Review Report

February 9, 2022
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	Herceptin Intravenous Infusion 60 Herceptin Intravenous Infusion 150
Non-proprietary Name	Trastuzumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	April 26, 2021
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 60 mg or 150 mg of trastuzumab (genetical recombination)
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of unresectable advanced or recurrent human epidermal growth factor receptor 2 (HER2)-positive colorectal 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 indication and dosage and administration shown below.

Indications

- ○ HER2-overexpressing breast cancer
- ○ Unresectable advanced or recurrent HER2-overexpressing gastric cancer
- ○ Unresectable advanced or recurrent HER2-positive salivary gland carcinoma
- ○ Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy

(Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

Dosage and Administration

For the treatment of HER2-overexpressing breast cancer, use Regimen A or B.

For the treatment of unresectable advanced or recurrent HER2-overexpressing gastric cancer, use Regimen B in combination with other antineoplastic drugs.

For the treatment of unresectable advanced or recurrent HER2-positive salivary gland carcinoma, use Regimen B in combination with docetaxel.

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, use Regimen B in combination with pertuzumab (genetical recombination).

Regimen A: The usual dose for adults is a loading dose of 4 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 2 mg/kg as intravenous infusions over ≥90 minutes once weekly.

Regimen B: The usual dose for adults is a loading dose of 8 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minutes every 3 weeks.

The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

(Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

December 27, 2021

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).

Products Submitted for Approval

(a) Brand Name	Herceptin Intravenous Infusion 60 Herceptin Intravenous Infusion 150
Non-proprietary Name	Trastuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	April 26, 2021
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 60 mg or 150 mg of trastuzumab (genetical recombination)
Proposed Indications	○ HER2-overexpressing breast cancer ○ Unresectable advanced or recurrent HER2-overexpressing gastric cancer ○ <u>Unresectable advanced or recurrent HER2-overexpressing colorectal cancer</u>

(Underline denotes additions.)

Proposed Dosage and Administration	For the treatment of HER2-overexpressing breast cancer, use Regimen A or B. For the treatment of unresectable advanced or recurrent HER2-overexpressing gastric cancer, use Regimen B in combination with other antineoplastic drugs. <u>For the treatment of unresectable advanced or recurrent HER2-overexpressing colorectal cancer, use Regimen B in combination with pertuzumab (genetical recombination).</u> Regimen A: The usual dose for adults is a loading dose of 4 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 2 mg/kg as intravenous infusions over ≥90 minutes once weekly. Regimen B: The usual dose for adults is a loading dose of 8 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by

subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minutes every 3 weeks.
The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

(Underline denotes additions.)

(b) Brand Name	Perjeta Intravenous Infusion 420 mg/14 mL
Non-proprietary Name	Pertuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	April 26, 2021
Dosage Form/Strength	Injection: Each 14 mL vial contains 420 mg of pertuzumab (genetical recombination).
Proposed indications	○ HER2-positive breast cancer ○ Unresectable advanced or recurrent HER2-positive colorectal cancer

(Underline denotes additions.)

Proposed Dosage and Administration

For the treatment of HER2-positive breast cancer, the usual loading dose for adults is 840 mg of pertuzumab (genetical recombination) administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab (genetical recombination) as 60-minute intravenous infusions every 3 weeks, in combination with trastuzumab (genetical recombination) and other antineoplastic drugs. For neo-adjuvant or adjuvant therapy, the maximum treatment period is 12 months. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer, the usual loading dose for adults is 840 mg of pertuzumab (genetical recombination) administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab (genetical recombination) as 60-minute intravenous infusions every 3 weeks, in combination with trastuzumab (genetical recombination). The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

(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 products

Both trastuzumab (genetical recombination) (hereafter, referred to as "TRA") and pertuzumab (genetical recombination) (hereafter, referred to as "PER") are humanized anti-HER2 monoclonal antibodies developed by Genentech Inc. in the US. TRA binds to subdomain IV, a juxta-membrane region of HER2's extracellular domain, and induces antibody-dependent cellular cytotoxicity (ADCC), etc., thereby inhibiting tumor growth. On the other hand, PER binds to subdomain II of HER2's extracellular domain to induce ADCC as well as to block HER2 dimerization and subsequently the activation of downstream signaling, thereby inhibiting tumor growth.

In Japan, TRA was approved for the indications of (a) "metastatic HER2-overexpressing breast cancer " in April 2001, (b) "adjuvant chemotherapy for HER2-overexpressing breast cancer" in February 2008, (c) "unresectable advanced or recurrent HER2-overexpressing gastric cancer" in March 2011, and (d) "unresectable advanced or recurrent HER2-positive salivary gland carcinoma" in November 2021. The above indications (a) and (b) were changed and combined into a single indication "HER2-overexpressing breast cancer" in November 2011.

PER was approved for the indication of "HER2-positive inoperable or recurrent breast cancer" in June 2013, which was changed to "HER2-positive breast cancer" in October 2018.

1.2 Development history etc.

During the clinical development of combination therapy with TRA and PER (hereafter, referred to as "TRA/PER therapy") for unresectable advanced or recurrent HER2-positive colorectal cancer, a Japanese phase II study in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer (TRIUMPH study) was initiated in January 2018. The clinical study was conducted as an investigator-initiated trial by the National Cancer Center Hospital East and other medical institutions, under the support of the Project Promoting Clinical Trials for Development of New Drugs by the Japan Agency for Medical Research and Development.

As of November 2021, TRA/PER therapy has not been approved for the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer in any country or region.

Based on the results of the TRIUMPH study serving as pivotal data, the applicant has recently filed partial change approval applications for TRA and PER to add an indication and dosage and administration for the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer.

2. Quality and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage. Therefore, no new data relating to quality were submitted.

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

Although the present application is intended for a new indication and a new dosage, no new data were submitted because nonclinical pharmacology data were considered to have been evaluated at the review of the initial application.

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

Although the present application is intended for a new indication and a new dosage, no new data were submitted because nonclinical pharmacokinetic data were considered to have been evaluated at the review of the initial application.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage. Therefore, no data relating to toxicity were submitted.

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

Although the present application is intended for a new indication and a new dosage, no new data were submitted because data relating to biopharmaceutic studies and associated analytical methods and clinical pharmacology were considered to have been evaluated at the review of the initial application.

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 the Japanese phase II study shown in Table 1. The applicant also submitted results from the Japanese phase II study and 2 non-interventional studies shown in Table 1, as reference data.

Table 1. Clinical studies on efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation data	Japan	TRIUMPH	II	Chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer	TRA/PER therapy 30 TBx group: 27 LBx group: 25	TRA[*1] and PER[*2] IV every 3 weeks	Efficacy Safety
					SCRUM-Japan Registry (evaluation) 6[*3]	Investigator's choice of therapy	
Reference data					SCRUM-Japan Registry (reference) 14		
	Foreign	PER001JP	Non-interventional	Chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer: (a) Patients who were enrolled in the MyPathway study and received TRA/PER therapy (b) Patients who were registered in Flatiron and Foundation Medicine's real-world clinico-genomic database, and received investigator's choice of therapy	75 (a) 57 (b) 18	(a) TRA[*1] and PER[*2] IV every 3 weeks (b) Investigator's choice of therapy	Efficacy
		SG42530	Non-interventional	Chemotherapy-treated patients with unresectable advanced or recurrent colorectal cancer, who were registered in Flatiron and Foundation Medicine's real-world clinico-genomic database, and received investigator's choice of therapy: (a) HER2-positive patients (b) HER2-negative patients	576 (a) 63 (b) 513	Investigator's choice of therapy	Efficacy

*1 A loading dose of 8 mg/kg as an intravenous infusion, followed by subsequent doses of 6 mg/kg as intravenous infusions every 3 weeks.
*2 A loading dose of 840 mg as an intravenous infusion, followed by subsequent doses of 420 mg as intravenous infusions every 3 weeks.
*3 Patients had to provide signed consent.

A summary of the clinical studies is presented below. Common adverse events other than deaths that were reported in the TRIUMPH study are detailed in Section "7.3 Adverse events reported in the clinical study."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, TRIUMPH study, January 2018 to March 2020)

An open-label, uncontrolled study was conducted at 7 sites in Japan to evaluate the efficacy and safety of TRA/PER therapy in chemotherapy-treated[1)] patients with unresectable advanced or recurrent HER2-positive colorectal cancer[2)] (target sample size, 25 patients each for the TBx group and LBx group).

[1)] Patients had to be refractory or intolerant to fluoropyrimidines, oxaliplatin (L-OHP), irinotecan hydrochloride hydrate (IRI), and anti-epidermal growth factor receptor (anti-EGFR) antibody therapy (cetuximab [Cmab] or panitumumab [Pmab]). Patient were enrolled regardless of prior treatments with angiogenic inhibitors such as bevacizumab (Bmab). Patients who had previously received HER2-targeted drugs were excluded.

[2)] Patients were enrolled in the study if their tumor tissue samples were confirmed to be *RAS* wild-type, and if they met either of the following conditions:
- In the central TBx test, the tumors were:
  (a) Found to have HER2 overexpression defined as a 3+ score by immunohistochemistry (IHC) ("Ventana I-View Pathway HER2 (4B5)," Roche Diagnostic K.K.); or,
  (b) Positive for HER2 by fluorescence *in situ* hybridization (FISH) ("Pathvision HER2 DNA Probe Kit," Abbott Japan LLC)
- In the central LBx test, a next-generation sequencing (NGS) analysis using "Guardant360" (Guardant Health) revealed that the tumors had *HER2* gene amplification (gene copy number ≥2.4) and were *RAS* wild-type (defined as a ratio of *RAS* mutations to the most frequently detected mutations of ≤30%) in cell-free DNAs).

Patients received (a) intravenous TRA as a loading dose of 8 mg/kg, followed by subsequent doses of 6 mg/kg every 3 weeks, in combination with (b) intravenous PER as a loading dose of 840 mg, followed by subsequent doses of 420 mg every 3 weeks. The treatment was continued until disease progression or a withdrawal criterion was met.

All 30 patients enrolled were treated with TRA/PER therapy. All of the patients were included in the safety analysis set. Patients who tested positive for HER2 in the tumor tissue biopsy (TBx test) (TBx group) and patients who tested positive for HER2 in the liquid biopsy using plasma (LBx test) (LBx group) constituted the efficacy analysis set.

