes
11			Chronic lymphocytic leukemia	-6	Resolving	Serious	Not related	Yes

No	Gender	Age	PT	Number of days to onset	Outcome	Seriousness	Relation-ship with Arzerra	Factors suspected of being associated with the event other than Arzerra
12	[redacted]		Therapeutic product effect incomplete	302	Not resolved	Non-serious	Related	No
13			Chronic lymphocytic leukemia	329	Death	Serious	Not related	Yes
14			Thrombo-cytopenia	103	Resolved	Serious	Related	Yes

Source:Listing 03_03

* The output is the sum of events described in the [Adverse events] page of the case report form and events described in the infusion reaction column of the [Status at each dose] page

10.6 Efficacy

Antitumor effects (tabulated by best response) in this study are shown in Table 10-51.

The response rate (CR + PR) in this study was 48.7% (145/298 patients).

Table 10-51 Antitumor effect (efficacy analysis set)

Best response	After the start of administration (unit: months)					
	<2	≥2 to <4	≥4 to <6	≥6	Unknown	Total
Response (CR + PR)	33(11.1%)	32(10.7%)	30(10.1%)	50(16.8%)	0(0.0%)	145(48.7%)
CR	7(2.3%)	14(4.7%)	13(4.4%)	20(6.7%)	0(0.0%)	54(18.1%)
PR	26(8.7%)	18(6.0%)	17(5.7%)	30(10.1%)	0(0.0%)	91(30.5%)
SD	52(17.4%)	13(4.4%)	10(3.4%)	15(5.0%)	0(0.0%)	90(30.2%)
PD	15(5.0%)	10(3.4%)	1(0.3%)	1(0.3%)	0(0.0%)	27(9.1%)
NE	21(7.0%)	2(0.7%)	0(0.0%)	1(0.3%)	12(4.0%)	36(12.1%)
Total	121(40.6%)	57(19.1%)	41(13.8%)	67(22.5%)	12(4.0%)	298(100.0%)

Source:Table 20

10.6.1 Efficacy analysis by patient factor

Efficacy by patient factor is shown in Table 10-52.

Among the 298 patients in the efficacy analysis set, the proportions of responders and non-responders were 48.66% (145 patients) and 51.34% (153 patients), respectively.

To examine factors that may affect the efficacy, efficacy analyses were performed by patient factor defined in Section 9.10.6. Analysis was based on the odds ratio (95% CI).

As a result, a difference was observed with the 95% CI of the odds ratio not including 1 for "hospitalization status (outpatient)," "complication (hepatic dysfunction) (yes)," "prior

treatment (yes)," "prior treatment (antineoplastic drugs) (yes)," "ECOG PS (2)," "ECOG PS (3)," "rituximab premedication (yes),"" prior anti-CD20 antibody therapy (yes)," and "concomitant medication (treatment of primary disease) (yes)." Patients with poor general condition, comorbidities, or a history of prior treatment could have decreased response to treatment.

Table 10-52 Antitumor effect by patient factor (efficacy analysis set)

Patient factor		Number of patients	Responders (partial response or better)	Non-responders	Response rate (%)	Odds ratio (95%CI)	
						OR	lower-upper
Efficacy analysis set		298	145	153	48.66	--	--
Gender	Male	184	83	101	45.11	--	--
	Female	114	62	52	54.39	1.451	(0.908 , 2.320)
	Unknown	0	0	0	-	--	--
Age	<15 years	0	0	0	-	-	(- , -)
Minimum = 44	≥15 to <65 years	72	32	40	44.44	--	--
Maximum = 91	≥65 years	223	111	112	49.78	1.239	(0.726 , 2.113)
	Unknown	3	2	1	66.67	--	--
Age (15 years)	<15 years	0	0	0	-	--	--
	≥15 years	295	143	152	48.47	-	(- , -)
	Unknown or not entered	3	2	1	66.67	--	--
Age (18 years)	<18 years	0	0	0	-	--	--
	≥18 years	295	143	152	48.47	-	(- , -)
	Unknown or not entered	3	2	1	66.67	--	--
Age (65 years)	<65 years	72	32	40	44.44	--	--
	≥65 years	223	111	112	49.78	1.239	(0.726 , 2.113)
	Unknown or not entered	3	2	1	66.67	--	--
Hospitalization status	Inpatient	266	124	142	46.62	--	--
	Outpatient	30	20	10	66.67	2.290	(1.033 , 5.078)
	Unknown	2	1	1	50.00	--	--
Disease duration	<1 year	42	19	23	45.24	--	--
	≥1 to <3 years	55	26	29	47.27	1.085	(0.485 , 2.430)
	≥3 to <6 years	71	39	32	54.93	1.475	(0.685 , 3.176)
	≥6 to <11 years	72	39	33	54.17	1.431	(0.666 , 3.072)
	≥11 years	36	15	21	41.67	0.865	(0.352 , 2.125)
	Unknown	22	7	15	31.82	--	--
Pregnancy	No	114	62	52	54.39	--	--
	Yes	0	0	0	-	-	(- , -)
	Unknown	0	0	0	-	--	--

