Review Report

August 21, 2020
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	Enhertu for Intravenous Drip Infusion 100 mg
Non-proprietary Name	Trastuzumab Deruxtecan (Genetical Recombination) (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 28, 2020
Dosage Form/Strength	Injection: each vial contains 107 mg of trastuzumab deruxtecan (genetical recombination)
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (10) Other drugs (under re-examination)
Items Warranting Special Mention	SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 5 of 2018 [*30 yaku*]; PSEHB/PED Notification No.0327-1 dated March 27, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy, 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 indications and dosage and administration shown below, with the following conditions. The incidence and risk factors for interstitial lung disease (ILD) should be further evaluated in the post-marketing surveillance.

Indications

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy

(Underline denotes additions.)

Dosage and Administration

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy

The usual adult dosage is 6.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been collected. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

July 8, 2020

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	Enhertu for Intravenous Drip Infusion 100 mg
Non-proprietary Name	Trastuzumab Deruxtecan (Genetical Recombination)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 28, 2020
Dosage Form/Strength	Injection: each vial contains 107 mg of trastuzumab deruxtecan (genetical recombination)
Proposed Indications	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments) Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy (Underline denotes additions.)
Proposed Dosage and Administration	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments) The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes. Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy The usual adult dosage is 6.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes. (Underline denotes additions.)

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

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) discovered by the applicant and consists of MAAL-9001, a humanized monoclonal antibody of immunoglobin G1 (IgG1) subclass targeting human epidermal growth factor receptor type 2 (HER2), that is bound via a peptide linker to MAAA-1181a, a topoisomerase I inhibitor derivative of exatecan. Trastuzumab deruxtecan binds to HER2 expressed on the tumor cell membrane. Upon internalization into the cell, the linker undergoes hydrolysis, releasing MAAA-1181a. The released MAAA-1181a is thought to induce deoxyribonucleic acid (DNA) damage, apoptosis, and other effects, leading to inhibition of tumor growth.

In Japan, trastuzumab deruxtecan was approved in March 2020 for the indication of "unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)."

1.2 Development history etc.

The following studies were conducted in the clinical development of trastuzumab deruxtecan for the treatment of unresectable advanced or recurrent HER2-positive gastric cancer. Study J101 was a global phase I study conducted by the applicant from September 2015 in patients with unresectable advanced or recurrent HER2-positive gastric cancer, etc. From November 2017, a global phase II study (Study J202) was conducted by the applicant in patients with unresectable advanced or recurrent HER2-positive gastric cancer that had progressed after ≥2 chemotherapy regimens including trastuzumab.

As of May 2020, for the indication of unresectable advanced or recurrent HER2-positive gastric cancer, trastuzumab deruxtecan has not been approved in any country or region.

In Japan, enrollment of patients in Studies J101 and J202 began in September 2015 and November 2017, respectively.

Recently, an application for partial change to the marketing approval of trastuzumab deruxtecan has been filed with the results from the pivotal J202 study.

In March 2018, trastuzumab deruxtecan was designated as a SAKIGAKE product (SAKIGAKE Drug Designation No.5 of 2018 [*30 yaku*]) with the intended indication of "unresectable advanced or recurrent HER2-overexpressing gastric cancer that has progressed after cancer chemotherapy.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Although the present application is for a new indication and a new dosage of trastuzumab deruxtecan, data relating to the quality of the drug product stability have been submitted. The results obtained so far from the stability study (e.g., long-term testing using 3 batches of the formulation[1)] manufactured by

1) The manufacturing site and scale of the formulation differ from those of the formulation manufactured by the approved process.

Process 1 for [redacted] months) suggest that (a) no significant changes in quality attributes including biological activity were observed either in the formulation manufactured by Process 1 or the formulation manufactured by the approved process; and (b) there were no significant differences in stability between the formulation manufactured by Process 1 and the formulation manufactured by the approved process. On the basis of the findings including the above, the applicant explained that the shelf life of the drug product will be extended up to 30 months based on the results of the long-term testing using 3 batches of the formulation manufactured by Process 1 for [redacted] months and that a commitment relating to shelf-life extension will be made.

On the basis of the submitted data, PMDA concluded that the applicant's explanation was acceptable.

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

The present application is for a new indication and a new dosage of trastuzumab deruxtecan, and non-clinical pharmacology data have already been evaluated at the initial approval; therefore, no new data were submitted.

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

The present application is for a new indication and a new dosage of trastuzumab deruxtecan, and non-clinical pharmacokinetic data have already been evaluated at the initial approval; therefore, no new data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication and a new dosage of trastuzumab deruxtecan, no data relating to toxicity testing were submitted.

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

The present application is for a new indication and a new dosage of trastuzumab deruxtecan, and data relating to biopharmaceutic studies and associated analytical methods have already been evaluated at the initial approval; therefore, no new data were submitted.

6.1 Clinical pharmacology

6.1.1 Global phase II study (CTD 5.3.5.1-1, Study J202 [ongoing since November 2017, data cut-off on November 8, 2019])

An open-label, randomized study was conducted in the primary cohort of 188 patients (125 were included in the pharmacokinetic [PK] analysis) with unresectable advanced or recurrent HER2-positive gastric cancer[2)] that had progressed after ≥2 chemotherapy regimens including trastuzumab to compare the efficacy and safety of trastuzumab deruxtecan with the efficacy and safety of the treatment of investigator's choice (IC).

2) Patients with gastroesophageal junction adenocarcinoma were also eligible for enrollment.

The dosage regimen was trastuzumab deruxtecan 6.4 mg/kg administered intravenously Q3W in 21-day cycles, and serum trastuzumab deruxtecan concentrations and other parameters were evaluated.

Table 1 shows the PK parameters of trastuzumab deruxtecan and MAAA-1181a.

Of the 123 subjects whose anti-drug antibodies against trastuzumab deruxtecan were measured after administration of the first dose of trastuzumab deruxtecan, the antibodies were detected in 9 subjects.

Table 1. PK parameters of trastuzumab deruxtecan and MAAA-1181a

Analyte	Cycle	n	C_{max} (μg/mL[*1])	t_{max}[*2] (h)	AUC_{last} (μg·day/mL[*3])	AUC_{21day} (μg·day/mL[*3])	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Trastuzumab deruxtecan	1	125	127 ± 28.4	3.93 (0.00, 7.15)	611 ± 150	612 ± 150[*4]	5.77 ± 1.37[*4]	10.4 ± 2.91[*4]	70.6 ± 16.5[*4]
	3	69	137 ± 31.1	4.00 (0.58, 7.25)	—	867 ± 213[*5]	7.46 ± 1.82[*5]	7.86 ± 1.87[*6]	71.9 ± 19.3[*5]
MAAA -1181a	1	125	12.1 ± 4.79	6.85 (3.75, 7.25)	46.7 ± 16.3	46.4 ± 16.1[*7]	5.50 ± 1.11[*8]	—	—
	3	69	9.08 ± 3.81	6.80 (3.78, 7.25)	—	42.0 ± 15.1[*9]	7.01 ± 1.65[*10]	—	—

Mean ± standard deviation; *1, values for MAAA-1181a are expressed in ng/mL; *2, median (range); *3, values for MAAA-1181a are expressed in ng·day/mL; *4, 124 subjects; *5, 66 subjects; *6, 68 subjects; *7, 107 subjects; *8, 98 subjects; *9, 54 subjects; *10, 50 subjects

6.1.2 PPK analysis

Population pharmacokinetic (PPK) analyses of trastuzumab deruxtecan and MAAA-1181a were performed based on the PK data of trastuzumab deruxtecan and MAAA-1181a (n = 808; 14,042 timepoints [serum trastuzumab deruxtecan concentration] and 14,119 timepoints [serum MAAA-1181a concentration]) from a Japanese phase I study (Study J102), global phase I studies (Studies J101 and A104), global phase II studies (Studies J202 and U201), and a foreign phase I study (Study A103) using a nonlinear mixed effects model (software, NONMEM Version 7.3). The results of the PPK analysis include the following:

- The analysis identified tumor type as the covariate[3)] on CL_{intact} and V_1 of trastuzumab deruxtecan, and on CL_{drug} and V_{drug} of MAAA-1181a.
- Table 2 shows the estimated exposure to trastuzumab deruxtecan and MAAA-1181a following administration of trastuzumab deruxtecan 6.4 mg/kg Q3W to patients with gastric cancer, or trastuzumab deruxtecan 5.4 mg/kg Q3W to patients with breast cancer.

3) The following covariates were tested for trastuzumab deruxtecan: tumor type, prior total gastrectomy, race, ALT, AST, total bilirubin, creatinine clearance (CLcr), and degree of hepatic impairment (National Cancer Institute [NCI] criteria) on elimination clearance of intact DS-8201a (CL_{intact}); and tumor type and race on central volume of distribution (V_1). Likewise, the following covariates were tested for MAAA-1181a: tumor type, race, CLcr, and degree of hepatic impairment (NCI criteria) on elimination clearance of released drug (MAAA-1181a) (CL_{drug}); and tumor type and race on released drug (MAAA-1181a) volume of distribution (V_{drug}).

Table 2. Estimated PK parameters of trastuzumab deruxtecan and MAAA-1181a in patients with gastric cancer or breast cancer

Analyte	Patient population (dose)	n	$C_{max,ss}$ (μg/mL[*1])	$C_{min,ss}$ (μg/mL[*1])	AUC_{ss} (μg·day/mL[*2])
Trastuzumab deruxtecan	Gastric cancer (6.4 mg/kg)	193	126	10.4	743
	Breast cancer (5.4 mg/kg)	270	125	11.2	743
MAAA-1181a	Gastric cancer (6.4 mg/kg)	193	5.22	0.465	32.9
	Breast cancer (5.4 mg/kg)	270	4.39	0.418	27.7

Geometric mean; *1, values for MAAA-1181a are expressed in ng/mL; *2, values for MAAA-1181a are expressed in ng·day/mL

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about clinical pharmacology was acceptable.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from a global phase I study and a global phase II study shown in Table 3. The applicant also submitted results from 4 studies (a Japanese phase I study, a global phase I study, a global phase II, and a foreign phase I study) as reference data (Table 3). These reference data were previously submitted when an application for initial approval of trastuzumab deruxtecan was filed and have already been evaluated; therefore, the details of these studies are not included in this report (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020).