The primary endpoint was the objective response rate, as assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, with a predetermined threshold objective response rate of 5%.[3)]

The target sample size determined at the start of the study was 18 patients each for the TBx group and LBx group, under the condition that the necessity of an increase in the sample size to 25 patients would be considered to increase the statistical power if patient enrollment goes smoothly.[4)] At 6 months after the start of patient enrollment, this predetermined condition was fulfilled. The sample size for each group was increased to 25 patients (August 8, 2018). In addition, the following were specified: (i) Even when the target sample size for either the TBx group or the LBx group was achieved, patient enrollment would be continued until the number of enrolled patients in the other group reached the target sample size; and, (ii) analyses would be conducted on the first enrolled 25 patients, who served as the primary analysis set, as well as on all enrolled patients.

On January 7, 2019, the numbers of patients evaluable for tumor response (complete response [CR] or partial response [PR]) reached 17 patients in the TBx group and 15 patients in the LBx group, and tumor response was confirmed in ≥5 patients in both groups. This result was considered to be adequate to determine whether the primary objective of the study had been achieved. Consequently, the statistical analysis plan was changed to specify that efficacy and safety analyses would be performed on patients in the TBx group and the LBx group as of January 7, 2019 (17 patients and 15 patients, respectively), instead of the target sample size (25 patients in each group) (Statistical Analysis Plan ver. 2.0, dated July 1, 2019). Meanwhile, the final analyses (data cutoff on March 31, 2020) were performed on all patients enrolled and treated with TRA/PER therapy (27 patients[5)] in the TBx group and 25 patients in the LBx group).[6)]

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3) The threshold objective response rate was determined based on the objective response rates of regorafenib and trifluridine (FTD)/tipiracil hydrochloride (TPI) (1.0% and 1.6%, respectively) observed in a global phase III study in patients with unresectable advanced or recurrent colorectal cancer that had progressed after ≥2 regimens of chemotherapies including fluoropyrimidines, L-OHP, IRI, and Bmab (and anti-EGFR antibody therapy [Cmab or Pmab] for patients with *KRAS* wild-type tumors) (*Lancet.* 2013;381:303-12, *N Engl J Med*. 2015;372:1909-19).

4) Patient enrollment was considered smooth where ≥13 patients has been enrolled or is expected to be enrolled shortly, at 1 year after enrollment of the first patient.

5) A total of 23 patients had IHC 3+ tumors (all 23 patients tested positive on FISH) and 27 patients had FISH-positive tumors (23 were scored as 3+ and 4 as 2+ by IHC).

6) Of the 30 patients, 29 patients underwent both the TBx test and the LBx test. Of these 29 patients, 22 were positive for HER2 in both tests, and were included in both the TBx group and the LBx group.

However, the analyses conducted using the 17 patients in the TBx group and 15 patients in the LBx group cannot be deemed as the prespecified analyses. Therefore, this review report focuses on the results of the final analyses conducted using all enrolled patients (data cutoff on March 31, 2020).

Table 2 shows the primary efficacy results based on the final analysis of the overall response rate, as assessed by the investigators according to RECIST ver 1.1 (data cutoff on March 31, 2020). In both the TBx group and the LBx group, the lower limit of the 95% confidence interval (CI) of the overall response rate exceeded the predetermined threshold overall response rate (5%). The overall response rates [95% CIs] in the first 25 patients enrolled in the TBx group and the LBx group were both 28.0% [12.1%, 49.4%] (7 of 25 patients) (data cutoff on March 31, 2020).[7)]

Table 2. Best overall response and objective response rates
(RECIST ver. 1.1, final efficacy analysis set, data cutoff on March 31, 2020)

Best overall response	n (%)	
	Investigator's assessment	
	TBx N = 27	LBx N = 25
CR	1 (3.7)	1 (4.0)
PR	7 (25.9)	6 (24.0)
SD	10 (37.0)	8 (32.0)
PD	9 (33.3)	10 (40.0)
NE	0	0
Response (CR + PR) (objective response rate [95% CI*])	8 (29.6% [13.8%, 50.2%])	7 (28.0% [12.1%, 49.4%])

* Clopper-Pearson method

The safety analysis revealed that deaths occurred in 2 of 30 patients (6.7%) during the treatment period or within 30 days after the last dose. The cause of all of these deaths was disease progression.

In the study, a SCRUM-Japan Registry group (evaluation), which comprised patients with unresectable advanced or recurrent colorectal cancer who were registered in the SCRUM-Japan Registry[8)] at 6 sites in Japan between November 28, 2017 and February 29, 2020, and met the same eligibility criteria[9)] as those in the TRIUMPH study, was established (target sample size undetermined). An analysis was conducted to compare the efficacy of TRA/PER therapy in the TRA/PER group with that of investigator's choice of therapy in the SCRUM-Japan Registry group (evaluation).

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7) The objective response rates [95% CIs] in the first enrolled 17 patients in the TBx group and the first enrolled 15 patients in the LBx group were 35.3% [14.2%, 61.7%] (6 of 17 patients) and 33.3% [11.8%, 61.6%] (5 of 15 patients), respectively (data cutoff on January 7, 2019).

8) A disease registry that was established according to a Project Promoting Clinical Trials for the Development of New Drugs entitled, "Constructing a cancer registry based on the nation-wide genome screening project (SCRUM-Japan) for new oncology agent development" adopted by the Japan Agency for Medical Research and Development. This registry enrolls patients with advanced solid tumors confirmed to have certain genetic abnormalities by cancer genomic profiling or other testing to prospectively accrue medical information (including images taken at specified intervals [6 to 10 weeks]).

9) Patients identified from the registry had to meet all of the following criteria:
- Confirmed to have *RAS* wild-type tumors by testing of tumor tissue samples
- Confirmed to have HER2-positive (according to the definition of HER2 positivity used in the TRIUMPH study) tumors by either a TBx test or an LBx test
- Are refractory or intolerant to fluoropyrimidines, L-OHP, IPI, and anti-EGFR antibody therapy (Cmab or Pmab) (regardless of prior treatments with angiogenic inhibitors such as Bmab)

Of 14 patients identified for the SCRUM-Japan Registry group (7 for the TBx group and 10 for the LBx group), 6 provided signed consent to participate in the study. Of these 6 patients, 5[10)] (4 in the TBx group and 2 in the LBx group) were evaluable for best overall response. The objective response rate, as assessed by the investigators according to RECIST ver. 1.1, in these 5 patients was 0% for both the TBx group and the LBx group (data cutoff on February 29, 2020).

7.2 Reference data

7.2.1 Japanese clinical study

7.2.1.1 Japanese phase II study (CTD 5.3.5.2-2, TRIUMPH study, January 2018 to March 2020)

Patients with unresectable advanced or recurrent HER2-positive colorectal cancer who were registered in the SCRUM-Japan Registry[8)] at 6 sites in Japan between November 28, 2017 and February 29, 2020, and met the same eligibility criteria[9)] as those in the TRIUMPH study constituted a SCRUM-Japan Registry group (reference) (target sample size undetermined). An analysis was conducted to compare the efficacy of the TRA/PER therapy in the TRA/PER group of the TRIUMPH study [see Section 7.1.1.1] with that of investigator's choice of therapy in the SCRUM-Japan Registry group (reference).

Of 14 patients (7 in the TBx group and 10 in the LBx group) identified for the SCRUM-Japan Registry group, 13 patients (6 in the TBx group and 9 in the LBx group)[11)] were evaluable for best overall response, irrespective of whether or not they had provided signed consent. The objective response rates, as assessed by the investigators according to RECIST ver. 1.1, in these 13 patients were 0% for both the TBx group and the LBx group (data cutoff on February 29, 2020) [for the objective response rates in the TRA/PER group of the TRIUMPH study, see Section 7.1.1.1].

7.2.2 Non-interventional studies

7.2.2.1 Non-interventional study (CTD 5.3.5.4-1, Study PER001JP)

A non-interventional study was conducted to compare the efficacy of TRA/PER therapy with that of investigator's choice of therapy in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer (target sample size undetermined).

Among patients with unresectable advanced or recurrent HER2-positive[12)] colorectal cancer who were enrolled in the MyPathway study[13)] between October 20, 2014 and June 22, 2017, a total of 57 patients receiving TRA/PER therapy (at the same dosage regimen as that used in the TRIUMPH study) constituted the TRA/PER group. The control group was composed of 18 patients with unresectable advanced or recurrent

[10)] The investigator's choice of therapies were FTD/TPI + Bmab in 3 patients, FTD/TPI in 1 patient, and folinate/fluorouracil/L-OHP (FOLFOX) + Bmab in 1 patient.

[11)] The investigator's choice of therapies were FTD/TPI + Bmab in 5 patients, FTD/TPI in 3 patients, regorafenib in 2 patients, S-1 in 1 patient, FOLFOX + Bmab in 1 patient, and fluorouracil/folinate/IRI (FOLFIRI) + Bmab in 1 patient.

[12)] The study enrolled patients who had a score of 3+ by IHC, tested positive on FISH or chromogenic *in situ* hybridization (CISH), or were positive for *HER2* gene amplification by NGS at the study site.

[13)] A foreign phase IIa study that evaluated the efficacy, safety, and other aspects of therapies targeting specified genetic abnormalities in patients with advanced solid tumors harboring such genetic abnormalities, who had previously received standard first-line treatments and for whom the targeted therapies were considered to be their best treatments (*Lancet Oncol.* 2019;20:518-30). Of the 57 patients allocated to the TRA/PER group of Study PER001JP, 53 patients received TRA/PER therapy as a third- or later-line treatment.

HER2-positive[14] colorectal cancer, who were registered in the real-world clinico-genomic database[15] established with data from Flatiron and Foundation Medicine, between January 1, 2011 and December 31, 2019, met the same eligibility criteria as those used in the MyPathway study, had been treated with ≥2 regimens of chemotherapies[16] including standard first-line treatments, and received investigator's choice of therapy.

