Report on the Deliberation Results

March 4, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Vyloy for I.V. Infusion 100 mg
Non-proprietary Name	Zolbetuximab (Genetical Recombination) (JAN*)
Applicant	Astellas Pharma Inc.
Date of Application	June 9, 2023

Results of Deliberation

In its meeting held on March 4, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN*)*

Review Report

February 19, 2024
Pharmaceuticals and Medical Devices Agency

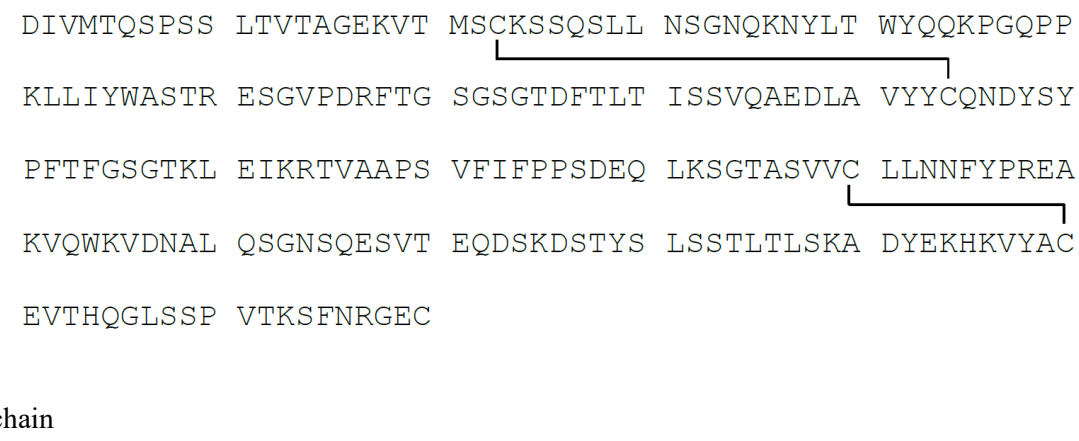
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Vyloy for I.V. Infusion 100 mg
Non-proprietary Name	Zolbetuximab (Genetical Recombination)
Applicant	Astellas Pharma Inc.
Date of Application	June 9, 2023
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection: Each vial contains 105 mg of Zolbetuximab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Zolbetuximab is a recombinant chimeric monoclonal antibody composed of variable regions derived from mouse anti-human claudin-18 isoform 2 monoclonal antibody and constant regions derived from human IgG1. Zolbetuximab is produced by Chinese hamster ovary cells. Zolbetuximab is a glycoprotein (molecular weight: ca. 150,000) composed of 2 H-chains (γ1-chains) consisting of 448 amino acid residues each and 2 L-chains (κ-chains) consisting of 220 amino acid residues each.

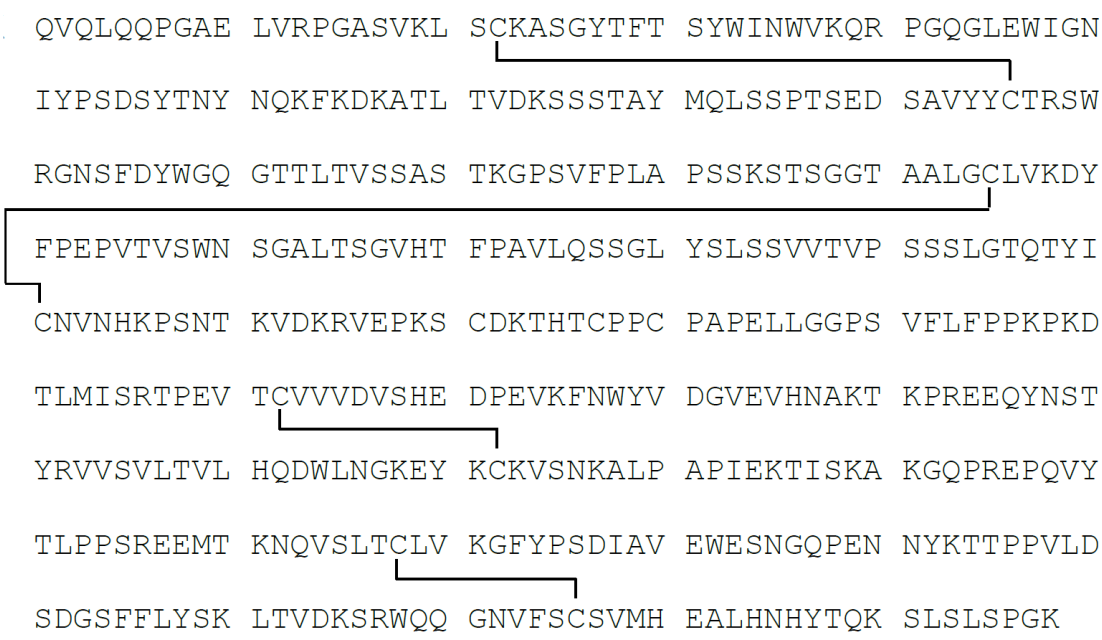
Structure

Amino acid sequence:

L-chain



H-chain



Intrachain disulfide bonds: Solid lines in the figure

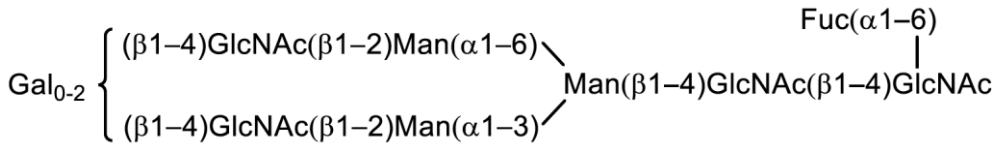
Interchain disulfide bonds: L-chain C220-H-chain C221, H-chain C227-H-chain C227, H-chain C230-H-chain C230

Partial pyroglutamate acid: H-chain Q1

Glycosylation site: H-chain N298

Partial processing: H-chain K448

Presumed main carbohydrate structure:



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6534}H_{10066}N_{1726}O_{2056}S_{44}$ (protein segment, 4 chains)
Molecular weight: ca. 150,000

Items Warranting Special Mention None

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of claudin-18 splice variant 2 (CLDN18.2)-positive unresectable advanced or recurrent gastric cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The occurrence of nausea and vomiting need to be further investigated via post-marketing surveillance.

Indication

CLDN18.2-positive unresectable advanced or recurrent gastric cancer

Dosage and Administration

In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion over at least 2 hours for the initial dose and then 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks for the subsequent doses.

Approval Condition

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

Attachment

Review Report (1)

December 7, 2023

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

Product Submitted for Approval

Brand Name	Vyloy for I.V. Infusion 100 mg
Non-proprietary Name	Zolbetuximab (Genetical Recombination)
Applicant	Astellas Pharma Inc.
Date of Application	June 9, 2023
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection: Each vial contains 105 mg of Zolbetuximab (Genetical Recombination).
Proposed Indication	CLDN18.2-positive locally advanced, unresectable or metastatic gastric cancer

Proposed Dosage and Administration

In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion for the initial single loading dose. The subsequent maintenance dose administered as an intravenous infusion is 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Zolbetuximab (genetical recombination) (hereinafter referred to as zolbetuximab) is a chimeric monoclonal antibody that is comprised of variable regions derived from mouse anti-human claudin-18 splice variant 2 (CLDN18.2) antibody and constant regions derived from human immunoglobulin (Ig)G1, discovered by Ganymed Pharmaceuticals AG in Germany.

Zolbetuximab binds to CLDN18.2, expressed on the cell membrane of gastric cancer cells, and thereby induces antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) against tumor cells expressing CLDN18.2, which is expected to inhibit tumor cell growth.

1.2 Development history, etc.

Outside Japan, Ganymed Pharmaceuticals AG in Germany initiated a foreign phase I study in patients with CLDN18.2-positive advanced gastric cancer (Study GM-IMAB-001 [Study 001]) in July 2009. Then, the applicant initiated global phase III studies in patients with CLDN18.2-positive and human epidermal growth factor receptor type 2 (HER2)-negative, unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy, Study 8951-CL-0301 (SPOTLIGHT study) and Study 8951-CL-0302 (GLOW study), in June and November 2018, respectively.

In the US and EU, applications for marketing approval (applications) based on the pivotal data from the SPOTLIGHT and GLOW studies were submitted in May and June 2023, respectively, and are currently under review.

As of October 2023, zolbetuximab has not been approved in any countries or regions.

In Japan, the applicant initiated a Japanese phase I study (Study 8951-CL-0104 [Study 0104]) in patients with CLDN18.2-positive advanced gastric cancer in June 2018. In addition, patient enrollment in the global phase III studies, the SPOTLIGHT and GLOW studies, was started in December 2018 and February 2019, respectively.

Recently, an application for zolbetuximab based on the pivotal data from the SPOTLIGHT and GLOW studies has been submitted.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Hybridoma cells were prepared by mouse myeloma cells with spleen cells isolated from mice that had been immunized using a vector encoding human CLDN18.2 extracellular domain, and an appropriate clone was selected from them based on the binding ability to CLDN18.2. From this clone, the gene sequence of a mouse antibody specific to CLDN18.2 was determined, and of this sequence, parts encoding the constant regions were replaced by the corresponding human sequences to obtain the gene sequence of a chimeric antibody. Using the obtained sequence, gene fragments encoding heavy and light chains were prepared and inserted into expression plasmids to obtain the gene expression constructs of

zolbetuximab. The concerned gene expression constructs were introduced into Chinese hamster ovary (CHO) cells, and from the transfected CHO cells, a clone appropriate for production of zolbetuximab was selected and used to prepare a master cell bank (MCB) and a working cell bank (WCB).

Characterization and purity tests on the MCB, WCB, and end of production cells (EOPCs) were performed in accordance with ICH Q5A(R1), Q5B, and Q5D guidelines. The results demonstrated genetic stability of the cells throughout the manufacturing period, and within a scope of items tested, neither viral nor non-viral adventitious agents were detected except for endogenous retrovirus-like particles, which are generally detected in rodent cell lines.

MCB and WCB are stored in [redacted]. There is no plan for generating a new MCB, but a new WCB will be generated as necessary.

2.1.2 Manufacturing process

The manufacturing process of the drug substance is comprised of seed culture, production culture, cell separation, [redacted] chromatography, [redacted] viral inactivation, [redacted], [redacted] chromatography, [redacted] chromatography, viral removal filtration, [redacted], filtration and filling, and storage and testing.

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] have been defined as critical process steps.

Process validation of the manufacturing process of the drug substance was performed at a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No animal- or human-derived raw materials are used in the manufacturing process of the drug substance, except for the host CHO cell line.

Purity tests were performed on the MCB, WCB, and EOPC [see Section 2.1.1]. In addition, unprocessed bulks at a commercial scale were subjected to tests for mycoplasma, bioburden, *in vitro* adventitious viruses, and minute virus of mice, but within a scope of items tested, neither viral nor non-viral adventitious agents were detected. These tests are included as in-process control tests for unprocessed bulks.

The purification process was studied for viral clearance using model viruses and was demonstrated to have certain robustness. (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Reovirus type 3	Pseudorabies virus
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] viral inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥17.09	≥12.23	≥15.13	≥13.99

[redacted]

2.1.4 Manufacturing process development

The following are the major changes made to the manufacturing process of the drug substance during development (the manufacturing processes are referred to as Process 1, Process 2, Process 3, Proposed Process 1, and Proposed Process 2). In the SPOTLIGHT and GLOW studies, the formulation manufactured from the drug substance of Process 3 was used.

- From Process 1 to Process 2: Establishment of a new MCB, introduction of the WCB, and changes to the manufacturing site, manufacturing scale, culture process, purification process, and formulation
- From Process 2 to Process 3: Changes to the manufacturing site, manufacturing scale, culture process, viral inactivation condition, viral removal filter, and primary container
- From Process 3 to Proposed Process 1: Change to a purification column
- From Proposed Process 1 to Proposed Process 2: Change to the manufacturing site

In response to a process change, comparability of quality attributes between pre-change and post-change drug substances was evaluated and has been demonstrated.

2.1.5 Characterization

2.1.5.1 Structure and characterization

Characterization was performed as shown in Table 2.

Table 2. Characterization attributes

Primary/higher order structure	Amino acid sequence, disulfide bond, free-thiol group content, post-translational modifications (N-terminal pyroglutamate form, oxidation form, succinimide form, deamidation form, C-terminal proline amidation form, C-terminal lysine adduct), secondary structure, tertiary structure, and thermostability
Physicochemical properties	Molecular weight, size variants, and charge variants
Carbohydrate structure	Glycosylation site, amount of glycosylation, and N-linked oligosaccharide profile
Biological properties	Binding activity to CLDN18.2
	Binding affinity to FcγR (FcγRI, FcγRIIa [H131 and R131], FcγRIIb/c, FcγRIIIa [F158 and V158]), FcRn, and C1q
	ADCC and CDC activity

Investigation on biological properties revealed mainly the following points:

- The binding activity of zolbetuximab to CLDN18.2 was confirmed by [redacted] method using CLDN18.2-expressing [redacted].
- ADCC activity of zolbetuximab was confirmed by a [redacted]-based bioluminescent assay using the target cells and effecter cells of CLDN18.2-positive [redacted] and [redacted], respectively, and by a reporter assay using the target cells and effecter cells of CLDN18.2-expressing [redacted] and [redacted], respectively.

- CDC activity of zolbetuximab was confirmed in an assay system using CLDN18.2-expressing [redacted] in the presence of [redacted].

2.1.5.2 Product-related substances/Product-related impurities

Based on characterization results in Section "2.1.5.1 Structure and characterization," [redacted] was considered a product-related substance, and Impurity A ([redacted] and [redacted]), Impurity B, and Impurity C were considered product-related impurities. Of product-related impurities, Impurity C is controlled by the manufacturing process, and [redacted], [redacted], and Impurity B are controlled by the specifications for the drug substance and drug product.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell deoxyribonucleic acid (DNA), Impurity D, Impurity E, Impurity F, Impurity G, and Impurity H were considered process-related impurities. All of the process-related impurities are demonstrated to be adequately removed in the manufacturing process. HCP is controlled by [redacted].

2.1.6 Control of drug substance

The proposed specifications for the drug substance include the content, description, identification (peptide mapping and capillary isoelectric focusing [cIEF]), pH, N-linked oligosaccharide profile, purity (size exclusion chromatography [SEC], capillary electrophoresis sodium dodecyl sulphate [CE-SDS] [[redacted]], and cIEF), bacterial endotoxins, microbial limits, potency ([redacted] and [redacted]), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows main stability studies of the drug substance.

Table 3. Main stability studies of the drug substance

	Number of batches*1	Storage condition	Studied period	Storage package
Long-term testing	3	-70 ± 10°C	36 months*2	Multiple-layer plastic bag using [redacted] as the inner layer
Accelerated testing	3	5 ± 3°C	6 months	
Stress testing	3	25 ± 2°C/60 ± 5%RH	6 months	

*1 Drug substance manufactured by Proposed Process 1;
*2 The testing is continued for up to [redacted] months.

Under the long-term storage condition, no clear changes in quality attributes were observed throughout the studied period.

Under the accelerated condition, [redacted] in [redacted] and [redacted] in [redacted] tended to increase.

Findings under the stress condition were an increasing trend of multimer peaks in SEC, increases of acidic peaks in cIEF and of [redacted] in [redacted] ([redacted]), elevation of [redacted], and decreases of [redacted] and [redacted].

Based on the above, a shelf life of 36 months has been proposed for the drug substance when stored in a multiple-layer plastic bag using [redacted] as the inner layer at -70°C ± 10°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a glass vial (20 mL), containing 105 mg of zolbetuximab. Excipients contained in the drug product are L-arginine, sucrose, polysorbate 80, and phosphoric acid. An excess volume of zolbetuximab is filled in each vial compared with the labeled amount so that, following reconstitution with 5.0 mL of water for injection, 100 mg of zolbetuximab (protein concentration after reconstitution is 20 mg/mL) can be obtained.

2.2.2 Manufacturing process

The manufacturing process of the drug product is comprised of drug solution preparation, sterile filtration and filling, lyophilization, crimping, and packaging/labeling/storage/testing.

[redacted] has been defined as critical process step.

Process validation of the manufacturing process for the drug product was performed at a commercial scale.

2.2.3 Manufacturing process development

The following are the major changes made to the manufacturing process of the drug product during development (the manufacturing processes are referred to as Process A, Process B, Proposed Process 1, and Proposed Process 2). In the SPOTLIGHT and GLOW studies, the formulation manufactured by Proposed Process 1 was used.

- From Process A to Process B: Changes to manufacturing scale and filling volume
- From Process B to Proposed Process 1: Changes to the manufacturing site, manufacturing scale, and drug solution preparation process
- From Proposed Process 1 to Proposed Process 2: Addition of a manufacturing site and changes to drug solution preparation and crimping processes

In response to a process change, comparability of quality attributes between pre-change and post-change drug products was evaluated and has been demonstrated.

2.2.4 Control of drug product

The proposed specifications for the drug product include the strength, description, identification (peptide mapping), osmolality, pH, purity (appearance of solution, SEC, CE-SDS [redacted], and cIEF), water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, potency ([redacted] and [redacted]), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows main stability studies of the drug product.

Table 4. Main stability studies of the drug product

	Number of batches[*1]	Storage condition	Studied period	Storage package
Long-term testing	3	5 ± 3°C	40 months[*2]	[redacted] rubber stopper and glass vial
Accelerated testing	3	25 ± 2°C/60 ± 5%RH	6 months	
Stress testing	3	40 ± 2°C/75 ± 5%RH	6 months	
Photostability testing	1	Overall illumination of ≥1.2 million lx·h and an integrated near ultraviolet energy of ≥200 W·h/m^2 at 25°C		

*1 Drug product manufactured by Proposed Process 1 using the drug substance manufactured by Proposed Process 1
*2 The testing is being continued for up to [redacted] months.

Under the long-term storage and accelerated conditions, no clear changes in quality attributes were observed throughout the studied period.

Findings under the stress condition were an increase of [redacted] in [redacted] and an increasing trend of [redacted] in [redacted].

Photostability testing showed that the drug product is photostable.

Based on the above, a shelf life of 40 months has been proposed for the drug product when stored at 2°C to 8°C, using the primary container of [redacted], [redacted] rubber stopper, and glass vial.

2.3 Quality control strategy

Through the following studies, a control method of quality attributes of zolbetuximab was established, using process parameter control, in-process control testing, and specifications in combination [for control of product-related and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs):
  Based on information, related knowledge, etc. obtained through development of zolbetuximab, the following CQAs were identified:

  CQAs of the drug substance: Primary sequence, description, content, potency ([redacted], [redacted], [redacted], and [redacted]), osmolality, excipients, pH, bioburden, bacterial endotoxins, mycoplasma, adventitious viral contamination, purity of the desired product, disulfide scrambling including free-thiol groups, [redacted], [redacted], oxidant, Impurity B, Impurity C, non-fucosylation, terminal galactose content, terminal N-acetyl-D-glucosamine content, terminal mannose content, terminal sialylation, glycosylated form, Impurity G, Impurity H, Impurity F, HCP, and DNA content

  CQAs of the drug product: Primary sequence, description, strength, potency ([redacted], [redacted], [redacted], and [redacted]), osmolality, excipients, pH, water content, insoluble particulate matter, integrity of the container closure system, bioburden, bacterial endotoxins, mycoplasma, adventitious viral contamination, sterility, purity of the desired product, disulfide scrambling including free-thiol groups, [redacted], [redacted], oxidant, Impurity B, Impurity C, non-fucosylation, terminal galactose content, terminal N-acetyl-D-

glucosamine content, terminal mannose content, terminal sialylation, and glycosylated form.

- Process characterization:
  Operating ranges of process parameters were investigated by a risk assessment and characterization of the process, and the process parameters affecting CQAs and process performance were identified.

2.R Outline of the review conducted by PMDA

Based on the data submitted and the considerations described in the following subsections, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.R.1 Novel excipients

The drug product contains phosphoric acid, a novel excipient, in an amount higher than those present in existing intravenous formulations.

2.R.1.1 Specifications and stability

Phosphoric acid in the drug product conforms to the specification of the Japanese Pharmaceutical Excipients, and PMDA found no problem in the specifications or stability.

2.R.1.2 Safety

Based on the submitted data, PMDA considered that phosphoric acid is unlikely to raise safety problems when used in the drug product as proposed, in terms of the amount and route of administration.

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

3.1 Primary pharmacodynamics

3.1.1 Binding to CLDN18.2 (CTD 4.2.1.1-1, 4.2.1.1-2, and 4.2.1.1-3)

The binding of zolbetuximab to the following cell lines was investigated by flow cytometry: The human CLDN18.2 or human claudin-18 splice variant 1 (CLDN18.1)[1)]-expressing human embryonic kidney HEK 293 cell line, human CLDN18.2-expressing CHO-K1 cell line, endogenous CLDN18.2-expressing human gastric cancer KATO-III and NUGC-4 cell lines, as well as the non-CLDN18.2 and CLDN18.1-expressing human breast cancer SK-BR-3 cell line. Zolbetuximab bound to human CLDN18.2-expressing cell lines (HEK293, CHO-K1, KATO-III, and NUGC-4 cell lines). On the other hand, zolbetuximab did not bind to the human CLDN18.1-expressing HEK293 cell line or the non-CLDN18.2 and CLDN18.1-expressing SK-BR-3 cell line.

The binding affinity of zolbetuximab to CLDN18.2 was investigated by flow cytometry using the following cell lines: The human, mouse, or cynomolgus monkey CLDN18.2-expressing HEK293 cell line as well as endogenous CLDN18.2-expressing KATO-III and NUGC-4 cell lines. Table 5 shows resultant dissociation constant (K_D) values of zolbetuximab.

1) A claudin family protein with 91% sequence homology to CLDN18.2

Table 5.Binding affinity of zolbetuximab to CLDN18.2

Cell line	Animal species	n	K_D value (nmol/L)
KATO-III	Human	2	9.93, 12.1
NUGC-4		2	17.6, 17.0
HEK293		9	2.90 ± 0.863
	Mouse	2	2.60, 2.22
	Cynomolgus monkey	3	2.73 ± 1.48

Mean ± standard deviation (SD) or individual values for n = 2

The binding site of zolbetuximab to human CLDN18.2 was investigated by flow cytometry, using the mutant CLDN18.2[2)]-expressing human embryonic kidney FreeStyle 293F cell line. The investigation suggested that 12 amino acid residues in the extracellular domain 1 of CLDN18.2 (at positions 30, 42, 43, 45, 48, 49, 50, 53, 56, 60, 62, and 63) were critical in its binding to zolbetuximab.

NUGC-4 and KATO-III cells treated with antineoplastic agents (EOF [epirubicin, oxaliplatin (L-OHP), and 5-fluorouracil (5-FU)] or FLO [5-FU, leucovorin, and L-OHP]) for 96 hours were evaluated for the binding of zolbetuximab by flow cytometry. Treatment with antineoplastic agents was found to increase the binding of zolbetuximab.

3.1.2 ADCC activity (CTD 4.2.1.1-1)

Using healthy adult peripheral blood mononuclear cells (PBMCs) as effector cells, zolbetuximab-induced ADCC against luciferase gene-transfected NUGC-4, KATO-III, and SK-BR-3 cell lines was investigated based on the luciferase activity. The 50% effective concentration (EC_{50}) of zolbetuximab against NUGC-4 and KATO-III cell lines (mean ± standard deviation [SD], n = 10) was 250.4 ± 128.8 and 105.4 ± 84.09 ng/mL, respectively. On the other hand, zolbetuximab did not induce ADCC against the non-CLDN18.2-expressing SK-BR-3 cell line.

Using healthy adult PBMCs as effector cells, an effect of treatment with antineoplastic agents (OF [L-OHP and 5-FU], EOF, or FLO)[3)] on zolbetuximab-induced ADCC against luciferase gene-transfected NUGC-4 and KATO-III cell lines was investigated based on the luciferase activity. Table 6 shows resultant EC_{50} of zolbetuximab.

Table 6. Zolbetuximab-induced ADCC after treatment with antineoplastic agents

Cell line	Antineoplastic combination	n	EC_{50} (ng/mL)
NUGC-4	—	8	668 ± 403
	OF	9	180 ± 166
	EOF	7	204 ± 202
	FLO	9	164 ± 111
KATO-III	—	9	1,231 ± 1,390
	OF	4	420 ± 458
	EOF	6	219 ± 129
	FLO	8	118 ± 141

Mean ± SD; —, Not applicable

3.1.3 CDC activity (CTD 4.2.1.1-1)

In the presence of human serum, zolbetuximab-induced CDC against the luciferase gene-transfected, human CLDN18.1 or CLDN18.2-expressing CHO-K1 cell line was investigated based on the luciferase

2) Mutant CLDN18.2 in which point mutation was introduced to substitute alanine or glycine for any of 87 amino acid residues in the extracellular domain of human CLDN18.2

3) NUGC-4 and KATO-III cell lines were treated with each antineoplastic combination for 96 and 120 hours, respectively.

activity. The EC_{50} of zolbetuximab against the human CLDN18.2-expressing CHO-K1 cell line (n = 1) was 178 ng/mL. On the other hand, zolbetuximab did not induce CDC against the human CLDN18.1-expressing CHO-K1 cell line.

In the presence of human serum, zolbetuximab-induced CDC against luciferase gene-transfected NUGC-4 and KATO-III cell lines was investigated based on the luciferase activity. The EC_{50} of zolbetuximab (mean ± SD, n = 9) was 29.8 ± 6.57 and 31.2 ± 6.32 μg/mL, respectively.

In the presence of human serum, an effect of treatment with antineoplastic agents (OF or EOF)[4] on zolbetuximab-induced CDC against luciferase gene-transfected NUGC-4 and KATO-III cell lines was investigated based on the luciferase activity. Table 7 shows resultant EC_{50} of zolbetuximab.

Table 7. Zolbetuximab-induced CDC after treatment with antineoplastic agents

Cell line	Antineoplastic combination	EC_{50} (μg/mL)
NUGC-4	—	78.7
	OF	19.9
	EOF	17.4
KATO-III	—	40.8
	OF	28.4
	EOF	19.1

n = 1 (individual value); —, Not applicable

3.1.4 Effects on immune system (CTD 4.2.1.1-4 and 4.2.1.1-5)

In mice subcutaneously transplanted with the mouse CLDN18.2-expressing mouse gastric cancer CLS-103 cell line (n = 10/group), effects of zolbetuximab, EOF, and zolbetuximab/EOF (zolbetuximab and EOF) on immune cell infiltration into the tumor tissue was investigated. Starting 4 days after transplantation, EOF[5] was intraperitoneally administered once weekly for 2 weeks, and zolbetuximab 200 μg was intravenously or intraperitoneally administered twice weekly for 3 weeks. At 18 days after transplantation, immune cell infiltration into the tumor tissue was investigated by flow cytometry. Increased infiltration of cluster of differentiation (CD)8-positive T cells was observed in the zolbetuximab/EOF group, compared with the control (phosphate-buffered saline) group, zolbetuximab group, and EOF group.

In mice subcutaneously transplanted with the mouse CLDN18.2-expressing CLS-103 cell line (n = 14 or 15/group), effects of zolbetuximab, OF, and zolbetuximab/OF (zolbetuximab and OF) on immune cell infiltration into the tumor tissue was investigated. Starting 2 days after transplantation, zolbetuximab 800 μg and OF[6] were intraperitoneally administered twice weekly for 2 weeks. At 16 days after transplantation, immune cell infiltration into the tumor tissue was investigated by flow cytometry. Statistically significant infiltration of CD8-positive T cells was observed in the zolbetuximab/OF group, compared with the control (phosphate-buffered saline) group ($P < 0.05$, Mann-Whitney U test).

4) NUGC-4 and KATO-III cell lines were treated with each antineoplastic combination for 72 and 48 hours, respectively.
5) Epirubicin 1.25 mg/kg, L-OHP 3.25 mg/kg, and 5-FU 56.25 mg/kg
6) L-OHP 1 mg/kg and 5-FU 30 mg/kg

3.1.5 Growth inhibitory effect against gastric cancer cell line (CTD 4.2.1.1-1, 4.2.1.1-4, and 4.2.1.1-5)

In nude mice subcutaneously transplanted with endogenous CLDN18.2, the epidermal growth factor receptor (EGFR), and HER2-expressing NUGC-4 cell line (n = 8 or 9/group), tumor growth inhibitory effect of zolbetuximab, cetuximab, and trastuzumab was investigated. Starting 6 days after transplantation, zolbetuximab, cetuximab, or trastuzumab 200 μg was administered twice weekly for 15 days. Of the 2 doses per week, one was given intravenously, and the other was given intraperitoneally. At 21 days after transplantation, tumor volume was calculated. Statistically significant tumor growth inhibitory effect was observed in the zolbetuximab group, compared with the control (isotype antibody or physiological saline) group, cetuximab group, and trastuzumab group (Figure 1).

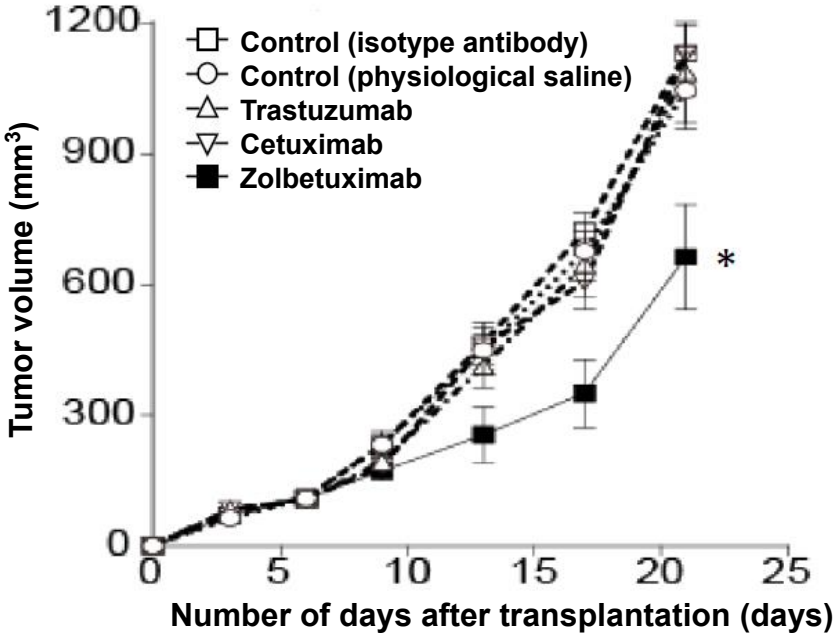


Figure 1. Tumor growth inhibitory effect of zolbetuximab, etc. in nude mice subcutaneously transplanted with NUGC-4 cell line

n = 8 or 9, Mean ± standard error; * Control, $P < 0.05$ to cetuximab and trastuzumab
(one-way analysis of variance and Tukey's multiple comparison test)

In mice subcutaneously transplanted with the mouse CLDN18.2-expressing CLS-103 cell line (n = 10/group), tumor growth inhibitory effect of zolbetuximab, EOF, and zolbetuximab/EOF was investigated. EOF[5] was intraperitoneally administered once weekly for 4 weeks starting 3 days after transplantation, zolbetuximab 800 μg was intravenously administered once weekly for 9 weeks starting 4 days after transplantation. At 17 days after transplantation, tumor volume was calculated. Statistically significant tumor growth inhibitory effect was observed in the zolbetuximab/EOF group compared with the zolbetuximab group and the EOF group ($P < 0.01$ for the zolbetuximab group and $P < 0.05$ for the EOF group, Kruskal-Wallis test and Dunn's multiple comparison test).

In mice subcutaneously transplanted with the mouse CLDN18.2-expressing CLS-103 cell line (n = 15/group), tumor growth inhibitory effect of zolbetuximab, OF, and zolbetuximab/OF was investigated. Starting 2 days after transplantation, zolbetuximab 800 μg and OF[6] were intraperitoneally administered

twice weekly for 2 weeks, and at 16 days after transplantation, tumor volume was calculated. Statistically significant tumor growth inhibitory effect was observed in the zolbetuximab/OF group compared with the zolbetuximab group and the OF group ($P < 0.05$ for the zolbetuximab group and $P < 0.01$ for the OF group, Student's t test).

3.2 Safety pharmacology

3.2.1 Effects on central nervous system (CTD 4.2.1.3-1)

A single dose of zolbetuximab 10, 30, or 100 mg/kg was intravenously administered to mice (n = 8/group), and effects on the central nervous system were investigated by the Irwin test. No effects of zolbetuximab were observed.

3.2.2 Effects on cardiovascular and respiratory systems

In a 4-week repeated-dose toxicity study [see Section 5.2] in cynomolgus monkeys (n = 6/group), zolbetuximab 10, 30, or 100 mg/kg was intravenously administered on Days 1, 8, 15, 22, and 29, and effects on the blood pressure, heart rate, electrocardiogram (ECG), and respiratory rate were investigated. No effects of zolbetuximab were observed.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations described in the following subsections, PMDA concluded that the applicant's explanation about non-clinical pharmacology of zolbetuximab is acceptable.

3.R.1 Mechanism of action and efficacy of zolbetuximab

The applicant's explanation about the mechanism of action of zolbetuximab and its efficacy against CLDN18.2-positive gastric cancer:

CLDN18.2 is expressed on normal gastric mucosal epithelial cells, contact adjacent cells closely, and thereby contributes to formation of tight junctions, which are involved in maintenance of cell polarity (*Gene.* 2011;481:83-92, *Mol Cell Biol.* 2001;21:7380-90). CLDN18.2 is also expressed on tumor tissues such as gastric cancer (*Clin Cancer Res.* 2008;14:7624-34). In a course of malignant transformation, CLDN18.2 is continuously expressed but becomes rather exposed on the cell membrane in tumor tissues owing to a change of cell polarity (*Biomark Res.* 2022;10:38).

Zolbetuximab is an anti-human CLDN18.2 chimeric monoclonal antibody, binds to CLDN18.2 on the cell membrane of tumor cells [see Section 3.1.1], and thereby is considered to inhibit tumor growth by inducing ADCC and CDC activities [see Sections 3.1.2 and 3.1.3].

In addition to the above mechanism of action, taking into account that zolbetuximab inhibited tumor growth in nude mice subcutaneously transplanted with the CLDN18.2-expressing human gastric cancer cell line [see Section 3.1.5], the efficacy of zolbetuximab against CLDN18.2-positive gastric cancer can be expected.

PMDA accepted the applicant's explanation.

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

Pharmacokinetics (PK) of zolbetuximab in animals was investigated in mice, monkeys, etc.

Zolbetuximab in (a) mouse and (b) monkey serum was quantified by (a) enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence (ECL) as well as (b) ECL and flow cytometry immunoassay (lower limit of quantification,[7] (a) 10 and 2 μg/mL as well as (b) 2 and 14 μg/mL). Anti-zolbetuximab antibodies in mouse and monkey serum were both detected by ELISA and ECL.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of zolbetuximab 10 mg/kg was intravenously administered to male monkeys, and zolbetuximab concentrations in serum were determined. C_{max}, AUC_{inf}, $t_{1/2}$, CL, and V_{ss} (mean ± SD) of zolbetuximab were 226 ± 10 μg/mL, 1,470 ± 100 μg•day/mL, 9.29 ± 3.91 day, 6.84 ± 0.52 mL/day/kg, and 82.1 ± 15.3 mL/kg, respectively.[8]

Anti-zolbetuximab antibody was detected in 3 of 5 monkeys.

4.1.2 Repeated-dose administration

Zolbetuximab 100, 200, or 300 mg/kg was intravenously administered QW to male and female mice for 13 weeks, and zolbetuximab concentrations in serum were determined (Table 8). No clear gender-related difference was observed in zolbetuximab exposure. The zolbetuximab exposure generally increased dose-proportionally over a range of the dose tested.

Anti-zolbetuximab antibody was not detected in any animal.

Table 8. PK parameters* of zolbetuximab (male and female mice, 13-week repeated intravenous administration)

Day of administration (Day)	Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_{168h} (μg•h/mL)	$t_{1/2}$ (h)
1	100	Male	2,140	85,800	123
		Female	1,930	84,200	184
	200	Male	3,620	136,000	102
		Female	4,310	141,000	123
	300	Male	9,450	233,000	68.3
		Female	9,890	231,000	87.6
92	100	Male	2,600	104,000	306
		Female	2,300	106,000	256
	200	Male	5,000	157,000	275
		Female	4,960	159,000	226
	300	Male	8,460	224,000	156
		Female	8,060	221,000	244

* The PK parameters were calculated from the mean serum zolbetuximab concentration (n = 3) at each time point.