Table 3. List of clinical studies on efficacy and safety

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Major endpoints
Evalua-tion	Global	J101	I	Part 1 Patients with unresectable or recurrent breast cancer, and patients with unresectable advanced or recurrent gastric cancer Part 2 2a, Patients with unresectable or recurrent HER2-positive[*1] breast cancer previously treated with T-DM1 2b, Patients with HER2-positive[*2] gastric cancer previously treated with trastuzumab 2c, Patients with unresectable or recurrent HER2 low-expressing[*3] breast cancer 2d, Patients with HER2-expressing[*4] advanced solid tumors (other than breast/gastric cancer), and HER2-mutated advanced solid tumors 2e, Patients with unresectable or recurrent HER2-expressing[*5] breast cancer	Part 1 27 Part 2 2a, 103 2b, 41 2c, 40 2d, 60 2e, 21	Part 1 Trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg IV infusion Q3W Part 2 Trastuzumab deruxtecan 5.4 or 6.4 mg/kg IV infusion Q3W	Efficacy Safety Tolerability PK

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Major endpoints
	Global	J202	II	Primary cohort Patients with unresectable advanced or recurrent HER2-positive[*2] gastric cancer that had progressed after ≥2 chemotherapy regimens including trastuzumab Exploratory cohort HER2-targeted treatment[*6] naïve patients with HER2-low expressing[*7] gastric cancer that had progressed after ≥2 chemotherapy regimens	Primary cohort: (1) 126 (2) 62 Exploratory cohort: Cohort 1, 21 Cohort 2, 24	Primary cohort (1) Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W (2) CPT-11 150 mg/m^2 IV infusion Q2W, or PTX 80 mg/m^2 IV infusion QW Exploratory cohort Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W	Efficacy Safety
Reference	Japan	J102	I	Patients with unresectable or recurrent HER2-expressing[*5] breast cancer	51	Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W	PK
	Global	A104	I	Patients with HER2-expressing[*5] advanced solid tumors	Cohort 1: 17 Cohort 2: 23	Cohort 1 Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W in combination with ritonavir Cohort 2 Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W in combination with itraconazole	PK
	Global	U201	II	Patients with unresectable or recurrent HER2-positive[*1] breast cancer previously treated with T-DM1	Part 1 PK stage, 65 Dose-finding stage, 54 Part 2 2a, 130 2b, 4	Part 1 PK stage: Trastuzumab deruxtecan 5.4, 6.4, or 7.4 mg/kg IV infusion Q3W Dose-finding stage: Trastuzumab deruxtecan 5.4 or 6.4 mg/kg IV infusion Q3W Part 2 Trastuzumab deruxtecan 5.4 mg/kg IV infusion Q3W	Efficacy Safety PK
	Foreign	A103	I	Patients with HER2-positive[*1] cancer shown below, previously treated with trastuzumab • unresectable or recurrent breast cancer • unresectable advanced or recurrent gastric cancer	12	Trastuzumab deruxtecan 6.4 mg/kg IV infusion Q3W	PK

*1, Defined as tumors scored as 3+ by immunohistochemistry (IHC) or *in situ* hybridization (ISH)-positive; *2, defined as tumors scored as 3+ by IHC, or tumors scored as 2+ by IHC and ISH-positive; *3, defined as tumors scored as 2+ by IHC and ISH-negative, tumors scored as 1+ by IHC and ISH-negative, or tumors scored as 1+ by IHC and ISH not evaluated; *4, defined as expression detected by IHC, ISH, next generation sequencing (NGS), or other methods; *5, defined as tumors scored as 1+, 2+, or 3+ by IHC, or ISH-positive; *6, treatment with agents targeting HER2 such as trastuzumab; *7, patients with tumors scored as 2+ by IHC and ISH-negative in Exploratory Cohort 1; patients with tumors scored as 1+ by IHC in Exploratory Cohort 2.

The following sections provide an outline of the clinical studies. Main adverse events other than deaths that occurred in the clinical studies are described in Section "7.2 Adverse events and other findings observed in clinical studies." The results data of Study J101 were previously submitted when an application for initial approval of trastuzumab deruxtecan was filed, and have already been evaluated; therefore, the details of these studies are not included in this report (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020).

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase I study (CTD 5.3.3.2-1, Study J101 [ongoing since September 2015, data cut-off on February 1, 2019])

An open-label, uncontrolled study was conducted at 14 study centers in 2 countries including Japan to assess the efficacy, safety, PK, and other aspects of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer,[2)] or other types of tumor[4)] (target sample size: Part 1, 18 subjects; Part 2a, 100 subjects; Part 2b, 40 subjects; Part 2c, 40 subjects; Part 2d, 60 subjects; Part 2e, 20 subjects).

The dosage regimens were as follows: in Part 1 (dose escalation stage), trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg intravenously Q3W; and in Parts 2a through 2e (dose expansion stage), trastuzumab deruxtecan 5.4 or 6.4 mg/kg intravenously Q3W. Treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

All 41 subjects (including 36 Japanese subjects) enrolled in Part 2b were included in the efficacy analyses. In Part 2b, 17 subjects (including 12 Japanese subjects) were assigned to the 5.4 mg/kg group and 24 subjects (all Japanese subjects) were assigned to the 6.4 mg/kg group. Of the 292 subjects enrolled in the study, 3 subjects who did not receive trastuzumab deruxtecan were excluded, and the remaining 289 subjects (including 178 Japanese subjects) were included in the safety analyses. Among these subjects, the number of patients with HER2-positive gastric cancer who received trastuzumab deruxtecan 5.4 mg/kg or 6.4 mg/kg as the initial dose was 19 (including 14 Japanese) subjects and 25 (all Japanese) subjects, respectively.

The first 21 days after the start of treatment in Part 1 was defined as the dose limiting toxicity (DLT) assessment period. No DLTs were observed, and the maximum tolerated dose (MTD) was not determined.

As the efficacy endpoints, which are the primary objective of Part 2, confirmed objective response rate by independent central review (ICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 and other measures of efficacy were specified.

Table 4 shows the results of confirmed objective response rate[5)] by ICR according to RECIST ver.1.1, one of the efficacy endpoints in Part 2b (data cut-off on February 1, 2019).

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4) The target populations enrolled in the study are shown below by part. Parts 1, 2c, 2d, and 2e enrolled patients refractory or intolerant to standard lines of treatment.
- Part 1: Patients with unresectable or recurrent breast cancer, and patients with unresectable advanced or recurrent gastric cancer.
- Part 2a: Patients with unresectable or recurrent HER2-positive (scored as 3+ by IHC or ISH-positive) breast cancer previously treated with T-DM1.
- Part 2b: Patients with HER2-positive (scored as 3+ by IHC, or scored as 2+ by IHC and ISH-positive) gastric cancer previously treated with trastuzumab.
- Part 2c: Patients with unresectable or recurrent HER2 low-expressing (scored as 2+ by IHC and ISH-negative, scored as 1+ by IHC and ISH-negative, or scored as 1+ by IHC and ISH not-evaluated) breast cancer.
- Part 2d: Patients with HER2-expressing (detected by e.g., IHC, ISH, NGS) advanced solid tumors (other than breast/gastric cancer), and *HER2*-mutated advanced solid tumors.
- Part 2e: Patients with unresectable or recurrent HER2-expressing (scored as 1+, 2+, or 3+ by IHC, or ISH-positive) breast cancer.

5) In the calculation, patients with response were defined as patients who achieved a confirmed response (defined as subjects with response further confirmed by imaging after ≥4 weeks from the first response confirmed as per RECIST ver.1.1).

Table 4. Best overall response and confirmed objective response rate (RECIST ver.1.1, Part 2b, efficacy analysis set, by ICR, data cut-off on February 1, 2019)

Best overall response	Number of subjects (%)	
	Trastuzumab deruxtecan 5.4 mg/kg (n = 17)	Trastuzumab deruxtecan 6.4 mg/kg (n = 24)
CR	0	1 (4.2)
PR	4 (23.5)	7 (29.2)
SD	9 (52.9)	13 (54.2)
PD	4 (23.5)	3 (12.5)
Response (CR + PR) (objective response rate % [95% CI*])	4 (23.5% [6.8, 49.9])	8 (33.3% [15.6, 55.3])

*, Clopper-Pearson method

During the treatment period and within 28 days of the last dose of trastuzumab deruxtecan, deaths occurred in 10 of 289 subjects (3.5%), including 5 deaths in Japanese subjects. Three of the 10 subjects died from disease progression. The causes of death other than disease progression were respiratory failure (3 subjects), pneumonitis (1 subject), mechanical ileus (1 subject), pneumonia aspiration (1 subject), and disseminated intravascular coagulation/febrile neutropenia/hepatic function abnormal (1 subject). Among these events, a causal relationship to trastuzumab deruxtecan could not be ruled out for respiratory failure (2 subjects), pneumonitis (1 subject), and disseminated intravascular coagulation/febrile neutropenia/hepatic function abnormal (1 subject) (the causes of death due to adverse events were identified as mechanical ileus [1 subject], pneumonia aspiration [1 subject], and disseminated intravascular coagulation/febrile neutropenia/hepatic function abnormal [1 subject] in Japanese subjects).

Of the patients with HER2-positive gastric cancer who received trastuzumab deruxtecan 6.4 mg/kg, deaths occurred in 1 of 25 subjects (4.0%). The cause of death in this patient (Japanese) was disease progression, and a causal relationship to trastuzumab deruxtecan was denied. There were no deaths in patients with HER2-positive gastric cancer who received trastuzumab deruxtecan 5.4 mg/kg.

7.1.1.2 Global phase II study (CTD 5.3.5.1-1, Study J202 [ongoing since November 2017, data cut-off on November 8, 2019])

An open-label, randomized study was conducted at 66 study centers in 2 countries including Japan in the primary cohort[6)] (target sample size, 180 subjects) in patients with unresectable advanced or recurrent HER2-positive[7)] gastric cancer[2)] that had progressed after ≥2 chemotherapy regimens[8)] including trastuzumab to compare the efficacy and safety of trastuzumab deruxtecan with the efficacy and safety of the treatment of IC.

The dosage regimens were as follows: in the trastuzumab deruxtecan group, trastuzumab deruxtecan 6.4 mg/kg intravenously Q3W, and in the IC group, (i) irinotecan hydrochloride hydrate (CPT-11) 150

6) The study consists of the primary cohort and exploratory cohort, which was aimed to evaluate the efficacy and safety of trastuzumab deruxtecan in HER2-targeted treatment naïve patients with HER2-low expressing (Exploratory cohort 1: patients with tumors scored as 2+ by IHC and ISH-negative; Exploratory cohort 2: patients with tumors scored as 1+ by IHC) gastric cancer that had progressed after ≥2 cancer chemotherapy regimens (target sample size, 20 subjects each in the Exploratory cohorts 1 and 2).

7) Defined as tumors scored as 3+ by IHC, or tumors scored as 2+ by IHC and ISH-positive.

8) Patients with prior fluoropyrimidine- and platinum-based chemotherapy regimens were enrolled.

mg/m^2 intravenously Q2W; or (ii) paclitaxel (PTX) 80 mg/m^2 intravenously QW for 3 consecutive weeks followed by a rest period of at least 2 weeks. Treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

Of the 188 subjects who were enrolled in the primary cohort of the study and randomized (126 subjects in the trastuzumab deruxtecan group and 62 subjects in the IC group), 187 subjects (125 subjects including 99 Japanese subjects in the trastuzumab deruxtecan group and 62 subjects including 50 Japanese subjects in the IC group) received at least 1 dose of the study drug and were included in the full analysis set (FAS). Of the187 subjects, 175 subjects who were identified by ICR to have targeted lesions at baseline (119 subjects including 95 Japanese subjects in the trastuzumab deruxtecan group and 56 subjects including 45 Japanese subjects in the IC group) were included in the response evaluable set (RES). The FAS and RES were included in the efficacy analyses,[9)] while the FAS was included in the safety analyses.