The primary endpoint of the study was overall survival (OS). Propensity score adjustment[17] was used to compare OS between the TRA/PER group and the control group. OS in the TRA/PER group was defined as the time from the date when TRA/PER therapy in the MyPathway study was started to the date of death. OS in the control group was defined as the time from the date when a new chemotherapy was started (the index date) after ≥2 regimens of chemotherapies including standard first-line treatments and after a diagnosis of HER2 positivity to the date of death. If a single patient received ≥2 new chemotherapies and had multiple index dates, OS data (records) for all of the index dates were included in the analyses. As a result, 56 records in the TRA/PER therapy and 27 records in the control group[18] were analyzed, based on a quasi population weighted using a propensity score-based standard mortality ratio weighting method (with the stabilized weight in the TRA/PER group deemed as 1).

Table 3 shows the results of OS as the primary efficacy endpoint (data cutoff on August 1, 2017 for the TRA/PER group and December 31, 2019 for the control group).

Table 3. OS (weighed quasi-population, data cutoff on August 1, 2017 for the TRA/PER group and December 31, 2019 for the control group)

	TRA/PER	Control
No. of patients	56.0	22.9
No. of events (%)	25.0 (44.6)	9.2 (40.2)
Median [95% CI] (months)	11.5 [7.7, 22.1]	9.7 [7.4, 22.2]
Hazard ratio [95% CI]*1	0.73 [0.18, 3.90]	

*1 A Cox proportional hazard model with the location of the primary tumor (right colon, transverse colon, left colon, colon [unknown site], vs. rectum), number of prior treatment regimens (<4 vs. ≥4), time from the diagnosis of progression or recurrence to the index date (continuous values), *KRAS* mutation status (positive vs. negative), prior anti-EGFR antibody therapy (Cmab alone, Pmab alone, both Cmab and Pmab, vs. neither Cmab nor Pmab), and treatment as explanatory variables. The hazard ratio [95% CI] based on a Cox proportional hazard model with treatment as the sole explanatory variable was 1.04 [0.43, 3.94].

7.2.2.2 Non-interventional study (CTD 5.3.5.4-2, Study SG42530)

A non-interventional study was conducted to compare patient characteristics, OS, and other aspects by HER2 status (positive vs. negative) in chemotherapy-treated patients with unresectable advanced or recurrent colorectal cancer (target sample size undetermined).

[14] Patients whose tumors were confirmed to have *HER2* gene amplification by a Foundation Medicine's comprehensive genomic profiling test ("FoundationOne" or "FoundationOne CDx") were enrolled.
[15] A database constructed using data from patients with cancer who underwent a Foundation Medicine's comprehensive genomic profiling test ("FoundationOne" or "FoundationOne CDx") and were registered in the medical information database by Flatiron.
[16] A fluoropyrimidine in combination with L-OHP or IRI was defined as a standard first-line treatment. Patients who had previously received HER2-targeted drugs were excluded.
[17] Propensity scores were estimated using a logistic model with age, location of the primary tumor, number of prior treatment regimens, time from the diagnosis of progression or recurrence to the index date, *KRAS* mutation status, and prior anti-EGFR antibody therapy as covariates.
[18] In the control group, the treatments chosen by the investigators in ≥2 records were regorafenib in 4 records, and FOLFOX + Bmab, FOLFOX + Cmab, and pembrolizumab (genetical recombination) in 2 records each.

Of patients who were registered in Flatiron and Foundation Medicine's real-world clinico-genomic database,[15] between January 1, 2011 and December 31, 2019, a total of 576 patients with unresectable advanced or recurrent HER2-positive[14] or -negative colorectal cancer (63 in the HER2-positive group and 513 in the HER2-negative group) who had previously received ≥1 regimens of chemotherapies were identified for analyses. OS was defined as the time from the date when a new chemotherapy was started after the first-line treatment (the index date) to the date of death. If a single patient received ≥2 new chemotherapies and had multiple index dates, OS data (records) for all of the index dates were included in analyses. As a result, analyses were conducted on 158 records in the HER2-positive group and 1181 records in the HER2-negative group.

The distributions of most patient characteristics did not differ substantially between the HER2-positive group and the HER2-negative group, with the exception of the proportion of patients with *KRAS* mutations, which clearly differed between the two groups (18% and 52%, respectively). The median OS [95% CI] was 11.2 [8.57, 15.08] months in the HER2-positive group and 9.92 [8.28, 10.87] months in the HER2-negative group (data cutoff on December 31, 2019).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the reviews presented below, PMDA concluded that a certain level of efficacy of TRA/PER therapy had been demonstrated in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer.

7.R.1.1 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint in the TRIUMPH study and the efficacy of TRA/PER therapy in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer:

Chemotherapy-treated patients with unresectable advanced or recurrent colorectal cancer can be expected to respond to treatments, thereby attaining improvements in clinical symptoms associated with disease progression (e.g., *J Clin Oncol*. 2009;27:1822-8). Achieving a response is thus clinically meaningful in this patient population; therefore, the objective response rate was selected as the primary endpoint in the TRIUMPH study.

The results of the TRIUMPH study showed that the investigator's assessment-based objective response rates [95% CIs], the primary endpoint, exceeded the predetermined threshold objective response rate (5%) in both the TBx group and the LBx group (29.6% [13.8%, 50.2%] and 28.0% [12.1%, 49.4%], respectively) [see Section 7.1.1.1]. The central assessment-based objective response rates [95% CIs] in the TBx group and the LBx group were 33.3% [16.5%, 54.0%] and 28.0% [12.1%, 49.4%], respectively.

Figure 1 shows the maximum tumor shrinkage (percent change of sum of diameters of target lesions), as assessed by the investigators according to RECIST ver. 1.1, in the TBx group and the LBx group of the

TRIUMPH study. The median duration of response[19] [95% CI] was 12.1 [2.8, not estimable] months in the TBx group and 8.1 [2.8, not estimable] in the LBx group.

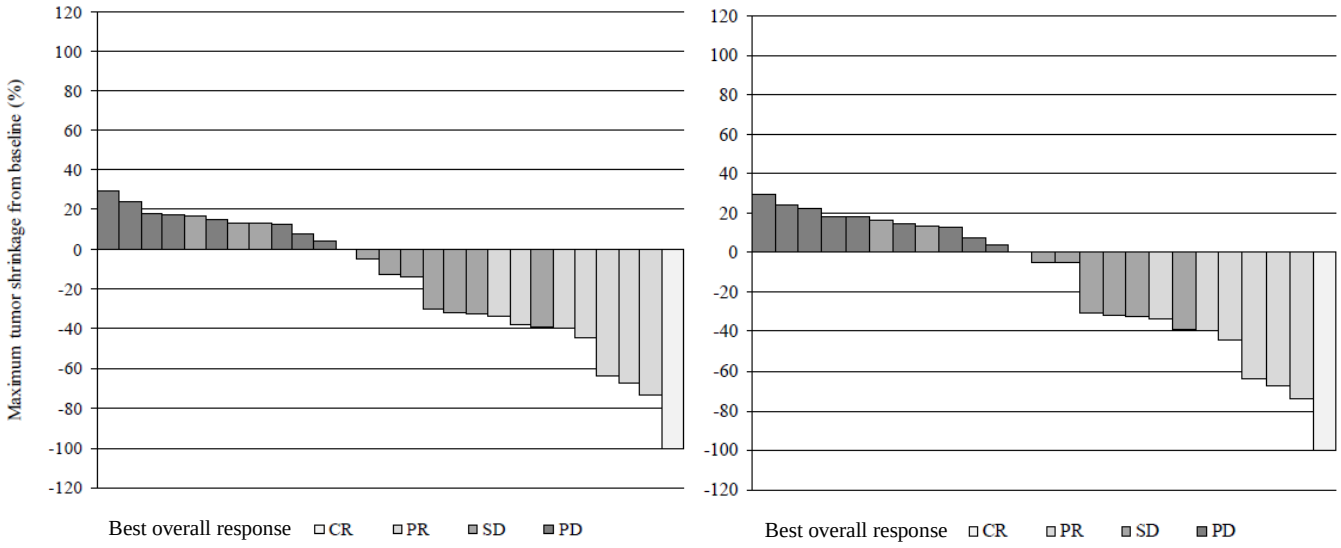

Figure 1. Maximum tumor shrinkage (percent change of sum of diameters of target lesions) (left, TBx group; right, LBx group) (RECIST ver. 1.1, investigator's assessment, data cutoff on March 31, 2020)

Because patients with unresectable advanced or recurrent HER2-positive colorectal cancer accounts for only 2% to 3% of all patients with colorectal cancers (e.g., *J Pathol*. 2016;238:562-70, *Br J Cancer*. 2014;111:1977-84), conducting a confirmatory study in patients with unresectable advanced or recurrent HER2-positive colorectal cancer was infeasible. Furthermore, no clinical study data on the efficacy of conventional treatments were available from Japanese patients with unresectable advanced or recurrent HER2-positive colorectal cancer. Under these circumstances, patients who were enrolled in a disease registry and met the same eligibility criteria as those for the TRIUMPH study were used to compare the efficacy of TRA/PER therapy with that of conventional treatments. The objective response rates of investigator's choice of therapy in 5 patients identified from the SCRUM-Japan Registry (4 in the TBx group and 2 in the LBx group) were 0% for both the TBx group and the LBx group [see Section 7.1.1.1]. There are limitations in interpreting the results of the analysis using a disease registry, due to the small number of patients evaluated, biases in patient characteristics that may affect the results of the analysis, and other factors. Nevertheless, TRA/PER therapy can be expected to be effective in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, taking into account available findings including the hazard ratio [95% CI] of 0.73 [0.18, 3.90] for propensity score-adjusted OS for the TRA/PER group versus the control group (investigator's choice of therapy) in Study PER001 JP [see Section 7.2.2.1].

PMDA's view:

The relationship between OS (the true endpoint) and the objective response rate has not been clarified in

[19] The duration of response was defined as the time from first response to progressive disease (PD) or death in patients experiencing a CR or PR. Patients who experienced neither a PD nor death event were censored at the final imaging assessment.

chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer. Thus, the potential of TRA/PER therapy to prolong survival in such patients cannot be evaluated based on the objective response rate (the primary endpoint) in the TRIUMPH study. Further, although the results in the SCRUM-Japan Registry group (evaluation) identified for the TRIUMPH study [see Section 7.1.1.1] may serve as reference information to support the efficacy of conventional treatments, there are limitations in interpreting the results of comparison of the registry group with the TRA/PER group, due to the very small number of patients evaluated, biases in patient characteristics which may affect the study results, and other factors.