[7] The lower limit of quantification in each study is as follows: (a) 10 μg/mL in the 13-week repeated intravenous dose study in mice and 2 μg/mL in the embryo-fetal development study in mice; and (b) 2 μg/mL in the single intravenous dose study in monkeys and 14 μg/mL in the 4-week repeated intravenous dose study in monkeys.

[8] PK parameters after administration of the zolbetuximab drug substance manufactured at [redacted]. C_{max}, AUC_{inf}, $t_{1/2}$, CL, and V_{ss} (mean ± SD) of zolbetuximab after administration of zolbetuximab drug substance manufactured at [redacted] were 287 ± 36 μg/mL, 1,590 ± 310 μg•day/mL, 9.35 ± 4.78 day, 6.45 ± 1.18 mL/day/kg, and 71.9 ± 16.4 mL/kg, and anti-zolbetuximab antibody was detected in 3 of 5 monkeys.

4.2 Distribution

The applicant's explanation about tissue distribution of zolbetuximab:
In view of volume of distribution of zolbetuximab in a single intravenous dose study in monkeys [see Section 4.1.1] and plasma volume (44.8 mL/kg) and extracellular water volume (208 mL/kg) in monkeys (*Pharm Res.* 1993;10:1093-5), zolbetuximab is considered to be hardly transferred into tissues and mainly distributed in extracellular fluid including plasma.

In an embryo-fetal development toxicity study in mice, zolbetuximab 100 or 300 mg/kg was intravenously administered to pregnant mice on Gestation Days 6 and 11, and placental transfer and fetal distribution of zolbetuximab were investigated. The serum zolbetuximab concentration ratio in fetuses to maternal animals at 168 hours after the administration on Gestation Day 11 was 11.2 and 8.48, respectively, indicating that zolbetuximab crosses the placenta and is distributed in fetuses.

4.3 Metabolism and excretion

The applicant's explanation about metabolism and excretion of zolbetuximab:
Zolbetuximab, which is an antibody drug, is considered to be eliminated through a proteolysis pathway.

Excretion of zolbetuximab into milk may occur because zolbetuximab has constant regions of human IgG1 and human IgG is excreted into milk (*Acta Paediatr*. 1992;81:113-8, etc.).

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacokinetics of zolbetuximab is acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

Because zolbetuximab was found to bind to human, mouse, and cynomolgus monkey CLDN18.2 to a similar extend [see Section 3.1.1], single- and repeated-dose toxicity studies in mice and cynomolgus monkeys and a developmental and reproductive toxicity study in mice were conducted.

5.1 Single-dose toxicity

Single intravenous dose toxicity studies in mice and cynomolgus monkeys were conducted (Table 9), and no acute toxicity was observed in either animal species. In a preliminary 2-week repeated intravenous dose toxicity study in mice, no acute toxicity was observed at up to the highest dose (400 mg/kg).

The approximate lethal dose by an intravenous route was determined to be >400 mg/kg in mice and >150 mg/kg in cynomolgus monkeys.

Table 9. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female mouse (NMRI)	Intravenous	0,*1 1, 10, 50, 100	None	>100	4.2.3.1-1
Female mouse (NMRI)	Intravenous	0,*1 30, 100	None	>100	4.2.3.1-2
Male and female cynomolgus monkeys	Intravenous	50, 150*2	None	>150	4.2.3.1-3

*1 Arginine-added phosphate-buffered saline
*2 The same animal received zolbetuximab 150 mg/kg in a dose-escalation manner 17 days after administration of zolbetuximab 50 mg/kg.

5.2 Repeated-dose toxicity

A 13-week repeated-dose toxicity study in mice and a 4-week repeated-dose toxicity study in cynomolgus monkeys were conducted (Table 10). In mice, fundic gland dilatation and mucosal hypertrophy in the gastric fundus were observed, but they did not accompany histopathological changes suggestive of gastric mucosal injury. In cynomolgus monkeys, vomiting was observed, but the incidence was low and not correlated to the dose. The findings in both animal species were therefore considered of low toxicological significance. The no observed adverse effect level (NOAEL) was determined to be 300 mg/kg/week in mice and 100 mg/kg/week in cynomolgus monkeys. At the NOAEL in the 13-week repeated-dose toxicity study in mice, zolbetuximab exposure (AUC_{168h}) was 232,743 (male) and 230,768 (female) μg•h/mL, which were both 8.5 times the clinical exposure.[9)] At the NOAEL in the 4-week repeated-dose toxicity study in cynomolgus monkeys, zolbetuximab exposure (AUC_{168h}) was 232,000 (male) and 202,000 (female) μg•h/mL, which were 8.5 and 7.4 times the clinical exposure.[9)]

Table 10. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose (mg/kg/week)	Major findings	NOAEL	Attached document CTD
Male and female mice (NMRI)	Intravenous	13 weeks (QW)	0,* 100, 200, 300	≥200: Fundic gland dilatation and mucosal hypertrophy in the gastric fundus	300	4.2.3.2-3
Male and female cynomolgus monkeys	Intravenous	4 weeks (QW)	0,* 10, 30, 100	10, 30: Vomiting	100	4.2.3.2-4

* 200 mmol/L Phosphoric acid solution containing arginine (pH 7.4)

5.3 Genotoxicity

Zolbetuximab, an antibody drug, would not interact directly with DNA or other chromosomal components, and no genotoxicity studies were conducted.

5.4 Carcinogenicity

Zolbetuximab is an antineoplastic agent intended to treat advanced cancer, and no carcinogenicity studies were conducted.

9) AUC_{21d} of zolbetuximab (81,840 μg•h/mL) in Japanese patients with gastric cancer receiving zolbetuximab 800/600 mg/m^2 Q3W, estimated based on the PPK analysis [see Section 6.2.5]

5.5 Reproductive and developmental toxicity

In the 13-week repeated-dose toxicity study in mice and 4-week repeated-dose toxicity study in cynomolgus monkeys, no effects on male or female reproductive organs were observed.

An embryo-fetal development study in mice was conducted (Table 11). No effects on the embryos or fetuses were observed, and the NOAEL was determined to be 300 mg/kg. The exposure (AUC_{120h}) at the concerned dose was 147,000 μg•h/mL, which was 1.8 times the clinical exposure.[9)]

Table 11. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg)	Major findings	NOAEL	Attached document CTD
Embryo-fetal development	Female Mouse (NMRI)	Intravenous	Gestation Days 6 and 11	0,* 100, 300	Maternal animal: None Embryo/fetus: None	Maternal animal (general toxicity): 300 Embryo/fetus: 300	4.2.3.5.2-3

* 0.02% polysorbate 80 solution

5.6 Other toxicity studies

5.6.1 Tissue cross-reactivity

A tissue cross-reactivity study using normal human tissues was conducted (Table 12). Zolbetuximab was found to bind to the cell membrane of the gastric mucosal epithelium. For other tissues, the positive reaction was observed in the cytoplasm in Kupffer cells, pancreas duct epithelium, epidermis, and splenic red pulp in the spleen, but it occurred in an intracellular site that cannot be reached by zolbetuximab. The applicant explained that toxicological significance was low.

Table 12. Tissue cross-reactivity

Test system	Test method	Positive tissues	Attached document CTD
Normal human tissues	Binding of FITC-labeled zolbetuximab (2, 5, and 10 μg/mL) to tissues was investigated using formalin fixed frozen human tissue specimens.	Cell membrane of the gastric mucosal epithelium and cytoplasm in Kupffer cells, pancreas duct epithelium, epidermis, and splenic red pulp in the spleen	4.2.3.7.7-5

5.6.2 Study for mechanism of vomiting-related toxicity development

A study for the mechanism of toxicity development in ferrets was conducted to investigate the mechanism of vomiting, which was observed in clinical studies of zolbetuximab (Table 13). The applicant explained that vomiting attributable to zolbetuximab is related to gastric mucosal injury and would be alleviated by fosaprepitant alone or fosaprepitant in combination with other antiemetics.

Table 13. Study for mechanism of toxicity development

Test system	Test method	Major findings	Attached document CTD
Male ferret	After single intravenous administration of zolbetuximab 1 mg/kg, • Vomiting episodes were counted until 6 hours post-dose. • Histopathological examination was performed on the stomach specimens collected at 15 minutes post-dose or just after the first vomiting episode, 6 hours, and 2 weeks post-dose.	Count of vomiting episodes: Vomiting frequently occurred until 1 hour post-dose, and then the frequency decreased until 6 hours post-dose. Histopathological examination: 15 minutes post-dose or just after the first vomiting episode: Cortical mucosal cell detachment and submucosal inflammation in the mucosa of the fundic gland and pyloric gland 6 hours post-dose: Epithelial deficiency, degeneration, necrosis, and regeneration of the mucosa in the fundic gland and pyloric gland, inflammatory cell infiltration in the lamina propria, mucosal atrophy, and submucosal inflammation 2 weeks post-dose: Mineralization in the pyloric gland	4.2.3.7.3-4
Male ferret	After a single-dose administration* of antiemetics (one of dexamethasone, ondansetron, fosaprepitant, and olanzapine or all of them in combination) and then single intravenous administration of zolbetuximab 1 mg/kg, • Vomiting episodes were counted until 6 hours post-dose. • Histopathological examination was performed on the stomach specimens.	Count of vomiting episodes: Dexamethasone, ondansetron, or fosaprepitant alone or all of the antiemetics in combination decreased the count of vomiting episodes. Histopathological examination: Antiemetics did not prevent severe gastric mucosal injury.	4.2.3.7.3-5
Male ferret	After a single-dose administration* of antiemetics (one of dexamethasone, ondansetron, fosaprepitant, and olanzapine, or combination of ondansetron and fosaprepitant) and then single intravenous administration of zolbetuximab at 1 mg/kg, • Vomiting episodes were counted until 6 hours post-dose. • Histopathological examination was performed on the stomach specimens.	Count of vomiting episodes: Fosaprepitant alone and combination of ondansetron and fosaprepitant decreased the count of vomiting episodes. Histopathological examination: Dexamethasone alone and combination of ondansetron and fosaprepitant tended to prevent severe gastric mucosal injury.	4.2.3.7.3-6

* Dexamethasone 20 mg/kg, ondansetron 3 mg/kg, and fosaprepitant 3 mg/kg were intravenously administered as a single dose, and olanzapine 0.03 mg/kg was intramuscularly administered as a single dose.

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about toxicity of zolbetuximab is acceptable.

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

Table 14 shows the detailed dosage regimens of zolbetuximab referred to as 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W in this section and Section "7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA."

Table 14. Dosage regimen of zolbetuximab

Regimen code	Dosage regimen of zolbetuximab
800/600 mg/m^2 Q3W	The initial dose of 800 mg/m^2 (body surface area) and subsequent doses of 600 mg/m^2 (body surface area) are administered as an intravenous infusion every 3 weeks.
800/400 mg/m^2 Q2W	The initial dose of 800 mg/m^2 (body surface area) and subsequent doses of 400 mg/m^2 (body surface area) are administered as an intravenous infusion every 2 weeks.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Zolbetuximab in human serum was quantified by ELISA (lower limit of quantification,[10] 1.00 µg/mL) and ECL (lower limit of quantification,[11] 1.00 and 5.00 µg/mL). Anti-zolbetuximab antibody in human serum was detected by ELISA[12] and ECL.[13]

6.2 Clinical pharmacology

PK of zolbetuximab in patients with gastric cancer was investigated after administration of zolbetuximab alone and concomitant use of zolbetuximab with FOLFOX (a combination of 5-FU, folinate [LV] or levofolinate [*l*-LV] [(*l*-)LV], and L-OHP) or pembrolizumab.

6.2.1 Japanese studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-3, Study 0104, June 2018 to June 2020)

An open-label, uncontrolled study was conducted to investigate PK, etc. of zolbetuximab in 18 patients with CLDN18.2-positive advanced gastric cancer (18 patients included in the PK analysis). Zolbetuximab was intravenously administered at 800/600 mg/m^2 in the Safety Part A and expansion part and at 1,000 mg/m^2 in the Safety Part B, Q3W for both doses, to determine serum zolbetuximab concentrations.

Table 15 shows PK parameters of zolbetuximab.

Table 15. PK parameters of zolbetuximab

Dosage regimen	Day of measurement (Day)	n	C_{max} (µg/mL)	t_{max}[*1] (day)	AUC_{21d} (µg•day/mL)	$t_{1/2}$ (day)
800/600 mg/m^2 Q3W	1	15	482 ± 113	0.211 (0.138, 0.349)	2,390 ± 639[*2]	8.82 ± 3.81
	43	10	391 ± 75.8	0.236 (0.106, 0.284)	2,110 ± 1,010[*3]	—
1000 mg/m^2 Q3W	1	3	805 ± 166	0.292 (0.203, 0.294)	2,360 ± 296	7.16 ± 2.35
	43	1	800	0.266	—	—

Mean ± SD (individual value for n = 1)
*[1] Median (minimum, maximum); *[2] n = 13; *[3] n = 7; —, Not calculated

6.2.2 Global study

6.2.2.1 Global phase II study (CTD 5.3.5.2-1, Study 8951-CL-0103 [Study 0103], ongoing since August 2018 [data cutoff on May 3, 2021])

An open-label, uncontrolled study was conducted to investigate PK, etc. of zolbetuximab in 54 patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer (54 patients included in the PK analysis). The dosage regimens were zolbetuximab 800/600 mg/m^2 Q3W in Cohort 1, zolbetuximab

[10] Lower limit of quantification in Studies 001 and 02
[11] Lower limit of quantification in Study 03, 1.00 µg/mL; lower limit of quantification in Studies 0103, 0104, and 0105, and SPOTLIGHT and GLOW studies, 5.00 µg/mL
[12] Used in Studies 001, 02, 04.
[13] Used in Studies 0103, 0104, 0105, 02, 03, and 04, and SPOTLIGHT and GLOW studies.

800/600 mg/m^2 Q3W in combination with FOLFOX in Cohort 2,[14] and zolbetuximab 800/600 mg/m^2 Q3W in combination with pembrolizumab in Cohort 3, and serum zolbetuximab concentrations were determined.

Table 16 shows PK parameters of zolbetuximab.

Table 16. PK parameters of zolbetuximab

	Day of measurement (Day)	n	C_{max} (μg/mL)	t_{max}*1 (day)	AUC_{21d} (μg•day/mL)	$t_{1/2}$ (day)
Zolbetuximab alone	1	30	448 ± 135*2	0.174 (0.0889, 0.355)*2	2,210 ± 842*2	8.72 ± 4.23*2
	43	12	362 ± 79.3	0.120 (0.0868, 0.247)	2,740 ± 1,320*3	—
Zolbetuximab/ FOLFOX	3	21	477 ± 82.3*4	0.150 (0.0382, 0.292)*5	1,900 ± 746*6	5.44 ± 1.82*4
	43	21	369 ± 50.6*7	0.183 (0.106, 0.872)*5	2,400 ± 1,010*8	—
Zolbetuximab/ pembrolizumab	1	3	433 ± 88.9	0.160 (0.151, 0.186)	2,930 ± 652	10.0 ± 4.22

Mean ± SD
*1 Median (minimum, maximum), *2 n = 23, *3 n = 11, *4 n = 16, *5 n = 18, *6 n = 15, *7 n = 17, *8 n = 14; —, Not calculated

6.2.3 Foreign studies

6.2.3.1 Foreign phase I study (CTD 5.3.3.2-1, Study 001, July 2009 to May 2010)

An open-label, uncontrolled study was conducted to investigate the PK, etc. of zolbetuximab in 15 patients with CLDN18.2-positive advanced gastric cancer, etc. (15 patients included in the PK analysis). A single dose of zolbetuximab at 33 to 1,000 mg/m^2 was intravenously administered, and serum zolbetuximab concentrations were determined.

Table 17 shows PK parameters of zolbetuximab. The zolbetuximab exposure generally increased dose-proportionally over a range of the dose tested.

Table 17. PK parameters of zolbetuximab

Dose (mg/m^2)	n	C_{max} (μg/mL)	t_{max}* (day)	AUC_{21d} (μg•day/mL)	$t_{1/2}$ (day)
33	3	15.1 ± 0.273	0.0826 (0.0792, 0.201)	111 ± 24.6	14.0 ± 0.728
100	3	58.7 ± 17.3	0.106 (0.101, 0.418)	392 ± 58.9	18.9 ± 8.00
300	3	170 ± 5.95	0.125 (0.0833, 0.208)	1,220 ± 311	21.7 ± 11.5
600	3	331 ± 36.7	0.211 (0.0833, 1.10)	1,750 ± 767	14.1 ± 7.76
1,000	3	517 ± 77.3	0.208 (0.0979, 0.232)	3,480 ± 372	13.1 ± 3.95

Mean ± SD
* Median (minimum, maximum)

6.2.3.2 Foreign phase I study (CTD 5.3.3.2-4, Study 8951-CL-0105 [Study 0105], October 2019 to January 2021)

An open-label, uncontrolled study was conducted in 13 patients with CLDN18.2-positive advanced gastric cancer (12 patients included in the PK analysis) to investigate PK, etc. of zolbetuximab. Zolbetuximab 800/600 mg/m^2 was administered Q3W, and serum zolbetuximab concentrations were determined.

Table 18 shows PK parameters of zolbetuximab.

[14] Only in Cycle 1 of the 3-week cycles, zolbetuximab was administered on Day 3.

Table 18. PK parameters of zolbetuximab

Day of measurement (Day)	n	C_{max} (μg/mL)	t_{max}*1 (day)	AUC_{21d} (μg•day/mL)	$t_{1/2}$ (day)
1	12	372 ± 61.1	0.220 (0.142, 0.347)	2,280 ± 559*2	7.87 ± 5.17*3
43	2	359, 484	0.347, 1.14	3,890, 5,510	—

Mean ± SD (individual values for n = 2)
*1 Median (minimum, maximum), *2 n = 7, *3 n = 11; —, Not calculated

6.2.4 Relationship of the exposure to variations of QT interval (QT)/QT interval corrected (QTc) interval

In a Japanese phase I study (Study 0104) and global phase II study (Study 0103), a linear mixed effect model was used to examine a relationship between serum zolbetuximab concentrations and changes from baseline in QT corrected by the Fridericia's correction formula (ΔQTcF) based on data from 44 patients in whom serum zolbetuximab concentrations were determined at the time of ECG. Although the result showed the relationship between serum zolbetuximab concentrations and ΔQTcF, the upper limit of the one-sided 95% confidence interval (CI) of ΔQTcF with C_{max} on the regimens of zolbetuximab 800/600 mg/m^2 Q3W and zolbetuximab 1,000 mg/m^2 Q3W (geometric mean, 446 and 792 μg/mL, respectively) were 9.38 and 17.9 ms, respectively.

The applicant's explanation:
In view of the above results and incidences of adverse events in clinical studies [see Sections 7.3.3 and 7.3.4], zolbetuximab, when used in accordance with the proposed dosage and administration, is unlikely to prolong the QT/QTc interval.

6.2.5 Population pharmacokinetic (PPK) analysis

A PPK analysis was performed using a nonlinear mixed effect model on PK data of zolbetuximab (5,066 measurement time points from 714 patients) obtained from Japanese study (Study 0104), global studies (Study 0103, SPOTLIGHT and GLOW studies), and foreign studies (Studies 001, 0105, 02, and 03) (NONMEM Version 7.5.0). The PK of zolbetuximab was described by a 2-compartment model with zero-order absorption and first-order elimination.

For CL, V1, and V2 of zolbetuximab, the following covariates were assessed: Body surface area, sex, age, race, albumin, serum creatinine, creatinine clearance (CrCL), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin, total tumor diameter, Eastern Cooperative Oncology Group Performance Status (ECOG PS), presence or absence of prior gastrectomy, presence or absence of measurable lesion, presence or absence of peritoneal metastasis, primary site (stomach or gastroesophageal junction), hepatic impairment,[15)] renal impairment,[16)] and concomitant medications. As a covariate for Q, body surface area was assessed. Of them, the following significant covariates for zolbetuximab were selected: Body surface area, sex, albumin, and presence or absence of prior gastrectomy for CL; body surface area for V1; body surface area and presence or absence of prior gastrectomy for V2; and body surface area for Q. Regarding an extent of the zolbetuximab exposure varied by the status of the selected covariates, the geometric mean ratio of C_{min} of zolbetuximab in patients with prior gastrectomy to that in patients without prior gastrectomy was 1.41 to 1.81, but ratios

15) Classified according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.
16) Renal function was assessed based on CrCL (mL/min) as follows: ≥90, normal; ≥60 and <90, mild impairment; ≥30 and <60, moderate impairment; and <30, severe impairment.

similarly indicative of extents of AUC and C_{max} varied by the presence or absence of prior gastrectomy as well as of the exposure varied by the status of body surface area, sex, and albumin were estimated to fall within a range from 0.80 to 1.25.[17)]

The applicant's explanation:
The above covariates are unlikely to have clinically relevant effects on PK of zolbetuximab, in view of the above results and the documented efficacy of zolbetuximab regardless of prior gastrectomy in the global phase III studies (SPOTLIGHT and GLOW studies).

6.2.6 Relationship of exposure to efficacy and safety

6.2.6.1 Relationship of exposure to efficacy

Using results from Study GM-IMAB-001-03 (Study 03) and the SPOTLIGHT and GLOW studies, a relationship of zolbetuximab exposure[18)] (C_{avg} throughout the treatment period, C_{min} after the first dose, C_{min} after the last dose, AUC_{21d} after the last dose, etc.) to the efficacy (progression free survival [PFS], overall survival [OS], etc.) was investigated. The result showed that PFS and OS tended to extend with increasing zolbetuximab exposure.

6.2.6.2 Relationship of exposure to safety

Using results from Study 03 and the SPOTLIGHT and GLOW studies, relationships of zolbetuximab exposure and infusion rate[18)] to adverse events were investigated. The results showed that the following incidences tended to increase: (a) Grade ≥3 nausea and vomiting, Grade ≥2 nausea and vomiting, infusion related reaction, etc., with increasing C_{max} of zolbetuximab after the first dose; (b) Grade ≥3 nausea and vomiting, Grade ≥2 nausea and vomiting, etc., with increasing C_{max} after the last dose; (c) Grade ≥2 nausea and vomiting, Grade ≥3 neutropenia, etc., with increasing AUC_{21d} after the last dose; (d) hypersensitivity reaction, etc. with increasing C_{avg} over a period from the first dose to onset of an adverse event; and (e) infusion related reaction with increasing infusion rate for the first dose.

6.2.7 Effects of renal and hepatic impairment on PK of zolbetuximab

No clinical studies have been conducted to investigate PK of zolbetuximab in patients with renal or hepatic impairment.

The applicant's explanation:
Renal or hepatic impairment is unlikely to affect the PK of zolbetuximab for the reasons given below.

- Zolbetuximab, an antibody drug, is considered to be eliminated through a proteolysis pathway.
- In the PPK analysis [see Section 6.2.5], the zolbetuximab exposure at steady state on the zolbetuximab 800/600 mg/m^2 Q3W regimen according to renal or hepatic function classification was estimated as follows:
  - The geometric mean ratios of C_{max} and AUC_{21d} in patients with mild and moderate renal impairment[16)] (298 and 109 patients, respectively) to those in patients with normal renal function

[17)] Body surface area and albumin: The geometric mean ratios of zolbetuximab exposure in patients with the 5 and 95 percentile parameter values to that in patients with the median
Sex: The geometric mean ratio of zolbetuximab exposure in female patients to that in male patients
[18)] Estimated by the PPK analysis [see Section 6.2.5].

(306 patients) [90% CI] were 1.05 [1.03, 1.07] and 1.08 [1.05, 1.11], and 1.11 [1.08, 1.14] and 1.14 [1.10, 1.18], respectively.

- The geometric mean ratios of C_{max} and AUC_{21d} in patients with mild and moderate hepatic impairment[15] (108 and 4 patients, respectively) to those in patients with normal hepatic function (602 patients) [90% CI] were 0.989 [0.966, 1.01] and 0.956 [0.924, 0.989], and 1.06 [0.941, 1.18] and 1.04 [0.879, 1.22], respectively.

6.2.8 Difference in PK between Japanese and non-Japanese patients

The applicant's explanation:

No clear difference in PK of zolbetuximab between Japanese and non-Japanese patients is expected, because C_{max} and AUC_{21d} of zolbetuximab after the first dose and multiple doses did not clearly differ between the Safety Part A and expansion part in the Japanese phase I study (Study 0104) and the foreign phase I study in Chinese patients (Study 0105) or Cohort 1 of the global phrase II study in non-Japanese patients (including Caucasian and Asian patients) (Study 0103) [see Sections 6.2.1.1, 6.2.2.1, and 6.2.3.2].

6.R Outline of the review conducted by PMDA

On the basis of the submitted data and the considerations described in the following subsections, PMDA concluded that the applicant's explanation about clinical pharmacology, etc. of zolbetuximab is acceptable.

6.R.1 Establishment of the dosage regimen based on a simulation using the PPK model

For the present application, the proposed dosage and administration is the zolbetuximab 800/400 mg/m^2 Q2W regimen based on the result of a simulation using the PPK model in addition to the zolbetuximab 800/600 mg/m^2 Q3W regimen, which was used in the SPOTLIGHT and GLOW studies.

The applicant's explanation about the rationale for the zolbetuximab 800/400 mg/m^2 Q2W regimen:

FOLFOX, which was concomitantly used with zolbetuximab in the SPOTLIGHT study, is administered Q2W. To improve convenience of using FOLFOX concomitantly, the dose of zolbetuximab appropriate for a Q2W regimen was investigated by a simulation using the PPK model [see Section 6.2.5]. The simulation presented PK parameters of zolbetuximab (estimates) with each regimen of the proposed dosage and administration in the overall population and Japanese population, which were included in the PPK analysis, as shown in Table 19.

Table 19. PK parameters of zolbetuximab (estimates)

Population	n	Dosage regimen*	42 days after the first dose			42 days at steady state		
			C_{max} (μg/mL)	AUC_{21d} (μg•day/mL)	C_{min} (μg/mL)	C_{max} (μg/mL)	AUC_{21d} (μg•day/mL)	C_{min} (μg/mL)
Overall	714	800/600 mg/m^2 Q3W	434 ± 96	2,263 ± 712	61.0 ± 33.4	425 ± 91	3,340 ± 1,246	101 ± 51
		800/400 mg/m^2 Q2W	434 ± 96	2,520 ± 777	73.8 ± 39.8	326 ± 74	3,349 ± 1,250	110 ± 54
Japanese	73	800/600 mg/m^2 Q3W	472 ± 78	2,314 ± 664	60.2 ± 31.1	454 ± 82	3,410 ± 1,158	102 ± 48
		800/400 mg/m^2 Q2W	472 ± 78	2,579 ± 726	72.8 ± 36.8	346 ± 69	3,419 ± 1,161	111 ± 50

Mean ± SD;
* Zolbetuximab was infused over 2 hours for either regimen.

In view of the following points, a difference in exposure between the regimens of the proposed dosage and administration is unlikely to affect the efficacy and safety of zolbetuximab, and any regimen of zolbetuximab may be selected according to concomitant chemotherapy.

- C_{avg} (value obtained by dividing AUC by the treatment period) remained similar either after the first dose or at steady state between the regimens of zolbetuximab 800/600 mg/m^2 Q3W and 800/400 mg/m^2 Q2W. This parameter reflects information on exposure throughout the treatment period and was used as an indicator of the exposure in the investigation of the relationship to efficacy.
- C_{max} with the zolbetuximab 800/400 mg/m^2 Q2W regimen did not tend to be higher than that with the zolbetuximab 800/600 mg/m^2 Q3W regimen either after the first dose or at steady state. This parameter was used as an indicator of the exposure in the investigation of the relationship to safety in view of frequently occurring timing of nausea and vomiting associated with zolbetuximab.
- For other PK parameters, the geometric mean ratios with the zolbetuximab 800/400 mg/m^2 Q2W regimen to that with the zolbetuximab 800/600 mg/m^2 Q3W regimen were mostly estimated to fall within a range from 0.80 to 1.25.

PMDA accepted the applicant's explanation. Appropriateness of the dosage regimen in view of the efficacy and safety of zolbetuximab in clinical studies is discussed in Section "7.R.5 Dosage and administration."

6.R.2 Effects of anti-zolbetuximab antibody on the PK of zolbetuximab

The applicant's explanation about effects of zolbetuximab in specimens on measurement of anti-zolbetuximab antibody:

In the measurement method of anti-zolbetuximab antibody, which was mainly used in the SPOTLIGHT and GLOW studies [see Section 6.1], the upper limit of zolbetuximab concentrations in specimens that did not affect the measurement result was 50 to 300 μg/mL[19] depending on the serum anti-zolbetuximab antibody concentrations. In these 2 studies, of 4,548 specimens at time points at which anti-zolbetuximab antibody was measured, 3,714 specimens were found to contain zolbetuximab at concentrations not more than the above upper limit. In view of this finding, zolbetuximab is unlikely to affect measurement of anti-zolbetuximab antibody.

[19] For positive control specimens containing anti-zolbetuximab antibody at 100, 250, and 500 ng/mL, the upper limit was 50, 200, and 300 μg/mL, respectively.

The applicant's explanation about the effect of anti-zolbetuximab antibody on the PK of zolbetuximab:
Development of anti-zolbetuximab antibody was investigated in all clinical studies. Of patients who received zolbetuximab in the SPOTLIGHT and GLOW studies and in whom development of anti-zolbetuximab antibody was evaluated (253 and 226 patients, respectively), anti-zolbetuximab antibody was detected in 8 patients (3.2%) and 13 patients (5.8%), respectively.

Table 20 shows serum zolbetuximab concentrations by development status of anti-zolbetuximab antibody in the SPOTLIGHT and GLOW studies. Although no clear differences in serum zolbetuximab concentration were observed between positive and negative patients, the number of patients positive for anti-zolbetuximab antibody was limited, and thus definite conclusion on the effect of anti-zolbetuximab antibody on the PK of zolbetuximab cannot be drawn at present.

Table 20. Serum zolbetuximab concentrations by development status of anti-zolbetuximab antibody

Study	Time point of measurement	Patients positive for anti-zolbetuximab antibody		Patients negative for anti-zolbetuximab antibody	
		n*	Serum zolbetuximab concentration (μg/mL)	n*	Serum zolbetuximab concentration (μg/mL)
SPOTLIGHT	Before the second dose	1	BQL	180	41.0 ± 37.1
	Before the fifth dose	3	30.8 ± 53.4	180	71.0 ± 49.7
	Before the ninth dose	2	BQL, 90.7	136	98.2 ± 50.6
	Before the 13th dose	2	BQL, 100	94	120 ± 64.6
	Before the 17th dose	1	146	56	134 ± 57.1
	30 days after the last dose	4	24.4 ± 48.8	78	57.7 ± 41.5
	90 days after the last dose	1	BQL	72	10.4 ± 12.7
GLOW	Before the second dose	8	6.31 ± 9.79	204	40.4 ± 31.1
	Before the fifth dose	1	15.9	156	75.8 ± 51.2
	Before the ninth dose	1	57.7	89	102 ± 57.5
	30 days after the last dose	5	27.9 ± 40.0	57	55.3 ± 48.3
	90 days after the last dose	1	BQL	43	9.90 ± 11.1

Mean ± SD (individual values for n = 1 or 2)
BQL (Below the quantification limit), <5.00 μg/mL
* Some patients were counted more than once.

PMDA's view:
PMDA accepted the applicant's explanation. Information on the effect of anti-zolbetuximab antibody on the PK of zolbetuximab, however, is limited, and thus the applicant should continue to collect the information and to provide the information to healthcare professionals when it becomes available.

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

The applicant submitted the evaluation and reference data on the efficacy and safety in the form of results from studies listed in Table 21.

Table 21. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Study population	No. of patients enrolled	Dosage regimen[*1]	Main endpoints
Evaluation	Japan	Study 0104	I	Patients with CLDN18.2-positive advanced gastric cancer	(a) 3 (b) 3 (c)12	(a) (c) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W (b) Intravenous administration of zolbetuximab 1,000 mg/m^2 Q3W	Tolerability Safety PK
	Global	Study 0103	II	(a) (c) Patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer who had received prior chemotherapy (b) Patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy	(a) 30 (b) 21 (c) 3	(a) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W (b) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W, in combination with FOLFOX[*2] (c) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W, in combination with pembrolizumab	Efficacy Safety
		SPOTLIGHT study	III	Patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy	565 (a) 283 (b) 282	Intravenous administration of (a) zolbetuximab 800/600 mg/m^2 or (b) placebo Q3W, in combination with FOLFOX	Efficacy Safety
		GLOW study	III	Patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy	507 (a) 254 (b) 253	Intravenous administration of (a) zolbetuximab 800/600 mg/m^2 or (b) placebo Q3W, in combination with CAPOX	Efficacy Safety
	Foreign	Study 001	I	Patients with CLDN18.2-positive advanced gastric cancer, etc.	15	A single intravenous administration of zolbetuximab 33-1,000 mg/m^2	Tolerability Safety PK
		Study 02	II	Patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer, etc.	(a) 4 (b) 6 (c) 44	(a) Intravenous administration of zolbetuximab 300 mg/m^2 Q2W (b) (c) Intravenous administration of zolbetuximab 600 mg/m^2 Q2W	Efficacy Safety
		Study 03	II	Patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy, etc.	(a) 85 (b) 79 (c) 88	(a) EOX (b) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W, in combination with EOX (c) Intravenous administration of zolbetuximab 1,000 mg/m^2 Q3W, in combination with EOX	Efficacy Safety
Reference	Foreign	Study 04	I	Patients with CLDN18.2-positive advanced gastric cancer, etc.	(a) 8 (b) 9 (c) 7 (d) 5	(a) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W, in combination with zoledronic acid (b) (c) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W, in combination with zoledronic acid and IL-2 (d) Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W	Tolerability Safety PK
		Study 0105	I	Patients with CLDN18.2-positive advanced gastric cancer	13	Intravenous administration of zolbetuximab 800/600 mg/m^2 Q3W	Tolerability Safety PK

*1 The dosage regimen of concomitant medications is not described.
*2 Only in Cycle 1 of the 3-week cycles, zolbetuximab was administered on Day 3.

Each clinical study is outlined below. Table 22 and Table 23 show the definition of CLDN18.2 positive and the dosage regimens of antineoplastic agents other than zolbetuximab used in each clinical study. The main adverse events other than deaths in each clinical study are described in Section “7.3 Adverse events observed in clinical studies.”

Table 22. Definition of CLDN18.2 positive used in each clinical study

Study	Staining intensity assessed as CLDN18.2 positive*
Study 001 Safety part of Study 0104 Study 0105	≥1+ in tumor cells
Cohort 3 of Study 0103 Study 02	≥2+ in ≥50% tumor cells
Study 03	≥2+ in ≥40% tumor cells
Study 04	2+ in ≥40% tumor cells or 3+ in tumor cells
Cohorts 1 and 2 of Study 0103 Expansion part of Study 0104 GLOW study SPOTLIGHT study	≥2+ in ≥75% tumor cells

* Central laboratory assessed the staining intensity by immunohistochemistry (IHC) based on CLDN18 staining intensity on the cell membrane and classified into 0 (no staining), 1+ (weak staining), 2+ (moderate staining), or 3+ (strong staining).