At the beginning of the study, the primary endpoint in the primary cohort of the study was the objective response rate[10)] by ICR according to RECIST ver.1.1. When a statistically significant result was obtained in the primary analysis, secondary endpoints were to be analyzed hierarchically starting from PFS followed by OS. After the start of the study, this was amended by taking into consideration that the evaluation of OS in the patient population is clinically meaningful. When a statistically significant result was obtained in the primary analysis of objective response rate, an analysis of OS only was to be performed hierarchically (Protocol version 3.0, dated [redacted], 20[redacted]). At the beginning of the study, the primary analysis of objective response rate was to be performed when all patients in the primary cohort completed tumor assessment at Week 18 after the start of study drug treatment. After the above amendment was made to the analysis, the primary analysis was to be performed at one of the following timepoints whichever came later (1) when all patients in the primary cohort have completed tumor assessment at Week 18; or (2) when approximately 108 OS-related events have occurred (Protocol version 3.0, dated [redacted], 20[redacted]). During the study, the results of Study J101 (data cut-off on August 10, 2018) suggested that time to onset of OS-related events in the trastuzumab deruxtecan group could be longer than previously estimated. Accordingly, the protocol was amended so that primary analysis of objective response rate would be performed when all patients in the primary cohort have completed tumor assessment at Week 24 (Protocol version 4.0, dated [redacted], 20[redacted]).

Table 5 shows the results of the objective response rate[10)] by ICR according to RECIST ver.1.1, the primary endpoint in the primary cohort of the study. The objective response rates were statistically significantly higher in the trastuzumab deruxtecan group than in the IC group (data cut-off on November 8, 2019).

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9) RES was the primary analysis set for objective response rate and disease control rate, while FAS was the primary analysis set for the other efficacy endpoints (e.g., OS).

10) In the calculation, patients with response were defined as patients who achieved response confirmed by at least 1 imaging exam regardless of being assessed as confirmed response (defined as subjects with response further confirmed by imaging after ≥4 weeks from the first response confirmed as per RECIST ver.1.1).

Table 5. Best overall response and objective response rate (RECIST ver.1.1, primary cohort, RES, by ICR, data cut-off on November 8, 2019)

Best overall response	Number of subjects (%)			
	Entire study population		Japanese subpopulation	
	Trastuzumab deruxtecan n = 119	IC n = 56	Trastuzumab deruxtecan n = 95	IC n = 45
CR	11 (9.2)	0	9 (9.5)	0
PR	50 (42.0)	8 (14.3)	39 (41.1)	7 (15.6)
SD	42 (35.3)	27 (48.2)	34 (35.8)	22 (48.9)
PD	14 (11.8)	17 (30.4)	12 (12.6)	14 (31.1)
NE	2 (1.7)	4 (7.1)	1 (1.1)	2 (4.4)
Response (CR + PR) (Objective response rate % [95% CI[*1]])	61 (51.3% [41.9, 60.5])	8 (14.3% [6.4, 26.2])	48 (50.5% [40.1, 60.9])	7 (15.6% [6.5, 29.5])
P-value (2-sided)[*2]	<0.0001[*3]			

*1, Clopper-Pearson method; *2, Cochran-Mantel-Haenszel test stratified by country (Japan, South Korea); *3, significance level (2-sided), 0.05

Table 6 shows the results of the confirmed objective response rate[5)] by ICR according to RECIST ver.1.1 as a supplementary analysis.

Table 6. Best overall response and confirmed objective response rate (RECIST ver.1.1, primary cohort, RES, by ICR, data cut-off on November 8, 2019)

Best overall response	Number of subjects (%)			
	Entire study population		Japanese subpopulation	
	Trastuzumab deruxtecan n = 119	IC n = 56	Trastuzumab deruxtecan n = 95	IC n = 45
CR	10 (8.4)	0	9 (9.5)	0
PR	41 (34.5)	7 (12.5)	33 (34.7)	6 (13.3)
SD	51 (42.9)	28 (50.0)	40 (42.1)	23 (51.1)
PD	14 (11.8)	17 (30.4)	12 (12.6)	14 (31.1)
NE	3 (2.5)	4 (7.1)	1 (1.1)	2 (4.4)
Response (CR + PR) (Objective response rate % [95% CI[*1]])	51 (42.9% [33.8, 52.3])	7 (12.5% [5.2, 24.1])	42 (44.2% [34.0, 54.8])	6 (13.3% [5.1, 26.8])
P-value (2-sided)[*2]	<0.0001			

*1, Clopper-Pearson method; *2, Cochran-Mantel-Haenszel test stratified by country (Japan, South Korea)

In the primary cohort, during the treatment period and within 47 days of the last dose of trastuzumab deruxtecan, deaths occurred in 8 of 125 subjects (6.4%) in the trastuzumab deruxtecan group and 7 of 62 subjects (11.3%) in the IC group (the deaths included 6 Japanese subjects each in both groups). Five subjects in the trastuzumab deruxtecan group and 7 subjects in the IC group died from disease progression. The causes of death other than disease progression were disseminated intravascular coagulation, large intestine perforation, and pneumonia in 1 subject each in the trastuzumab deruxtecan group. A causal relationship to trastuzumab deruxtecan could not be ruled out for the event of pneumonia. (Among Japanese subjects, the cause of death other than disease progression was disseminated intravascular coagulation in 1 subject in the trastuzumab deruxtecan group.)

Of the patients who were enrolled in the exploratory cohort and received at least 1 dose of trastuzumab deruxtecan (20 [including 16 Japanese] subjects in Cohort 1 and 24 [including 17 Japanese] subjects in Cohort 2), deaths during the treatment period and within 47 days of the last dose of trastuzumab deruxtecan occurred in 2 of 20 subjects (10.0%) in Cohort 1 and 1 of 24 subjects (4.2%) in Cohort 2, all

of which were due to disease progression, and a causal relationship to trastuzumab deruxtecan was denied.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

Of the evaluation data submitted, PMDA concluded that the primary cohort of Study J202, the global phase II study which was conducted to compare the efficacy and safety of trastuzumab deruxtecan with those of IC in patients with unresectable advanced or recurrent HER2-positive gastric cancer that had progressed after ≥2 chemotherapy regimens including trastuzumab, is the important clinical study for evaluating the efficacy and safety of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy. Therefore, PMDA decided to evaluate the efficacy and safety reviews mainly focusing on Study J202.

In addition, PMDA decided to review the efficacy in Japanese patients from the standpoint of consistency between the entire study population and Japanese subpopulation in the primary cohort in Study J202 based on principles including "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012), and "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 discussions, PMDA concluded that trastuzumab deruxtecan has a certain degree of efficacy in the treatment of patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab.

7.R.2.1 Establishment of control group

The applicant's explanation about the establishment of the control group in the primary cohort of Study J202:

At the planning of Study J202, standard treatments had not been specified for patients with unresectable advanced or recurrent gastric cancer that has progressed after ≥2 chemotherapy regimens in treatment guidelines published in Japan including Japanese Gastric Cancer Treatment Guidelines issued by the Japanese Gastric Cancer Association (preliminary version in October 2015), which stated that in patients with good performance status, treatment with agents that had not been used in first- or second-line treatment was to be considered. In patients with HER2-positive gastric cancer, the recommended first-line regimen was trastuzumab combined with fluoropyrimidine- and platinum-based chemotherapy, while the recommended second-line regimens include paclitaxel plus ramucirumab (genetical recombination) (PTX/RAM), or monotherapy with PTX, docetaxel hydrate (DTX), CPT-11, or RAM. Given that PTX/RAM was the most strongly recommended regimen among the above options for second-line treatment, together with data including the results of a clinical study (*J Clin Oncol.* 2013;31:4438-44) which compared CPT-11 alone with PTX alone, it was considered that CPT-11 or

PTX alone was used as the standard third-line treatment. In the control group in Study J202, it was therefore decided that the investigator would choose the regimen from either CPT-11 or PTX monotherapy for each subject.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint for the primary cohort in Study J202 and the efficacy of trastuzumab deruxtecan in the study population of the primary cohort:
It has been reported that when response is achieved, the quality of life (QOL), performance status, and other measures of patients with unresectable advanced or recurrent gastric cancer can be expected to improve as a result of tumor shrinkage (*J Clin Oncol.* 2007;25:3210-6). Because achieving response is considered clinically meaningful for the patient population, objective response rate[10)] was selected as the primary endpoint for the primary cohort of Study J202.

In the primary cohort of Study J202, the objective response rate, the primary endpoint, was statistically significantly higher in the trastuzumab deruxtecan group than in the IC group. In the Japanese subpopulation, the objective response rate tended to be higher in the trastuzumab deruxtecan group than in the IC group [see Section 7.1.1.2].

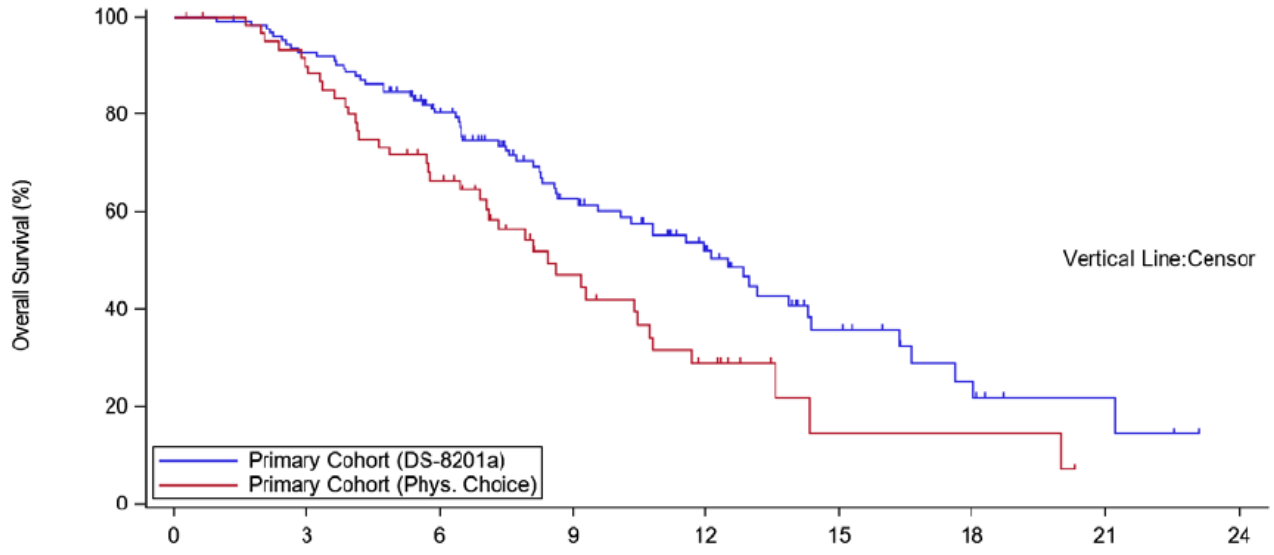
In the primary cohort of Study J202, when the results for objective response rate, the primary endpoint, were statistically significant, hypothesis testing of OS, one of the secondary endpoints, was also to be conducted hierarchically [see Section 7.1.1.2]; in addition, the following analyses were to be conducted: (a) the interim analysis at the primary analysis of objective response rate for the purpose of efficacy evaluation, and (b) the final analysis when 133 OS-related events have occurred. For control of type I error rates associated with the implementation of the interim analysis, the O'Brien-Fleming type alpha spending function based on the Lan-DeMets method was to be used.