Nevertheless, PMDA concluded that a certain level of efficacy of TRA/PER therapy had been demonstrated in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, taking into consideration the facts that: (i) both TRA and PER are HER2-targeted antibody drugs, and (ii) the objective response rates of TRA/PER therapy in the TRIUMPH study exceeded the study results for conventional treatments (described below), which was clinically significant.

- In a global phase III study conducted to evaluate the efficacy and safety of regorafenib versus placebo in patients with unresectable advanced or recurrent colorectal cancer that had progressed after ≥2 regimens of chemotherapies including fluoropyrimidines, L-OHP, IRI, and Bmab (and anti-EGFR antibody therapy [Cmab or Pmab] for patients with *KRAS* wild-type tumors), the investigator's assessment-based objective response rate in the regorafenib group was 1.0% (*Lancet.* 2013;381:303-12).
- In a global phase III study conducted to evaluate the efficacy and safety of FTD/TPI therapy versus placebo in patients with unresectable advanced or recurrent colorectal cancer who were resistant or intolerant to ≥2 regimens of chemotherapies including fluoropyrimidines, L-OHP, IRI, and Bmab (and anti-EGFR antibody therapy [Cmab or Pmab] for patients with *KRAS* wild-type tumors), the investigator's assessment-based objective response rate in the FTD/TPI group was 1.6% (*N Engl J Med.* 2015;372:1909-19).

7.R.2 Safety

PMDA's view based on the reviews in the subsections below:

Adverse events requiring special attention in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer during TRA/PER therapy are adverse events identified as those of special interests at the regulatory reviews for the approved indications of (a) TRA and (b) PER. Chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer should be closely monitored for the onset of these adverse events during TRA/PER therapy.

(a) Cardiac disorder: infusion reaction; interstitial pneumonia and lung disorder; haematotoxicity; hepatic failure and liver disorder; renal disorder; coma, cerebrovascular disorder, and brain oedema; infection; tumour lysis syndrome; and oligohydramnios (see "Review Report for Herceptin Intravenous Infusion 60, Herceptin Intravenous Infusion 150" dated October 21, 2021," etc.)

(b) Neutropenia/leukopenia, diarrhoea and mucositis, cardiac disorder, infusion reaction, interstitial lung disease, rash, hypersensitivity/anaphylaxis, and tumour lysis syndrome (see "Review Report for Perjeta Intravenous Infusion 420 mg/14 mL dated August 3, 2018," etc.)

Although patients on TRA/PER therapy should be monitored for the onset of the above-mentioned adverse events, TRA/PER therapy is tolerable in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, as long as the patients are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through appropriate measures such as the monitoring and management of adverse events, and the interruption of TRA and PER.

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of TRA/PER therapy in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, based on the safety data obtained in the TRIUMPH study:

Table 4 presents a summary of the safety data from the TRA/PER group of the TRIUMPH study.

Table 4. Summary of safety (TRIUMPH study)

	n (%)
	TRA/PER (N = 30)
All adverse events	30 (100)
Grade ≥3 adverse events	8 (26.7)
Adverse events leading to death	0
Serious adverse events	5 (16.7)
Adverse events leading to drug discontinuation	1 (3.3)
Adverse events leading to drug interruption	0

In the TRIUMPH study, adverse events of any grade reported with an incidence of ≥10% were infusion related reaction in 14 patients (46.7%), diarrhoea in 12 patients (40.0%), decreased appetite in 5 patients (16.7%), nausea, stomatitis, and nasopharyngitis in 4 patients (13.3%) each, and malaise, pyrexia, oedema peripheral, pneumonia, anaemia, and rhinitis allergic in 3 patients (10.0%) each. Grade ≥3 adverse events reported with an incidence of ≥5% were anaemia and hypokalaemia in 2 patients (6.7%) each. Serious adverse events were infusion related reaction in 2 patients (6.7%), and cellulitis, pneumonia, ejection fraction decreased, osteitis, and dyspnoea in 1 patient (3.3%) each. An adverse event (ejection fraction decreased) led to drug discontinuation in 1 patient (3.3%). No adverse events led to death or drug interruption.

The applicant's explanation about the differences in the safety profiles of TRA and PER between patients with unresectable advanced or recurrent colorectal cancer (TRIUMPH study) and patients treated with TRA/PER therapy at the same dosage regimen as that used in the TRIUMPH study (i.e., intravenous TRA as a loading dose of 8 mg, followed by subsequent doses of 6 mg/kg every 3 weeks; intravenous PER as a loading dose of 840 mg, followed by subsequent doses of 420 mg every 3 weeks) for the approved indications in a global phase III study in patients with chemotherapy-naïve inoperable or recurrent breast cancer (CLEOPATRA study) and a global phase III study in patients with resected breast cancer (APHINITY study):

Table 5 shows the incidences of adverse events in the TRA/PER group of the TRIUMPH study, the TRA/PER/docetaxel hydrate (DTX) group of the CLEOPATRA study, and the TRA/PER/chemotherapy group[20] of the APHINITY study.

Table 5. Summary of safety (TRIUMPH, CLEOPATRA, and APHINITY studies)

	n (%)		
	TRIUMPH study (colorectal cancer)	CLEOPATRA study (inoperable or recurrent breast cancer)	APHINITY study (resected breast cancer)
	TRA/PER N = 30	TRA/PER/DTX N = 407	TRA/PER/chemotherapy N = 2364
All adverse events	30 (100)	406 (99.8)	2361 (99.9)
Grade ≥3 adverse events	8 (26.7)	302 (74.2)	1518 (64.2)
Adverse events leading to death	0	8 (2.0)	10 (0.4)
Serious adverse events	5 (16.7)	140 (34.4)	692 (29.3)
Adverse events leading to drug discontinuation	1 (3.3)	25 (6.1)	166 (7.0)
Adverse events leading to drug interruption	0	183 (45.0)	725 (30.7)

The adverse event of any grade with a ≥10% higher incidence in the TRIUMPH study than in either the CLEOPATRA study or the APHINITY study was infusion related reaction (14 patients [46.7%] in the TRIUMPH study, 11 patients [2.7%] in the CLEOPATRA study, and 90 patients [3.8%] in the APHINITY study). The serious adverse event with a ≥5% higher incidence in the TRIUMPH study than in either the CLEOPATRA study or the APHINITY study was infusion related reaction (2 patients [6.7%], 0 patients, and 3 patients [0.1%]). There were no Grade ≥3 adverse events or adverse events leading to death, drug discontinuation, or drug interruption, with a ≥5% higher incidence in the TRIUMPH study than in either the CLEOPATRA study or the APHINITY study.

PMDA's view:

Although infusion related reaction was reported more frequently in the TRIUMPH study than in patients treated for the approved indications, the difference in the use of prophylactic corticosteroids[21] might have partly contributed to the higher incidence of the adverse event in the TRIUMPH study. Infusion related reaction is a known adverse event of both TRA and PER, and the outcome of even serious cases was "resolved." In addition, the incidence of adverse events leading to death or serious adverse events did not tend to be higher in patients enrolled in the TRIUMPH study than in patients treated for the approved indications. In view of these findings, TRA/PER therapy is tolerable in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through appropriate measures such as the monitoring and management of adverse events, and the interruption of TRA and PER. However, the incidence of infusion related reaction in the TRIUMPH study and other relevant information should be appropriately communicated to healthcare professionals through the package insert and other materials.

[20] One of the following chemotherapy regimens, (a) to (e), was chosen by the investigators:
(a) Fluorouracil + epirubicin hydrochloride (EPI) + cyclophosphamide hydrate (CPA) (FEC therapy), (b) fluorouracil + doxorubicin hydrochloride (ADM) + CPA (FAC therapy), (c) ADM + CPA (AC therapy), (d) EPI + CPA (EC therapy), and (e) DTX + carboplatin

[21] The percentages of patients who received corticosteroids prophylactically or concomitantly were 30.0% (9 of 30 patients) in the TRIUMPH study, 77.1% (310 of 402 patients) in the CLEOPATRA study, and 82.2% (1944 of 2364 patients) in the APHINITY study. There were no reports of infusion related reaction from 9 patients who received prophylactic corticosteroids in the TRIUMPH study.

7.R.3 Clinical positioning and indication

In the present partial change application, the applicant proposed the indications of TRA and PER, as shown in the table below. After the submission of the present application, the applicant explained that the statements in the "Precautions Concerning Indications" sections would be modified as presented in the table below.

	Indications	Precautions Concerning Indications
TRA	Unresectable advanced or recurrent HER2-overexpressing colorectal cancer	• Testing for HER2 overexpression should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing, using an approved *in vitro* diagnostic or medical device. • The efficacy and safety of TRA have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of TRA as an adjuvant chemotherapy have not been established. • The efficacy and safety of TRA have not been established in the treatment of *RAS*-mutated tumors. • The efficacy and safety of TRA have not been established in the treatment of *BRAF*-mutated tumors.
PER	Unresectable advanced or recurrent HER2-positive colorectal cancer	• Testing for HER2 should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing, using an approved *in vitro* diagnostic or medical device. • The efficacy and safety of PER have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of PER in the adjuvant setting have not been established. • The efficacy and safety of PER have not been established in the treatment of *RAS*-mutated tumors. • The efficacy and safety of PER have not been established in the treatment of *BRAF*-mutated tumors.

PMDA's view:

Based on the reviews in Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the subsections presented below, the "Indications" and the "Precautions Concerning Indications" sections for TRA and PER should include the following statements.

	Indications	Precautions Concerning Indications
TRA	Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy	• TRA should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test. • The efficacy and safety of TRA have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of TRA have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of TRA as an adjuvant therapy have not been established. • Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based adequate knowledge of the efficacy and safety of TRA, after carefully considering the choice of alternative therapies.
PER	Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy	• PER should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test. • The efficacy and safety of PER have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of PER have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of PER in the adjuvant setting have not been established. • Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of PER, after carefully considering the choice of alternative therapies.