Table 23. List of dosage regimens of antineoplastic agents other than zolbetuximab used in each clinical study

	Dosage regimen
CAPOX	In a 3-week cycle, L-OHP 130 mg/m^2 was intravenously administered on Day 1, and Cape 1,000 mg/m^2 was orally administered BID on Days 1 through 14 (L-OHP was administered for up to 8 cycles).
EOX	In a 3-week cycle, epirubicin 50 mg/m^2 and L-OHP 130 mg/m^2 were administered on Day 1, and Cape 625 mg/m^2 was orally administered BID on Days 1 through 21 (medications were repeated for up to 8 cycles).
FOLFOX	In a 2-week cycle, L-OHP 85 mg/m^2 and LV 400 mg/m^2 or *l*-LV 200 mg/m^2 were intravenously administered, and 5-FU 400 mg/m^2 was intravenously administered as a bolus dose followed by continuous intravenous infusion of 5-FU 2,400 mg/m^2 on Day 1 (L-OHP is administered for up to 12 cycles).
IL-2	In 3-week cycles, aldesleukin 1,000,000 units (Arm 2 of Study 04) or 3,000,000 units (Arm 3 of Study 04) was subcutaneously administered on Days 1 through 3 of Cycles 1 and 3.
Zoledronic acid	In 3-week cycles, zoledronic acid 4 mg was intravenously administered on Day 1 of Cycles 1 and 3.
Pembrolizumab	Pembrolizumab 200 mg was intravenously administered Q3W.

7.1 Evaluation data

7.1.1 Japanese study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2-3, Study 0104, June 2018 to June 2020)

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, and PK of zolbetuximab in patients with CLDN18.2-positive advanced gastric cancer[20] (target sample size, up to 6 patients in the Safety Part A, up to 6 patients in the Safety Part B, 20 patients in the expansion part) at a single study site in Japan.

Zolbetuximab was intravenously administered Q3W at 800/600 mg/m^2 in the Safety Part A and expansion part and at 1,000 mg/m^2 in the Safety Part B and continued until disease progression was documented or the criteria for treatment discontinuation were met.

All of 18 patients enrolled in the study (3 in the Safety Part A, 3 in the Safety Part B, 12 in the expansion part) received zolbetuximab and were included in the safety analysis.

In the Safety Parts A and B, dose-limiting toxicity (DLT) was evaluated until 22 days after the first dose of zolbetuximab. In either Safety Part A or B, no DLT was observed.

[20] Patients with adenocarcinoma of the gastroesophageal junction were also enrolled.

Deaths occurred in 1 of 3 patients (33.3%) in the Safety Part A, 1 of 3 patients (33.3%) in the Safety Part B, and 6 of 12 patients (50%) in the expansion part during the zolbetuximab treatment or within 90 days after the last dose, and were all caused by disease progression or primary disease.

7.1.2 Global studies

7.1.2.1 Global phase II study (CTD 5.3.5.2-1, Study 0103, ongoing since August 2018 [data cutoff on May 3, 2021])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of zolbetuximab alone, zolbetuximab/FOLFOX (a combination of zolbetuximab and FOLFOX), and zolbetuximab/pembrolizumab (a combination of zolbetuximab and pembrolizumab) in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer[21] (target sample size, 20 patients in Cohort 1, 12 patients in Cohort 2, 12 patients in Cohort 3) at 14 study sites in 6 countries or regions including Japan.

The dosage regimens, which were all administered intravenously, were zolbetuximab 800/600 mg/m^2 Q3W in Cohort 1, zolbetuximab 800/600 mg/m^2 Q3W in combination with FOLFOX in Cohort 2, and zolbetuximab 800/600 mg/m^2 Q3W in combination with pembrolizumab in Cohort 3, and the treatment was continued until disease progression was documented or the criteria for treatment discontinuation were met.

All of 54 patients enrolled in the study (30 in Cohort 1, 21 in Cohort 2, 3 in Cohort 3) received zolbetuximab and were included in the safety analysis (Japanese patients, 0 in Cohort 1, 0 in Cohort 2, 3 in Cohort 3).

Deaths occurred in 3 of 30 patients (10.0%) in Cohort 1 during the treatment with the study drug or within 30 days after the last dose, but no death occurred in Cohort 2 or 3. Causes of the deaths were sepsis in 2 patients and intestinal obstruction in 1 patient, and a causal relationship to the study drug was denied for all of them.

7.1.2.2 Global phase III study (CTD 5.3.5.1-1, SPOTLIGHT study, ongoing since June 2018 [data cutoff on September 9, 2022])

A randomized, double-blind, controlled study was conducted to compare the efficacy and safety of zolbetuximab with those of the placebo, used in combination with FOLFOX for both, in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer[22] who had not received prior chemotherapy[23] (target sample size, 550 patients) at 232 study sites in 20 countries or regions including Japan.

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[21] The following patients were enrolled in the cohorts:
- Cohorts 1 and 3: Patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer (including adenocarcinoma of the gastroesophageal junction) who had received ≥2 lines of prior chemotherapy
- Cohort 2: Patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer (including adenocarcinoma of the gastroesophageal junction) who had not received prior chemotherapy

[22] Patients with adenocarcinoma of the gastroesophageal junction were also enrolled.

[23] Patients with recurrent disease were allowed to be enrolled if the last dose of a preoperative or postoperative adjuvant therapy occurred ≥6 months before randomization.

Zolbetuximab 800/600 mg/m^2 or placebo was intravenously administered Q3W in combination with FOLFOX, and L-OHP was repeated for up to 12 cycles, and other study drugs were continued until disease progression was documented or the criteria for treatment discontinuation were met.

All of 565 patients who were enrolled and randomized in the study (283 in the zolbetuximab group, 282 in the placebo group) were included in the full analysis set (FAS) and also in the efficacy analysis (Japanese patients, 32 in the zolbetuximab group, 33 in the placebo group). Of these, 557 patients (279 in the zolbetuximab group, 278 in the placebo group) were included in the safety analysis (Japanese patients, 31 in the zolbetuximab group, 32 in the placebo group), and the remaining 8 patients who did not receive the study drug (4 in the zolbetuximab group, 4 in the placebo group) were excluded.

The primary endpoint in the study was PFS assessed by the independent review committee (IRC) based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. Table 24 shows a statistical analysis plan for the study and major changes.

Table 24. Statistical analysis plan for SPOTLIGHT study and major changes

	Protocol version 1 (dated January 31, 2018)	Protocol version 5 (dated October 18, 2021)
Primary endpoint	PFS assessed by the IRC based on RECIST ver.1.1	(no changes)
Secondary endpoint	OS • Test would be performed if the null hypothesis for PFS is rejected.	(no changes)
Target sample size	550 patients • PFS: The assumption comprised of 368 events, a hazard ratio of 0.67, and a significance level (one-sided) of 0.025 would have a power of 97%. • OS: The assumption comprised of 396 events, a hazard ratio of 0.75, and a significance level (one-sided) of 0.025 would have a power of 81%.	550 patients (no changes) • PFS: The assumption comprised of 300 events, a hazard ratio of 0.67, and a significance level (one-sided) of 0.025 would have a power of 93.4%. • OS: (no changes)
Analysis timepoint	Primary analysis on PFS: When approximately 368 PFS events are observed Interim analysis on OS: When the primary analysis on PFS is performed Final analysis on OS: When 396 OS events are observed	Primary analysis on PFS: When approximately 300 PFS events are observed Interim analysis and final analysis on OS: (no changes)
Reason for the changes	(not applicable)	Accumulation of the PFS events was slower than initially assumed, and the analysis timepoint was predicted to reach ≥12 months later than initially planned. The number of events required for the primary analysis on PFS was changed.

For the interim analysis on OS, the type I error probability was adjusted according to an O'Brien-Fleming α-spending function by the Lan-DeMets algorithm.

Results from the primary analysis on PFS (data cutoff on September 9, 2022), the primary efficacy endpoint, and the Kaplan-Meier curve are as shown in Table 25 and Figure 2, demonstrating superiority of zolbetuximab over placebo.

Table 25. Results from the primary analysis on PFS
(assessed by the IRC, FAS, data cutoff on September 9, 2022)

	Zolbetuximab	Placebo
Number of patients	283	282
Number of events (%)	146 (51.6)	167 (59.2)
Median [95% CI] (months)	10.6 [8.90, 12.5]	8.67 [8.21, 10.3]
Hazard ratio [95% CI][*1]	0.751 [0.598, 0.942]	
P value (one-sided)[*2]	0.0066	

*1 A Cox proportional hazard model stratified by region (Asia or non-Asia), number of organs with metastasis (≤2 or ≥3), and prior gastrectomy (with or without)
*2 Stratified log-rank test (stratified by the same factors as those in the Cox proportional hazard model), a significance level (one-sided) of 0.025

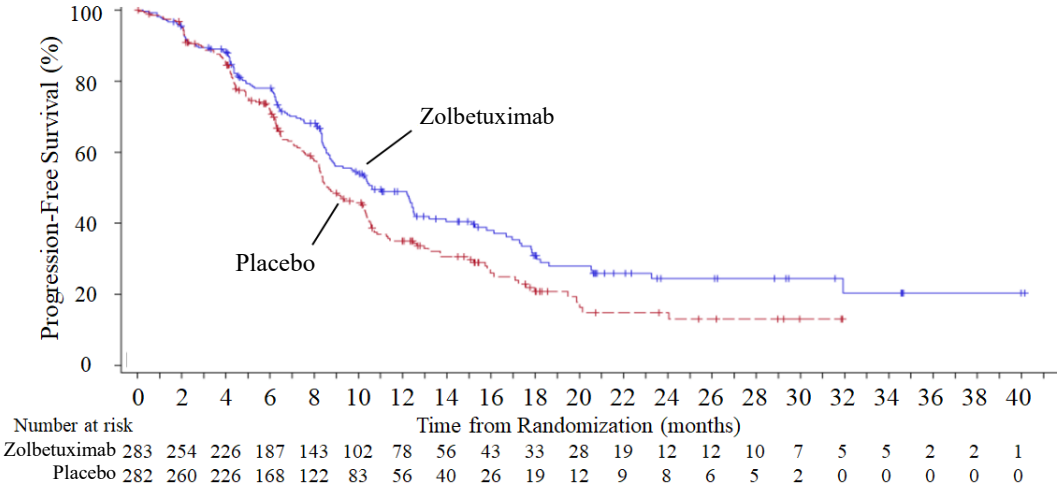

Figure 2. Kaplan-Meier curve of PFS at the time of the primary analysis
(assessed by the IRC, FAS, data cutoff on September 9, 2022)

A statistically significant difference shown in the primary analysis on PFS led to a test on OS, one of the secondary endpoints. Results from the interim analysis on OS (data cutoff on September 9, 2022) and the Kaplan-Meier curve are as shown in Table 26 and Figure 3, statistically demonstrating that zolbetuximab significantly extended OS compared with placebo.

Table 26. Results from interim analysis on OS (FAS, data cutoff on September 9, 2022)

	Zolbetuximab	Placebo
Number of patients	283	282
Number of events (%)	149 (52.7)	177 (62.8)
Median [95% CI] (months)	18.2 [16.4, 22.9]	15.5 [13.5, 16.5]
Hazard ratio [95% CI][*1]	0.750 [0.601, 0.936][*2]	
P value (one-sided)[*3]	0.0053	

*1 A Cox proportional hazard model stratified by region (Asia or non-Asia), number of organs with metastasis (≤2 or ≥3), and prior gastrectomy (with or without)
*2 The significance level in the interim analysis corresponds to 97.3% CI [0.585, 0.963]
*3 Stratified log-rank test (stratified by the same factors as those in the Cox proportional hazard model), a significance level (one-sided) of 0.0135

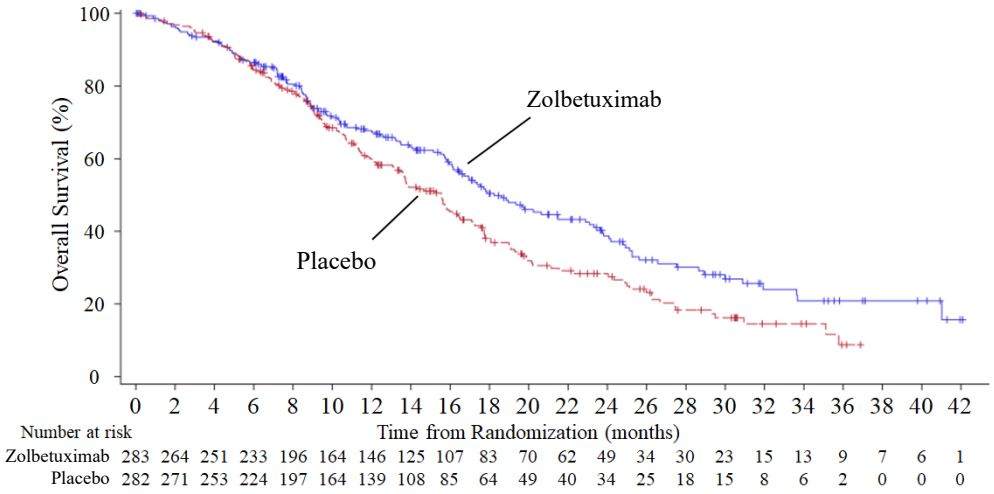

Figure 3. Kaplan-Meier curve of OS at the time of the interim analysis (FAS, data cutoff on September 9, 2022)

Deaths occurred in 22 of 279 patients (7.9%) in the zolbetuximab group and 24 of 278 patients (8.6%) in the placebo group during the treatment with the study drug or within 30 days after the last dose. Causes of the deaths other than disease progression (9 patients in the zolbetuximab group, 12 patients in the placebo group) were respiratory failure in 2 patients, death, pneumonia/acute myocardial infarction/disseminated intravascular coagulation, pneumonia/acute respiratory failure/pulmonary sepsis, encephalopathy/septic shock, upper gastrointestinal haemorrhage, sepsis, acute hepatic failure, coronavirus disease (COVID-19) pneumonia, intestinal obstruction, neutropenic sepsis, and small intestinal obstruction in 1 patient each in the zolbetuximab group; and death, pneumonia, acute myocardial infarction, acute respiratory distress syndrome, cardio-respiratory arrest, abscess soft tissue, cardiac arrest, cerebral haemorrhage, gastrointestinal haemorrhage, gastrointestinal obstruction, general physical health deterioration, and intestinal perforation in 1 patient each in the placebo group. A causal relationship to the study drug could not be ruled out for acute hepatic failure, pneumonia/acute myocardial infarction/disseminated intravascular coagulation, neutropenic sepsis, respiratory failure, and sepsis in 1 patient each in the zolbetuximab group; and cardiac arrest, pneumonia, death, and general physical health deterioration in 1 patient each in the placebo group.

Of the above, deaths in the Japanese subgroup occurred in 2 patients in the zolbetuximab group and 1 patient in the placebo group. Causes of the deaths other than disease progression (1 patient in the zolbetuximab group) were pneumonia/acute myocardial infarction/disseminated intravascular coagulation in 1 patient in the zolbetuximab group and cerebral haemorrhage in 1 patient in the placebo group. A causal relationship to the study drug could not be ruled out for pneumonia/acute myocardial infarction/disseminated intravascular coagulation in 1 patient in the zolbetuximab group.

7.1.2.3 Global phase III study (CTD 5.3.5.1-2, GLOW study, ongoing since November 2018 [data cutoff on October 7, 2022])

A randomized, double-blind, controlled study was conducted to compare the efficacy and safety of zolbetuximab with those of the placebo, used in combination with CAPOX for both, in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer[22)] who had

not received prior chemotherapy[23] (target sample size, 500 patients) at 166 study sites in 18 countries or regions including Japan.

Zolbetuximab 800/600 mg/m^2 or placebo was intravenously administered Q3W in combination with CAPOX, and L-OHP was repeated for up to 8 cycles, and other study drugs were continued until disease progression was documented or the criteria for treatment discontinuation were met.

All of 507 patients who were enrolled and randomized in the study (254 in the zolbetuximab group, 253 in the placebo group) were included in the FAS and also in the efficacy analysis (Japanese patients, 24 in the zolbetuximab group, 27 in the placebo group). In addition, 503 patients[24] (254 in the zolbetuximab group, 249 in the placebo group) were included in the safety analysis (Japanese patients, 24 in the zolbetuximab group, 27 in the placebo group), and the remaining 4 patients who did not receive the study drug (1 in the zolbetuximab group, 3 in the placebo group) were excluded.

The primary endpoint in the study was PFS assessed by the IRC based on the RECIST ver.1.1. Table 27 shows a statistical analysis plan for the study and major changes.

Table 27. Statistical analysis plan for GLOW study and major changes

	Protocol version 1 (dated April 26, 2018)	Protocol version 5 (dated October 18, 2021)
Primary endpoint	PFS assessed by the IRC based on RECIST ver.1.1	(no changes)
Secondary endpoint	OS • Test would be performed if the null hypothesis for PFS is rejected.	(no changes)
Target sample size	550 patients • PFS: The assumption comprised of 344 events, a hazard ratio of 0.67, and a significance level (one-sided) of 0.025 would have a power of 96%. • OS: The assumption comprised of 386 events, a hazard ratio of 0.75, and a significance level (one-sided) of 0.025 would have a power of 80%.	550 patients (no changes) • PFS: The assumption comprised of 300 events, a hazard ratio of 0.67, and a significance level (one-sided) of 0.025 would have a power of 93.4%. • OS: (no changes)
Analysis timepoint	Primary analysis on PFS: When approximately 344 PFS events are observed Interim analysis on OS: When the primary analysis on PFS is performed Final analysis on OS: When 386 OS events are observed	Primary analysis on PFS: When 300 PFS events are observed Interim analysis and final analysis on OS: (no changes)
Reason for the changes	(not applicable)	Accumulation of the PFS events was slower than initially assumed, and the analysis timepoint was predicted to reach ≥12 months later than initially planned. The number of events required for the primary analysis on PFS was changed.

For the interim analysis on OS, the type I error probability was adjusted according to an O'Brien-Fleming α-spending function by the Lan-DeMets algorithm.

Results from the primary analysis on PFS (data cutoff on October 7, 2022), the primary efficacy endpoint, and the Kaplan-Meier curve are as shown in Table 28 and Figure 4, demonstrating superiority of zolbetuximab over placebo.

[24] One patient who had been randomized to the placebo group but received zolbetuximab was handled as one in the zolbetuximab group.

Table 28. Results from the primary analysis on PFS (assessed by the IRC, FAS, data cutoff on October 7, 2022)

	Zolbetuximab	Placebo
Number of patients	254	253
Number of events (%)	137 (53.9)	172 (68.0)
Median [95% CI] (months)	8.21 [7.46, 8.84]	6.80 [6.14, 8.08]
Hazard ratio [95% CI][*1]	0.687 [0.544, 0.866]	
P value (one-sided)[*2]	0.0007	

*1 A Cox proportional hazard model stratified by region (Asia or non-Asia), number of organs with metastasis (≤2 or ≥3), and prior gastrectomy (with or without)
*2 Stratified log-rank test (stratified by the same factors as those in the Cox proportional hazard model), a significance level (one-sided) of 0.025

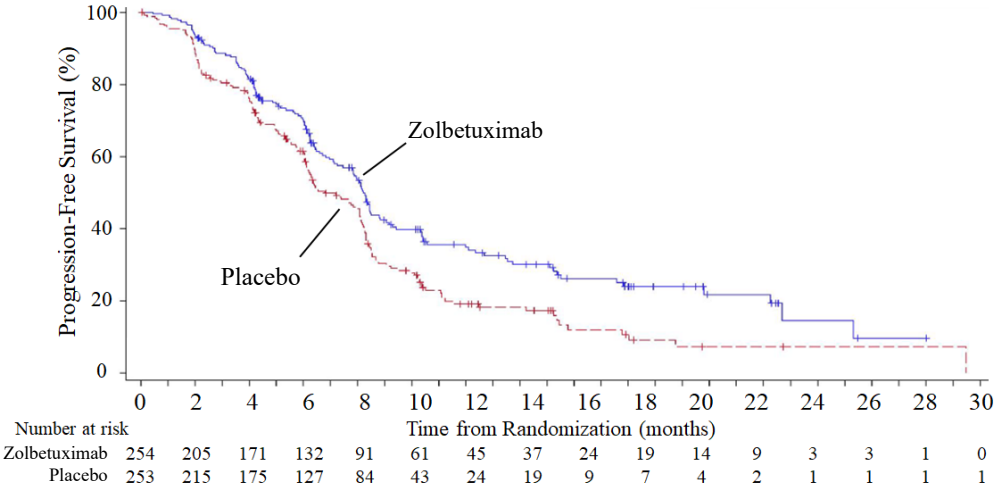

Figure 4. Kaplan-Meier curve of PFS at the time of the primary analysis (assessed by the IRC, FAS, data cutoff on October 7, 2022)

A statistically significant difference shown in the primary analysis on PFS led to a test on OS, one of the secondary endpoints. Results from the interim analysis on OS (data cutoff on October 7, 2022) and the Kaplan-Meier curve are as shown in Table 29 and Figure 5, statistically demonstrating that zolbetuximab significantly extended OS compared with placebo.

Table 29. Results from interim analysis on OS (FAS, data cutoff on October 7, 2022)

	Zolbetuximab	Placebo
Number of patients	254	253
Number of events (%)	144 (56.7)	174 (68.8)
Median [95% CI] (months)	14.4 [12.3, 16.5]	12.2 [10.3, 13.7]
Hazard ratio [95% CI][*1]	0.771 [0.615, 0.965][*2]	
P value (one-sided)[*3]	0.0118	

*1 A Cox proportional hazard model stratified by region (Asia or non-Asia), number of organs with metastasis (≤2 or ≥3), and prior gastrectomy (with or without)
*2 The significance level in the interim analysis corresponds to 97.3% CI [0.598, 0.994];
*3 Stratified log-rank test (stratified by the same factors as those in the Cox proportional hazard model), a significance level (one-sided) of 0.0135

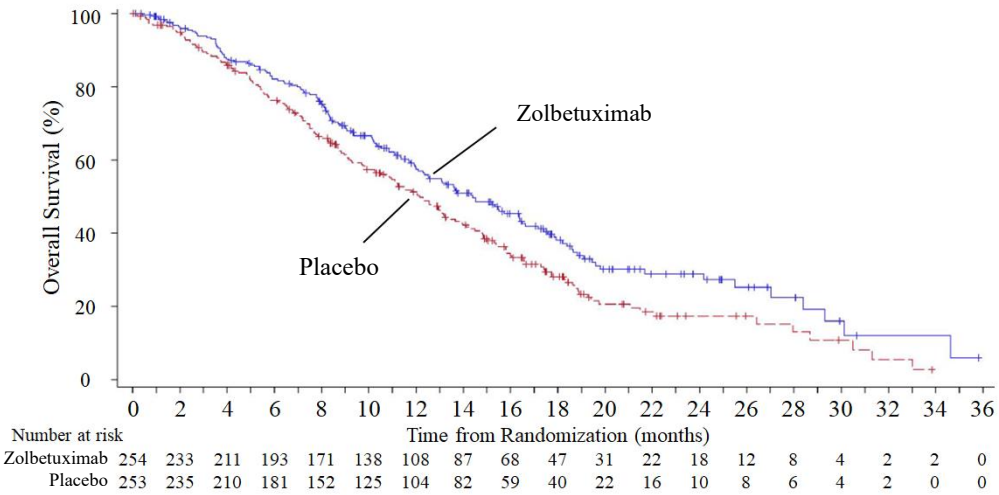

Figure 5. Kaplan-Meier curve of OS at the time of the interim analysis (FAS, data cutoff on October 7, 2022)

Deaths occurred in 27 of 254 patients (10.6%) in the zolbetuximab group and 32 of 249 patients (12.9%) in the placebo group during the treatment with the study drug or within 30 days after the last dose. Causes of the deaths other than disease progression (7 patients in the zolbetuximab group, 13 patients in the placebo group) were death, septic shock, upper gastrointestinal haemorrhage, and cerebral haemorrhage in 2 patients each, sepsis/platelet count decreased, disseminated intravascular coagulation/haemorrhagic ascites, pneumonia, abdominal infection, acute respiratory distress syndrome, cardio-respiratory arrest, dyspnoea, gastric perforation, Klebsiella sepsis, procedural complication, sudden death, and syncope in 1 patient each in the zolbetuximab group; and acidosis/septic shock, pneumonia/respiratory failure, febrile neutropenia/lower respiratory tract infection viral, hyperkalaemia/renal failure, death, pneumonia, septic shock, upper gastrointestinal haemorrhage, abdominal infection, cardio-respiratory arrest, dyspnoea, neutropenic sepsis, diarrhoea, escherichia infection, haematemesis, metastases to meninges, mucosal infection, pleural effusion, and pulmonary embolism in 1 patient each in the placebo group. A causal relationship to the study drug could not be ruled out for septic shock, procedural complication, cerebral haemorrhage, sepsis/platelet count decreased, syncope, and upper gastrointestinal haemorrhage in 1 patient each in the zolbetuximab group; and diarrhoea, death, haematemesis, septic shock, febrile neutropenia/lower respiratory tract infection viral, neutropenic sepsis, and mucosal infection in 1 patient each in the placebo group.

Of the above, death in the Japanese subgroup occurred in 1 patient in the placebo group, and the cause was malignant neoplasm progression, for which a causal relationship to the study drug was denied.

7.1.3 Foreign studies

7.1.3.1 Foreign phase I study (CTD 5.3.3.2-1, Study 001, July 2009 to May 2010)

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, and PK of zolbetuximab in patients with CLDN18.2-positive advanced gastric cancer[25)] (target sample size, 15 patients) at 6 study sites outside Japan.

[25)] Patients with esophageal cancer were also enrolled. In Latvia, pre-enrollment assessment for CLDN18.2 expression status was not mandatory, and enrollment required provision of tissue specimens. One patient enrolled in the 300 mg/m^2 cohort was later found negative for CLDN18.2.

Zolbetuximab 33, 100, 300, 600, or 1,000 mg/m^2 was intravenously administered as a single dose.

All of 15 patients enrolled in the study (3 in the 33 mg/m^2 cohort, 3 in the 100 mg/m^2 cohort, 3 in the 300 mg/m^2 cohort, 3 in the 600 mg/m^2 cohort, 3 in the 1,000 mg/m^2 cohort) received zolbetuximab and were included in the safety analysis.

DLT was evaluated until 28 days after the first dose of zolbetuximab. No DLT was observed at any dose.

No death occurred during the zolbetuximab treatment or within 28 days after the last dose.

7.1.3.2 Foreign phase II study (CTD 5.3.5.2-2, Study GM-IMAB-001-02 [Study 02], September 2010 to August 2015 [data cutoff on August 13, 2015])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of zolbetuximab in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer[26] (target sample size, 3 patients in Cohort 1, 3 patients in Cohort 2, 19 patients in Cohort 3) at 21 study sites outside Japan.

Zolbetuximab was intravenously administered Q2W at 300 mg/m^2 in Cohort 1 and at 600 mg/m^2 in Cohorts 2 and 3 and continued until disease progression was documented or the criteria for treatment discontinuation were met.

A total of 54 patients who were enrolled in the study and received zolbetuximab (4 in Cohort 1, 6 in Cohort 2, 44 in Cohort 3)[27] were included in the safety analysis. Of the safety analysis set, 43 patients in whom the efficacy data were available (3 in Cohort 1, 3 in Cohort 2, 37 in Cohort 3) were included in the efficacy analysis.

The primary endpoint in the study was the response rate assessed by the investigators based on RECIST ver.1.0 or 1.1 at Week 11 of the zolbetuximab treatment and 7 to 9 weeks after the last dose of zolbetuximab.

Results on the response rate (data cutoff on August 13, 2015), the primary efficacy endpoint, are as shown in Table 30.

Table 30. Response rate
(RECIST ver.1.0 or 1.1, assessed by the investigator, efficacy analysis set, data cutoff on August 13, 2015)

	Response rate [95% CI] (%)	
	300 mg/m^2 n = 3	600 mg/m^2 n = 40
Week 11 of the zolbetuximab treatment	0	7.7 [0.95, 24.13]
7 to 9 weeks after the last dose of zolbetuximab	0	5.3 [0.13, 26.03]

[26] Patients with cancer of the gastroesophageal junction and patients with lower esophageal adenocarcinoma were also enrolled.
[27] Because many patients dropped out of the study before the fifth dose, patients more than the target sample size were enrolled.

No death occurred in Cohort 1 during the treatment with the study drug or within 28 days after the last dose, but of 50 patients who were enrolled in Cohorts 2 and 3 and received zolbetuximab 600 mg/m^2, 10 patients (20.0%) died. Causes of the deaths other than disease progression (5 patients) were general physical condition decreased in 3 patients and renal failure and respiratory failure in 1 patient each, and a causal relationship to the study drug was denied for all of them.

7.1.3.3 Foreign phase II study (CTD 5.3.5.1-3, Study 03, July 2012 to January 2019 [efficacy data cutoff on December 18, 2015, safety data cutoff on January 31, 2019])

A randomized, open-label, controlled study was conducted to compare the efficacy and safety of EOX (a combination of epirubicin, L-OHP, and capecitabine) with those of zolbetuximab/EOX (a combination of zolbetuximab and EOX) in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer[28)] who had not received prior chemotherapy (target sample size, not specified) at 46 study sites outside Japan.

EOX was administered in Arm 1, and zolbetuximab 800/600 mg/m^2 or 1,000 mg/m^2 was intravenously administered Q3W in combination with EOX in Arms 2 and 3, respectively, and the treatment was continued until disease progression was documented or the criteria for treatment discontinuation were met.

Of 252 patients enrolled in the study (85 in Arm 1, 79 in Arm 2, 88 in Arm 3), 246 patients (84 in Arm 1, 77 in Arm 2, 85 in Arm 3) were included in the efficacy and safety analyses, and the remaining 6 patients (1 in Arm 1, 2 in Arm 2, 3 in Arm 3) who did not receive the study drug were excluded.

The primary endpoint in the study was PFS centrally assessed by independent review based on RECIST ver.1.1.

Results from the primary analysis on PFS (data cutoff on December 18, 2015), the primary efficacy endpoint, and the Kaplan-Meier curve are as shown in Table 31 and Figure 6.

Table 31. Results from the primary analysis on PFS (centrally assessed by independent review, efficacy analysis set, data cutoff on December 18, 2015)

	Arm 1 EOX	Arm 2 Zolbetuximab 800/600 mg/m^2/EOX	Arm 3 Zolbetuximab 1,000 mg/m^2/EOX
Number of patients	84	77	85
Number of events (%)	62 (73.8)	42 (54.5)	49 (57.6)
Median [95% CI] (months)	5.3 [4.1, 7.1]	7.5 [5.6, 10.3]	7.1 [5.6, 8.0]
Hazard ratio [95% CI]*	—	0.45 [0.30, 0.69]	0.57 [0.39, 0.85]

* A Cox proportional hazard model stratified by measurable lesion (yes or no) and proportion of CLDN18.2-positive tumor cells (<70%, ≥70%) at baseline

28) Patients with cancer of the gastroesophageal junction and patients with esophageal adenocarcinoma were also enrolled.

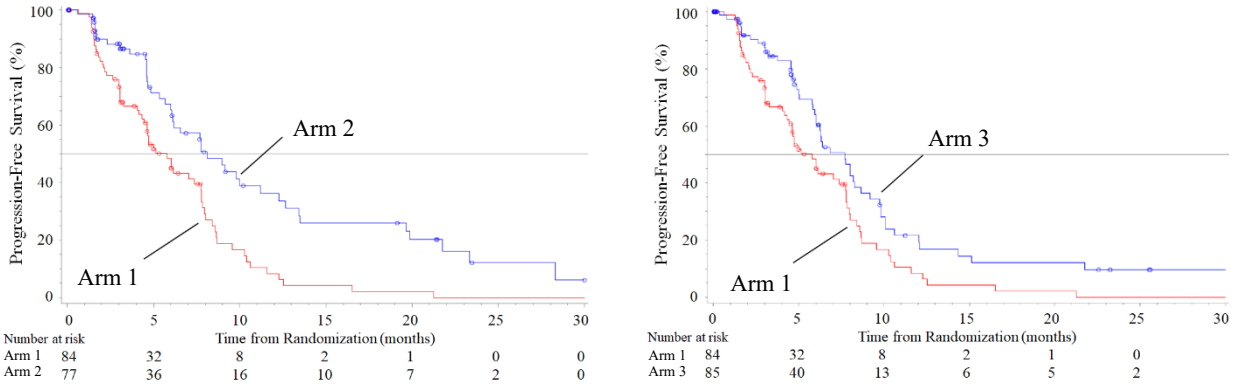

Figure 6. Kaplan-Meier curve of PFS at the time of the primary analysis (centrally assessed by independent review, efficacy analysis set, data cutoff on December 18, 2015)

Deaths occurred in 15 of 84 patients (17.9%) in Arm 1, 8 of 77 patients (10.4%) in Arm 2, and 9 of 85 patients (10.6%) in Arm 3 during the treatment with the study drug or within 6 months after the last dose. Causes of the deaths other than disease progression (8 patients in Arm 1, 3 patients in Arm 2, 4 patients in Arm 3) were gastric haemorrhage in 2 patients, ileus, death, general physical condition decreased, renal failure, and pulmonary artery thrombosis in 1 patient each in Arm 1, cardiopulmonary failure, multi-organ failure, sudden death, oesophageal adenocarcinoma, and cerebrovascular accident in 1 patient each in Arm 2, and pulmonary embolism in 2 patients, cardiac failure, sepsis, and acute renal failure/respiratory failure in 1 patient each in Arm 3. A causal relationship to the study drug could not be ruled out for pulmonary embolism in 1 patient in Arm 3.

7.2 Reference data

7.2.1 Foreign studies

7.2.1.1 Foreign phase I study (CTD 5.3.3.2-2, Study GM-IMAB-001-04 [Study 04], October 2012 to October 2014)

Deaths occurred in 2 of 7 patients (28.6%) in Arm 1, 3 of 9 patients (33.3%) in Arm 2, 1 of 7 patients (14.3%) in Arm 3, and 1 of 5 patients (20.0%) in Arm 4 during the treatment with the study drug or within 3 months after the last dose. Causes of the deaths other than disease progression (1 patient each in Arms 1 and 2) were general physical health decreased in 1 patient in Arm 1, dehydration and Escherichia infection in 1 patient each in Arm 2, general physical health decreased in 1 patient in Arm 3, and cerebrovascular accident/dyspnoea in 1 patient in Arm 4. A causal relationship to the study drug was denied for all events.

7.2.1.2 Foreign phase I study (CTD 5.3.3.2-4, Study 0105, October 2019 to January 2021)

Deaths occurred in 1 of 12 patients (8.3%) during the zolbetuximab treatment or within 30 days after the last dose. The cause of death was intestinal obstruction, and a causal relationship to the study drug was denied.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the pivotal study for evaluation of the efficacy and safety of zolbetuximab was the global phase III studies in patients with CLDN18.2-positive

and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy (SPOTLIGHT and GLOW studies), and decided to evaluate the submitted data focusing on these studies. PMDA decided to evaluate the efficacy in Japanese patients systematically based on data in the SPOTLIGHT and GLOW studies in accordance with the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Amendment to 'Basic Principles on Global Clinical Trials (Reference Cases)'" (Administrative Notice dated December 10, 2021), and "Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

7.R.2 Efficacy

On the basis of the following review, PMDA has concluded that zolbetuximab/chemotherapy (a combination of zolbetuximab and chemotherapy) shows the efficacy in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy.

7.R.2.1 Setting of the control group

The applicant's explanation about the rationale for the control group in the SPOTLIGHT and GLOW studies:

For the following reasons, FOLFOX and CAPOX were used as comparators in the SPOTLIGHT and GLOW studies:

- At the time of planning the SPOTLIGHT and GLOW studies, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer (NCCN guideline, v.1.2018) recommended combinations of fluoro pyrimidine antineoplastic agents and platinum antineoplastic agents (FOLFOX, CAPOX, etc.) as the first-line therapies in patients with unresectable advanced or recurrent gastric cancer.
- At the time of planning the SPOTLIGHT and GLOW studies, the Japanese gastric cancer treatment guidelines edited by the Japanese Gastric Cancer Association (Japanese treatment guideline) (2018 version) recommended CAPOX, FOLFOX, etc. as the first-line therapies in patients with unresectable advanced or recurrent gastric cancer.

The applicant specified the L-OHP treatment period as up to 12 cycles in combination with FOLFOX and up to 8 cycles with CAPOX in the SPOTLIGHT and GLOW studies, respectively.

