Report on the Deliberation Results

May 21, 2013
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Perjeta Intravenous Infusion 420 mg/14 mL
[Non-proprietary name]	Pertuzumab (Genetical Recombination)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	May 25, 2012

[Results of deliberation]
In the meeting held on April 25, 2013, the Second Committee on New Drugs concluded that the product may be approved and that these results should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The Committee pointed out that a post-marketing clinical study should be conducted to further clarify the efficacy of the product in Japanese patients. Therefore, instead of the preplanned cohort study aimed at further clarification of efficacy in Japanese patients, a more detailed analysis is required. For this purpose, the applicant should conduct a single-arm post-marketing clinical study to confirm the progression-free survival period in patients with HER2-positive inoperable or recurrent breast cancer.

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

(JAN*) **Japanese Accepted Name (modified INN)*

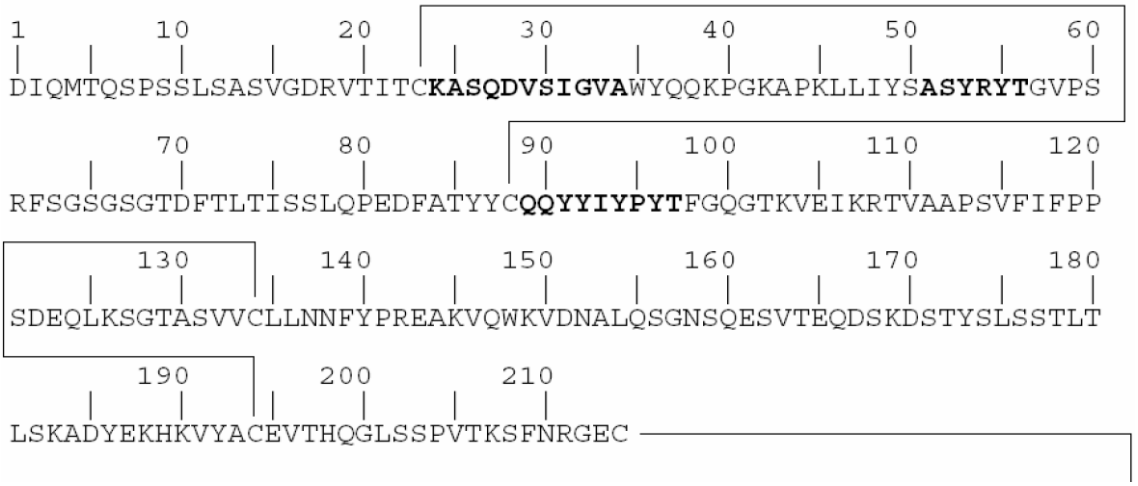
Review Report

April 9, 2013
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Perjeta Intravenous Infusion 420 mg/14 mL
[Non-proprietary name]	Pertuzumab (Genetical Recombination)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	May 25, 2012
[Dosage form/Strength]	Injection: Each vial contains 420 mg Pertuzumab (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

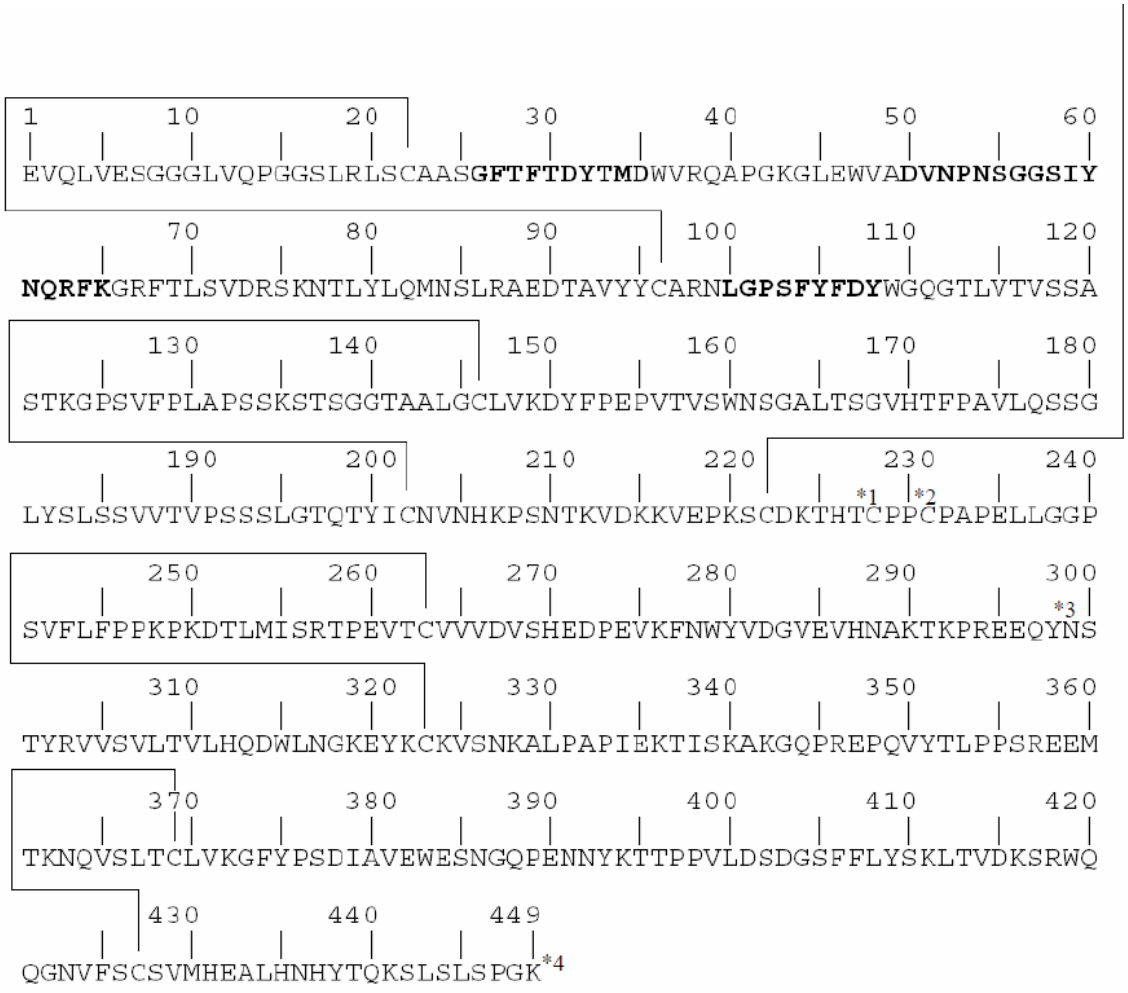
[Amino acid sequence]



Light chain

(Continued on the next page)

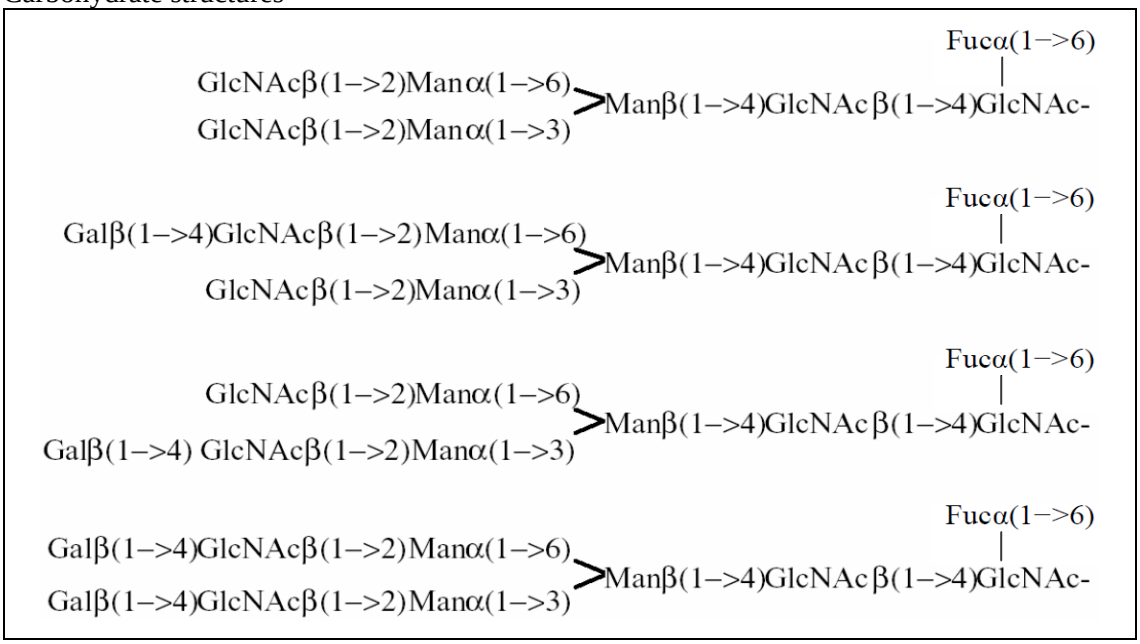
Intramolecular disulfide bond: solid line
Complementarity-determining region: bold type



Heavy chain

Intramolecular disulfide bond: solid line
Intermolecular disulfide bonds: *1 (Cys^{228} in heavy chain – Cys^{228} in heavy chain), *2 (Cys^{231} in heavy chain – Cys^{231} in heavy chain)
Complementarity-determining region: bold type
Glycosylation site: *3 (Asn^{299})
Partial deficiency: *4 (Lys^{449})

Carbohydrate structures



Gal: galactose, GlcNAc: N-acetylglucosamine, Man: mannose, Fuc: fucose

Molecular formula:	$C_{6476}H_{9974}N_{1710}O_{2016}S_{44}$
Molecular weight:	Approx. 148,000
Chemical name:	Pertuzumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-HER2 monoclonal antibody and framework regions and constant regions derived from human IgG1. Pertuzumab is produced in Chinese hamster ovary cells. Pertuzumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chain (γ1-chain) molecules consisting of 449 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 214 amino acid residues each.

[Items warranting special mention] None

[Reviewing office] Office of New Drug V

Review Results

April 9, 2013

[Brand name]	Perjeta Intravenous Infusion 420 mg/14 mL
[Non-proprietary name]	Pertuzumab (Genetical Recombination)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	May 25, 2012

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with HER2-positive inoperable or recurrent breast cancer has been demonstrated and its safety is acceptable in view of its observed benefits. The safety concerns such as febrile neutropenia and interstitial lung disease as well as the efficacy of the product in Japanese patients need to be further investigated in the clinical studies.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]	HER2-positive inoperable or recurrent breast cancer
[Dosage and administration]	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 a 60-minute infusion every 3 weeks, in combination with trastuzumab (genetical recombination) and other antineoplastic drugs. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

Review Report (1)

March 1, 2013

I. Product Submitted for Registration

[Brand name]	Perjeta for Intravenous Infusion 420 mg/14 mL
[Non-proprietary name]	Pertuzumab (Genetical Recombination)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	May 25, 2012
[Dosage form/Strength]	Injection: Each vial contains 420 mg of Pertuzumab (Genetical Recombination).
[Proposed indication]	HER2-positive inoperable or recurrent breast cancer
[Proposed dosage and administration]	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 Pertsuzumab (Genetical Recombination) as 60-minute infusions every 3 weeks, in combination with other antineoplastic drugs. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Drug overview

Human epidermal growth factor receptor type 2 (HER2) is a receptor tyrosine kinase belonging to the epidermal growth factor receptor (EGFR) family. The endogenous ligand of HER2 has not been identified. HER2 is considered to form a homodimer or a heterodimer with an activated receptor of another EGFR family, thereby activating the signal transduction pathway downstream, resulting in the regulation of cell growth and differentiation, etc. In tumor cells, such as those of breast cancer, overexpression of HER2 protein and amplification of HER2 gene are observed. Trastuzumab (genetical recombination) ("trastuzumab"), an anti-HER2 antibody, and lapatinib tosilate hydrate, a chemically synthesized drug with HER2 tyrosine kinase-inhibiting activity, are used clinically in Japan and overseas.

Pertuzumab (Genetical Recombination) (hereafter referred to as "pertuzumab") is a humanized anti-HER2 monoclonal antibody developed by Genentech Inc. in the US, the company that invented trastuzumab. Unlike trastuzumab which binds to subdomain IV of HER2 located close to the cell membrane, pertuzumab is considered to bind to subdomain II, the region essential for HER2 dimer formation, thereby inhibiting heterodimer formation, resulting in suppression of tumor growth.

1.(2) Development history etc.

In foreign countries, a phase I study (Study TOC2297g) involving patients with solid tumor was initiated in November 2001 by Genentech Inc. After Study TOC2297g, the developer considered that pertuzumab, unlike trastuzumab, may be effective not only against HER2-overexpressing cancers but also against low-expressing cancers. To test this possibility, 5 phase II studies of pertuzumab monotherapy were conducted in patients with HER2 low-expressing breast cancer and patients with ovarian cancer, non-small cell lung cancer, and prostate cancer, which are

expected to express HER2. However, these 5 studies failed to show the sufficient efficacy of pertuzumab. Therefore, starting in May 2006, a phase II study (Study BO17929) was conducted by F. Hoffmann-La Roche, Ltd. (Roche) in which pertuzumab was administered in combination with trastuzumab to breast cancer patients with high-expressing HER2 who had previously received trastuzumab therapy. Subsequently, a phase III study (Study WO20698 [the CLEOPATRA study]) was commenced in February 2008 in which pertuzumab, trastuzumab, and docetaxel hydrate were administered in combination to patients with HER2-positive breast cancer.

With the data from the pivotal study CLEOPATRA, a marketing application for pertuzumab was submitted by Roche in the EU in November 2011 and by Genentech Inc. in the US in December 2011. In the US, pertuzumab was approved for the following indication: "PERJETA is indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease." In the EU, pertuzumab is currently under review.

As of December 2012, pertuzumab is approved in 4 countries or regions for indications related to breast cancer.

In Japan, the applicant initiated a phase I study (Study JO17076) involving patients with solid tumor in June 2004 and completed it in August 2005. However, by the time of the completion, no sufficient efficacy had been obtained in foreign clinical studies of pertuzumab monotherapy. The applicant therefore suspended the development of pertuzumab until they obtained the results of clinical studies including BO17929 to decide whether or not to resume the development. Subsequently, the applicant obtained the results of BO17929 study in [redacted] 20[redacted] and, upon confirming that the results were favorable, decided to participate in the CLEOPATRA study. After these processes, the global clinical study CLEOPATRA was initiated also in Japan in July 2009, which was 1 year and 5 months after the initiation of the study.

In May 2012, the application for pertuzumab was submitted based on the results from the pivotal study CLEOPATRA.

The brand name proposed at the submission was "Perjeta for Intravenous Infusion 420 mg/14 mL", but was changed to "Perjeta Intravenous Infusion 420 mg/14 mL" from the point of view of clinical safety.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Preparation and control of cell substrate

Hybridoma cells expressing murine anti human-HER2 monoclonal antibody were prepared by fusion of murine myeloma cells with spleen cells of a BALB/c mouse immunized with cells expressing HER2. The complementarity determining region was identified from the genetic information of the hybridoma cells, based on which the base sequence of the variable region of the humanized antibody was designed. The variable region thus designed was further modified to [redacted], by [redacted] of [redacted] to [redacted], and then linked to the constant region of human immunoglobulin G1 (IgG1) to design the amino acid sequence and the base sequence of humanized anti-HER2 antibody. The gene fragments encoding the heavy and light chains of humanized anti-HER2 antibody were inserted into a vector to prepare a gene expression construct, which was then introduced into Chinese hamster ovary (CHO) cells, from which the cell line appropriate for pertuzumab production was selected. The master cell bank (MCB) was prepared from this cell line, and the working cell bank (WCB) was prepared from the MCB.

The MCB, WCB, and cells cultured to the limit of the *in vitro* cell age (CAL) were subjected to characterization tests (isozymes analysis, restriction endonuclease cleavage analysis, gene copy number, cDNA sequence, peptide mapping analysis), and their genetic stability during the manufacturing period was confirmed.

For MCB, WCB, and CAL, purity tests (sterility test, mycoplasma testing [culture test and DNA staining]), adventitious virus test (*in vitro*), latent virus free test (*in vivo*), rodent parvovirus test (*in vitro*), retrovirus test by co-culture, reverse transcriptase activity test, retroviral infection test, murine antibody production test, hamster antibody production test, and observation by transmission electron microscopy) were performed. For unprocessed/non-purified bulk, characterization tests (isozymes analysis), purity test (mycoplasma test [culture method and DNA staining]), bioburden, adventitious virus test (*in vitro*), rodent parvovirus test (*in vitro*, polymerase chain reaction [PCR]), reverse transcriptase activity test, retroviral infection test, and observation by transmission electron microscopy were performed. As a result, no adventitious virus or nonviral infectious substance was detected within the range of the items tested, except the endogenous retrovirus-like particles commonly observed in rodent-derived cell lines.

Appropriate storage conditions are determined for MCB and WCB, and the storage stability of MCB and WCB are confirmed by viability of cells and [redacted] after thawing. WCB is regenerated as appropriate [redacted] of MCB [redacted].

2.A.(1).2) Manufacturing process

The drug substance is manufactured by a process comprising seed culture, inoculation culture, production culture, harvesting, [redacted] chromatography, viral inactivation, [redacted] chromatography, [redacted] for viral removal, [redacted] chromatography, [redacted] filtration, and the final filtration. The solution obtained after the final filtration process is handled as the drug substance and stored at ≤ -20°C in a [redacted] tank. This manufacturing process was developed using quality by design (QbD), and a design space (DS) with identified critical process parameters (CPPs) is defined in the manufacturing process [see "2.A.(4) Quality by design (QbD)"].

The critical processes are identified as [redacted], [redacted] chromatography, viral inactivation by [redacted], and [redacted] chromatography.

The manufacturing process of the drug substance was evaluated at the pilot scale and at the commercial scale.

2.A.(1).3) Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, peptone derived from pigs of American origin is used as a component of the medium used in the production culture process, and this material has been confirmed to conform with the Standards for Biological Ingredients.

MCB, WCB, CAL, and unprocessed/non-purified bulk have been tested for viral safety [see "2.A.(1).1) Preparation and control of cell substrate"]. The following in-process control tests have been established: rodent parvovirus test (PCR method) for the production culture fluid; and rodent parvovirus test (PCR method and *in vitro*), bioburden test, mycoplasma test (culture method and DNA staining), and adventitious virus test (*in vitro*) for pre-harvest fluid.

Viral clearance test was performed using model viruses for the purification process. Results showed that the process had sufficient capacity to remove viruses.

Results of viral clearance test

Manufacturing process	Virus reduction factor (log_{10})		
	Xenotropic mouse leukemia virus	Mouse minute virus	Simian virus 40
[redacted] Chromatography*1	[redacted]	[redacted]	[redacted]
Viral inactivation*2	[redacted]	[redacted]	[redacted]
[redacted] for viral removal*3	[redacted]	[redacted]	[redacted]
[redacted] chromatography*4	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥20.24	≥6.40	≥6.14

*1: The value obtained from 1 test with an unused resin or that from 1 test with the resin that had been used [redacted] times, whichever was lower.
*2: The lower of the values obtained from the test repeated twice at [redacted]°C
*3: The value obtained from 1 test using [redacted] in [redacted] [redacted] chromatography process as [redacted] and [redacted] of [redacted] or that from 1 test using [redacted], whichever was lower.
*4: The value obtained from 1 test with an unused resin or that from 1 test with the resin that had been used [redacted] times, whichever was lower.

2.A.(1).4) Manufacturing process development (comparability)

The summary of manufacturing changes made throughout the process of development of the drug substance are as follows (each process is designated as manufacturing processes A, B, C, D [proposed manufacturing process]):

- Change from manufacturing process A to B: Changes in [redacted], [redacted], and [redacted] in [redacted] chromatography process, etc.
- Change from manufacturing process B to C: Changes in [redacted], [redacted], [redacted], [redacted] and [redacted] in [redacted] process, [redacted] in [redacted] and [redacted] chromatography processes, [redacted] in [redacted] process, [redacted], etc.
- Change from manufacturing process C to D: Changes in [redacted] etc.

The comparability of the quality attributes of the drug substance was evaluated before and after these changes in the manufacturing process.

2.A.(1).5) Characteristics

2.A.(1).5).i) Structure/Composition

(a) Primary structure

- The amino acid sequence determined by trypsin digestion under reducing conditions and by peptide mapping of Asp-N digest was identical with that estimated from the cDNA base sequence.
- Peptide mapping after trypsin digestion under reducing conditions showed that most of C-terminal lysine of the heavy chain was deleted. A mutant protein with [redacted] at the N-terminus of the light chain (impurity A) was detected in a trace amount.

(b) Higher order structure

- Peptide mapping after trypsin digestion under non-reducing conditions and peptide mapping of Lys-C digest showed that pertuzumab has 2 and 4 disulfide bonds within the light chain and the heavy chain, respectively, and that pertuzumab has 2 and 1 disulfide bonds between the heavy chains and between the heavy chain and the light chain, respectively.
- Hydrophobic interaction chromatography of the non-denatured sample showed 2 main peaks, one indicating the homodimer (not containing [redacted]) and the other indicating the heterodimer containing [redacted] in one of the Fab domains. The sample digested with carboxypeptidase B and papain showed the peak of a modified Fab containing [redacted] with [redacted] and [redacted] not forming [redacted].

- Ellman's analysis showed that 1 mole of pertuzumab contains [redacted] to [redacted] moles of free thiols.
- Fourier transform infrared spectrophotometry showed the β sheet-rich secondary structure characteristic to IgG1.

(c) Carbohydrate structure

- Peptide mapping after trypsin digestion under reducing condition and SDS-capillary electrophoresis (CE-SDS) showed that an *N*-linked oligosaccharide is bound to asparagine residue at position 299 in ≥[redacted]% of the heavy chains.
- Glycosylation analysis confirmed the presence of G0, G1, and G2, which are fucosylated biantennary glycans with 0 to 2 galactose units attached to the terminals, which accounted for [redacted]% to [redacted]%, [redacted]% to [redacted]%, and [redacted]% to [redacted]%, respectively, of the total glycans. The analysis also showed the presence of non-fucosylated forms of G0 glycans(G0-F), G0 glycan devoid of either of *N*-acetylglucosamine (GlcNAc) units (G0-GlcNAc), and high mannose-type glycans (Man5), each of which accounted for ≤[redacted]% of the total glycans.
- Analysis of sialic acid content showed that 1 mole of pertuzumab contained [redacted] to [redacted] moles of *N*-acetylneuraminic acid. *N*-glycolylneuraminic acid was not detected.

(d) Physicochemical properties

Molecular weight

- The molecular weight of pertuzumab estimated from electrospray ionization mass spectrometry was almost identical with the theoretical molecular weight predicted from amino acid sequence and the glycan structure.

Electrophoresis

- SDS-polyacrylamide gel electrophoresis (SDS-PAGE) under non-reducing conditions showed the minor bands of approximately [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] Da, in addition to the major band of approximately [redacted] Da indicating the monomer. SDS-PAGE under reducing conditions showed the minor bands of approximately [redacted], [redacted], [redacted], [redacted], and [redacted] Da, in addition to the main bands of approximately [redacted] and [redacted] Da indicating the heavy and light chains, respectively.
- CE-SDS with laser-induced fluorescence detector showed, under non-reducing conditions, the minor peaks indicating high molecular weight variants and low molecular weight variants, in addition to the main peak ([redacted]%-[redacted]%) and, under reducing conditions, the peak indicating a non-glycosylated heavy chain, in addition to the 2 main peaks indicating the heavy and light chains.
- Imaged capillary isoelectric focusing showed, in addition to the main peak, peaks in the acidic and basic regions, confirming the presence of charge variants of acidic and basic molecular species.
- Capillary isoelectric focusing showed that pertuzumab had an isoelectric point of [redacted].

Liquid chromatography

- Size exclusion chromatography (SEC) showed peaks of high molecular weight variants and low molecular weight variants of the assembly such as dimers, in addition to the main peak of the monomer.
- Ion exchange chromatography (IEC) showed, in addition to the main peak, peaks of acidic molecular species mainly containing impurities B, C, and D; and basic molecular species containing impurities E and F, dimer, impurities C and A.

Other

- Extinction coefficient ([redacted] nm) was [redacted] mL/(mg·cm).

(e) Biological properties

Functional analysis of Fab

- Enzyme-linked immunosorbent assay (ELISA) confirmed the binding of pertuzumab with HER2.
- Pertuzumab inhibited the growth of breast cancer-derived [redacted] cell line low-expressing HER2 (1+ by immunohistochemistry [IHC] staining).
- Cell growth-inhibitory activity and HER2-binding activity of samples subjected to stress conditions (stored at 40°C for 3 or 6 weeks, acidic condition [pH [redacted]], basic condition [pH [redacted]], photoirradiation [1.20 × 10^6 lux·h], [redacted]% [redacted]) were determined to be comparable to those of pertuzumab.

Functional analysis of Fc

- Pertuzumab bound to complement C1q, but did not show complement-dependent cytotoxicity (CDC) against [redacted] cell line or human breast cancer-derived [redacted] cell line. The applicant explained the reason for the failure of pertuzumab to show CDC activity in these cell lines, as follows: these human breast cancer cell lines express CD59, decay accelerating factor, and membrane cofactor protein which inhibit complement C1q-mediated cytolysis (*Clin Exp Immunol.* 1999;115:13-8).
- Competitive binding assay using non-radioactive, light-emitting, homogenous assay format with beads confirmed the binding of pertuzumab with FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIa, as well as with neonatal Fc receptor (FcRn).
- Pertuzumab did not show antibody-dependent cell-mediated cytotoxicity (ADCC) against [redacted] cell line, whereas it exhibited ADCC activity against [redacted] cell line high-expressing HER2 (3+ by IHC) and against human breast cancer-derived [redacted] cell line. The applicant explained that pertuzumab induces ADCC activity against human breast cancer-derived cells in a manner dependent on HER2 expression level [see "2.B On ADCC activity"].

(f) Product-related substances

In risk assessment and characterization to identify critical quality attributes (CQAs), biological properties such as cell growth-inhibitory activity, ADCC activity, and HER2-binding activity were investigated on each molecular species separated. However, none of them were identified as product-related substances.

2.A.(1).5).ii) Impurities

(a) Process-related impurities

Host cell-derived impurities (host cell-derived protein and DNA) and purification process-derived impurities (protein A leached from the column) were handled as process-related impurities, all of which have been confirmed to be sufficiently removed during the manufacturing process.

Among raw materials used for cell culture and purification process, [redacted], [redacted], [redacted], [redacted], and [redacted] have been confirmed to be sufficiently removed during the manufacturing process, with their levels in the product kept below their permitted daily level of ingestion.

(b) Product-related impurities

Charge variants (acidic and basic molecular species) and molecular weight variants (high and low molecular weight variants) were handled as product-related impurities. The product-related impurities are controlled by specifications for the drug substance and for the drug product.

2.A.(1).6) Control of drug substance

The proposed specifications for the drug substance are content, description, identification (peptide

mapping), osmotic pressure, pH, [redacted], purity (CE-SDS, SEC), bacterial endotoxin, microbial limits, [redacted], assay (protein content), and potency in biological assay (cell growth-inhibitory activity). [redacted] was added during the review process [see "2.B ADCC activity"].

2.A.(1).7) Stability of the drug substance

The main stability tests for the drug substance are as shown in the table below.

Outline of main stability tests for drug substance

	Manufacturing process	Number of batches	Storage conditions	Storage period	Storage configuration
Long-term testing	Process C	3	-20 ± 5°C	48 months	[redacted]-mL stainless steel tank
	Process D			[redacted] months*	
Accelerated testing	Process C	3	5 ± 3°C	6 months	
	Process D				
Stress testing	Process C	3	40 ± 2°C 75 ± 5%RH	1 month	[redacted]-mL glass vials
	Process D				

* Ongoing

The long-term testing and the accelerated testing did not show any significant change in the quality attributes of pertuzumab throughout the storage period.

The stress testing showed a decrease in the content of the main peak, as measured by SEC and IEC.

Based on the above results, a shelf life of 36 months has been proposed for the drug substance when stored at ≤-20°C in a [redacted] tank. The long-term testing of the drug substance manufactured by process D will be continued up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Drug product, formulation, and formulation development

The drug product is a solution for injection containing 420 mg of pertuzumab, supplied in each 20-mL glass vial. The drug product also contains, as excipients, L-histidine, glacial acetic acid, purified sucrose, and polysorbate 20. The secondary packaging component is a paperboard carton.

2.A.(2).2) Manufacturing process

The drug product is manufactured by a process comprising drug solution preparation, sterile filtration, filling and stoppering, capping, inspection, packaging and labeling, storage, and testing. The manufacturing process was developed using QbD [see "2.A.(4) Quality by design (QbD)"].

[redacted] and [redacted] processes are defined as critical processes.

The manufacturing process was evaluated at the commercial scale production.

2.A.(2).3) Manufacturing process development (comparability)

During the process of the development of the drug product, changes were made to the formulation [see "2.A.(1).4) Manufacturing process development (comparability)"] and to the manufacturing site (from [redacted] [plant A] to [redacted] [plant B]). The comparability of the quality attributes of the drug product was evaluated before and after the change in the manufacturing process.

2.A.(2).4) Control of drug product

The proposed specifications for the drug product include content, description, identification (capillary zone electrophoresis), osmotic pressure, pH, purity test (IEC, SEC), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, assay (protein content), and potency in biological assay (cell growth-inhibitory activity).

2.A.(2).5) Stability of the drug product

The main stability tests for the drug product are as shown in the table below.