The interim analysis results of OS (data cut-off on November 8, 2019) and the Kaplan-Meier curves are presented in Table 7 and Figure 1, respectively. A statistically significant extension of OS was observed in the trastuzumab deruxtecan group compared with the IC group.

Table 7. Interim analysis results of OS (primary cohort, FAS, data cut-off on November 8, 2019)

	Trastuzumab deruxtecan	IC
Number of subjects	125	62
Number of events (%)	62 (49.6)	39 (62.9)
Median [95% CI] (months)	12.5 [9.6, 14.3]	8.4 [6.9, 10.7]
Hazard ratio [95% CI][*1]	0.59 [0.39, 0.88]	
P-value (2-sided)[*2]	0.0097	

*1, A stratified Cox proportional hazards model using region (Japan, South Korea) as the stratification factor; *2, the stratified log-rank test (using a stratification factor similar to the Cox proportional hazards model); significance level (2-sided), 0.0202



Subjects at risk	Time from randomization (months)								
Trastuzumab deruxtecan	125	115	88	54	33	14	7	3	0
IC	62	54	37	19	10	2	2	0	0

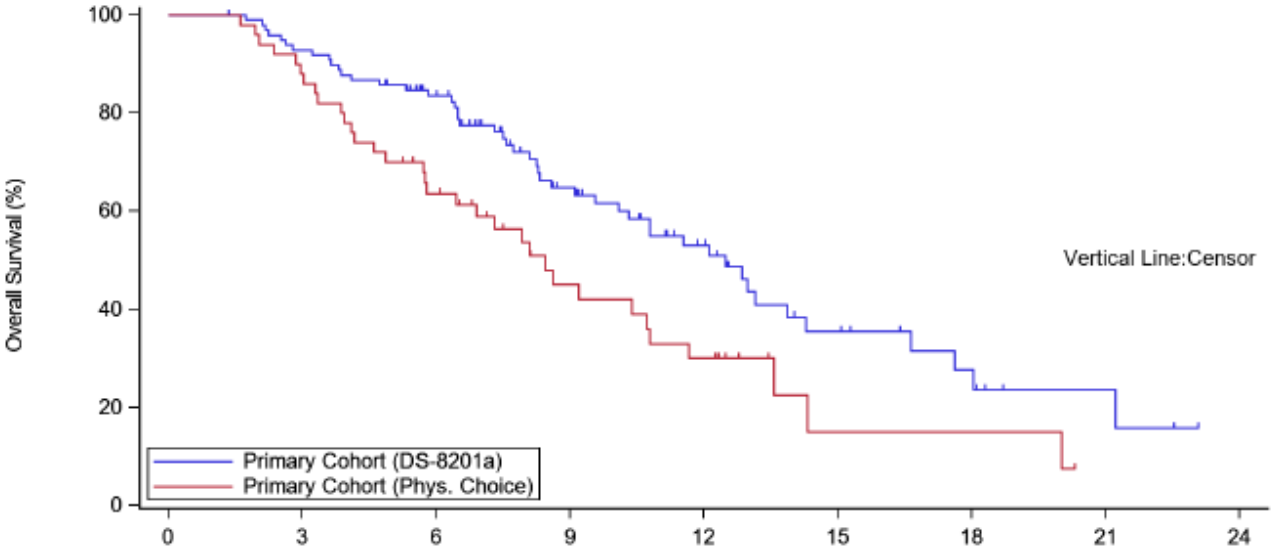
Figure 1. The Kaplan-Meier curves for OS at the interim analysis (primary cohort, FAS, data cut-off on November 8, 2019)

The interim analysis results of OS and the Kaplan-Meier curves for the Japanese subpopulation in the primary cohort in Study J202 are shown in Table 8 and Figure 2, respectively.

Table 8. The analysis results of OS in the Japanese subpopulation (primary cohort, FAS, data cut-off on November 8, 2019)

	Trastuzumab deruxtecan	IC
Number of subjects	99	50
Number of events (%)	48 (48.5)	33 (66.0)
Median [95% CI] (months)	12.5 [9.6, 14.3]	8.4 [5.8, 10.8]
Hazard ratio [95% CI][*1]	0.57 [0.36, 0.89]	
P-value (2-sided)[*2]	0.0121	

*1, unstratified Cox proportional hazards model; *2, unstratified log-rank test



Subjects at risk	Time from randomization (months)								
Trastuzumab deruxtecan	99	91	72	43	26	12	7	3	0
IC	50	44	29	15	10	2	2	0	0

Figure 2. The Kaplan-Meier curves for OS in the Japanese subpopulation at the interim analysis (primary cohort, FAS, data cut-off on November 8, 2019)

Taking into account several factors including the following, trastuzumab deruxtecan is expected to be effective in the treatment of patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab:

- The objective response rate[10] according to RECIST ver.1.1, the primary endpoint for the primary cohort in Study J202, was statistically significantly higher in the trastuzumab deruxtecan group than in the IC group, and it is also considered that the objective response rate achieved is clinically meaningful.
- In the primary cohort of Study J202, statistical tests were performed for the OS, one of the secondary endpoints, according to the pre-specified hierarchical procedure, and a statistically significant extension of OS was observed in the trastuzumab deruxtecan group compared with the IC group.
- Trastuzumab deruxtecan is a HER2-targeted ADC [see Section 1.1], and has characteristics including (a) a high drug-to-antibody ratio, (b) high stability in blood, and (c) high membrane permeability of MAAA-1181a, exerting an antitumor effect also on neighboring tumor cells not bound by trastuzumab deruxtecan (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020). Therefore, trastuzumab deruxtecan is expected to have efficacy in patients with unresectable advanced or recurrent gastric cancer refractory to chemotherapy including trastuzumab, which is a conventional HER2-targeted treatment.

PMDA's discussion:

The effect of trastuzumab deruxtecan on prolongation of life in the patient population is difficult to evaluate based solely on the results of the primary cohort in Study J202, a phase II study that evaluated

the objective response rate as the primary endpoint. Nevertheless, the applicant's explanation about the efficacy of trastuzumab deruxtecan above is understandable. PMDA concluded that the results demonstrated that trastuzumab deruxtecan has a certain degree of efficacy in the treatment of patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events and other findings observed in clinical studies"]

On the basis of the discussions in the following sections, PMDA considered that adverse events that require particular attention when trastuzumab deruxtecan is used in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy are the adverse events that were determined to require particular attention at the time of review for the approved indication, i.e., ILD, myelosuppression, infusion reaction, hepatic dysfunction, and cardiac disorder (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020). Therefore, when using trastuzumab deruxtecan, patients should be monitored particularly closely for these adverse events.

Although the use of trastuzumab deruxtecan requires particular caution for the adverse events mentioned above, PMDA concluded that patients should be able to tolerate trastuzumab deruxtecan provided that appropriate steps including monitoring and control of adverse events and dose modification are taken by a physician with sufficient knowledge and experience in cancer chemotherapy, and that safety management measures can be ensured by utmost attention and control measures for serious adverse events including ILD.

7.R.3.1 Safety profiles of trastuzumab deruxtecan

The applicant's explanation about the safety profile of trastuzumab deruxtecan based on the safety data from the primary cohort of Study J202:

Table 9 summarizes the safety data from the primary cohort of Study J202.[11)]

11) The detailed classification of events captured as each adverse event are as follows:
- ILD: events classified as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) "interstitial lung disease," "pneumonitis," "acute interstitial pneumonitis," and "organising pneumonia."
- Abdominal pain: events classified as MedDRA PTs "abdominal discomfort," "abdominal pain," "abdominal pain lower," and "abdominal pain upper."
- Anaemia: events classified as MedDRA PTs "anaemia," "haemoglobin decreased," "red blood cell count decreased," and "haematocrit decreased."
- Lymphocyte count decreased: events classified as MedDRA PTs "lymphocyte count decreased" and "lymphopenia."
- Neutrophil count decreased: events classified as MedDRA PTs "neutrophil count decreased" and "neutropenia."
- White blood cell count decreased: events classified as MedDRA PTs "white blood cell count decreased" and "leukopenia."
- Platelet count decreased: events classified as MedDRA PTs "platelet count decreased" and "thrombocytopenia."
- Stomatitis: events classified as MedDRA PTs "stomatitis," "aphthous ulcer," "mouth ulceration," "oral mucosa erosion," and "oral mucosa blistering."

Table 9. Summary of safety data (primary cohort of Study J202)

	Number of subjects (%)	
	Trastuzumab deruxtecan n = 125	IC n = 62
All adverse events	125 (100)	61 (98.4)
Grade ≥3 adverse events	107 (85.6)	35 (56.5)
Adverse events leading to death	8 (6.4)	2 (3.2)
Serious adverse events	55 (44.0)	15 (24.2)
Adverse events leading to treatment discontinuation	19 (15.2)	4 (6.5)
Adverse events leading to dose interruption	78 (62.4)	23 (37.1)
Adverse events leading to dose reduction	40 (32.0)	21 (33.9)

Adverse events of any grade with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥10% were nausea (79 subjects [63.2%] in the trastuzumab deruxtecan group and 29 subjects [46.8%] in the IC group), neutrophil count decreased (79 subjects [63.2%], 22 subjects [35.5%]), decreased appetite (75 subjects [60.0%], 28 subjects [45.2%]), anaemia (72 subjects [57.6%], 19 subjects [30.6%]), platelet count decreased (49 subjects [39.2%], 4 subjects [6.5%]), malaise (43 subjects [34.4%], 10 subjects [16.1%]), vomiting (33 subjects [26.4%], 5 subjects [8.1%]), lymphocyte count decreased (27 subjects [21.6%], 2 subjects [3.2%]), ILD (13 subjects [10.4%], 0 subjects), and oedema peripheral (13 subjects [10.4%], 0 subjects). Grade ≥3 adverse events with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥5% were neutrophil count decreased (64 subjects [51.2%], 15 subjects [24.2%]), anaemia (47 subjects [37.6%], 14 subjects [22.6%]), white blood cell count decreased (26 subjects [20.8%], 7 subjects [11.3%]), platelet count decreased (14 subjects [11.2%], 2 subjects [3.2%]), and lymphocyte count decreased (14 subjects [11.2%], 1 subject [1.6%]). Serious adverse events with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥3% were decreased appetite (13 subjects [10.4%], 1 subject [1.6%]), ILD (5 subjects [4.0%], 0 subjects), and dehydration (4 subjects [3.2%], 0 subjects). Adverse events leading to treatment discontinuation of the study drug with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥3% were ILD (7 subjects [5.6%], 0 subjects). Adverse events leading to dose interruption of the study drug with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥3% were neutrophil count decreased (35 subjects [28.0%], 7 subjects [11.3%]), anaemia (14 subjects [11.2%], 2 subjects [3.2%]), decreased appetite (11 subjects [8.8%], 2 subjects [3.2%]), platelet count decreased (5 subjects [4.0%], 0 subjects), fatigue (4 subjects [3.2%], 0 subjects), pneumonia (4 subjects [3.2%], 0 subjects), ILD (4 subjects [3.2%], 0 subjects), and lymphocyte count decreased (4 subjects [3.2%], 0 subjects). Adverse events leading to dose reduction of the study drug with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥3% were decreased appetite (12 subjects [9.6%], 3 subjects [4.8%]). There were no adverse events leading to death with an incidence higher in the trastuzumab deruxtecan group than in the IC group by ≥3%.