The applicant's explanation about the reasons for setting the treatment period:

The upper limit was not specified on the L-OHP treatment period in the clinical studies that supported the recommendations for combination of fluoro pyrimidine antineoplastic agents and L-OHP in the treatment guidelines in and outside Japan. The median number of 3-week cycles actually used in clinical studies was 6 to 7 cycles (corresponding to 4.5 to 5.5 months), and the median actual treatment period using 2-week cycles in clinical studies was 5 months (*N Engl J Med.* 2008;358:36-46, *Ann Oncol.* 2015;26:141-8, etc.); and the extended use of L-OHP might lead to aggravation of peripheral nervous toxicity. Taking account of the above, the L-OHP treatment period was specified as up to 12 and 8 cycles (corresponding to approximately 6 months for both) in the SPOTLIGHT and GLOW studies, respectively. In the SPOTLIGHT and GLOW studies, the (median) L-OHP treatment period in the

placebo group was 4.9 and 3.9 months in the overall population and 4.5 and 3.7 months in the Japanese subgroup, which were similar to the above treatment period in the clinical studies that supported the recommendations in the guidelines. In observational research in patients with unresectable advanced or recurrent gastric cancer who had received the first-line therapy containing fluoro pyrimidine antineoplastic agents and platinum antineoplastic agents and undergone ≥2 sessions of tumor assessment, discontinuation of only the platinum antineoplastic agents before disease progression would not pose a risk of disease progression compared with their continuation to disease progression[29] (*Clin Transl Oncol.* 2020;22:734-50). Therefore, the specified L-OHP treatment period in the SPOTLIGHT and GLOW studies was also justified.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint in the SPOTLIGHT and GLOW studies:
Extended PFS was accompanied by extended time to worsening of clinical symptoms and deterioration of quality of life (QOL) owing to disease progression in multiple clinical studies in patients with unresectable advanced or recurrent gastric cancer (*J Clin Oncol.* 2007;25:3210-6, etc.). In view of this finding, extended PFS in the concerned patient population can be expected to lead to maintained QOL and thus is considered clinically meaningful. The primary endpoint in the SPOTLIGHT and GLOW studies was specified as PFS.

The applicant's explanation about the efficacy of zolbetuximab/chemotherapy in the SPOTLIGHT and GLOW studies:

SPOTLIGHT study

Results on PFS assessed by the IRC based on RECIST ver.1.1, the primary endpoint, demonstrated the superiority of zolbetuximab over placebo. The statistical test on OS performed in a hierarchical procedure showed that zolbetuximab significantly extended OS than placebo [see Section 7.1.2.2].

Results from the primary analysis on PFS and the Kaplan-Meier curve in the Japanese subgroup in the SPOTLIGHT study are as shown in Table 32 and Figure 7. Results from the interim analysis on OS and the Kaplan-Meier curve are as shown in Table 33 and Figure 8.

Table 32. Results from the primary analysis on PFS in the Japanese subgroup: SPOTLIGHT study (assessed by the IRC, FAS, data cutoff on September 9, 2022)

	Zolbetuximab	Placebo
Number of patients	32	33
Number of events (%)	12 (37.5)	17 (51.5)
Median [95% CI] (months)	18.1 [8.64, —]	8.28 [6.28, 10.6]
Hazard ratio [95% CI]*	0.493 [0.223, 1.09]	

—, Not estimable
* A Cox proportional hazard model stratified by number of organs with metastasis (≤2 or ≥3) and prior gastrectomy (with or without)

[29] In the HER2-negative population, 37.5% of patients who continued platinum antineoplastic agents until disease progression achieved 12-month PFS, while 46.6% of patients who discontinued only platinum antineoplastic agents before that achieved 12-month PFS. The multivariate analysis showed the hazard ratio [95% CI] of PFS in patients who discontinued only platinum antineoplastic agents before disease progression compared with patients who continued platinum antineoplastic agents until disease progression was 1.07 [0.69, 1.65], and the discontinuation of only platinum antineoplastic agents before disease progression did not clearly decrease PFS.

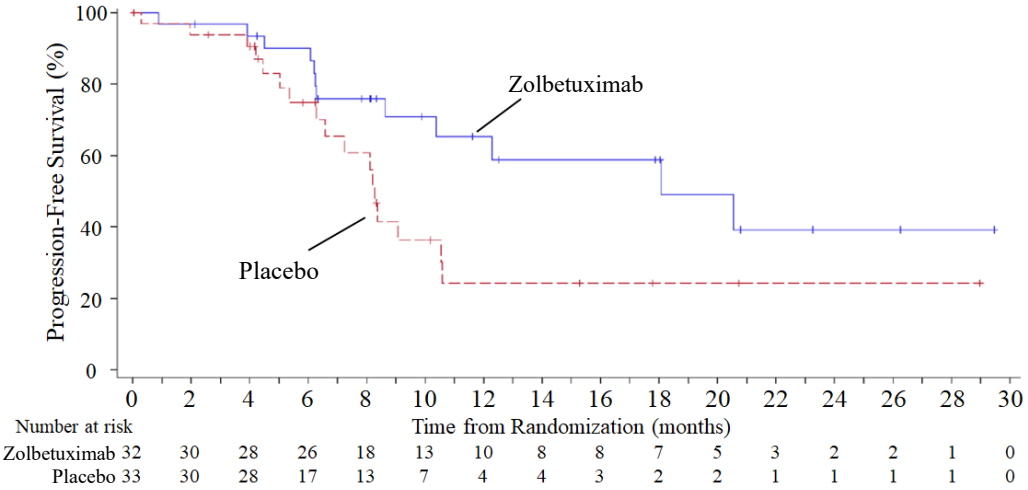

Figure 7. Kaplan-Meier curve of PFS in the Japanese subgroup at the time of the primary analysis: SPOTLIGHT study
(assessed by the IRC, FAS, data cutoff on September 9, 2022)

Table 33. Results from the interim analysis on OS in the Japanese subgroup: SPOTLIGHT study
(FAS, data cutoff on September 9, 2022)

	Zolbetuximab	Placebo
Number of patients	32	33
Number of events (%)	23 (71.9)	27 (81.8)
Median [95% CI] (months)	23.1 [16.4, 25.3]	17.7 [9.63, 25.1]
Hazard ratio [95% CI]*	0.719 [0.389, 1.33]	

* A Cox proportional hazard model stratified by number of organs with metastasis (≤2 or ≥3) and prior gastrectomy (with or without)

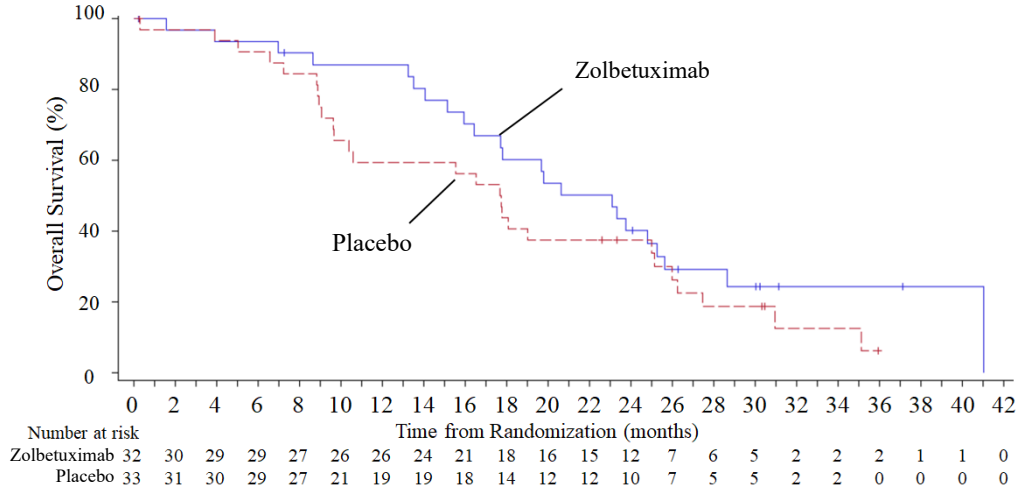

Figure 8. Kaplan-Meier curve of OS in the Japanese subgroup at the time of the interim analysis: SPOTLIGHT study
(FAS, data cutoff on September 9, 2022)

GLOW study

Results on PFS assessed by the IRC based on RECIST ver.1.1, the primary endpoint, demonstrated superiority of zolbetuximab over placebo. The statistical test on OS performed in a hierarchical procedure showed that zolbetuximab significantly extended OS compared with placebo [see Section 7.1.2.3].

Results from the primary analysis on PFS and the Kaplan-Meier curve in the Japanese subgroup in the GLOW study are as shown in Table 34 and Figure 9. Results from the interim analysis on OS and the Kaplan-Meier curve are as shown in Table 35 and Figure 10.

Table 34. Results from the primary analysis on PFS in the Japanese subgroup: GLOW study (assessed by the IRC, FAS, data cutoff on October 7, 2022)

	Zolbetuximab	Placebo
Number of patients	24	27
Number of events (%)	7 (29.2)	16 (59.3)
Median [95% CI] (months)	20.8 [8.11, —]	8.28 [6.01, 9.07]
Hazard ratio [95% CI]*	0.352 [0.119, 1.04]	

—, Not estimable
* A Cox proportional hazard model stratified by number of organs with metastasis (≤2 or ≥3) and prior gastrectomy (with or without)

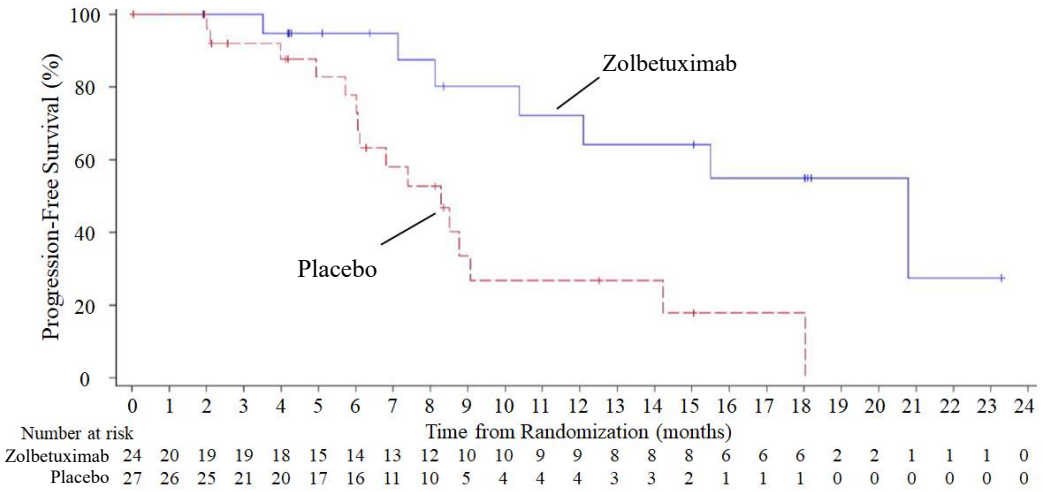

Figure 9. Kaplan-Meier curve of PFS in the Japanese subgroup at the time of the primary analysis: GLOW study (assessed by the IRC, FAS, data cutoff on October 7, 2022)

Table 35. Results from the interim analysis on OS in the Japanese subgroup: GLOW study (FAS, data cutoff on October 7, 2022)

	Zolbetuximab	Placebo
Number of patients	24	27
Number of events (%)	13 (54.2)	19 (70.4)
Median [95% CI] (months)	24.2 [13.1, 27.0]	14.7 [9.07, 18.3]
Hazard ratio [95% CI]*	0.494 [0.219, 1.11]	

* A Cox proportional hazard model stratified by number of organs with metastasis (≤2 or ≥3) and prior gastrectomy (with or without)

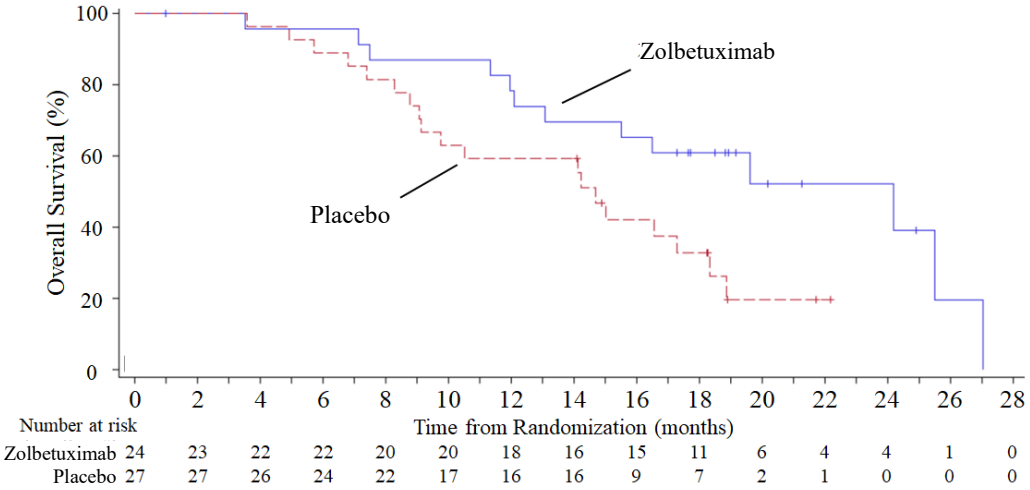

Figure 10. Kaplan-Meier curve of OS in the Japanese subgroup at the time of the interim analysis: GLOW study
(FAS, data cutoff on October 7, 2022)

The applicant's explanation about the efficacy of zolbetuximab/chemotherapy by primary site:
Table 36 shows results on PFS and OS by primary site in the pooled analysis of the SPOTLIGHT and GLOW studies. The efficacy of zolbetuximab tended to differ between patients with gastric cancer and patients with cancer of the gastroesophageal junction. While the reason for this different trend remains unknown, there are no data suggesting that tumor biological characteristics and CLDN18.2 expression status could differ depending on the primary site. In view of these facts, the above results from the subgroup analysis are not considered to deny the efficacy of zolbetuximab in patients with cancer of the gastroesophageal junction.

Table 36. Results on PFS and OS by primary site
(pooled analysis of the SPOTLIGHT and GLOW studies)

Endpoint	Primary site	Treatment	n	Median [95% CI] (months)	Hazard ratio*1 [95% CI]	*P* value for interaction*2
PFS	Stomach	Zolbetuximab	438	9.79 [8.48, 12.0]	0.648 [0.543, 0.774]	0.0087
		Placebo	419	7.85 [6.57, 8.25]		
	Gastroesophageal junction	Zolbetuximab	99	8.34 [6.41, 9.95]	1.11 [0.774, 1.58]	
		Placebo	116	9.23 [8.18, 10.5]		
OS	Stomach	Zolbetuximab	438	17.0 [15.5, 18.8]	0.690 [0.580, 0.822]	0.0472
		Placebo	419	13.2 [11.4, 14.2]		
	Gastroesophageal junction	Zolbetuximab	99	15.5 [11.8, 17.5]	1.05 [0.738, 1.49]	
		Placebo	116	15.8 [12.3, 17.2]		

*1 A non-stratified Cox proportional hazard model
*2 A Cox proportional hazard model stratified by region, number of organs with metastasis, prior gastrectomy, and study (SPOTLIGHT or GLOW study)

PMDA's view:
PMDA accepted the applicant's explanation and, for the following reasons, concluded that the efficacy of zolbetuximab/chemotherapy in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy was demonstrated.

- In the SPOTLIGHT and GLOW studies, the results on PFS, the primary endpoint, demonstrated superiority of zolbetuximab over placebo, and the statistical test on OS performed in a hierarchical procedure showed that zolbetuximab significantly extended OS than the placebo.

- Because results on PFS and OS in the Japanese subgroup did not tend to differ from those in the overall population, the efficacy of zolbetuximab can be expected in Japanese patients as well.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events observed in clinical studies"]

PMDA's view:

On the basis of the following review, as adverse events requiring special attention during use of zolbetuximab/chemotherapy are nausea and vomiting, infusion reaction, and hypersensitivity.

Although the above adverse events require attention during treatment, zolbetuximab/chemotherapy will be tolerable when appropriate measures, such as monitoring and controlling of adverse events and interruption of zolbetuximab, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of zolbetuximab/chemotherapy based on the safety data obtained from the SPOTLIGHT and GLOW studies:

Table 37 shows the outline of the safety profile in the SPOTLIGHT and GLOW studies.

Table 37. Outline of the safety (SPOTLIGHT and GLOW studies)

	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
All adverse events	278 (99.6)	277 (99.6)	251 (98.8)	244 (98.0)
Grade ≥3 adverse events	242 (86.7)	216 (77.7)	185 (72.8)	174 (69.9)
Adverse events leading to death	22 (7.9)	24 (8.6)	27 (10.6)	32 (12.9)
Serious adverse events	125 (44.8)	121 (43.5)	120 (47.2)	124 (49.8)
Adverse events leading to treatment discontinuation*1	120 (43.0)	106 (38.1)	79 (31.1)	63 (25.3)
Zolbetuximab or placebo	55 (19.7)	30 (10.8)	51 (20.1)	36 (14.5)
Cape, 5-FU, (*l*-)LV or L-OHP	104 (37.3)	103 (37.1)	73 (28.7)	60 (24.1)
Adverse events leading to treatment interruption*1	228 (81.7)	156 (56.1)	181 (71.3)	128 (51.4)
Zolbetuximab or placebo	208 (74.6)	111 (39.9)	140 (55.1)	71 (28.5)
Cape, 5-FU, (*l*-)LV or L-OHP	155 (55.6)	136 (48.9)	134 (52.8)	121 (48.6)
Adverse events leading to dose reduction*2	143 (51.3)	122 (43.9)	113 (44.5)	99 (39.8)
Adverse events leading to slower infusion rate*3	45 (16.1)	6 (2.2)	45 (17.7)	1 (0.4)

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 38 and Table 39 show adverse events for which the incidence was higher in the zolbetuximab group than in the placebo group of the SPOTLIGHT and GLOW studies. There were no adverse events leading to death of which the incidence was ≥2% higher in the zolbetuximab group than in the placebo group. In the GLOW study, there were no adverse events leading to discontinuation of the study drug of which the incidence was ≥3% higher in the zolbetuximab group than in the placebo group.

Table 38. Adverse events for which the incidence was higher in the zolbetuximab group than in the placebo group (safety analysis set, SPOTLIGHT study)

PT (MedDRA ver.25.0)	Number of patients (%)	
	Zolbetuximab n = 279	Placebo n = 278
All-grade adverse events[*1]		
Nausea	230 (82.4)	169 (60.8)
Vomiting	188 (67.4)	99 (35.6)
Decreased appetite	131 (47.0)	93 (33.5)
Oedema peripheral	49 (17.6)	26 (9.4)
Abdominal pain upper	47 (16.8)	32 (11.5)
Hypoalbuminaemia	43 (15.4)	17 (6.1)
Hypocalcaemia	30 (10.8)	9 (3.2)
Grade ≥3 adverse events[*2]		
Neutropenia	79 (28.3)	65 (23.4)
Nausea	45 (16.1)	18 (6.5)
Vomiting	45 (16.1)	16 (5.8)
Asthenia	20 (7.2)	7 (2.5)
Hypoalbuminaemia	11 (3.9)	2 (0.7)
Serious adverse events[*3]		
Vomiting	23 (8.2)	13 (4.7)
Nausea	19 (6.8)	11 (4.0)
Febrile neutropenia	8 (2.9)	1 (0.4)
Adverse events leading to treatment discontinuation[*2,4]		
Vomiting	20 (7.2)	1 (0.4)
Nausea	18 (6.5)	3 (1.1)
Adverse events leading to treatment interruption[*2,4]		
Nausea	106 (38.0)	9 (3.2)
Vomiting	92 (33.0)	7 (2.5)
Abdominal pain	17 (6.1)	3 (1.1)
Hypertension	17 (6.1)	2 (0.7)
Abdominal pain upper	14 (5.0)	0
Asthenia	12 (4.3)	3 (1.1)
Adverse events leading to dose reduction[*2,5]		
Neutropenia	42 (15.1)	32 (11.5)
Adverse events leading to slower infusion rate[*2,6]		
Nausea	30 (10.8)	1 (0.4)
Vomiting	21 (7.5)	1 (0.4)

*1 Events with a ≥5% higher incidence in the zolbetuximab group than in the placebo group
*2 Events with a ≥3% higher incidence in the zolbetuximab group than in the placebo group
*3 Events with a ≥2% higher incidence in the zolbetuximab group than in the placebo group
*4 Adverse events leading to discontinuation or interruption of any of the study drugs
*5 Adverse events leading to dose reduction of any of 5-FU, (*l*-)LV, and L-OHP
*6 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 39. Adverse events for which the incidence was higher in the zolbetuximab group than in the placebo group (safety analysis set, GLOW study)

PT (MedDRA ver.25.0)	Number of patients (%)	
	Zolbetuximab n = 254	Placebo n = 249
All-grade adverse events[*1]		
Nausea	174 (68.5)	125 (50.2)
Vomiting	168 (66.1)	77 (30.9)
Decreased appetite	105 (41.3)	84 (33.7)
Hypoalbuminaemia	57 (22.4)	35 (14.1)
Neutropenia	50 (19.7)	35 (14.1)
Weight decreased	50 (19.7)	25 (10.0)
Oedema peripheral	26 (10.2)	6 (2.4)
Grade ≥3 adverse events[*2]		
Vomiting	31 (12.2)	9 (3.6)
Nausea	22 (8.7)	6 (2.4)
Neutropenia	18 (7.1)	7 (2.8)
Decreased appetite	17 (6.7)	4 (1.6)
Serious adverse events[*3]		
Decreased appetite	10 (3.9)	3 (1.2)
Adverse events leading to treatment interruption[*2,4]		
Vomiting	70 (27.6)	12 (4.8)
Nausea	55 (21.7)	9 (3.6)
Neutropenia	31 (12.2)	19 (7.6)
Neutrophil count decreased	19 (7.5)	11 (4.4)
Adverse events leading to dose reduction[*2,5]		
Nausea	14 (5.5)	6 (2.4)
Vomiting	11 (4.3)	3 (1.2)
Adverse events leading to slower infusion rate[*2,6]		
Nausea	26 (10.2)	0
Vomiting	26 (10.2)	0

*1 Events with a ≥5% higher incidence in the zolbetuximab group than in the placebo group
*2 Events with a ≥3% higher incidence in the zolbetuximab group than in the placebo group
*3 Events with a ≥2% higher incidence in the zolbetuximab group than in the placebo group
*4 Adverse events leading to interruption of any of the study drugs
*5 Adverse events leading to dose reduction of either Cape or L-OHP
*6 Adverse events leading to slower infusion rate of zolbetuximab or placebo

PMDA's view:

All-grade and Grade ≥3 adverse events as well as serious adverse events for which the incidence was higher in the zolbetuximab group than in the placebo group of the SPOTLIGHT and GLOW studies are highly likely to occur during use of zolbetuximab, and thus patients receiving zolbetuximab should be carefully monitored for these events in consideration of their association with zolbetuximab. Most of these events, however, were manageable by interruption of zolbetuximab. In view of the above findings, PMDA concluded that zolbetuximab/chemotherapy is tolerable when appropriate measures, such as monitoring and controlling of adverse events and interruption of zolbetuximab are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.2 Safety in patients with or without prior gastrectomy

Because CLDN18.2 is mainly expressed in the stomach, the safety profile of zolbetuximab may differ depending on prior gastrectomy.

The applicant's explanation about the safety of zolbetuximab/chemotherapy in patients with or without prior gastrectomy based on the safety data in the SPOTLIGHT and GLOW studies:

Table 40 and Table 41 shows the outline of the safety in patients with or without prior gastrectomy in the SPOTLIGHT and GLOW studies.

Table 40. Outline of the safety in patients with or without prior gastrectomy (SPOTLIGHT study)

	Number of patients (%)			
	Patients without prior gastrectomy		Patients with prior gastrectomy	
	Zolbetuximab n = 197	Placebo n = 196	Zolbetuximab n = 82	Placebo n = 82
All adverse events	196 (99.5)	195 (99.5)	82 (100)	82 (100)
Grade ≥3 adverse events	173 (87.8)	150 (76.5)	69 (84.1)	66 (80.5)
Adverse events leading to death	19 (9.6)	19 (9.7)	3 (3.7)	5 (6.1)
Serious adverse events	93 (47.2)	87 (44.4)	32 (39.0)	34 (41.5)
Adverse events leading to treatment discontinuation*1	85 (43.1)	72 (36.7)	35 (42.7)	34 (41.5)
Adverse events leading to treatment interruption*1	162 (82.2)	108 (55.1)	66 (80.5)	48 (58.5)
Adverse events leading to dose reduction*2	94 (47.7)	77 (39.3)	49 (59.8)	45 (54.9)
Adverse events leading to slower infusion rate*3	36 (18.3)	4 (2.0)	9 (11.0)	2 (2.4)

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 41. Outline of the safety in patients with or without prior gastrectomy (GLOW study)

	Number of patients (%)			
	Patients without prior gastrectomy		Patients with prior gastrectomy	
	Zolbetuximab n = 181	Placebo n = 183	Zolbetuximab n = 73	Placebo n = 66
All adverse events	180 (99.4)	178 (97.3)	71 (97.3)	66 (100)
Grade ≥3 adverse events	135 (74.6)	128 (69.9)	50 (68.5)	46 (69.7)
Adverse events leading to death	23 (12.7)	29 (15.8)	4 (5.5)	3 (4.5)
Serious adverse events	86 (47.5)	90 (49.2)	34 (46.6)	34 (51.5)
Adverse events leading to treatment discontinuation*1	58 (32.0)	48 (26.2)	21 (28.8)	15 (22.7)
Adverse events leading to treatment interruption*1	131 (72.4)	89 (48.6)	50 (68.5)	39 (59.1)
Adverse events leading to dose reduction*2	80 (44.2)	68 (37.2)	33 (45.2)	31 (47.0)
Adverse events leading to slower infusion rate*3	37 (20.4)	0	8 (11.0)	1 (1.5)

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of either Cape or L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 42 shows adverse events for which the incidence was higher in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group of the SPOTLIGHT study. In the zolbetuximab group, there were no adverse events leading to death of which the incidence was ≥2% higher in patients without prior gastrectomy than in patients with prior gastrectomy.

Table 42. Adverse events for which the incidence was higher in patients without prior gastrectomy than in patients with prior gastrectomy (SPOTLIGHT study)

PT (MedDRA ver.25.0)	Number of patients (%)			
	Patients without prior gastrectomy		Patients with prior gastrectomy	
	Zolbetuximab n = 197	Placebo n = 196	Zolbetuximab n = 82	Placebo n = 82
All-grade adverse events[*1]				
Vomiting	149 (75.6)	72 (36.7)	39 (47.6)	27 (32.9)
Constipation	76 (38.6)	86 (43.9)	23 (28.0)	26 (31.7)
Hypoalbuminaemia	40 (20.3)	13 (6.6)	3 (3.7)	4 (4.9)
Grade ≥3 adverse events[*2]				
Vomiting	38 (19.3)	11 (5.6)	7 (8.5)	5 (6.1)
Nausea	35 (17.8)	13 (6.6)	10 (12.2)	5 (6.1)
Hypertension	14 (7.1)	9 (4.6)	1 (1.2)	1 (1.2)
Serious adverse events[*2]				
Vomiting	22 (11.2)	9 (4.6)	1 (1.2)	4 (4.9)
Nausea	17 (8.6)	8 (4.1)	2 (2.4)	3 (3.7)
Adverse events leading to slower infusion rate[*2,3]				
Vomiting	18 (9.1)	1 (0.5)	3 (3.7)	0

*1 Events with a ≥10% higher incidence in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group
*2 Events with a ≥5% higher incidence in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 43 shows adverse events for which the incidence was higher in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group of the GLOW study. In the zolbetuximab group, there were no (i) adverse events leading to death with a ≥2% higher incidence, (ii) serious adverse events with a ≥5% higher incidence; or (iii) adverse events leading to slower infusion rate of zolbetuximab or placebo with a ≥5% higher incidence in patients without prior gastrectomy than in patients with prior gastrectomy.

Table 43. Adverse events for which the incidence was higher in patients without prior gastrectomy than in patients with prior gastrectomy (GLOW study)

PT (MedDRA ver.25.0)	Number of patients (%)			
	Patients without prior gastrectomy		Patients with prior gastrectomy	
	Zolbetuximab n = 181	Placebo n = 183	Zolbetuximab n = 73	Placebo n = 66
All-grade adverse events[*1]				
Nausea	131 (72.4)	90 (49.2)	43 (58.9)	35 (53.0)
Vomiting	130 (71.8)	54 (29.5)	38 (52.1)	23 (34.8)
Grade ≥3 adverse events[*2]				
Vomiting	26 (14.4)	9 (4.9)	5 (6.8)	0

*1, Events with a ≥10% higher incidence in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group
*2, Events with a ≥5% higher incidence in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group

PMDA's view:

PMDA confirmed that the incidence of adverse events other than nausea and vomiting in patients without prior gastrectomy was similar to that in patients with prior gastrectomy. For vomiting and nausea, the incidence of serious adverse events was higher in patients without prior gastrectomy than in patients with prior gastrectomy. This finding is further discussed in Section "7.R.3.4 Nausea and vomiting."

7.R.3.3 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation about differences in safety of zolbetuximab/chemotherapy between Japanese and non-Japanese patients based on safety data obtained from the SPOTLIGHT and GLOW studies:

Table 44 shows the outline of the safety in Japanese and non-Japanese patients in the zolbetuximab group of the SPOTLIGHT and GLOW studies.

Table 44. Outline of the safety in Japanese and non-Japanese patients (zolbetuximab group in the SPOTLIGHT and GLOW studies)

	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Japanese patients n = 31	Non-Japanese patients n = 248	Japanese patients n = 24	Non-Japanese patients n = 230
All adverse events	31 (100)	247 (99.6)	24 (100)	227 (98.7)
Grade ≥3 adverse events	24 (77.4)	218 (87.9)	14 (58.3)	171 (74.3)
Adverse events leading to death	2 (6.5)	20 (8.1)	0	27 (11.7)
Serious adverse events	10 (32.3)	115 (46.4)	7 (29.2)	113 (49.1)
Adverse events leading to treatment discontinuation[*1]	13 (41.9)	107 (43.1)	5 (20.8)	74 (32.2)
Zolbetuximab	5 (16.1)	50 (20.2)	2 (8.3)	49 (21.3)
Cape, 5-FU, (*l*-)LV or L-OHP	11 (35.5)	93 (37.5)	5 (20.8)	68 (29.6)
Adverse events leading to treatment interruption[*1]	27 (87.1)	201 (81.0)	18 (75.0)	163 (70.9)
Zolbetuximab	24 (77.4)	184 (74.2)	15 (62.5)	125 (54.3)
Cape, 5-FU, (*l*-)LV or L-OHP	14 (45.2)	141 (56.9)	17 (70.8)	117 (50.9)
Adverse events leading to dose reduction[*2]	21 (67.7)	122 (49.2)	10 (41.7)	103 (44.8)
Adverse events leading to slower infusion rate[*3]	6 (19.4)	39 (15.7)	4 (16.7)	41 (17.8)

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab

Table 45 and Table 46 show adverse events for which the incidence was higher in Japanese patients than in non-Japanese patients in the zolbetuximab group of the SPOTLIGHT and GLOW studies. In either study, there were no adverse events leading to death with a ≥5% higher incidence in Japanese patients than in non-Japanese patients. There were no serious adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients in the SPOTLIGHT study or adverse events leading to slower infusion rate of zolbetuximab with a ≥5% higher incidence in Japanese patients than in non-Japanese patients in the GLOW study.

Table 45. Adverse events for which the incidence was higher in Japanese patients than in non-Japanese patients (zolbetuximab group in SPOTLIGHT study)

PT (MedDRA ver.25.0)	Number of patients (%)	
	Japanese patients n = 31	Non-Japanese patients n = 248
All-grade adverse events[*1]		
Peripheral sensory neuropathy	23 (74.2)	83 (33.5)
Decreased appetite	22 (71.0)	109 (44.0)
Neutrophil count decreased	18 (58.1)	77 (31.0)
Malaise	11 (35.5)	10 (4.0)
Hiccups	8 (25.8)	8 (3.2)
Grade ≥3 adverse events[*2]		
Neutrophil count decreased	17 (54.8)	52 (21.0)
Adverse events leading to treatment discontinuation[*2,3]		
Neutrophil count decreased	6 (19.4)	12 (4.8)
Adverse events leading to treatment interruption[*2,3]		
Neutrophil count decreased	6 (19.4)	24 (9.7)
Decreased appetite	3 (9.7)	6 (2.4)
Drug hypersensitivity	2 (6.5)	1 (0.4)
Adverse events leading to dose reduction[*2,4]		
Neutrophil count decreased	9 (29.0)	28 (11.3)
Decreased appetite	6 (19.4)	5 (2.0)
Febrile neutropenia	2 (6.5)	3 (1.2)
Malaise	2 (6.5)	0
Adverse events leading to slower infusion rate[*2,5]		
Vomiting	5 (16.1)	16 (6.5)

*1 Events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients
*2 Events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients
*3 Adverse events leading to discontinuation or interruption of any of the study drugs
*4 Adverse events leading to dose reduction of any of 5-FU, (*l*-)LV, and L-OHP
*5 Adverse events leading to slower infusion rate of zolbetuximab

Table 46. Adverse events for which the incidence was higher in Japanese patients than in non-Japanese patients (zolbetuximab group in GLOW study)

PT (MedDRA ver.25.0)	Number of patients (%)	
	Japanese patients n = 24	Non-Japanese patients n = 230
All-grade adverse events[*1]		
Peripheral sensory neuropathy	19 (79.2)	37 (16.1)
Grade ≥3 adverse events[*2]		
Decreased appetite	3 (12.5)	14 (6.1)
Diarrhoea	3 (12.5)	12 (5.2)
Hypoalbuminaemia	3 (12.5)	5 (2.2)
Neutropenia	3 (12.5)	15 (6.5)
Hepatic function abnormal	2 (8.3)	0
Serious adverse events[*2]		
Decreased appetite	3 (12.5)	7 (3.0)
Hepatic function abnormal	2 (8.3)	0
Adverse events leading to treatment discontinuation[*2,3]		
Neutropenia	2 (8.3)	2 (0.9)
Peripheral sensory neuropathy	2 (8.3)	3 (1.3)
Adverse events leading to treatment interruption[*2,3]		
Nausea	8 (33.3)	47 (20.4)
Decreased appetite	4 (16.7)	8 (3.5)
Diarrhoea	3 (12.5)	12 (5.2)
Neutrophil count decreased	3 (12.5)	16 (7.0)
Hypoalbuminaemia	2 (8.3)	2 (0.9)
Infusion site extravasation	2 (8.3)	0
Adverse events leading to dose reduction[*2,4]		
Neutropenia	3 (12.5)	8 (3.5)

*1 Events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients
*2 Events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients
*3 Adverse events leading to discontinuation or interruption of any of the study drugs
*4 Adverse events leading to dose reduction of either Cape or L-OHP

The applicant's explanation about adverse events for which the incidence was higher in Japanese patients than in non-Japanese patients:

- In both studies, the incidence of peripheral sensory neuropathy was higher in Japanese patients than in non-Japanese patients, but the higher incidence might have been influenced by L-OHP included in the concomitant chemotherapy. L-OHP is known to pose a risk of peripheral sensory neuropathy, which is manageable by interruption, etc. Peripheral sensory neuropathy associated with zolbetuximab/chemotherapy is also manageable.
- Although the incidence of neutrophil count decreased was higher in Japanese patients than in non-Japanese patients in the SPOTLIGHT study, the incidence of neutropenia was higher in non-Japanese patients than in Japanese patients. Overall evaluation on these related events does not indicate any clear difference between Japanese and non-Japanese patients.
- The incidences of decreased appetite, hiccups, and malaise were higher in Japanese patients than in non-Japanese patients. Although the reasons for the higher incidences remain unknown, serious events were limited. These events are manageable by interruption of zolbetuximab and concomitant chemotherapy.

PMDA's view:

Although there were limitations to compare safety profiles between Japanese and non-Japanese patients due to the limited number of Japanese patients who received zolbetuximab, there were events with a higher incidence in Japanese patients than in non-Japanese patients in the SPOTLIGHT and GLOW

studies, and attention should be paid to these events during the use of zolbetuximab. However, examinations of related events, such as neutrophil count decreased and neutropenia, in which the incidence was higher in Japanese patients than in non-Japanese patients have shown no clear differences between Japanese and non-Japanese patients; and possible influences of concomitant chemotherapy is also considered. PMDA concluded that zolbetuximab is tolerable in Japanese patients, considering that zolbetuximab is used by physicians with adequate knowledge and experience in cancer chemotherapy.