Outline of the stability tests for drug product

	Manufacturing site	Manufacturing process of drug substance	Number of batches	Storage conditions	Storage period	Storage configuration
Long-term testing	Plant A	Process C	3	5 ± 3°C	48 months	Glass vials
	Plant B	Process D			[redacted] months[*1]	
Accelerated testing	Plant A	Process C	3	25 ± 2°C 60 ± 5% RH	6 months	
	Plant B	Process D			6 months	
Stress testing	Plant B	Process D	3	40 ± 2°C 75 ± 5% RH	1 month	
Photostability testing	Plant B	Process D	1	≥1.20 × 10^6 lux·h ≥200W·h/m^2 as integrated near UV energy		Glass vials and glass vials light-shielded with aluminum foil
Temperature cycle test	Plant B	Process D	1	5 ± 3°C ([redacted] days) → cycles[*2] → 5 ± 3°C ([redacted] days) ([redacted] days in total)		Glass vials

*1: Ongoing

*2: [redacted] ± 3°C ([redacted]days) → [redacted] ± 2°C ([redacted] days), [redacted] ± 3°C ([redacted]days) → 25 ± 2°C/60 ± 5%RH ([redacted]days) → [redacted] ± 5°C ([redacted] days) → 30 ± 2°C/75 ± 5% RH ([redacted] days) → 5 ± 3°C ([redacted] days) → 25 ± 2°C/60 ± 5% RH ([redacted] days)

The long-term testing did not show any significant change in the quality attributes of the drug product throughout the storage period.

The acceleration testing showed a decrease in the content of the main peak, as measured by IEC and SEC.

The stress testing showed a change in the description (color) and decrease in the content of the main peak, measured by IEC and SEC.

The photostability testing showed a decrease in the content of the main peak measured by IEC and SEC in samples that were not protected from light, whereas no significant changes in the quality attributes were observed in samples that were wrapped in aluminum foil and protected from light.

The temperature cycle test did not show any significant changes in the quality attributes throughout the storage period.

From the above results, the shelf life of 36 months has been proposed for the drug product when stored at 5 ± 3°C with light protection. The long-term testing of the drug product manufactured at plant B will be continued up to 36 months.

2.A.(3) Reference materials

The reference material is selected from among the batches of the drug substance and stored at [redacted]°C. The stability of the reference material during storage is checked at least every [redacted] years.

The proposed specifications for the reference material include content, description, identification (peptide mapping, capillary zone electrophoresis), [redacted], osmotic pressure, pH, purity test (CE-SDS [reducing], IEC, SEC), [redacted], assay (protein content), and potency in biological assay (cell growth-inhibitory activity). During the course of the review, [redacted] was added to the specifications [see "2.B: ADCC activity"].

In the regeneration of the reference material, the following characterization studies are conducted to evaluate the primary structure, charge heterogeneity, and post-translational modifications: mass spectrometry, peptide mapping after trypsin digestion (under reducing conditions), capillary electrophoresis for glycosylation analysis, and CE-SDS (non-reducing), or alternative methods.

2.A.(4) Quality by design (QbD)

Pertuzumab was developed using the QbD approach whereby mainly the following investigations were performed. During the course of the review, [redacted] was identified as a critical quality attribute (CQA).

- Identification of [redacted], pH, excipient concentrations, protein concentration, osmotic pressure, viruses, bioburden, mycoplasma, bacterial endotoxin, description, particulates, and sterility.
- Characterization of manufacturing process and identification of critical process parameters (CPPs)
- Construction of design space (DS)
- Construction of strategies for tests to control each quality attribute
- Evaluation of the robustness of the strategies for quality control tests

2.B. Outline of the review by PMDA

Based on the submitted data and on the results of the following review, PMDA concludes that currently the quality of the drug substance and the drug product is appropriately controlled. The applicant has requested the change in the shelf life of the drug product based on the updated results of the stability tests, and the details are currently under review.

During the review process, [redacted] was added to CQAs. The applicant is currently performing re-evaluation to identify CPPs, and the review results on the re-evaluation will be described in Review Report (2). PMDA is continuing the review of the appropriateness of applying DS to the manufacturing process of pertuzumab by the QbD approach.

ADCC activity

In light of the observation in the characterization of pertuzumab that pertuzumab exhibited ADCC activity in a manner dependent on HER2 expression level, pertuzumab may exhibit the clinical effect via its ADCC activity. Therefore, PMDA asked the applicant to include and control ADCC activity, or glycans that are reported to affect ADCC activity (e.g., *J Biol Chem.* 2001;276:6591-604, *J Biol Chem.* 2003;278:3466-74, *J Biol Chem.* 2006;281:5032-6), as a specification, in addition to the potency in biological assay (cell growth-inhibitory activity) included in the proposed specifications.

The applicant responded that [redacted] would be included in the specifications for the drug substance and that [redacted] would be added to CQAs.
Taking account of the strong correlation between [redacted] and ADCC activity of pertuzumab

and the unlikeliness of the drug product manufacturing process affecting [redacted], PMDA accepted the applicant's response that [redacted] would be included in the specifications for the drug substance and [redacted] would be controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

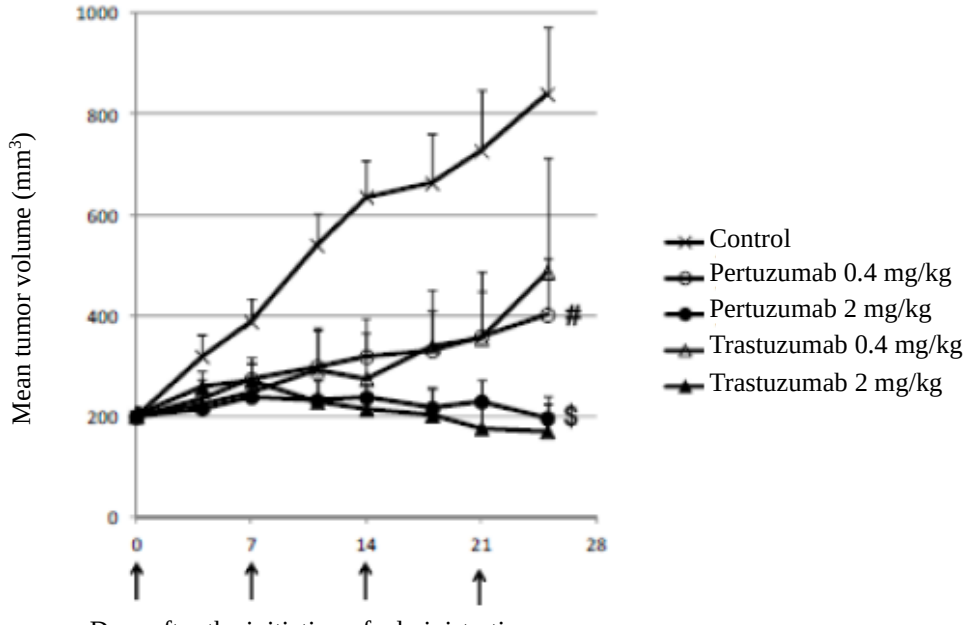
3.(i).A. Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Tumor growth inhibition effect

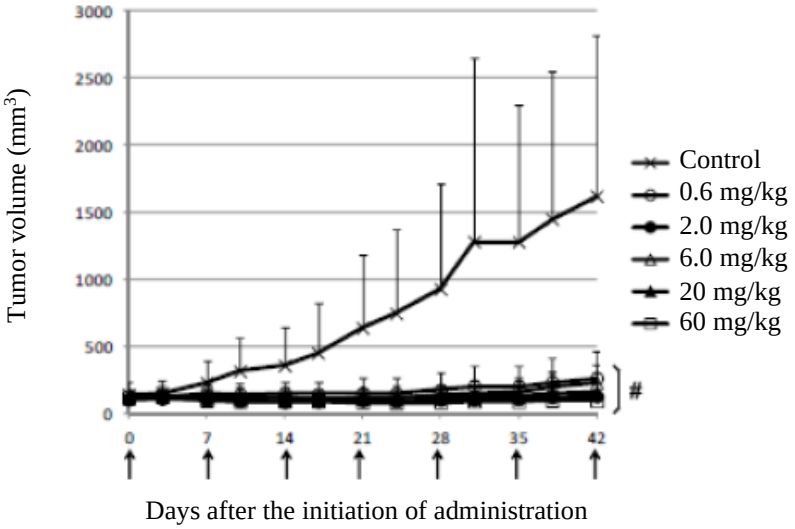
i) Growth-inhibitory effect on breast cancer cell line expressing HER2 and breast cancer-derived tumor tissue (Reports 1041202, 1041204)

Tumor growth-inhibitory effect of pertuzumab (genetical recombination) (hereafter referred to as pertuzumab) was investigated using athymic mice (nude mice) subcutaneously transplanted with human breast cancer-derived BT474JB cell line high-expressing (3+ by immunohistochemical [IHC] staining) human epidermal growth factor receptor (HER) type 2 (HER2; HER2 homologue is called ErbB2). Starting on Post-transplantation Day 16 when the tumor volume reached approximately 200 mm^3, pertuzumab was administered intravenously once weekly for a total of 4 doses at the initial dose of 0.8 mg/kg and at the subsequent doses of 0.4 mg/kg (if the initial and subsequent doses are different, the doses are abbreviated, e.g., 0.8/0.4 mg/kg. The doses in the figure showing tumor volume indicates the subsequent dose levels of each administration), or at 4/2 mg/kg, and tumor volume was measured (the figure below). A statistically significant inhibition of tumor growth was observed in the pertuzumab group compared with the control group. Humanized monoclonal antibody that does not bind to HER2 protein (rhuMAb E25) was used as the negative control and trastuzumab (genetical recombination) (trastuzumab) as the positive control.



Tumor growth-inhibitory effect of pertuzumab and trastuzumab (BT474JB cell line)
Mean + standard error (SE), n = 9 (number of animals that received the initial dose), "↑" indicates the day of pertuzumab or trastuzumab administration, #: $P = 0.0274$ (Wilcoxon test) against control group (rhuMAb E25), $: $P = 0.0006$ (Wilcoxon test) against control group (rhuMAb E25)

Tumor growth-inhibitory effect of pertuzumab was investigated using nude mice subcutaneously transplanted with human breast cancer-derived tumor tissue MAXF449 low-expressing HER2 (1+ by IHC). Starting on Post-transplantation Day 33 when the transplanted tumor volume reached approximately 100 to 200 mm^3, pertuzumab (1.2/0.6, 4/2, 12/6, 40/20, 120/60 mg/kg) was administered intraperitoneally once weekly for a total of 7 doses, and the tumor volume was measured (the figure below). A statistically significant inhibition of tumor growth was observed in the pertuzumab group compared with the control group. rhuMAb E25 was used as the control.



Tumor growth-inhibitory effect of pertuzumab
(MAXF449 human breast cancer-derived tumor tissue)

Mean + standard deviation (SD), n = 9-11, "↑" indicates the day of pertuzumab administration,
#: *P* <0.0001 (Wilcoxon test) against control group

The applicant explained that the above results demonstrated the tumor growth-inhibitory effect of pertuzumab on the HER2-expressing human breast cancer cell line and in mice transplanted with breast cancer-derived tumor tissue.

ii) Growth-inhibitory effect on tumor tissue derived from breast cancer patients (Report 1043264)

Tumor tissues (6 types including MAXF449), which were derived from breast cancer patients and confirmed by IHC to express HER2, were subcutaneously transplanted to nude mice, and pertuzumab (100 mg/kg) was administered to the mice intraperitoneally once or twice weekly for a total of 3 to 15 doses. Tumor growth-inhibitory effect was evaluated using "%T/C" calculated according to the following equation as the index. Of these tumor tissue types, except HER2 low-expressing MAXF449 (1.0 by IHC), 5 (HER2 expression levels of 0.4-2.44 by IHC) showed %T/C values of ≥50% whereas a %T/C value of 13% was noted in the mice transplanted with MAXF449, demonstrating the tumor growth-inhibitory effect. When pertuzumab (120/60 mg/kg) was administered to MAXF449-transplanted mice once weekly for 6 doses, %T/C value was 7%, demonstrating a tumor growth-inhibitory effect.

$$\%T/C = \frac{\text{Percent change of tumor volume from the time of initial dose to the time point of tumor volume measurement in pertuzumab group}}{\text{Percent change of tumor volume from the time of initial dose to the time point of tumor volume measurement in control group}} \times 100$$

3.(i).A.(1).2 Mechanism of action

i) Binding characteristics to HER2/ErbB2 (Report [redacted]-249-1821)

Affinity of pertuzumab and trastuzumab to human and monkey HER2/ErbB2, forcedly expressed in monkey kidney-derived COS-7 cell line, was investigated by radioimmunoassay using ^{125}I-labeled pertuzumab and trastuzumab. Dissociation constant (Kd) of pertuzumab and trastuzumab was 0.8 and 0.65 nmol/L, respectively, for human receptor and 0.53 and 0.72 nmol/L, respectively, for monkey receptor.

ii) Growth-inhibitory effect on HER2-expressing cancer cell lines (Reports 1041203, 1041201, 1043265, 1043263)

Growth-inhibitory effect of pertuzumab on tumors other than breast cancer was investigated using nude mice subcutaneously transplanted with HER2 high-expressing (3+ by IHC) human non-small cell lung cancer (NSCLC)-derived Calu-3 cell line and severe combined immunodeficiency (SCID) mice subcutaneously transplanted with HER2 low-expressing (1+ by IHC) human NSCLC-derived NCI-H522 cell line. Tumor growth-inhibitory effect of pertuzumab was observed in mice transplanted with these cell lines.

Pertuzumab (100 mg/kg) was administered intraperitoneally once or twice weekly for a total of 2 to 9 doses to nude mice subcutaneously transplanted with human ovarian cancer (2 types) or human NSCLC (17 types)-derived tissues expressing HER2 (0.5-2.6 by IHC), and growth-inhibitory effect on tumors other than breast cancer was investigated using %T/C, as was the case with the investigation using breast cancer patients-derived tissue (Report 1043264). As a result, tumor growth-inhibitory effect of pertuzumab was observed in mice transplanted with any of 4 types of the examined NSCLC-derived tissues with HER2 expression level 0.9 to 2.1 by IHC (%T/C value, 29%-46%). The data submitted in this new drug application also include other studies on the growth-inhibitory effect using human ovarian cancer (2 types) and human NSCLC (1 type)-derived tissues, but since HER2 expression level was unknown in these tumor tissues, results of these studies are omitted here.

iii) Growth-inhibitory effect on trastuzumab-resistant murine breast cancer-derived cell line (Report 1041193)

The applicant has confirmed that Founder 2-134R, a cell line derived from mammary adenocarcinoma of transgenic mice engineered to overexpress [redacted] HER2 gene in the mammary tissue was resistant to 4D5, the parent antibody of trastuzumab.

Tumor growth-inhibitory effect of pertuzumab was investigated using nude mice subcutaneously transplanted with Founder 2-134R cell line. As a result, pertuzumab inhibited tumor growth in a dose-dependent manner.

3.(i).A.(2) Safety pharmacology (Report [redacted]-377-1821, [redacted]-458-1821)

As safety pharmacology studies, repeat dose toxicity studies (7-week and 26-week administration studies) were conducted in cynomolgus monkeys to evaluate the effect of pertuzumab (15, 50, 150 mg/kg) on (a) the central nervous system (general symptoms/behavior, body temperature), (b) respiratory system (respiratory rate), and (c) cardiovascular system (blood pressure, electrocardiogram (ECG), heart rate) [see "3.(iii).A.(2).1 Seven-week repeat intravenous dose toxicity study in monkeys" and "3.(iii).A.(2).2 Twenty-six-week repeat intravenous dose toxicity study in monkeys", respectively]. Throughout the period of both studies, there were no effects of pertuzumab on either of the parameters listed in (a) to (c) above.

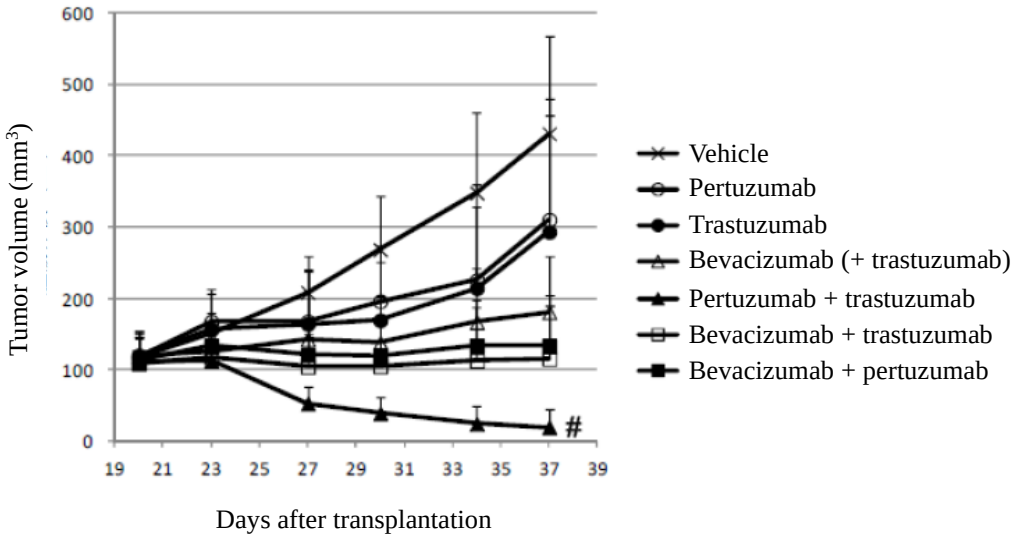
3.(i).A.(3) Studies on pharmacodynamic interactions

3.(i).A.(3).1) Concomitant use of pertuzumab with trastuzumab (Reports 1021305, 1019398)

KPL-4 cell line derived from human breast cancer high-expressing HER2 (3+ by IHC) was orthotopically transplanted to SCID mice, and starting from Post-transplantation Day 21 when the volume of the transplanted tumor reached 50 to 200 mm^3, pertuzumab, trastuzumab, or bevacizumab (genetical recombination) (bevacizumab) was administered intraperitoneally according to the following dosage regimens, and tumor growth-inhibitory effect by dosage regimen was investigated (the figure below). A statistically significant tumor growth-inhibitory effect was observed in the pertuzumab/trastuzumab combination therapy group compared with the trastuzumab alone group (P = 0.0001, Wilcoxon test).

- Administration of either pertuzumab or trastuzumab only
- Sequential concomitant use of bevacizumab with trastuzumab*
- Concomitant use of pertuzumab with trastuzumab
- Concomitant use of pertuzumab with bevacizumab
- Concomitant use of bevacizumab with trastuzumab

*: Trastuzumab was started from Post-transplantation Day 57. The duration of concomitant use of trastuzumab is not shown in the figure because it is irrelevant for the evaluation of pertuzumab.



Tumor growth-inhibitory effect of concomitant use of pertuzumab with trastuzumab (KPL-4 cell line)

Mean + SD, n = 10, #: P = 0.0001 (Wilcoxon test) for pertuzumab/trastuzumab combination therapy group relative to trastuzumab alone group at 37 day after transplantation

In a similar manner, tumor growth-inhibitory effect of pertuzumab/trastuzumab combination was investigated using nude mice subcutaneously transplanted with Calu-3 cell line. As a result, an enhanced tendency of tumor growth inhibitory effect was observed in the pertuzumab/trastuzumab combination therapy group compared with the trastuzumab alone group.

The applicant explained that the above results suggested the enhancement of tumor growth-inhibitory effect of pertuzumab/trastuzumab combination compared with trastuzumab alone.

3.(i).A.(3).2) Concomitant use of pertuzumab with capecitabine (Reports 1015439, 1011230, 1011232, 1016330, 1043266, 1043267, 1009892, 1011974)

HER2-expressing MAXF583 (1.5 by IHC) and MAXF574 (confirmed by fluorescent *in situ* hybridization [FISH]), which were patient-derived breast cancer tissues, were subcutaneously transplanted to nude mice. Starting on Post-transplantation Day 21 (MAXF583) or 13 (MAXF574) when the mean diameter of the transplanted tumor reached 5 to 8 mm, pertuzumab and capecitabine (Cape) were concomitantly administered, and tumor growth-inhibitory effect was investigated. In MAXF583-tranplanted mice, a statistically significant tumor growth-inhibitory effect was observed in the pertuzumab/Cape combination therapy group compared with the Cape alone group ($P < 0.002$, Mann-Whitney-Wilcoxon test). In MAXF574-transplanted mice, pertuzumab/Cape combination therapy tended to enhance the tumor growth-inhibitory effect.

HER2-expressing human NSCLC-derived QG-56 cell lines (confirmed by Western blotting [*J Thorac Oncol* 2009;4:1066-74] and IHC [0+] [*Clin Cancer Res* 2005;11:5300-9]) and Calu-3 cell line (3+ by IHC), human ovarian cancer-derived IGROV-1 cell line (confirmed by Western blotting, *Anticancer Drugs* 2009;20:450-60), and patient-derived colon cancer tissue CXF264 (1.75 by IHC) were subcutaneously transplanted to mice, and pertuzumab was concomitantly administered with paclitaxel, Cape, gemcitabine hydrochloride, cisplatin, erlotinib hydrochloride, or irinotecan hydrochloride hydrate to investigate the tumor growth-inhibitory effect. In all mice transplanted with cell lines or tissues other than CXF264, concomitant use of pertuzumab with the above antineoplastic drugs tended to enhance the tumor growth-inhibitory effect.

The data submitted in the application also include studies on the growth-inhibitory effect of concomitant use of pertuzumab with other antineoplastic drugs using human ovarian cancer-derived tissue (1 type), but since HER2 expression level was unknown in this tumor tissue, results of these studies are omitted here.

3.(i).B. Outline of the review by PMDA

Based on the submitted data and on the following discussion, PMDA has concluded that pertuzumab is expected to be effective in the patients with HER2-positive breast cancer.

Mechanism of action

The applicant explained the pharmacologic characteristics and the mechanism of action of pertuzumab as well as the similarity and dissimilarity of pertuzumab with trastuzumab, an antibody that targets HER2, as is the case with pertuzumab, as follows:

Pertuzumab is reported to have antibody-dependent cell-mediated cytotoxicity (ADCC) (*Cancer Res* 2009;69:9330-6), probably by the same mechanism as that of trastuzumab.

However, it is reported based on the results of X-ray crystallography that, unlike trastuzumab which binds to HER2 sub-domain IV proximate to the cell membrane (*Nature.* 2003;421:756-60), pertuzumab binds to sub-domain II of the extracellular domain that is essential for ligand-induced HER2 heterodimer formation (*Cancer Cell.* 2002;2:127-37). Therefore, it is considered that pertuzumab inhibits the heterodimer (HER2/HER3) formation induced by heregulin (HRG), a ligand for HER3, thereby inhibiting the phosphorylation of HER2 tyrosine kinase and the activation of the downstream phosphatidylinositol-3-kinase (PI3K)-Akt pathway and mitogen-activated protein kinase (MAPK) pathway (*Cancer Cell.* 2002;2:127-37), resulting in the inhibition of tumor cell growth. This is the mechanism of action unique to pertuzumab and not shared by trastuzumab. In contrast, trastuzumab is thought to exhibit its tumor cell growth-inhibitory effect by inhibiting the release of the extracellular domain of HER2 which leads to HER2 activation (*Cancer Res.* 2001;61:4744-9) and inhibiting the ligand-independent HER2 signal transduction through the inhibition of ligand-independent HER2/HER3 interaction (*Cancer Cell.* 2009;15:429-40).

Founder 2-134R cell line derived from mammary adenocarcinoma of transgenic mice engineered to overexpress HER2 gene in the mammary tissue, was resistant to 4D5, the parent antibody of trastuzumab, whereas pertuzumab inhibited the growth of this cell line in a dose-dependent manner [see "3.(i).A.(1).2).iii) Growth-inhibitory effect on trastuzumab-resistant murine breast cancer-derived cell line"]. The applicant considered that Founder 2-134R cell line has become resistant to 4D5 by [redacted].
Pertuzumab, in contrast, binds to sub-domain II of HER2, thereby inhibiting the tumor growth mainly by inhibiting the ligand-dependent HER2 signal transduction.

These results suggest that pertuzumab acts through a mechanism partially different from that of trastuzumab. In light of the finding that concomitant use of pertuzumab with trastuzumab brought about a statistically significant enhancement of tumor growth-inhibitory effect compared with trastuzumab alone [see "3.(i)A.(3).1) Concomitant use of pertuzumab with trastuzumab"], concomitant use of pertuzumab and trastuzumab is expected to be more effective in inhibiting the tumor growth in clinical settings as well.

PMDA considers as follows:
The applicant's explanation on the pharmacokinetic characteristics and the mechanism of action of pertuzumab as well as the similarity and dissimilarity between pertuzumab and trastuzumab are acceptable based on the submitted data and published reports.

PMDA also accepted the applicant's explanation that concomitant use of pertuzumab and trastuzumab is expected to be more effective in inhibiting the tumor growth.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A. Summary of the submitted data

Pharmacokinetics (PK) of pertuzumab was investigated in mice, rats, and monkeys.

3.(ii).A.(1) Analytical methods

3.(ii).A.(1).1) Measurement of pertuzumab

Serum pertuzumab concentrations in mice, rats, and monkeys were measured by enzyme-linked immunosorbent assay (ELISA) using immobilized recombinant HER2 extracellular domain (p185 HER2 extracellular domain [ECD]) and [redacted]-labeled mouse anti-[redacted] antibody.

3.(ii).A.(1).2) Measurement of anti-pertuzumab antibody

Anti-pertuzumab antibody in monkey serum was measured by ELISA using immobilized pertuzumab, [redacted] pertuzumab, and [redacted]-labeled [redacted].

3.(ii).A.(2) Absorption

3.(ii).A.(2).1) Single-dose administration

Following a single intravenous dose of pertuzumab (3, 30, 90 mg/kg) or single intraperitoneal dose (30 mg/kg) to male mice, serum pertuzumab concentration was measured (the table below). Following the intravenous administration, pertuzumab was eliminated in a biphasic manner. In each treatment group, $t_{1/2}$ (arithmetic mean) was 11.4 to 15.7 days, showing a gradual elimination. The applicant explained that CL was higher in the 90 mg/kg group than in the 3 and 30 mg/kg groups, whereas $t_{1/2}$ was longer in the 3 mg/kg group than in the 30 and 90 mg/kg groups, failing to show consistency among parameters, with no clear conclusion on the linearity of PK.

Bioavailability (F) following intraperitoneal administration was 91.3%.

PK parameters following a single intravenous or intraperitoneal dose of pertuzumab to male mice

Route of administration	Dose (mg/kg)	n	t_{max} (day)	C_{max} (mg/mL)	AUC_{inf} (mg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)
i.v.	3	3[*1]	-	0.0593	0.538	15.7	5.58	50.6	124
	30	3[*1]	-	0.672	4.80	11.4	6.25	44.6	102
	90	3[*1]	-	1.56	9.75	11.6	9.23	57.9	148
i.p.	30	1-3[*1]	0.285	0.293	4.38	15.3	6.85[*2]	93.4[*3]	-

PK parameters were calculated by a 2-compartment model.
*1: Number of animals at each measuring time point
*2: CL/F, *3: V_c/F

Following a single intravenous dose of pertuzumab (3, 30, 90 mg/kg) to male rats, serum pertuzumab concentration was measured (the table below). Following the intravenous administration, pertuzumab was eliminated in a biphasic manner. In each treatment group, $t_{1/2}$ (arithmetic mean) was 8.92 to 9.22 days, showing a gradual elimination. The applicant explained that CL tended to be lower in the 3 mg/kg group compared with the 30 and 90 mg/kg groups, whereas $t_{1/2}$ (the table below) and the mean residence time (12.6, 11.5, and 12.3 days [arithmetic means] in the 3, 30, and 90 mg/kg groups, respectively) were comparable among treatment groups, which suggested that PK was roughly linear within the dose range from 3 to 90 mg/kg.

PK parameters following a single intravenous dose of pertuzumab to male rats

Dose (mg/kg)	n	C_{max} (mg/mL)	AUC_{inf} (mg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)
3	6	0.112 ± 0.0186	0.443 ± 0.129	9.22 ± 0.782	7.24 ± 1.97	27.4 ± 5.24	91.3 ± 27.1
30	5	0.956 ± 0.350	4.03 ± 1.93	8.92 ± 3.16	9.46 ± 5.54	36.0 ± 16.1	93.7 ± 23.0
90	6	2.07 ± 0.211	9.17 ± 1.75	9.05 ± 1.77	10.1 ± 1.78	44.0 ± 4.45	121 ± 9.88

Arithmetic mean ± SD, PK parameters were calculated according to a 2-compartment model.

Following a single intravenous dose of pertuzumab (3, 30 mg/kg) to female nude mice subcutaneously transplanted with Founder 2-134R cell line and in non-transplanted female nude mice, serum pertuzumab concentrations were measured (the table below). At both doses, CL was higher in transplanted mice than in non-transplanted mice. The applicant explained that in transplanted mice, pertuzumab may be eliminated not only via the target antigen-independent pathway, but also via the antigen-dependent elimination mediated by the binding of pertuzumab to HER2 ECD released from the cell membrane and to HER2 expressed on the cell membrane.

PK parameters following a single intravenous dose of pertuzumab to non-transplanted and transplanted female nude mice

Animal species	Dose (mg/kg)	n	C_{max} (mg/mL)	AUC_{inf} (mg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)
Non-transplanted mice	3	2-3[*]	0.0653	0.649	16.7	4.62	46.0	107
	30	3[*]	0.437	5.730	30.3	5.24	68.7	176
Transplanted mice	3	1-3[*]	0.0658	0.169	5.15	17.8	45.6	109
	30	3[*]	0.436	1.875	4.15	16.0	68.9	82.8

PK parameters were calculated according to a 2-compartment model.
*: number of animals at each measuring time point

Following a single intravenous dose of pertuzumab (15, 50, 150 mg/kg) or single subcutaneous dose (50 mg/kg) to male and female monkeys, serum pertuzumab concentrations were measured (the table below). Following the intravenous administration, pertuzumab was eliminated in a biphasic manner. In each treatment group, $t_{1/2}$ (arithmetic mean) was 9.89 to 10.4 days, showing a gradual elimination. The applicant explained that CL was roughly constant regardless of dose, suggesting that PK was linear within the dose range from 15 to 150 mg/kg.

F was 81.5% following subcutaneous administration.