The applicant's explanation about the difference between the safety profile of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy and that in the patient population for the previously approved indication:
The safety data for the primary cohort in Study J202 and the trastuzumab deruxtecan group in Study U201, the global phase II study conducted in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 are summarized in Table 10.[11)]

Table 10. Summary of safety data in patients with gastric cancer and patients with breast cancer

	Number of subjects (%)	
	Gastric cancer (primary cohort in Study J202)	Breast cancer (Study U201)
	Trastuzumab deruxtecan 6.4 mg/kg n = 125	Trastuzumab deruxtecan 5.4 mg/kg n = 184
All adverse events	125 (100)	183 (99.5)
Grade ≥3 adverse events	107 (85.6)	94 (51.1)
Adverse events leading to death	8 (6.4)	9 (4.9)
Serious adverse events	55 (44.0)	36 (19.6)
Adverse events leading to treatment discontinuation	19 (15.2)	15 (8.2)
Adverse events leading to dose interruption	78 (62.4)	57 (31.0)
Adverse events leading to dose reduction	40 (32.0)	37 (20.1)

Adverse events of any grade with an incidence higher in patients with gastric cancer (trastuzumab deruxtecan 6.4 mg/kg Q3W) than in patients with breast cancer (trastuzumab deruxtecan 5.4 mg/kg Q3W, the approved regimen for patients with breast cancer) by ≥10% were neutrophil count decreased (79 subjects [63.2%] in the gastric cancer patient group and 57 subjects [31.0%] in the breast cancer patient group), decreased appetite (75 subjects [60.0%], 53 subjects [28.8%]), anaemia (72 subjects [57.6%], 48 subjects [26.1%]), platelet count decreased (49 subjects [39.2%], 32 subjects [17.4%]), white blood cell count decreased (47 subjects [37.6%], 36 subjects [19.6%]), malaise (43 subjects [34.4%], 5 subjects [2.7%]), pyrexia (30 subjects [24.0%], 13 subjects [7.1%]), lymphocyte count decreased (27 subjects [21.6%], 23 subjects [12.5%]), and hypoalbuminaemia (18 subjects [14.4%], 6 subjects [3.3%]). Grade ≥3 adverse events with an incidence higher in patients with gastric cancer than in patients with breast cancer by ≥5% were neutrophil count decreased (64 subjects [51.2%], 32 subjects [17.4%]), anaemia (47 subjects [37.6%], 12 subjects [6.5%]), white blood cell count decreased (26 subjects [20.8%], 9 subjects [4.9%]), decreased appetite (21 subjects [16.8%], 3 subjects [1.6%]), lymphocyte count decreased (14 subjects [11.2%], 10 subjects [5.4%]), and platelet count decreased (14 subjects [11.2%], 6 subjects [3.3%]). Serious adverse events with an incidence higher in patients with gastric cancer than in patients with breast cancer by ≥3% were decreased appetite (13 subjects [10.4%], 0 subjects), ILD (5 subjects [4.0%], 1 subject [0.5%]), and dehydration (4 subjects [3.2%], 0 subjects). Adverse events leading to dose interruption of trastuzumab deruxtecan with an incidence higher in patients with gastric cancer than in patients with breast cancer by ≥3% were neutrophil count decreased (35 subjects [28.0%], 25 subjects [13.6%]), anaemia (14 subjects [11.2%], 7 subjects [3.8%]), decreased appetite (11 subjects [8.8%], 0 subjects), white blood cell count decreased (10 subjects [8.0%], 4 subjects [2.2%]), malaise (5 subjects [4.0%], 0 subjects), pneumonia (4 subjects [3.2%], 0 subjects), and lymphocyte count decreased (4 subjects [3.2%], 0 subjects). Adverse events leading to dose reduction of trastuzumab deruxtecan with an incidence higher in patients with gastric cancer than in patients with breast cancer by ≥3% were neutrophil count decreased (16 subjects [12.8%], 4 subjects [2.2%]), decreased appetite (12 subjects [9.6%], 2 subjects [1.1%]), and malaise (4 subjects [3.2%], 0 subjects). There were no adverse events leading to death or treatment discontinuation of trastuzumab deruxtecan with an incidence higher in patients with gastric cancer than in patients with breast cancer by ≥3%.

Furthermore, in the clinical study of trastuzumab deruxtecan, in order to comprehensively evaluate adverse events suspected of being cases of ILD, reported adverse events classified in any of the following were evaluated by the independent ILD adjudication committee[12]: standardised MedDRA queries (SMQ) "interstitial lung disease (narrow and some broad terms)," MedDRA PTs "respiratory failure," and "acute respiratory failure."

Adverse events classified in the above categories were summarized. Table 11 shows the incidence of ILD events which were assessed by the independent ILD adjudication committee as being causally related to trastuzumab deruxtecan among patients with gastric cancer (primary cohort in Study J202) and patients with breast cancer (Study U201) who received trastuzumab deruxtecan. Of the patients who developed ILD, 11 of 12 subjects with gastric cancer and 7 of 15 subjects with breast cancer were Japanese patients.

Table 11. Incidence of ILD in patients with gastric cancer and patients with breast cancer (ILD causally related to trastuzumab deruxtecan as assessed by the ILD adjudication committee)

	Number of subjects (%)	
	Gastric cancer (primary cohort in Study J202)	Breast cancer (Study U201)
	Trastuzumab deruxtecan 6.4 mg/kg n = 125	Trastuzumab deruxtecan 5.4 mg/kg n = 184
All Grade ILD	12 (9.6)	15 (8.2)
Grade ≥3 ILD	3 (2.4)	4 (2.2)
ILD leading to death	0	4 (2.2)
Serious ILD	5 (4.0)	4 (2.2)

PMDA's discussion:

In the primary cohort in Study J202, some adverse events occurred at a higher incidence in the trastuzumab deruxtecan group compared with the IC group. When compared with the patient population for the previously approved indication, some adverse events occurred at a higher incidence in patients with gastric cancer in the study. These adverse events are either previously known adverse events associated with trastuzumab deruxtecan or considered to have been developed in association with the primary disease. Adverse events that tended to occur at a higher incidence in patients with gastric cancer compared with the patient population for the previously approved indication were primarily myelosuppression-related events; however, the incidence of myelosuppression-related events that led to death, and the incidence of myelosuppression-related events classified as serious adverse events did not differ greatly between these 2 patient populations, and these events were well-managed by dose modification, supportive care, and other measures. The incidence of ILD in patients with gastric cancer did not differ markedly from that in the patient population for the previously approved indication.

Taking into account several factors including the above, there are no additional safety problems requiring caution specifically for the use of trastuzumab deruxtecan in patients with gastric cancer. Therefore, PMDA concluded that patients with gastric cancer should be able to tolerate trastuzumab

12) The independent ILD adjudication committee was composed of thoracic tumor specialists, respiratory specialists, and radiologists from Japan and the US. The committee reviewed and adjudicated suspected cases of ILD. When a case was diagnosed as ILD by the committee, the onset date, severity, causal relationship to trastuzumab deruxtecan, and causal relationship to death were adjudicated independent of the investigator.

deruxtecan provided that appropriate steps including monitoring and control of adverse events and dose interruption/reduction are taken by a physician with sufficient knowledge and experience in cancer chemotherapy, and that safety management can be ensured by utmost attention and control measures for serious adverse events including ILD.

7.R.4 Clinical positioning and indications

The proposed indication of trastuzumab deruxtecan was specified as "unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy." The "Precautions Concerning Indications" section included the following statements:

- Eligible patients for trastuzumab deruxtecan are those who have received prior chemotherapy regimens including trastuzumab.
- The efficacy and safety of trastuzumab deruxtecan as first- or second-line therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as adjuvant therapy have not been established.

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy" and at the same time, to include the following cautionary statements in the "Precautions Concerning Indications" section:

- The efficacy and safety of trastuzumab deruxtecan in patients with no prior chemotherapy including trastuzumab (genetical recombination) have not been established.
- The efficacy and safety of trastuzumab deruxtecan as first- or second-line therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

7.R.4.1 Clinical positioning and indications of trastuzumab deruxtecan

In the latest clinical practice guidelines and representative textbooks of clinical oncology published in Japan and other countries, no descriptions of trastuzumab deruxtecan on the treatment of unresectable advanced or recurrent gastric cancer were found.

The applicant's explanation about clinical positioning of trastuzumab deruxtecan and the indications:
The results of the primary cohort of Study J202 suggest that trastuzumab deruxtecan can be positioned as a treatment option for patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab.

In light of the current situation where no clinical study data have been obtained regarding the clinical benefits of adjuvant treatment with trastuzumab deruxtecan, the use of trastuzumab deruxtecan as adjuvant therapy is not recommended.

In the primary cohort of Study J202, eligible patients were those with gastric cancer that had progressed after ≥2 chemotherapy regimens including trastuzumab. No clinical data from studies have been obtained to assess the clinical benefits of trastuzumab deruxtecan in (a) patients with no prior treatment with trastuzumab; or (b) patients undergoing first- or second-line therapy, and therefore, the use of trastuzumab deruxtecan in these patients is not recommended.

On the basis of the above, the proposed indication of trastuzumab deruxtecan was specified as "unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy" while giving precautionary advice in the "Precautions Concerning Indications" section to the following effect:

- Eligible patients for trastuzumab deruxtecan are those who have received prior chemotherapy regimens including trastuzumab.
- The efficacy and safety of trastuzumab deruxtecan as first- or second-line therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as adjuvant therapy have not been established.