In the following subsections, PMDA reviewed the safety results in studies including the SPOTLIGHT and GLOW studies with the focus on adverse events with a higher incidence in the zolbetuximab group.

7.R.3.4 Nausea and vomiting

The applicant's explanation about nausea and vomiting associated with zolbetuximab:
Events classified into "nausea," "vomiting," "vomiting projectile," "retching,"[30] and "cyclic vomiting syndrome," preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA), were tabulated as nausea and vomiting.

Table 47 and Table 48 show incidences of nausea and vomiting in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of nausea and vomiting was 1 (1, 755) in the zolbetuximab group and 10 (1, 326) in the placebo group of the SPOTLIGHT study, and 1 (1, 217) in the zolbetuximab group and 3 (1, 253) in the placebo group of the GLOW study.

Table 47. Incidences of nausea and vomiting (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea and vomiting*	249 (89.2)	61 (21.9)	188 (67.6)	24 (8.6)	208 (81.9)	42 (16.5)	149 (59.8)	10 (4.0)
Nausea	230 (82.4)	45 (16.1)	169 (60.8)	18 (6.5)	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	188 (67.4)	45 (16.1)	99 (35.6)	16 (5.8)	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)
Retching	6 (2.2)	1 (0.4)	3 (1.1)	0	1 (0.4)	0	0	0

* All events included in tabulation

[30] Gagging

Table 48. Incidences of serious nausea and vomiting (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal nausea and vomiting	0	0	0	0
Serious nausea and vomiting	28 (10.0)	16 (5.8)	21 (8.3)	13 (5.2)
Vomiting	23 (8.2)	13 (4.7)	15 (5.9)	11 (4.4)
Nausea	19 (6.8)	11 (4.0)	11 (4.3)	6 (2.4)
Retching	1 (0.4)	1 (0.4)	0	0
Serious nausea and vomiting for which a causal relationship to the study drug cannot be ruled out	24 (8.6)	6 (2.2)	20 (7.9)	11 (4.4)
Vomiting	19 (6.8)	4 (1.4)	14 (5.5)	8 (3.2)
Nausea	17 (6.1)	3 (1.1)	11 (4.3)	6 (2.4)
Retching	1 (0.4)	1 (0.4)	0	0
Nausea and vomiting leading to treatment discontinuation[*1]	27 (9.7)	3 (1.1)	11 (4.3)	5 (2.0)
Vomiting	20 (7.2)	1 (0.4)	9 (3.5)	4 (1.6)
Nausea	18 (6.5)	3 (1.1)	6 (2.4)	3 (1.2)
Retching	1 (0.4)	0	0	0
Nausea and vomiting leading to treatment interruption[*1]	134 (48.0)	12 (4.3)	92 (36.2)	16 (6.4)
Nausea and vomiting leading to dose reduction[*2]	14 (5.0)	10 (3.6)	20 (7.9)	7 (2.8)
Nausea and vomiting leading to slower infusion rate[*3]	40 (14.3)	1 (0.4)	37 (14.6)	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

The clinical study data submitted for the present application were found to include no Grade ≥4 serious nausea or vomiting for which a causal relationship to zolbetuximab could not be ruled out.

In the SPOTLIGHT and GLOW studies, the incidence of nausea and vomiting was higher in patients without prior gastrectomy than in patients with prior gastrectomy in the zolbetuximab group [see Section 7.R.3.2].

The applicant's explanation about risk factors of nausea and vomiting during use of zolbetuximab in view of the above finding:
Table 49 and Table 50 show incidences of events classified into MedDRA PTs of "nausea" and "vomiting" according to prior gastrectomy (patients without prior gastrectomy, patients with prior partial gastrectomy, and patients with prior total gastrectomy). The incidences of nausea and vomiting tended to be higher in patients without prior gastrectomy than in patients with prior partial gastrectomy or with prior total gastrectomy. Prior gastrectomy, however, is not considered as a risk factor of nausea and vomiting during use of zolbetuximab, because (a) a difference in incidence of nausea or vomiting between the groups varied from study to study; and (b) comparison in incidence between patients with partial gastrectomy and patients without prior gastrectomy did not indicate any consistent and substantial trend.

Table 49. Incidences of nausea and vomiting in patients with or without prior gastrectomy (SPOTLIGHT study)

PT (MedDRA ver.25.0)	Number of patients (%)					
	Patients without prior gastrectomy		Patients with prior partial gastrectomy		Patients with prior total gastrectomy	
	Zolbetuximab n = 197	Placebo n = 196	Zolbetuximab n = 41	Placebo n = 42	Zolbetuximab n = 41	Placebo n = 40
All-grade adverse events						
Nausea	166 (84.3)	113 (57.7)	35 (85.4)	29 (69.0)	29 (70.7)	27 (67.5)
Vomiting	149 (75.6)	72 (36.7)	22 (53.7)	14 (33.3)	17 (41.5)	13 (32.5)
Grade ≥3 adverse events						
Nausea	35 (17.8)	13 (6.6)	8 (19.5)	4 (9.5)	2 (4.9)	1 (2.5)
Vomiting	38 (19.3)	11 (5.6)	4 (9.8)	3 (7.1)	3 (7.3)	2 (5.0)
Serious adverse events						
Nausea	17 (8.6)	8 (4.1)	1 (2.4)	1 (2.4)	1 (2.4)	2 (5.0)
Vomiting	22 (11.2)	9 (4.6)	1 (2.4)	1 (2.4)	0	3 (7.5)
Adverse events leading to slower infusion rate*						
Nausea	23 (11.7)	1 (0.5)	5 (12.2)	0	2 (4.9)	0
Vomiting	18 (9.1)	1 (0.5)	2 (4.9)	0	1 (2.4)	0

* Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 50. Incidences of nausea and vomiting in patients with or without prior gastrectomy (GLOW study)

PT (MedDRA ver.25.0)	Number of patients (%)					
	Patients without prior gastrectomy		Patients with prior partial gastrectomy		Patients with prior total gastrectomy	
	Zolbetuximab n = 181	Placebo n = 183	Zolbetuximab n = 47	Placebo n = 29	Zolbetuximab n = 26	Placebo n = 37
All-grade adverse events						
Nausea	131 (72.4)	90 (49.2)	28 (59.6)	14 (48.3)	15 (57.7)	21 (56.8)
Vomiting	130 (71.8)	54 (29.5)	31 (66.0)	11 (37.9)	7 (26.9)	12 (32.4)
Grade ≥3 adverse events						
Nausea	18 (9.9)	6 (3.3)	3 (6.4)	0	1 (3.8)	0
Vomiting	26 (14.4)	9 (4.9)	5 (10.6)	0	0	0
Serious adverse events						
Nausea	9 (5.0)	6 (3.3)	2 (4.3)	0	0	0
Vomiting	12 (6.6)	10 (5.5)	3 (6.4)	1 (3.4)	0	0
Adverse events leading to slower infusion rate*						
Nausea	21 (11.6)	0	5 (10.6)	0	0	0
Vomiting	21 (11.6)	0	5 (10.6)	0	0	0

* Adverse events leading to slower infusion rate of zolbetuximab or placebo

The applicant's explanation about antiemetic medication for management of nausea and vomiting associated with zolbetuximab:

In the SPOTLIGHT and GLOW studies, neurokinin $(NK)_1$ or 5-hydroxytryptamine $(5\text{-}HT)_3$ receptor antagonists were recommended as antiemetics, and no or minimum use of corticosteroids was allowed for the reasons described below. Use of antihistamines for antiemetic medication was not specified.

- NK_1 and $5\text{-}HT_3$ receptor antagonists are standard antiemetics used during chemotherapy.
- Corticosteroids may weaken ADCC of zolbetuximab.

In the SPOTLIGHT and GLOW studies, proportions of patients in the zolbetuximab group who received antiemetics before the first dose of zolbetuximab for primary prevention were 64.5% and 55.9% for NK_1 receptor antagonists, 94.3% and 98.4% for $5\text{-}HT_3$ receptor antagonists, 18.3% and 20.1% for antihistamines, and 29.7% and 33.1% for corticosteroids, respectively. Table 51 and Table 52 show incidences of nausea and vomiting on the day of the first dose according to using or not using antiemetic medication for the primary prevention.

Table 51. Incidences of nausea and vomiting on the day of the first dose by the use of antiemetics for the primary prevention (SPOTLIGHT study)

Antiemetic*	Use	No. of patients	Number of patients (%)		
			All-grade nausea and vomiting	Grade ≥3 nausea and vomiting	Serious nausea and vomiting
NK_1 receptor antagonists	Yes	180	108 (60.0)	14 (7.8)	5 (2.8)
	No	96	60 (62.5)	15 (15.6)	5 (5.2)
5-HT_3 receptor antagonists	Yes	263	162 (61.6)	29 (11.0)	10 (3.8)
	No	13	6 (46.2)	0	0
Antihistamines	Yes	51	31 (60.8)	6 (11.8)	1 (2.0)
	No	225	137 (60.9)	23 (10.2)	9 (4.0)
Corticosteroids	Yes	83	44 (53.0)	9 (10.8)	1 (1.2)
	No	193	124 (64.2)	20 (10.4)	9 (4.7)

* Of 8 patients who did not receive any of the above antiemetics, 4 patients experienced nausea and vomiting.

Table 52. Incidences of nausea and vomiting on the day of the first dose by the use of antiemetics for the primary prevention (GLOW study)

Antiemetic*	Use	No. of patients	Number of patients (%)		
			All-grade nausea and vomiting	Grade ≥3 nausea and vomiting	Serious nausea and vomiting
NK_1 receptor antagonists	Yes	142	80 (56.3)	10 (7.0)	5 (3.5)
	No	111	74 (66.7)	9 (8.1)	1 (0.9)
5-HT_3 receptor antagonists	Yes	250	152 (60.8)	18 (7.2)	5 (2.0)
	No	3	2 (66.7)	1 (33.3)	1 (33.3)
Antihistamines	Yes	51	28 (54.9)	3 (5.9)	0
	No	202	126 (62.4)	16 (7.9)	6 (3.0)
Corticosteroids	Yes	84	46 (54.8)	6 (7.1)	0
	No	169	108 (63.9)	13 (7.7)	6 (3.6)

* Of 2 patients who did not receive any of the above antiemetics, 2 patients experienced nausea and vomiting.

The hazard ratio of zolbetuximab to placebo in the subgroup of patients receiving corticosteroids was 0.785 in the SPOTLIGHT study and 0.592 in the GLOW study for PFS, and 0.674 in the SPOTLIGHT study and 0.646 in the GLOW study for OS, the above is an exploratory analysis, and interpretation of the results are considered to have limitations, which had a similar trend to those in the overall population (0.751 in the SPOTLIGHT study and 0.687 in the GLOW study for PFS, and 0.750 in the SPOTLIGHT study and 0.771 in the GLOW study for OS).

Taking account of these findings, NK_1 and 5-HT_3 receptor antagonists should be recommended to prevent nausea and vomiting during use of zolbetuximab, as specified in the SPOTLIGHT and GLOW studies. Thus, there is no need to restrict the use of antihistamines and corticosteroids administered at the discretion of attending physicians.

PMDA's view:

The submitted clinical study data showed that the incidences of Grade ≥3 nausea and vomiting and nausea and vomiting leading to treatment discontinuation or interruption tended to be higher in the zolbetuximab group than in the placebo group; and multiple patients experienced serious nausea and vomiting for which a causal relationship to zolbetuximab could not be ruled out. Taking account of the above, attention should be paid to nausea and vomiting during the use of zolbetuximab. Accordingly, the applicant should raise caution among healthcare professionals appropriately by providing the package insert information, etc. on incidences of nausea and vomiting and the related management method in the clinical studies.

Regarding a risk of nausea and vomiting in patient with or without prior gastrectomy, the following findings were obtained, although the number of patients with prior gastrectomy is limited, requiring careful examination: (a) The incidence of nausea and vomiting tended to be higher in patients without prior gastrectomy than in patients with prior gastrectomy generally in both the SPOTLIGHT and GLOW studies; and (b) furthermore, in the subgroup of patients with prior gastrectomy, the incidence of nausea and vomiting tended to be higher in patients with prior partial gastrectomy than in patients with prior total gastrectomy. The above information, which is considered important in managing nausea and vomiting during use of zolbetuximab, should be provided to healthcare professionals through materials.

The presented results show little evidence on the use of specific antiemetics recommended during zolbetuximab treatment, therefore, information about settings of the clinical studies, incidences of nausea and vomiting by type of antiemetics in the clinical studies, and efficacy in patients using or not using corticosteroids should be provided through materials to help attending physicians select antiemetics.

7.R.3.5 Infusion reaction

The applicant's explanation about infusion reaction associated with zolbetuximab:
The following events that were classified into MedDRA PTs and occurred on the day or the following day of zolbetuximab treatment were tabulated as infusion reaction: "Abdominal pain," "abdominal pain upper," "administration related reaction," "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "angioedema," "asthenia," "back pain," "blood pressure increased," "bronchospasm," "chest discomfort," "chest pain," "chills," "cough," "diarrhoea," "dizziness," "drug eruption," "drug hypersensitivity," "dyspepsia," "dyspnoea," "epiglottic oedema," "erythema," "fatigue," "fixed eruption," "flushing," "headache," "hot flush," "hyperhidrosis," "hypertension," "hypotension," "immediate post-injection reaction," "infusion related hypersensitivity reaction," "infusion related reaction," "injection related reaction," "laryngeal oedema," "laryngospasm," "laryngotracheal oedema," "malaise," "non-cardiac chest pain," "pruritus," "pyrexia," "rash," "salivary hypersecretion," "tachycardia," and "urticaria."

Table 53 and Table 54 show incidences of infusion reaction in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of infusion reaction was 2 (1, 615) in the zolbetuximab group and 39 (1, 377) in the placebo group of the SPOTLIGHT study, and 2 (1, 519) in the zolbetuximab group and 22 (1, 848) in the placebo group of the GLOW study.

Table 53. Incidences of infusion reaction (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction*	179 (64.2)	36 (12.9)	129 (46.4)	10 (3.6)	141 (55.5)	18 (7.1)	107 (43.0)	7 (2.8)
Fatigue	44 (15.8)	6 (2.2)	31 (11.2)	2 (0.7)	19 (7.5)	1 (0.4)	20 (8.0)	1 (0.4)
Diarrhoea	38 (13.6)	0	43 (15.5)	3 (1.1)	26 (10.2)	2 (0.8)	35 (14.1)	2 (0.8)
Abdominal pain	35 (12.5)	6 (2.2)	23 (8.3)	0	17 (6.7)	0	17 (6.8)	0
Asthenia	27 (9.7)	3 (1.1)	25 (9.0)	1 (0.4)	21 (8.3)	2 (0.8)	15 (6.0)	0
Hypertension	26 (9.3)	12 (4.3)	11 (4.0)	4 (1.4)	15 (5.9)	6 (2.4)	5 (2.0)	2 (0.8)
Abdominal pain upper	24 (8.6)	2 (0.7)	5 (1.8)	0	12 (4.7)	0	4 (1.6)	0
Pyrexia	14 (5.0)	0	9 (3.2)	0	13 (5.1)	1 (0.4)	4 (1.6)	0
Chills	13 (4.7)	2 (0.7)	2 (0.7)	0	10 (3.9)	0	4 (1.6)	0
Dizziness	13 (4.7)	0	5 (1.8)	0	7 (2.8)	0	6 (2.4)	0
Dyspepsia	11 (3.9)	1 (0.4)	5 (1.8)	0	5 (2.0)	0	3 (1.2)	0
Headache	11 (3.9)	0	13 (4.7)	0	3 (1.2)	0	3 (1.2)	0
Back pain	10 (3.6)	0	4 (1.4)	0	3 (1.2)	0	4 (1.6)	0
Cough	9 (3.2)	0	6 (2.2)	0	2 (0.8)	0	0	0
Malaise	8 (2.9)	0	2 (0.7)	0	23 (9.1)	1 (0.4)	18 (7.2)	0
Dyspnoea	7 (2.5)	0	6 (2.2)	0	6 (2.4)	0	1 (0.4)	0
Hypotension	7 (2.5)	0	5 (1.8)	0	7 (2.8)	1 (0.4)	2 (0.8)	0
Pruritus	7 (2.5)	0	12 (4.3)	0	5 (2.0)	0	4 (1.6)	0
Salivary hypersecretion	7 (2.5)	0	0	0	7 (2.8)	0	0	0
Chest pain	6 (2.2)	0	0	0	1 (0.4)	0	0	0
Hyperhidrosis	6 (2.2)	1 (0.4)	1 (0.4)	0	2 (0.8)	0	1 (0.4)	0
Blood pressure increased	5 (1.8)	3 (1.1)	0	0	1 (0.4)	0	1 (0.4)	0
Chest discomfort	5 (1.8)	1 (0.4)	0	0	9 (3.5)	0	5 (2.0)	0
Erythema	5 (1.8)	0	7 (2.5)	0	2 (0.8)	0	2 (0.8)	0
Flushing	5 (1.8)	0	4 (1.4)	0	4 (1.6)	0	0	0
Hot flush	5 (1.8)	0	3 (1.1)	0	0	0	0	0
Infusion related reaction	5 (1.8)	1 (0.4)	2 (0.7)	0	11 (4.3)	0	2 (0.8)	0
Non-cardiac chest pain	5 (1.8)	0	1 (0.4)	0	4 (1.6)	0	0	0
Rash	5 (1.8)	0	5 (1.8)	0	4 (1.6)	0	3 (1.2)	0
Tachycardia	4 (1.4)	0	0	0	1 (0.4)	0	1 (0.4)	0
Drug hypersensitivity	3 (1.1)	1 (0.4)	2 (0.7)	0	1 (0.4)	0	3 (1.2)	1 (0.4)
Bronchospasm	1 (0.4)	0	0	0	0	0	0	0
Anaphylactic reaction	0	0	1 (0.4)	0	3 (1.2)	3 (1.2)	4 (1.6)	2 (0.8)
Laryngospasm	0	0	1 (0.4)	0	0	0	2 (0.8)	0
Urticaria	0	0	5 (1.8)	1 (0.4)	0	0	0	0
Drug eruption	0	0	0	0	2 (0.8)	1 (0.4)	0	0

* All events included in tabulation

Table 54. Incidences of serious infusion reaction (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal infusion reaction	0	0	0	0
Serious infusion reaction	4 (1.4)	4 (1.4)	6 (2.4)	7 (2.8)
Serious infusion reaction for which a causal relationship to the study drug cannot be ruled out	4 (1.4)	3 (1.1)	4 (1.6)	6 (2.4)
Pyrexia	2 (0.7)	1 (0.4)	0	0
Abdominal pain	1 (0.4)	1 (0.4)	0	0
Chest pain	1 (0.4)	0	0	0
Hyperhidrosis	1 (0.4)	0	0	0
Hypotension	1 (0.4)	0	1 (0.4)	0
Infusion related reaction	1 (0.4)	0	1 (0.4)	0
Fatigue	0	1 (0.4)	0	0
Anaphylactic reaction	0	0	2 (0.8)	1 (0.4)
Flushing	0	0	1 (0.4)	0
Malaise	0	0	1 (0.4)	1 (0.4)
Pruritus	0	0	1 (0.4)	0
Diarrhoea	0	0	0	2 (0.8)
Drug hypersensitivity	0	0	0	1 (0.4)
Laryngospasm	0	0	0	1 (0.4)
Infusion reaction leading to treatment discontinuation[*1]	8 (2.9)	5 (1.8)	13 (5.1)	2 (0.8)
Abdominal pain[*2]	0	0	3 (1.2)	0
Anaphylactic reaction[*2]	0	0	3 (1.2)	1 (0.4)
Chest discomfort[*2]	0	0	2 (0.8)	1 (0.4)
Malaise[*2]	0	0	2 (0.8)	0
Infusion reaction leading to treatment interruption[*1]	79 (28.3)	18 (6.5)	44 (17.3)	10 (4.0)
Abdominal pain[*3]	16 (5.7)	0	10 (3.9)	0
Hypertension[*3]	16 (5.7)	1 (0.4)	1 (0.4)	1 (0.4)
Abdominal pain upper[*3]	13 (4.7)	0	4 (1.6)	0
Chills[*3]	8 (2.9)	0	6 (2.4)	1 (0.4)
Headache[*3]	6 (2.2)	1 (0.4)	1 (0.4)	0
Infusion related reaction[*3]	2 (0.7)	2 (0.7)	5 (2.0)	0
Infusion reaction leading to dose reduction[*4]	2 (0.7)	4 (1.4)	9 (3.5)	7 (2.8)
Infusion reaction leading to slower infusion rate[*5]	7 (2.5)	1 (0.4)	11 (4.3)	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events reported by ≥2 patients in the zolbetuximab group
*3 Adverse events reported by ≥2% of patients in the zolbetuximab group
*4 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*5 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 55 shows details of patients who experienced a serious infusion reaction for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 55. List of patients who experienced a serious infusion reaction for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	6[redacted]	Female	FOLFOX	Chest pain	2	22	2	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Abdominal pain	3	105	1	Interruption	Resolved
				Hyperhidrosis	3	105	1	Interruption	Resolved
	6[redacted]	Male	FOLFOX	Infusion related reaction	2	36	3	Unchanged	Resolved
GLOW	6[redacted]	Female	CAPOX	Anaphylactic reaction	3	1	2	Discontinuation	Resolved
	5[redacted]	Male	CAPOX	Flushing	1	29	1	Discontinuation	Resolved
				Pruritus	1	29	1	Discontinuation	Resolved
				Malaise	1	29	1	Discontinuation	Resolved
				Hypotension	1	29	1	Discontinuation	Resolved
	7[redacted]	Male	CAPOX	Infusion related reaction	2	134	2	Unchanged	Resolved
0103	6[redacted]	Male	None	Drug hypersensitivity	2	24	2	Discontinuation	Resolved
	5[redacted]	Male	FOLFOX	Infusion related reaction	2	3	1	Interruption	Resolved

* MedDRA ver.25.0 (SPOTLIGHT and GLOW studies), MedDRA ver.23.0 (Study 0103)

In the SPOTLIGHT and GLOW studies, premedication to suppress infusion reaction during use of zolbetuximab was not specified. Proportions of patients in the zolbetuximab group who received antihistamines or corticosteroids before the first dose of zolbetuximab were 25.4% in the SPOTLIGHT study and 37.0% in the GLOW study for antihistamines, and 32.3% in the SPOTLIGHT study and 36.6% in the GLOW study for corticosteroids.

PMDA's view:
The submitted clinical study data showed that multiple patients experienced a serious infusion reaction for which a causal relationship to zolbetuximab could not be ruled out; and the incidences of Grade ≥3 infusion reaction, etc. were higher in the zolbetuximab group than in the placebo group, therefore, attention should be paid to infusion reaction during use of zolbetuximab. Accordingly, the applicant should raise caution among healthcare professionals appropriately by providing the package insert information, etc. on incidences of infusion reaction and the related management method in the clinical studies.

7.R.3.6 Hypersensitivity

The applicant's explanation about hypersensitivity associated with zolbetuximab:
Events classified into MedDRA standardised MedDRA queries (SMQ) of "hypersensitivity" were tabulated as hypersensitivity.

Table 56 and Table 57 show incidences of hypersensitivity in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of hypersensitivity was 41 (1, 520) in the zolbetuximab group and 59 (1, 706) in the placebo group of the SPOTLIGHT study, and 26.5 (1, 519) in the zolbetuximab group and 48 (1, 256) in the placebo group of the GLOW study.

Table 56. Incidences of hypersensitivity reported by ≥2% of patients in any group (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity*	133 (47.7)	20 (7.2)	125 (45.0)	6 (2.2)	58 (22.8)	7 (2.8)	45 (18.1)	7 (2.8)
Stomatitis	58 (20.8)	7 (2.5)	57 (20.5)	3 (1.1)	8 (3.1)	0	7 (2.8)	0
Pruritus	24 (8.6)	0	24 (8.6)	0	9 (3.5)	0	8 (3.2)	0
Rash	18 (6.5)	1 (0.4)	22 (7.9)	0	5 (2.0)	0	6 (2.4)	1 (0.4)
Rash maculo-papular	8 (2.9)	0	15 (5.4)	1 (0.4)	5 (2.0)	0	7 (2.8)	0
Flushing	7 (2.5)	0	5 (1.8)	0	4 (1.6)	0	0	0
Erythema	7 (2.5)	0	10 (3.6)	0	3 (1.2)	0	3 (1.2)	0
Conjunctivitis	7 (2.5)	0	3 (1.1)	0	1 (0.4)	0	1 (0.4)	0
Infusion related reaction	6 (2.2)	2 (0.7)	5 (1.8)	0	11 (4.3)	0	2 (0.8)	0
Mouth ulceration	6 (2.2)	1 (0.4)	3 (1.1)	0	4 (1.6)	0	2 (0.8)	1 (0.4)
Dermatitis acneiform	6 (2.2)	0	2 (0.7)	0	2 (0.8)	0	0	0
Urticaria	4 (1.4)	0	9 (3.2)	1 (0.4)	4 (1.6)	0	0	0
Drug hypersensitivity	4 (1.4)	1 (0.4)	6 (2.2)	0	2 (0.8)	0	3 (1.2)	1 (0.4)

* All events included in tabulation

Table 57. Incidences of serious hypersensitivity (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal hypersensitivity	3 (1.1)	0	0	1 (0.4)
Respiratory failure	2 (0.7)	0	0	1 (0.4)
Acute respiratory failure	1 (0.4)	0	0	0
Fatal hypersensitivity for which a causal relationship to the study drug cannot be ruled out	1 (0.4)	0	0	0
Respiratory failure	1 (0.4)	0	0	0
Serious hypersensitivity	11 (3.9)	2 (0.7)	8 (3.1)	6 (2.4)
Acute respiratory failure	3 (1.1)	0	0	0
Respiratory failure	3 (1.1)	0	1 (0.4)	2 (0.8)
Hypersensitivity	1 (0.4)	0	0	0
Infusion related reaction	1 (0.4)	0	2 (0.8)	0
Lip swelling	1 (0.4)	0	0	0
Rash	1 (0.4)	0	0	0
Stomatitis	1 (0.4)	1 (0.4)	0	0
Anaphylactic reaction	0	0	2 (0.8)	1 (0.4)
Cutaneous vasculitis	0	0	1 (0.4)	0
Drug hypersensitivity	0	1 (0.4)	0	1 (0.4)
Flushing	0	0	1 (0.4)	0
Laryngospasm	0	0	0	1 (0.4)
Mouth ulceration	0	0	0	1 (0.4)
Pruritus	0	0	1 (0.4)	0
Skin necrosis	0	0	1 (0.4)	0
Swollen tongue	0	0	1 (0.4)	0
Serious hypersensitivity for which a causal relationship to the study drug cannot be ruled out	4 (1.4)	2 (0.7)	7 (2.8)	4 (1.6)
Infusion related reaction	1 (0.4)	0	2 (0.8)	0
Lip swelling	1 (0.4)	0	0	0
Respiratory failure	1 (0.4)	0	0	0
Stomatitis	1 (0.4)	1 (0.4)	0	0
Drug hypersensitivity	0	1 (0.4)	0	1 (0.4)
Anaphylactic reaction	0	0	2 (0.8)	1 (0.4)
Cutaneous vasculitis	0	0	1 (0.4)	0
Flushing	0	0	1 (0.4)	0
Pruritus	0	0	1 (0.4)	0
Skin necrosis	0	0	1 (0.4)	0
Swollen tongue	0	0	1 (0.4)	0
Laryngospasm	0	0	0	1 (0.4)
Mouth ulceration	0	0	0	1 (0.4)
Hypersensitivity leading to treatment discontinuation*1	10 (3.6)	12 (4.3)	7 (2.8)	2 (0.8)
Hypersensitivity leading to treatment interruption*1	22 (7.9)	17 (6.1)	15 (5.9)	7 (2.8)
Hypersensitivity leading to dose reduction*2	8 (2.9)	2 (0.7)	4 (1.6)	0
Hypersensitivity leading to slower infusion rate*3	2 (0.7)	0	1 (0.4)	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 58 shows details of patients who experienced serious hypersensitivity for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 58. List of patients who experienced serious hypersensitivity for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	7[redacted]	Male	FOLFOX	Respiratory failure	4	281	14	Unchanged	Not resolved
					5	294	1	Unchanged	Death
	7[redacted]	Female	FOLFOX	Stomatitis	3	151	17	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Lip swelling	3	48	2	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Infusion related reaction	2	36	3	Unchanged	Resolved
GLOW	6[redacted]	Female	CAPOX	Anaphylactic reaction	3	1	2	Discontinuation	Resolved
	4[redacted]	Female	CAPOX	Cutaneous vasculitis	3	30	8	Unchanged	Resolved
	5[redacted]	Male	CAPOX	Flushing	1	29	1	Discontinuation	Resolved
				Pruritus	1	29	1	Discontinuation	Resolved
				Swollen tongue	1	29	1	Discontinuation	Resolved
	5[redacted]	Male	CAPOX	Infusion related reaction	1	4	8	Interruption	Resolved
	7[redacted]	Male	CAPOX	Infusion related reaction	2	134	2	Unchanged	Resolved
0103	6[redacted]	Male	None	Drug hypersensitivity	2	24	2	Discontinuation	Resolved
	7[redacted]	Male	None	Anaphylactic reaction	3	36	2	Discontinuation	Resolved
	5[redacted]	Male	FOLFOX	Infusion related reaction	2	3	1	Interruption	Resolved

* MedDRA ver.25.0 (SPOTLIGHT and GLOW studies), MedDRA ver.23.0 (Study 0103)

PMDA's view:

The submitted clinical study data showed that hypersensitivity including Grade ≥3 events occurred during use of zolbetuximab at a certain incidence; and multiple patients experienced serious hypersensitivity for which a causal relationship to zolbetuximab could not be ruled out, therefore, attention should be paid to hypersensitivity during use of zolbetuximab. Accordingly, the applicant should raise caution among healthcare professionals appropriately by providing the package insert information, etc. on incidences of hypersensitivity and the related management method in the clinical studies.

7.R.3.7 Others

(a) Blood disorder

The applicant's explanation about blood disorder associated with zolbetuximab:

Events classified into MedDRA SMQ of "haematopoietic cytopenias (broad)," "haematopoietic leukopenia (broad)," and "haematopoietic thrombocytopenia (broad)" and MedDRA PTs of "febrile neutropenia," "haemophagocytic lymphohistiocytosis," "idiopathic neutropenia," "neutropenia," "neutropenic colitis," "neutropenic infection," "neutropenic sepsis," "neutrophil count decreased," and "thrombosis with thrombocytopenia syndrome" were tabulated as blood disorder.

Table 59 and Table 60 show incidences of blood disorder in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of blood disorder was 23 (1, 356) in the zolbetuximab group and 22 (1, 238) in the placebo group of the SPOTLIGHT study, and 47 (1, 407) in the zolbetuximab group and 45 (2, 551) in the placebo group of the GLOW study.

Table 59. Incidences of blood disorder (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood disorder*	214 (76.7)	157 (56.3)	217 (78.1)	143 (51.4)	169 (66.5)	78 (30.7)	157 (63.1)	72 (28.9)
Neutropenia	102 (36.6)	79 (28.3)	94 (33.8)	65 (23.4)	50 (19.7)	18 (7.1)	35 (14.1)	7 (2.8)
Anaemia	100 (35.8)	24 (8.6)	104 (37.4)	26 (9.4)	90 (35.4)	27 (10.6)	91 (36.5)	28 (11.2)
Neutrophil count decreased	95 (34.1)	69 (24.7)	91 (32.7)	69 (24.8)	70 (27.6)	26 (10.2)	59 (23.7)	24 (9.6)
White blood cell count decreased	50 (17.9)	8 (2.9)	46 (16.5)	16 (5.8)	51 (20.1)	5 (2.0)	39 (15.7)	9 (3.6)
Platelet count decreased	40 (14.3)	3 (1.1)	49 (17.6)	6 (2.2)	61 (24.0)	19 (7.5)	60 (24.1)	20 (8.0)
Thrombocytopenia	28 (10.0)	4 (1.4)	45 (16.2)	4 (1.4)	28 (11.0)	7 (2.8)	31 (12.4)	7 (2.8)
Leukopenia	15 (5.4)	7 (2.5)	12 (4.3)	3 (1.1)	17 (6.7)	0	8 (3.2)	1 (0.4)
Febrile neutropenia	8 (2.9)	8 (2.9)	1 (0.4)	1 (0.4)	0	0	3 (1.2)	3 (1.2)
Lymphocyte count decreased	5 (1.8)	0	4 (1.4)	0	8 (3.1)	0	5 (2.0)	2 (0.8)
Haemoglobin decreased	3 (1.1)	2 (0.7)	0	0	0	0	0	0
Lymphopenia	3 (1.1)	0	5 (1.8)	0	1 (0.4)	1 (0.4)	1 (0.4)	0
Neutropenic sepsis	1 (0.4)	1 (0.4)	0	0	0	0	1 (0.4)	1 (0.4)
Agranulocytosis	0	0	0	0	1 (0.4)	1 (0.4)	0	0
Eosinopenia	0	0	0	0	0	0	1 (0.4)	0
Red blood cell count decreased	0	0	0	0	0	0	2 (0.8)	0

* All events included in tabulation

Table 60. Incidences of serious blood disorder (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal blood disorder	1 (0.4)	0	1 (0.4)	2 (0.8)
Fatal blood disorder for which a causal relationship to the study drug cannot be ruled out	1 (0.4)	0	1 (0.4)	2 (0.8)
Neutropenic sepsis	1 (0.4)	0	0	1 (0.4)
Platelet count decreased	0	0	1 (0.4)	0
Febrile neutropenia	0	0	0	1 (0.4)
Serious blood disorder	18 (6.5)	12 (4.3)	20 (7.9)	18 (7.2)
Serious blood disorder for which a causal relationship to the study drug cannot be ruled out	18 (6.5)	7 (2.5)	14 (5.5)	12 (4.8)
Febrile neutropenia	8 (2.9)	1 (0.4)	0	1 (0.4)
Neutropenia	6 (2.2)	3 (1.1)	3 (1.2)	1 (0.4)
Anaemia	4 (1.4)	1 (0.4)	2 (0.8)	3 (1.2)
Neutropenic sepsis	1 (0.4)	0	0	1 (0.4)
Neutrophil count decreased	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)
Thrombocytopenia	1 (0.4)	0	0	2 (0.8)
Platelet count decreased	0	0	8 (3.1)	6 (2.4)
White blood cell count decreased	0	0	1 (0.4)	1 (0.4)
Leukopenia	0	0	0	1 (0.4)
Blood disorder leading to treatment discontinuation*1	37 (13.3)	33 (11.9)	13 (5.1)	13 (5.2)
Blood disorder leading to treatment interruption*1	92 (33.0)	94 (33.8)	73 (28.7)	62 (24.9)
Blood disorder leading to dose reduction*2	87 (31.2)	77 (27.7)	50 (19.7)	44 (17.7)
Blood disorder leading to slower infusion rate*3	0	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 61 shows details of patients who experienced Grade ≥3 serious blood disorder for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 61. List of patients who experienced Grade ≥3 serious blood disorder for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	5[redacted]	Male	FOLFOX	Febrile neutropenia	3	15	4	Unchanged	Resolved
	6[redacted]	Female	FOLFOX	Neutropenia	4	25	3	Unchanged	Resolved
	5[redacted]	Male	FOLFOX	Anaemia	3	12	Unknown	Interruption	Not resolved
				Febrile neutropenia	3	12	3	Interruption	Resolved
	5[redacted]	Male	FOLFOX	Neutropenic sepsis	5	50	1	Discontinuation	Death
	6[redacted]	Male	FOLFOX	Neutropenia	3	92	7	Interruption	Resolved
	4[redacted]	Female	FOLFOX	Neutropenia	4	15	2	Unchanged	Resolved
	4[redacted]	Female	FOLFOX	Febrile neutropenia	3	16	6	Unchanged	Resolved
	4[redacted]	Female	FOLFOX	Febrile neutropenia	3	20	5	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Neutrophil count decreased	4	19	3	Unchanged	Resolved
GLOW	6[redacted]	Male	CAPOX	Anaemia	3	26	10	Unchanged	Resolving
	7[redacted]	Male	CAPOX	Platelet count decreased	5	41	1	Unchanged	Death
				White blood cell count decreased	4	20	14	Unchanged	Not resolved
	7[redacted]	Male	CAPOX	Platelet count decreased	3	29	Unknown	Interruption	Not resolved
	6[redacted]	Male	CAPOX	Platelet count decreased	3	27	9	Unchanged	Resolving
	6[redacted]	Female	CAPOX	Platelet count decreased	4	66	5	Interruption	Not resolved
	6[redacted]	Male	CAPOX	Platelet count decreased	4	164	5	Interruption	Resolving
	5[redacted]	Male	CAPOX	Neutropenia	4	36	4	Unchanged	Resolved
0103	4[redacted]	Male	None	Anaemia	3	22	2	Unchanged	Resolved

* MedDRA ver.25.0 (SPOTLIGHT and GLOW studies), MedDRA ver.23.0 (Study 0103)

PMDA's view:

Although the submitted clinical study data showed that serious blood disorder for which a causal relationship to zolbetuximab could not be ruled out occurred, no special caution about blood disorder is required at present on the precondition that information on blood disorder in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) The incidences of fatal blood disorder and serious blood disorder did not tend to be clearly higher in the zolbetuximab group than in the placebo group; and (b) for most of the events, an influence of concomitant chemotherapy cannot be ruled out. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(b) Skin disorder

The applicant's explanation about skin disorder associated with zolbetuximab:

Events classified into MedDRA SMQ of "severe cutaneous adverse reactions (broad)" and MedDRA system organ class (SOC) of "skin and subcutaneous tissue disorders" were tabulated as skin disorder.