PK parameters following a single intravenous or subcutaneous dose of pertuzumab to male and female monkeys

Route of administration	Dose (mg/kg)	n	t_{max} (day)	C_{max} (mg/mL)	AUC_{inf} (mg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)
i.v.	15	4*1	-	0.403 ± 0.0330	3.05 ± 0.405	10.4 ± 1.52	4.98 ± 0.625	37.4 ± 3.06	68.1 ± 6.25
	50	4*1	-	1.62 ± 0.122	9.64 ± 0.941	9.89 ± 0.759	5.23 ± 0.553	30.9 ± 2.32	68.7 ± 5.87
	150	4*1	-	4.580 ± 0.992	28.7 ± 1.60	10.0 ± 0.973	5.24 ± 0.287	33.9 ± 7.07	72.7 ± 6.34
s.c.	50	4*1	2.28 ± 0.286	0.536 ± 0.0412	7.86 ± 0.673	10.6 ± 1.46	6.40 ± 0.561*2	53.0 ± 17.6*3	-

Arithmetic mean ± SD, PK parameters were calculated according to a 2-compartment model.
*1: Results obtained from 2 males and 2 females were combined, *2: CL/F, *3:V_c/F

3.(ii).A.(2).2) Repeat dose administration

Following repeated intravenous administration of pertuzumab (15, 50, 150 mg/kg) to male and female monkeys once weekly for a total of 7 doses, serum pertuzumab concentrations were measured (the table below). No significant sex difference was observed in PK parameters at any of the doses. The maximum concentration during the repeat administration period ($C_{max-obs}$) and AUC from Day 0 to Day 48 of administration (AUC_{0-48}) increased with dose, whereas in the 150 mg/kg group, they were less than proportional to dose. CL after the last dose was higher in the 150 mg/kg group compared with the 15 and 50 mg/kg groups. V_c and V_{ss} after the last dose were roughly the same among treatment groups.

In all dose groups, serum pertuzumab concentration increased with repeated administration, with time to reach $C_{max-obs}$ ($t_{max-obs}$) (arithmetic mean) being 35 to 42 days. The ratio of AUC from Day 42 to Day 48 (AUC_{42-48}) to AUC from Day 0 to Day 7 (AUC_{0-7}) was 2.00, 2.03, and 1.65, respectively, in the 15, 50, and 150 mg/kg, showing no marked accumulation. CL, V_c, V_{ss}, and $t_{1/2}$ after the last dose were similar to those after single dose in the 15 and 50 mg groups [see "3.(ii)A.(2).1) Single-dose administration"], whereas in the 150 mg/kg group, CL was higher after the last dose compared with the value after single dose.

Anti-pertuzumab antibody in serum was measured before the initiation of pertuzumab administration and at Days 49 and 80. No anti-pertuzumab antibody was detected from any of the samples tested.

PK parameters following 7-week repeat intravenous administration of pertuzumab to male and female monkeys

Dose (mg/kg)	Sex	n	$C_{max\text{-}obs}$*1 (mg/mL)	$AUC_{0\text{-}7}$*1 (mg·day/mL)	$AUC_{42\text{-}48}$*1 (mg·day/mL)	$AUC_{0\text{-}48}$*1 (mg·day/mL)	$t_{1/2}$*2 (day)	CL*2 (mL/day/kg)	V_c*2 (mL/kg)	V_{ss}*2 (mL/kg)
15	Male	4	0.705 ± 0.0966	1.24 ± 0.0659	2.69 ± 0.35	19.2 ± 1.55	11.0 ± 2.85	4.88 ± 0.795	38.4 ± 1.41	71.5 ± 5.75
	Female	4	0.721 ± 0.0301	1.38 ± 0.0883	2.55 ± 0.212	19.7 ± 1.22	7.89 ± 1.36	5.30 ± 0.555	32.9 ± 0.222	57.3 ± 4.50
50	Male	4	2.11 ± 0.194	3.62 ± 0.374	7.30 ± 0.486	53.2 ± 2.50	10.4 ± 3.79	6.05 ± 0.712	41.6 ± 3.96	82.8 ± 15.7
	Female	4	2.310 ± 0.307	3.98 ± 0.360	8.05 ± 0.887	61.0 ± 6.11	10.9 ± 1.98	5.31 ± 0.711	38.2 ± 3.32	76.8 ± 12.4
150	Male	6	5.860 ± 0.818	10.2 ± 1.77	18.0 ± 2.72	152 ± 18.4	9.21 ± 1.93	7.17 ± 1.31	40.8 ± 4.12	87.0 ± 19.2
	Female	6	5.510 ± 0.625	11.3 ± 0.993	17.0 ± 1.54	147 ± 13.0	7.06 ± 1.14	7.68 ± 0.832	40.3 ± 3.60	70.9 ± 8.36

Arithmetic mean ± SD

*1: calculated by model-independent analytical method; *2: calculated by 2-compartment model using serum pertuzumab concentration after the last dose

Following repeated intravenous administration of pertuzumab (15, 50, 150 mg/kg) to male and female monkeys once weekly for a total of 26 doses, serum pertuzumab concentrations were measured (the table below). No significant sex difference was observed in PK parameters of pertuzumab at any doses tested. $C_{max\text{-}obs}$ and AUC from Day 0 to Day 182 ($AUC_{0\text{-}182}$) increased with dose, whereas in the 150 mg/kg group, they were less than proportional to dose. At all doses tested, AUC reached steady state at 1 to 2 months after the initiation of administration, with $t_{max\text{-}obs}$ (arithmetic mean) being 118 to 135 days. CL after the last dose in the 15 and 50 mg groups was similar to that observed after single dose [see "3.(ii).A.(2).1) Single-dose administration"], whereas in the 150 mg/kg group, CL was higher after repeated administration than after single dose administration; the value was also higher compared with the 15 mg and 50 mg groups.

PK parameter values (arithmetic means) of pertuzumab were calculated by a 2-compartment model using serum pertuzumab concentration after the last dose in animals for observation during the recovery period in the 150 mg/kg group. $t_{1/2}$ was 10.6 days, CL was 6.31 mL/day/kg, V_c was 38.4 mL/kg, and V_{ss} was 79.6 mL/kg; results were thus similar to those observed following the 7-week repeated administration. V_c was similar to the plasma volume of monkeys (44.8 mL/kg) (*Pharm Res.* 1993;10:1093-5), and V_{ss} was smaller compared with the volume of the extracellular fluid and the total body water (208 and 693 mL/kg, respectively) and close to the plasma volume in monkeys. Based on the above, the applicant explained the tissue distribution of pertuzumab was low.

Anti-pertuzumab antibody in serum was measured before the initiation of pertuzumab administration and Day 1 to 239. No anti-pertuzumab antibody was detected from any of the samples tested.

PK parameters following 26-week repeated intravenous administration of pertuzumab to male and female monkeys

Dose (mg/kg)	Sex	n	$C_{max\text{-}obs}$ (mg/mL)	$AUC_{0\text{-}7}$ (mg·day/mL)	$AUC_{176\text{-}182}$ (mg·day/mL)	$AUC_{0\text{-}182}$ (mg·day/mL)	CL* (mL/day/kg)
15	Male	4	0.861 ± 0.0896	1.28 ± 0.201	3.57 ± 0.536	98.1 ± 12.5	4.48 ± 0.450
	Female	4	0.864 ± 0.125	1.25 ± 0.130	3.88 ± 0.736	96.1 ± 15.9	3.58 ± 0.306
50	Male	4	2.840 ± 0.322	4.08 ± 0.130	12.9 ± 2.72	308 ± 42.7	4.00 ± 0.773
	Female	3	2.810 ± 0.397	3.90 ± 0.465	11.2 ± 1.09	257 ± 83.5	4.49 ± 0.441
150	Male	6	7.710 ± 1.33	11.4 ± 0.962	24.6 ± 3.89	769 ± 83.4	6.23 ± 0.940
	Female	6	6.97 ± 0.986	10.6 ± 1.01	20.1 ± 5.73	677 ± 65.8	8.12 ± 2.95

Arithmetic mean ± SD, PK parameters were calculated by a model-independent analytical method. *: CL after the last dose.

In the above repeat dose study in monkeys, CL in the 150 mg/kg group was higher compared with the 15 and 50 mg/kg groups. It was also higher compared with the value observed after single dose at 150 mg/kg.

The applicant explained the mechanism of these results as follows:
Endogenous IgG, by binding to neonatal Fc receptor (FcRn), escapes from degradation within cells and is released into the blood again, thus maintaining its blood concentration (recycling mechanism) (*Clin Pharmacokinet* 2010;49:633-59, *Clin Pharmacokinet* 2010;49:493-507). This recycling system appears to work also in the elimination process of pertuzumab, an antibody (IgG) drug [see "3.(ii).A.(4) Metabolism and excretion"]. γ-Globulin concentration in monkey serum is 6.35 to 18.9 mg/mL (*Biological reference data book on experimental animals* [Soft Science Inc., 1989]) (Note: serum IgG concentration is not reported). Given the $C_{max\text{-}obs}$ value observed in the above repeat dose study in monkeys, it is likely that serum total IgG concentration (including pertuzumab) increased after pertuzumab administration. As a result, in the pertuzumab 150 mg/kg repeat dose group which showed the highest increase in total IgG concentration, it is inferred that IgG-recycling mechanism may have become saturated, resulting in the increase in CL of pertuzumab.

3.(ii).A.(3) Distribution

Pertuzumab (30, 100, 150 mg/kg) was administered intravenously to monkeys on Gestation Day 19, followed by intravenous administration of pertuzumab (10, 33.3, 100 mg/kg) twice weekly from Gestation Day 26 to 50 for a total of 8 doses, and pertuzumab concentrations in the serum of mother animals and fetuses were measured on Gestation Day 100. In the 10, 33.3, and 100 mg/kg groups (initial dose 30, 100, and 150 mg/kg, respectively), pertuzumab concentration in the serum of mother animals was 10.3, 30.0, and 143 μg/mL, respectively, and the concentration in the serum of fetuses was 8.88, 10.5, and 42.5 μg/mL, respectively. Thus, the ratio of serum pertuzumab concentration in fetuses to that in mother animals was 0.294, 0.399, and 0.338, respectively. Thus, the applicant explained that pertuzumab was transferred to the fetuses through the placenta.

Tissue distribution of pertuzumab was not investigated.

3.(ii).A.(4) Metabolism and excretion

It is reported that, similar to endogenous IgG, antibody (IgG) drugs are incorporated into cells by the pathway mediated by the binding to the target antigen in vivo or the pathway independent of binding to the target antigen, where they are degraded into peptides and amino acids, then excreted into urine or recycled for use in the living body (*Clin Pharmacokinet.* 2010;49:493-507). The applicant explained that since pertuzumab is also considered to undergo metabolism and excretion similar to those of endogenous IgG, the studies on the metabolism and excretion of pertuzumab can be omitted.

The applicant also explained as follows:
No study was conducted on the excretion of pertuzumab into breast milk. However, since it is known that human IgG is excreted into breast milk (*The Journal of Pediatric Infectious Diseases and Immunology.* 2010;22:403-7, *J Anim Sci*. 2009;87:3-9), cautions will be provided in the package insert to instruct nursing women to discontinue breast feeding when using pertuzumab.

3.(ii).A.(5) Pharmacokinetic interactions

Following intravenous administration of pertuzumab or bevacizumab (30 mg/kg each) alone, or the combination of the two drugs to male rats, serum pertuzumab and bevacizumab concentrations were measured. Time-course changes in serum concentration and PK parameters after combined administration were similar to those observed after administration of either drug alone. Thus, the applicant explained that no pharmacokinetic interactions were observed between these drugs.

3.(ii).A.(6) Effect of change in the manufacturing process of the drug substance on PK

During the development process of the drug substance, the manufacturing process was changed as shown in (a) to (d) below [see "2.A.(1).4) Manufacturing process development (comparability)"].

(a) Change from manufacturing process A to B (change of [redacted], etc.)
(b) Change from manufacturing process B to C# [Note: differs from process C in [redacted]] (change of [redacted])
(c) Change from manufacturing process B to C (changes of [redacted], [redacted], etc.)
(d) Change from manufacturing process C to D (change of [redacted], etc.)

In order to evaluate the effect of the changes described in above (a), (b), and (c) on the PK of pertuzumab, the formulations (30 mg/kg) manufactured using the post- and pre-change drug substances were administered intravenously to male rats in a single dose, and serum pertuzumab concentration was measured (the table below). (Note: in the evaluation for change (a), formulations manufactured using the manufacturing process A [31.4 mg/kg] and manufacturing process B [29.7 mg/kg] were used). The applicant explained that results showed that there was no significant difference in the time-course changes in serum pertuzumab concentration or PK parameters in the comparison of the formulations.

PK parameters in male rats following single intravenous dose of formulations manufactured using the drug substances before and after change in the manufacturing process

Change	Manufacturing process of drug substance	C_{max} (μg/mL)	AUC_{0-14}* (μg·day/mL)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)
(a)	Process A	709 ± 105	-	3060 ± 623	8.36 ± 2.59	10.7 ± 2.26	45.2 ± 7.66	120 ± 40.5
	Process B	580 ± 74.7	-	2750 ± 641	8.30 ± 2.44	11.3 ± 2.40	52.0 ± 6.71	126 ± 41.2
(b)	Process B	711 ± 70.3	2457 ± 318	3380 ± 1010	8.02 ± 2.74	9.54 ± 2.48	55.0 ± 10.3	97.6 ± 9.99
	Process C#	801 ± 80.8	2486 ± 214	3600 ± 1000	8.19 ± 3.22	8.96 ± 2.51	54.5 ± 11.4	92.3 ± 12.3
(c)	Process B	972 ± 60.6	2862 ± 202	3810 ± 597	7.48 ± 1.53	8.05 ± 1.33	50.4 ± 6.46	81.4 ± 5.82
	Process C	895 ± 86.8	2900 ± 355	3880 ± 947	7.35 ± 2.37	8.13 ± 1.78	44.4 ± 12.9	78.2 ± 12.3

Arithmetic mean ± SD, n = 12,
PK parameters were calculated according to a 2-compartment model.
*: calculated by a model-independent analytical method.

3.(ii).A.(7) Anti-pertuzumab antibody

No anti-pertuzumab antibody was detected in repeat dose studies in monkeys [see "3.(ii)A.(2).2) Repeat dose administration"]. It is shown that the sensitivity of the assay method used in these studies to measure serum anti-pertuzumab antibody decreases if pertuzumab is present at a concentration of ≥1.0 μg/mL. In the 7- and 26-week repeat dose studies in monkeys, serum pertuzumab concentration in individual animals was ≥100 and ≥46 μg/mL, respectively, at the time point of anti-pertuzumab antibody measurement, raising a possibility that the results with

anti-pertuzumab antibody measurement were false-negative. Thus, the applicant explained that it is unclear whether or not anti-pertuzumab antibody was produced in monkey, but in either of the studies, there were no animals that showed more rapid disappearance of pertuzumab compared with other animals used in the studies, showing that all animals were exposed to a constant level of pertuzumab.

3.(ii).B. Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concluded that the applicant's explanation on absorption, distribution, metabolism, and excretion is acceptable.

Tissue distribution of pertuzumab

PMDA asked the applicant to explain the reason for not investigating the tissue distribution of pertuzumab.

The applicant responded as follows:

In light of the following observations, pertuzumab, a humanized IgG1 monoclonal antibody, was expected to be distributed mainly inside the vascular vessels (in blood) and in tissues expressing HER2/ErbB2 protein, therefore the applicant considered that investigation on tissue distribution can be omitted.

- Comparison of V_c and V_{ss} observed in the 7- and 26-week repeated administration in monkeys with plasma volume, the volume of the extracellular fluid, and the total body water suggests that pertuzumab is poorly distributed in tissues [see "3.(ii).A.(2).2) Repeat administration"].
- In the cross-reactivity test using normal tissues of humans and cynomolgus monkeys, cross-reactivity of pertuzumab was observed only in those tissues that are expected to express HER2/ErbB2 protein [see "3.(iii).A.(7).2) Tissue cross-reactivity test using normal tissues of humans and cynomolgus monkeys"].

PMDA considers as follows:

Although the results of a tissue distribution study in a relevant animal species are useful for predicting potential toxicities in clinical use etc., a tissue distribution study of pertuzumab is not considered essential at present for the following reasons. PMDA accepted the response of the applicant.

- Pertuzumab is expected to be distributed mainly inside the blood vessels, with only poor distribution in tissues.
- Sufficient knowledge has been obtained on the distribution in human tissues and organs that express HER2.
- The safety profile of pertuzumab in humans has been sufficiently validated.

3.(iii) Summary of toxicology studies

3.(iii).A. Summary of the submitted data

In vivo toxicology studies of pertuzumab were conducted in cynomolgus monkeys, for the following reasons:

- Tissue cross-reactivity of pertuzumab is similar between humans and monkeys.
- The amino acid sequence of the extracellular domain of human HER2 protein is highly homologous (99%) with that of cynomolgus monkey ErbB2 protein (Report [redacted]-249-1821).
- In an *in vitro* test system, it has been shown that pertuzumab binding to human HER2 and that to monkey ErbB2 have similar binding affinity [see "3.(i).A.(1).2).i) Binding characteristics to HER2/ErbB2"].

3.(iii).A.(1) Single dose toxicity study

No single dose toxicity study was conducted. Instead, acute toxicity of pertuzumab was investigated based on the results from the initial dose to the high dose group in a repeat dose toxicity study in cynomolgus monkeys. In the 7-week repeated dose intravenous toxicity study, diarrhea was observed in 2 females of the 150 mg/kg group after the initial dose, but no death occurred during the study throughout the repeated administration period. In the 4-week repeated dose subcutaneous toxicity study, pertuzumab was administered at doses of up to 250 mg/kg, but no treatment-related findings were observed.

From these results, the approximate lethal dose was determined to be >150 mg/kg in intravenous administration and >250 mg/kg in subcutaneous administration.

3.(iii).A.(2) Repeat dose toxicity studies

3.(iii).A.(2).1) Seven-week repeat dose intravenous toxicity study in monkeys

Pertuzumab (0 [vehicle], 15, 50, 150 mg/kg) was administered intravenously to cynomolgus monkeys (4 or 6 each of males and females per group) once weekly for a total of 7 doses to investigate the repeat dose toxicity of pertuzumab. In 2 each of males and females in the control (vehicle) group and the 150 mg/kg group, the treatment period was followed by a 4-week recovery period to investigate the recovery. No death occurred during the administration period.

As changes in clinical observations, diarrhea (watery stools, amorphous stool) were found sporadically in any dose groups including the control (vehicle) group; the incidence tended to be higher in the pertuzumab groups but the symptoms were nonserious in all the animals. The diarrhea was not accompanied by other toxicity findings or dehydration. No pertuzumab-related toxicity findings were observed in ophthalmological examination, heart rate, blood pressure, ECG, hematology, blood coagulation test, clinical chemistry (including troponin T and creatine kinase isozymes), urinalysis, necropsy, or histopathological examination. No anti-pertuzumab antibody was detected in the serum of monkeys. During the 4-week recovery period, diarrhea tended to resolve both in the control (vehicle) group and the 150 mg/kg group.

Based on the above results, the no observed adverse effect level (NOAEL) was determined to be 150 mg/kg.

3.(iii).A.(2).2) Twenty six-week repeat dose intravenous toxicity study in monkeys

Pertuzumab (0 [vehicle], 15, 50, 150 mg/kg) was administered intravenously to cynomolgus monkeys (4 or 6 each of males and females per group) once weekly for a total of 27 doses to investigate the repeat dose toxicity of pertuzumab. In 2 each of males and females in the control (vehicle) group and the 150 mg/kg group, the treatment period was followed by an 8-week recovery period to investigate the recovery. No death occurred during the administration period.

One female animal in the 50 mg/kg group showed aggravation of general conditions probably caused by dehydration induced by incessant diarrhea, and was euthanized (on Day 126 after the initiation of administration) because the symptoms did not respond to treatment such as fluid replacement. Two additional animals (1 male in the 15 mg/kg group, 1 female in the 150 mg/kg group) also experienced repeated diarrhea and were treated with fluid replacement. Diarrhea was observed in all groups including the control (vehicle) group, with the incidence tending to be higher in the pertuzumab groups. In 1 female of the control (vehicle) group and 3 animals (1 male, 2 females) in the 150 mg/kg group, diarrhea (watery stools, amorphous stools) continued even during the recovery period. The clinical chemistry findings showed a slight increase in blood urea nitrogen (BUN) in the pertuzumab groups; increased BUN was also observed in the 150 mg/kg group at the end of the recovery period (56 days after the end of administration). No pertuzumab-

related toxicity findings were observed in weight, body temperature, respiratory rate, blood pressure, ECG, hematology, blood coagulation test, urinalysis, serum testosterone, serum troponin, organ weights, necropsy, or histopathological examination.

Thus, diarrhea and increased BUN were observed in all pertuzumab groups, from which NOAEL was determined to be <15 mg/kg. The mean C_{trough} in the 15 mg/kg group on Day 182 after the initiation of administration was 340 μg/mL, which was 5.5 times the clinical exposure level.*

*: The value observed in Cycle 9 in Japanese subjects enrolled in the substudy of the global phase III study.

3.(iii).A.(2).3) Four-week repeat dose subcutaneous toxicity study in monkeys

Pertuzumab (0 [vehicle], 250 mg/kg) was administered subcutaneously to cynomolgus monkeys (3 females per group) once weekly for a total of 5 doses. No death occurred during the administration period. No treatment-related toxicity findings were observed in general symptoms, weight, hematology or clinical chemistry (histopathology was not performed), neither were any gross toxicity findings observed at the site of administration.

3.(iii).A.(3) Genotoxicity

Since pertuzumab is a biotechnological drug, no genotoxicity study was conducted.

3.(iii).A.(4) Carcinogenicity

Since pertuzumab is a biotechnological drug and is indicated for inoperable or recurrent breast cancer, no carcinogenicity test was conducted.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

In the repeat intravenous dose toxicity studies in cynomolgus monkeys, histopathological examination was performed on the genital organs of males and females. No pertuzumab-related toxicity findings were observed.

3.(iii).A.(5).2) Study of embryo-fetal development in monkeys

Following an intravenous administration of pertuzumab (0 [vehicle], 30, 100, 150 mg/kg [control (vehicle), low dose, medium dose, and high dose, respectively]) to cynomolgus monkeys (12 females per group) on Gestation Day 19, the drug (0 [vehicle], 10, 33.3, 100 mg/kg [control (vehicle), low dose, medium dose, and high dose, respectively]) was administered intravenously twice weekly for a total of 8 doses. Cesarean section was performed on Gestation Day 100.

Toxicity findings observed in fetuses were abortion or embryo-fetal death (pertuzumab groups), decreased amniotic fluid volume (pertuzumab groups), decreased fetal weight (medium and high dose groups), hyperextension or hyperflexion of limbs (medium and high dose groups), decreased heart weight (medium and high dose groups), ventricular septal defect (medium dose group), and ventricular wall thinning (medium and high dose groups), decreased lung weight (pertuzumab groups), decreased lung size (medium and high dose groups), decreased kidney weight (pertuzumab groups), and renal aplasia detected by histopathological examination of fetuses (pertuzumab groups). The mean C_{trough} in mother animals of the low dose group on Gestation Day 50 was 390 μg/mL, which was 6.3 times the clinical exposure level.*

*: The value observed in Cycle 9 in Japanese subjects enrolled in the substudy of global phase III study.

3.(iii).A.(6) Local tolerance

No local tolerance study was conducted. However, gross examination (i.v. and s.c. injections) and histopathological examination (i.v. injection) of the administration site in the repeat dose toxicity studies showed no treatment-related toxicity findings.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Hemolytic effect and hemocompatibility in humans and cynomolgus monkey

Pertuzumab (0 [vehicle], 5.4, 10.8, 21.6 mg/mL) caused no hemolysis of red blood cells in the whole blood of humans or cynomolgus monkeys, nor did it coagulate or precipitate the plasma or serum of humans or cynomolgus monkeys.

3.(iii).A.(7).2) Tissue cross-reactivity test using normal tissues of humans and cynomolgus monkeys

Cross-reactivity of pertuzumab was investigated using frozen sections of normal tissues of humans and cynomolgus monkeys by IHC. The tissues that showed cross-reactivity with pertuzumab were identical with those reported to express HER2 (*Oncogene.* 1990;5:953-62).

3.(iii).B. Outline of the review by PMDA

Based on the submitted data and on the following discussion, PMDA has concluded that pertuzumab could be used clinically. However, because teratogenicity was observed in the study for effects of pertuzumab on embryo-fetal development in monkeys, the product should not be used in pregnant or possibly pregnant women.

3.(iii).B.(1) Administration of pertuzumab to pregnant women or women who may possibly be pregnant

PMDA asked the applicant to explain the relationship between the toxicity findings (abnormalities in kidney, lung, and heart, and oligohydramnios) observed in fetuses in the study for effects of pertuzumab on embryo-fetal development in monkeys and the pharmacological action of pertuzumab.

The applicant responded as follows:

In the study for effects of pertuzumab on embryo-fetal development in monkeys, decreased weight and aplasia of fetal kidney were found even in the low dose group. In light of the following reports, these toxicities may be due to the pharmacological action of pertuzumab. Also, the study for effects of pertuzumab on embryo-fetal development in monkeys showed oligohydramnios even in the low dose group. Oligohydramnios is known to be caused, among other causes, by malformation of the urinary system of fetuses (*Obstetrical and Gynecological Therapy.* 2007;94:886-93), which suggests that oligohydramnios observed after pertuzumab administration is a change associated with the aplasia of fetal kidney.

- HER2 expression is observed in the kidney of human fetuses (*Oncogene.* 1990;5:953-62).
- Epidermal growth factor receptor (EGFR) family plays important roles in the growth, differentiation, and morphogenesis of kidney cells (*BioFactors.* 1998;7:323-35, *J Am Soc Nephrol.* 2012;23:112-22).

Decreased fetal lung weight was observed in pertuzumab groups and decreased lung size in medium and high dose groups. It is reported that expression of HER2 and HER3 proteins are observed in the lung of human fetuses during the second trimester pregnancy and that activation of these receptors is related to the division and growth of lung epithelial cells of fetuses (*Am J Respir Cell Mo Biol.* 2000;22:432-40). Therefore, it cannot be excluded that the abnormalities in fetal lung may have been caused by the pharmacological action of pertuzumab. However, judging from the report that pulmonary hypoplasia occurs if the amniotic fluid of pregnant rats is reduced by paracentesis (*Am J Physiol Lung Cell Mol Physiol.* 2002;282:L431-9), the observed pulmonary abnormalities are likely to be changes secondary to oligohydramnios.

Decreased heart weight, ventricular septal defect, and ventricular wall thinning in fetuses also were found in medium and high dose groups. In light of the following reports, these toxicity findings may possibly have been caused by the direct pharmacological action of pertuzumab on the growth and differentiation of fetal heart.

- In rodents, neu (which corresponds to human HER2) plays an important role in embryonic development (*Nature* 1995;378:394-8, *Mol Cell Neurosci* 1996;7:247-62), and $P185^{neu}$ gene knock-out mice show embryonic death during the early stage of development and cardiac trabecular defect (*Nature.* 1995;378:394-8, *Recent Prog Horm Res.* 2004;59:1-12).
- ErbB2 is expressed in heart muscle cells of mouse embryos aged 9.5 or 10.5 days and plays important roles in the growth, differentiation, and function of the heart (*Semin Cell Dev Biol.* 2010;21:929-35, *Adv Anat Embryol Cell Biol.* 2007;190:1-65, *Dev Dyn.* 2011;240:1322-34).

PMDA asked the applicant to explain the possibility of the above toxicity findings observed in monkey fetuses occurring in humans and the appropriateness of administering pertuzumab to pregnant women or women who may possibly be pregnant.

The applicant responded as follows:
Based on the following observations, the possibility cannot be excluded that renal aplasia caused by the pharmacological action of pertuzumab, oligohydramnios and pulmonary hypoplasia associated with the renal aplasia, and abnormalities of the heart may occur in human fetuses. Therefore, it is not recommended to administer pertuzumab to pregnant women or women who may possibly be pregnant. However, with consideration given to the seriousness of the disease for which pertuzumab is indicated, the applicant considers it appropriate to provide the opportunity to use pertuzumab only if the expected therapeutic benefits outweigh the possible risks associated with treatment, upon providing (a) information on the results of nonclinical studies (e.g., abortion, embryo-fetal death, abnormalities of visceral organs, oligohydramnios) and (b) a caution that the safety in pregnant women or women who may possibly be pregnant has not been established.

- In the study for effects of pertuzumab on embryo-fetal development in monkeys, the estimated serum pertuzumab concentration in the animals of the low dose group that showed renal aplasia and oligohydramnios was 2.5 to 3.5 times the estimated serum pertuzumab concentration in human fetuses, and the NOAEL in embryos and fetuses is currently unknown.
- The estimated serum pertuzumab concentration in human fetuses (63-90 μg/mL) exceeds 20 μg/mL, the level that is supposed to exhibit tumor growth-inhibitory activity.

PMDA considers as follows:
PMDA accepted the applicant's response on the relationship between the toxicity findings in fetuses observed in the study for effects of pertuzumab on embryo-fetal development in monkeys and the pharmacological action of pertuzumab, and on the possibility of these toxicities occurring in humans. On the other hand, given the following, toxicity findings observed in monkeys may occur in the clinical use of pertuzumab. Therefore, it is inappropriate to use pertuzumab in pregnant women or women who may possibly be pregnant.

- Toxicity findings observed in monkeys may possibly have been caused by the pharmacological action of pertuzumab.
- The serum pertuzumab concentration in human fetuses is estimated to exceed the level that is required for the manifestation of the pharmacological effect of pertuzumab.

3.(iii).B.(2) Effect of pertuzumab on testis

Histopathological examination showed no spermatogenesis in any of males in the 7-week repeat dose toxicity study in cynomolgus monkeys nor in any animals in the 26-week repeat dose toxicity study in cynomolgus monkeys, except for 2 animals each in the control (vehicle) group and the 150 mg/kg group. Based on these results, PMDA asked the applicant to explain the effect of pertuzumab on testis.