No clinical data have been obtained to compare the efficacy and safety of trastuzumab deruxtecan versus the efficacy and safety of conventional therapies other than CPT-11 and PTX (e.g., nivolumab, trifluridine/tipiracil hydrochloride [FTD/TPI]) to choose a suitable therapy between trastuzumab deruxtecan and conventional therapies in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens. Nevertheless, based on data including the results from the primary cohort of Study J202 and results from the clinical studies of the conventional therapies shown below, it is considered that trastuzumab deruxtecan will show higher efficacy compared with conventional therapies, and therefore trastuzumab deruxtecan should take precedence over the other therapies.

- In the latest clinical practice guidelines published in Japan and other countries, nivolumab and FTD/TPI are recommended as third-line therapy for treatment of unresectable advanced or recurrent gastric cancer. In clinical studies conducted in patients with unresectable advanced or recurrent gastric cancer that had progressed after ≥2 standard chemotherapy regimens, objective response rates with the above agents are reported as follows:
  - In a global phase III study (the ATTRACTION-2 study) conducted to compare the efficacy and safety of nivolumab with those of placebo, the objective response rate in the nivolumab group assessed by the investigator was 11.2% (30 of 268 subjects) (*Lancet.* 2017;390:2461-71).
  - In a global phase III study (the TAGS study) conducted to compare the efficacy and safety of FTD/TPI with those of placebo, the objective response rate in the FTD/TPI group assessed by the investigator was 4.5% (13 of 290 subjects) (*Lancet Oncol.* 2018;19:1437-48).

PMDA's discussion:
PMDA largely accepted the applicant's explanation above. However, in the present partial change application, the efficacy of trastuzumab deruxtecan has been examined based on the results of the primary cohort of Study J202, in which the objective response rate was evaluated as the primary endpoint, and no confirmatory study results on the effect of trastuzumab deruxtecan on prolongation of life have been obtained. Taking this and other factors into consideration, it is difficult to conclusively state that whether the use of trastuzumab deruxtecan should take precedence over the conventional therapies other than CPT-11 and PTX, such as nivolumab and FTD/TPI. Not only trastuzumab deruxtecan, but a thorough consideration of other treatment options is necessary, and therefore PMDA concluded that it is appropriate to state clearly in the "Precautions Concerning Indications" section to the effect that whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after a thorough consideration of other treatment options.

On the basis of the above, PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy" and include in the "Precautions Concerning Indications" section the cautionary statements shown below:

- The efficacy and safety of trastuzumab deruxtecan in patients with no prior chemotherapy including trastuzumab have not been established.
- The efficacy and safety of trastuzumab deruxtecan as first- or second-line therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

7.R.5 Dosage and administration

The proposed dosage and administration of trastuzumab deruxtecan for the treatment of unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy was "The usual adult dosage is 6.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes." In the "Precautions Concerning Dosage and Administration" section, statements to the effect of the following were specified (the details of the precautions are identical to those of the approved indication, except for the recommended dose level reductions and treatment discontinuation).

- The efficacy and safety of trastuzumab deruxtecan in combination with other antineoplastic agents have not been established.

- Dose interruption, reduction, or treatment discontinuation of trastuzumab deruxtecan for adverse reactions.

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the regimen of trastuzumab deruxtecan and the "Precautions for Dosage and Administration" section without modifying the proposed statements.

7.R.5.1 Dosage and administration of trastuzumab deruxtecan

The applicant's explanation of the proposed dosage and administration of trastuzumab deruxtecan for patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy:

The dosage and administration for the primary cohort of Study J202 was specified based on the clinical study results shown below and other information.

- In Part 1 of Study J101, trastuzumab deruxtecan 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg was administered intravenously Q3W. While the MTD of trastuzumab deruxtecan was not determined, 5.4 and 6.4 mg/kg were selected as the dose levels for Part 2 of Study J101 taking the relationship between efficacy/safety and exposure into account.
- On the basis of the factors including the following results obtained in Part 2b of Study J101, 6.4 mg/kg was selected as the dose level for the primary cohort in Study J202.
  - The objective response rate in the 6.4 mg/kg group tended to be higher than that in the 5.4 mg/kg group [see Section 7.1.1.1] and tumor response tended to last longer (median progression free survival [PFS]: 4.3 months in the 5.4 mg/kg group and 8.2 months in the 6.4 mg/kg group).
  - Although the incidence of Grade ≥3 adverse events tended to be higher in the 6.4 mg/kg group than in the 5.4 mg/kg group, the events were well-managed by dose interruption, dose reduction, and other measures.

The results of the primary cohort of Study J202 demonstrated the clinical benefits of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy. In addition to the data from 5 clinical studies (Studies J101, J102, A103, A104, and U201) used for the previous PPK analysis, which was evaluated for the previously approved indication (see Review Report of Enhertu for Intravenous Drip Infusion 100 mg, dated February 17, 2020), data from Study J202 were added and a PPK analysis and an exposure-response analysis were performed. On the basis of the results of these analyses as shown below, the 6.4 mg/kg Q3W regimen was proposed as the dosage and administration for this partial change application. This is because the 6.4 mg/kg Q3W regimen is expected to demonstrate higher efficacy in patients with gastric cancer compared to the 5.4 mg/kg Q3W regimen and this dose is seemed to be still well-tolerated.

- The exposure levels of trastuzumab deruxtecan following intravenous administration of trastuzumab deruxtecan 6.4 mg/kg Q3W to patients with gastric cancer was similar to the exposure

levels of the dosage and administration approved for breast cancer (trastuzumab deruxtecan 5.4 mg/kg Q3W intravenously) to patients with breast cancer [see Section 6.1.2].

- In the exposure-response analysis[13] on efficacy in patients with HER2-positive gastric cancer, the objective response rate tended to increase as the C_{min} at steady state of trastuzumab deruxtecan increased.
- In the exposure-response analysis[14] on safety, the incidence of ILD of any Grade and Grade ≥3 ILD tended to increase as trastuzumab deruxtecan AUC or C_{max} at steady state increased; however, the incidence of ILD following administration of trastuzumab deruxtecan 6.4 mg/kg Q3W to patients with gastric cancer was estimated to be similar to that of trastuzumab deruxtecan 5.4 mg/kg Q3W to patients with breast cancer.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose modification of trastuzumab deruxtecan

The applicant's explanation of the dose modification of trastuzumab deruxtecan:

The criteria for dose interruption, reduction, and treatment discontinuation, as well as the recommended dose level reductions and treatment discontinuation for the primary cohort of Study J202 are similar to those used in Study U201, the pivotal study (global phase II) evaluated for the approved indication, conducted in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1. The results of Study J202 demonstrated the clinical benefits of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer that had progressed after cancer chemotherapy. For the present partial change application, no revision would be necessary to the approved indication version of "Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions" in the "Precautions Concerning Dosage and Administration" section. Phrases and recommended dose levels which were used in the primary cohort of Study J202 have been added to the table of dose level reductions and treatment discontinuation as shown below (underline denotes additions to the descriptions of the approved indication).

Dose level for reductions and treatment discontinuation

Indication	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)	Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy
Dose reduction level	Dose	Dose
Usual dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Treatment discontinuation	If 3.2 mg/kg is not tolerated, discontinue treatment	If 4.4 mg/kg is not tolerated, discontinue treatment.

PMDA accepted the applicant's explanation.

13) Data from Studies J101 and J202 were used.
14) Data from Studies J101, J102, A103, A104, U201, and J202 were used.

7.R.6 Post-marketing investigations

The applicant's explanation on the post-marketing investigations:

There was no marked difference between the safety profile of trastuzumab deruxtecan in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy and that in the patients with unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy, and the incidence of ILD in patients with gastric cancer was similar to that in patients with breast cancer [see Section 7.R.3].

As with the ongoing post-marketing surveillance for patients with breast cancer, the applicant has planned to conduct post-marketing surveillance in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy to keep track of the occurrence of ILD in clinical practice, and investigate risk factors, while defining ILD as a safety specification. This planned surveillance will cover all patients who will be receiving trastuzumab deruxtecan.

A sample size of 650 has been specified to secure ≥50 patients who develop ILD to keep track of the occurrence of ILD in patients with gastric cancer, taking into account the incidence of ILD in the primary cohort of Study J202.

A follow-up period of 12 months was selected, taking into account the time to onset of ILD was within 12 months of the start of trastuzumab deruxtecan treatment in the primary cohort of Study J202 except for 1 patient (non-serious).

PMDA's discussion:

Taking into account factors including those shown below, the safety specification for the post-marketing surveillance should include ILD, as specified by the applicant. It was therefore concluded that post-marketing surveillance should be conducted in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy, covering all patients who will be receiving trastuzumab deruxtecan for a specified period after the market launch, to immediately gather safety data in an unbiased manner, and the obtained safety data should be provided promptly to healthcare professionals.

- Given the discussions in Section "7.R.3 Safety" and examination of ILD at the review for the indication of breast cancer, investigation of risk factors for ILD associated with trastuzumab deruxtecan is of primary importance.
- The results of post-marketing surveillance for patients with breast cancer covering all patients have not been obtained.

The planned sample size should be modified to account for the investigation of risk factors for ILD, one of the surveillance objectives. The follow-up period proposed by the applicant is acceptable.

7.2 Adverse events and other findings observed in clinical studies

The following sections discuss main adverse events from the results of clinical studies submitted for safety evaluation, except for those that resulted in death, which are discussed in Section "7.1 Evaluation data."

7.2.1 Global phase II study (Study J202)

7.2.1.1 Primary cohort

Adverse events occurred in 125 of 125 subjects (100%) in the trastuzumab deruxtecan group, and 61 of 62 subjects (98.4%) in the IC group. A causal relationship to the study drug could not be ruled out for events that occurred in 122 of 125 subjects (97.6%) in the trastuzumab deruxtecan group and 56 of 62 subjects (90.3%) in the IC group. Table 12 shows adverse events with an incidence of ≥20% in at least 1 group.