7.R.3.1 Clinical positioning and indication of TRA/PER therapy

Representative clinical practice guidelines and leading clinical oncology textbooks published in and outside of Japan contain descriptions on TRA/PER therapy for chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, which are as shown below.

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (hereinafter referred to as "NCCN Guidelines") (Colon Cancer) (v.3.2021):
  TRA/PER therapy is recommended as a second- or later-line treatment option for patients with unresectable advanced or recurrent HER2-positive, *RAS* wild-type, and *BRAF* wild-type colon cancer.
- NCCN Guidelines (Rectal Cancer) (v.2.2021):
  TRA/PER therapy is recommended as a second- or later-line treatment option for patients with unresectable advanced or recurrent HER2-positive, *RAS* wild-type, and *BRAF* wild-type rectal cancer.

The applicant's explanation about the background and reason for using combination therapy with TRA and PER in the TRIUMPH study:

For the following reasons, the combination of TRA and PER was considered to have a higher antitumor effect than TRA or PER monotherapy, and was thus selected. The preliminary results from Study NCCH1901,[22)] which was initiated after the start of the TRIUMPH study, revealed that TRA monotherapy yielded an objective response rate of 0% (0 of 3 patients) in patients with unresectable advanced or recurrent HER2-positive colorectal cancer that had progressed after standard treatments (as of September 22, 2021).

- Given the following findings, TRA was expected to have a higher antitumor effect when used in combination with other HER2-targeted drugs, than when used as a monotherapy.

[22)] A specified clinical research study involving patients with solid tumors that are confirmed by a comprehensive genomic profiling test to harbor specific genetic alterations, in which unapproved drugs targeting the genetic alterations are used in patients who propose the off-label use of such drugs, under the patient-proposed healthcare system. The clinical research study intends to collect treatment course data.

- TRA and PER bind to different sites on HER2 [see Section 1.1], and thus are considered to have partly different mechanisms of action. In mouse models xenografted with cells derived from patients with HER2-positive breast cancer and from patients with HER2-positive non-small-cell lung cancer (NSCLC), TRA/PER therapy had higher antitumor effects than TRA monotherapy (*Cancer Res.* 2009;69:9330-6).
- In a mouse model xenografted with cells derived from patients with HER2-positive colorectal cancer, combination therapy with TRA and lapatinib (a tyrosine kinase inhibitor that targets EGFR and HER2) had a higher antitumor effect than TRA or lapatinib monotherapy (*Clin Cancer Res.* 2015;21:5519-31). In a foreign phase II study that evaluated the efficacy and safety of combination therapy with TRA and lapatinib in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive and *KRAS* wild-type colorectal cancer (HERACLES study), the objective response rate was 29.6% (8 of 27 patients) (*Lancet Oncol.* 2016;17:738-46).

- Since PER had failed to show efficacy when used as a monotherapy in multiple clinical studies in patients with solid tumors, a clinical development was initiated for PER in combination with TRA. A clinical study in patients with HER2-positive breast cancer successfully demonstrated PER's add-on effect to TRA-based chemotherapy (see "Review Report for Perjeta Intravenous Infusion 420 mg/14 mL dated April 9, 2013").
- The interim analysis of the MyPathway study showed that the objective response rate of TRA/PER therapy in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer was 38% (13 of 34 patients) (*J Clin Oncol.* 2017;35(4 Suppl):676).

The applicant's explanation about the clinical positioning and indication of TRA/PER therapy in the treatment of unresectable advanced or recurrent colorectal cancer:
In view of the results of the TRIUMPH study [see Sections 7.R.1 and 7.R.2] and other findings, TRA/PER therapy can be positioned as a treatment option for patients with unresectable advanced or recurrent HER2-positive colorectal cancer.

Patients enrolled in the TRIUMPH study had to be refractory or intolerant to fluoropyrimidines, L-OHP, and IRI as standard treatments for unresectable advanced or recurrent colorectal cancer. For this reason, TRA/PER therapy cannot be recommended for patients who have not received these treatments. In addition, while the TRIUMPH study enrolled patients with or without *BRAF* mutations, only a single patient had *BRAF*-mutated cancer, who achieved a best overall response of stable disease (SD) in the study. The Japanese Society for Cancer of the Colon and Rectum Guidelines for the Treatment of Colorectal Cancer (hereinafter referred to as the "Japanese clinical practice guidelines") (2019 edition, preliminary edition as of November 2020) recommend combination therapies including BRAF inhibitors such as encorafenib for the treatment of chemotherapy-treated patients with unresectable advanced or recurrent BRAF V600E-mutated colorectal cancer. Taking these recommendations into account, TRA/PER therapy cannot be recommended for patients with *BRAF*-mutated colorectal cancer. In addition, because no clinical studies have thus far evaluated the

efficacy and safety of TRA/PER therapy as an adjuvant therapy, TRA/PER therapy cannot be recommended as an adjuvant therapy.

The applicant provided the following opinion on the use of TRA/PER therapy in (a) patients with *RAS*-mutated colorectal cancer and (b) patients who have not previously received anti-EGFR antibody therapy, who were excluded from the TRIUMPH study.

(a) Patients with *RAS*-mutated colorectal cancer:

Based on the following and other findings, TRA/PER therapy cannot be expected to be effective in patients with *RAS*-mutated colorectal cancer. Furthermore, the TRIUMPH study enrolled only patients with *RAS* wild-type colorectal cancer. In light of these facts, TRA/PER therapy cannot be recommended for patients with *RAS*-mutated colorectal cancer.

- TRA and PER, both of which target HER2, cannot be expected to be effective in patients with *RAS*-mutated colorectal cancer, in view of the following reports: (i) In patients with *RAS*-mutated colorectal cancer, constitutive activation of EGFR downstream signaling pathway is likely to result in the poor anti-tumor effect of anti-EGFR antibody therapy (*J Clin Oncol.* 2003;21:2787-99); (ii) All anti-EGFR antibody drugs that have been approved for the treatment of colorectal cancer in Japan were indicated for use in patients with RAS wild-type colorectal cancer (e.g., Japanese clinical practice guidelines [2016 edition]); and, (iii) RAS protein is a common downstream signaling molecule of EGFR and HER2 (*J Clin Oncol.* 2003;21:2787-99).
- The interim analysis of the MyPathway study showed that the objective response rate of TRA/PER therapy was 52% (13 of 25 patients) in patients with *KRAS* wild-type colorectal cancer, as compared with 0% (0 of 9 patients) in patients with *KRAS*-mutated colorectal cancer (*J Clin Oncol.* 2017;35(4 Suppl):676).

Patients with unresectable advanced or recurrent colorectal cancer need to undergo *RAS* mutation testing for identification of the eligibility for anti-EGFR antibody therapy before initiating a first-line treatment (Japanese clinical practice guidelines [2019 edition]). Thus, patients who have previously received anti-EGFR antibody therapy, who are eligible for TRA/PER therapy, should have been confirmed to have a RAS wild-type tumor before starting their first-line treatments.

The applicant's opinion on the need to reconfirm that the tumor remains RAS wild-type using samples taken after anti-EGFR antibody therapy:

The emergence of *RAS* mutations is observed in appropriately 40% to 60% of patients treated with anti-EGFR antibody therapy, and this is reported to be a main mechanism by which colorectal tumors acquire resistance to anti-EGFR antibodies (e.g., *Nature.* 2012;486:537-40). In view of this and other findings, in the TRIUMPH study, the efficacy of TRA/PER therapy was evaluated in patients allocated to the LBx group, in which patients were confirmed to have HER2-positive and *RAS* wild-type colorectal cancer[23)] by testing in blood samples taken after anti-EGFR antibody therapy. However, the objective response rate of TRA/PER therapy in the LBx group did not substantially differ from that in patients allocated to the TBx group, in which patients were confirmed to have HER2-positive and *RAS* wild-type colorectal cancer by testing in tumor tissue samples taken before anti-EGFR antibody therapy [see Section 7.1.1.1]. Taking into consideration the above results and the following findings, reconfirming *RAS* mutation status using a sample taken after anti-EGFR antibody therapy in patients who have been confirmed to have HER2-positive colorectal cancer using a sample taken at any time before the start of TRA/PER therapy is less necessary.

- *RAS* mutations and *HER2* gene amplification contribute in a mutually independent manner to the development of resistance to anti-EGFR antibody therapy (*Cancer Discov.* 2011;6:508-23). Since tumors are unlikely to acquire both *RAS* mutations and *HER2* gene amplification, which are the independent mechanisms of resistance to anti-EGFR antibody therapy, neither patients whose tumors are already HER2-positive before the start of anti-EGFR antibody therapy nor patients whose tumors become HER2-positive after the start of anti-ECFR antibody therapy are likely to have *RAS* mutations.
- A total of 27 patients were confirmed to have a *RAS* wild-type and HER2-positive colorectal cancer by testing in tumor tissue samples taken before the start of anti-EGFR antibody therapy and then enrolled in the TRIUMPH study. Of the 27 patients, 8 tested negative for HER2 in blood samples taken after anti-EGFR antibody therapy, and 1 of these 8 patients was confirmed to have *RAS* mutations by testing in the blood sample taken after anti-EGFR antibody therapy. However, given the following results from the patient, tumor heterogeneity might have affected the results of tissue tumor sample testing. It cannot be concluded from the results from this single patient that the likelihood of *RAS* mutations occurring after anti-EGFR antibody therapy in patients who tested positive for HER2 before the start of the therapy should be considered.
  - The tumor tissue sample had HER2 expression defined as IHC 2+, and the IHC staining was uneven and low.
  - The tumor tissue sample tested positive on FISH, but the blood sample tested negative for HER2.
- In 22 patients with unresectable advanced or recurrent *RAS* wild-type and HER2-negative colorectal cancer, the *RAS* mutation status and *HER2* gene amplification status were assessed when the disease progressed after anti-EGFR antibody therapy. The assessment results showed that none of these patients

[23)] In a foreign phase II study that evaluated the efficacy and safety of combination therapy with TRA and lapatinib in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive and *KRAS* wild-type colorectal cancer (HERACLES study), the variant allele frequency was ≤30% in all patients with a best overall response of PR, but it was >30% in all patients with a best overall response of SD or PD. Based on this and other findings, in the TRIUMPH study, *RAS* wild-type was defined as a *RAS* variant allele frequency of ≤30%.

experienced the co-occurrence of *RAS* mutations and *HER2* gene amplification (*Clin Cancer Res.* 2017;23:2414-22).