The applicant responded as follows:

Although the role of HER2 in the testis formation and spermatogenesis is unknown, it is reported that, in the adult testis, HER2 protein is expressed in the spermatogonium, primary spermatocytes, oval spermatids, Sertoli cells, Leydig cells, and seminiferous tubule cells (*Fertil Steril.* 2011;95:2725-8), which suggests possible roles of HER2 in multiple spermatogenic processes. It is also reported that steroid synthesis in Leydig cells is regulated by epidermal growth factor (EGF) (*J Biol Chem.* 2008;283:27525-33), which suggests the possibility that HER2 regulates steroid synthesis by forming a heterodimer with activated EGFR. Thus, pertuzumab may exhibit toxicity in the testis.

However, if the following points are taken into account, it cannot be determined that pertuzumab affects the testis. Also, given the restricted passage of IgG through the blood-testis barrier (*Pharmacol Rev.* 2012;64:16-64, *Casarett and Doull's Toxicology, The basic science of poisons.* 6th ed. McGraw-Hill; 2001), pertuzumab is unlikely to affect spermatogenesis.

- Although histopathological examination showed no spermatogenesis in any of males in the 7-week repeat dose toxicity study, evaluation of testis weight based on the relationship between testis weight and histopathological maturation (*J Pharm Toxicol Method.* 2010;61:32-7, *Toxicol Pathol.* 2012;40:935-42) suggested that some of the animals were in sexual maturation period although they had not reached full maturity.
- In the 26-week repeat dose toxicity study, histopathological examination showed spermatogenesis in 1 of 4 animals each in the control (vehicle) group and the 150 mg/kg group at the end of administration, and in 1 of 2 animals each in the control (vehicle) group and the 150 mg/kg group at the end of the recovery period. No abnormality was observed in the testis weight, pathological findings of the testis, or serum testosterone concentration in the 2 animals in the 150 mg/kg group.
- In the 26-week repeat dose toxicity study, sperm analysis was performed in 1 of 4 animals each in the control (vehicle) group and the 150 mg/kg group at the end of administration. As a result, no effect of pertuzumab was observed on the sperm motility or count.
- In the tissue cross-reactivity test of pertuzumab using the normal tissues of humans and cynomolgus monkeys, expression of HER2 protein in the testis was not detected.

PMDA considers as follows:

When the following two points are taken into account, the possibility of pertuzumab affecting the testis cannot be excluded. However, given that the possibility of pertuzumab being transferred into the seminiferous tubules is low, it is unlikely that the effect of pertuzumab pose any clinically significant problem. PMDA therefore accepted the response of the applicant.

- It is reported that HER2 protein, the target molecule of pertuzumab, is expressed in the testis (*Fertil Steril.* 2011;95:2725-8).
- In the repeat dose toxicity studies, the effect of pertuzumab on the testis was investigated only in a limited number of animals.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A. Summary of the submitted data

4.(i).A.(1) Analytical method

4.(i).A.(1).1) Assay of pertuzumab

During the early stage of development, human serum concentration of pertuzumab (genetical recombination) (hereafter referred to as pertuzumab) was measured by enzyme-linked immunosorbent assay (ELISA) (lower limit of quantitation, 400 ng/mL) using the extracellular domain of immobilized recombinant human epidermal growth factor receptor type 2 (p185 HER2 extracellular domain) and [redacted] ([redacted])-labeled anti-[redacted] ([redacted])-[redacted] antibody. In the global phase III study (Study WO20698 [CLEOPATRA study]), serum concentration of pertuzumab was measured by ELISA (lower limit of quantitation, 150 ng/mL) using immobilized anti-idiotypic monoclonal antibody against pertuzumab, [redacted]-labeled anti-[redacted] monoclonal antibody, and [redacted]-labeled [redacted]. This ELISA allows pertuzumab measurement even in the presence of trastuzumab (genetical recombination) (trastuzumab).

4.(i).A.(1).2) Assay of anti-pertuzumab antibody

During the early stage of the development, anti-pertuzumab antibody in human serum was measured by ELISA using immobilized pertuzumab, [redacted]-labeled pertuzumab, and [redacted]-labeled [redacted] (measurement sensitivity for positive control [cynomolgus monkey anti-pertuzumab antibody] in the absence of pertuzumab, 30 ng/mL). In subsequent studies, the antibody was measured by electrochemical luminescence assay (ECLA) using [redacted], [redacted]-labeled pertuzumab, and [redacted]-labeled pertuzumab. The ECLA was used to minimize the effect of drugs coexisting in the serum (measurement sensitivity for positive control [cynomolgus monkey anti-pertuzumab antibody] in the absence of pertuzumab, 18 ng/mL). In the CLEOPATRA study, the antibody was measured by a revised ELISA using immobilized [redacted], [redacted]-labeled pertuzumab, [redacted]-labeled pertuzumab, and [redacted]-labeled anti-[redacted] antibody (measurement sensitivity for positive control [anti-idiotypic monoclonal antibody against pertuzumab] in the absence of pertuzumab, 8 ng/mL).

For samples that were positive for anti- pertuzumab antibody in the above assays, an absorption test was performed using pertuzumab. Based on the results of the test, presence or absence of anti-pertuzumab antibody was finally determined.

4.(i).A.(1).3) Test for HER2 expression

HER2 expression in tumor tissues was mainly investigated by fluorescent *in situ* hybridization (FISH) using HER2 FISH pharmDx kit (manufactured by DAKO Ltd.) or PathVysion (manufactured by Abbott Molecular Inc.), and by immunohistochemical (IHC) staining using HercepTest (manufactured by DAKO Ltd.).

4.(i).A.(2) Changes of drug substance manufacturing process during the development

During the process of the drug substance development, the manufacturing process underwent changes [see "2.A.(1).4) Manufacturing process development (comparability)"]. Of the clinical studies submitted in this application, the CLEOPATRA study and part of the foreign phase II study (Study BO17929) were conducted using the formulation produced by manufacturing process C, part of the foreign phase I study (Study TOC2297g) was conducted using the formulation produced by manufacturing process A, and other clinical studies were conducted using the formulation produced by manufacturing process B. The formulation produced by manufacturing process D was submitted for registration.

Comparability of the quality attributes was evaluated between formulations at the time of each

change of the manufacturing process from A to D. As a result, the applicant determined that the drug substance was comparable between before and after each change.

4.(i).B. Outline of the review by PMDA

Assay method for anti-pertuzumab antibody

PMDA asked the applicant to explain the possible effect of pertuzumab in testing samples on the measurement of anti-pertuzumab antibody.

The applicant responded as follows:
With the revised ELISA used in the CLEOPATRA study, the detection of anti-idiotypic monoclonal antibody against pertuzumab, in serum obtained from breast cancer patients, was possible with a measurement sensitivity of 500 ng/mL in the presence of 60 μg/mL of pertuzumab, whereas the anti-idiotypic antibody could not be detected in the presence of ≥80 μg/mL of pertuzumab. In the CLEOPATRA study, PK of pertuzumab was investigated in some of the patients, which showed the serum trough concentration of 63.6 ± 48.1 to 94.1 ± 30.6 μg/mL (arithmetic mean ± standard deviation [SD]) [see "4.(ii).A.(8) Substudy of global phase III study"]. These results suggest the possibility that, in the CLEOPATRA study, pertuzumab in test samples may have interfered with the measurement of anti-pertuzumab antibody, resulting in false negative findings.

In other studies in which anti-pertuzumab antibody was measured by ELISA or ECLA, pertuzumab in the test samples may have interfered with the measurement of anti-pertuzumab antibody, as was the case with the CLEOPATRA study.

Next, since pertuzumab and trastuzumab were concomitantly administered in the CLEOPATRA study, PMDA asked the applicant to explain the possibilities that (a) trastuzumab in test samples may have affected the measurement of anti-pertuzumab antibody, and (b) anti-trastuzumab antibody may have affected the measurement of anti-pertuzumab antibody.

The applicant responded as follows:
As regards (a), the revised ELISA allowed the detection of monoclonal anti-idiotypic antibody against pertuzumab (16 ng/mL) in healthy adult-derived serum in the presence of 200 μg/mL of trastuzumab. In the CLEOPATRA study, the trough concentration (arithmetic mean ± SD) of trastuzumab in the pertuzumab/trastuzumab combination therapy group was approximately 23.7 ± 12.3 μg/mL, which suggests that trastuzumab in test samples was unlikely to have affected the measurement of anti-pertuzumab antibody.

As regards (b) in contrast, since trastuzumab and pertuzumab have the same structure of IgG framework region (*Cancer Cell* 2004;5:317-28), the revised ELISA may detect anti-trastuzumab antibody that has the same framework region as the epitope, as anti-pertuzumab antibody.

PMDA considers as follows:
With the anti-pertuzumab antibody assay methods employed in the submitted clinical studies, pertuzumab in test samples and anti-trastuzumab antibody may have affected the results of the measurement of anti-pertuzumab antibody. Therefore, the assessment of the serum concentration of anti-pertuzumab antibody should be carefully determined based on the above results [see "4.(ii).B.(4) Anti- pertuzumab antibody"].

4.(ii) Summary of clinical pharmacology studies

4.(ii).A. Summary of the submitted data

PK of pertuzumab (in treatment with pertuzumab alone or in combination with other antineoplastic drugs) was investigated in cancer patients.

4.(ii).A.(1) Foreign phase I study (5.3.3.2-2, Study TOC2297g [November 2001 to August 2003])

An open-label, uncontrolled study was conducted in 21 patients with advanced solid tumors to investigate the maximum tolerated dose (MTD), safety, and PK of Pertuzumab. Pertuzumab (0.5, 2.0, 5.0, 10.0, 15.0 mg/kg) was intravenously administered over 90 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted) every 3 weeks, and serum pertuzumab concentration was measured (the table below).

Pertuzumab was eliminated in a monophasic manner in the 0.5 mg/kg group and in a biphasic manner in the 2.0 to 15.0 mg/kg groups. In each of 2.0 to 15.0 mg/kg groups, $t_{1/2\ terminal}$ ($t_{1/2}$ of the elimination phase, arithmetic mean) was 14.9 to 22.3 days. CL and $t_{1/2\ terminal}$ were similar among 2.0 to 15.0 mg/kg groups. The 0.5 mg/kg group, in contrast, had a greater CL value and a smaller $t_{1/2\ terminal}$ value compared with other dose groups, showing non-linear PK of pertuzumab. V_c was similar among all the dose groups, and almost comparable to the plasma volume in the human body (42.8 mL/kg) (*Pharm Res.* 1993;10:1093-5).

The applicant explained the reason for the non-linear PK of pertuzumab as follows:
Pertuzumab is considered to be eliminated by the pathway mediated by the binding to the target antigen and by the pathway independent of binding to the target antigen [see "3.(ii).A.(4) Metabolism and excretion"]. At pertuzumab doses exceeding 0.5 mg/kg, the elimination pathway mediated by binding to the target antigen appears to have become saturated, resulting in a decreased and roughly constant CL value.

PK parameters of pertuzumab in Cycle 1

Dose (mg/kg)	n	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)	$t_{1/2\ initial}$ *1 (days)	$t_{1/2\ terminal}$ *2 (days)	AUC (μg·day/mL)	C_{max} (μg/mL)
0.5	3	13.1 ± 5.5	43.6 ± 4.6	-	-	2.6 ± 0.9	43.1 ± 17.8	11.5 ± 1.20
2.0	3	3.74 ± 1.28	35.5 ± 3.5	69.5 ± 13.7	0.96 ± 0.99	14.9 ± 1.1	569.4 ± 169.0	55.1 ± 5.30
5.0	4	3.52 ± 0.85	39.7 ± 6.2	74.1 ± 30.4	1.09 ± 0.74	17.2 ± 10.3	1478 ± 349.4	125.8 ± 17.5
10.0	3	2.69 ± 0.92	38.4 ± 5.3	73.4 ± 13.6	1.23 ± 0.90	22.3 ± 9.9	3959 ± 1110	257.2 ± 34.2
15.0	8	3.68 ± 1.47	42.8 ± 7.9	85.3 ± 36.7	1.50 ± 1.17	18.6 ± 8.8	4503 ± 1245	358.5 ± 68.83

Arithmetic mean ± SD,
PK parameters were calculated by a 1-compartment model in 0.5 mg/kg group and by a 2-compartment model in 2.0 to 15.0 mg/kg groups.
*1: $t_{1/2}$ in the distribution phase, *2: $t_{1/2}$ in the elimination phase

4.(ii).A.(2) Japanese phase I study (5.3.3.2-1, Study JO17076 [June 2004 to August 2005])

An open-label, uncontrolled study was conducted in 18 patients with advanced solid tumors to investigate the MTD, safety, and PK of pertuzumab. Pertuzumab (5, 10, 15, 20, 25 mg/kg) was intravenously administered over 90 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted) every 3 weeks, and serum pertuzumab concentration was measured (the table below).

The applicant explained as follows:
AUC_{last}, AUC_{inf}, and C_{max} increased proportionally with dose, whereas CL, V_{ss}, and $t_{1/2}$ remained comparable regardless of the dose, showing linear PK of pertuzumab over the dose range from 5 to 25 mg/kg. During the multiple doses, the cumulative coefficient in Cycles 2 and 3, calculated

from the trough concentration, was 1.70 and 2.30, respectively, which was similar to the value predicted from $t_{1/2}$ following the initial dose.

PK parameters of pertuzumab in Cycle 1

Dose (mg/kg)	n	CL (mL/day/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (days)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)
5	3	5.62 ± 0.82	90.2 ± 12.8	11.1 ± 0.5	608 ± 112	902 ± 121	105 ± 32.4
10	3	4.82 ± 1.53	93.7 ± 18.7	14.4 ± 2.7	1400 ± 447	2230 ± 773	181 ± 32.6
15	3	4.25 ± 1.66	94.1 ± 40.9	16.8 ± 4.0	2350 ± 852	3970 ± 1740	320 ± 73.2
20	3	4.87 ± 0.58	99.6 ± 10.8	15.0 ± 2.6	2640 ± 193	4150 ± 507	340 ± 51.3
25	6	4.54 ± 1.66	94.7 ± 12.3	16.3 ± 5.9	3730 ± 893	6060 ± 1900	498 ± 108

Arithmetic mean ± SD
PK parameters were calculated by a model-independent analytical method.

4.(ii).A.(3) Foreign phase II study (5.3.5.4-2, Study BO16934 [February 2003 to December 2004])

An open-label, randomized, comparative study was conducted in 78 patients with HER2-low expressing (negative on FISH and 0/1+/2+ by IHC) distant metastatic or recurrent breast cancer (77 patients included in PK analysis) to investigate the efficacy and safety of pertuzumab. Pertuzumab was intravenously administered every 3 weeks, at the loading dose of 840 mg followed by 420 mg, or at the fixed dose of 1050 mg throughout the study, and serum pertuzumab concentration was measured. Pertuzumab was administered over 90 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted).

PK parameter values following the loading dose of pertuzumab were as shown in the table below. The applicant explained that when pertuzumab was administered at the loading dose of 840 mg, followed by 420 mg, the peak serum pertuzumab concentration and the trough concentration reached the steady state before Cycle 2.

PK parameters of pertuzumab in Cycle 1

Dose (mg/kg)	n	CL (mL/day)	V_{ss} (mL)	$t_{1/2}$ (days)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)
840	40	270 (42)[*1]	4122 (40)[*1]	12.2 (31)[*1]	2517 (36)	3598 (39)[*1]	289 (37)
1050	37	247 (36)[*2]	3527 (39)[*2]	11.4 (36)[*2]	3465 (30)	4750 (32)[*2]	409 (39)

Arithmetic mean (coefficient of variation [CV] [%])
PK parameters were calculated by a model-independent analytical method
*1: n = 38; *2: n = 36

4.(ii).A.(4) Foreign phase I study (5.3.3.2-5, Study BO17021 [April 2004 to January 2006])

An open-label, uncontrolled study was conducted in 19 patients with advanced solid tumors to investigate the MTD and safety of concomitant use of pertuzumab with docetaxel hydrate (DTX). Pertuzumab was intravenously administered every 3 weeks, at the loading dose of 840 mg followed by 420 mg, or at the fixed dose of 1050 mg throughout the study. Both treatments were given in combination with DTX (60, 75, or 100 mg/m^2 every 3 weeks), and serum pertuzumab concentration and plasma DTX concentration were measured. Pertuzumab was administered over 90 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted). In Cycle 1, DTX was to be administered on Day 1 and pertuzumab on Day 2 and, from Cycle 2, both drugs were to be administered on Day 1 (DTX immediately after pertuzumab) of each cycle.

PK parameter values of pertuzumab were as shown in the table below. The applicant explained that, in both dosage regimens, $t_{1/2}$ was greater in Cycle 2 compared with that in Cycle 1, probably

because the blood sampling time point was different in Cycle 2.

The applicant also explained that V_{ss} and $t_{1/2}$ of DTX slightly increased or prolonged following the combined administration (Cycle 2) than those following administration of DTX alone (Cycle 1), whereas CL, AUC_{inf}, and C_{max} were similar between the dosage regimens, and time-course change in plasma DTX concentration was also similar between the dosage regimens.

PK parameters of pertuzumab

Dose (mg)	Cycle	n	CL (mL/day)	V_{ss} (mL)	$t_{1/2}$ (days)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)
840	1	11	329 ± 97	5355 ± 1680	12.13 ± 5.40	1749 ± 543	2796 ± 967	255 ± 84
420	2	10	169 ± 60	4233 ± 1555	19.10 ± 9.49	1491 ± 472	2762 ± 892	150 ± 43
1050	1	8	282 ± 83	5214 ± 1386	13.36 ± 4.18	2390 ± 584	3951 ± 919	301 ± 93
1050	2	7	167 ± 49	4672 ± 1221	22.08 ± 12.89	3500 ± 551	6856 ± 2335	368 ± 79

Arithmetic mean ± SD
PK parameters were calculated by a model-independent analytical method (treatment groups with different DTX doses were combined).

PK parameters of DTX

Dose		Cycle	n	CL ($mL/h/m^2$)	V_{ss} (mL/m^2)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)
DTX (mg/m^2)	Pertuzumab (mg)								
60	-	1	6	33,128 ± 4396	786,981 ± 218,139	16.9 ± 5.22	1838 ± 244	1642 ± 274	0.63 ± 0.21
60	1050	2	6	35,813 ± 6216	1,023,569 ± 335,711	19.7 ± 4.65	1734 ± 409	1695 ± 331	0.89 ± 0.24
75	-	1	6	22,013 ± 7031	410,174 ± 184,216	12.7 ± 3.46	3744 ± 1304	3128 ± 859	0.57 ± 0.16
75	840/420*	2	6	23,747 ± 8175	566,759 ± 361,946	15.2 ± 5.11	3496 ± 1211	2722 ± 912	0.83 ± 0.16
100	-	1	5	18,913 ± 7245	254,233 ± 85,054	9.59 ± 2.34	5930 ± 2137	5450 ± 1867	0.90 ± 0.00
100	840/420	2	4	22,976 ± 12,679	428,863 ± 283,977	12.8 ± 6.13	5218 ± 2216	4705 ± 1871	0.70 ± 0.23

Arithmetic mean ± SD
Pertuzumab 1050 mg/DTX 75 mg/m^2 combination therapy group was excluded from PK analysis because of the limited number of patients (2 patients).
*: Loading dose of 840 mg, followed by 420 mg

4.(ii).A.(5) Foreign phase I study (5.3.3.2-4, Study BO17003 [January 2004 to May 2005])

An open-label, uncontrolled study was conducted in 18 patients with advanced solid tumors to investigate the MTD and safety of concomitant use of pertuzumab with capecitabine (Cape). Pertuzumab (1050 mg) was intravenously administered over 90 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted) every 3 weeks in combination with Cape (825, 1000, or 1250 mg/m^2 twice daily from Day 1 to 14, followed by a 1-week withdrawal), and the concentrations of the following substances were measured: pertuzumab in serum; and Cape and its metabolites (5'-deoxy-5-fluorocytidine [5'-DFCR], doxifluridine [5'-DFUR], fluorouracil [5-FU], α-fluoro-β-alanine [FBAL]) in plasma. A single dose of Cape alone was to be administered 7 days before the initiation of Cycle 1.

In Cycle 1 of pertuzumab/Cape combination therapy, PK parameters of pertuzumab (calculated by combining treatment groups of different Cape doses) were as follows (arithmetic mean ± SD): CL 283 ± 98 mL/day, V_{ss} 5202 ± 1007 mL, $t_{1/2}$ 14.6 ± 41 days, AUC_{last} 2743 ± 744 μg·day/mL, AUC_{inf} 4097 ± 1282 μg·day/mL, and C_{max} 355 ± 59 μg/mL.

PK parameters ($t_{1/2}$, t_{max}, C_{max}, AUC) of Cape and its metabolites showed high inter-subject variability, whereas AUC and $t_{1/2}$ of 5-FU, the active metabolite, did not show any marked difference after administration of Cape alone (7 days before the initiation of Cycle 1) and after concomitant use with pertuzumab (Day 1 of Cycle 1). Based on the above, the applicant explained that concomitant use of pertuzumab with Cape does not significantly affect the activation of Cape to 5-FU or metabolism of 5-FU.

4.(ii).A.(6) Foreign phase I study (5.3.5.4-10, Study WO20024 [September 2006 to December 2008])

An open-label, uncontrolled study was conducted in 15 patients with locally advanced or distant metastatic non-small cell lung cancer (NSCLC) to investigate the MTD and safety of concomitant use of pertuzumab with erlotinib hydrochloride (erlotinib). Pertuzumab (loading dose of 840 mg, followed by 420 mg) was intravenously administered over 60 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the second and subsequent doses if no safety problem was noted) every 3 weeks in combination with erlotinib (100 or 150 mg once daily from 8 days before the initiation of Cycle 1), and serum pertuzumab concentration and plasma erlotinib concentration were measured.

PK parameters (calculated by combining treatment groups with different erlotinib doses) of pertuzumab in Cycle 2 of pertuzumab/erlotinib combination therapy were as follows (arithmetic mean ± SD): C_{max} 231 ± 55.3 μg/mL, $AUC_{0\text{-}21d}$ (AUC from Day 0 to 21) 1780 ± 340 μg·day/mL, AUC_{inf} 3000 ± 815 μg·day/mL, CL 240 ± 50 mL/day, V_{ss} 4900 ± 1300 mL, and $t_{1/2}$ 17.9 ± 2.18 days.

PK parameters ($t_{1/2}$, t_{max}, C_{max}, $AUC_{0\text{-}24h}$, CL_{ss}, V_{ss}) of erlotinib showed high inter-subject variability, whereas $AUC_{0\text{-}24h}$ of erlotinib in erlotinib 100 mg group (comparison in 150 mg group could not be done because of the limited number of patients) did not show any marked difference after administration of erlotinib alone (1 day before the initiation of Cycle 1) and after concomitant use with pertuzumab (Day 1 of Cycle 2). Thus, the applicant explained that concomitant use of pertuzumab with erlotinib does not significantly affect the PK of erlotinib.

4.(ii).A.(7) Foreign phase II study (5.3.5.4-9, Study TOC3258g [January 2005 to September 2007])

An open-label, randomized study was conducted in 130 patients with ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer (31 patients included in PK analysis) to investigate the efficacy and safety of concomitant use of pertuzumab or placebo with gemcitabine hydrochloride (GEM). Pertuzumab (loading dose of 840 mg, followed by 420 mg thereafter) was intravenously administered over 60 ± 10 minutes (the dosing duration could be reduced to 30 ± 10 minutes in the third and subsequent doses if no safety problem was noted) every 3 weeks in combination with GEM (800 mg/m^2 once weekly for 2 weeks, followed by 1-week withdrawal), and serum pertuzumab concentration and plasma concentrations of GEM and its metabolite (2',2'-difluorodeoxyuridine [dFdU]) were measured.

The serum trough and peak concentrations of pertuzumab reached the steady state roughly before Cycle 2, with the trough concentration (arithmetic mean ± SD) in Cycles 2 and 3 being 57.1 ± 18.9 and 54.4 ± 16.4 μg/mL, respectively, and the peak concentration, 188 ± 56.1 and 192 ± 27.7 μg/mL, respectively.

For $AUC_{5\text{-}30min}$ (AUC from 5 to 30 minutes after dosing) of GEM and AUC_{all} (AUC from 5 to 125 minutes after dosing) of dFdU on Day 1 of Cycle 2, the ratio of the geometric mean (90% confidence interval [CI]) of pertuzumab/GEM combination therapy group to that of GEM alone group was 0.886 [0.625, 1.26] and 0.968 [0.854, 1.10], respectively. Although $AUC_{5\text{-}30min}$ of GEM

showed high inter-subject variability, based on the above results, the applicant explained that concomitant use of pertuzumab with GEM does not significantly affect PK of GEM and dFdU.

4.(ii).A.(8) Substudy of global phase III study (5.3.5.1-1, 5.3.5.1-2, 5.3.3.2-3, 5.3.4.2-1; substudy of Study WO20698 [CLEOPATRA] [February 2008 to May 2011])

As a substudy of the double-blind, randomized comparative study in patients with HER2-positive distant metastatic or recurrent breast cancer conducted to investigate the efficacy and safety of pertuzumab or placebo added to trastuzumab/DTX combination (pertuzumab combination therapy group or placebo combination therapy group, respectively), parameters including PK of administered drugs were evaluated in 40 patients who consented to participate in PK measurement. Pertuzumab (loading dose of 840 mg, followed by 420 mg) or placebo was intravenously administered over ≥60 minutes (the dosing duration could be reduced to 30 minutes in the second and subsequent doses if no safety problem was noted) every 3 weeks in combination with trastuzumab (loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks) and DTX (75 mg/m^2 [the dose could be increased to 100 mg/m^2 from Cycle 2 at the discretion of the investigator if tolerability was confirmed in Cycle 1]), and serum pertuzumab and trastuzumab concentrations and plasma DTX concentration were measured. In Cycle 1, pertuzumab was to be administered on Day 1, and trastuzumab and DTX on Day 2. If tolerability was confirmed in Cycle 1, all drugs could be administered on Day 1 of each of the subsequent cycles.

Under concomitant use with trastuzumab and DTX, the peak serum concentration of pertuzumab (arithmetic mean ± SD) was 263 ± 56.5 μg/mL in Cycle 1 and 183 ± 33.5 to 221 ± 32.0 μg/mL in Cycle 3 to 15, and the trough concentration (arithmetic mean ± SD) was 63.6 ± 48.1 to 94.1 ± 30.6 μg/mL in Cycle 1 to 15. Both peak and trough concentrations tended to increase slightly with cycle number in Cycle 3 and the subsequent cycles, but roughly remained within similar ranges.

Under concomitant use with DTX and placebo, peak serum concentration (arithmetic mean [coefficient of variation (CV) %]) of trastuzumab was 201 μg/mL (33.3) in Cycle 1 and 151 μg/mL (22.5) in Cycle 3, and the trough concentration was 24.0 μg/mL (40.2) in Cycle 3. In the pertuzumab combination therapy group, the peak trastuzumab concentration was 177 μg/mL (17.7) in Cycle 1 and 133 μg/mL (38.3) in Cycle 3, and the trough concentration was 23.7 μg/mL (52.0) in Cycle 3. For the peak concentration in Cycles 1 and 3 and the trough concentration in Cycle 3, the geometric mean ratios (%) [90% CI] of the pertuzumab combination therapy group to the placebo combination therapy group were 90.3 [78.1, 104.3], 81.0 [62.7, 104.7], and 95.9 [70.7, 130.1], respectively, showing no marked difference in the concentrations between the placebo combination therapy group and the pertuzumab combination therapy group.

Under concomitant use with trastuzumab, PK parameters of DTX in Cycle 1 were as shown in the table below. For AUC_{last}, AUC_{inf}, and C_{max}, the geometric mean ratios (%) [90% CI] of the pertuzumab combination therapy group to the placebo combination therapy group were 104.9 [73.9, 148.9], 101.4 [75.7, 136.0], and 92.5 [65.2, 131.2], respectively, showing no marked difference in these parameter values between the placebo combination therapy group and the pertuzumab combination therapy group. The time course of the plasma DTX concentration in Cycle 1 was similar between the pertuzumab combination therapy group and the placebo combination therapy group.

PK parameters of DTX in Cycle 1

Treatment group	n	CL (L/h)	V_{ss} (L)	$t_{1/2}$ (h)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)
Placebo combination therapy group	14	57.8*1 (45.0)	272*1 (98.4)	11.8*1 (21.7)	2334 (48.9)	2649*1 (46.1)	2250 (53.7)
Pertuzumab combination therapy group	18	52.3*2 (39.7)	253*2 (65.7)	13.0*2 (22.2)	2625 (67.8)	2961*2 (59.4)	2346 (88.5)

Geometric mean (CV%), excluding patients deemed inappropriate for PK analysis (3 patients in the placebo combination therapy group, 2 patients in the pertuzumab combination therapy group).
*1: n = 11, *2: n = 15.

In addition to the clinical studies described in "4.(ii).A.(1) Foreign phase I study (Study TOC2297g)" to "4.(ii).A.(8) Substudy of global phase III study (substudy of the CLEOPATRA study)," the following studies were conducted in foreign cancer patients and serum pertuzumab concentrations were measured following the administration of pertuzumab alone: 2 foreign phase II studies (Studies TOC2689g and BO17004) in which pertuzumab was administered at the loading dose of 840 mg followed by 420 mg every 3 weeks, or the fixed dose of 1050 mg every 3 weeks, and 2 foreign phase II studies (Studies TOC2682g and TOC2572g) in which pertuzumab was administered at the loading dose of 840 mg followed by 420 mg every 3 weeks. PK data obtained were subjected to analysis of population pharmacokinetics (PPK) [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PKK)"].

4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)

Based on PK data of 444 cancer patients (3890 points) obtained from 12 studies, foreign phase I studies (Studies TOC2297g [excluding 0.5 mg/kg group], BO17003, BO17021, WO20024), a Japanese phase I study (Study JO17076), foreign phase II studies (Studies TOC2689g, BO16934, BO17004, TOC2682g, TOC2572g, TOC3258g), and a foreign phase III study (substudy of the CLEOPATRA study), PPK analysis was performed using a 2-compartment model with the first-order elimination process by nonlinear mixing effect model (NONMEM version 7.1.2), and a PPK model was constructed. As covariates of PK parameters (CL, V_c, V_p) of pertuzumab, the following parameters were investigated: age, lean body mass, sex, ethnicity (Japanese patient or non-Japanese patient), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum bilirubin, serum albumin, alkaline phosphatase (ALP), serum creatinine, Eastern Cooperative Oncology Group Performance Status (ECOG PS), type of cancer (breast cancer or other than breast cancer), number of metastases, presence or absence of liver metastasis, and presence or absence of history of receiving concomitant chemotherapy. After the completion of the above analysis, it was found that some of the patient data had not been included in the analysis. These data were added and, based on PK data of 481 patients (4525 points) in total, PPK parameter estimation, etc., was performed.