Patient factor		Number of patients	Responders (partial response or better)	Non-responders	Response rate (%)	Odds ratio (95%CI)	
						OR	lower-upper
Noteworthy constitution/predisposition to hypersensitivity	No	260	124	136	47.69	--	--
	Yes	38	21	17	55.26	1.355	(0.684 , 2.686)
	Drug	27	15	12	55.56	--	--
	Food	8	5	3	62.50	--	--
	Other	7	2	5	28.57	--	--
	Unknown	0	0	0	-	--	--
Past medical history	No	184	94	90	51.09	--	--
	Yes	114	51	63	44.74	0.775	(0.485 , 1.239)
	Unknown	0	0	0	-	--	--
Past medical history (hepatic dysfunction)	No	294	143	151	48.64	--	--
	Yes	4	2	2	50.00	1.056	(0.147 , 7.597)
	Unknown	0	0	0	-	--	--
Past medical history (cardiac dysfunction)	No	286	137	149	47.90	--	--
	Yes	12	8	4	66.67	2.175	(0.641 , 7.385)
	Unknown	0	0	0	-	--	--
Past medical history (renal dysfunction)	No	290	142	148	48.97	--	--
	Yes	8	3	5	37.50	0.625	(0.147 , 2.665)
	Unknown	0	0	0	-	--	--
Past medical history (pulmonary dysfunction)	No	297	144	153	48.48	--	--
	Yes	1	1	0	100.00	-	(- , -)
	Unknown	0	0	0	-	--	--
Complication	No	131	64	67	48.85	--	--
	Yes	167	81	86	48.50	0.986	(0.624 , 1.558)
	Unknown	0	0	0	-	--	--
Complication (hepatic dysfunction)	No	270	137	133	50.74	--	--
	Yes	28	8	20	28.57	0.388	(0.165 , 0.912)
	Unknown	0	0	0	-	--	--
Complication (cardiac dysfunction)	No	275	133	142	48.36	--	--
	Yes	23	12	11	52.17	1.165	(0.497 , 2.730)
	Unknown	0	0	0	-	--	--
Complication (renal dysfunction)	No	263	131	132	49.81	--	--
	Yes	35	14	21	40.00	0.672	(0.328 , 1.378)
	Unknown	0	0	0	-	--	--
Complication (pulmonary dysfunction)	No	295	145	150	49.15	--	--
	Yes	3	0	3	0.00	-	(- , -)
	Unknown	0	0	0	-	--	--
HBV infection	No	36	20	16	55.56	--	--
	Yes	79	42	37	53.16	0.908	(0.411 , 2.005)
	Unknown	183	83	100	45.36	--	--
Prior treatment	No	120	69	51	57.50	--	--
	Yes	178	76	102	42.70	0.551	(0.345 , 0.880)
	Unknown	0	0	0	-	--	--
Prior treatment (antineoplastic drugs)	No	124	70	54	56.45	--	--
	Yes	174	75	99	43.10	0.584	(0.367 , 0.930)
	Unknown	0	0	0	-	--	--