Table 62 and Table 63 show incidences of skin disorder in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of skin disorder was 36 (1, 436) in the zolbetuximab group and 43 (1, 404) in the placebo group of the SPOTLIGHT study, and 42.5 (1, 425) in the zolbetuximab group and 35.5 (1, 605) in the placebo group of the GLOW study.

Table 62. Incidences of skin disorder reported by ≥2% of patients in any group (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorder*	185 (66.3)	19 (6.8)	176 (63.3)	13 (4.7)	114 (44.9)	13 (5.1)	104 (41.8)	15 (6.0)
Stomatitis	58 (20.8)	7 (2.5)	57 (20.5)	3 (1.1)	8 (3.1)	0	7 (2.8)	0
Paraesthesia	44 (15.8)	6 (2.2)	46 (16.5)	4 (1.4)	13 (5.1)	1 (0.4)	11 (4.4)	0
Palmar-plantar erythrodysaesthesia syndrome	24 (8.6)	3 (1.1)	19 (6.8)	2 (0.7)	41 (16.1)	4 (1.6)	49 (19.7)	9 (3.6)
Pruritus	24 (8.6)	0	24 (8.6)	0	9 (3.5)	0	8 (3.2)	0
Alopecia	21 (7.5)	0	21 (7.6)	0	7 (2.8)	0	4 (1.6)	0
Rash	18 (6.5)	1 (0.4)	22 (7.9)	0	5 (2.0)	0	6 (2.4)	1 (0.4)
Dry skin	17 (6.1)	0	12 (4.3)	0	2 (0.8)	0	1 (0.4)	0
Hypoaesthesia	11 (3.9)	0	11 (4.0)	1 (0.4)	30 (11.8)	1 (0.4)	30 (12.0)	0
Hyperhidrosis	9 (3.2)	1 (0.4)	5 (1.8)	0	2 (0.8)	0	1 (0.4)	0
Dysaesthesia	8 (2.9)	0	13 (4.7)	2 (0.7)	7 (2.8)	0	5 (2.0)	0
Rash maculo-papular	8 (2.9)	0	15 (5.4)	1 (0.4)	5 (2.0)	0	7 (2.8)	0
Conjunctivitis	7 (2.5)	0	3 (1.1)	0	1 (0.4)	0	1 (0.4)	0
Erythema	7 (2.5)	0	10 (3.6)	0	3 (1.2)	0	3 (1.2)	0
Flushing	7 (2.5)	0	5 (1.8)	0	4 (1.6)	0	0	0
Contusion	6 (2.2)	1 (0.4)	2 (0.7)	0	0	0	0	0
Dermatitis acneiform	6 (2.2)	0	2 (0.7)	0	2 (0.8)	0	0	0
Herpes zoster	6 (2.2)	1 (0.4)	3 (1.1)	0	2 (0.8)	0	1 (0.4)	1 (0.4)
Mouth ulceration	6 (2.2)	1 (0.4)	3 (1.1)	0	4 (1.6)	0	2 (0.8)	1 (0.4)
Urticaria	4 (1.4)	0	9 (3.2)	1 (0.4)	4 (1.6)	0	0	0
Night sweats	2 (0.7)	0	6 (2.2)	1 (0.4)	0	0	0	0
Skin hyperpigmentation	1 (0.4)	0	8 (2.9)	0	4 (1.6)	0	2 (0.8)	0
Pigmentation disorder	1 (0.4)	0	0	0	6 (2.4)	0	3 (1.2)	0

* All events included in tabulation

Table 63. Incidences of serious skin disorder (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal skin disorder	0	0	0	0
Serious skin disorder	7 (2.5)	4 (1.4)	8 (3.1)	2 (0.8)
Serious skin disorder for which a causal relationship to the study drug cannot be ruled out	3 (1.1)	1 (0.4)	5 (2.0)	1 (0.4)
Hyperhidrosis	1 (0.4)	0	0	0
Lip swelling	1 (0.4)	0	0	0
Stomatitis	1 (0.4)	1 (0.4)	0	0
Cutaneous vasculitis	0	0	1 (0.4)	0
Flushing	0	0	1 (0.4)	0
Paraesthesia	0	0	1 (0.4)	0
Pruritus	0	0	1 (0.4)	0
Skin necrosis	0	0	1 (0.4)	0
Skin toxicity	0	0	1 (0.4)	0
Swollen tongue	0	0	1 (0.4)	0
Wound complication	0	0	1 (0.4)	0
Mouth ulceration	0	0	0	1 (0.4)
Skin disorder leading to treatment discontinuation*1	9 (3.2)	11 (4.0)	9 (3.5)	2 (0.8)
Skin disorder leading to treatment interruption*1	21 (7.5)	17 (6.1)	19 (7.5)	19 (7.6)
Skin disorder leading to dose reduction*2	19 (6.8)	9 (3.2)	19 (7.5)	18 (7.2)
Skin disorder leading to slower infusion rate*3	2 (0.7)	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 64 shows details of patients who experienced serious skin disorder for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 64. List of patients who experienced serious skin disorder for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	7[redacted]	Female	FOLFOX	Stomatitis	3	151	17	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Lip swelling	3	48	2	Unchanged	Resolved
	6[redacted]	Male	FOLFOX	Hyperhidrosis	3	105	1	Interruption	Resolved
GLOW	7[redacted]	Male	CAPOX	Wound complication	2	52	44	Interruption	Resolved
	4[redacted]	Female	CAPOX	Cutaneous vasculitis	3	30	8	Unchanged	Resolved
	5[redacted]	Male	CAPOX	Flushing	1	29	1	Discontinuation	Resolved
				Paraesthesia	1	29	1	Discontinuation	Resolved
				Pruritus	1	29	1	Discontinuation	Resolved
				Swollen tongue	1	29	1	Discontinuation	Resolved

* MedDRA ver.25.0

PMDA's view:

Although the submitted clinical study data showed that serious skin disorder for which a causal relationship to zolbetuximab could not be ruled out occurred, no special caution about skin disorder is required at present on the precondition that information on skin disorder in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) All of the events resolved in a relatively short period of time; and (b) the incidence of skin disorder did not tend to be clearly higher in the zolbetuximab group than in the placebo group. The applicant, however, should continue to gather

information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(c) Gastrointestinal disorder (other than nausea and vomiting)

The applicant's explanation about gastrointestinal disorder (other than nausea and vomiting) associated with zolbetuximab:

Events classified into MedDRA SMQs of "gastrointestinal nonspecific inflammation and dysfunctional conditions (broad),"[31] "gastrointestinal ulceration (narrow)," and "noninfectious diarrhoea (broad)," MedDRA high level term (HLT) of "stomatitis and ulceration," and MedDRA PTs of "abdominal discomfort," "abdominal distension," "abdominal pain," "abdominal pain lower," "abdominal pain upper," "abdominal symptom," "abdominal tenderness," "epigastric discomfort," and "gastrointestinal pain" were tabulated as gastrointestinal disorder (other than nausea and vomiting).

Table 65 and Table 66 show incidences of gastrointestinal disorder (other than nausea and vomiting) in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of gastrointestinal disorder (other than nausea and vomiting) was 14 (1, 618) in the zolbetuximab group and 16 (1, 502) in the placebo group of the SPOTLIGHT study, and 9 (1, 448) in the zolbetuximab group and 23 (1, 329) in the placebo group of the GLOW study.

Table 65. Incidences of gastrointestinal disorder (other than nausea and vomiting) reported by ≥3% of patients in any group (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorder (other than nausea and vomiting)*	213 (76.3)	42 (15.1)	224 (80.6)	30 (10.8)	159 (62.6)	23 (9.1)	155 (62.2)	31 (12.4)
Diarrhoea	110 (39.4)	12 (4.3)	122 (43.9)	9 (3.2)	80 (31.5)	15 (5.9)	86 (34.5)	18 (7.2)
Constipation	99 (35.5)	3 (1.1)	112 (40.3)	2 (0.7)	39 (15.4)	0	52 (20.9)	0
Abdominal pain	67 (24.0)	12 (4.3)	82 (29.5)	6 (2.2)	40 (15.7)	1 (0.4)	54 (21.7)	4 (1.6)
Stomatitis	58 (20.8)	7 (2.5)	57 (20.5)	3 (1.1)	8 (3.1)	0	7 (2.8)	0
Abdominal pain upper	47 (16.8)	4 (1.4)	32 (11.5)	0	23 (9.1)	0	13 (5.2)	1 (0.4)
Dyspepsia	26 (9.3)	1 (0.4)	18 (6.5)	0	12 (4.7)	0	8 (3.2)	1 (0.4)
Dysphagia	21 (7.5)	3 (1.1)	22 (7.9)	8 (2.9)	9 (3.5)	3 (1.2)	9 (3.6)	1 (0.4)
Abdominal distension	16 (5.7)	3 (1.1)	22 (7.9)	0	14 (5.5)	2 (0.8)	15 (6.0)	2 (0.8)
Gastrooesophageal reflux disease	12 (4.3)	0	15 (5.4)	0	9 (3.5)	0	4 (1.6)	0
Abdominal discomfort	9 (3.2)	0	7 (2.5)	0	6 (2.4)	0	8 (3.2)	0
Chest pain	9 (3.2)	0	5 (1.8)	0	2 (0.8)	0	2 (0.8)	0
Non-cardiac chest pain	9 (3.2)	1 (0.4)	11 (4.0)	0	6 (2.4)	0	1 (0.4)	0

* All events included in tabulation

[31] Except MedDRA PTs of "nausea," "vomiting," "vomiting projectile," and "retching"

Table 66. Incidences of serious gastrointestinal disorder (other than nausea and vomiting) (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal gastrointestinal disorder (other than nausea and vomiting)	0	0	0	1 (0.4)
Fatal gastrointestinal disorder (other than nausea and vomiting) for which a causal relationship to the study drug cannot be ruled out	0	0	0	1 (0.4)
Diarrhoea	0	0	0	1 (0.4)
Serious gastrointestinal disorder (other than nausea and vomiting)	16 (5.7)	23 (8.3)	19 (7.5)	23 (9.2)
Serious gastrointestinal disorder (other than nausea and vomiting) for which a causal relationship to the study drug cannot be ruled out	9 (3.2)	6 (2.2)	12 (4.7)	12 (4.8)
Diarrhoea	7 (2.5)	2 (0.7)	7 (2.8)	8 (3.2)
Abdominal pain	1 (0.4)	2 (0.7)	0	0
Chest pain	1 (0.4)	0	0	0
Stomatitis	1 (0.4)	1 (0.4)	0	0
Dysphagia	0	1 (0.4)	1 (0.4)	0
Enteritis	0	1 (0.4)	0	1 (0.4)
Colitis	0	0	2 (0.8)	0
Abdominal distension	0	0	1 (0.4)	0
Dyspepsia	0	0	1 (0.4)	0
Enterocolitis	0	0	0	2 (0.8)
Mouth ulceration	0	0	0	1 (0.4)
Gastrointestinal disorder (other than nausea and vomiting) leading to treatment discontinuation[*1]	7 (2.5)	5 (1.8)	11 (4.3)	4 (1.6)
Gastrointestinal disorder (other than nausea and vomiting) leading to treatment interruption[*1]	52 (18.6)	14 (5.0)	38 (15.0)	20 (8.0)
Gastrointestinal disorder (other than nausea and vomiting) leading to dose reduction[*2]	15 (5.4)	7 (2.5)	13 (5.1)	15 (6.0)
Gastrointestinal disorder (other than nausea and vomiting) leading to slower infusion rate[*3]	3 (1.1)	0	5 (2.0)	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 67 shows details of patients who experienced Grade ≥3 serious gastrointestinal disorder (other than nausea and vomiting) for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 67. List of patients who experienced Grade ≥3 serious gastrointestinal disorder for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	7[redacted]	Female	FOLFOX	Diarrhoea	3	151	17	Unchanged	Resolved
				Stomatitis	3	151	17	Unchanged	Resolved
	6[redacted]	Male		Diarrhoea	3	48	2	Unchanged	Resolved
	6[redacted]	Male		Abdominal pain	3	105	1	Interruption	Resolved
	4[redacted]	Female		Diarrhoea	3	14	5	Unchanged	Resolved
GLOW	7[redacted]	Male	CAPOX	Colitis	3	124	3	Unchanged	Resolved
	7[redacted]	Male		Diarrhoea	3	22	5	Unchanged	Resolved
	6[redacted]	Male		Abdominal distension	3	147	Unknown	Interruption	Not resolved
0103	3[redacted]	Female	None	Abdominal pain	3	5	6	Unchanged	Resolved

* MedDRA ver.25.0 (SPOTLIGHT and GLOW studies), MedDRA ver.23.0 (Study 0103)

PMDA's view:

Although the submitted clinical study data showed that serious gastrointestinal disorder (other than nausea and vomiting) for which a causal relationship to zolbetuximab could not be ruled out occurred, no special caution about gastrointestinal disorder (other than nausea and vomiting) is required at present on the precondition that information on gastrointestinal disorder in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) Most of the events resolved in a relatively short period of time; and (b) the incidence of gastrointestinal disorder (other than nausea and vomiting) did not tend to be clearly higher in the zolbetuximab group than in the placebo group. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(d) Fluid retention

The applicant's explanation about fluid retention associated with zolbetuximab:

Events classified into MedDRA SMQ of "haemodynamic oedema, effusions and fluid overload (narrow)" and MedDRA HLTs of "total fluid volume increased" and "protein metabolism disorders NEC" were tabulated as fluid retention.

Table 68 and Table 69 show incidences of fluid retention in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of fluid retention was 43 (1, 1,051) in the zolbetuximab group and 99 (1, 371) in the placebo group of the SPOTLIGHT study, and 26 (3, 546) in the zolbetuximab group and 64 (2, 865) in the placebo group of the GLOW study.

Table 68. Incidences of fluid retention (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Fluid retention*	97 (34.8)	15 (5.4)	59 (21.2)	7 (2.5)	82 (32.3)	16 (6.3)	63 (25.3)	18 (7.2)
Oedema peripheral	49 (17.6)	2 (0.7)	26 (9.4)	0	26 (10.2)	1 (0.4)	6 (2.4)	0
Hypoalbuminaemia	43 (15.4)	11 (3.9)	17 (6.1)	2 (0.7)	57 (22.4)	8 (3.1)	35 (14.1)	4 (1.6)
Oedema	7 (2.5)	0	2 (0.7)	0	4 (1.6)	0	3 (1.2)	0
Hypoproteinaemia	6 (2.2)	0	2 (0.7)	0	6 (2.4)	0	4 (1.6)	0
Ascites	5 (1.8)	1 (0.4)	12 (4.3)	3 (1.1)	9 (3.5)	5 (2.0)	16 (6.4)	8 (3.2)
Peripheral swelling	4 (1.4)	0	3 (1.1)	0	2 (0.8)	1 (0.4)	0	0
Pleural effusion	4 (1.4)	1 (0.4)	6 (2.2)	2 (0.7)	5 (2.0)	1 (0.4)	7 (2.8)	5 (2.0)
Generalised oedema	2 (0.7)	1 (0.4)	0	0	2 (0.8)	0	0	0
Fluid retention	1 (0.4)	0	0	0	0	0	0	0
Gastrointestinal oedema	1 (0.4)	0	0	0	0	0	0	0
Joint effusion	1 (0.4)	0	0	0	0	0	0	0
Joint swelling	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0	1 (0.4)	0
Lymphoedema	1 (0.4)	0	0	0	0	0	0	0
Pulmonary oedema	1 (0.4)	0	1 (0.4)	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Swelling	1 (0.4)	0	0	0	0	0	0	0
Acute pulmonary oedema	0	0	1 (0.4)	0	0	0	0	0
Localised oedema	0	0	1 (0.4)	0	0	0	0	0
Mouth swelling	0	0	1 (0.4)	0	0	0	0	0
Pericardial effusion	0	0	2 (0.7)	1 (0.4)	0	0	0	0
Retroperitoneal oedema	0	0	0	0	1 (0.4)	0	0	0
Gravitational oedema	0	0	0	0	0	0	1 (0.4)	1 (0.4)
Pelvic fluid collection	0	0	0	0	0	0	1 (0.4)	0

* All events included in tabulation

Table 69. Incidences of serious fluid retention (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal fluid retention	0	0	0	1 (0.4)
Fatal fluid retention for which a causal relationship to the study drug cannot be ruled out	0	0	0	0
Serious fluid retention	5 (1.8)	4 (1.4)	8 (3.1)	15 (6.0)
Serious fluid retention for which a causal relationship to the study drug cannot be ruled out	1 (0.4)	0	3 (1.2)	3 (1.2)
Oedema peripheral	1 (0.4)	0	1 (0.4)	0
Hypoalbuminaemia	0	0	1 (0.4)	1 (0.4)
Peripheral swelling	0	0	1 (0.4)	0
Pleural effusion	0	0	0	2 (0.8)
Fluid retention leading to treatment discontinuation*1	1 (0.4)	1 (0.4)	0	6 (2.4)
Fluid retention leading to treatment interruption*1	9 (3.2)	0	6 (2.4)	2 (0.8)
Fluid retention leading to dose reduction*2	1 (0.4)	0	0	1 (0.4)
Fluid retention leading to slower infusion rate*3	0	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 70 shows details of patients who experienced serious fluid retention for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 70. List of patients who experienced serious fluid retention for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	6[redacted]	Male	FOLFOX	Oedema peripheral	2	48	2	Unchanged	Resolved
GLOW	7[redacted]	Male	CAPOX	Oedema peripheral	3	141	8	Unchanged	Resolving
	6[redacted]	Male	CAPOX	Hypoalbuminaemia	2	116	4	Unchanged	Resolving
					2	132	30	Unchanged	Resolving
	6[redacted]	Male	CAPOX	Peripheral swelling	3	147	Unknown	Unchanged	Not resolved

* MedDRA ver.25.0

PMDA's view:

Although the submitted clinical study data showed that the incidence of fluid retention tended to be higher in the zolbetuximab group than in the placebo group, no special caution about fluid retention is required at present on the precondition that information on fluid retention in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) Most of the events were Grade ≤2; and (b) the incidence of serious fluid retention did not tend to be clearly higher in the zolbetuximab group than in the placebo group. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(e) Electrolyte abnormality

The applicant's explanation about electrolyte abnormality associated with zolbetuximab:

Events classified into MedDRA HLT of "water and electrolyte analyses NEC" and MedDRA PTs of "blood calcium decreased," "blood calcium increased," "blood magnesium decreased," "blood magnesium increased," "blood phosphorus decreased," "blood phosphorus increased," "blood potassium decreased," "blood potassium increased," "blood sodium decreased," "blood sodium increased," "calcium deficiency," "hypercalcaemia," "hyperkalaemia," "hypermagnesaemia,"

"hypernatraemia," "hyperphosphataemia," "hypocalcaemia," "hypokalaemia," "hypomagnesaemia," "hyponatraemia," "hypophosphataemia," and "magnesium deficiency" were tabulated as electrolyte abnormality.

Table 71 and Table 72 show incidences of electrolyte abnormality in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of electrolyte abnormality was 42 (2, 862) in the zolbetuximab group and 56 (2, 578) in the placebo group of the SPOTLIGHT study, and 44 (1, 596) in the zolbetuximab group and 56 (2, 231) in the placebo group of the GLOW study.

Table 71. Incidences of electrolyte abnormality reported by ≥1% of patients in any group (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Electrolyte abnormality*	87 (31.2)	34 (12.2)	66 (23.7)	19 (6.8)	57 (22.4)	18 (7.1)	52 (20.9)	25 (10.0)
Hypokalaemia	50 (17.9)	16 (5.7)	41 (14.7)	10 (3.6)	36 (14.2)	14 (5.5)	36 (14.5)	16 (6.4)
Hypocalcaemia	30 (10.8)	6 (2.2)	9 (3.2)	0	13 (5.1)	0	12 (4.8)	1 (0.4)
Hypophosphataemia	17 (6.1)	8 (2.9)	13 (4.7)	7 (2.5)	8 (3.1)	3 (1.2)	7 (2.8)	2 (0.8)
Hyponatraemia	14 (5.0)	6 (2.2)	10 (3.6)	2 (0.7)	15 (5.9)	4 (1.6)	18 (7.2)	9 (3.6)
Hypomagnesaemia	11 (3.9)	1 (0.4)	11 (4.0)	0	4 (1.6)	1 (0.4)	5 (2.0)	1 (0.4)
Hyperkalaemia	8 (2.9)	2 (0.7)	1 (0.4)	1 (0.4)	4 (1.6)	1 (0.4)	2 (0.8)	1 (0.4)
Blood potassium decreased	3 (1.1)	1 (0.4)	1 (0.4)	0	2 (0.8)	0	0	0
Blood magnesium decreased	1 (0.4)	0	3 (1.1)	0	1 (0.4)	0	0	0

* All events included in tabulation

Table 72. Incidences of serious electrolyte abnormality (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal electrolyte abnormality	0	0	0	1 (0.4)
Fatal electrolyte abnormality for which a causal relationship to the study drug cannot be ruled out	0	0	0	0
Serious electrolyte abnormality	8 (2.9)	3 (1.1)	6 (2.4)	8 (3.2)
Serious electrolyte abnormality for which a causal relationship to the study drug cannot be ruled out	3 (1.1)	2 (0.7)	3 (1.2)	6 (2.4)
Hypokalaemia	2 (0.7)	1 (0.4)	3 (1.2)	6 (2.4)
Hyponatraemia	1 (0.4)	0	1 (0.4)	0
Hypercalcaemia	0	1 (0.4)	0	0
Hypophosphataemia	0	1 (0.4)	1 (0.4)	0
Electrolyte abnormality leading to treatment discontinuation*1	3 (1.1)	2 (0.7)	2 (0.8)	0
Electrolyte abnormality leading to treatment interruption*1	11 (3.9)	5 (1.8)	6 (2.4)	3 (1.2)
Electrolyte abnormality leading to dose reduction*2	4 (1.4)	5 (1.8)	1 (0.4)	2 (0.8)
Electrolyte abnormality leading to slower infusion rate*3	0	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 73 shows details of patients who experienced Grade ≥3 serious electrolyte abnormality for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 73. List of patients who experienced Grade ≥3 serious electrolyte abnormality for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	6[redacted]	Female	FOLFOX	Hypokalaemia	3	76	8	Interruption	Resolving
	6[redacted]	Male	FOLFOX	Hypokalaemia	3	152	4	Interruption	Resolving
					3	176	2	Unchanged	Resolving
GLOW	7[redacted]	Male	CAPOX	Hypokalaemia	3	124	Unknown	Interruption	Not resolved
0103	4[redacted]	Male	None	Hyponatraemia	3	10	2	Unchanged	Resolved

* MedDRA ver.25.0

PMDA's view:

Although the submitted clinical study data showed that serious electrolyte abnormality for which a causal relationship to zolbetuximab could not be ruled out occurred, no special caution about electrolyte abnormality is required at present on the precondition that information on electrolyte abnormality in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) Most of the events resolved within a short period; and (b) the incidence of electrolyte abnormality did not tend to be clearly higher in the zolbetuximab group than in the placebo group. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(f) Hypertension

The applicant's explanation about hypertension associated with zolbetuximab:

Events classified into MedDRA SMQ of "hypertension (narrow)" were tabulated as hypertension.

Table 74 and Table 75 show incidences of hypertension in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of hypertension was 1 (1, 327) in the zolbetuximab group and 59.5 (1, 329) in the placebo group of the SPOTLIGHT study, and 1 (1, 184) in the zolbetuximab group and 118.5 (1, 848) in the placebo group of the GLOW study.

Table 74. Incidences of hypertension (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension*	39 (14.0)	19 (6.8)	22 (7.9)	10 (3.6)	15 (5.9)	6 (2.4)	8 (3.2)	3 (1.2)
Hypertension	31 (11.1)	15 (5.4)	22 (7.9)	10 (3.6)	15 (5.9)	6 (2.4)	7 (2.8)	3 (1.2)
Blood pressure increased	5 (1.8)	3 (1.1)	0	0	1 (0.4)	0	1 (0.4)	0
Blood pressure diastolic increased	1 (0.4)	0	0	0	0	0	0	0
Hypertensive crisis	1 (0.4)	0	0	0	0	0	0	0
Postoperative hypertension	1 (0.4)	1 (0.4)	0	0	0	0	0	0
Procedural hypertension	1 (0.4)	1 (0.4)	0	0	0	0	0	0

* All events included in tabulation

Table 75. Incidences of serious hypertension (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal hypertension	0	0	0	0
Serious hypertension	1 (0.4)	1 (0.4)	0	0
Serious hypertension for which a causal relationship to the study drug cannot be ruled out	1 (0.4)	0	0	0
Hypertensive crisis	1 (0.4)	0	0	0
Hypertension leading to treatment discontinuation*1	2 (0.7)	1 (0.4)	0	0
Hypertension leading to treatment interruption*1	21 (7.5)	2 (0.7)	1 (0.4)	1 (0.4)
Hypertension leading to dose reduction*2	0	0	1 (0.4)	0
Hypertension leading to slower infusion rate*3	0	0	3 (1.2)	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 76 shows details of patients who experienced serious hypertension for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 76. List of patients who experienced serious hypertension for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	5[redacted]	Female	FOLFOX	Hypertensive crisis	2	1	2	Interruption	Resolved

* MedDRA ver.25.0

PMDA's view:
Although the submitted clinical study data showed that serious hypertension for which a causal relationship to zolbetuximab could not be ruled out occurred, no special caution about hypertension is required at present on the precondition that information on hypertension in the clinical studies be provided in the package insert, etc. in view of the following finding: The number of patients who experienced hypertension including serious event is limited. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(g) Infection
The applicant's explanation about infection associated with zolbetuximab:
Events classified into MedDRA SOC of "infections and infestations" were tabulated as infection.

Table 77 and Table 78 show incidences of infection in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of infection was 101.5 (1, 838) in the zolbetuximab group and 92 (2, 752) in the placebo group of the SPOTLIGHT study, and 94.5 (1, 541) in the zolbetuximab group and 72.5 (4, 561) in the placebo group of the GLOW study.

Table 77. Incidences of infection reported by ≥2% of patients in any group (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection*	112 (40.1)	27 (9.7)	95 (34.2)	25 (9.0)	70 (27.6)	23 (9.1)	68 (27.3)	30 (12.0)
COVID-19	21 (7.5)	1 (0.4)	25 (9.0)	2 (0.7)	11 (4.3)	2 (0.8)	11 (4.4)	3 (1.2)
Urinary tract infection	16 (5.7)	2 (0.7)	8 (2.9)	0	7 (2.8)	1 (0.4)	6 (2.4)	1 (0.4)
Pneumonia	13 (4.7)	6 (2.2)	14 (5.0)	9 (3.2)	12 (4.7)	7 (2.8)	10 (4.0)	6 (2.4)
Nasopharyngitis	8 (2.9)	0	7 (2.5)	0	4 (1.6)	0	1 (0.4)	0
Conjunctivitis	7 (2.5)	0	3 (1.1)	0	1 (0.4)	0	1 (0.4)	0
Herpes zoster	6 (2.2)	1 (0.4)	3 (1.1)	0	2 (0.8)	0	1 (0.4)	1 (0.4)
Oral candidiasis	5 (1.8)	0	14 (5.0)	0	3 (1.2)	0	3 (1.2)	0
Urinary tract infection bacterial	3 (1.1)	1 (0.4)	6 (2.2)	0	0	0	0	0

* All events included in tabulation

Table 78. Incidences of serious infection (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal infection	6 (2.2)	2 (0.7)	6 (2.4)	9 (3.6)
Fatal infection for which a causal relationship to the study drug cannot be ruled out	3 (1.1)	1 (0.4)	2 (0.8)	4 (1.6)
Neutropenic sepsis	1 (0.4)	0	0	1 (0.4)
Pneumonia	1 (0.4)	1 (0.4)	0	0
Sepsis	1 (0.4)	0	1 (0.4)	0
Septic shock	0	0	1 (0.4)	1 (0.4)
Lower respiratory tract infection viral	0	0	0	1 (0.4)
Mucosal infection	0	0	0	1 (0.4)
Serious infection	29 (10.4)	23 (8.3)	25 (9.8)	21 (8.4)
Serious infection for which a causal relationship to the study drug cannot be ruled out	5 (1.8)	3 (1.1)	3 (1.2)	7 (2.8)
Atypical pneumonia	1 (0.4)	0	0	0
Neutropenic sepsis	1 (0.4)	0	0	1 (0.4)
Pneumonia	1 (0.4)	2 (0.7)	0	0
Sepsis	1 (0.4)	0	1 (0.4)	0
Urinary tract infection	1 (0.4)	0	0	0
Bacteraemia	0	1 (0.4)	0	0
Device related infection	0	0	1 (0.4)	0
Septic shock	0	0	1 (0.4)	1 (0.4)
Biliary tract infection	0	0	0	1 (0.4)
Lower respiratory tract infection	0	0	0	1 (0.4)
Lower respiratory tract infection viral	0	0	0	1 (0.4)
Mucosal infection	0	0	0	1 (0.4)
Peritonitis	0	0	0	1 (0.4)
Urinary tract infection bacterial	0	0	0	1 (0.4)
Infection leading to treatment discontinuation*1	8 (2.9)	4 (1.4)	6 (2.4)	7 (2.8)
Infection leading to treatment interruption*1	33 (11.8)	18 (6.5)	15 (5.9)	16 (6.4)
Infection leading to dose reduction*2	2 (0.7)	0	3 (1.2)	1 (0.4)
Infection leading to slower infusion rate*3	0	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

Table 79 shows details of patients who experienced serious infection for which a causal relationship to zolbetuximab could not be ruled out in the clinical study data submitted for the present application.

Table 79. List of patients who experienced serious infection for which a causal relationship to zolbetuximab could not be ruled out

Study	Age	Sex	Concomitant chemotherapy	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on zolbetuximab	Outcome
SPOTLIGHT	5[redacted]	Male	FOLFOX	Neutropenic sepsis	5	50	1	Discontinuation	Death
	3[redacted]	Female	FOLFOX	Sepsis	5	155	1	Discontinuation	Death
	7[redacted]	Male	FOLFOX	Pneumonia	5	119	1	Discontinuation	Death
	7[redacted]	Male	FOLFOX	Urinary tract infection	3	28	2	Unchanged	Resolved
GLOW	7[redacted]	Male	CAPOX	Sepsis	5	41	1	Discontinuation	Death

* MedDRA ver.25.0

PMDA's view:

Although the submitted clinical study data showed that events of serious infection, including fatal infection for which a causal relationship to zolbetuximab could not be ruled out, occurred, no special caution about infection is required at present on the precondition that information on infection in the clinical studies be provided in the package insert, etc. in view of the following findings: (a) The incidence of infection did not tend to be clearly higher in the zolbetuximab group than in the placebo group; and (b) concomitant chemotherapy is also suspected to influence development of infection. The applicant, however, should continue to gather information in post-marketing settings and to provide the obtained safety information to healthcare professionals.

(h) Interstitial lung disease (ILD)

The applicant's explanation about ILD associated with zolbetuximab:

Events classified into MedDRA SMQ of "interstitial lung disease (broad)" were tabulated as ILD.

Table 80 and Table 81 show incidences of ILD in the SPOTLIGHT and GLOW studies. The median time (minimum, maximum) (days) to the first onset of ILD was 226.5 (187, 503) in the zolbetuximab group and 198 (65, 333) in the placebo group of the SPOTLIGHT study, and 131 (121, 141) in the zolbetuximab group and 5 (5, 5) in the placebo group of the GLOW study.

Table 80. Incidences of ILD (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)							
	SPOTLIGHT study				GLOW study			
	Zolbetuximab n = 279		Placebo n = 278		Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD*	6 (2.2)	0	5 (1.8)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)
Interstitial lung disease	3 (1.1)	0	1 (0.4)	0	0	0	0	0
Pneumonitis	2 (0.7)	0	3 (1.1)	0	0	0	0	0
Pulmonary fibrosis	1 (0.4)	0	0	0	0	0	0	0
Acute respiratory distress syndrome	0	0	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)

* All events included in tabulation

Table 81. Incidences of serious ILD (SPOTLIGHT and GLOW studies)

PT (MedDRA ver.25.0)	Number of patients (%)			
	SPOTLIGHT study		GLOW study	
	Zolbetuximab n = 279	Placebo n = 278	Zolbetuximab n = 254	Placebo n = 249
Fatal ILD	0	1 (0.4)	1 (0.4)	0
Fatal ILD for which a causal relationship to the study drug cannot be ruled out	0	0	0	0
Serious ILD	0	1 (0.4)	2 (0.8)	1 (0.4)
Serious ILD for which a causal relationship to the study drug cannot be ruled out	0	0	0	0
ILD leading to treatment discontinuation*1	1 (0.4)	2 (0.7)	0	1 (0.4)
ILD leading to treatment interruption*1	0	2 (0.7)	0	0
ILD leading to dose reduction*2	0	0	0	0
ILD leading to slower infusion rate*3	0	0	0	0

*1 Adverse events leading to discontinuation or interruption of any of the study drugs
*2 Adverse events leading to dose reduction of any of Cape, 5-FU, (*l*-)LV, and L-OHP
*3 Adverse events leading to slower infusion rate of zolbetuximab or placebo

The clinical study data submitted for the present application showed no serious ILD for which a causal relationship to zolbetuximab could not be ruled out.

PMDA's view:
No special caution about ILD is required at present in view of the following findings: (a) The submitted clinical study data showed no serious ILD for which a causal relationship to zolbetuximab could not be ruled out; and (b) the incidence of ILD did not tend to be clearly higher in the zolbetuximab group than in the placebo group.

7.R.4 Clinical positioning and indication

The proposed indication of zolbetuximab was "CLDN18.2-positive locally advanced, unresectable or metastatic gastric cancer." For the Precautions Concerning Indication section, the following statements were proposed:

- Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive in a testing by adequately experienced pathologists or testing at qualified laboratories using approved *in vitro* diagnostics.Note)

  Note) Approved *in vitro* diagnostics for CLDN18 detection are available. CLDN18.2 positivity can be determined by the concerned *in vitro* diagnostics when gastric cancer tissue is confirmed to be CLDN18 positive.
- Appropriate patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of zolbetuximab.
- The efficacy and safety of zolbetuximab in patients with HER2-positive tumor have not been established.
- The efficacy and safety of zolbetuximab used for the second-line or subsequent therapy have not been established.
- The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

As a result of the reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA has concluded that the indication of zolbetuximab should be "CLDN18.2-positive unresectable,

advanced or recurrent gastric cancer" with the following cautionary statements included in the Precautions Concerning Indication section:

- Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive[Note)] in a testing by adequately experienced pathologists or testing at qualified laboratories, after fully understanding the definition of CLDN18.2 positive presented in the "Clinical Studies" section. The testing should be performed using approved *in vitro* diagnostics or medical devices.