Results of the analysis were as follows:

- As statistically significant covariates, lean body mass and serum albumin were selected for CL, and lean body mass for the distribution volume of the central compartment (V_c) and for the distribution volume of the peripheral compartment (V_p). CL increased in patients with a high lean body mass and decreased in patients with high serum albumin. V_c and V_p increased in patients with a high lean body mass.
- In the final model, CL was 0.235L/day, V_c was 3.11 L, inter-compartmental clearance (Q) was 0.534 L/day, and V_p was 2.46 L in patients with body weight of 48 kg and serum albumin of 3.9 g/dL. Inter-individual variability of CL, V_c, and V_p was 34.1%, 18.5%, and 45.9%, respectively. $t_{1/2\ terminal}$ was estimated to be 18.0 days.

Although the above results showed that lean body mass and serum albumin were covariates that

affect the PK of pertuzumab, the applicant explained that pertuzumab dose adjustment for these covariates were unnecessary for the following reasons: (a) comparison with the extent of the inter-individual variability in the whole population suggests that the effect of lean body mass and serum albumin on the PK of pertuzumab is limited, and (b) examination based on the results of the CLEOPATRA study did not show any clear effect of these covariates on the efficacy or safety of pertuzumab.

4.(ii).A.(10) Effect of pertuzumab on QT interval

In the substudy of the CLEOPATRA study, effect of pertuzumab on QT interval was investigated based on ECG data at a total of 347 points obtained from 37 patients (20 patients in the pertuzumab combination therapy group, 17 patients in the placebo combination therapy group). Taking account of the following results, the applicant explained that pertuzumab is not considered to have a marked effect on QT interval.

- QT interval corrected by Fridericia's method (QTcF) exceeded 450 ms in 0 and 2 patients (<480 ms in both) in the pertuzumab combination therapy group and the placebo combination therapy group, respectively. The incidence of abnormal ECG was similar between the pertuzumab combination therapy group and the placebo combination therapy group, with no findings suggestive of arrhythmogenic effect of pertuzumab being observed.
- No clear correlation was observed between serum pertuzumab concentration and change in QTcF from baseline (ΔQTcF), and the maximum ΔQTcF did not exceed 30 ms at any observation time points in Cycle 1 or 3.
- In Cycle 1, the point estimate of difference in ΔQTcF between the pertuzumab combination therapy group and the placebo combination therapy group (ΔΔQTcF) was <5 ms, and the upper confidence limit of 90% CI did not exceed 10 ms. In Cycle 3, in contrast, the point estimate of ΔΔQTcF exceeded 5 ms and the upper confidence limit of 90% CI exceeded 10 ms. However, the increased ΔΔQTcF appears to have been chiefly contributed by variations of ΔQTcF in the placebo combination therapy group.

4.(ii).A.(11) Anti-pertuzumab antibody

Anti-pertuzumab antibody was investigated in the following studies: TOC2297g (23 patients), BO16934 (80 patients), BO17004 (70 patients) by ELISA; BO17931 (85 patients), JO17076 (18 patients), TOC2572g (46 patients), TOC2664g (1 patient), TOC2682g (41 patients), TOC2689g (115 patients), TOC3258g (64 patients), WO20024 (15 patients) by ECLA; and CLEOPATRA (403 patients) by revised ELISA.

In 11 studies except the CLEOPATRA study, there were no anti-pertuzumab antibody-positive patients observed before pertuzumab administration, whereas after pertuzumab administration, the antibody was positive in 1 of 46 patients (2.2%) in Study BO17931 and in 1 of 27 patients (3.7%) in Study TOC2572g. In the pertuzumab combination therapy group of the CLEOPATRA study, anti-pertuzumab antibody was positive in 11 of 386 patients (2.8%); the antibody was positive in 5 of 384 patients (1.3%) before pertuzumab administration, 9 of 375 patients (2.4%) during the administration, and 5 of 194 patients (2.6%) after the last dose. In 4 of 5 patients who were determined to be antibody-positive before pertuzumab administration, the response is considered to be false-positive because they were negative after pertuzumab administration. In the placebo combination therapy group of the CLEOPATRA study, anti-pertuzumab antibody was positive in 23 of 372 patients (6.2%). However, the applicant explained that these false positive reactions were possibly due partly to the detection of anti-trastuzumab antibody by the revised ELISA [see "4.(i).B Assay method for anti-pertuzumab antibody"].

Among patients who became positive for anti-pertuzumab antibody after pertuzumab administration, 2 patients, one in Study TOC2572g and the other in the CLEOPATRA study, participated in the study of PK of pertuzumab. In the patient in Study TOC2572g (judged positive

on Day 41 after treatment initiation), the peak serum concentration of pertuzumab in Cycle 1 was 242 μg/mL, which was similar to the mean peak concentration at the same time point in all patients examined including this patient (265.1 μg/mL). In contrast, the trough concentration in Cycle 1 (at the last blood sampling point for this patient which was performed on Day 22 after treatment initiation) was 2.71 μg/mL, which was markedly lower compared with the mean trough concentration at the same time point (45.8 μg/mL). In the patient in the CLEOPATRA study (judged positive on Day 192 after treatment initiation), the trough and peak concentrations of pertuzumab on Day 172 were 40.8 and 196 μg/mL, respectively, which tended to be lower than, or similar to, the mean values at the same time point (75.5 and 196 μg/mL, respectively). However, serum pertuzumab concentration in this patient tended to be lower than the mean level even at time points where anti-pertuzumab antibody was negative.

Based on the above, the applicant explained as follows:
These results suggest that, in the patient in Study TOC2572g, anti-pertuzumab antibody may have caused the decrease in pertuzumab concentration. However, since only 2 antibody-positive patients were evaluated for PK of pertuzumab, no conclusion can be derived on the effect of anti-pertuzumab antibody on the PK of pertuzumab.

4.(ii).A.(12) Applicant's discussions

4.(ii).A.(12).1) Pharmacokinetic interactions

(a) Effect of other antineoplastic drugs on PK of pertuzumab

Following the administration of pertuzumab alone, CL, V_{ss}, and $t_{1/2}$ of pertuzumab were 0.232 to 0.308 L/day, 4.88 to 7.05 L, and 11.1 to 22.3 days, respectively, in Study TOC2297g (except 0.5 mg/kg group) and Study JO17076 [see "4.(ii).A.(1) Foreign phase I study (Study TOC2297g)" and "4.(ii).A. (2) Japanese phase I study (Study JO17076)"], and 0.247 to 0.270 L/day, 3.53 to 5.23 L, and 11.4 to 19.3 days, respectively, in Studies BO16934 and BO17004 [see "4.(ii).A.(3) Foreign phase II study (Study BO16934)"]. Following the concomitant administrations of pertuzumab with DTX in Study BO17021, with Cape in Study BO17003, and with erlotinib in Study WO20024, CL, V_{ss}, and $t_{1/2}$ of pertuzumab were 0.240 to 0.329 L/day, 4.90 to 5.36 L, and 12.1 to 17.9 days, respectively [see "4.(ii).A.(4) Foreign phase I study (Study BO17021)" to "4.(ii).A.(6) Foreign phase I study (Study WO20024)"], showing no marked differences compared with those observed following the administration of pertuzumab alone.

Following the administration of pertuzumab alone (loading dose of 840 mg, followed by 420 mg), the trough concentration of pertuzumab (in Cycle 3) in Studies TOC2689g, TOC2682g, and TOC2572g was 66.5, 53.1, and 38.0 μg/mL, respectively. Under concomitant use with GEM in Study TOC3258g, the trough concentration of pertuzumab (in Cycle 2) was 57.1 μg/mL, and under concomitant use with trastuzumab and DTX in the substudy of the CLEOPATRA study, the trough concentration of pertuzumab (in Cycle 3) was 63.6 μg/mL; thus, the trough concentration of pertuzumab under these conditions did not show any marked difference compared with the concentration following the administration of pertuzumab alone.

Furthermore, in the PPK analysis, "presence or absence of concomitant chemotherapy" was not selected as a covariate affecting the PK of pertuzumab [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)"].

These results suggest that concomitant use with trastuzumab, DTX, etc. does not have any apparent effect on the PK of pertuzumab.

(b) Effect of pertuzumab on PK of other antineoplastic drugs

In Study BO17021, neither time-course change of plasma DTX concentration nor PK parameters of DTX showed any marked difference between administration of DTX alone and concomitant use with pertuzumab [see "4.(ii).A.(4) Foreign phase I study (Study BO17021)"]. In the substudy

of the CLEOPATRA study, no marked difference was observed in peak serum concentration of trastuzumab and trough concentration of trastuzumab, as well as in plasma DTX concentration or PK parameters of DTX between the placebo combination therapy group and the pertuzumab combination therapy group [see "4.(ii).A.(8) Substudy of global phase III study (substudy of the CLEOPATRA study)"]. These results suggest that pertuzumab does not have any marked effect on the PK of trastuzumab or DTX.

Also, pertuzumab is considered not to have any marked effect on the PK of Cape, erlotinib, or GEM [see "4.(ii).A.(5) Foreign phase I study (Study BO17003)" to "4.(ii).A.(7) Foreign phase II study (Study TOC3258g)"].

4.(ii).A.(12).2) Effect of impaired hepatic or renal function on PK of pertuzumab

No clinical study was conducted in patients with hepatic or renal impairment to evaluate the PK of pertuzumab. However, the applicant considers it unnecessary to adjust pertuzumab dose in patients with hepatic or renal impairment because impaired hepatic or renal function is unlikely to affect the PK of pertuzumab, an antibody drug, for the following reasons.

- It is considered that antibody drugs are, like endogenous IgG, incorporated into cells by the pathway mediated by the binding to the target antigen or the pathway independent of binding to the target antigen, where they are degraded, and that metabolism in the liver, such as by CYP450 or UDP-glucuronosyltransferase, renal excretion, and biliary excretion are not directly involved in the elimination of antibody drugs (e.g., *Annu Rev Pharmacol Toxicol.* 2011;51:359-72, *J Pharm Sci.* 2012;101:4367-82).
- In PPK analysis, indices of hepatic function (ALT, AST, total serum bilirubin, ALP) and the index of renal function (serum creatinine) were not identified as covariates for PK parameters (CL, V_c, V_p) of pertuzumab [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)"].
- Using the post-hoc parameters obtained in the above PPK analysis, serum trough concentration under steady state in multiple administration of pertuzumab (loading dose of 840 mg, followed by 420 mg every 3 weeks) was calculated, and data were classified according to the severity of renal impairment (normal, creatinine clearance ≥80 mL/min; mild, <80 mL/min to ≥50 mL/min; moderate, <50 mL/min to ≥30 mL/min; severe, <30 mL/min). As a result, the trough concentration was within a similar range among patients with normal renal function (241 patients), those with mild impairment (158 patients), those with moderate impairment (38 patients), and those with severe impairment (3 patients), which suggested that renal function impairment does not affect the PK of pertuzumab.

4.(ii).B. Outline of the review by PMDA

4.(ii).B.(1) PK of pertuzumab in Japanese and foreign populations

The applicant explained that there were no clear difference in the PK of pertuzumab between Japanese and foreign populations for the following reasons:

- PK data for 5, 10, and 15 mg/kg pertuzumab groups were compared between the Japanese phase I study (Study JO17076) and the foreign phase I study (Study TOC2297g). The dose-adjusted time-course profile of serum pertuzumab concentration was similar between the 2 studies at all doses tested. PK parameter values (calculated by a 2-compartment model using the combined data of 5 to 15 mg/kg groups) in Japanese and foreign subjects were as follows (arithmetic mean ± SD): CL, 273 ± 92.8 and 256 ± 106 mL/day, respectively; V_c, 2830 ± 728 and 2930 ± 643 mL; and V_{ss}, 5220 ± 1240 and 5620 ± 1480 mL; thus the values were similar in Japanese and foreign subjects.
- PK data were compared between Japanese (4 patients) and foreign patients (15 patients) in the substudy of the CLEOPATRA study. The peak serum concentration (arithmetic mean)

in each of Cycle 1 to 15 was 195 to 272 μg/mL in Japanese patients and 181 to 260 μg/mL in foreign patients, showing similar values. The trough concentration (arithmetic mean) in each of Cycle 3 to 9 was 52.8 to 62.3 μg/mL in Japanese patients and 53.6 to 79.9 μg/mL in foreign patients, showing approximately similar values. In Cycles 12 and 15, the trough concentration (arithmetic mean ± SD) was 60.9 ± 26.7 and 59.2 ± 19.0 μg/mL, respectively, in Japanese patients, and 98.7 ± 25.4 and 107 ± 22.7 μg/mL, respectively, in foreign patients, showing higher values in foreign patients. These differences were possibly caused by inter-individual variability, taking account of the reduced number of foreign patients who proceeded to Cycle 12 and subsequent cycles (9 patients in Cycle 12, 8 patients in Cycle 15).

- In PPK analysis, ethnicity (Japanese patients and non-Japanese patients) was not selected as a covariate affecting the PK of pertuzumab [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)"].

PMDA considers as follows:
Based on the results of the Japanese and foreign phase I studies (Studies JO17076 and TOC2297g), there is no clear difference in PK between Japanese and foreign patients following a single dose administration of pertuzumab at the same dose per body weight. Also, based on the results of the substudy of the CLEOPATRA study, there is no clear difference in the peak or trough concentration up to Cycle 9 between Japanese and foreign patients when the recommended clinical dose of pertuzumab (loading dose of 840 mg, followed by 420 mg) is administered every 3 weeks, although the number of Japanese patients studied was limited. In contrast, the above substudy showed higher trough concentrations in Cycle 12 and subsequent cycles in foreign patients compared with Japanese patients. However, since the comparison was conducted between limited numbers of patients, it is difficult to reach a conclusion whether or not the observed difference was due to the ethnic difference between Japanese and foreign patients.

In light of the facts that (a) PK data of Japanese patients treated with multiple administration of pertuzumab at the recommended clinical dose were obtained from only 4 patients, and that (b) the relationship between the exposure level of pertuzumab and its efficacy is unclear [see "4.(ii).B.(3) Relationship between the exposure level of pertuzumab and efficacy or safety"] and the CLEOPATRA study failed to illustrate consistency in the efficacy between the Japanese population and the total population [see "4.(iii).B.(2).4) Efficacy in Japanese patients"], information allowing the evaluation of the difference in PK between Japanese and foreign patients should be collected in future, focusing on PK data obtained from multiple-dose administration at the recommended clinical dose.

4.(ii).B.(2) Determination of dosage and administration
In the foreign phase I study (Study TOC2297g), which was the first clinical study conducted using pertuzumab, the drug was adjusted according to body weight, whereas in subsequent studies including the CLEOPATRA study, pertuzumab was administered at a fixed dose. PMDA asked the applicant to explain the reason for changing the dosage regimen to fixed dosage regimen.

The applicant responded as follows:
In Study TOC2297g, pertuzumab was administered up to 15 mg/kg body weight, but did not reach the maximum tolerated dose. Therefore, in the subsequent clinical studies, pertuzumab was administered by the "loading dose of 840 mg (which corresponds to 12 mg/kg in patients weighing 70 kg), followed by 420 mg (6 mg/kg) every 3 weeks from the second dose," which is the fixed dosage required to reach the target serum trough concentration of 20 μg/mL determined from the results of a xenograft model, based on the PK data of Study TOC2297g. A PPK model was constructed based on PK data obtained from Study TOC2297g and from foreign phase II studies conducted with fixed doses (Studies TOC2689g and BO16934), and simulation was performed. Results showed that the trough concentration at the steady state was similar between

the fixed dose stated above and the body weight-adjusted dose (loading dose of 12.2 mg/kg, followed by 6.1 mg/kg), and was predicted that the trough concentration would exceed the target level in ≥90% of patients under both dosage regimens (*Pharm Res.* 2006;23:1275-84). From these results, the applicant considered that there was no clear evidence supporting the superiority of the weight-adjusted dose to the fixed dose, and adopted the fixed dose in the CLEOPATRA study and other studies.

Next, PMDA pointed out the observation that lean body mass was identified as a covariate affecting the PK of pertuzumab in PPK analysis [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)"], and asked the applicant to explain the appropriateness of using the fixed dose as the proposed dosage and administration.

The applicant responded as follows:
Using the above PPK model, a simulation was performed to estimate the exposure level (C_{max}, AUC, trough concentration) in individual patients at steady state following the administration at the fixed dose (loading dose of 840 mg, followed by 420 mg) every 3 weeks. Comparison by lean body mass (by subpopulation divided by quartile point) showed that although the exposure level decreased with the increase in lean body mass, C_{min} was predicted to exceed the target level in roughly ≥90% of patients. In fact, in clinical studies with fixed dose administration stated above, the observed trough concentration exceeded the target trough level in almost all patients.

In addition, the relationship between body weight and efficacy or safety was investigated based on the results of the CLEOPATRA study. The value for progression-free survival (PFS) assessed by the independent review facility (IRF) was calculated by the baseline body weight (for each of subgroups devided by quartile point). The hazard ratio [95% CI] of PFS was in the pertuzumab combination therapy group to that in the placebo combination therapy group, in the increasing order of body weight, 0.62 [0.42, 0.91], 0.48 [0.32, 0.70], 0.69 [0.47, 1.02], and 0.76 [0.52, 1.09], showing a tendency of increase with body weight. However, the hazard ratio was the lowest in the population with the second lowest body weight, failing to show clear relationship between body weight and efficacy. Furthermore, comparison of adverse events with an incidence of ≥10% and of adverse events of Grade ≥3 among subpopulations by baseline body weights did not show any clear relationship between body weight and safety.

Based on the above results, the applicant considered that there were no clear difference in efficacy or safety among patients with differing body weight, and therefore considered it appropriate to set the fixed dose (loading dose of 840 mg, followed by 420 mg) as the proposed dosage and administration.

PMDA considers that, although the clinical significance of serum pertuzumab concentration exceeding the target trough concentration (20 μg/mL) is unclear [see "4.(ii).B.(3) Relationship between the exposure level of pertuzumab and efficacy or safety"], there is no necessity to adjust the dose for body weight, and accepted the applicant's response.

4.(ii).B.(3) Relationship between the exposure level of pertuzumab and efficacy or safety

PMDA asked the applicant to explain the relationship between the exposure level of pertuzumab and efficacy or safety.

The applicant responded as follows:
In the CLEOPATRA study, PK of pertuzumab was investigated in only 20 patients in the pertuzumab combination therapy group. However, since there are no other clinical data available to allow the investigation of the relationship between the exposure level of pertuzumab and efficacy or safety, the predicted exposure level was calculated for all patients enrolled in the

CLEOPATRA study using the PPK model [see "4.(ii).A.(9) Analysis of population pharmacokinetics (PPK)"], and the relationship with efficacy or safety was analyzed in an exploratory manner.

4.(ii).B.(3).1) Relationship between exposure level of pertuzumab and efficacy

The relationship between the predicted exposure level of pertuzumab by patient (C_{max}, AUC, trough concentration) and (a) PFS assessed by IRF or (b) overall survival (OS) was plotted on a scatter diagram and evaluated visually. As a result, no clear relationship was observed between the predicted exposure level and PFS (IRF assessment) or OS.

4.(ii).B.(3).2) Relationship between exposure level of pertuzumab and safety

Patients were divided into subgroups by quartile point of the predicted exposure level of pertuzumab (C_{max}, AUC, trough concentration), and adverse events were tabulated for each subgroup. Results showed no clear relationship between the predicted exposure level and the incidence of adverse events.

PMDA considers as follows:

Although the presented study results did not show any clear relationship between the exposure level of pertuzumab and efficacy or safety, since the results were obtained using information including the predicted exposure level, it is difficult to reach a conclusion on the relationship between the exposure level and efficacy or safety based solely on these results. The relationship should be investigated in more close detail in future when new clinical study data are accumulated.

4.(ii).B.(4) Anti-pertuzumab antibody

PMDA asked the applicant to explain the possible effect of anti-pertuzumab antibody on the safety and efficacy of pertuzumab.

The applicant responded as follows:

As regards the effect of anti-pertuzumab antibody on the safety of pertuzumab, the antibody was detected in 2 of 366 patients (0.5%) in a total of 11 phase I and phase II studies, and these patients experienced Grade 3 hypersensitivity reaction, for which a causal relationship to anti-pertuzumab antibody was not ruled out. In the pertuzumab combination therapy group in the CLEOPATRA study, 3 patients among those positive for anti-pertuzumab antibody had hypersensitivity reaction, but these events were considered not related to the antibody. These results suggest that, although there are only limited data on anti-pertuzumab antibody-positive patients, the incidence of the adverse events possibly caused by the antibody is low and that the anti-pertuzumab antibody is unlikely to have a marked effect on the safety of pertuzumab.

As regards the effect of anti-pertuzumab antibody on the efficacy of pertuzumab, the effect was investigated based on the results of the CLEOPATRA study. However, anti-pertuzumab antibodies were positive in only 11 of 386 patients (2.8%) in the pertuzumab combination therapy group, which precluded any conclusion on the effect of anti-pertuzumab antibody on the efficacy of the drug. In the pertuzumab combination therapy group, the median PFS (IRF assessment) tended to be shorter in anti-pertuzumab antibody-positive patients than in negative patients, but a similar tendency was also observed in the placebo combination therapy group. In addition, PFS tended to be prolonged by the addition of pertuzumab even in anti-pertuzumab antibody-positive patients as observed in negative patients.

PMDA considers as follows:

As regards the effect of anti-pertuzumab antibody on the safety of pertuzumab, taking into account that, in the CLEOPATRA study, the incidence of hypersensitivity/anaphylaxis did not tend to be higher in the pertuzumab combination therapy group compared with the placebo combination therapy group in the total population including anti-pertuzumab antibody-negative patients [see

"4.(iii).B.(3).8) Hypersensitivity/anaphylaxis"], the possibility of anti-pertuzumab antibody causing a safety problem in clinical use is low. However, it should be noted that, in the clinical studies submitted, (i) there were only a limited number of anti-pertuzumab antibody-positive patients in the pertuzumab group and (ii) some antibody-positive patients experienced hypersensitivity reaction. As regards the effect of the antibody on the efficacy of pertuzumab, it is difficult to reach a conclusion because, in the CLEOPATRA study, (i) the number of anti-pertuzumab antibody-positive patients in the pertuzumab combination therapy group were limited and (ii) it is possible that anti-trastuzumab antibody-positive patients may have been included in anti-pertuzumab antibody-positive patients.

With consideration given to the above points and the following reasons, it is necessary to continue to collect information on the effect of anti-pertuzumab antibody on the safety of pertuzumab, etc., and to take appropriate measures such as providing the relevant information if new findings become available.

- The effect of anti-pertuzumab antibody on the PK of pertuzumab is unclear [see "4.(ii).A.(11) Anti-pertuzumab antibody"].
- By the assay methods for anti-pertuzumab antibody employed in the clinical studies, pertuzumab and anti-pertuzumab antibody in test samples may affect the results of an assay [see "4.(i).B Assay method for anti-pertuzumab antibody"].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

As the efficacy and safety evaluation data, the results from a total of 4 studies including a Japanese phase I study, a global phase III study, a foreign phase I study, and a foreign phase II study were submitted. As the reference data, the results from a total of 12 studies including 3 phase I studies, 8 phase II studies, and 1 extended study, all conducted in foreign countries, were submitted.

List of clinical studies on efficacy and safety

Category	Region	Study	Phase	Study population	No. of subjects enrolled	Outline of dosage and administration	Primary endpoints
Evaluation	Japan	JO17076	I	Patients with solid tumors	18	Pertuzumab (5, 10, 15, 20, or 25 mg/kg) every 3 weeks	Safety PK
	Global	WO20698 [CLEOPATRA]	III	Patients with distant metastatic or HER2-positive recurrent breast cancer who had not received chemotherapy	808 (a) 402 (b) 406	In combination with trastuzumab (loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks) and DTX (75 mg/m^2 every 3 weeks), (a) pertuzumab (loading dose of 840 mg, followed by 420 mg) or (b) placebo, every 3 weeks	Efficacy Safety
	Foreign	TOC2297g	I	Patients with solid tumors	21	Pertuzumab (0.5, 2.0, 5.0, 10.0, or 15.0 mg/kg) every 3 weeks	Safety PK
		BO17929	II	Patients with distant metastatic or HER2-positive recurrent breast cancer who had received chemotherapy with trastuzumab	95 (a) 66 (b) 29	(a) Cohorts 1 and 2: Pertuzumab (loading dose of 840 mg, followed by 420 mg) in combination with trastuzumab (at the same dosage regimen as that in prior treatment) every 3 weeks* (b) Cohort 3: Pertuzumab (loading dose of 840 mg, followed by 420 mg) every 3 weeks	Efficacy Safety
Reference	Foreign	BO17003	I	Patients with solid tumors	19	Pertuzumab (1050 mg) in combination with Cape (825, 1000, or 1250 mg/m^2 twice daily orally for 14 days, followed by a 7-day withdrawal) at 3-week intervals	Safety PK
		BO17021	I	Patients with solid tumors	19	Pertuzumab (1050 mg throughout, or loading dose of 840 mg, followed by 420 mg) in combination with DTX (60, 75, or 100 mg/m^2) every 3 weeks	Safety PK
		WO20697 [NEOSPHERE]	II	Patients with locally advanced, inflammatory or HER2-positive early breast cancer	417 (a) 107 (b) 107 (c) 107 (d) 96	(a) Group A: Concomitant use with trastuzumab and DTX (b) Group B: Pertuzumab (loading dose of 840 mg, followed by 420 mg) in combination with trastuzumab and DTX every 3 weeks (c) Group C: Pertuzumab (loading dose of 840 mg, followed by 420 mg) in combination with trastuzumab every 3 weeks (d) Group D: Pertuzumab (loading dose of 840 mg, followed by 420 mg) in combination with DTX every 3 weeks • Trastuzumab: Loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks • DTX: 75 mg/m^2 every 3 weeks	Safety
		BO16934	II	Patients with distant metastatic or HER2 low-expressing recurrent breast cancer who had received chemotherapy	79 (a) 41 (b) 38	(a) Group A: Pertuzumab (loading dose of 840 mg, followed by 420 mg) every 3 weeks (b) Group B: Pertuzumab (1050 mg) every 3 weeks	Safety
		TOC2689g	II	Patients with ovarian cancer	129 (a) 65 (b) 64	(a) Cohort 1: Same as group A in Study BO16934 (b) Cohort 2: Same as group B in Study BO16934	Safety
		TOC2572g	II	Patients with non-small cell lung cancer	51	Same as group A in BO16934 study	Safety
		BO17004	II	Patients with prostate cancer	68 (a) 35 (b) 33	(a) Cohort 1: Same as group A in BO16934 study (b) Cohort 2: Same as group B in BO16934 study	Safety
		TOC2682g	II	Patients with prostate cancer	42	Same as group A in Study BO16934	Safety

Category	Region	Study	Phase	Study population	No. of subjects enrolled	Outline of dosage and administration	Primary endpoints
		BO17931	II	Patients with ovarian cancer	152 (a) 75 (b) 77	(a) Group A: CBDCA and PTX or GEM (b) Group B: Pertuzumab (loading dose of 840 mg, followed by 420 mg) every 3 weeks in combination with CBDCA and PTX or GEM • CBDCA: On Day 1, AUC 5 (in combination with PTX) or AUC 4 (in combination with PTX) every 3 weeks • PTX: 175 mg/m^2 on Day 1 every 3 weeks • GEM: 1000 mg/m^2 on Days 1 and 8 every 3 weeks	Safety
		TOC3258g	II	Patients with ovarian cancer	131 (a) 65 (b) 66	In combination with GEM (800 mg/m^2 on Days 1 and 8 every 3 weeks), (a) pertuzumab (loading dose of 840 mg, followed by 420 mg) or (b) placebo, every 3 weeks	Safety
		WO20024	I	Patients with non-small cell lung cancer	17	Pertuzumab (loading dose of 840 mg, followed by 420 mg) in combination with erlotinib hydrochloride (100 or 150 mg, once daily oral administration) every 3 weeks	Safety PK
		TOC2664g	Extended administration	Patients with ovarian cancer	3	The same dosage regimen as in Study TOC2689g or TOC3258	Safety

DTX: docetaxel hydrate, Cape: capecitabine, CBDCA: carboplatin, PTX: paclitaxel, GEM: gemcitabine hydrochloride, *: In Cycle 1, trastuzumab was administered on Day 1 and pertuzumab on Day 2, and in the subsequent cycles, both drugs were administered on Day 1 of each cycle.

The outline of each clinical study was as described below.

The main adverse events excluding deaths observed in individual clinical studies are presented in "4.(iv) Adverse events observed in clinical studies" and results of PK are presented in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

[Evaluation data]

(1) Japanese clinical study

Japanese phase I study (5.3.3.2-1, Study JO17076 [June 2004 to August 2005])

An open-label, uncontrolled study was conducted at a single center in Japan involving patients with advanced solid tumors (target sample size, 18-30) to investigate the MTD, safety, and PK of pertuzumab.

Pertuzumab (5, 10, 15, 20, 25 mg/kg) was to be intravenously administered every 3 weeks.

All of the 18 patients enrolled into the study received pertuzumab and were included in the safety analysis.

The treatment period up to the end of Cycle 1 was defined as the period for dose limiting toxicity (DLT) evaluation, where tolerability, etc., was evaluated. As a result, DLT was observed only in 1 of 6 patients in the 25 mg/kg group (gamma-glutamyltransferase increased), with MTD not reached.

As regards safety, no death occurred during the treatment period or during the follow-up (until 28 days after the last administration of the study drug).