Table 12. Adverse events with an incidence of ≥20% in at least 1 group

SOC PT (MedDRA ver.20.1)	Number of subjects (%)			
	Trastuzumab deruxtecan n = 125		IC n = 62	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	125 (100)	107 (85.6)	61 (98.4)	35 (56.5)
Gastrointestinal disorders				
Nausea	79 (63.2)	6 (4.8)	29 (46.8)	1 (1.6)
Diarrhoea	40 (32.0)	3 (2.4)	20 (32.3)	1 (1.6)
Vomiting	33 (26.4)	0	5 (8.1)	0
Constipation	30 (24.0)	0	14 (22.6)	0
Metabolism and nutrition disorders				
Decreased appetite	75 (60.0)	21 (16.8)	28 (45.2)	8 (12.9)
Blood and lymphatic system disorders				
Anaemia	71 (56.8)	47 (37.6)	19 (30.6)	14 (22.6)
Investigations				
Neutrophil count decreased	77 (61.6)	62 (49.6)	21 (33.9)	14 (22.6)
White blood cell count decreased	47 (37.6)	26 (20.8)	21 (33.9)	7 (11.3)
Platelet count decreased	47 (37.6)	14 (11.2)	4 (6.5)	2 (3.2)
Lymphocyte count decreased	27 (21.6)	14 (11.2)	2 (3.2)	1 (1.6)
General disorders and administration site conditions				
Malaise	43 (34.4)	1 (0.8)	10 (16.1)	0
Pyrexia	30 (24.0)	0	10 (16.1)	0
Fatigue	27 (21.6)	9 (7.2)	15 (24.2)	2 (3.2)
Skin and subcutaneous tissue disorders				
Alopecia	28 (22.4)	0	9 (14.5)	0

Serious adverse events occurred in 55 of 125 subjects (44.0%) in the trastuzumab deruxtecan group and 15 of 62 subjects (24.2%) in the IC group. Serious adverse events that occurred in ≥3 subjects in each group were decreased appetite in 13 of 125 subjects (10.4%); anaemia and dehydration in 4 of 125 subjects each (3.2%); disease progression, jaundice cholestatic, pyrexia, pneumonia, tumour haemorrhage, and pneumonitis in 3 of 125 subjects each (2.4%) in the trastuzumab deruxtecan group. Among these events, a causal relationship to the study drug could not be ruled out for decreased appetite in 8 subjects; anaemia, dehydration, pyrexia, and pneumonitis in 3 subjects each; pneumonia and tumour haemorrhage in 1 subject each.

Adverse events led to treatment discontinuation of the study drug in 19 of 125 subjects (15.2%) in the trastuzumab deruxtecan group and 4 of 62 subjects (6.5%) in the IC group. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each group were pneumonitis in 5 of 125 subjects (4.0%); ILD, anaemia, and pneumonia in 2 of 125 subjects each (1.6%) in the trastuzumab deruxtecan group; and neutrophil count decreased in 2 of 62 subjects (3.2%) in the IC group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonitis in 5 subjects; ILD in 2 subjects; anaemia and pneumonia in 1 subject each in the trastuzumab deruxtecan group; and neutrophil count decreased in 2 subjects in the IC group.

7.2.1.2 Exploratory cohort

Adverse events occurred in all subjects. Adverse events in which a causal relationship to trastuzumab deruxtecan could not be ruled out occurred in 19 of 20 subjects (95.0%) in Cohort 1 and 24 of 24 subjects (100%) in Cohort 2. Adverse events with an incidence of ≥50% in each cohort were decreased appetite in 13 of 20 subjects (65.0%), nausea in 11 of 20 (55.0%), and anaemia in 10 of 20 subjects (50.0%) in Cohort 1; nausea in 19 of 24 subjects (79.2%), decreased appetite in 18 of 24 subjects (75.0%), and neutrophil count decreased in 12 of 24 subjects (50.0%) in Cohort 2.

Serious adverse events occurred in 6 of 20 subjects (30.0%) in Cohort 1 and 11 of 24 subjects (45.8%) in Cohort 2. Serious adverse events that occurred in ≥2 subjects in each cohort were decreased appetite and disease progression in 2 subjects each (10.0%) in Cohort 1; decreased appetite in 4 subjects (16.7%), gastric haemorrhage in 2 subjects (8.3%) in Cohort 2. A causal relationship to trastuzumab deruxtecan could not be ruled out for decreased appetite in 1 subject in Cohort 1; decreased appetite in 2 subjects, and gastric haemorrhage in 1 subject in Cohort 2.

Adverse events led to treatment discontinuation of trastuzumab deruxtecan in 2 of 20 subjects (10.0%) in Cohort 1 and 1 of 24 subjects (4.2%) in Cohort 2. Adverse events leading to treatment discontinuation of trastuzumab deruxtecan were ILD and disease progression in 1 subject each (5.0%) in Cohort 1, and hyperglycaemia in 1 subject (4.2%) in Cohort 2. A causal relationship to trastuzumab deruxtecan could not be ruled out for ILD in 1 subject in Cohort 1.

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 investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that trastuzumab deruxtecan has a certain level of efficacy in the treatment of unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy, and that trastuzumab deruxtecan has acceptable safety in view of its benefits. Trastuzumab deruxtecan is clinically meaningful because it offers a new treatment option for patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy. PMDA considers that several issues including the indications and dosage and administration require further discussion.

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

Review Report (2)

August 20, 2020

Product Submitted for Approval

Brand Name	Enhertu for Intravenous Drip Infusion 100 mg
Non-proprietary Name	Trastuzumab Deruxtecan (Genetical Recombination)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	April 28, 2020

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 the primary cohort of Study J202, a global phase II study conducted in patients with unresectable advanced or recurrent HER2-positive gastric cancer that had progressed after ≥2 chemotherapy regimens including trastuzumab, the objective response rate by ICR according to RECIST ver.1.1 and the 95% CI, the primary endpoint, was statistically significantly higher in the trastuzumab deruxtecan group than in the IC group (CPT-11 or PTX), and the objective response rate achieved is clinically meaningful.

In view of the discussions in Section "7.R.2 Efficacy" in Review Report (1), the findings, including the above objective response rate achieved following administration of trastuzumab deruxtecan, which is characterized by a high drug-to-antibody ratio, demonstrate that trastuzumab deruxtecan has a certain level of efficacy in the treatment of patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

In view of the discussions in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that adverse events that require particular attention when trastuzumab deruxtecan is used in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after ≥2 chemotherapy regimens including trastuzumab are the adverse events that were determined to require

particular attention at the time of review for the approved indication (i.e., ILD, myelosuppression, infusion reaction, hepatic dysfunction, and cardiac disorder).

Although the use of trastuzumab deruxtecan requires particular caution for the adverse events mentioned above, PMDA concluded that patients should be able to tolerate trastuzumab deruxtecan provided that appropriate steps including monitoring and control of adverse events and dose modification are taken by a physician with sufficient knowledge and experience in cancer chemotherapy, and that safety management measures can be ensured by utmost attention and control measures for serious adverse events including ILD.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indications

In view of the discussions in Section "7.R.4 Clinical positioning and indications" in Review Report (1), PMDA concluded that it is appropriate to specify the indication of trastuzumab deruxtecan as "unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy" and at the same time, to include the cautionary statements shown below in the "Precautions Concerning Indications" section:

Precautions Concerning Indications

- The efficacy and safety of trastuzumab deruxtecan in patients who have not previously received chemotherapy including trastuzumab have not been established.
- The efficacy and safety of trastuzumab deruxtecan as first- or second-line therapy have not been established.
- The efficacy and safety of trastuzumab deruxtecan as adjuvant therapy have not been established.
- Whether a patient is eligible for treatment with trastuzumab deruxtecan should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough understanding of the efficacy and safety of trastuzumab deruxtecan, while carefully examining other treatment options for the patient.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

On the basis of the above, PMDA instructed the applicant to specify the "Indications" and the "Precautions Concerning Indications" sections as shown above, and the applicant agreed with the instruction.

1.4 Dosage and administration

In view of the discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration of trastuzumab deruxtecan should be specified as "The usual adult dosage is 6.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-

tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes." and at the same time, to include the following cautionary statements in the "Precautions Concerning Dosage and Administration" section.

Precautions Concerning Dosage and Administration (Underline denotes additions to the descriptions of the approved indication)

- The efficacy and safety of trastuzumab deruxtecan in combination with other antineoplastic agents have not been established.
- If the patient develops an adverse reaction following administration of trastuzumab deruxtecan, the dose of trastuzumab deruxtecan must be interrupted, reduced, or treatment with trastuzumab deruxtecan must be discontinued based on the following criteria.

Dose levels for reductions and treatment discontinuation

Indication	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)	Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy
Dose reduction level	Dose	Dose
Usual dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Treatment discontinuation	If 3.2 mg/kg is not tolerated, discontinue treatment	If 4.4 mg/kg is not tolerated, discontinue treatment.

Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions

Adverse reaction	Severity[Note)]		Action
Interstitial lung disease			Discontinue treatment.
Left ventricular ejection fraction (LVEF) decreased	LVEF ≥40% and ≤45%	Absolute decrease from baseline is <10%	Consider dose interruption. Repeat LVEF assessment within 3 weeks.
		Absolute decrease from baseline is ≥10% and ≤20%	Interrupt dose, and repeat LVEF assessment within 3 weeks. If the absolute decrease in LVEF from baseline has not recovered to <10%, discontinue treatment.
	LVEF <40% or absolute decrease from baseline is >20%		Interrupt dose, and repeat LVEF assessment within 3 weeks. If LVEF remains <40%, or absolute decrease from baseline is >20%, discontinue treatment.
Symptomatic congestive heart failure			Discontinue treatment.
QT interval prolongation	Grade 3		Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level and resume treatment.
	Grade 4		Discontinue treatment.
Infusion reaction	Grade 1		Reduce infusion rate by 50%. If no other symptoms develop, administer at the original infusion rate in subsequent infusions.
	Grade 2		Temporarily stop treatment until resolved to Grade ≤1. If treatment is resumed, reduce infusion rate by 50%. Administer at the reduced infusion rate in subsequent infusions.
	Grade 3 or 4		Discontinue treatment.
Neutrophil count decreased	Grade 3		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. Or, resume treatment at the same dose level.
	Grade 4		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment.
Febrile neutropenia			Interrupt dose until resolved. After resolved, reduce dose by 1 level, and resume treatment.
Anaemia	Grade 3		Interrupt dose until resolved to Grade ≤2. After resolved, resume treatment at the same dose level.
	Grade 4		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment.
Platelet count decreased	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level, and resume treatment.
Total bilirubin increased	Grade 2		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, reduce dose by 1 level, and resume treatment. If resolved in >7 days, discontinue treatment.
	Grade 4		Discontinue treatment.
Diarrhoea or colitis	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤3 days, resume treatment at the same dose level. If resolved in >3 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Discontinue treatment.
Other adverse reactions	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Discontinue treatment.

Note), toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

On the basis of the above, PMDA instructed the applicant to specify the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as shown above.

The applicant's response:

The recommended dose level reductions and treatment discontinuation will be specified according to the request by modifying the details as shown below:

Dose level for reductions and treatment discontinuation

Indication	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)	Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy
Usual dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Treatment discontinuation	If 3.2 mg/kg is not tolerated, discontinue treatment	If 4.4 mg/kg is not tolerated, discontinue treatment.

PMDA accepted the applicant's response.

1.5 Risk management plan (draft)

The applicant has planned to conduct post-marketing surveillance in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy, covering all patients who will be receiving trastuzumab deruxtecan with a planned sample size of 650 and a follow-up period of 12 months to keep track of the occurrence of ILD in clinical practice and to investigate risk factors, while defining ILD as a safety specification.