  Note) CLDN18.2 positivity can be determined when gastric cancer tissue is confirmed to be CLDN18 positive.
- Zolbetuximab should be used in patients with HER2-negative tumor.
- The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

7.R.4.1 Clinical positioning of zolbetuximab and intended population

Japan and foreign treatment guidelines and representative textbooks on clinical oncology were found to have no descriptions about use of zolbetuximab for treatment of patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy.

The applicant's explanation about (a) clinical positioning of zolbetuximab and (b) CLDN18.2 test for selecting appropriate patients for zolbetuximab:

(a) Clinical positioning of zolbetuximab:

Because the efficacy of zolbetuximab/EOX tended to be high in patients with high CLDN18.2-expressing tumor in Study 03,[32)] the SPOTLIGHT and GLOW studies included patients with CLDN18.2-positive tumor. The studies demonstrated that zolbetuximab/chemotherapy was clinically useful in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy [see Sections 7.R.2 and 7.R.3], and thus zolbetuximab/chemotherapy can be positioned as a treatment option for the concerned patients. Use of zolbetuximab/chemotherapy in patients with HER2-positive tumor and patients with prior chemotherapy, on the other hand, is not recommended, because no clinical study data on the efficacy and safety of zolbetuximab/chemotherapy in these patient populations are available. Use of zolbetuximab/chemotherapy in postoperative adjuvant chemotherapy is not recommended either, because no clinical study data on the efficacy and safety of zolbetuximab/chemotherapy used as postoperative adjuvant chemotherapy are available.

The SPOTLIGHT and GLOW studies also included patients with cancer of the gastroesophageal junction. The concerned information will be included in the Clinical Studies section in the package insert, and the cautionary statement that appropriate patients should be selected by physicians with a full understanding of the information presented in the Clinical Studies section will be included in the Precautions Concerning Indication section.

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32) The hazard ratio [95% CI] of PFS in Arm 2 (zolbetuximab 800/600 mg/m^2/EOX) to that in Arm 1 (EOX) was 0.40 [0.25, 0.65] in (i) patients with ≥70% tumor cells being CLDN18.2-stained at ≥2+ intensity and 0.71 [0.32, 1.57] in (ii) patients with 40% to 69% tumor cells being CLDN18.2-stained at ≥2+ intensity.

(b) CLDN18.2 test:

In the SPOTLIGHT and GLOW studies, a central laboratory performed immunohistochemistry (IHC) using "VENTANA CLDN18 (43-14A) RxDx Assay for research" (Ventana Medical Systems, Inc.) to stain CLDN18 on the cell membrane of tumor cells, patients with ≥75% tumor cells stained at the moderate (2+) to strong (3+) intensity were enrolled, and the efficacy and safety of zolbetuximab were evaluated [see Sections 7.1.2.2 and 7.1.2.3]. Because the primary antibody of "VENTANA CLDN18 (43-14A) RxDx Assay for research" binds to both CLDN18.1 and CLDN18.2 isoforms, tumor cells expressing either CLDN18.1 or CLDN18.2 isoform will test positive for CLDN18. However, the applicant considers that gastric cancer tissues that have tested positive for CLDN18 using "VENTANA CLDN18 (43-14A) RxDx Assay for research" can be deemed as CLDN18.2-positive tissues in view of the following findings: Of gastric cancer tissues evaluable for CLDN18.1 expression level, 99% (196 of 198 preparations) expressed CLDN18.2 predominantly compared with CLDN18.1, and the median expression level of CLDN18.2 was >90 times that of CLDN18.1 (*Ann Oncol.* 2021;32 Suppl 3:S138).

Based on the above, patients eligible for zolbetuximab should be selected using "VENTANA OptiView CLDN18 (43-14A)" (Roche Diagnostics K.K.) which employs the same test method as that of "VENTANA CLDN18 (43-14A) RxDx Assay for research." The concerned information will be included in the Precautions Concerning Indication section as the cautionary statement.

In view of the above (a) and (b), the package insert included details (e.g., primary site) of the patients in the SPOTLIGHT and GLOW studies in the Clinical Studies section, provided the following cautionary statements in the Precautions Concerning Indication section, and specified the indication of zolbetuximab as "CLDN18.2-positive locally advanced, unresectable or metastatic gastric cancer."

- Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive in a testing by adequately experienced pathologists or testing at qualified laboratories using approved *in vitro* diagnostics.[Note)]

  Note) Approved *in vitro* diagnostics for CLDN18 detection are available. CLDN18.2 positivity can be determined by the concerned *in vitro* diagnostics when gastric cancer tissue is confirmed to be CLDN18 positive.
- Appropriate patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of zolbetuximab.
- The efficacy and safety of zolbetuximab in patients with HER2-positive tumor have not been established.
- The efficacy and safety of zolbetuximab used for the second-line or subsequent therapy have not been established.
- The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

The applicant's explanation about choice between nivolumab/chemotherapy (combination of nivolumab and chemotherapy) or zolbetuximab/chemotherapy for patients with CLDN18.2-positive and HER2-negative unresectable, advanced or recurrent gastric cancer who had not received prior chemotherapy,

considering that recommendation level of nivolumab/chemotherapy can differ depending on the programmed cell death-ligand 1 (PD-L1) expression status:

- For patients with combined positive score (CPS) ≥5, there are no results from clinical studies comparing the efficacy and safety of zolbetuximab/chemotherapy with those of nivolumab/chemotherapy, and the appropriate choice remains unknown at present. Treatment choice should be made according to the individual patient's condition by physicians with understanding of the efficacy and safety of these treatments.
- For patients with CPS <5, an add-on effect of nivolumab to chemotherapy alone in patients with CPS <5 was limited (*Lancet.* 2021;398:27-40), but zolbetuximab/chemotherapy was demonstrated to be clinically useful in the SPOTLIGHT and GLOW studies, which included patients with CLDN18.2-positive tumor irrespective of PD-L1 expression status. Zolbetuximab/chemotherapy should be firstly used.

PMDA's view:

PMDA generally accepted the applicant's explanation. However, in the SPOTLIGHT and GLOW studies, patients with "≥75% tumor cells of which cell membrane was CLDN18-stained at the moderate to strong intensity" were selected as patients with CLDN18.2 positive, and zolbetuximab/chemotherapy was demonstrated to be clinically useful in this patient population. In selecting appropriate patients, the above information is important. The Clinical Studies section in the package insert should include the definition of CLDN18.2 positive used in both studies, and the Precautions Concerning Indication section should include the cautionary statement that zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive after fully understanding the Clinical Studies section. Any special remark does not have to be attached to the cautionary statement that the efficacy and safety of zolbetuximab used for the second-line or subsequent therapy have not been established.

Based on the above, the Indication and Precautions Concerning Indication section should be specified after some modifications as shown below.

Indication

CLDN18.2-positive unresectable advanced or recurrent gastric cancer

Precautions Concerning Indication

- Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive[Note)] in a testing by adequately experienced pathologists or testing at qualified laboratories, after fully understanding the definition of CLDN18.2 positive presented in the "Clinical Studies" section. The testing should be performed using approved *in vitro* diagnostics or medical devices.

  Note) CLDN18.2 positivity can be determined when gastric cancer tissue is confirmed to be CLDN18 positive.
- Zolbetuximab should be used in patients with HER2-negative tumor.
- The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

7.R.5 Dosage and administration

The proposed dosage and administration of zolbetuximab was "In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion for the initial single loading dose. The subsequent maintenance dose administered as an intravenous infusion is 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks." For the Precautions Concerning Dosage and Administration section, the following statements were proposed:

- Zolbetuximab should be administered as an intravenous infusion over ≥2 hours.[Note 1)] The infusion should be started at a rate slower than that calculated to complete it in 2 hours (see the table below). The infusion rate should be increased gradually with tolerability being monitored.

Recommended infusion rate of zolbetuximab

Dose		Starting infusion rate [Note 2)] (First 30-60 minutes after the start of the infusion)	Subsequent infusion rate
Initial single loading dose	800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
Maintenance dose	600 mg/m^2 (every 3 weeks)	75 mg/m^2/h	150-300 mg/m^2/h
	400 mg/m^2 (every 2 weeks)	50 mg/m^2/h	100-200 mg/m^2/h

Note 1) If the infusion time exceeds 6 hours from end of preparation of infusion solution, the remaining solution must be discarded and a new infusion solution must be reprepared.
Note 2) If no adverse drug reactions have occurred in the first 30 to 60 minutes after the start of the infusion, the infusion rate may be subsequently increased with tolerability being monitored.

- The efficacy and safety of zolbetuximab alone, without other antineoplastic agents, have not been established.
- Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.
- If zolbetuximab and other antineoplastic agents are administered on the same day, administration of zolbetuximab should be completed before that of other antineoplastic agents.
- Guide for interruption and discontinuation of zolbetuximab at the occurrence of adverse drug reactions

As a result of the reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA has concluded that the Dosage and Administration of zolbetuximab should be "In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion over at least 2 hours for the initial dose and then 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks for the subsequent doses" with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

- The infusion rate of zolbetuximab may be gradually increased after 30 to 60 minutes after the start of the infusion with reference to the table below, if the infusion is well-tolerated.

Dose	Infusion rate	
	Up to 30-60 minutes after the start of the infusion	Subsequent infusion rate
800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150-300 mg/m^2/h
400 mg/m^2	50 mg/m^2/h	100-200 mg/m^2/h

- Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.
- Guide for interruption and discontinuation of zolbetuximab at the occurrence of adverse drug reactions [see Section 7.R.5.2].

7.R.5.1 Dosage and administration of zolbetuximab

The applicant's explanation about the rationale for the proposed dosage and administration of zolbetuximab:

The SPOTLIGHT and GLOW studies were conducted with the dosage regimen based on the following clinical study results and demonstrated that zolbetuximab/chemotherapy was clinically useful in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy [see Sections 7.R.2 and 7.R.3]. On the basis of the settings in the concerned studies and results from the simulation using the PPK model [see Section 6.R.1], the dosage regimen of zolbetuximab was specified.

- The foreign phase I study in patients with CLDN18.2-positive advanced gastric cancer (Study 001) confirmed that single doses of zolbetuximab 600 and 1,000 mg/m^2 were tolerated [see Section 7.1.3.1].
- The foreign phase II study in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer (Study 02) showed that the efficacy of zolbetuximab 600 mg/m^2 Q2W tended to be higher than that of zolbetuximab 300 mg/m^2 Q2W [see Section 7.1.3.2].
- Serum zolbetuximab concentrations were estimated to be below 50 μg/mL (concentrations expected to exert ADCC and CDC) at 14 days after administration of zolbetuximab 600 mg/m^2, and the initial loading dose of zolbetuximab 800 mg/m^2 was considered appropriate.
- The foreign phase II study in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer (Study 03) showed that the efficacy of zolbetuximab 800/600 mg/m^2 Q3W tended to be higher than that of zolbetuximab 1,000 mg/m^2 Q3W, both in combination with EOX [see Section 7.1.3.3].
- The Japanese phase I study (Study 0104) showed that zolbetuximab 800/600 mg/m^2 Q3W did not cause DLT and was tolerated in Japanese patients [see Section 7.1.1.1].

Cautionary statement on the infusion rate of zolbetuximab will be included in the Precautions Concerning Dosage and Administration section with reference to the following settings in the SPOTLIGHT and GLOW studies:

- Zolbetuximab should be administered as an intravenous infusion over ≥2 hours. The infusion rate should be gradually increased or reduced with the tolerability being monitored. The recommended infusion rate is as shown in the table below.

Dose	From the start of the infusion to 30 minutes after that	From 30 to 60 minutes after that	≥60 minutes after that
800 mg/m^2	100 mg/m^2/h	200 mg/m^2/h	300-400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150 mg/m^2/h	225-300 mg/m^2/h

Based on the above, the dosage regimen of zolbetuximab was "In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion for the initial single loading dose. The subsequent maintenance dose administered as an intravenous infusion is 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks" with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

- Zolbetuximab should be administered as an intravenous infusion over ≥2 hours.[Note 1)] The infusion should be started at a rate slower than that calculated to complete it in 2 hours (see the table below). The infusion rate should be increased gradually with tolerability being monitored.

Recommended infusion rate of zolbetuximab

Dose		Starting infusion rate[Note 2)] (First 30-60 minutes after the start of the infusion)	Subsequent infusion rate
Initial single loading dose	800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
Maintenance dose	600 mg/m^2 (every 3 weeks)	75 mg/m^2/h	150-300 mg/m^2/h
	400 mg/m^2 (every 2 weeks)	50 mg/m^2/h	100-200 mg/m^2/h

Note 1) If the infusion time exceeds 6 hours from end of preparation of infusion solution, the remaining solution must be discarded and a new infusion solution must be reprepared.
Note 2) If no adverse drug reactions have occurred in the first 30 to 60 minutes after the start of the infusion, the infusion rate may be subsequently increased with tolerability being monitored.

- The efficacy and safety of zolbetuximab alone, without other antineoplastic agents, have not been established.
- Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.
- If zolbetuximab and other antineoplastic agents are administered on the same day, administration of zolbetuximab should be completed before that of other antineoplastic agents.

PMDA's view:
PMDA generally accepted the applicant's explanation. However, the cautionary statement that the efficacy and safety of zolbetuximab, without other antineoplastic agents, have not been established is considered unnecessary, because the dosage regimen clearly specifies that zolbetuximab is administered in combination with other antineoplastic agents. Actions to be taken if the zolbetuximab infusion time exceeds 6 hours and the administration sequence of zolbetuximab and other antineoplastic agents should be included in the Precautions Concerning Use section of the package insert or information materials appropriately provided to healthcare professionals, but not in the Precautions Concerning Dosage and Administration section.

Based on the above, the Dosage and Administration and Precautions Concerning Dosage and Administration sections should be specified after some modifications as shown below.

Dosage and Administration

In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion over at least 2 hours for the initial dose and then 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks for the subsequent doses.

Precautions Concerning Dosage and Administration

- The infusion rate of zolbetuximab may be gradually increased after 30 to 60 minutes after the start of the infusion with reference to the table below, if the infusion is well-tolerated.

Dose	Infusion rate	
	Up to 30-60 minutes after the start of the infusion	Subsequent infusion rate
800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150-300 mg/m^2/h
400 mg/m^2	50 mg/m^2/h	100-200 mg/m^2/h

- Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.

7.R.5.2 Guide for treatment interruption and discontinuation

The applicant's explanation about the guide for interruption and discontinuation of zolbetuximab:

In the SPOTLIGHT and GLOW studies, the criteria for interruption and discontinuation of zolbetuximab at the occurrence of adverse drug reactions were specified and applied, and thereby zolbetuximab/chemotherapy was demonstrated to be clinically useful. The Precautions Concerning Dosage and Administration section was therefore proposed to include the guide for interruption and discontinuation of zolbetuximab based on the criteria specified in the SPOTLIGHT and GLOW studies with the following modifications.

- In both studies, if Grade 2 hypersensitivity reaction[33)] or infusion related reaction[34)] occurred, infusion rate of zolbetuximab for the next dose was reduced, but the slower infusion rate applied after occurrence of the concerned event did not make clear differences in incidence of adverse events on the day of zolbetuximab treatment.[35)] The slower infusion rate of zolbetuximab for the next dose will not be specified.
- In both studies, zolbetuximab was continued even after occurrence of Grade 2 nausea or vomiting, but in view of the incidences of nausea and vomiting in the studies, more careful measures were considered necessary. The following instruction will be therefore specified: If Grade 2 nausea or vomiting occurred, zolbetuximab should be interrupted until the symptom resolves to Grade 1.
- In both studies, the criteria related to posterior reversible encephalopathy syndrome were specified, but no such events occurred in clinical studies. No specific criteria will be specified.

33) "Hypersensitivity reaction" was defined as anaphylactic reaction or drug hypersensitivity.

34) "Infusion related reaction" was defined as events assessed as an infusion related reaction by the investigator.

35) In the subgroup of patients who experienced Grade 2 hypersensitivity reaction or infusion related reaction during use of zolbetuximab 600 mg/m^2, the incidence of all-grade adverse events on the day of the next zolbetuximab treatment was 16.7% (4 of 24) of patients treated at the slower infusion rate and 19.0% (4 of 21) of patients treated at the original infusion rate in the SPOTLIGHT study and 28.6% (4 of 14) of patients treated at the slower infusion rate and 33.3% (2 of 6) of patients treated at the original infusion rate in the GLOW study. The incidence of Grade ≥3 adverse events on the day of the next zolbetuximab treatment was 0% and 0% in the SPOTLIGHT study and 7.1% (1 of 14) of patients and 0% in the GLOW study. On the day of the next zolbetuximab treatment, none of the serious adverse events, adverse events leading to death, and adverse events leading to discontinuation of zolbetuximab occurred in either study.

- In both studies, the criteria related to blood disorder were specified, but the relevant events were considered to have been influenced by other antineoplastic agents. No specific criteria will be specified.
- In both studies, interruption or discontinuation of zolbetuximab was specified if Grade ≥3 of other non-hematologic toxicities occurred, but in view of other potential causes for the relevant events, individually arranged measures should be recommended. No specific criteria will be specified.

PMDA's view:
PMDA generally accepted the applicant's explanation. The applicant does not propose to specify the slower infusion rate of zolbetuximab for the next dose after occurrence of Grade 2 hypersensitivity reaction or infusion related reaction. PMDA considers it acceptable in view of the instruction for the infusion rate of zolbetuximab, which is allowed to be gradually increased for any dose.

Based on the above, the guide for interruption and discontinuation of zolbetuximab at the occurrence of adverse drug reactions should be specified after some modifications as shown below.
- If any adverse drug reaction occurs after use of zolbetuximab, interruption or discontinuation of zolbetuximab, and other actions should be considered by referring to the table below.

Guide for interruption or discontinuation of zolbetuximab, and other actions at the occurrence of adverse drug reactions

Adverse drug reaction	Severity*	Action
Hypersensitivity or infusion reaction	Grade 2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	Anaphylaxis Suspected anaphylaxis Grade ≥3	Discontinue zolbetuximab.
Nausea	Grade ≥2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
Vomiting	Grade 2 or 3	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	Grade 4	Discontinue zolbetuximab.

* Graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
The applicant plans to conduct a post-marketing surveillance in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer to investigate the post-marketing safety of zolbetuximab under routine clinical use.

The safety specification in the surveillance will include an infusion related reaction including nausea and vomiting in view of particularly high incidences of nausea and vomiting in the SPOTLIGHT and GLOW studies, and the incidence of these reactions in clinical use and risk factors will be investigated.

A target sample size is 600 patients in view of the incidence of the infusion related reaction in the SPOTLIGHT and GLOW studies.

An observation period is 54 weeks in view of the time to onset of nausea and vomiting, which frequently occurred as an infusion related reaction in the SPOTLIGHT and GLOW studies.

PMDA's view:
Because the safety information of zolbetuximab in Japanese patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer is limited, the applicant should implement the post-marketing surveillance to gather the safety information of zolbetuximab under routine clinical use.

The safety specification in the surveillance should include nausea and vomiting based on the review in Section "7.R.3 Safety," and incidences of the concerned events (including incidences by type of antiemetic used) in post-marketing settings should be investigated.

Details of the method for gathering the information, including potentially conducting a database survey, should continue to be examined.

7.3 Adverse events observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections "7.1 Evaluation data" and "7.2 Reference data." The following subsections summarize major adverse events other than deaths.

7.3.1 Japanese phase I study (Study 0104)

Adverse events occurred in 3 of 3 patients (100%) in Safety Part A, 3 of 3 patients (100%) in Safety Part B, and 11 of 12 patients (91.7%) in expansion part, and adverse events for which a causal relationship to zolbetuximab could not be ruled out were observed in 3 of 3 patients (100%) in Safety Part A, 3 of 3 patients (100%) in Safety Part B, and 11 of 12 patients (91.7%) in expansion part. Table 82 shows adverse events reported by ≥2 patients in any part.

Table 82. Adverse events reported by ≥2 patients in any part

SOC PT (MedDRA ver.20.1)	Number of patients (%)					
	Safety Part A n = 3		Safety Part B n = 3		Expansion part n = 12	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	1 (33.3)	3 (100)	1 (33.3)	11 (91.7)	1 (8.3)
Gastrointestinal disorders						
Abdominal pain upper	3 (100)	0	0	0	5 (41.7)	0
Nausea	2 (66.7)	0	2 (66.7)	0	7 (58.3)	0
Vomiting	2 (66.7)	0	1 (33.3)	0	4 (33.3)	0
Constipation	1 (33.3)	0	0	0	3 (25.0)	0
Abdominal pain	0	0	2 (66.7)	0	1 (8.3)	0
General disorders and administration site conditions						
Malaise	2 (66.7)	0	1 (33.3)	0	2 (16.7)	0
Metabolism and nutrition disorders						
Decreased appetite	3 (100)	0	3 (100)	0	8 (66.7)	0
Hypoalbuminaemia	0	0	0	0	2 (16.7)	1 (8.3)

Neither serious adverse events nor adverse events leading to discontinuation of zolbetuximab occurred in any part.

7.3.2 Global phase II study (Study 0103)

Adverse events occurred in 30 of 30 patients (100%) in Cohort 1, 21 of 21 patients (100%) in Cohort 2, and 3 of 3 patients (100%) in Cohort 3, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 24 of 30 patients (80.0%) in Cohort 1, 21 of 21 patients (100%) in Cohort 2, and 3 of 3 patients (100%) in Cohort 3. Table 83 shows adverse events with an incidence of ≥35% in any cohort.

Table 83. Adverse events with an incidence of ≥35% in any cohort

SOC PT (MedDRA ver.23.0)	Number of patients (%)					
	(a) Cohort 1 n = 30		(b) Cohort 2 n = 21		(c) Cohort 3 n = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	30 (100)	15 (50.0)	21 (100)	20 (95.2)	3 (100)	1 (33.3)
Blood and lymphatic system disorders						
Neutropenia	0	0	8 (38.1)	6 (28.6)	0	0
Gastrointestinal disorders						
Nausea	19 (63.3)	2 (6.7)	19 (90.5)	1 (4.8)	2 (66.7)	0
Abdominal pain	12 (40.0)	3 (10.0)	7 (33.3)	2 (9.5)	0	0
Vomiting	11 (36.7)	2 (6.7)	14 (66.7)	2 (9.5)	1 (33.3)	0
Constipation	5 (16.7)	0	6 (28.6)	0	2 (66.7)	0
Diarrhoea	3 (10.0)	0	8 (38.1)	1 (4.8)	1 (33.3)	0
General disorders and administration site conditions						
Pyrexia	6 (20.0)	1 (3.3)	6 (28.6)	2 (9.5)	2 (66.7)	0
Fatigue	2 (6.7)	0	8 (38.1)	1 (4.8)	0	0
Investigations						
Neutrophil count decreased	2 (6.7)	0	9 (42.9)	7 (33.3)	1 (33.3)	1 (33.3)
Metabolism and nutrition disorders						
Decreased appetite	7 (23.3)	0	9 (42.9)	1 (4.8)	2 (66.7)	0

Serious adverse events occurred in 12 of 30 patients (40.0%) in Cohort 1, 11 of 21 patients (52.4%) in Cohort 2, and 0 patients in Cohort 3. Table 84 shows serious adverse events reported by ≥2 patients in any cohort.

Table 84. Serious adverse events reported by ≥2 patients in any cohort

PT (MedDRA ver.23.0)	Number of patients (%)					
	(a) Cohort 1 n = 30		(b) Cohort 2 n = 21		(c) Cohort 3 n = 3	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	12 (40.0)	6 (20.0)	11 (52.4)	3 (14.3)	0	0
Sepsis	2 (6.7)	0	1 (4.8)	0	0	0
Intestinal obstruction	2 (6.7)	0	0	0	0	0
Vomiting	1 (3.3)	1 (3.3)	3 (14.3)	1 (4.8)	0	0
Abdominal pain	1 (3.3)	1 (3.3)	2 (9.5)	0	0	0

Adverse events leading to discontinuation of the study drug occurred in 5 of 30 patients (16.7%) in Cohort 1, 14 of 21 patients (66.7%) in Cohort 2, and 0 patients in Cohort 3. Table 85 shows adverse events leading to discontinuation of the study drug reported by ≥2 patients in any cohort.

Table 85. Adverse events leading to discontinuation of the study drug reported by ≥2 patients in any cohort

PT (MedDRA ver.23.0)	Number of patients (%)					
	(a) Cohort 1 n = 30		(b) Cohort 2 n = 21		(c) Cohort 3 n = 3	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	5 (16.7)	3 (10.0)	14 (66.7)	12 (57.1)	0	0
Neutropenia	0	0	4 (19.0)	4 (19.0)	0	0
Peripheral sensory neuropathy	0	0	3 (14.3)	3 (14.3)	0	0
Hypokalaemia	0	0	2 (9.5)	1 (4.8)	0	0
Neutrophil count decreased	0	0	2 (9.5)	2 (9.5)	0	0

7.3.3 Global phase III study (SPOTLIGHT study)

Adverse events occurred in 278 of 279 patients (99.6%) in the zolbetuximab group and 277 of 278 patients (99.6%) in the placebo group, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 277 of 279 patients (99.3%) in the zolbetuximab group and 268 of 278 patients (96.4%) in the placebo group. Table 86 shows adverse events with an incidence of ≥10% in either group.

Table 86. Adverse events with an incidence of ≥10% in either group

SOC PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 279		Placebo n = 278	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	278 (99.6)	242 (86.7)	277 (99.6)	216 (77.7)
Blood and lymphatic system disorders				
Neutropenia	102 (36.6)	79 (28.3)	94 (33.8)	65 (23.4)
Anaemia	100 (35.8)	24 (8.6)	104 (37.4)	26 (9.4)
Thrombocytopenia	28 (10.0)	4 (1.4)	45 (16.2)	4 (1.4)
Gastrointestinal disorders				
Nausea	230 (82.4)	45 (16.1)	169 (60.8)	18 (6.5)
Vomiting	188 (67.4)	45 (16.1)	99 (35.6)	16 (5.8)
Diarrhoea	110 (39.4)	12 (4.3)	122 (43.9)	9 (3.2)
Constipation	99 (35.5)	3 (1.1)	112 (40.3)	2 (0.7)
Abdominal pain	67 (24.0)	12 (4.3)	82 (29.5)	6 (2.2)
Stomatitis	58 (20.8)	7 (2.5)	57 (20.5)	3 (1.1)
Abdominal pain upper	47 (16.8)	4 (1.4)	32 (11.5)	0
General disorders and administration site conditions				
Fatigue	78 (28.0)	17 (6.1)	91 (32.7)	14 (5.0)
Asthenia	74 (26.5)	20 (7.2)	64 (23.0)	7 (2.5)
Pyrexia	54 (19.4)	1 (0.4)	48 (17.3)	1 (0.4)
Oedema peripheral	49 (17.6)	2 (0.7)	26 (9.4)	0
Investigations				
Neutrophil count decreased	95 (34.1)	69 (24.7)	91 (32.7)	69 (24.8)
Weight decreased	55 (19.7)	5 (1.8)	54 (19.4)	2 (0.7)
White blood cell count decreased	50 (17.9)	8 (2.9)	46 (16.5)	16 (5.8)
AST increased	49 (17.6)	4 (1.4)	44 (15.8)	7 (2.5)
Platelet count decreased	40 (14.3)	3 (1.1)	49 (17.6)	6 (2.2)
ALT increased	34 (12.2)	2 (0.7)	47 (16.9)	7 (2.5)
Metabolism and nutrition disorders				
Decreased appetite	131 (47.0)	16 (5.7)	93 (33.5)	9 (3.2)
Hypokalaemia	50 (17.9)	16 (5.7)	41 (14.7)	10 (3.6)
Hypoalbuminaemia	43 (15.4)	11 (3.9)	17 (6.1)	2 (0.7)
Hypocalcaemia	30 (10.8)	6 (2.2)	9 (3.2)	0
Musculoskeletal and connective tissue disorders				
Back pain	34 (12.2)	0	30 (10.8)	0
Nervous system disorders				
Peripheral sensory neuropathy	106 (38.0)	11 (3.9)	118 (42.4)	15 (5.4)
Paraesthesia	44 (15.8)	6 (2.2)	46 (16.5)	4 (1.4)
Dysgeusia	41 (14.7)	1 (0.4)	40 (14.4)	0
Dizziness	36 (12.9)	0	27 (9.7)	1 (0.4)
Headache	31 (11.1)	2 (0.7)	35 (12.6)	1 (0.4)
Psychiatric disorders				
Insomnia	29 (10.4)	1 (0.4)	25 (9.0)	0
Respiratory, thoracic and mediastinal disorders				
Cough	28 (10.0)	0	28 (10.1)	0
Dyspnoea	20 (7.2)	3 (1.1)	32 (11.5)	6 (2.2)
Vascular disorders				
Hypertension	31 (11.1)	15 (5.4)	22 (7.9)	10 (3.6)

Serious adverse events occurred in 125 of 279 patients (44.8%) in the zolbetuximab group and 121 of 278 patients (43.5%) in the placebo group. Table 87 shows serious adverse events reported by ≥6 patients in either group.

Table 87. Serious adverse events reported by ≥6 patients in either group

PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 279		Placebo n = 278	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	125 (44.8)	66 (23.7)	121 (43.5)	41 (14.7)
Vomiting	23 (8.2)	19 (6.8)	13 (4.7)	4 (1.4)
Nausea	19 (6.8)	17 (6.1)	11 (4.0)	3 (1.1)
Malignant neoplasm progression	10 (3.6)	0	12 (4.3)	0
Diarrhoea	8 (2.9)	7 (2.5)	4 (1.4)	2 (0.7)
Febrile neutropenia	8 (2.9)	8 (2.9)	1 (0.4)	1 (0.4)
Intestinal obstruction	7 (2.5)	1 (0.4)	3 (1.1)	0
Pyrexia	7 (2.5)	2 (0.7)	6 (2.2)	1 (0.4)
Neutropenia	6 (2.2)	6 (2.2)	3 (1.1)	3 (1.1)
Pneumonia	6 (2.2)	1 (0.4)	8 (2.9)	2 (0.7)
Pulmonary embolism	6 (2.2)	0	4 (1.4)	1 (0.4)
Abdominal pain	5 (1.8)	1 (0.4)	9 (3.2)	2 (0.7)
General physical health deterioration	2 (0.7)	0	6 (2.2)	2 (0.7)

Adverse events leading to discontinuation of the study drug occurred in 120 of 279 patients (43.0%) in the zolbetuximab group and 106 of 278 patients (38.1%) in the placebo group. Table 88 shows adverse events leading to discontinuation of the study drug reported by ≥5 patients in either group.

Table 88. Adverse events leading to discontinuation of the study drug reported by ≥5 patients in either group

PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 279		Placebo n = 278	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	120 (43.0)	106 (38.0)	106 (38.1)	82 (29.5)
Vomiting	20 (7.2)	19 (6.8)	1 (0.4)	1 (0.4)
Peripheral sensory neuropathy	19 (6.8)	19 (6.8)	21 (7.6)	19 (6.8)
Nausea	18 (6.5)	18 (6.5)	3 (1.1)	3 (1.1)
Neutrophil count decreased	18 (6.5)	18 (6.5)	14 (5.0)	14 (5.0)
Neutropenia	14 (5.0)	14 (5.0)	13 (4.7)	13 (4.7)
Decreased appetite	7 (2.5)	7 (2.5)	3 (1.1)	2 (0.7)
Fatigue	5 (1.8)	5 (1.8)	3 (1.1)	2 (0.7)
Paraesthesia	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)

7.3.4 Global phase III study (GLOW study)

Adverse events occurred in 251 of 254 patients (98.8%) in the zolbetuximab group and 244 of 249 patients (98.0%) in the placebo group, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 246 of 254 patients (96.9%) in the zolbetuximab group and 234 of 249 patients (94.0%) in the placebo group. Table 89 shows adverse events with an incidence of ≥10% in either group.

Table 89. Adverse events with an incidence of ≥10% in either group

SOC PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 254		Placebo n = 249	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	251 (98.8)	185 (72.8)	244 (98.0)	174 (69.9)
Blood and lymphatic system disorders				
Anaemia	90 (35.4)	27 (10.6)	91 (36.5)	28 (11.2)
Neutropenia	50 (19.7)	18 (7.1)	35 (14.1)	7 (2.8)
Thrombocytopenia	28 (11.0)	7 (2.8)	31 (12.4)	7 (2.8)
Gastrointestinal disorders				
Nausea	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)
Diarrhoea	80 (31.5)	15 (5.9)	86 (34.5)	18 (7.2)
Abdominal pain	40 (15.7)	1 (0.4)	54 (21.7)	4 (1.6)
Constipation	39 (15.4)	0	52 (20.9)	0
General disorders and administration site conditions				
Fatigue	34 (13.4)	7 (2.8)	42 (16.9)	9 (3.6)
Pyrexia	34 (13.4)	1 (0.4)	23 (9.2)	0
Asthenia	33 (13.0)	7 (2.8)	32 (12.9)	3 (1.2)
Malaise	31 (12.2)	1 (0.4)	22 (8.8)	0
Oedema peripheral	26 (10.2)	1 (0.4)	6 (2.4)	0
Investigations				
Neutrophil count decreased	70 (27.6)	26 (10.2)	59 (23.7)	24 (9.6)
AST increased	63 (24.8)	6 (2.4)	72 (28.9)	7 (2.8)
Platelet count decreased	61 (24.0)	19 (7.5)	60 (24.1)	20 (8.0)
White blood cell count decreased	51 (20.1)	5 (2.0)	39 (15.7)	9 (3.6)
Weight decreased	50 (19.7)	1 (0.4)	25 (10.0)	1 (0.4)
ALT increased	48 (18.9)	2 (0.8)	52 (20.9)	7 (2.8)
Metabolism and nutrition disorders				
Decreased appetite	105 (41.3)	17 (6.7)	84 (33.7)	4 (1.6)
Hypoalbuminaemia	57 (22.4)	8 (3.1)	35 (14.1)	4 (1.6)
Hypokalaemia	36 (14.2)	14 (5.5)	36 (14.5)	16 (6.4)
Nervous system disorders				
Peripheral sensory neuropathy	56 (22.0)	1 (0.4)	56 (22.5)	6 (2.4)
Hypoaesthesia	30 (11.8)	1 (0.4)	30 (12.0)	0
Psychiatric disorders				
Insomnia	27 (10.6)	0	16 (6.4)	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	41 (16.1)	4 (1.6)	49 (19.7)	9 (3.6)

Serious adverse events occurred in 120 of 254 patients (47.2%) in the zolbetuximab group and 124 of 249 patients (49.8%) in the placebo group. Table 90 shows serious adverse events reported by ≥6 patients in either group.

Table 90. Serious adverse events reported by ≥6 patients in either group

PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 254		Placebo n = 249	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	120 (47.2)	68 (26.8)	124 (49.8)	56 (22.5)
Vomiting	15 (5.9)	14 (5.5)	11 (4.4)	8 (3.2)
Nausea	11 (4.3)	11 (4.3)	6 (2.4)	6 (2.4)
Decreased appetite	10 (3.9)	9 (3.5)	3 (1.2)	3 (1.2)
Malignant neoplasm progression	9 (3.5)	1 (0.4)	13 (5.2)	0
Platelet count decreased	8 (3.1)	8 (3.1)	6 (2.4)	6 (2.4)
Diarrhoea	7 (2.8)	7 (2.8)	10 (4.0)	8 (3.2)
Upper gastrointestinal haemorrhage	7 (2.8)	4 (1.6)	4 (1.6)	1 (0.4)
Hypokalaemia	6 (2.4)	3 (1.2)	6 (2.4)	6 (2.4)
Pneumonia	6 (2.4)	0	5 (2.0)	0
Anaemia	5 (2.0)	2 (0.8)	6 (2.4)	3 (1.2)
Abdominal pain	3 (1.2)	0	6 (2.4)	0
Pulmonary embolism	2 (0.8)	1 (0.4)	8 (3.2)	3 (1.2)
Pleural effusion	1 (0.4)	0	7 (2.8)	2 (0.8)

Adverse events leading to discontinuation of the study drug occurred in 79 of 254 patients (31.1%) in the zolbetuximab group and 63 of 249 patients (25.3%) in the placebo group. Table 91 shows adverse events leading to discontinuation of the study drug reported by ≥5 patients in either group.