Patient factor		Number of patients	Responders (partial response or better)	Non-responders	Response rate (%)	Odds ratio (95%CI)	
						OR	lower-upper
Prior treatment (hematopoietic stem cell transplantation)	No	292	143	149	48.97	--	--
	Yes	6	2	4	33.33	0.521	(0.094 , 2.889)
	Unknown	0	0	0	-	--	--
Disease stage (Rai stage)	0	16	9	7	56.25	--	--
	I	35	18	17	51.43	0.824	(0.251 , 2.706)
	II	41	27	14	65.85	1.500	(0.461 , 4.881)
	III	44	26	18	59.09	1.123	(0.354 , 3.570)
	IV	150	60	90	40.00	0.519	(0.183 , 1.468)
	Unknown	12	5	7	41.67	--	--
Disease stage (Binet stage)	A	23	15	8	65.22	--	--
	B	72	40	32	55.56	0.667	(0.251 , 1.769)
	C	194	86	108	44.33	0.425	(0.172 , 1.048)
	Unknown	9	4	5	44.44	--	--
ECOG PS	0	129	76	53	58.91	--	--
	1	109	57	52	52.29	0.764	(0.457 , 1.278)
	2	34	7	27	20.59	0.181	(0.073 , 0.446)
	3	20	5	15	25.00	0.232	(0.080 , 0.678)
	4	6	0	6	0.00	-	(- , -)
	Unknown	0	0	0	-	--	--
Number of lines of Arzerra treatment	First-line	15	8	7	53.33	--	--
	Second-line	117	64	53	54.70	1.057	(0.360 , 3.104)
	Third-line	104	51	53	49.04	0.842	(0.285 , 2.491)
	Other	0	0	0	-	-	(- , -)
	Unknown	62	22	40	35.48	--	--
Rituximab premedication	No	245	129	116	52.65	--	--
	Yes	53	16	37	30.19	0.389	(0.206 , 0.736)
Prior anti-CD20 antibody therapy	No	124	70	54	56.45	--	--
	Yes	169	73	96	43.20	0.587	(0.368 , 0.936)
	Unknown	5	2	3	40.00	--	--
Concomitant medications	No	75	42	33	56.00	--	--
	Yes	223	103	120	46.19	0.674	(0.398 , 1.142)
	Unknown	0	0	0	-	--	--
Concomitant medication (treatment of primary disease)	No	184	92	92	50.00	--	--
	Yes	39	11	28	28.21	0.393	(0.185 , 0.836)
	Unknown	75	42	33	56.00	--	--
Concomitant medication (prevention of infection)	No	22	9	13	40.91	--	--
	Yes	201	94	107	46.77	1.269	(0.519 , 3.102)
	Unknown	75	42	33	56.00	--	--
Concomitant therapies	No	292	145	147	49.66	--	--
	Yes	6	0	6	0.00	-	(- , -)
	Unknown	0	0	0	-	--	--

Source:Table 19

* Past medical history and complications of “hepatic dysfunction,”“ cardiac dysfunction,” “renal dysfunction,” and“ pulmonary dysfunction” were not those described in the case report forms but were those identified using the MedDRA PT code list prepared by NPKK.

10.6.2 Patients with special background

10.6.2.1 Children (<15 years)

Among the 298 patients in the efficacy analysis set, administration to children (<15 years old) was not observed.

10.6.2.2 Elderly (≥65 years)

Among the 298 patients in the efficacy analysis set, 223 were elderly patients (≥65 years).

The response rate in elderly patients was 49.78%, which was not markedly different from that in non-elderly patients, 44.44%.

10.6.2.3 Pregnant women

Among the 298 patients in the efficacy analysis set, use in pregnant women was not observed.

10.6.2.4 Patients complicated with renal dysfunction

Among the 298 patients in the efficacy analysis set, 35 patients were complicated with renal dysfunction.

The response rate in patients complicated with renal dysfunction was 40.00%, which was not markedly different from 49.81% in patients not complicated with renal dysfunction.

10.6.2.5 Patients complicated with hepatic dysfunction

Among the 298 patients in the efficacy analysis set, 28 patients were complicated with hepatic dysfunction.

The response rate in patients complicated with hepatic dysfunction was 28.57%, which was lower than 50.74% in patients not complicated with hepatic dysfunction.

11 Discussion

11.1 Summary of study results

- This study was started on 24 May 2013, and 347 patients were registered by 05 April 2022.
- The safety analysis set consisted of 302 patients, and the efficacy analysis set consisted of 298 patients.
- Among the 302 patients in the safety analysis set, there were more men (62.25%, 188 patients) than women (37.75%, 114 patients). Patients aged ≥65 years accounted for 74.83% (226 patients). No patients aged <15 years were reported.
- In the safety analysis set (302 patients), the total number of doses of Arzerra was 11 to 12 in approximately 50% of patients. The dose of the first dose was 300 mg in many patients, and the mean doses per 1 dose of the second to eighth doses and the ninth and subsequent doses were both 2,000 mg. Patients received Arzerra according to the dosage and administration described in the package insert.