(b) Patients who have not previously received anti-EGFR antibody therapy

When the TRIUMPH study was being planned, the Japanese clinical practice guidelines (2016 edition) and other guidelines recommended anti-EGFR antibody therapy (Cmab or Pmab) alone or in combination with IRI as a treatment option for patients with unresectable advanced or recurrent *RAS* wild-type colorectal cancer who were refractory or intolerant to fluoropyrimidines, L-OHP, and IRI, and had not previously received anti-EGFR antibody therapy. The reported objective response rates of these treatments ranged from 20% to 26% (e.g., *Lancet Onco*l. 2014;15:569-79). On the other hand, the objective response rate [95% CI] of TRA/PER therapy provided from the interim analysis of the MyPathway study at the time was 38% [22%, 56%] (13 of 34 patients), showing that the lower limit of the 95% CI was below the objective response rate of the recommended treatments. For this and other reasons, patients who had previously received anti-EGFR antibody therapy were selected as the target population of the TRIUMPH study. However, in view of the following reports, there is little need to restrict the intended population of TRA/PER therapy to patients who had previously received anti-EGFR antibody therapy.

- After the start of the TRIUMPH study, patients with unresectable advanced or recurrent HER2-positive colorectal cancer were reported to have a lower response to anti-EGFR antibody therapy than those with HER2-negative tumors (e.g., *Int J Mol Sci.* 2021;22:6813, *JCO Precis Oncol.* 2019;3:1-13). Based on these reports and other findings, the NCCN Guidelines (Colon Cancer, v.3.2021; Rectal Cancer, v.2.2021) included a statement to the effect that HER2 positivity was a possible predictor of resistance to anti-EGFR antibody therapy.
- In the MyPathway study, the objective response rates of TRA/PER therapy were 36% (11 of 31 patients) in patients with prior anti-EGFR antibody therapy and 50% (6 of 12 patients) in those without such prior therapy, showing no clear difference (*Lancet Oncol.* 2019;20:518-30).

Based on the above, the indication of TRA was proposed as “unresectable advanced or recurrent HER2-overexpressing colorectal cancer,” and the indication of PER was proposed as “unresectable advanced or recurrent HER2-positive colorectal cancer,” with the statements presented in the table below included in the proposed “Precautions Concerning Indications” section.

	Precautions Concerning Indications
TRA	• The efficacy and safety of TRA have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of TRA as an adjuvant chemotherapy have not been established. • The efficacy and safety of TRA have not been established in the treatment of *RAS*-mutated tumors. • The efficacy and safety of TRA have not been established in the treatment of *BRAF*-mutated tumors.
PER	• The efficacy and safety of PER have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of PER in the adjuvant setting have not been established. • The efficacy and safety of PER have not been established in the treatment of *RAS*-mutated tumors. • The efficacy and safety of PER have not been established in the treatment of *BRAF*-mutated tumors.

PMDA's view:

Since there are no clinical study data on the efficacy and safety of TRA/PER therapy in chemotherapy-naïve patients with unresectable advanced or recurrent HER2-positive colorectal cancer, the "Indications" section should clarify that the intended population of TRA/PER therapy is patients with colorectal cancer that has progressed after cancer chemotherapy.

Further, clinical study data on the efficacy and safety of TRA/PER therapy in patients with unresectable advanced or recurrent HER2-positive and *BRAF*-mutated colorectal cancer are limited. At present, this precludes drawing a definitive conclusion on the clinical benefit of TRA/PER therapy in such patients. In addition, the Japanese clinical practice guidelines (2019 edition) and other guidelines recommend that patients with unresectable advanced or recurrent colorectal cancer should undergo *BRAF* mutation testing before initiating their first-line treatments, and that patients with confirmed *BRAF* mutations should receive combination therapies including BRAF inhibitors as the second- or later-line treatments. TRA/PER therapy will be used by physicians with sufficient knowledge and experience in cancer chemotherapy. In view of the above facts, there is currently little need to provide precautionary advice regarding the use of TRA/PER therapy in patients with HER2-positive and *BRAF*-mutated colorectal cancer.

The applicant's explanation about the use of TRA/PER therapy in patients with *RAS*-mutated colorectal cancer is acceptable. Meanwhile, the applicant's explanation about the use of TRA/PER therapy for patients who have not previously received anti-EGFR antibody therapy is partly understandable, but not completely satisfactory. Given that (i) the intended population of TRA/PER therapy should be the target population of the TRIUMPH study, and (ii) the present partial change approval application evaluated the efficacy of TRA/PER therapy mainly based on objective response rates, but not on its prolonged survival effect, the "Clinical Studies" section of the package insert should include information, such as prior treatment history in the target population of the TRIUMPH study, with a precautionary statement in the "Precautions Concerning Indications" section that the use of TRA/PER therapy should be decided cautiously, after carefully considering the choice of alternative therapies.

Based on the above, PMDA concluded that the indication of TRA and PER should be "unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy," with the statements presented in the table below included in the "Precautions Concerning Indications" sections. Although the approved indications of TRA included the wording "HER2 overexpressing," current clinical practice guidelines use the wording "HER2-positive," not only when more than a specified amount of HER2 protein is detected by IHC testing, but also when HER2 gene amplification is identified by *in situ* hybridization (ISH) testing. Thus, the wording "HER2 overexpressing" in the proposed indication for colorectal cancer should be modified to "HER2-positive."

	Precautions Concerning Indications
TRA	• The efficacy and safety of TRA have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of TRA have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of TRA as an adjuvant therapy have not been established. • Eligible patients should be selected by physicians with a full understanding of the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of TRA, after carefully considering the choice of alternative therapies.
PER	• The efficacy and safety of PER have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of PER have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of PER in the adjuvant setting have not been established. • Eligible patients should be selected by physicians with a full understanding of the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of PER, after carefully considering the choice of alternative therapies.

7.R.3.2 HER2 testing

As companion diagnostics intended to assist in identifying eligibility for TRA/PER therapy, Roche Diagnostics K.K. and Abbott Japan LLC have filed partial change approval applications for "Ventana ultraView Pathway HER2 (4B5)" and the "Pathvision HER-2 DNA Probe Kit," respectively. In addition, Guardant Health is scheduled to file a partial change approval application for "Guardant360 CDx."

The applicant's explanation about the HER2 test used to identify eligible patients for TRA/PER therapy:
In the TRIUMPH study, the TBx test was performed by a central laboratory, as (a) an IHC test using "Ventana I-View Pathway HER2 (4B5)"(Roche Diagnostics K.K.) and/or as (b) a FISH test using the "Pathvision HER-2 DNA Probe Kit" (Abbott Japan LLC). For the following reasons, the HER2 positivity criteria for the IHC and FISH tests in colorectal cancer were set according to the guidelines for the pathological diagnosis of breast cancer. Specifically, patients with colorectal cancer whose tumors were scored as 3+ by the IHC test (a), or whose tumors tested positive on the FISH test (b) were categorized as HER2-positive patients and included in the TBx group. In addition, (c) the LBx test using "Guardant360" (Guardant Health) was performed by a central laboratory, and patients with colorectal cancer whose had *HER2* gene amplification (*HER2* gene copy number ≥2.4[24)]) were categorized as HER2-positive patients and included in the LBx group.

- Studies on the association between *HER2* gene amplification and prognosis in patients with unresectable advanced or recurrent colorectal cancer showed a good concordance between IHC and FISH results for

[24)] This corresponded to the higher 50% of the *HER2* gene copy number gains detected using Guardant360 in samples from patients with cancer.

HER2 positivity, when the results were determined using the diagnostic criteria based on the guidelines for the pathological diagnosis of breast cancer (Guidelines for HER2 testing in breast cancer, 2014, 4th edition, Breast Cancer HER2 Testing Pathology Group) (*Clin colorectal cancer*. 2018;17:198-205,[25)] J*CO Precis Oncol*. 2020; 4: 6-19).

The results of the TRIUMPH study demonstrated: (i) a certain level of efficacy and the acceptable safety of TRA/PER therapy in both the TBx group and the LBx group [see Sections 7.R.1.1 and 7.R.2.1], and (ii) a good concordance between the above 2 testing methods, (a) and (b), for HER2 positivity, with no clear difference between the objective response rate in patients enrolled based on the results of test (a) (34.8%) and that in patients enrolled based on the results of test (b) (29.6%). Based on these results and other findings, identifying eligible patients for TRA/PER therapy using one of the tests (a), (b), and (c) is considered appropriate. "Ventana ultraView Pathway HER2 (4B5)," for which Roche Diagnostics K.K. has filed a partial change approval application was shown to provide a 100% concordance rate with "Ventana I-View Pathway HER2 (4B5)," in an equivalence study using samples from patients with colorectal cancer. The diagnostic kit is expected to appropriately identify patients in whom the efficacy and safety of TRA/PER therapy can be promising.

Based on the above results, eligible patients for TRA/PER therapy should be identified using "Ventana ultraView Pathway HER2 (4B5)," "Pathvision HER-2 DNA Probe Kit," or "Guardant360 CDx." This information will be included in the "Precautions Concerning Indications" section.

PMDA's view:

The applicant's explanation is generally acceptable. A statement modified as shown below should be included in the "Precautions Concerning Indications" section. The detailed results of HER2 testing (IHC and FISH tests) in patients allocated to the TBx group of the TRIUMPH study [see Section 7.1.1.1] should be appropriately communicated to healthcare professionals through the package insert and other materials.

- TRA/PER therapy should be administered to patients with HER2-positive colorectal cancer confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test.

7.R.4 Dosage and administration

The proposed "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections are presented below.

[25)] The study results were published after the start of the TRIUMPH study.