Table 91. Adverse events leading to discontinuation of the study drug reported by ≥5 patients in either group

PT (MedDRA ver.25.0)	Number of patients (%)			
	Zolbetuximab n = 254		Placebo n = 249	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	79 (31.1)	55 (21.7)	63 (25.3)	39 (15.7)
Vomiting	9 (3.5)	9 (3.5)	4 (1.6)	3 (1.2)
Nausea	6 (2.4)	6 (2.4)	3 (1.2)	2 (0.8)
Diarrhoea	5 (2.0)	5 (2.0)	2 (0.8)	2 (0.8)
Peripheral sensory neuropathy	5 (2.0)	5 (2.0)	5 (2.0)	5 (2.0)
Platelet count decreased	5 (2.0)	5 (2.0)	3 (1.2)	3 (1.2)
Neutropenia	4 (1.6)	3 (1.2)	5 (2.0)	5 (2.0)

7.3.5 Foreign phase I study (Study 001)

Adverse events occurred in 3 of 3 patients (100%) in 33 mg/m^2 cohort, 3 of 3 patients (100%) in 100 mg/m^2 cohort, 2 of 3 patients (66.7%) in 300 mg/m^2 cohort, 2 of 3 patients (66.7%) in 600 mg/m^2 cohort, and 3 of 3 patients (100%) in 1,000 mg/m^2 cohort, and adverse events for which a causal relationship to zolbetuximab could not be ruled out were observed in 0 patients in 33 mg/m^2 cohort, 3 of 3 patients (100%) in 100 mg/m^2 cohort, 1 of 3 patients (33.3%) in 300 mg/m^2 cohort, 1 of 3 patients (33.3%) in 600 mg/m^2 cohort, and 3 of 3 patients (100%) in 1,000 mg/m^2 cohort. Adverse events reported by ≥2 patients in each cohort were vomiting and decreased appetite in 2 patients (66.7%) each in 100 mg/m^2 cohort and vomiting, fatigue, and γ-glutamyl transpeptidase (GTP) increased in 2 patients (66.7%) each in 1,000 mg/m^2 cohort (none in 33 mg/m^2, 300 mg/m^2, and 600 mg/m^2 cohorts).

Serious adverse events occurred in 0 patients each in 33 mg/m^2 and 100 mg/m^2 cohorts, 1 of 3 patients (33.3%) in 300 mg/m^2 cohort, 1 of 3 patients (33.3%) in 600 mg/m^2 cohort, and 0 patients in 1,000 mg/m^2 cohort. Observed serious adverse events were odynophagia in 300 mg/m^2 cohort and urinary retention in 600 mg/m^2 cohort, and a causal relationship to zolbetuximab was denied for both of them.

No adverse events leading to discontinuation of zolbetuximab occurred.

7.3.6 Foreign phase I study (Study 04)

Adverse events occurred in 7 of 7 patients (100%) in Arm 1, 9 of 9 patients (100%) in Arm 2, 6 of 7 patients (85.7%) in Arm 3, and 4 of 5 patients (80.0%) in Arm 4, and adverse events for which a causal relationship to zolbetuximab could not be ruled out were observed in 3 of 7 patients (42.9%) in Arm 1, 6 of 9 patients (66.7%) in Arm 2, 4 of 7 patients (57.1%) in Arm 3, and 4 of 5 patients (80.0%) in Arm 4. Adverse events reported by ≥3 patients in each arm were anaemia, fatigue, and back pain in 3 patients (42.9%) each in Arm 1, nausea and vomiting in 6 patients (66.7%) each, fatigue in 4 patients (44.4%), and pyrexia and cough in 3 patients (33.3%) each in Arm 2, nausea and vomiting in 4 patients (57.1%) each and fatigue, decreased appetite, and dyspnea in 3 patients (42.9%) each in Arm 3, and vomiting in 4 patients (80.0%) and nausea in 3 patients (60.0%) in Arm 4.

Serious adverse events occurred in 3 of 7 patients (42.9%) in Arm 1, 5 of 9 patients (55.6%) in Arm 2, 2 of 7 patients (28.6%) in Arm 3, and 3 of 5 patients (60.0%) in Arm 4. There were no serious adverse events reported by ≥2 patients in any arm.

Adverse events leading to discontinuation of zolbetuximab occurred in 1 of 7 patients (14.3%) in Arm 1, 5 of 9 patients (55.6%) in Arm 2, 2 of 7 patients (28.6%) in Arm 3, and 2 of 5 patients (40.0%) in Arm 4. There were no adverse events leading to discontinuation of zolbetuximab reported by ≥2 patients in any arm.

7.3.7 Foreign phase II study (Study 02)

Adverse events occurred in 4 of 4 patients (100%) in Cohort 1 and 48 of 50 patients (96.0%) in Cohorts 2 and 3, and adverse events for which a causal relationship to zolbetuximab could not be ruled out were observed in 3 of 4 patients (75.0%) in Cohort 1 and 41 of 50 patients (82.0%) in Cohorts 2 and 3. Table 92 shows adverse events reported by ≥2 patients in Cohort 1 or adverse events with an incidence of ≥20% in Cohorts 2 and 3.

Table 92. Adverse events reported by ≥2 patients in (a) Cohort 1 or adverse events with an incidence of ≥20% in (b) Cohorts 2 and 3

SOC PT (MedDRA ver.20.0)	Number of patients (%)			
	(a) Cohort 1 n = 4		(b) Cohorts 2 and 3 n = 50	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	2 (50.0)	48 (96.0)	34 (68.0)
Gastrointestinal disorders				
Nausea	2 (50.0)	1 (25.0)	32 (64.0)	7 (14.0)
Vomiting	2 (50.0)	2 (50.0)	29 (58.0)	10 (20.0)
Constipation	1 (25.0)	0	13 (26.0)	0
Diarrhoea	0	0	14 (28.0)	3 (6.0)
General disorders and administration site conditions				
Fatigue	1 (25.0)	0	22 (44.0)	2 (4.0)
Asthenia	0	0	12 (24.0)	4 (8.0)
Oedema peripheral	0	0	12 (24.0)	1 (2.0)
General physical health deterioration	0	0	10 (20.0)	4 (8.0)
Metabolism and nutrition disorders				
Decreased appetite	0	0	16 (32.0)	2 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Tumour pain	3 (75.0)	0	3 (6.0)	2 (4.0)

Serious adverse events occurred in 1 of 4 patients (25.0%) in Cohort 1 and 24 of 50 patients (48.0%) in Cohorts 2 and 3. Serious adverse events reported by ≥2 patients in each cohort were general physical health deterioration and malignant neoplasm progression in 5 patients (10.0%) each, and diarrhoea, nausea, pleural effusion, and vomiting in 3 patients (6.0%) each in Cohorts 2 and 3 (none in Cohort 1). A causal relationship to zolbetuximab could not be ruled out for nausea in 2 patients and vomiting in 3 patients.

Adverse events leading to discontinuation of zolbetuximab occurred in 1 of 4 patients (25.0%) in Cohort 1 and 10 of 50 patients (20.0%) in Cohorts 2 and 3. Adverse events leading to discontinuation of zolbetuximab reported by ≥2 patients in each cohort were general physical health deterioration and nausea in 2 patients (4.0%) each in Cohorts 2 and 3 (none in Cohort 1). A causal relationship to zolbetuximab could not be ruled out for nausea in 2 patients.

7.3.8 Foreign phase II study (Study 03)

Adverse events occurred in 84 of 84 patients (100%) in Arm 1, 74 of 77 patients (96.1%) in Arm 2, and 85 of 85 patients (100%) in Arm 3, and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 80 of 84 patients (95.2%) in Arm 1, 74 of 77 patients (96.1%) in Arm 2, and 83 of 85 patients (97.6%) in Arm 3. Table 93 shows adverse events with an incidence of ≥20% in any arm.

Table 93. Adverse events with an incidence of ≥20% in any arm

SOC PT (MedDRA ver.15.0)	Number of patients (%)					
	(a) Arm 1 n = 84		(b) Arm 2 n = 77		(c) Arm 3 n = 85	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	84 (100)	54 (64.3)	74 (96.1)	54 (70.1)	85 (100)	58 (68.2)
Blood and lymphatic system disorders						
Anaemia	30 (35.7)	6 (7.1)	35 (45.5)	9 (11.7)	40 (47.1)	10 (11.8)
Neutropenia	29 (34.5)	18 (21.4)	34 (44.2)	25 (32.5)	40 (47.1)	25 (29.4)
Gastrointestinal disorders						
Nausea	64 (76.2)	4 (4.8)	63 (81.8)	5 (6.5)	70 (82.4)	2 (2.4)
Vomiting	46 (54.8)	3 (3.6)	52 (67.5)	8 (10.4)	66 (77.6)	10 (11.8)
Diarrhoea	31 (36.9)	3 (3.6)	14 (18.2)	3 (3.9)	16 (18.8)	2 (2.4)
Abdominal pain upper	18 (21.4)	1 (1.2)	7 (9.1)	0	8 (9.4)	1 (1.2)
General disorders and administration site conditions						
Asthenia	19 (22.6)	2 (2.4)	19 (24.7)	2 (2.6)	17 (20.0)	2 (2.4)
Fatigue	17 (20.2)	3 (3.6)	24 (31.2)	5 (6.5)	21 (24.7)	7 (8.2)
Pyrexia	17 (20.2)	0	9 (11.7)	0	9 (10.6)	0
Investigations						
Weight decreased	26 (31.0)	3 (3.6)	25 (32.5)	9 (11.7)	25 (29.4)	3 (3.5)
Metabolism and nutrition disorders						
Decreased appetite	19 (22.6)	2 (2.4)	15 (19.5)	0	16 (18.8)	1 (1.2)
Nervous system disorders						
Headache	18 (21.4)	2 (2.4)	12 (15.6)	0	13 (15.3)	1 (1.2)
Skin and subcutaneous tissue disorders						
Alopecia	17 (20.2)	1 (1.2)	22 (28.6)	0	22 (25.9)	1 (1.2)

Serious adverse events occurred in 27 of 84 patients (32.1%) in Arm 1, 19 of 77 patients (24.7%) in Arm 2, and 17 of 85 patients (20.0%) in Arm 3. Table 94 shows serious adverse events reported by ≥2 patients in any arm.

Table 94. Serious adverse events reported by ≥2 patients in any arm

PT (MedDRA ver.15.0)	Number of patients (%)					
	(a) Arm 1 n = 84		(b) Arm 2 n = 77		(c) Arm 3 n = 85	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	27 (32.1)	5 (6.0)	19 (24.7)	8 (10.4)	17 (20.0)	5 (5.9)
Neoplasm malignant	7 (8.3)	0	3 (3.9)	0	4 (4.7)	0
Gastric haemorrhage	3 (3.6)	0	0	0	0	0
Febrile neutropenia	2 (2.4)	2 (2.4)	2 (2.6)	2 (2.6)	0	0
Nausea	2 (2.4)	2 (2.4)	1 (1.3)	1 (1.3)	0	0
Pulmonary embolism	2 (2.4)	1 (1.2)	0	0	2 (2.4)	1 (1.2)
Renal failure	2 (2.4)	0	0	0	0	0
Pneumonia	0	0	2 (2.6)	0	1 (1.2)	0

Adverse events leading to discontinuation of the study drug occurred in 16 of 84 patients (19.0%) in Arm 1, 13 of 77 patients (16.9%) in Arm 2, and 12 of 85 patients (14.1%) in Arm 3. Table 95 shows adverse events leading to discontinuation of the study drug reported by ≥2 patients in any arm.

Table 95. Adverse events leading to discontinuation of the study drug reported by ≥2 patients in any arm

PT (MedDRA ver.15.0)	Number of patients (%)					
	(a) Arm 1 n = 84		(b) Arm 2 n = 77		(c) Arm 3 n = 85	
	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out	All adverse events	Adverse events for which a causal relationship to the study drug cannot be ruled out
All adverse events	16 (19.0)	4 (4.8)	13 (16.9)	9 (11.7)	12 (14.1)	8 (9.4)
Vomiting	2 (2.4)	0	4 (5.2)	3 (3.9)	2 (2.4)	2 (2.4)
General physical health deterioration	2 (2.4)	0	1 (1.3)	1 (1.3)	2 (2.4)	0
Nausea	1 (1.2)	0	2 (2.6)	2 (2.6)	0	0
Neoplasm malignant	1 (1.2)	0	1 (1.3)	0	2 (2.4)	0
Asthenia	0	0	2 (2.6)	2 (2.6)	1 (1.2)	1 (1.2)
Weight decreased	0	0	2 (2.6)	1 (1.3)	0	0

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

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

The inspections is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspections is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that zolbetuximab has efficacy in the treatment of CLDN18.2-positive unresectable advanced or recurrent gastric cancer, and that zolbetuximab has acceptable safety in view of its benefits. Zolbetuximab is a drug with a new active ingredient, which is expected to inhibit tumor cell growth by binding to CLDN18.2, expressed on the membrane of gastric cancer cells and thereby inducing ADCC and CDC against tumor cells expressing CLDN18.2 and considered as a clinically meaningful treatment option for patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer. PMDA considers that the safety, the dosage regimen, and other matters should be further discussed.

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

Review Report (2)

February 15, 2024

Product Submitted for Approval

Brand Name	Vyloy for I.V. Infusion 100 mg
Non-proprietary Name	Zolbetuximab (Genetical Recombination)
Applicant	Astellas Pharma Inc.
Date of Application	June 9, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

In view of the discussion presented in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has concluded that global phase III studies in patients with CLDN18.2-positive and HER2-negative unresectable advanced or recurrent gastric cancer who had not received prior chemotherapy (SPOTLIGHT and GLOW studies) demonstrated the efficacy of zolbetuximab/chemotherapy in this patient population with the results on PFS and OS, the primary and secondary endpoints, presented below.

- In both studies, the results from the primary analysis on PFS demonstrated superiority of zolbetuximab over placebo.
- In both studies, the results from the interim analysis on OS using a statistical test in a hierarchical procedure showed that zolbetuximab significantly extended OS compared with placebo.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion and raised the following comments.

- The efficacy of zolbetuximab/chemotherapy by primary site tended to differ between patients with gastric cancer and patients with cancer of the gastroesophageal junction in both the SPOTLIGHT

and GLOW studies[36]; and furthermore, the pooled analysis of the SPOTLIGHT and GLOW studies suggested an interaction between the treatment and primary site [see Table 36 in the Review Report (1)]. In view of the above, the efficacy of zolbetuximab/chemotherapy in patients with cancer of the gastroesophageal junction should be carefully evaluated. The safety of zolbetuximab/chemotherapy in patients with cancer of the gastroesophageal junction should be investigated in the post-marketing surveillance.

Based on the above discussion at the Expert Discussion, PMDA asked the applicant to explain factors that might have caused the efficacy to differ by the primary site.

The applicant's response:
The prevalence of gastric cancer and cancer of the gastroesophageal junction differs by race; the prevalence of gastric cancer is higher in Asians than in non-Asians, while that of cancer of the gastroesophageal junction is higher in non-Asians (*Digestion.* 2022;103:29-36, *Curr Gastroenterol Rep.* 2017;19:36). In the SPOTLIGHT and GLOW studies, the efficacy of zolbetuximab/chemotherapy differed among regions.[37] In response to this finding, the efficacy in the Asian and non-Asian subgroups was evaluated by primary site (Table 96), and the efficacy of zolbetuximab/chemotherapy tended to differ between the Asian and non-Asian subgroups, suggesting that in addition to the primary site, the race might have influenced the efficacy of zolbetuximab/chemotherapy. The CLDN18.2 expression level was similar between the cancers of different primary sites in the SPOTLIGHT and GLOW studies.[38] Based on this finding, CLDN18.2 expression is unlikely to affect the difference in efficacy of zolbetuximab between cancers of different primary sites.

[36] The hazard ratio [95% CI] of PFS in the zolbetuximab group to that in the placebo group was 0.69 [0.53, 0.89] in the subgroup of patients with gastric cancer and 1.02 [0.65, 1.59] in the subgroup of patients with cancer of the gastroesophageal junction in the SPOTLIGHT study and 0.62 [0.48, 0.79] in the subgroup of patients with gastric cancer and 1.35 [0.73, 2.50] in the subgroup of patients with cancer of the gastroesophageal junction in the GLOW study. The hazard ratio [95% CI] of OS, determined in the same manner, was 0.67 [0.52, 0.86] in the subgroup of patients with gastric cancer and 1.07 [0.69, 1.67] in the subgroup of patients with cancer of the gastroesophageal junction in the SPOTLIGHT study and 0.72 [0.57, 0.91] in the subgroup of patients with gastric cancer and 1.01 [0.56, 1.82] in the subgroup of patients with cancer of the gastroesophageal junction in the GLOW study.

[37] In the pooled analysis of the SPOTLIGHT and GLOW studies, the hazard ratio [95% CI] of PFS in the zolbetuximab group to that in the placebo group was 0.57 [0.45, 0.72] in the Asian region and 0.87 [0.70, 1.07] in the non-Asian region. The hazard ratio [95% CI] of OS, determined in the same manner, was 0.67 [0.53, 0.84] in the Asian region and 0.83 [0.67, 1.02] in the non-Asian region.

[38] In the CLDN18.2-positive patient population, patients with ≥75% and <90% tumor cells being CLDN18-membranous staining intensity ≥2+ accounted for 39.0% to 44.3% and patients with ≥90% tumor cells being CLDN18-membranous staining intensity ≥2+ accounted for 55.7% to 61.0% in the subgroup of patients with cancer of the gastroesophageal junction, and 41.8% to 45.0% and 54.8% to 57.9%, respectively, in the subgroup of patients with gastric cancer.

Table 96. Results on PFS and OS by primary site and race (pooled analysis of the SPOTLIGHT and GLOW studies)

Endpoint	Primary site	Race	Treatment	No. of patients	Median [95% CI] (months)	Hazard ratio* [95% CI]
PFS	Gastric cancer	Asian	Zolbetuximab	219	10.4 [8.64, 12.7]	0.55 [0.43, 0.71]
			Placebo	219	6.57 [6.14, 8.15]	
		Non-Asian	Zolbetuximab	219	8.54 [8.21, 10.5]	0.76 [0.59, 0.98]
			Placebo	200	8.25 [7.33, 9.20]	
	Cancer of the gastroesophageal junction	Asian	Zolbetuximab	27	8.11 [6.18, 23.3]	0.80 [0.38, 1.69]
			Placebo	29	7.95 [6.05, 8.38]	
		Non-Asian	Zolbetuximab	72	8.34 [6.24, 10.3]	1.28 [0.85, 1.94]
			Placebo	87	10.3 [8.48, 11.3]	
OS	Gastric cancer	Asian	Zolbetuximab	219	17.4 [15.7, 19.7]	0.66 [0.52, 0.84]
			Placebo	219	13.1 [11.2, 14.9]	
		Non-Asian	Zolbetuximab	219	17.0 [12.3, 19.5]	0.71 [0.56, 0.92]
			Placebo	200	13.3 [10.7, 14.7]	
	Cancer of the gastroesophageal junction	Asian	Zolbetuximab	27	17.7 [11.8, 33.7]	0.60 [0.30, 1.21]
			Placebo	29	11.5 [8.94, 26.3]	
		Non-Asian	Zolbetuximab	72	13.3 [9.69, 16.1]	1.28 [0.85, 1.93]
			Placebo	87	15.8 [13.1, 17.8]	

* Non-stratified Cox proportional hazard model

Regarding factors causing the efficacy of zolbetuximab/chemotherapy to differ between Asian and non-Asian, the following suggest that more patients in the Asian subgroup than in the non-Asian subgroup continued zolbetuximab by taking measures such as the slower infusion rate, etc. and avoided treatment interruption or discontinuation, potentially causing the difference in therapeutic effect between these subgroups.

- The pooled analysis of the SPOTLIGHT and GLOW studies revealed that patients who discontinued the study because of adverse events accounted for 9.1% (23 of 254) of patients in the zolbetuximab group and 6.3% (16 of 255) of patients in the placebo group in the Asian subgroup and 18.7% (53 of 283) of patients in the zolbetuximab group and 4.6% (13 of 280) of patients in the placebo group in the non-Asian subgroup. An imbalance was observed between the treatment groups in the non-Asian subgroup.
- The pooled analysis of the SPOTLIGHT and GLOW studies revealed that in the Asian and non-Asian subgroups (253 and 280 patients, respectively) (in the same order hereinafter), 14.6% and 24.6% experienced adverse events leading to discontinuation of zolbetuximab; 57.3% and 72.5% experienced adverse events leading to interruption of zolbetuximab; and 20.9% and 13.2% experienced adverse events leading to the slower infusion rate.

Regarding factors causing the efficacy of zolbetuximab/chemotherapy to differ between patients with gastric cancer and patients with cancer of the gastroesophageal junction, the exploratory subgroup analysis, of which results may have limitations in discussion, revealed that race and treatment status in addition to the primary site might have influenced the efficacy of zolbetuximab/chemotherapy. At present, therefore, the efficacy of zolbetuximab/chemotherapy in patients with cancer of the gastroesophageal junction would not be denied.

PMDA's view:

The applicant's explanation about factors causing the efficacy to differ by primary site is understandable to some extent. At present, factors have not been identified, but potential involvement of multiple factors was suggested. In view of such current status, the applicant should provide information on the results

by primary site and race in the SPOTLIGHT and GLOW studies through materials. In view of discussion at the Expert Discussion, the applicant should continue to gather information on the safety by primary site in the post-marketing surveillance [see Section 1.5].

1.2 Safety

In view of the discussion presented in Section "7.R.3 Safety" in the Review Report (1), PMDA has concluded that adverse events requiring special attention during use of zolbetuximab/chemotherapy are nausea and vomiting, infusion reaction, and hypersensitivity.

PMDA has also concluded that although attention should be paid to the above adverse events during use of zolbetuximab, zolbetuximab/chemotherapy is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures , such as monitoring and controlling of adverse events, and the interruption of zolbetuximab,.

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

1.3 Clinical positioning and indication

In view of the discussion presented in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA has concluded that the indication of zolbetuximab should be "CLDN18.2-positive unresectable, advanced or recurrent gastric cancer" with the following cautionary statements included in the Precautions Concerning Indication section.

- Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive[Note)] in a testing by adequately experienced pathologists or testing at qualified laboratories, after fully understanding the definition of CLDN18.2 positive presented in the "Clinical Studies" section. The testing should be performed using approved *in vitro* diagnostics or medical devices.
  Note) CLDN18.2 positivity can be determined when gastric cancer tissue is confirmed to be CLDN18 positive.
- Zolbetuximab should be used in patients with HER2-negative tumor.
- The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

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

PMDA instructed the applicant to specify the Indication and the Precautions Concerning Indication section as described above. The applicant agreed to do as instructed.

1.4 Dosage and administration

In view of the discussion presented in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA has concluded that the Dosage and Administration of zolbetuximab should be "In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion over at least 2 hours for the initial dose and then 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface

area) every 2 weeks for the subsequent doses" with the following cautionary statements included in the Precautions Concerning Dosage and Administration section:

- The infusion rate of zolbetuximab may be gradually increased after 30 to 60 minutes after the start of the infusion with reference to the table below, if the infusion is well-tolerated.

Dose	Infusion rate	
	Up to 30-60 minutes after the start of the infusion	Subsequent infusion rate
800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150-300 mg/m^2/h
400 mg/m^2	50 mg/m^2/h	100-200 mg/m^2/h

- Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.
- If any adverse drug reaction occurs after use of zolbetuximab, interruption or discontinuation of zolbetuximab, and other actions should be considered by referring to the table below.

Guide for interruption or discontinuation of zolbetuximab, and other actions at the occurrence of adverse drug reactions

Adverse drug reaction	Severity*	Action
Hypersensitivity or infusion reaction	Grade 2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	Anaphylaxis Suspected anaphylaxis Grade ≥3	Discontinue zolbetuximab.
Nausea	Grade ≥2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
Vomiting	Grade 2 or 3	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	Grade 4	Discontinue zolbetuximab.

* Graded according to NCI-CTCAE v5.0.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion and raised the following comments.

- The zolbetuximab 800/400 mg/m^2 Q2W regimen can be established based on results from the simulation using the PPK model, but the safety data with this regimen are not available. It is important to confirm the safety of this regimen in the post-marketing surveillance.

In view of the above discussion at the Expert Discussion, PMDA has concluded that the applicant is required to gather the safety information on the zolbetuximab 800/400 mg/m^2 Q2W regimen in the post-marketing surveillance [see Section 1.5].

PMDA instructed the applicant to specify the Dosage and Administration and the Precautions Concerning Dosage and Administration section as described above. The applicant agreed to do as instructed.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer who have received zolbetuximab/chemotherapy to investigate the post-marketing safety of zolbetuximab/chemotherapy in clinical use. The safety specification includes the infusion related reaction including nausea and vomiting. The planned sample size is 600 patients and the observation period is 54 weeks.

In view of the discussion presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that the post-marketing surveillance should be conducted to collect the safety information on zolbetuximab/chemotherapy in clinical use. PMDA further concluded on the surveillance plan as follows:

- The safety specification should be nausea and vomiting, and incidences of the concerned events (including incidences by type of antiemetic used) in post-marketing settings should be investigated.
- Details of the method for gathering the information should be continuously examined, including potentially conducting a post-marketing database survey.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion and commented that the safety by primary site and during the zolbetuximab 800/400 mg/m^2 Q2W regimen should be confirmed in the post-marketing surveillance in view of the discussion about the efficacy and dosage regimen.

On the basis of the above review and discussion at the Expert Discussion, PMDA instructed the applicant to re-examine the implementation plan for the surveillance.

The applicant's response:

- The safety specification for the surveillance will include nausea and vomiting.
- As a result of the examination of the method for gathering the information, the applicant will implement a use-results survey as the post-marketing surveillance to investigate the safety of zolbetuximab in clinical use, for the following reasons:
  - Because antiemetic will be administered to prevent nausea and vomiting, it is difficult to define their onset as an outcome based on prescription of antiemetic in the post-marketing database survey.
  - Information about the infusion rate of zolbetuximab is also important in evaluating control of nausea and vomiting for appropriateness. Although the concerned information may not be gathered in the post-marketing database survey, it can be gathered in the use-results survey by including the relevant survey items in a survey form.
- In view of the incidences of nausea and vomiting in the clinical studies, the planned sample size and observation period of the surveillance will be 600 patients and 54 weeks, respectively.

PMDA accepted the applicant's response. In addition, PMDA considers it possible to gather the safety information by primary site and during the zolbetuximab 800/400 mg/m^2 Q2W regimen in the above use-results survey.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for zolbetuximab should include the safety specification presented in Table 97, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 98 and Table 99.

Table 97. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypersensitivity • Infusion reaction • Nausea and vomiting	None	None
Efficacy specification		
None		

Table 98. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey in patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer	None	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals

Table 99. Outline of use-results survey (draft)

Objective	To capture incidences, etc. of nausea and vomiting in clinical use
Survey method	Survey method that registers consecutive patients
Population	Patients with CLDN18.2-positive unresectable advanced or recurrent gastric cancer
Observation period	54 weeks
Target sample size	600 patients
Main survey items	Safety specification: Nausea and vomiting Other main survey items: Patient characteristics (age, sex, primary site, medical history, and complications, etc.), treatment status of zolbetuximab (dose, infusion rate [at the start of the infusion, at 30-60 minutes after the start, at the resumption after treatment interruption], etc.), use of antiemetic (type of antiemetic, etc.), concomitant therapies (chemotherapy, presence or absence of radiation therapy, etc.), adverse events, etc.

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

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

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following finding was present in CTD 5.3.5.1-1, although it does not have a considerable impact on the overall evaluation of the study. PMDA notified the applicant of it as a finding requiring corrective action.

Finding requiring corrective action

Applicant

- The applicant did not check the maintenance status of blindness in the study in a timely manner.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that the clinical studies had been conducted in compliance with GCP overall, and there were no obstacles to conducting its review based on the application documents submitted. However, the following findings were present at some of the study sites and the sponsor, although they do not have a considerable impact on the overall evaluation of the studies. PMDA notified heads of the study sites and the sponsor of them as findings requiring corrective action.

Findings requiring corrective action

Sponsor

- Inconsistencies between case report forms and source documents of some of the subjects were not identified by monitoring.

Study sites

- Additional written informed consent to continued participation in the clinical study using the revised written information was not obtained from some of the subjects.
- Inconsistencies between case report forms and source documents were found in some of the subjects.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition, provided that the package insert includes appropriate cautionary statements; information about the proper use is appropriately disseminated in post-marketing settings; and zolbetuximab is properly used by physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. The product is a drug with a new active ingredient, and the re-examination period is 8 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

CLDN18.2-positive unresectable advanced or recurrent gastric cancer

Dosage and Administration

In combination with other antineoplastic agents, the usual adult dosage is 800 mg/m^2 (body surface area) of zolbetuximab (genetical recombination) administered as an intravenous infusion over at least 2 hours for the initial dose and then 600 mg/m^2 (body surface area) every 3 weeks or 400 mg/m^2 (body surface area) every 2 weeks for the subsequent doses.

Approval Condition

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

Warnings

The product should be administered only to patients considered appropriate to receive treatment with the product by physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. Prior to treatment, the benefits and risks of the treatment should be thoroughly explained to the patient or their family member, and consent should be obtained.

Contraindication

Patients with a history of serious hypersensitivity to the product or any of the excipients

Precautions Concerning Indication

1. Zolbetuximab should be used in patients with tumor confirmed to be CLDN18.2 positive[Note)] in a testing by adequately experienced pathologists or testing at qualified laboratories, after fully understanding the definition of CLDN18.2 positive presented in the "Clinical Studies" section. The testing should be performed using approved *in vitro* diagnostics or medical devices.

   Note) CLDN18.2 positivity can be determined when gastric cancer tissue is confirmed to be CLDN18 positive.
2. Zolbetuximab should be used in patients with HER2-negative tumor.
3. The efficacy and safety of zolbetuximab have not been established for use in postoperative adjuvant chemotherapy.

Precautions Concerning Dosage and Administration

1. The infusion rate of zolbetuximab may be gradually increased after 30 to 60 minutes after the start of the infusion with reference to the table below, if the infusion is well-tolerated.

Dose	Infusion rate	
	Up to 30-60 minutes after the start of the infusion	Subsequent infusion rate
800 mg/m^2	100 mg/m^2/h	200-400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150-300 mg/m^2/h
400 mg/m^2	50 mg/m^2/h	100-200 mg/m^2/h

2. Other antineoplastic agents to be concomitantly used should be selected with a full understanding of the information presented in the "Clinical Studies" section.
3. If any adverse drug reaction occurs after use of zolbetuximab, interruption or discontinuation of zolbetuximab, and other actions should be considered by referring to the table below.

Guide for interruption or discontinuation of zolbetuximab, and other actions at the occurrence of adverse drug reactions

Adverse drug reaction	Severity[Note)]	Action
Hypersensitivity or infusion reaction	Grade 2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	• Anaphylaxis • Suspected anaphylaxis • Grade ≥3	Discontinue zolbetuximab.
Nausea	Grade ≥2	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
Vomiting	Grade 2 or 3	Interrupt zolbetuximab until the reaction resolves to Grade ≤1. After recovery, resume the infusion at the slower rate. For the next dose, use prophylactic medication, and then administer zolbetuximab as recommended in the infusion rate table.
	Grade 4	Discontinue zolbetuximab.

Note) Graded according to NCI-CTCAE ver.5.0.

Appendix

List of Abbreviations

5-FU	5-fluorouracil
5-HT	5-hydroxytryptamine
800/400 mg/m^2 Q2W regimen	The initial dose of 800 mg/m^2 (body surface area) and subsequent doses of 400 mg/m^2 (body surface area) are administered as an intravenous infusion every 2 weeks.
800/600 mg/m^2	800 mg/m^2 for the initial dose, 600 mg/m^2 for the subsequent doses
800/600 mg/m^2 Q3W regimen	The initial dose of 800 mg/m^2 (body surface area) and subsequent doses of 600 mg/m^2 (body surface area) are administered as an intravenous infusion every 3 weeks.
ADCC	antibody dependent cellular cytotoxicity
ADCP	antibody dependent cell-mediated phagocytosis
ALT	alanine aminotransferase
Application	Application for marketing approval
AST	aspartate aminotransferase
BID	bis in die
BQL	below the quantification limit
C1q	subcomponent of complement C1
Cape	Capecitabine
CAPOX	Co-administration of Cape and L-OHP
CD	cluster of differentiation
CDC	complement dependent cytotoxicity
CE-SDS	capillary electrophoresis sodium dodecyl sulphate
Cetuximab	Cetuximab (Genetical Recombination)
Chemotherapy	CAPOX or FOLFOX
CHO	Chinese hamster ovary
CI	confidence interval
cIEF	capillary isoelectric focusing
CLDN18	claudin-18
CLDN18.1	claudin-18 splice variant 1
CLDN18.2	claudin-18 splice variant 2
COVID-19	coronavirus disease
CPS	combined positive score
CQA	critical quality attribute
CrCL	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOF	Epirubicin, L-OHP, and 5-FU
EOPC	end of production cell
EOX	Co-administration of epirubicin, L-OHP, and capecitabine
Epirubicin	Epirubicin hydrochloride
ETFE	ethylene-tetrafluoroethylene

FAS	full analysis set
FcRn	neonatal Fc receptor
FcγR	fc gamma receptor
FITC	fluorescein isothiocyanate
FLO	5-FU, leucovorin, and L-OHP
FOLFOX	Co-administration of 5-FU, (*l*-)LV, and L-OHP
GLOW study	Study 8951-CL-0302
HCP	host cell protein
HER2	human epidermal growth factor receptor type 2
HLT	high level term
ICH Q5A(R1) guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B guideline	"Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D guideline	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
Ig	Immunoglobulin
IHC	immunohistochemistry
IL-2	interleukin-2
ILD	interstitial lung disease
IRC	independent review committee
Japanese treatment guideline	Japanese gastric cancer treatment guidelines edited by the Japanese Gastric Cancer Association
K_D	dissociation constant
LV	Folinate
l-LV	Levofolinate
(*l*-)LV	*l*-LV or LV
L-OHP	oxaliplatin
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MSX	L-methionine sulfoximine
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Gastric Cancer
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
Nivolumab	Nivolumab (Genetical Recombination)
Nivolumab/chemotherapy	Combination of nivolumab and chemotherapy
NK	neurokinin
OF	L-OHP and 5-FU
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-L1	programmed cell death-ligand 1
Pembrolizumab	Pembrolizumab (Genetical Recombination)
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics

PS	performance status
PT	preferred term
QOL	quality of life
QT	QT interval
QTc	QT interval corrected
ΔQTcF	Changes from baseline in QT corrected by the Fridericia's correction formula
QW	quaque 1 week
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RH	relative humidity
SEC	size exclusion chromatography
SMQ	standardised MedDRA queries
SOC	system organ class
SPOTLIGHT study	Study 8951-CL-0301
Study 001	Study GM-IMAB-001
Study 0103	Study 8951-CL-0103
Study 0104	Study 8951-CL-0104
Study 0105	Study 8951-CL-0105
Study 02	Study GM-IMAB-001-02
Study 03	Study GM-IMAB-001-03
Study 04	Study GM-IMAB-001-04
Trastuzumab	Trastuzumab (Genetical Recombination)
WCB	working cell bank
Zolbetuximab	Zolbetuximab (Genetical Recombination)
Zolbetuximab/CAPOX	Combination of zolbetuximab and CAPOX
Zolbetuximab/EOF	Zolbetuximab and EOF
Zolbetuximab/EOX	Combination of zolbetuximab and EOX
Zolbetuximab/FOLFOX	Combination of zolbetuximab and FOLFOX
Zolbetuximab/OF	Zolbetuximab and OF
Zolbetuximab/chemotherapy	Combination of zolbetuximab and chemotherapy
Zolbetuximab/pembrolizumab	Combination of zolbetuximab and pembrolizumab
Zoledronic acid	Zoledronic acid hydrate
γ-GTP	γ-glutamyl transpeptidase