11.1.1 Safety

- Among the 302 patients in the safety analysis set, the incidence of adverse drug reactions was 67.55% (204 patients). Common adverse drug reactions (≥5.00%) were rash in 16.56% (50 patients), pyrexia in 15.56% (47 patients), chills and urticaria in 8.94% (27 patients) each, neutrophil count decreased in 6.29% (19 patients), and dyspnoea in 5.96% (18 patients). In 223 patients evaluated in the overseas phase II study (OMB111773) conducted by the time of approval, adverse drug reactions were observed in 67% (149 patients). Common adverse drug reactions observed in the clinical studies were neutropenia in 30% (13 patients), chills in 9% (21 patients), rash in 9% (20 patients), and pyrexia, fatigue, and urticaria in 7% (15 patients) each. Of neutrophil count decreased (2/9 Japanese [22%] and 4/223 non-Japanese [2%]) and hyperglycaemia (2/9 Japanese [22%] and 5/223 non-Japanese [2%]] whose incidences were higher in Japanese patients than in non-Japanese patients in the Japanese and Korean phase I/II study (OMB112758) and the overseas phase II study (OMB111773), hyperglycaemia was not observed in this study. The incidence of adverse drug reactions in this study was comparable to the results of clinical studies, and the types of common adverse drug reactions were similar.
- Among the 302 patients in the safety analysis set, the incidence of serious adverse drug reactions was 13.91% (42 patients). Common serious adverse drug reactions (≥1.00%) were pneumonia in 1.99% (6 patients), neutrophil count decreased in 1.66% (5 patients), and white blood cell count decreased in 1.32% (4 patients). In 223 patients evaluated in the overseas phase II study (OMB111773) conducted by the time of approval, serious adverse drug reactions were observed in 17% (38 patients). Common serious adverse drug reactions observed in the clinical studies were neutropenia in 5% (11 patients), pneumonia in 3% (6 patients), and sepsis in 1% (3 patients). The incidence of serious adverse drug reactions in this study was comparable to the results of clinical studies, and no adverse drug reactions requiring special attention were observed.
- Among the 302 patients in the safety analysis set, the incidence of adverse events leading to treatment discontinuation was 24.83% (75 patients). Common adverse events leading to treatment discontinuation (≥1.00%) were chronic lymphocytic leukaemia (worsening) in 9.93% (30 patients), neutrophil count decreased in 1.99% (6 patients), pneumonia in 1.66% (5 patients), and vomiting in 1.32% (4 patients). In the overseas phase II study (OMB111773) conducted by the time of approval, adverse events leading to treatment discontinuation were observed in 30 of 223 evaluated patients, and the incidence was 13%. The most common adverse events leading to treatment discontinuation were pneumonia in 3% (6 patients), and sepsis and disease progression in 1% (3 patients) each. In this study, more patients discontinued treatment due to worsening of primary disease than in the clinical studies, but the incidence of other adverse events leading to treatment discontinuation and the most common adverse events leading to treatment discontinuation were similar to those in the clinical studies.
- Among the 302 patients in the safety analysis set, the incidence of adverse events related to infusion reactions was 50.99% (154 patients). Common infusion reactions (≥5.00%) were rash in 14.90% (45 patients), pyrexia in 13.91% (42 patients), chills in 8.94% (27 patients), urticaria in 8.61% (26 patients), and dyspnoea in 5.63% (17 patients). In the overseas phase II study (OMB111773) conducted by the time of approval, adverse events related to infusion reactions were observed in 153 of 223 evaluated patients, and the

incidence was 69%. Common infusion reactions were cough and pain in 11% (24 patients) each, dyspnoea and rash in 10% (22 patients) each, fatigue and chills in 9% (20 patients) each, and anaphylactoid event in 9% (19 patients). The incidence of infusion reactions in this study was lower than that in the clinical studies, and common infusion reactions were similar. In this study, no serious infusion reactions leading to death were observed. However, there have been overseas post-marketing spontaneous reports of cases in which serious infusion reactions occurred and led to death. The possibility of occurrence of infusion reactions is described in the "Warnings," "Precautions Concerning Dosage and Administration," and Precautions "Important Precautions" and "Clinically Significant Adverse Reactions " sections of the package insert. Patients should be carefully monitored for clinical symptoms and vital signs (blood pressure, pulse rate, respiratory rate, etc.) during and after treatment with Arzerra.