	Dosage and administration	Precautions concerning dosage and administration
TRA	For the treatment of unresectable advanced or recurrent HER2-overexpressing colorectal cancer, use Regimen B in combination with PER. Regimen B: The usual dose for adults is a loading dose of 8 mg/kg (body weight) of TRA as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minutes every 3 weeks. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.	• The dosage and administration to be used in case where the scheduled dosing is delayed (same as that for the approved indications)
PER	For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer, the usual loading dose for adults is 840 mg of PER administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of PER as 60-minute intravenous infusions every 3 weeks, in combination with TRA. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.	• The efficacy and safety of PER monotherapy have not been established (same as that for the approved indications). • The dosage and administration to be used in case where the scheduled dosing is delayed (same as that for the approved indications)

As a result of the reviews described in Sections "7.R.1 Efficacy," "7.R.2 Safety," and "7.R.3 Clinical positioning and indication," and the subsection below, PMDA concluded that the dosage and administration of TRA and PER for the treatment of unresectable advanced or recurrent colorectal cancer should be modified as presented below, with the proposed statements included in the "Precautions Concerning Dosage and Administration" section.

TRA

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, use Regimen B in combination with PER.

Regimen B:

The usual dose for adults is a loading dose of 8 mg/kg (body weight) of TRA as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minutes every 3 weeks.

The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

PER

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, the usual loading dose for adults is 840 mg of PER administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of PER as 60-minute intravenous infusions every 3 weeks, in combination with TRA. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

7.R.4.1 Dosage and administration of TRA and PER

The applicant's explanation about the dosage and administration of TRA and PER in the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer:

In the TRIUMPH study, TER and PER were administered according to the same dosage regimens for the respective approved indications (breast cancer and gastric cancer [Regimen B] for TRA, and breast cancer for

PER), and the results of the study showed that TRA/PER therapy had a certain level of efficacy and acceptable safety in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer. Based on these results, the same dosage and administration of TEA and PER as those for the approved indications, which were used in the TRIUMPH study, were proposed in the present partial change approval application. No clinical study data were available from chemotherapy-treated patients with unresectable advanced or recurrent colorectal cancer (i.e., the target population of the TRIUMPH study) who received TRA or PER monotherapy, or TRA and PER in combination with any other antineoplastic drugs. Therefore, therapy with the combination of TRA and PER was only proposed in the present application.

PMDA's view:
The applicant's explanation is acceptable. The proposed dosage and administration should be modified as shown below, in accordance with the modified indications of TRA and PER [see Section 7.R.3.1].

TRA
For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, use Regimen B in combination with PER.
Regimen B:
The usual dose for adults is a loading dose of 8 mg/kg (body weight) of TRA as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 6 mg/kg as intravenous infusion over ≥90 minutes every 3 weeks.
The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

PER
For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, the usual loading dose for adults is 840 mg of PER administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of PER as 60-minute infusions every 3 weeks, in combination with TRA. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

7.R.5 Post-marketing investigations
The applicant's explanation:
The applicant will collect safety information through routine pharmacovigilance activities, considering that no new safety issues have been identified in the present partial change approval application and that it is unnecessary to conduct post-marketing surveillance aiming at evaluating the safety and other aspects of TRA/PER therapy in patients with unresectable advanced or recurrent HER2-positive colorectal cancer immediately after approval of the present application. This stance is based on the following reasons.

- Most of the adverse events reported in the TRIUMPH study were known adverse events associated with TRA or PER. The safety profile of TRA/PER therapy did not clearly differ between patients treated in the TRIUMPH study and those treated for the approved indications [see Section 7.R.2].

- The post-marketing surveillance for the approved indications has been completed, and a certain amount of safety information has been collected from Japanese patients treated with TRA/PER therapy.

PMDA accepted the applicant's explanation.

7.3 Adverse events reported in clinical studies

The following subsection summarizes common adverse events other than deaths in the clinical study data submitted for the safety evaluation. Deaths are detailed in Section "7.1 Evaluation data."

7.3.1 Japanese phase II study (TRIUMPH study)

Adverse events were reported by all of the patients in the TRA/PER group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 24 of 30 patients (80.0%). Adverse events reported with an incidence of ≥10% were infusion related reaction in 14 patients (46.7%), diarrhoea in 12 patients (40.0%), decreased appetite in 5 patients (16.7%), nausea, stomatitis, and nasopharyngitis in 4 patients (13.3%) each, and malaise, pyrexia, oedema peripheral, pneumonia, anaemia, and rhinitis allergic in 3 patients (10.0%) each.

Serious adverse events were reported in 5 of 30 patients (16.7%). The reported serious adverse events were infusion related reaction in 2 patients (6.7%), and cellulitis, pneumonia, ejection fraction decreased, osteitis, and dyspnoea in 1 patient (3.3%) each. A causal relationship to the study drug could not be ruled out for the infusion related reaction in 2 patients and ejection fraction decreased in 1 patient.

An adverse event led to drug discontinuation in 1 of 30 patients (3.3%). The adverse event was ejection fraction decreased, for which a causal relationship to the study drug could not be ruled out.

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 new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that TRA/PER therapy has a certain level of efficacy in the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy and that TRA/PER therapy has acceptable safety in view of its benefits. TRA/PER therapy is clinically meaningful because it offers a new treatment option for patients with unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy. The clinical positioning and other aspects of TRA/PER therapy should be further evaluated.

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

Review Report (2)

February 9, 2022

Products Submitted for Approval

(a) Brand Name	Herceptin Intravenous Infusion 60 Herceptin Intravenous Infusion 150
Non-proprietary Name	Trastuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	April 26, 2021

(b) Brand Name	Perjeta Intravenous Infusion 420 mg/14 mL
Non-proprietary Name	Pertuzumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	April 26, 2021

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 TRIUMPH study in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, the objective response rates [95% CIs], as assessed by the investigators according to the RECIST ver. 1.1, which was the primary endpoint, were 29.6% [13.8%, 50.2 %] (8 of 27 patients) in the TBx group and 28.0% [12.1%, 49.4%] (7 of 25 patients) in the LBx group.

As a result of its review described in Section “7.R.1 Efficacy” of the Review Report (1), PMDA has concluded that a certain level of efficacy of TRA/ PER therapy had been demonstrated in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer, in view of findings including the results of the TRIUMPH study, which showed that the objective response rates of TRA/PER therapy exceeded the clinical study results of conventional treatments and thus were clinically significant.

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

1.2 Safety

As a result of its review described in Section "7.R.2 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer during TRA/PER therapy are adverse events identified as those of special interests at the regulatory reviews for the approved indications of (a) TRA and (b) PER. Chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer should be closely monitored for the onset of these events during TRA/PER therapy.

(a) Cardiac disorder; infusion reaction; interstitial pneumonia and lung disorder; haematotoxicity; hepatic failure and liver disorder; renal disorder; coma, cerebrovascular disorder, and brain oedema; infection; tumour lysis syndrome; and oligohydramnios
(b) Neutropenia/leukopenia, diarrhoea and mucositis, cardiac disorder, infusion reaction, interstitial lung disease, rash, hypersensitivity/anaphylaxis, and tumour lysis syndrome

In addition, PMDA has concluded that TRA/PER therapy, despite these adverse events requiring special attention, is tolerable in chemotherapy-treated patients with unresectable advanced or recurrent HER2-positive colorectal cancer as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy, through monitoring and management of adverse events, interruption of TRA and PER, or other appropriate measures.

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

1.3 Clinical positioning and indication

As a result of its review described in Section "7.R.3 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the statements presented in the table below should be included in the "Indications" and "Precautions Concerning Indications" sections of the package inserts for TRA and PER.

	Indications	Precautions Concerning Indications
TRA	Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy	• TRA should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test. • The efficacy and safety of TRA have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of TRA have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of TRA as an adjuvant therapy have not been established. • Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of TRA, after carefully considering the choice of alternative therapies.
PER	Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy	• PER should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test. • The efficacy and safety of PER have not been established in patients with *RAS*-mutated tumors. • The efficacy and safety of PER have not been established in patients with no prior treatments with fluoropyrimidines, L-OHP, and IRI. • The efficacy and safety of PER in the adjuvant setting have not been established. • Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of PER, after carefully considering the choice of alternative therapies.

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

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

1.4 Dosage and administration

As a result of its review described in Section "7.R.4 Dosage and administration" of the Review Report (1), PMDA has concluded that the statements presented in the table below should be included in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections of the package inserts for TRA and PER.

	Dosage and administration	Precautions concerning dosage and administration
TRA	For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, use Regimen B in combination with PER. Regimen B: The usual dose for adults is a loading dose of 8 mg/kg (body weight) of TRA as an intravenous infusion over ≥90 minute once daily, followed by subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minutes every 3 weeks. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.	• The dosage and administration to be used in case where the scheduled dosing is delayed (same as that for the approved indications)
PER	For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, the usual loading dose for adults is 840 mg of PER administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of PER as 60-minute intravenous infusions every 3 weeks, in combination with TRA. The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.	• The efficacy and safety of PER monotherapy have not been established (same as that for the approved indications). • The dosage and administration to be used in case where the scheduled dosing is delayed (same as that for the approved indications)

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

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

1.5 Post-marketing investigations

As a result of its review described in Section "7.R.5 Post-marketing investigations" of the Review Report (1), PMDA has concluded that there is little need to conduct post-marketing surveillance aimed at evaluating the safety and other aspects of TRA/PER therapy in patients with unresectable advanced or recurrent HER2-positive colorectal cancer immediately after approval of the present application, and that safety information may be collected through routine pharmacovigilance activities.

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

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved with the indications and the dosage and administration shown below, provided that the necessary precautions are included in the package inserts and information about the proper use of the products is appropriately disseminated to healthcare professionals in the post-marketing setting, and provided that the products are properly used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions that are fully capable of responding to emergencies.

Herceptin Intravenous Infusion 60 and Herceptin Intravenous Infusion 150

Indications

(Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

- HER2-overexpressing breast cancer
- Unresectable advanced or recurrent HER2-overexpressing gastric cancer
- <u>Unresectable advanced or recurrent HER2-positive salivary gland carcinoma</u>
- <u>Unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy</u>

Dosage and administration (Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

For the treatment of HER2-overexpressing breast cancer, use Regimen A or B.

For the treatment of unresectable advanced or recurrent HER2-overexpressing gastric cancer, use Regimen B in combination with other antineoplastic drugs.

<u>For the treatment of unresectable advanced or recurrent HER2-positive salivary gland carcinoma, use Regimen B in combination with docetaxel.</u>

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, use Regimen B in combination with pertuzumab (genetical recombination).