(2) Global clinical study

Global phase III study (5.3.5.1-1, 5.3.5.1-2, 5.3.3.2-3, 5.3.4.2-1; Study WO20698 [CLEOPATRA] [February 2008 – ongoing (data cut-off date, May 13, 2011)])

A double-blind, randomized, comparative study was conducted in 204 centers in 25 countries including Japan involving patients with distant metastatic or recurrent HER2-positive breast cancer who had not received chemotherapy* (target sample size, 800) to investigate the efficacy and safety of concomitant use of pertuzumab or placebo added to trastuzumab/DTX combination therapy.

*: Patients who had not received treatment with antineoplastic drugs such as EGFR inhibitors or anti-HER2 antibodies, or treatments with ≥2 regimens of hormone drugs

Pertuzumab (loading dose of 840 mg, followed by 420 mg) or placebo was to be intravenously administered every 3 weeks in combination with trastuzumab (loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks) and DTX* (75 mg/m^2 every 3 weeks). In Cycle 1, pertuzumab and placebo were to be administered on Day 1, and trastuzumab and DTX on Day 2. If tolerability was confirmed in Cycle 1, all the three drugs could be administered on Day 1 in Cycle 2 and subsequent cycles. Even if DTX was discontinued because of adverse events, administration of pertuzumab or placebo in combination with trastuzumab could be continued until disease progression or occurrence of unacceptable adverse events. However, if either of pertuzumab, placebo, or trastuzumab was discontinued, all other study drugs were also to be discontinued.

*: DTX could be increased up to 100 mg/m^2 at the discretion of the investigator if, for a longer period than one cycle, no toxicity events specified in the protocol (febrile neutropenia, Grade 4 neutropenia lasting for >5 days, neutrophil count decrease to <100/μL for >1 day, other non-hematological toxicity of Grade >2) occur and symptoms observed were controlable. Before Cycle 6, DTX was to be discontinued only if disease progression or unacceptable adverse events occurred, and in Cycle 6 and the subsequent cycles, DTX could be continued at the discretion of the investigator.

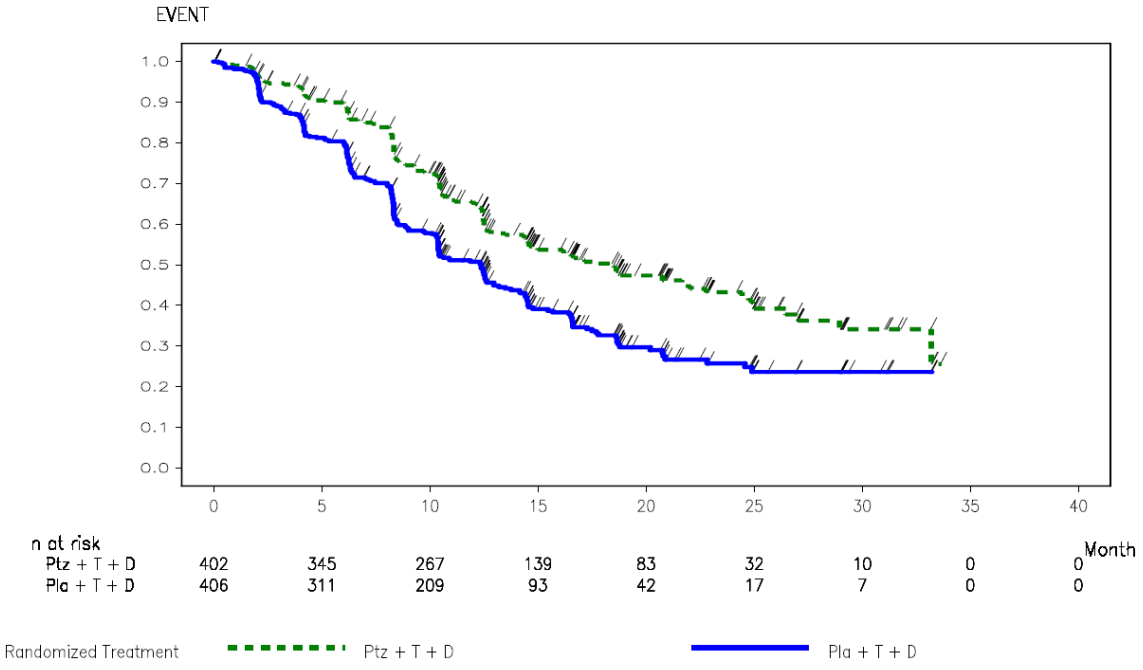
All of the 808 patients enrolled into the study (402 patients in the pertuzumab combination therapy group, 406 patients in the placebo combination therapy group) were included in the intent-to-treat (ITT) population for efficacy analysis. Of patients in the ITT population, 4 patients (2 patients in the pertuzumab combination therapy group, 2 patients in the placebo combination therapy group) did not receive the study drug. Eight patients assigned to the placebo combination therapy group received the treatment of the pertuzumab combination therapy, and 1 patient assigned to the pertuzumab combination therapy group received the treatment of the placebo combination therapy. As a result, a total of 804 patients who received the legitimate treatment for the respective group (407 patients in the pertuzumab combination therapy group, 397 patients in the placebo combination therapy group) were included in the safety analysis.

As regards the efficacy, the final analysis of PFS based on the assessment of IRF, which was the parameter defined as the primary endpoint of the study, was performed. For testing the hypothesis defined before the initiation of the study, the superiority of the pertuzumab combination therapy group over the placebo combination therapy group, was assessed. Results of the final analysis of PFS (IRF assessment) and the Kaplan-Meier curve in each group were as shown in the table and figure below.

Final analysis results of PFS (ITT population, IRF assessment, data cut-off date May 13, 2011)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	402	406
Number of deaths or aggravation (%)	191 (47.5)	242 (59.6)
Median [95% CI] (months)	18.5 [14.6, 22.8]	12.4 [10.4, 13.2]
Hazard ratio*1 [95% CI]	0.62 [0.51, 0.75]	
P value (two-sided) *2	< 0.0001	

*1: Cox proportional hazard model adjusted for stratification factors (prior treatment status and region)
*2: Stratified log-rank test (stratified by prior treatment status and region)



Kaplan-Meier curve of PFS (ITT population, IRF assessment, data cut-off May 13, 2011)

As regards safety, death occurred in 10 patients in the pertuzumab combination therapy group and in 12 patients in the placebo combination therapy group during the treatment period or within 42 days after the last dose. The causes of these deaths, except those due to disease progression (2 patients in the pertuzumab combination therapy group, 3 patients in the placebo combination therapy group) were, in the pertuzumab combination therapy group, febrile neutropenia (3 patients), sepsis, respiratory tract infection, somnolence, death, and intestinal perforation (1 patient each); and in the placebo combination therapy group, intestinal perforation and myocardial infarction (2 patients each), and pneumonia, sepsis, gastrointestinal haemorrhage, cerebrovascular accident, and hepatic failure (1 patient each). A causal relationship to pertuzumab or placebo could not be ruled out for febrile neutropenia in 3 patients and respiratory tract infection and somnolence in 1 patient each in the pertuzumab combination therapy group, and for intestinal perforation in 2 patients and myocardial infarction, pneumonia, sepsis, and cerebrovascular accident in 1 patient each in the placebo combination therapy group.

(3) Foreign clinical studies

1) Foreign phase I study (5.3.3.2-2, Study TOC2297g [November 2001 to August 2003])

An open-label, uncontrolled study was conducted in 2 centers overseas involving patients with advanced solid tumors (target sample size, 18-30) to investigate the MTD, safety, and PK of

pertuzumab.

Pertuzumab (0.5, 2.0, 5.0, 10, 15 mg/kg) was to be intravenously administered every 3 weeks.

All of the 21 patients enrolled into the study received pertuzumab and were included in the safety analysis.

The treatment period up to the end of Cycle 1 was defined as the period for DLT evaluation, where tolerability, etc., was evaluated. As a result, DLT was observed only in 1 of 8 patients of the 15 mg/kg group (gastrointestinal haemorrhage), with MTD not reached.

As regards safety, death occurred in 1 patient of the 0.5 mg/kg group during the treatment period or within 28 days after the last administration. The cause of the death was disease progression, and its causal relationship to pertuzumab was ruled out.

2) Foreign phase II study (5.3.5.2-1, 5.3.5.2-2; Study BO17929 [May 2006 to November 2010])

An open-label, uncontrolled study was conducted in 16 centers overseas involving patients with distant metastatic or recurrent HER2-positive breast cancer who had received chemotherapy with trastuzumab (target sample sizes; 58 patients in cohorts 1 and 2, 27 patients in cohort 3) to evaluate the efficacy and safety of pertuzumab.

In cohorts 1 and 2, pertuzumab (loading dose of 840 mg, followed by 420 mg) was to be intravenously administered every 3 weeks in combination with trastuzumab (the same dosage regimen as in their prior treatment, i.e., loading dose of 4 mg/kg followed by 2 mg/kg every 1 week, or loading dose of 8 mg/kg followed by 6 mg/kg every 3 weeks). In Cycle 1 of cohorts 1 and 2, trastuzumab was to be administered on Day 1 and pertuzumab on Day 2 and, in Cycle 2 and the subsequent cycles in cohorts 1 and 2, both drugs were to be administered on Day 1 of each cycle. In cohort 3, pertuzumab (loading dose of 840 mg, followed by 420 mg) was to be intravenously administered every 3 weeks and, if treatment effect was not observed or disease progression occurred, concomitant use of trastuzumab was permitted.

All of the 95 patients enrolled into the study (66 patients in cohorts 1 and 2, 29 patients in cohort 3) received pertuzumab and were included in the efficacy and safety analyses.

As regards efficacy, the response rate (the primary endpoint) and the clinical benefit response (CBR) rate were as shown in the table below.

Best overall effect, response rate, CBR rate (RECIST, data cut-off date, November 30, 2010)

Best overall effect	Cohorts 1 and 2 N = 66	Cohort 3 (monotherapy period) N = 29
Complete response (CR)	4 (6.1%)	0
Partial response (PR)	12 (18.2%)	1 (3.4%)
Stable disease (SD)	17 (25.8%)	2 (6.9%)
Disease progression (PD)	33 (50.0%)	26 (89.7%)
Unevaluable/no evaluation data	0	0
Response rate[*1] [80% CI]	24.2% [17.4, 32.3]	3.4% [0.4, 12.8]
CBR rate[*2] [80% CI]	50.0% [41.5, 58.5]	10.3% [3.9, 21.6]

*1: CR + PR, *2: CR + PR + SD that lasted for ≥8 cycles

Death occurred in 1 patient in cohorts 1 and 2, and 1 patient in cohort 3 during the treatment period or within 28 days after the last administration. The causes of the deaths were coma hepatic in the patient in cohorts 1 and 2 and hepatorenal failure in the patient in cohort 3. A causal

relationship to pertuzumab was ruled out for both events.

[Reference data]
Foreign clinical studies

1) Foreign phase I study (5.3.3.2-4, Study BO17003 [January 2004 to May 2005])

An open-label, uncontrolled study was conducted in 2 centers overseas involving patients with advanced solid tumors (target sample size, 15-18) to investigate the MTD, safety, and PK in concomitant use of pertuzumab with Cape.

Of 19 patients enrolled into the study, 18 patients who received pertuzumab were included in the safety analysis. Death during the treatment period or within 4 weeks after the last dose occurred in 1 patient in the pertuzumab/Cape 825 mg/m^2 group. The death was due to disease progression, and its causal relationship to pertuzumab was ruled out.

2) Foreign phase I study (5.3.3.2-5, Study BO17021 [April 2004 to January 2006])

An open-label, uncontrolled study was conducted in 2 centers overseas involving patients with advanced solid tumors (target sample size, 15-18) to investigate the MTD, safety, and PK in concomitant use of pertuzumab with DTX.

All of the 19 patients enrolled into the study received pertuzumab. Death during the treatment period or within 4 weeks after the last dose occurred in 1 patient in the pertuzumab 420 mg/DTX 100 mg/m^2 group. The death was due to disease progression, and its causal relationship to pertuzumab was ruled out.

3) Foreign phase II study (5.3.5.4-1, Study WO20697 [NEOSPHERE] [December 2007 – ongoing (data cut-off date, December 22, 2009)])

An open-label, randomized study was conducted in 59 centers overseas involving patients with locally advanced, inflammatory or HER2-positive early breast cancer (target sample size, 400) to investigate the efficacy and safety of trastuzumab plus DTX (group A), pertuzumab and trastuzumab plus DTX (group B), pertuzumab and trastuzumab (group C), and pertuzumab plus DTX (group D).

Of 417 patients enrolled into the study, 416 patients treated with the study drugs (107 patients in the group A, 107 patients in the group B, 108 patients in the group C, 94 patients in the group D) were included in the safety analysis. Death during the treatment period or within 28 days after the last dose occurred in 1 patient in the group B. The death was caused by hepatitis fulminant, and its causal relationship to the study drug could not be ruled out.

4) Foreign phase II study (5.3.5.4-2, Study BO16934 [February 2003 to December 2004])

An open-label, randomized study was conducted in 18 centers overseas involving patients with HER2 low-expressing (negative on FISH, and 0/1+/2+ by IHC), distant metastatic or recurrent breast cancer (target sample size, 120) to investigate the efficacy and safety of pertuzumab (group A, loading dose of 840 mg, maintenance dose of 420 mg; group B, 1050 mg).

Of 79 patients enrolled into the study, 78 patients who received pertuzumab (41 patients in the group A, 37 patients in the group B) were included in the safety analysis. Death during the treatment period or within 7 weeks after the last dose occurred in 3 patients in the group A and in 2 patients in the group B. The deaths were all due to disease progression, and their causal relationship to pertuzumab was ruled out.

5) Foreign phase II study (5.3.5.4-3, Study TOC2689g [May 2003 to July 2004])
An open-label, uncontrolled study was conducted in 13 centers overseas involving patients with refractory advanced or recurrent ovarian cancer (target sample size, 120) to investigate the efficacy and safety of pertuzumab.

Of 129 patients enrolled into the study, 123 patients who received pertuzumab (61 patients in cohort 1, 62 patients in cohort 2) were included in the safety analysis. Death during the treatment period or within 30 days after the last dose occurred in 3 patients in cohort 1 and 5 patients in cohort 2. The deaths were all due to disease progression, and their causal relationship to pertuzumab was ruled out.

6) Foreign phase II study (5.3.5.4-4, Study TOC2572g [July 2003 to April 2005])
An open-label, uncontrolled study was conducted in 10 centers overseas involving patients with recurrent NSCLC (target sample size, 40) to investigate the efficacy and safety of pertuzumab.

Of 51 patients enrolled into the study, 43 patients who received pertuzumab were included in the safety analysis. Death during the treatment period or within 28 (±7) days after the last dose occurred in 5 patients. Except 3 deaths due to disease progression, the causes of the deaths were pulmonary embolism/sepsis/pneumonia and acute respiratory distress syndrome in 1 patient each. For acute respiratory distress syndrome, a causal relationship to pertuzumab could not be ruled out.

7) Foreign phase II study (5.3.5.4-5, Study BO17004 [September 2003 to March 2005])
An open-label, uncontrolled study was conducted in 9 centers overseas involving patients with hormone-refractory prostate cancer who had not received chemotherapy (target sample size, 100) to investigate the efficacy and safety of pertuzumab.

All 68 patients enrolled into the study (35 patients in cohort A, 33 patients in cohort B) received pertuzumab. Death during the treatment period or within 7 weeks after the last dose occurred in 4 patients of cohort A. Except 3 deaths due to disease progression, the death of the remaining 1 case was due to haemolytic uraemic syndrome, and its causal relationship to pertuzumab could not be ruled out.

8) Foreign phase II study (5.3.5.4-6, Study TOC2682g [April 2003 to October 2004])
An open-label, uncontrolled study was conducted in 6 centers overseas involving patients with castration-resistant prostate cancer (target sample size, 45) to investigate the efficacy and safety of pertuzumab.

Of 42 patients enrolled into the study, 41 patients who received pertuzumab were included in the safety analysis. Death during the treatment period or within 30 days after the last dose occurred in 1 patient. The death was due to disease progression, and its causal relationship to pertuzumab was ruled out.

9) Foreign phase II study (5.3.5.4-7, 5.3.5.4-8; Study BO17931 [December 2005 to March 2011])
An open-label, uncontrolled study was conducted in 27 centers overseas involving patients with platinum antineoplastic drug-sensitive, recurrent ovarian cancer (target sample size, 148) to investigate the efficacy and safety of pertuzumab.

Of 152 patients enrolled into the study, 149 patients who received the study drug (74 patients in the group A, 75 patients in the group B) were included in the safety analysis. Death during the treatment period or within 28 days after the last dose occurred in 1 patient in group A and 2 patients in group B. Except 2 deaths due to disease progression (1 patient each in groups A and

B), the death in 1 patient in group B was caused by gastrointestinal haemorrhage, and its causal relationship to pertuzumab could not be ruled out.

10) Foreign phase II study (5.3.5.4-9, Study TOC3258g [January 2005 to September 2007])

A double-blind, randomized study was conducted in 30 centers overseas involving patients with platinum antineoplastic drug-resistant ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer (target sample size, 130) to investigate the efficacy and safety of concomitant use of pertuzumab or placebo with GEM.

Of 131 patients enrolled into the study, 130 patients who received pertuzumab or placebo (65 patients in the pertuzumab group, 65 patients in the placebo group) were included in the safety analysis. Death during the treatment period or within 30 days after the last dose occurred in 3 patients in the pertuzumab group and 3 patients in the placebo group. Except 3 deaths (2 patients in the pertuzumab group, 1 patient in the placebo group) due to disease progression, the causes of deaths were renal failure acute in 1 patient in the pertuzumab group, sepsis and infection in 1 patient each in the placebo group, and their causal relationship to pertuzumab or placebo was ruled out.

11) Foreign phase I study (5.3.5.4-10, Study WO20024 [September 2006 to December 2008])

An open-label, uncontrolled study was conducted in 3 centers overseas involving patients with locally advanced or distant metastatic NSCLC who had received cancer treatment of ≥1 regimen (target sample size, 15) to investigate the MTD and safety in concomitant use of pertuzumab with erlotinib.

Of 17 patients enrolled into the study, 15 patients who received pertuzumab (6 patients in cohort 1, 9 patients in cohort 2) were included in the safety analysis. Death during the treatment period or within 28 days after the last dose occurred in 1 patient in cohort 2. The death was a sudden death, and its causal relationship to pertuzumab was ruled out.

12) Foreign extended study (5.3.5.4-11, Study TOC2664g [May 2005 to October 2007])

An open-label, uncontrolled study was conducted in patients who had received pertuzumab alone or in combination with other drugs in the phase II study conducted by Genentech Inc (target sample size, 100) to evaluate the safety of pertuzumab.

All of the 3 patients enrolled into the study received pertuzumab. No death occurred during the treatment period or within 30 days after the last dose.

4.(iii).B. Outline of the review by PMDA

4.(iii).B.(1) Data for review

PMDA determined that the most important clinical study for evaluating the efficacy and safety of pertuzumab, among the submitted data, is the global phase III study (CLEOPATRA) involving patients with distant metastatic or recurrent HER2-positive breast cancer who had not received chemotherapy, and performed evaluation mainly based on the data of this study.

4.(iii).B.(2) Efficacy

As a result of the following review, PMDA has concluded that the efficacy of pertuzumab in patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy has been demonstrated.

4.(iii).B.(2).1) Use of control group

PMDA asked the applicant to explain the reason for using a placebo/trastuzumab/DTX

combination therapy group as the control group in the CLEOPATRA study.

The applicant responded as follows:
Textbooks available in Japan and foreign countries (*DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 8th ed. PA, USA: Lippincott Williams & Wilkins; 2008, *Clinical Oncology update*. 1st ed. Nankodo Co., Ltd.; 2006) state that concomitant use of trastuzumab and chemotherapy is useful for treating patients with HER2-positive distant metastatic or recurrent breast cancer who had not received chemotherapy, and recommend DTX, paclitaxel (PTX), vinorelbine ditartrate, and platinum antineoplastic drugs as chemotherapeutic agents to be concomitantly administered. Also, randomized comparative studies have demonstrated the clinical usefulness of the two taxane antineoplastic drugs, DTX and PTX, in combination with trastuzumab in patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy (*J Clin Oncol*. 2005;23:4265-74, *N Engl J Med*. 2001;344:783-92).

Based on the above, a taxane antineoplastic drug was selected as the chemotherapeutic agent to be concomitantly administered in the CLEOPATRA study. In the treatment of breast cancer, PTX is commonly administered every week whereas DTX is administered every 3 weeks. Therefore, DTX was selected for convenience. Thus, placebo/trastuzumab/DTX combination therapy group was selected as the control group for the CLEOPATRA study.

PMDA accepted the response of the applicant.

4.(iii).B.(2).2) Efficacy endpoints
PMDA asked the applicant to explain the reason for selecting PFS as the primary efficacy endpoint of the CLEOPATRA study.

The applicant responded as follows:
Although, in general, there is a limitation for using PFS as a surrogate endpoint for OS, a substantially prolonged PFS has a clinical significance because it (i) indicates the prolongation of the period taken for the disease to progress and of the period free of symptoms associated with disease progression, and (ii) allows delay in the initiation of the next chemotherapy (*J Clin Oncol.* 2008;26:1987-92, *J Clin Oncol.* 2009;27:2874-80).

Also, PFS is generally superior to OS since it allows evaluation of the efficacy in a smaller number of patients within a shorter observation period, and that it can compare the efficacy of drugs in a more genuine manner because it is not affected by the treatment performed after disease progression (European Medicines Agency. Evaluation of Medicines for Human Use. Committee for Medicinal Products for Human Use. Guideline on the Evaluation of Anticancer Medicinal Products in Man. London, 14 December 2005).

The guidance of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on the evaluation of antineoplastic drugs require, as conditions for accepting PFS as the primary endpoint, that (a) OS be included as a secondary endpoint and the treatment effect of OS be estimated at a sufficient precision to ensure the non-inferiority of the active drug group to the control group, and that (b) the clinical study be designed in an appropriate manner to minimize the risk of bias in the evaluation of PFS [see "U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2007," and "European Medicines Agency. Evaluation of Medicines for Human Use. Committee for Medicinal Products for Human Use. Guideline on the Evaluation of Anticancer Medicinal Products in Man. London, 14 December 2005"].

PMDA considers as follows:
Prolongation of PFS in treatment of patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy has a certain clinical significance, and PFS could possibly evaluate the efficacy of drugs. However, given that the true objective of the treatment is to prolong the life of patients, PMDA has concluded that the efficacy should be evaluated not only by PFS data but also in a comprehensive manner by including the data of OS.

4.(iii).B.(2).3) Results of efficacy evaluation

In the CLEOPATRA study, superiority of the pertuzumab combination therapy group to the placebo combination therapy group in PFS based on the IRF assessment was evaluated [see "4.(iii).A.[evaluation data] (2) Global study"]. PFS results based on the assessment made by the attending physician, performed as sensitivity analysis, were as shown in the table below.

Results of final analysis of PFS
(ITT population, assessed by attending physician, data cut-off date, May 13, 2011)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	402	406
Number of deaths or aggravations (%)	201 (50.0)	250 (61.6)
Median [95% CI] (months)	18.5 [16.1, 21.1]	12.4 [10.4, 13.2]
Hazard ratio *1 [95% CI]	0.65 [0.54, 0.78]	
P value (two-sided) *2	< 0.0001	

*1: Cox proportional hazard model adjusted for stratification factors (prior treatment status and region)
*2: Stratified long-rank test (stratified by prior treatment status and region)

A planned interim analysis was performed on OS, which was one of the secondary endpoints, at the final time point for PFS analysis (data cut-off date, May 13, 2011). Efficacy evaluation was performed using O'Brien-Fleming α-spending function based on the method of Lan and DeMets. As a result, the hazard ratio of the pertuzumab combination therapy group to the placebo combination therapy group [95% CI] was 0.64 [0.47, 0.88], failing to meet the predefined efficacy criteria ($P = 0.0050$, two-sided significance level of 0.0012).

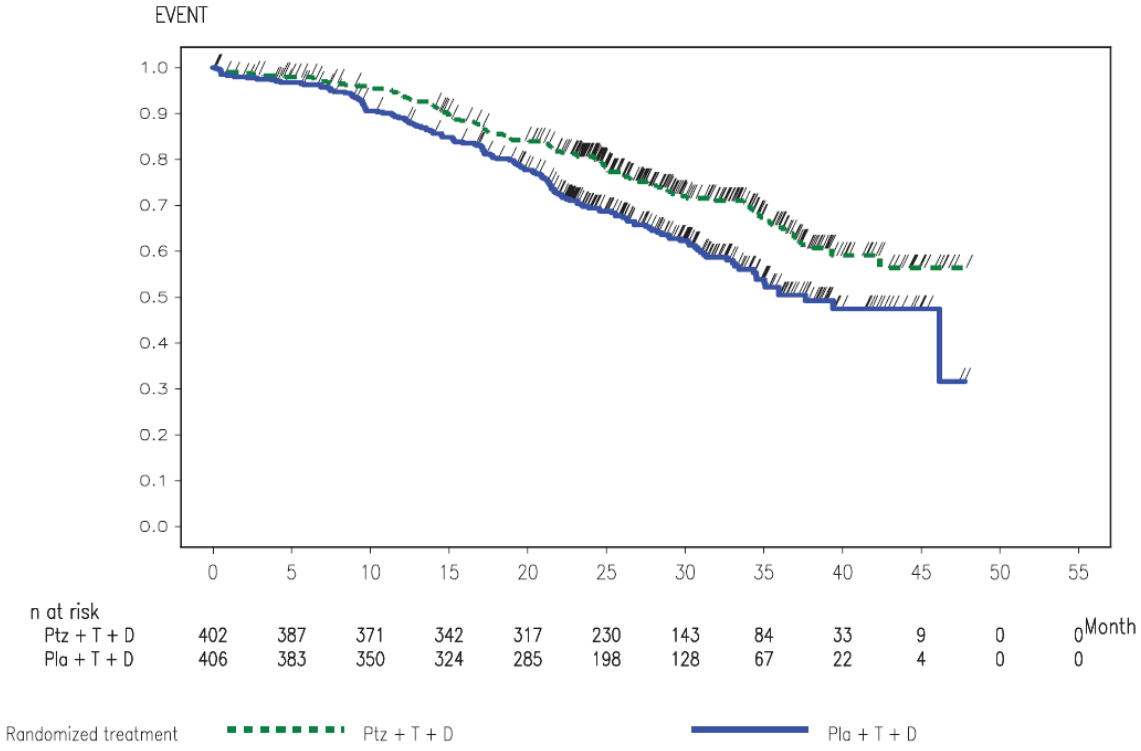
In the course of the review of pertuzumab at EMA, the Agency required the applicant to submit the results of an additional analysis of OS for the reason that the number of the events was insufficient in the interim analysis of OS performed at the time point of the last analysis of PFS. Therefore, the protocol and the statistical analysis plan of the CLEOPATRA study were amended ([redacted], 20[redacted]) and the second interim analysis of OS was performed (data cut-off date, May 14, 2012). Results fulfilled the efficacy criteria (two-sided significance level of 0.0138) (the table below).

As regards to the OS, since the second interim analysis showed prolongation of OS, patients who had been continuing the treatment in the placebo combination therapy group were given the option of switching to pertuzumab. The study is being continued until the target number of 385 events are observed.

Results of the second interim analysis on OS (ITT population, data cut-off date, May 14, 2012)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	402	406
Death (%)	113 (28.1)	154 (37.9)
Median [95% CI] (months)	NE [42.4, NE]	37.6 [34.3, NE]
Hazard ratio*1 [95% CI]	0.66 [0.52, 0.84]	
P value (two-sided) *2	0.0008*3	

NE: not estimable
*1: Cox proportional hazard model adjusted for stratification factors (prior treatment status and region)
*2: Stratified long-rank test (stratified by prior treatment status and region)
*3: Efficacy criterion was set at two-sided significance level of 0.0138.



Kaplan-Meier curves of OS (ITT population, data cut-off date, May 14, 2012)

PMDA considers as follows:
The CLEOPATRA study demonstrated (a) the superiority of the pertuzumab combination therapy group to the placebo combination therapy group in terms of PFS (IRF assessment) and (b) prolongation of OS in the pertuzumab combination therapy group compared with the placebo combination therapy group, as shown in the results of the second interim analysis. Therefore, PMDA has concluded that the efficacy of pertuzumab has been demonstrated in patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy.

4.(iii).B.(2).4) Efficacy in Japanese patients

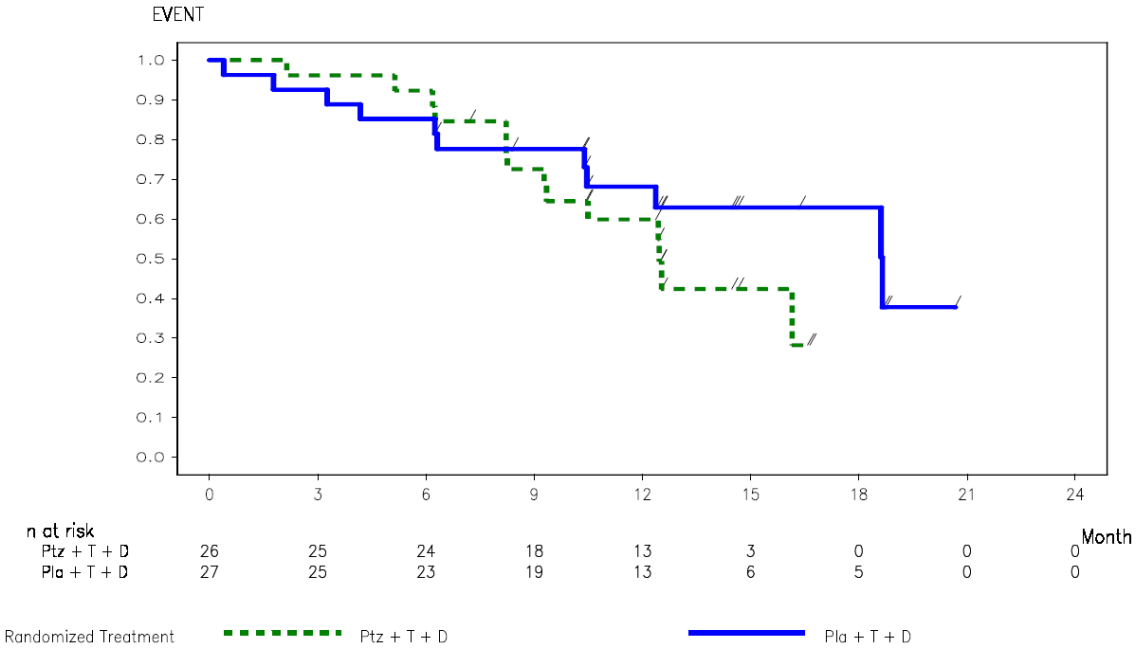
In the CLEOPATRA study, it had been pre-specified that results of PFS (IRF assessment), the primary endpoint, in the Japanese population should be considered to be consistent with those of the total population "if the point estimate of the hazard ratio of the pertuzumab combination therapy group to the placebo combination therapy group in the Japanese population is <1.00."