- The incidence of adverse events specified as priority study items other than infusion reactions was 17.55% (53 patients) for adverse events related to infections. Common adverse events (top 3) were pneumonia in 4.97% (15 patients), bronchitis and herpes zoster in 2.32% (7 patients) each, and sepsis in 1.66% (5 patients). In the overseas phase II study (OMB111773) conducted by the time of approval, infections were observed in 162 of 223 evaluated patients, and the incidence was 73%. Common adverse events were upper respiratory tract infection in 29% (64 patients), pneumonia in 21% (46 patients), and bronchitis in 12% (26 patients). Infections leading to death were pneumonia in 3.13% (7 patients) and sepsis in 2.69% (6 patients). The incidence of adverse events related to infections in this study was lower than that in the clinical studies. In addition, there were deaths, but the events were also observed in the clinical studies. Adverse events related to hematotoxicity were observed in 16.23% (49 patients). Common adverse events (top 3) were neutrophil count decreased in 6.29% (19 patients), anaemia in 3.97% (12 patients), and white blood cell count decreased in 2.98% (9 patients). In the overseas phase II study (OMB111773) conducted by the time of approval, adverse events related to blood and lymphatic system disorders were observed in 81 of 223 evaluated patients, and the incidence was 36%. Common adverse events were anaemia in 17% (39 patients), neutropenia in 17% (37 patients), and thrombocytopenia in 4% (10 patients). The incidence of adverse events related to hematotoxicity in this study was lower than that in the clinical studies. The incidence of adverse events of tumour lysis syndrome was 1.66% (5 patients). In the overseas phase II study (OMB111773) conducted by the time of approval, tumour lysis syndrome was observed in 1 of 223 evaluated patients, and the incidence was 0.45%. The incidence of adverse events of tumour lysis syndrome in this study was comparable to that in the clinical studies. Also for the adverse events of intestinal obstruction, skin disorder, cardiac disorder, blood pressure decreased, hepatic dysfunction/jaundice, renal disorder, and interstitial lung disease set out as other priority study items, there were no findings to particularly note in this study. For all of them, the "Clinically Significant Adverse Reactions" section of Precautions in the package insert has included descriptions including the implementation of periodic tests to call attention, and no additional measures are thought to be necessary at the present point in time.
- The results of the factorial analysis of the incidence of adverse drug reactions showed that the 95% CI of the odds ratio did not include 1 for the following 5 factors: "past medical history (yes)," "prior treatment (yes)," "prior treatment (antineoplastic drugs) (yes),"

"ECOG PS (2)," and "concomitant medication (yes)." No new safety concerns were identified for any of the factors.

- Rash and pyrexia were also observed as common adverse drug reactions in patients with special characteristics (elderly, hepatic dysfunction, and renal dysfunction). No adverse drug reactions specific to these patients were observed.

Based on the above, compared to the clinical studies, there were no new notable adverse drug reactions or new safety concerns requiring precautions.

11.1.2 Efficacy

- The response rate (CR + PR) in this study was 48.7% (145/298 patients). The response rate in this study was lower than the response rate (CR + CRi + nPR + PR), 78% (7/9 patients), based on the independent review in Japanese subjects in the Japanese and Korean phase I/II study (OMB112758). In the overseas phase II study (OMB111773), the rate of PR or better was 46% (95/207 patients) in patients with chronic lymphocytic leukemia.
- The response rate was low in patients with hepatic dysfunction among patients with special characteristics, but no new concerns were observed also in patients with other special characteristics (elderly and patients with renal dysfunction), showing a certain level of efficacy.
- Although it is impossible to make a definitive comparison because the patient characteristics are different between the clinical studies and this study, it is considered that a certain response under the conditions of actual use was shown.

11.2 Limitations

This is an observational study with no comparator group and does not collect information on patients who have not been exposed to Arzerra. Therefore, there are limitations to the inference about causality between exposure to Arzerra and the outcome.

11.3 Interpretation

Although limitations of the study methods as described in "11.2 Limitations" were identified, it is considered that this study successfully confirmed the safety and efficacy of Arzerra under the conditions of actual use.

11.4 Generalizability

Since this study included all patients treated with Arzerra, it is considered to generally reflect the safety and efficacy in patients treated with Arzerra in Japan.

12 Other information

The following documents are attached.

Attachment 1: Protocol Version 2.20

Attachment 2: Implementation Guideline Version 2.10

Attachment 3: Statistical Analysis Plan Version 5

Appendix 4: Analysis Results

13 Conclusion

Based on the results of this study, no new concerns about the safety or efficacy of Arzerra under the conditions of actual use or issues to be particularly addressed were identified.

14 References

Cheson BD (2010) Ofatumumab, a novel anti-CD20 monoclonal antibody for the treatment of B-cell malignancies.J Clin Oncol; 28(21):3525-30.

15 Appendices

Not applicable