Regimen A: The usual dose for adults is a loading dose of 4 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 2 mg/kg as intravenous infusions over ≥90 minutes once weekly.

Regimen B: The usual dose for adults is a loading dose of 8 mg/kg (body weight) of trastuzumab (genetical recombination) as an intravenous infusion over ≥90 minutes once daily, followed by subsequent doses of 6 mg/kg as intravenous infusions over ≥90 minute every 3 weeks s.

The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

Warnings (No change)

1. Trastuzumab-containing chemotherapy should be administered only to patients, who are considered eligible for the therapy, under the supervision of physicians with thorough knowledge and experience with cancer chemotherapy in medical institutions that are fully capable of responding to emergencies. Prior to the start of therapy, consent must be obtained from the patient or his/her family members who are fully informed of the efficacy and risks of the therapy.
2. Serious cardiac disorders such as cardiac failure occurred in patients treated with trastuzumab, and some of the patients had fatal outcomes. Cardiac function must be assessed prior to the initiation of treatment. In addition, cardiac assessments (e.g., echocardiography) should be performed to closely monitor the patient's conditions (including the change in left ventricular ejection fraction [LVEF]) during the treatment. In particular, the following patients require frequent cardiac assessments (e.g., echocardiography).
   - Patients who are receiving or have previously received anthracyclines
   - Patients who are undergoing radiation therapy to the chest
   - Patients with symptoms of cardiac failure
   - Patients with a history or presence of coronary artery disease (e.g., myocardial infarction, angina)
   - Patients with a history or presence of hypertension
3. Infusion reaction frequently occurs during dosing or within 24 hours after the start of dosing of trastuzumab. Some cases led to serious adverse drug reactions such as anaphylaxis or lung disorder (e.g., bronchospasm, severe blood pressure decreased, and acute respiratory distress syndrome), and then to fatal outcomes. Since these adverse drug reactions can easily become serious in patients with a history or presence of dyspnoea at rest (due to metastases to the lungs, cardiovascular diseases, etc.), trastuzumab should be administered cautiously, while the patients are monitored carefully.

Contraindication (No change)

Patients with a history of hypersensitivity to trastuzumab or any of the excipients

Precautions Concerning Indications (Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

~~All indications~~HER2-overexpressing breast cancer

1. Testing for HER2 overexpression should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing.

Unresectable advanced or recurrent HER2 overexpressing gastric cancer

2. Testing for HER2 overexpression should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing.
3. The efficacy and safety of trastuzumab as an adjuvant ~~chemo~~therapy have not been established.
4. Eligible patients should be selected by a physician with a full understanding of the information presented in the "Clinical Studies" section, including the primary sites and tissue types in the gastroesophageal junction region.

Unresectable advanced or recurrent HER2-positive salivary gland carcinoma

5. Trastuzumab should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test.

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

6. Trastuzumab should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test.
7. The efficacy and safety of trastuzumab have not been established in patients with *RAS*-mutated tumors.
8. The efficacy and safety of trastuzumab have not been established in patients with no prior treatments with fluoropyrimidines, oxaliplatin, and irinotecan hydrochloride hydrate.
9. The efficacy and safety of trastuzumab as an adjuvant therapy have not been established.
10. Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of trastuzumab, after carefully considering the choice of alternative therapies.

Precautions Concerning Dosage and Administration (Underline denotes additions. Double-underline denotes additions made as of November 25, 2021, after the submission of the present application.)

All indications

1. If the scheduled dosing is delayed for some reason, it is advisable to administer trastuzumab according to the following procedure:
   1.1 If the dose is delayed by ≤1 week, administer 2 mg/kg in Regimen A or 6 mg/kg in Regimen B.
   1.2 If the dose is delayed by >1 week, administer the re-loading dose (4 mg/kg in Regimen A or 8 mg/kg in Regimen B). For the subsequent doses, administer 2 mg/kg once weekly in Regimen A or 6 mg/kg every 3 weeks in Regimen B.

HER2-overexpressing breast cancer

2. The following cautions should be exercised when using trastuzumab as an adjuvant ~~chemotherapy~~therapy.

2.1 The efficacy and safety of treatment beyond 1 year have not been established.

2.2 Trastuzumab should be administered under the supervision of a physician with a full understanding of the information presented in the "Clinical Studies" section.

Unresectable advanced or recurrent HER2-overexpressing gastric cancer

3. Treatment with trastuzumab should be initiated as combination therapy with other antineoplastic drugs. The concomitant antineoplastic drugs must be selected by a physician with a full understanding of the information presented in the "Clinical Studies" section.

Perjeta Intravenous Infusion 420 mg/14 mL

Indications (Underline denotes additions.)

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

Dosage and administration (Underline denotes additions.)

For the treatment of HER2-positive breast cancer, the usual loading dose for adults is 840 mg of pertuzumab (genetical recombination) administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab (genetical recombination) as 60-minute intravenous infusions every 3 weeks, in combination with trastuzumab (genetical recombination) and other antineoplastic drugs. For neo-adjuvant or adjuvant therapy, the maximum treatment period is 12 months. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

For the treatment of unresectable advanced or recurrent HER2-positive colorectal cancer that has progressed after cancer chemotherapy, the usual loading dose for adults is 840 mg of pertuzumab (genetical recombination) administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab (genetical recombination) as 60-minute intravenous infusions every 3 weeks, in combination with trastuzumab (genetical recombination). The infusion time for the subsequent doses may be reduced to 30 minutes, if the loading dose is well tolerated.

Warning (No change)

Pertuzumab-containing chemotherapy should be administered only to patients, who are considered eligible for the therapy, under the supervision of physicians with a thorough knowledge and experience in cancer chemotherapy in medical institutions that are fully capable of responding to emergencies. Prior to initiation of the therapy, consent must be obtained from the patient or his/her family member who are fully informed of the efficacy and risks of the therapy.

Contraindications (No change)

1. Patients with a history of hypersensitivity to pertuzumab or any of the excipients
2. Pregnant women or women who may possibly be pregnant

Precautions Concerning Indications (Underline denotes additions.)

HER2-positive breast cancer

1. Testing for HER2 should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing.
2. The efficacy and safety of pertuzumab have not been established in patients with resected early HER2-positive breast cancer at a low risk of recurrence (i.e., patients with no lymph node metastases). Pertuzumab should be administered to patients who are at a high risk of recurrence.

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

3. Pertuzumab should be administered to patients with HER2-positive tumors confirmed by tests performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing. An approved *in vitro* diagnostic or medical device should be used in the test.
4. The efficacy and safety of pertuzumab have not been established in patients with *RAS*-mutated tumors.
5. The efficacy and safety of pertuzumab have not been established in patients with no prior treatments with fluoropyrimidines, oxaliplatin, and irinotecan hydrochloride hydrate.
6. The efficacy and safety of pertuzumab in the adjuvant setting have not been established.
7. Eligible patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section including the prior treatment history of patients enrolled in the clinical study, based on adequate knowledge of the efficacy and safety of pertuzumab, after carefully considering the choice of alternative therapies.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

All indications

1~~3~~. The efficacy and safety of pertuzumab monotherapy have not been established.

2~~4~~. If the scheduled dosing is delayed for some reason, it is advisable to administer pertuzumab according to the following procedure:

2~~4~~.1 If 6 weeks have not passed since the previous administration, administer 420 mg.

2~~4~~.2 If ≥6 weeks have passed since the previous administration, administer the re-loading dose of 840 mg. For the subsequent doses, administer 420 mg every 3 weeks.

HER2-positive breast cancer

3~~1~~. When pertuzumab is administered after the discontinuation of antineoplastic drugs other than trastuzumab, pertuzumab should be concomitantly administered with trastuzumab.

4~~2~~. Antineoplastic drugs other than trastuzumab to be concomitantly administered with pertuzumab should be selected by a physician with a thorough understanding of the information presented in the "Clinical Studies" section.

List of Abbreviations

ADM	doxorubicin hydrochloride
APHINITY study	BO25126 study
Bmab	bevacizumab (genetical recombination)
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRAF V600E mutation	a mutation of the BRAF gene in which valine is substituted by glutamic acid at position 600
CI	confidence interval
CISH	chromogenic *in situ* hybridization
CLEOPATRA study	WO20698 study
Cmab	cetuximab (genetical recombination)
CPA	cyclophosphamide hydrate
CR	complete response
DTX	docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EPI	epirubicin hydrochloride
FISH	fluorescence *in situ* hybridization
FOLFIRI/Bmab	combination therapy with fluorouracil, folinate, and IRI, plus Bmab
FOLFOX/Bmab	combination therapy with fluorouracil, folinate, and L-OHP, plus Bmab
FOLFOX/Cmab	combination therapy with fluorouracil, folinate, and L-OHP, plus Cmab
FTD/TPI	a fixed-dose combination of trifluridine and tipiracil hydrochloride
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
IRI	irinotecan hydrochloride hydrate
ISH	*in situ* hybridization
Japanese clinical practice guidelines	the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of colorectal cancer
KRAS gene	Kirsten rat sarcoma viral oncogene homolog
lapatinib	lapatinib tosilate hydrate
LBx test	liquid biopsy using plasma
LBx group	a group of patients who had a positive LBx test result
L-OHP	oxaliplatin
NCCN Guidelines (Colon Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer
NCCN Guidelines (Rectal Cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Rectal Cancer
NE	not evaluable
NGS	next generation sequencing
OS	overall survival
partial change approval application	application for partial change of marketing approval
PD	progressive disease
PER	pertuzumab (genetical recombination)
Pmab	panitumumab (genetical recombination)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
Q3W	quaque 3 weeks
RAS gene	rat sarcoma viral oncogene homologue
RECIST	Response Evaluation Criteria in Solid Tumors

regorafenib	regorafenib hydrate
SD	stable disease
S-1	a fixed-dose combination of tegafur, gimeracil, and oteracil potassium
TBx test	tumor tissue biopsy
TBx group	a group of patients who had a positive TBx test result
TRA	trastuzumab (genetical recombination)
TRA/PER	a combination of TRA and PER
TRA/PER/DTX	a combination of TRA, PER, and DTX
TRIUMPH study	EPOC1602 study