Results of PFS (IRF assessment) of Japanese patients in the CLEOPATRA study were as shown in the table below.

Results of analysis of PFS in Japanese patients
(ITT population, IRF assessment, data cut-off date, May 13, 2011)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	26	27
Number of death or aggravation (%)	14 (53.8)	11 (40.7)
Median [95% CI] (months)	12.5 [9.3, NE]	18.7 [10.5, NE]
Hazard ratio*1 [95% CI]	1.63 [0.70, 3.78]	
P value (two-sided) *2	0.2564	

NE: not estimable
*1: Cox proportional hazard model adjusted for stratification factor (prior treatment status)
*2: Stratified log-rank test (stratified by prior treatment status)



Kaplan-Meier curves of PFS in Japanese patients (ITT population, data cut-off date, May 13, 2011)

PFS (assessed by physician in charge) of Japanese patients in the CLEOPATRA study were as shown in the table below.

Results of analysis of PFS in Japanese patients
(ITT population, assessed by physician in charge, data cut-off date, May 13, 2011)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	26	27
Number of death or aggravation (%)	13 (50.0)	10 (37.0)
Median [95% CI] (months)	16.2 [10.3, NE]	NE [10.5, NE]
Hazard ratio*1 [95% CI]	1.29 [0.56, 2.95]	
P value (two-sided) *2	0.5509	

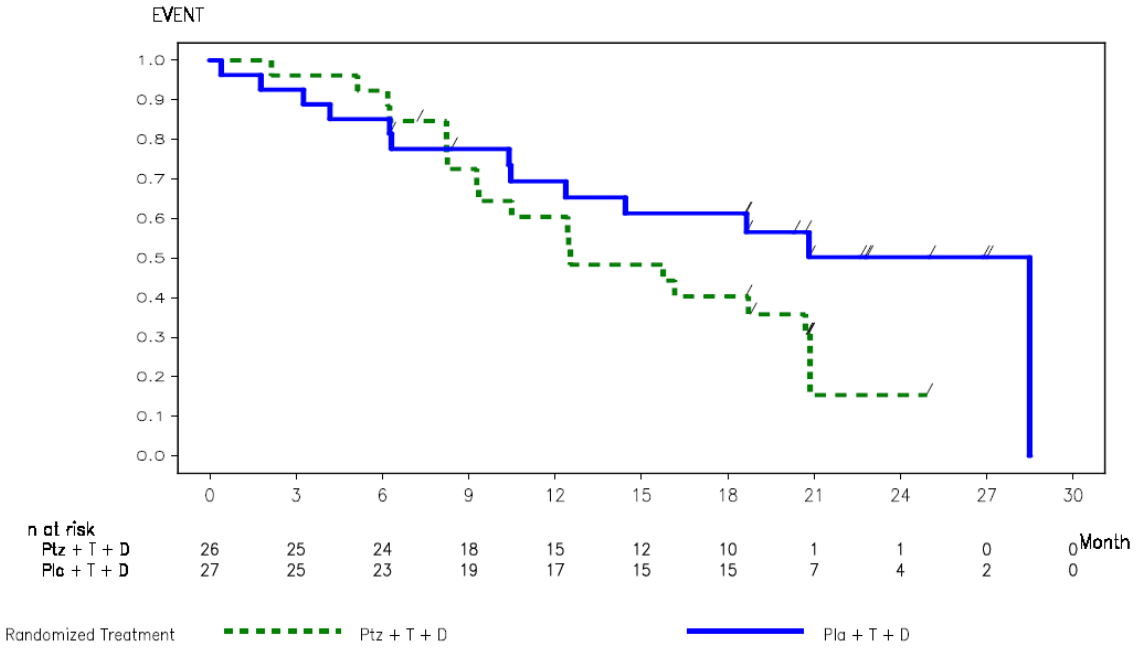
NE: not estimable
*1: Cox proportional hazard model adjusted for stratification factor (prior treatment status)
*2: Stratified log-rank test (stratified by prior treatment status)

At the time point where Japanese patients participated in the CLEOPATRA study, it was speculated that, assuming that the efficacy (hazard ratio) expected for the Japanese population is similar to that for the total population, the consistent results would be obtained at the conditional probability of 80% provided that 30 events are observed in Japan. However, it turned out to be that the event number for Japanese patients was unlikely to reach 30 events at the time point of the last PFS analysis in the total population. Therefore, the requirement of the protocol was amended (■■, 20■) so that the study be continued under blinded conditions for an additional analysis until the number of events for PFS (IRF assessment) in Japanese patients reached 30. The results of the additional analysis of PFS (IRF assessment) in Japanese patients were as follows.

Results of additional analysis of PFS in Japanese patients
(ITT population, IRF assessment, data cut-off date, January 27, 2012)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	26	27
Number of deaths or aggravations (%)	18 (69.2)	13 (48.1)
Median [95% CI] (months)	12.5 [9.3, 20.7]	28.5 [12.4, 28.5]
Hazard ratio*1 [95% CI]	1.92 [0.91, 4.04]	
P value (two-sided) *2	0.0871	

*1: Cox proportional hazard model adjusted for stratification factor (prior treatment status)
*2: Stratified log-rank test (stratified by prior treatment status)



Kaplan-Meier curves of PFS in Japanese patients
(ITT population, data cut-off date, January 27, 2012)

The consistency of PFS analysis results in the Japanese population with those of the total population in the CLEOPATRA study was not able to be confirmed, and PMDA asked the applicant to explain the efficacy in Japanese patients.

The applicant responded as follows:
Because of the small sample size of Japanese patients enrolled in the CLEOPATRA study, there is a limitation to conduct further analysis. With this reservation, the discrepancy in the distribution of the following background factors between the treatment groups in the Japanese population was

observed in the following parameters: visceral disease status (visceral or non-visceral disease), HER2 expression level assessed by IHC, ECOG PS, and hormone receptor (ER/PgR) expression level. Results of Cox regression analysis of the total population suggested that visceral disease status, HER2 expression level assessed by IHC, and ECOG PS were factors affecting PFS (prognostic factors).

Simultaneous distribution of prognostic factors in the Japanese population (ITT population)

Visceral disease	HER2 expression level	ECOG PS	Pertuzumab combination therapy group (N = 26)*	Placebo combination therapy group (N = 27)*
yes	2+	0	6 (23.1)	0
Yes	2+	1	1 (3.8)	0
Yes	3+	0	15 (57.7)	9 (33.3)
Yes	3+	1	0	5 (18.5)
No	2+	0	2 (7.7)	1 (3.7)
No	2+	1	0	0
No	3+	0	2 (7.7)	11 (40.7)
No	3+	1	0	1 (3.7)

*: Number of patients (%)

Data of the Japanese population and the non-Japanese population were adjusted by background factor using the Cox proportional hazard models: (a) data were adjusted by background factor that had been specified in advance as the prognostic factors in the statistical analysis plan (the factors region and ethnicity were excluded because of the evaluation of the Japanese population) (model 1), (b) ECOG PS was used as an adjusting factor in addition to those used in model 1 (model 2), and (c) data were adjusted by visceral disease status, HER2 expression level assessed by IHC, and ECOG PG, the three factors suggested as prognostic factors from the analysis of data of the entire population (model 3). The resulting hazard ratios [95% CI] were as follows. As regards the goodness of fit of the model in Japanese patients, the –2-fold value of the logarithmic maximum likelihood (logarithmic maximum likelihood) and Akaike's Information Criterion (AIC) were 200.350 and 212.350 in model 1, 187.704 and 201.704 in model 2, and 188.610 and 196.610 in model 3, respectively.

Results of multivariate analysis of PFS (ITT population, IRF assessment) (data cut-off date, January 27, 2012)

	Model 1	Model 2	Model 3
Covariates	Prior treatment status Age Visceral disease status Hormone receptor expression level HER2 expression level assessed by IHC	Prior treatment status Age Visceral disease status Hormone receptor expression level HER2 expression level assessed by IHC ECOG PS	Visceral disease status HER2 expression level assessed by IHC ECOG PS
Japanese patients*	1.08 [0.41, 2.80]	1.99 [0.66, 6.03]	1.91 [0.69, 5.27]
Non-Japanese patients*	0.58 [0.48, 0.71]	0.59 [0.48, 0.72]	0.60 [0.49, 0.73]

*: Hazard ratio [95% CI]

The degree of effect in which the data of individual patients have on the results under the condition of these models was investigated. As a result, the hazard ratio varied within the range from 0.88 to 1.28 in model 1, from 1.61 to 2.38 in model 2, and from 1.61 to 2.38 in model 3. The logarithmic maximum likelihood varied within the range from 190.093 to 200.151 in model 1, from 176.241 to 187.598 in model 2, and from 178.147 to 188.518 in model 3. In addition, effects on each

variable included in the model (DFBETA statistics) and on the entire model (LD and LMAX statistics) were investigated. As a result, the same patients showed greater variations in each statistic and tended to develop events in a relatively early stage, whereas no consistent characteristics were observed in the background factors considered in the model. By assuming that the same results would be obtained in the Japanese population and in the total population, the probability of the point estimate of the hazard ratio in the pertuzumab combination therapy group relative to the placebo combination therapy group being <1.00 was calculated, with consideration given to the effect and distribution of prognostic factors. Results showed that the probability was approximately 75% to 80%, indicating that the probability of the point estimate of the hazard ratio in the Japanese population being >1.00 was approximately 20% to 25%.

Using the total population, the difference in efficacy between Japanese and non-Japanese patients was investigated using (a) a multivariate analysis model with "Japanese/non-Japanese patients" added as a factor to the 3 multivariate analysis models above, and (b) a multivariate analysis model with "Japanese/non-Japanese patients" and "interactions between treatment group and Japanese/non-Japanese patients" added as factors to the 3 multivariate analysis models above. Results were as shown in the table below. It was suggested, from model 2, that there were interactions between the efficacy in the Japanese population and the non-Japanese population, at a two-sided significance level of 5%.

Results of multivariate analysis of PFS in the total population (ITT population, IRF assessment) (data cut-off date, January 27, 2012)

	Model 1		Model 2		Model 3	
	(a)	(b)	(a)	(b)	(a)	(b)
Treatment group (pertuzumab combination vs. placebo combination)*	0.612 [0.504, 0.742]	0.579 [0.474, 0.708]	0.623 [0.513, 0.756]	0.588 [0.481, 0.719]	0.631 [0.522, 0.763]	0.600 [0.493, 0.731]
Prior treatment (yes vs. no)*	0.927 [0.765, 1.123]	0.929 [0.766, 1.126]	0.939 [0.774, 1.138]	0.942 [0.777, 1.142]	—	—
Region (Asia vs. Europe)*	0.760 [0.308, 1.875]	0.766 [0.311, 1.891]	0.744 [0.301, 1.835]	0.749 [0.304, 1.849]	—	—
Region (North America vs. Europe)*	0.812 [0.603, 1.091]	0.814 [0.605, 1.094]	0.822 [0.611, 1.107]	0.826 [0.613, 1.112]	—	—
Region (South America vs. Europe)*	0.842 [0.610, 1.162]	0.842 [0.610, 1.162]	0.867 [0.629, 1.195]	0.867 [0.629, 1.195]	—	—
Age (≥65 vs. <65)*	0.868 [0.658, 1.145]	0.875 [0.663, 1.154]	0.867 [0.658, 1.144]	0.875 [0.663, 1.153]	—	—
Race (Asian vs. White)*	1.019 [0.419, 2.477]	1.011 [0.416, 2.459]	1.107 [0.418, 2.474]	1.010 [0.415, 2.458]	—	—
Race (Black vs. White)*	1.134 [0.684, 1.881]	1.120 [0.675, 1.858]	1.167 [0.704, 1.932]	1.152 [0.695, 1.909]	—	—
Race (Others vs. White)	0.757 [0.435, 1.316]	0.758 [0.436, 1.318]	0.787 [0.453, 1.370]	0.791 [0.455, 1.377]	—	—
Visceral disease (yes vs. no)*	0.590 [0.455, 0.764]	0.611 [0.471, 0.792]	0.617 [0.476, 0.800]	0.642 [0.494, 0.834]	—	—
Hormone receptor expression (positive vs. negative)*	0.801 [0.659, 0.974]	0.785 [0.645, 0.955]	0.782 [0.643, 0.952]	0.766 [0.629, 0.933]	0.633 [0.493, 0.813]	0.653 [0.508, 0.840]
HER2 expression level (0/1+ vs. 3+)*	1.378 [0.435, 4.363]	1.403 [0.443, 4.443]	1.521 [0.479, 4.822]	1.553 [0.490, 4.927]	1.616 [0.602, 4.344]	1.631 [0.607, 4.383]
HER2 expression level (2+ vs. 3+)*	1.888 [1.410, 2.530]	1.831 [1.365, 2.458]	1.951 [1.456, 2.615]	1.889 [1.407, 2.537]	1.791 [1.354, 2.369]	1.734 [1.308, 2.300]
ECOG PS*	—	—	0.694 [0.568, 0.848]	0.689 [0.564, 0.842]	0.695 [0.572, 0.845]	0.691 [0.568, 0.840]
Japanese/non-Japanese patients*	0.996 [0.660, 1.502]	0.684 [0.376, 1.244]	1.136 [0.748, 1.727]	0.768 [0.421, 1.401]	0.983 [0.677, 1.427]	0.684 [0.388, 1.206]

Interactions between treatment group and Japanese/non-Japanese patients (pertuzumab combination therapy and Japanese vs. other)*	—	2.120 [0.993, 4.526]	—	2.219 [1.039, 4.740]	—	2.083 [0.982, 4.418]
Difference in likelihood ratio test statistic	3.832		4.302		3.720	
Difference in Score statistic	4.136		4.752		3.720	
Difference in Wald statistic	3.839		4.437		3.433	

*: Hazard ratio [95% CI]

Based on the above analytical results, the applicant explained as follows:
Results obtained from this study suggested that the efficacy of pertuzumab in the Japanese population may differ from that obtained in the total population and the non-Japanese population, which suggests the presence of interactions, depending on the model used for investigation.

However, because of the limited number of patients in the Japanese population and the non-uniformity in the distribution of important prognostic factors between the treatment groups, the results in all models were substantially affected by the observed values in individual patients. Therefore, the possibility cannot be excluded that consistent results were not obtained even though the levels in the efficacy are similar between the Japanese population and the total population and the non-Japanese population, depending on the degree of bias in the sampling distribution. In all models studied, the hazard ratio of the pertuzumab combination therapy group to the placebo combination therapy group in the Japanese population had a wide 95% CI, and the 95% CI of the Japanese population overlapped with that of the total population and the non-Japanese population. Thus, the obtained data may not robustly contradict the consistency of the results in the Japanese population with those of the total population or the non-Japanese population.

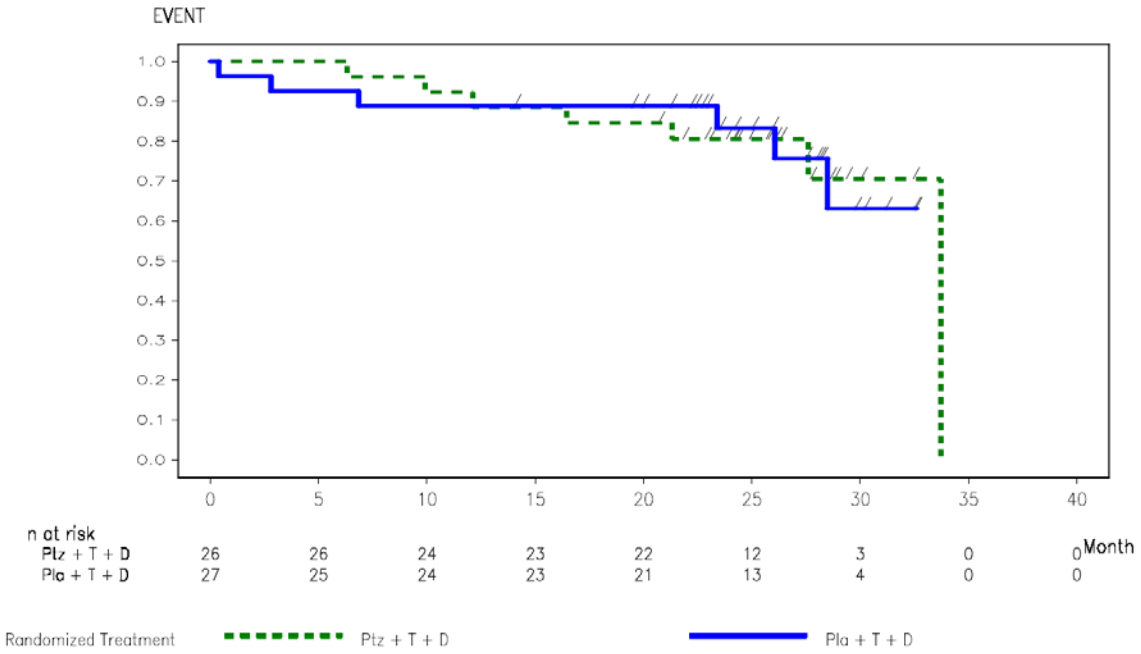
Next, in order to confirm (a) the results of the second interim analysis of OS in the Japanese population in the CLEOPATRA study and (b) whether or not there were any death in Japanese patients by the administration of pertuzumab, PMDA asked the applicant to explain the details of the causes of deaths at the time point of the analysis.

The applicant responded as follows:
Results of the second interim analysis of OS in the Japanese population are shown in the table below. At the time point of the second interim analysis of OS, death occurred in 7 patients in the pertuzumab combination therapy group and in 6 patients in the placebo combination therapy group. In all patients in the pertuzumab combination therapy group, death occurred due to disease progression, and in the placebo combination therapy group, death occurred in 4 patients due to disease progression and 1 patient each from pneumonia/febrile neutropenia and drowning.

Result of the second interim analysis of OS in Japanese patients (ITT, data cut-off date, May 14, 2012)

	Pertuzumab combination therapy group	Placebo combination therapy group
Number of patients	26	27
Death (%)	7 (26.9)	6 (22.2)
Median [95%CI] (months)	33.7 [27.6, 33.7]	NE [28.5, NE]
Hazard ratio*1 [95% CI]	1.17 [0.36, 3.88]	
P value (two-sided) *2	0.7924	

NE: not estimable
*1: Cox proportional hazard model adjusted for stratification factor (prior treatment status)
*2: Stratified log-rank test (stratified by prior treatment status)



Kaplan-Meier curves of OS in Japanese patients (ITT population, data cut-off date, May 14, 2012)

PMDA considers as follows:
The investigation of efficacy of pertuzumab in Japanese patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy in the CLEOPATRA study failed to demonstrate the consistency of results between the Japanese population and the total population, as assessed by the pre-specified endpoint PFS. The applicant explained that the inconsistency was possibly caused by the small sample size in the Japanese population and the non-uniformity in the distribution of the prognostic factors between the treatment groups, and PMDA considers the applicant's explanation acceptable.

However, although it is difficult to evaluate the degree of effect in which non-uniformity in the distribution of the prognostic factors may impose upon on the results from the reason that the events observed in the Japanese population was limited in number, it is practically impossible to conclude, from the results of the CLEOPATRA study, that pertuzumab is expected to be effective in Japanese patients, for the following reasons: (a) analytical results suggest the presence of interactions of treatment effect (PFS) with ethnicity (Japanese population vs. non-Japanese population), and (b) estimation of the treatment effect in the Japanese population based on the multivariate analysis models taking account of prognostic factors also failed to clearly show the efficacy of pertuzumab.

Clinical usefulness of pertuzumab in Japanese patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy should be examined also based on the results of the entire CLEOPATRA study, and was presented in "4.(iii).B.(4) Clinical positioning."

4.(iii).B.(3) Safety [see "4.(iv) Adverse events, etc., observed in clinical studies" for adverse events]

As a result of the reviews described below, PMDA considers that caution for the following adverse events is required in administering pertuzumab: neutropenia/leukopenia, diarrhoea/mucositis,

cardiac disorder, infusion reaction, interstitial lung disease, rash, and hypersensitivity/anaphylaxis. Thus, attention should be paid to the occurrence of these events in using pertuzumab.

However, PMDA has concluded that pertuzumab is tolerable for Japanese patients with breast cancer provided that monitoring and control of adverse events as well as the temporary withdrawal, dose reduction, or discontinuation of pertuzumab and/or concomitant medication are performed in an appropriate manner by physicians with sufficient knowledge and experience in cancer chemotherapy.

4.(iii).B.(3).1) Safety profile

Based on the safety information obtained in the pertuzumab combination therapy group and the placebo combination therapy group in the CLEOPATRA study, the applicant explained the safety profile of pertuzumab as follows:

The safety in the pertuzumab combination therapy group and the placebo combination therapy group in the CLEOPATRA study is summarized in the table below.

Summary of safety (the CLEOPATRA study)

	Number of patients (%)	
	Pertuzumab combination therapy group N = 407	Placebo combination therapy group N = 397
All adverse events	406 (99.8)	391 (98.5)
Adverse events of Grade ≥3	302 (74.2)	289 (72.8)
Serious adverse events	140 (34.4)	104 (26.2)
Adverse events leading to treatment discontinuation	119 (29.2)	110 (27.7)
Adverse events leading to withdrawal or dose reduction	244 (60.0)	211 (53.1)

Among adverse events reported by ≥10% of patients in any group, those that occurred with ≥5% higher incidence in the pertuzumab combination therapy group than in the placebo combination therapy group were diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin. Among adverse events reported by ≥10% of patients in any group, adverse events of Grade ≥3 occurring in any group with ≥5% incidence, and also with a higher incidence in the pertuzumab combination therapy group than in the placebo combination therapy group were neutropenia, febrile neutropenia, and diarrhoea (the table below).

Adverse events with an incidence of ≥10% in any group (the CLEOPATRA study)

Event	Number of patients (%)			
	Pertuzumab combination therapy group N = 407		Placebo combination therapy group N = 397	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Number of patients with event	406 (99.8)	302 (74.2)	391 (98.5)	289 (72.8)
Alopecia	248 (60.9)	0	240 (60.5)	1 (0.3)
Diarrhoea	272 (66.8)	32 (7.9)	184 (46.3)	20 (5.0)
Neutropenia	215 (52.8)	199 (48.9)	197 (49.6)	182 (45.8)
Nausea	172 (42.3)	5 (1.2)	165 (41.6)	2 (0.5)
Fatigue	153 (37.6)	9 (2.2)	146 (36.8)	13 (3.3)
Rash	137 (33.7)	3 (0.7)	96 (24.2)	3 (0.8)
Asthenia	106 (26.0)	10 (2.5)	120 (30.2)	6 (1.5)
Decreased appetite	119 (29.2)	7 (1.7)	105 (26.4)	6 (1.5)
Oedema peripheral	94 (23.1)	2 (0.5)	119 (30.0)	3 (0.8)
Vomiting	98 (24.1)	6 (1.5)	95 (23.9)	6 (1.5)
Mucosal inflammation	113 (27.8)	6 (1.5)	79 (19.9)	4 (1.0)
Myalgia	93 (22.9)	4 (1.0)	95 (23.9)	3 (0.8)
Nail disorder	93 (22.9)	5 (1.2)	91 (22.9)	1 (0.3)

Event	Number of patients (%)			
	Pertuzumab combination therapy group N = 407		Placebo combination therapy group N = 397	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Anaemia	94 (23.1)	10 (2.5)	75 (18.9)	14 (3.5)
Neuropathy peripheral	86 (21.1)	11 (2.7)	80 (20.2)	7 (1.8)
Cough	87 (21.4)	2 (0.5)	74 (18.6)	1 (0.3)
Constipation	61 (15.0)	0	99 (24.9)	4 (1.0)
Leukopenia	74 (18.2)	50 (12.3)	81 (20.4)	58 (14.6)
Headache	85 (20.9)	5 (1.2)	67 (16.9)	2 (0.5)
Pyrexia	76 (18.7)	5 (1.2)	71 (17.9)	2 (0.5)
Stomatitis	77 (18.9)	2 (0.5)	61 (15.4)	1 (0.3)
Dysgeusia	75 (18.4)	0	62 (15.6)	0
Arthralgia	63 (15.5)	1 (0.2)	64 (16.1)	3 (0.8)
Upper respiratory tract infection	68 (16.7)	3 (0.7)	53 (13.4)	0
Dyspnoea	57 (14.0)	4 (1.0)	62 (15.6)	8 (2.0)
Lacrimation increased	57 (14.0)	0	55 (13.9)	0
Pain in extremity	62 (15.2)	2 (0.5)	47 (11.8)	1 (0.3)
Insomnia	54 (13.3)	0	53 (13.4)	0
Abdominal pain	57 (14.0)	0	49 (12.3)	3 (0.8)
Peripheral sensory neuropathy	49 (12.0)	2 (0.5)	56 (14.1)	1 (0.3)
Back pain	55 (13.5)	6 (1.5)	46 (11.6)	4 (1.0)
Nasopharyngitis	48 (11.8)	0	51 (12.8)	1 (0.3)
Dizziness	51 (12.5)	2 (0.5)	48 (12.1)	0
Pruritus	57 (14.0)	0	40 (10.1)	0
Dyspepsia	49 (12.0)	0	48 (12.1)	0
Oedema	46 (11.3)	2 (0.5)	50 (12.6)	4 (1.0)
Febrile neutropenia	56 (13.8)	56 (13.8)	30 (7.6)	30 (7.6)
Paraesthesia	37 (9.1)	1 (0.2)	40 (10.1)	3 (0.8)
Dry skin	43 (10.6)	0	17 (4.3)	0

PMDA considers as follows:
As for the adverse events requiring caution, no additional events other than those observed in the placebo combination therapy group were observed in the pertuzumab group. Therefore, PMDA has concluded that concomitant use of pertuzumab (in pertuzumab/trastuzumab/DTX combination) was well-tolerated. However, attention should be paid to events that occurred with a higher incidence in the pertuzumab combination therapy group than in the placebo combination therapy group. Among these events, febrile neutropenia which was Grade ≥3 and occurred with ≥5% higher incidence than in the placebo combination therapy group requires particular caution because it may result in a serious outcome.

In the CLEOPATRA study, trastuzumab, an antibody that targets HER2 as is the case with pertuzumab, was administered to both the pertuzumab combination therapy group and placebo combination therapy group. Since the pharmacological action of trastuzumab resembles that of pertuzumab, the toxicity caused by pertuzumab in the pertuzumab combination therapy group may not have been clearly detected. Therefore, the safety profile of pertuzumab was examined using the data from the foreign phase II study in patients with ovarian cancer (Study BO17931) which compared the outcomes of patients receiving the standard chemotherapy not containing trastuzumab and those receiving pertuzumab in combination with the standard chemotherapy [see "4.(iii).A [reference data] Foreign clinical studies 9) Foreign phase II study (Study BO17931)"]. PMDA confirmed that pertuzumab caused no additional events requiring caution, other than those observed with trastuzumab.

4.(iii).B.(3).2) Difference in safety between Japanese and foreign patients
The applicant explained the difference in the safety of pertuzumab between Japanese and foreign patients, as follows:

In the CLEOPATRA study, adverse events reported by ≥10% of patients in either Japanese or foreign patients were as shown in the table below.

In the pertuzumab combination therapy group of the CLEOPATRA study, events that occurred with ≥20% higher incidence in Japanese patients than in foreign patients were alopecia, nausea, fatigue, rash, decreased appetite, nail disorder, constipation, pyrexia, stomatitis, dysgeusia, arthralgia, lacrimation increased, pruritus, oedema, dry skin, palmar-plantar erythrodysaesthesia syndrome, weight decreased, and pleural effusion. In the pertuzumab combination therapy group, Grade ≥3 events with ≥5% higher incidence in Japanese patients than in foreign patients were diarrhoea, nausea, decreased appetite, and febrile neutropenia.

In the pertuzumab combination therapy group of the CLEOPATRA study, events that occurred with ≥20% higher incidence in foreign patients than in Japanese patients were neutropenia and mucosal inflammation. In the pertuzumab combination therapy group, Grade ≥3 events with ≥5% higher incidence in foreign patients than in Japanese patients were neutropenia and leukopenia.