In view of the discussions in Section "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that a survey should be conducted in patients with unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy, covering all patients who will be receiving trastuzumab deruxtecan for a specified period after the market launch, to gather safety data in an unbiased manner without delay, and the safety data so obtained should be provided promptly to healthcare professionals. The details of the surveillance plan were determined as follows:

- The planned sample size should be modified to account for the investigation of risk factors for ILD, one of the surveillance objectives.
- The safety specification and follow-up period of the surveillance proposed by the applicant are acceptable.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

On the basis of the above discussions, PMDA instructed the applicant to review the surveillance plan.

The applicant's response:

A planned sample size of 900 was chosen to allow investigation of risk factors that may affect the development of ILD.

PMDA accepted the applicant's response.

On the basis of the above discussions, PMDA concluded that the current risk management plan (draft) for trastuzumab deruxtecan should include the safety specification presented in Table 13, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 14 and Table 15.

Table 13. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Myelosuppression • Infusion reaction	• Cardiac dysfunction (cardiac failure, LVEF decreased) • Hepatic dysfunction • Embryo-fetal toxicities	None
Efficacy specification		
None		

In this partial change application, no changes have been made since the initial approval.

Table 14. Summary of additional pharmacovigilance activities, surveillance/studies on efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance in patients with unresectable or recurrent HER2-positive breast cancer • Early post-marketing phase vigilance in patients with unresectable advanced or recurrent HER2-positive gastric cancer • Specified drug use-results survey in patients with unresectable or recurrent HER2-positive breast cancer (all-case surveillance) • Specified drug use-results survey in patients with unresectable advanced or recurrent HER2-positive gastric cancer (all-case surveillance) • Post-marketing clinical study in patients with unresectable or recurrent HER2-positive breast cancer previously treated with T-DM1 (extension study of U201 Part 2a)	None	• Disseminate data gathered during early post-marketing phase vigilance conducted in patients with unresectable or recurrent HER2-positive breast cancer • Disseminate data gathered during early post-marketing phase vigilance conducted in patients with unresectable advanced or recurrent HER2-positive gastric cancer • Disseminate information promptly regarding the latest status of ILD occurrence • Organize and disseminate information materials for healthcare professionals • Organize and disseminate information materials for patients

Underline denotes activities to be implemented for the new indication that is to be added through the application

Table 15. Outline of post-marketing surveillance plan (draft)

Objective	To keep track of the occurrence of ILD in clinical practice, and investigate risk factors
Survey method	All case surveillance
Population	All patients who have received trastuzumab deruxtecan
Follow-up period	12 months
Planned sample size	900 patients
Main survey items	Safety specification: ILD Other main survey items: patient characteristics (e.g., sex, age, current/past smoking status, prior treatment for primary disease, medical history, complications), status of treatment with trastuzumab deruxtecan

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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 conditions for approval shown below, provided that precautionary statement is included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and that trastuzumab deruxtecan is properly used only under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of providing adequate emergency medical care. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until March 24, 2028).

Indications (Underline denotes additions)

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

<u>Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy</u>

Dosage and Administration (Underline denotes additions)

<u>Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)</u>

The usual adult dosage is 5.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy

The usual adult dosage is 6.4 mg/kg (body weight) of trastuzumab deruxtecan (genetical recombination) administered as an intravenous infusion over 90 minutes every 3 weeks. If the first infusion is well-tolerated, subsequent infusions can be administered over a shorter infusion time with a minimum infusion time of 30 minutes.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to keep track of information on patient characteristics until data from a specified number of patients have been collected. Furthermore, data on the safety and efficacy of the product should be collected as soon as possible, and measures to ensure proper use of the product should also be taken.

Warnings (No change)

1. The product should be administered only to patients who are considered eligible for its use under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at a medical institution capable of providing adequate emergency medical care. Prior to the start of therapy, the benefits and risks associated with the product (in particular, initial symptoms of interstitial lung disease, precautions during treatment, and information including reported fatal cases) should be thoroughly explained to the patient or his/her family members and consent must be obtained.
2. The product should be used in cooperation with physicians with sufficient expertise in respiratory diseases because there have been reports of patients who died after experiencing interstitial lung disease associated with the product. During treatment, patients should be closely monitored for initial symptoms (e.g., dyspnea, cough, and pyrexia), and examined by regular arterial oxygen saturation (SpO_2) level, chest X-ray, chest computed tomography (CT), and other tests. In the event of an abnormality being found, administration of the product should be discontinued and appropriate actions such as introduction of corticosteroid therapy should be taken.
3. Prior to the start of treatment with the product, the patient's eligibility for the treatment should be carefully determined after performing chest CT as well as patient interview, and confirming that the patient has no current or history of interstitial lung disease.

Contraindication (No change)

Patients with medical history of hypersensitivity to any of the ingredients of the product

Precautions Concerning Indications (Underline denotes additions)

Common to both indications

1. Whether a patient is eligible for treatment with the product should be decided only after becoming fully familiar with the details in the "Clinical Studies" section, and gaining a thorough

understanding of the efficacy and safety of the product, while carefully examining other treatment options for the patient.

Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)

2. The efficacy and safety of the product in patients who have not previously received trastuzumab (genetical recombination), taxane-based chemotherapy, and trastuzumab emtansine (genetical recombination) have not been established.
3. The efficacy and safety of the product as a neoadjuvant or adjuvant therapy have not been established.

Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy

4. The efficacy and safety of the product in patients with no prior chemotherapy including trastuzumab (genetical recombination) have not been established.
5. The efficacy and safety of the product as first- or second-line therapy have not been established.
6. The efficacy and safety of the product as adjuvant therapy have not been established.

Precautions Concerning Dosage and Administration (Underline denotes additions and strikethrough denotes deletions)

1. The efficacy and safety of the product in combination with other antineoplastic agents have not been established.
2. If the patient develops an adverse reaction following administration of the product, the dose of the product must be interrupted, reduced, or treatment with the product must be discontinued based on the following criteria.

Dose levels for reductions and treatment discontinuation

Indication	Unresectable or recurrent HER2-positive breast cancer previously treated with chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments)	Unresectable advanced or recurrent HER2-positive gastric cancer that has progressed after cancer chemotherapy
~~Dose reduction level~~	~~Dose~~	
Usual dose	5.4 mg/kg	6.4 mg/kg
First dose reduction	4.4 mg/kg	5.4 mg/kg
Second dose reduction	3.2 mg/kg	4.4 mg/kg
Treatment discontinuation	If 3.2 mg/kg is not tolerated, discontinue treatment	If 4.4 mg/kg is not tolerated, discontinue treatment.

Criteria for dose interruption, reduction, or treatment discontinuation for adverse reactions

Adverse reaction	Severity[Note)]		Action
Interstitial lung disease			Discontinue treatment.
Left ventricular ejection fraction (LVEF) decreased	LVEF ≥40% and ≤45%	Absolute decrease from baseline is <10%	Consider dose interruption. Repeat LVEF assessment within 3 weeks.
		Absolute decrease from baseline is ≥10% and ≤20%	Interrupt dose, and repeat LVEF assessment within 3 weeks. If the absolute decrease in LVEF from baseline has not recovered to <10%, discontinue treatment.
	LVEF <40% or absolute decrease from baseline is >20%		Interrupt dose, and repeat LVEF assessment within 3 weeks. If LVEF remains <40%, or absolute decrease from baseline is >20%, discontinue treatment.
Symptomatic congestive heart failure			Discontinue treatment.
QT interval prolongation	Grade 3		Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level and resume treatment.
	Grade 4		Discontinue treatment.
Infusion reaction	Grade 1		Reduce infusion rate by 50%. If no other symptoms develop, administer at the original infusion rate in subsequent infusions.
	Grade 2		Temporarily stop treatment until resolved to Grade ≤1. If treatment is resumed, reduce infusion rate by 50%. Administer at the reduced infusion rate in subsequent infusions.
	Grade 3 or 4		Discontinue treatment.
Neutrophil count decreased	Grade 3		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment. Or, resume treatment at the same dose level.
	Grade 4		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment.
Febrile neutropenia			Interrupt dose until resolved. After resolved, reduce dose by 1 level, and resume treatment.
Anaemia	Grade 3		Interrupt dose until resolved to Grade ≤2. After resolved, resume treatment at the same dose level.
	Grade 4		Interrupt dose until resolved to Grade ≤2. After resolved, reduce dose by 1 level, and resume treatment.
Platelet count decreased	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Interrupt dose until resolved to Grade ≤1. After resolved, reduce dose by 1 level, and resume treatment.
Total bilirubin increased	Grade 2		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, reduce dose by 1 level, and resume treatment. If resolved in >7 days, discontinue treatment.
	Grade 4		Discontinue treatment.
Diarrhoea or colitis	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤3 days, resume treatment at the same dose level. If resolved in >3 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Discontinue treatment.
Other adverse reactions	Grade 3		Interrupt dose until resolved to Grade ≤1. If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, reduce dose by 1 level, and resume treatment.
	Grade 4		Discontinue treatment.

Note), toxicity grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver.4.03.

Appendix

List of Abbreviations

ADC	antibody-drug conjugate
application	application for marketing approval
AUC_{ss}	area under the concentration-time curve at steady state
CLcr	creatinine clearance
CL_{drug}	elimination clearance of released drug (MAAA-1181a)
CL_{intact}	elimination clearance of intact DS-8201a
$C_{max,ss}$	maximum serum concentration at steady state
C_{min}	minimum serum concentration
$C_{mim,ss}$	minimum serum concentration at steady state
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DTX	docetaxel hydrate
FAS	full analysis set
FTD/TPI	trifluridine/tipiracil hydrochloride
HER2	human epidermal growth factor receptor type 2
IC	investigator's choice
ICR	independent central review
Ig	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
ISH	*in situ* hybridization
Japanese Gastric Cancer Treatment Guidelines	Japanese Gastric Cancer Treatment Guidelines issued by Japanese Gastric Cancer Association
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
nivolumab	nivolumab (genetical recombination)
OS	overall survival
partial change application	application for partial change approval
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
PTX	paclitaxel
PTX/RAM	paclitaxel plus ramucirumab (genetical recombination)
QOL	quality of life
QW	quaque a week
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
RAM	ramucirumab (genetical recombination)
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable set
SD	stable disease
SMQ	standardised MedDRA queries

SOC	system organ class
Study A103	Study DS8201-A-A103
Study A104	Study DS8201-A-A104
Study J101	Study DS8201-A-J101
Study J102	Study DS8201-A-J102
Study J202	Study DS8201-A-J202
Study U201	Study DS8201-A-U201
T-DM1	trastuzumab emtansine (genetical recombination)
the ATTRACTION-2 study	Study ONO-4538-12
the TAGS study	Study TO-TAS-102-302
trastuzumab	trastuzumab (genetical recombination)
trastuzumab deruxtecan	trastuzumab deruxtecan (genetical recombination)
V_{drug}	released drug (MAAA-1181a) volume of distribution
V_{ss}	volume of distribution at steady state
V_1	central volume of distribution