Adverse events with incidence of ≥10% of patients in either Japanese or foreign patients (the CLEOPATRA study)

Event	Number of patients (%)							
	Pertuzumab combination therapy group				Placebo combination therapy group			
	Japanese patients N =26		Foreign patients N = 381		Japanese patients N =27		Foreign patients N = 370	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Alopecia	25 (96.2)	0	223 (58.5)	0	23 (85.2)	0	217 (58.6)	1 (0.3)
Diarrhoea	22 (84.6)	4 (15.4)	250 (65.6)	28 (7.3)	22 (81.5)	2 (7.4)	162 (43.8)	18 (4.9)
Neutropenia	8 (30.8)	8 (30.8)	207 (54.3)	191 (50.1)	9 (33.3)	9 (33.3)	188 (50.8)	173 (46.8)
Nausea	16 (61.5)	2 (7.7)	156 (40.9)	3 (0.8)	9 (33.3)	0	156 (42.2)	2 (0.5)
Fatigue	19 (73.1)	1 (3.8)	134 (35.2)	8 (2.1)	21 (77.8)	2 (7.4)	125 (33.8)	11 (3.0)
Rash	18 (69.2)	0	119 (31.2)	3 (0.8)	23 (85.2)	0	73 (19.7)	3 (0.8)
Asthenia	4 (15.4)	1 (3.8)	102 (26.8)	9 (2.4)	4 (14.8)	0	116 (31.4)	6 (1.6)
Decreased appetite	20 (76.9)	2 (7.7)	99 (26.0)	5 (1.3)	16 (59.3)	3 (11.1)	89 (24.1)	3 (0.8)
Oedema peripheral	6 (23.1)	1 (3.8)	88 (23.1)	1 (0.3)	5 (18.5)	2 (7.4)	114 (30.8)	1 (0.3)
Vomiting	6 (23.1)	1 (3.8)	92 (24.1)	5 (1.3)	5 (18.5)	0	90 (24.3)	6 (1.6)
Mucosal inflammation	0	0	113 (29.7)	6 (1.6)	0	0	79 (21.4)	4 (1.1)
Myalgia	8 (30.8)	0	85 (22.3)	4 (1.0)	6 (22.2)	0	89 (24.1)	3 (0.8)
Nail disorder	17 (65.4)	0	76 (19.9)	5 (1.3)	17 (63.0)	0	74 (20.0)	1 (0.3)
Anaemia	6 (23.1)	1 (3.8)	88 (23.1)	9 (2.4)	2 (7.4)	0	73 (19.7)	14 (3.8)
Neuropathy peripheral	7 (26.9)	1 (3.8)	79 (20.7)	10 (2.6)	8 (29.6)	0	72 (19.5)	7 (1.9)
Cough	6 (23.1)	0	81 (21.3)	2 (0.5)	2 (7.4)	0	72 (19.5)	1 (0.3)
Constipation	15 (57.7)	0	46 (12.1)	0	11 (40.7)	0	88 (23.8)	4 (1.1)
Leukopenia	1 (3.8)	1 (3.8)	73 (19.2)	49 (12.9)	1 (3.7)	1 (3.7)	80 (21.6)	57 (15.4)
Headache	10 (38.5)	0	75 (19.7)	5 (1.3)	6 (22.2)	0	61 (16.5)	2 (0.5)
Pyrexia	20 (76.9)	1 (3.8)	56 (14.7)	4 (1.0)	9 (33.3)	0	62 (16.8)	2 (0.5)
Stomatitis	14 (53.8)	0	63 (16.5)	2 (0.5)	11 (40.7)	0	50 (13.5)	1 (0.3)
Dysgeusia	16 (61.5)	0	59 (15.5)	0	15 (55.6)	0	47 (12.7)	0
Arthralgia	11 (42.3)	0	52 (13.6)	1 (0.3)	10 (37.0)	1 (3.7)	54 (14.6)	2 (0.5)
Upper respiratory tract infection	0	0	68 (17.8)	3 (0.8)	0	0	53 (14.3)	0
Dyspnoea	2 (7.7)	0	55 (14.4)	4 (1.0)	5 (18.5)	0	57 (15.4)	8 (2.2)
Lacrimation increased	9 (34.6)	0	48 (12.6)	0	5 (18.5)	0	50 (13.5)	0
Pain in extremity	3 (11.5)	0	59 (15.5)	2 (0.5)	3 (11.1)	0	44 (11.9)	1 (0.3)
Insomnia	5 (19.2)	0	49 (12.9)	0	6 (22.2)	0	47 (12.7)	0
Abdominal pain	1 (3.8)	0	56 (14.7)	0	1 (3.7)	0	48 (13.0)	3 (0.8)
Peripheral sensory neuropathy	6 (23.1)	1 (3.8)	43 (11.3)	1 (0.3)	8 (29.6)	0	48 (13.0)	1 (0.3)
Back pain	6 (23.1)	0	49 (12.9)	6 (1.6)	2 (7.4)	0	44 (11.9)	4 (1.1)
Nasopharyngitis	6 (23.1)	0	42 (11.0)	0	11 (40.7)	0	40 (10.8)	1 (0.3)
Dizziness	6 (23.1)	0	45 (11.8)	2 (0.5)	3 (11.1)	0	45 (12.2)	0
Pruritus	14 (53.8)	0	43 (11.3)	0	6 (22.2)	0	34 (9.2)	0
Dyspepsia	0	0	49 (12.9)	0	2 (7.4)	0	46 (12.4)	0

Event	Number of patients (%)							
	Pertuzumab combination therapy group				Placebo combination therapy group			
	Japanese patients N =26		Foreign patients N = 381		Japanese patients N =27		Foreign patients N = 370	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Oedema	15 (57.7)	1 (3.8)	31 (8.1)	1 (0.3)	18 (66.7)	2 (7.4)	32 (8.6)	2 (0.5)
Febrile neutropenia	5 (19.2)	5 (19.2)	51 (13.4)	51 (13.4)	7 (25.9)	7 (25.9)	23 (6.2)	23 (6.2)
Bone pain	0	0	39 (10.2)	1 (0.3)	0	0	39 (10.5)	2 (0.5)
Paraesthesia	6 (23.1)	1 (3.8)	31 (8.1)	0	3 (11.1)	0	37 (10.0)	3 (0.8)
Abdominal pain upper	4 (15.4)	0	33 (8.7)	1 (0.3)	4 (14.8)	0	35 (9.5)	0
Epistaxis	7 (26.9)	0	30 (7.9)	0	3 (11.1)	0	31 (8.4)	0
Dry skin	9 (34.6)	0	34 (8.9)	0	3 (11.1)	0	14 (3.8)	0
Palmar-plantar erythrodysaesthesia syndrome	11 (42.3)	1 (3.8)	17 (4.5)	2 (0.5)	8 (29.6)	0	14 (3.8)	1 (0.3)
Weight decreased	12 (46.2)	0	22 (5.8)	0	6 (22.2)	1 (3.7)	10 (2.7)	0
Chills	3 (11.5)	0	30 (7.9)	0	1 (3.7)	0	14 (3.8)	0
Rhinorrhoea	3 (11.5)	0	23 (6.0)	0	1 (3.7)	0	20 (5.4)	0
Pleural effusion	8 (30.8)	0	13 (3.4)	1 (0.3)	5 (18.5)	0	18 (4.9)	5 (1.4)
Muscle spasms	3 (11.5)	0	26 (6.8)	1 (0.3)	2 (7.4)	0	13 (3.5)	0
Paronychia	4 (15.4)	0	25 (6.6)	0	1 (3.7)	0	13 (3.5)	1 (0.3)
Hot flush	2 (7.7)	0	19 (5.0)	0	4 (14.8)	0	17 (4.6)	1 (0.3)
Conjunctivitis	1 (3.8)	0	22 (5.8)	0	3 (11.1)	0	14 (3.8)	0
Weight increased	5 (19.2)	1 (3.8)	8 (2.1)	0	10 (37.0)	0	11 (3.0)	0
Influenza like illness	6 (23.1)	0	14 (3.7)	1 (0.3)	2 (7.4)	0	6 (1.6)	0
Hypoaesthesia	4 (15.4)	0	12 (3.1)	0	0	0	11 (3.0)	0
Infusion related reaction	3 (11.5)	0	8 (2.1)	0	1 (3.7)	0	9 (2.4)	1 (0.3)
Face oedema	4 (15.4)	0	7 (1.8)	0	0	0	7 (1.9)	0
Dermatitis	4 (15.4)	0	8 (2.1)	1 (0.3)	0	0	5 (1.4)	0
Malaise	2 (7.7)	0	3 (0.8)	0	4 (14.8)	0	6 (1.6)	0
Cheilitis	4 (15.4)	0	4 (1.0)	0	2 (7.4)	0	1 (0.3)	0
Injection site reaction	3 (11.5)	0	1 (0.3)	0	2 (7.4)	0	5 (1.4)	1 (0.3)
Eye discharge	3 (11.5)	0	2 (0.5)	0	1 (3.7)	0	1 (0.3)	0
Ocular surface disease	3 (11.5)	0	0	0	2 (7.4)	0	0	0
Pharyngeal inflammation	1 (3.8)	0	1 (0.3)	0	3 (11.1)	0	0	0

PMDA considers as follows:

There were no significant differences in the types of adverse events that occurred in Japanese patients and in foreign patients after pertuzumab combination therapy. Among adverse events (all Grades) that occurred with ≥20% higher incidence in Japanese patients than foreign patients, Grade ≥3 adverse events occurred only in ≤2 Japanese patients, and only 1 Japanese patient experienced a serious adverse event (pyrexia). As regards Grade ≥3 adverse events that showed a tendency of a higher incidence in Japanese patients than in foreign patients, there was no significant difference in the incidence between the pertuzumab combination therapy group and the placebo combination therapy group, except diarrhoea and nausea, and Grade ≥3 diarrhoea and nausea did not result in treatment discontinuation in any of the Japanese patients. In the pertuzumab combination therapy group of the CLEOPATRA study, 11.5% (3 of 26 patients) of Japanese patients and 6.1% (25 of 407 patients) of foreign patients discontinued the treatment because of adverse events. Although the data suggest a higher discontinuation rate in Japanese patients, serious adverse events were observed in 30.8% (8 of 26 patients) of Japanese patients and in 34.4% (140 of 407 patients) of foreign patients, indicating a comparable incidence between the two ethnic groups.

Based on these results, PMDA has concluded that pertuzumab combination therapy (pertuzumab/trastuzumab/DTX) is tolerable for Japanese patients. However, it is necessary to appropriately provide information on adverse events with different incidence between Japanese patients and foreign patients. Also, because of the limited number of patients who were treated with pertuzumab before regulatory submission, there is no sufficient information accumulated on

the safety of pertuzumab in Japanese patients. Therefore, investigation should be performed after the market launch to collect information on the safety of pertuzumab in Japanese patients [see "4.(iii).B.(7) Post-marketing investigations"].

4.(iii).B.(3).3) Neutropenia/leukopenia

The applicant explained pertuzumab-induced neutropenia/leukopenia as follows:

In the CLEOPATRA study, leukopenia (adverse event corresponding to "Haematopoietic Leukopenia [narrow]" in the Standardised MedDRA Queries) were observed in 254 of 407 patients (62.4%) in the pertuzumab combination therapy group and in 231 of 397 patients (58.2%) in the placebo combination therapy group. Of these patients, 237 of 407 patients (58.2%) and 211 of 397 patients (53.1%), respectively, had Grade ≥3 leukopenia. Febrile neutropenia was observed in 56 of 407 patients (13.8%) in the pertuzumab combination therapy group and in 30 of 397 patients (7.6%) in the placebo combination therapy group. "Infection associated with leukopenia"* was observed in 51 of 407 patients (12.5%) in the pertuzumab combination therapy group and in 39 of 397 patients (9.8%) in the placebo combination therapy group, and "infection associated with febrile neutropenia"* was observed in 14 of 407 patients (3.4%) in pertuzumab combination therapy group and in 3 of 397 patients (0.8%) in the placebo combination therapy group.

*: Among adverse events of MedDRA System Organ Class "Infections and infestations," infection-related event that occurred within 14 days after the onset of Grade ≥3 leukopenia were defined as "infection associated with leukopenia" and those that occurred within 14 days after the onset of febrile neutropenia were defined as "infection associated with febrile neutropenia."

PMDA considers as follows:

The incidences of leukopenia and febrile neutropenia tended to be higher in the pertuzumab combination therapy group than in the placebo combination therapy group, and there were patients who died of febrile neutropenia (3 of 407 patients [0.7%] in the pertuzumab combination therapy group, 1 of 397 patients [0.3%] in the placebo combination therapy group). Therefore, patients should be appropriately monitored for possible occurrence of neutropenia/leukopenia during the treatment with pertuzumab. Particular caution is required against the occurrence of these events during pertuzumab administration. It is necessary to caution about such information including these events leading to infection in some patients.

As regards haematotoxicity other than neutropenia/leukopenia (anaemia, thrombocytopenia), caution is included in the package insert of trastuzumab, an antibody that targets HER2 as is the case with pertuzumab. However, neither of these events occurred more frequently in the pertuzumab combination therapy group than in the placebo combination therapy group; Grade ≥3 anaemia was observed in 10 of 407 patients [2.5%] in the pertuzumab combination therapy group and in 14 of 397 patients [3.5%] in the placebo combination therapy group, and Grade ≥3 thrombocytopenia in no patient in the pertuzumab combination therapy group and in 2 of 397 patients [0.5%] in the placebo combination therapy group. Therefore, PMDA considers that it is unnecessary at present to provide the same level of caution against these adverse events as against neutropenia/leukopenia.

4.(iii).B.(3).4) Diarrhoea/mucositis

The applicant explained pertuzumab-induced diarrhoea/mucositis as follows:

In the CLEOPATRA study, diarrhoea was observed in 272 of 407 patients (66.8%) in the pertuzumab combination therapy group and in 184 of 397 patients (46.3%) in the placebo combination therapy group. Among these patients, 32 of 407 patients (7.9%) and 20 of 397 patients (5.0%), respectively, had Grade ≥3 diarrhoea, and 6 of 407 patients (1.5%) and 2 of 397 patients (0.5%), respectively, discontinued the treatment. Diarrhoea/mucositis occurred during Cycle 1 in 60.3% (164 of 272 patients) in the pertuzumab combination therapy group and in 43.5% (80 of 184 patients) in the

placebo combination therapy group. The median time to the first occurrence was 7.0 and 22.0 days, respectively, showing a tendency of earlier occurrence in the pertuzumab combination therapy group.

In the CLEOPATRA study, "Mucositis of Gastrointestinal Tract"* (Mucositis) in Adverse Event Group Term (AEGT) defined by F. Hoffmann-La Roche, Ltd. (Roche) was observed in 198 of 407 patients (48.6%) in the pertuzumab combination therapy group and in 147 of 397 patients (37.0%) in the placebo combination therapy group. Among these patients, 12 of 407 patients (2.9%) and 7 of 397 patients (1.8%), respectively, had Grade ≥3 events. No patients discontinued the treatment.

*: Mucositis in AEGT defined by Roche includes the following MedDRA Preferred Terms: anal inflammation, aphthous stomatitis, cheilitis, colitis, colitis erosive, colitis ulcerative, diarrhoea haemorrhagic, duodenitis, duodenitis haemorrhagic, enterocolitis, enterocolitis haemorrhagic, erosive duodenitis, erosive oesophagitis, gastritis, gastritis erosive, gastritis haemorrhagic, gastroduodenitis, gastroduodenitis haemorrhagic, gastroenteritis, gastrointestinal erosion, gastrointestinal inflammation, gastrointestinal tract irritation, gastrooesophagitis, gingival erosion, gingival ulceration, gingivitis, gingivitis ulcerative, glossitis, haemorrhagic erosive gastritis, mouth ulceration, mucosal erosion, mucosal inflammation, oesophageal irritation, oesophagitis, oesophagitis haemorrhagic, oesophagitis ulcerative, oral mucosa erosion, palatitis, periproctitis, pharyngeal erosion, pharyngeal inflammation, pharyngitis, proctitis, proctitis ulcerative, proctocolitis, stomatitis, stomatitis haemorrhagic, stomatitis necrotising.

PMDA considers as follows:
Only a small number of patients discontinued the treatment with pertuzumab because of diarrhoea, and no patient discontinued the treatment because of mucositis. However, since the incidence of diarrhoea/mucositis tended to be higher in the pertuzumab combination therapy group than in the placebo combination therapy group, caution should be exercised against the occurrence of these adverse events in administering pertuzumab.

4.(iii).B.(3).5) Cardiac disorders

The applicant explained pertuzumab-induced cardiac disorders as follows:
In the CLEOPATRA study, cardiac disorders (MedDRA System Organ Class) were observed in 59 of 407 patients (14.5%) in the pertuzumab combination therapy group and in 65 of 397 patients (16.4%) in the placebo combination therapy group. Among these patients, 6 of 407 patients (1.5%) and 15 of 397 patients (3.8%), respectively, had Grade ≥3 cardiac disorders, and 5 of 407 patients (1.2%) and 6 of 397 patients (1.5%), respectively, discontinued the treatment. Left ventricular dysfunction (MedDRA Preferred Term [PT]) was observed in 18 of 407 patients (4.4%) in the pertuzumab combination therapy group and in 33 of 397 patients (8.3%) in the placebo combination therapy group. Among these patients, 5 of 397 patients (1.2%) and 11 of 407 patients (2.8%), respectively, had Grade ≥3 left ventricular dysfunction, and 6 of 407 patients (1.5%) and 8 of 397 patients (2.0%), respectively, discontinued the treatment (excluding those who discontinued only DTX).

In the CLEOPATRA study, diagnosis of symptomatic left ventricular contractile dysfunction was made by the investigator in 4 of 407 patients (1.0%) in the pertuzumab combination therapy group and in 7 of 397 patients (1.8%) in the placebo combination therapy group. Among these patients, 4 of 407 patients (1.0%) and 6 of 397 patients (1.5%), respectively, discontinued the treatment, and 3 patients and 5 patients, respectively, recovered at the data cut-off time point (May 31, 2011). Diagnosis of symptomatic left ventricular contractile dysfunction was made by IRF in 4 of 407 patients (1.0%) and 4 of 397 patients (1.0%), respectively (diagnoses by the investigator were identical to those by IRF in all the 4 patients in pertuzumab combination therapy group and in 2 of the 7 patients in placebo combination therapy group). Among these patients, 1 of 407 patients and 2 of 397 patients, respectively, recovered at the data cut-off time point (May 31, 2011). Decreased left ventricular ejection fraction (LVEF) (decreased by ≥10 points from baseline, and was <50%)

was observed in 15 of 393 patients (3.8%) in the pertuzumab combination therapy group and in 25 of 379 patients (6.6%) in the placebo combination therapy group. Cardiac failure congestive* was observed in 17 of 407 patients (4.2%) and in 29 of 397 patients (7.3%), respectively.

*: Serious adverse events classified as "Cardiac Failure (wide)" in the Standardised MedDRA Queries, and LVEF that decreased by ≥10 points from baseline and was <50%, were defined as "cardiac failure congestive."

Risk factors for cardiac failure congestive were investigated based on the information obtained from 60 patients who developed the disease among 1412 patients receiving pertuzumab in any of the clinical studies submitted for this new drug application. The table below shows possible risk factors for cardiac failure congestive investigated. Among the patients who developed cardiac failure congestive, the percentage of patients with a history of treatment with anthracycline antineoplastic drugs or radiotherapy was higher compared with that of the total population, which suggested that treatment history with anthracycline antineoplastic drugs or radiotherapy is a risk factor for cardiac failure congestive following pertuzumab treatment.

Risk factors for cardiac failure congestive
(patients receiving pertuzumab in any of the clinical studies submitted)

	All the patients who received pertuzumab N = 1412	Patients who developed heart failure congestive N = 60
Female	1237 (87.6%)	48 (80.0%)
Age >75 years	72 (5.1%)	7 (11.7%)
Baseline LVEF <55%	136 (9.6%)	7 (11.7%)
Smoking history	NA	NA
Hypertension[*1]	376 (26.6%)	15 (25.0%)
Diabetes mellitus[*2]	124 (8.8%)	4 (6.7%)
Other potential risk factors for cardiac failure[*3]	NA	20 (33.3%)
Oral administration of antihypertensive drugs or anti-heart disease drugs[*4]	NA	22 (36.7%)
History of treatment with anthracycline antineoplastic drugs	421 (29.8%)	31 (51.7%)
History of radiotherapy	441 (31.2%)	35 (58.3%)[*5]
Without above risk factors[*6]	NA	12 (20.0%)

NA: Not Available
*1: History of "hypertension" in MedDRA PT
*2: History of "hyperglycemia" or "diabetes mellitus" in Standardised MedDRA Queries
*3: History of any of the following: coronary artery disease, cardiac valve disorder, arrhythmia, cardiac failure, myocarditis, pericardial disorder, intravascular stent placement, hypothyroidism, hyperthyroidism and hyperlipidaemia
*4: Angiotensin converting enzyme inhibitors, β-blockers, calcium blockers, antianginal drugs, thiazide diuretics, angiotensin II antagonists, antiarrhythmic drugs, diuretics, loop diuretics, antihypertensive drugs, cardiac glycosides, aldosterone antagonists, platelet aggregation inhibitors, and statins
*5: Irradiation of the thoracic wall or the mediastinum
*6: Without any of the following: potential cardiac risk factors including smoking history, hypertension, and diabetes mellitus; oral administration of antihypertensive drugs or anti-heart disease drugs; treatment history with anthracycline antineoplastic drugs or radiotherapy

PMDA considers as follows:
The incidence of cardiac disorders did not tend to be higher in the pertuzumab combination therapy group than in the placebo combination therapy group. However, in light of the facts that cardiac disorders are known as adverse events requiring particular caution in patients receiving trastuzumab, an antibody that targets HER2 as is the case with pertuzumab, and that among adverse events leading to treatment discontinuation in the CLEOPATRA study (excluding patients who discontinued only DTX), left ventricular dysfunction was the most frequent adverse events (6 of 407 patients in the pertuzumab combination therapy group, 8 of 397 patients in the placebo combination therapy group), caution should be exercised against occurrence of cardiac disorders.

Patients should be monitored for cardiac function not only before and during treatment with pertuzumab but also after the last dose. Also, since some of those patients known to have a high risk for cardiac disorder such as heart failure congestive (patients with a treatment history with anthracycline antineoplastic drugs or thoracic radiotherapy, patients with symptoms of cardiac failure, patients with past or current coronary artery disease [e.g., myocardial infarction, angina pectoris], patients with past or current hypertension, etc.) were excluded from the CLEOPATRA study,* it is necessary to monitor these patients with particular attention and to raise caution about the risks so that they are addressed in an appropriate manner. Although no information on the appropriate monitoring period after last dose of pertuzumab for cardiac function is available, it is necessary to provide the information that, in the CLEOPATRA study, monitoring of cardiac function after the end of the treatment was required every 6 months during the first year, and once every year up to 3 years afterwards.

*: In the CLEOPATRA study, the patients with the followings were excluded: baseline LVEF <50%, treatment history with anthracycline antineoplastic drugs exceeding a specified dose, uncontrollable hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg), angina unstable, history of cardiac failure congestive, history of serious arrhythmia requiring treatment, history of myocardial infarction within past 6 months, history of LVEF decline to <50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy.

4.(iii).B.(3).6) Infusion reaction

The applicant investigated pertuzumab-induced infusion reactions regarding (a) adverse events that occurred during intravenous infusion of pertuzumab or placebo, (b) adverse events that occurred on the day of intravenous infusion of pertuzumab or placebo including those that occurred during the intravenous infusion, and (c) adverse events that occurred up to the next day of intravenous infusion of pertuzumab or placebo including those that occurred during the intravenous infusion.

The applicant explained as follows:

During the intravenous infusion of pertuzumab or placebo, adverse events occurred in 36 of 407 patients (8.8%) in the pertuzumab combination therapy group and in 20 of 397 patients (5.0%) in the placebo combination therapy group. Of these patients, 1 of 407 patients (0.2%) and 1 of 397 patients (0.3%), respectively, had Grade ≥3 adverse events. Events (all Grades) reported by ≥2 patients in either group were chills, pyrexia, fatigue, hypersensitivity, drug hypersensitivity, nausea, pruritus, erythema, hypertension, and dyspnoea. These events occurred during Cycle 1 in 16 of 407 patients (3.9%) in the pertuzumab combination therapy group and in 8 of 397patients (2.0%) in the placebo combination therapy group, and during Cycle 2, in 7 of 398 patients (1.8%) and in 5 of 385 patients (1.3%), respectively.

On the day of intravenous infusion of pertuzumab or placebo, including during the intravenous infusion, adverse events occurred in 337 of 407 patients (82.8%) in the pertuzumab combination therapy group and in 312 of 397 patients (78.6%) in the placebo combination therapy group. Of these events, Grade ≥3 adverse events occurred in 50 of 407 patients (12.3%) and 42 of 397 patients (10.6%), respectively. Adverse events (all Grades) that occurred with ≥10% incidence in any group and with ≥5% higher incidence in the pertuzumab combination therapy group than in the placebo combination therapy group were diarrhoea and alopecia. These events occurred during Cycle 1 (only pertuzumab or placebo was administered on Day 1) in 78 of 407 patients (19.2%) in the pertuzumab combination therapy group and in 58 of 397 patients (14.6%) in the placebo combination therapy group, and during Cycle 2 (3 drugs were administered on Day 1), in 134 of 398 patients (33.7%) and in 112 of 385 patients (29.1%), respectively.

Up to the next day of intravenous infusion of pertuzumab or placebo, including during the intravenous infusion, adverse events occurred in 359 of 407 patients (88.2%) in the pertuzumab combination therapy group and in 338 of 397 patients (85.1%) in the placebo combination therapy

group. Of these patients, 67 of 407 patients (16.5%) and 59 of 397 patients (14.9%), respectively, had Grade ≥3 adverse events. Adverse events (all Grades) that occurred with ≥10% incidence in any group and with ≥5% higher incidence in the pertuzumab combination therapy group than in the placebo combination therapy group were diarrhoea and alopecia. These events occurred during Cycle 1 in 182 of 407 patients (44.7%) in the pertuzumab combination therapy group and in 155 of 397 patients (39.0%) in the placebo combination therapy group, and during Cycle 2, in 170 of 398 patients (42.7%) and in 163 of 385 patients (42.3%), respectively.

In Cycle 1 of the CLEOPATRA study, pertuzumab or placebo was to be administered on Day 1, and trastuzumab and DTX on Day 2, and only patients who were found to tolerate the treatment could receive the 3 drugs on Day 1 of Cycle 2 and subsequent cycles [see "4.(iii).A. [Evaluation data] (2) Global study"]. PMDA asked the applicant to explain whether or not it is appropriate to administer 3 drugs of pertuzumab, trastuzumab, and DTX, on Day 1 of Cycle 1.

The applicant responded as follows:
In the CLEOPATRA study, administration of trastuzumab and DTX on Day 1 of Cycle 1 was avoided in order to obtain the data for evaluating the presence or absence of pertuzumab-induced infusion reaction. Results showed that, in Cycle 1, the incidence of adverse events occurring during pertuzumab or placebo infusion was low in both groups and did not show any significant difference between the groups, suggesting that pertuzumab has only a low risk of causing infusion reaction. Also, in Cycle 2 and the subsequent cycles, administration of the 3 drugs on the same day did not cause any events to occur with a substantially increased incidence during each treatment.

The foreign phase II study (Study WO20697) in which pertuzumab, trastuzumab, and DTX were given on Day 1 of Cycle 1 showed that (a) adverse events occurred during pertuzumab infusion only in 7 of 107 patients (6.5%) and that (b) although adverse events occurred on the next day of administration of pertuzumab in 45 of 107 patients (42.1%), Grade ≥3 events were observed in only 3 of 107 patients (2.8%). These results suggest that there is only a low risk of infusion reaction even if all the 3 drugs, pertuzumab, trastuzumab, and DTX, are given on Day 1 of Cycle 1.

Based on the above, the applicant considers it appropriate to administer the 3 drugs, pertuzumab, trastuzumab, DTX, on Day 1 of all cycles, including Cycle 1.

PMDA considers as follows:
The incidence of adverse events was higher in the pertuzumab combination therapy group than in the placebo combination therapy group for all of the following period: (a) during the intravenous infusion of pertuzumab or placebo, (b) on the day of intravenous infusion of pertuzumab or placebo, including the duration of the infusion, and (c) up to the next day of intravenous infusion of pertuzumab or placebo, including the duration of the infusion. Therefore, attention should be paid to the events related to infusion reaction in the pertuzumab treatment.

However, since there was no significant difference in the incidence of Grade ≥3 adverse events between the pertuzumab combination therapy group and the placebo combination therapy group, suggesting the tolerability of pertuzumab, PMDA considers that the applicant's explanation that all the 3 drugs (pertuzumab, trastuzumab, DTX) may be administered on Day 1 of Cycle 1 is acceptable.

4.(iii).B.(3).7) Interstitial lung disease

The applicant explained pertuzumab-induced interstitial lung disease as follows:
In the CLEOPATRA study, interstitial lung disease (adverse events corresponding to "Interstitial Lung Disease [narrow]" in the Standardised MedDRA Queries) was observed in 9 of 407 patients (2.2%) in the pertuzumab combination therapy group (breakdown by MedDRA PTs: pneumonitis

[4], interstitial lung disease [2], lung infiltration [1], pulmonary fibrosis [1], and pulmonary toxicity [1]), and in 6 of 397 patients (1.5%) in the placebo combination therapy group (breakdown by MedDRA PTs: pneumonitis [2], lung infiltration [1], pulmonary fibrosis [1], alveolitis [1], and bronchiolitis [1]). Of these patients, 3 of 407 patients (0.7%) and 2 of 397 patients (0.5%), respectively, had Grade ≥3 events.

In the pertuzumab combination therapy group, interstitial lung disease (MedDRA PT) in 2 patients and pneumonitis in 1 patient were regarded as serious adverse events for which a causal relationship to the study drug could not be ruled out, and administration of pertuzumab was discontinued in 1 patient with interstitial lung disease (which occurred on Day 58 after the initiation of pertuzumab administration).

In Japanese patients in the CLEOPATRA study, interstitial lung disease was observed in 2 of 26 patients (7.7%) in the pertuzumab combination therapy group (breakdown by MedDRA PT: interstitial lung disease and pulmonary fibrosis [1 each]); administration of pertuzumab was discontinued in the patient with interstitial lung disease. No interstitial lung disease was reported in the placebo combination therapy group.

PMDA considers as follows:
Interstitial lung disease (adverse events corresponding to "Interstitial Lung Disease [narrow]" in the Standardised MedDRA Queries) were observed in 16 of 1412 patients receiving pertuzumab in any of the clinical studies submitted for this application. Although no fatal cases were reported in those patients, in light of the facts that fatal lung disorder has been reported with trastuzumab, an antibody that targets HER2 as is the case with pertuzumab, and that interstitial lung disease tended to occur with a higher incidence in Japanese patients than in foreign patients and the serious cases were observed, particular caution should be exercised in administering pertuzumab, particularly to Japanese patients.

4.(iii).B.(3).8) Hypersensitivity/anaphylaxis

The applicant explained pertuzumab-induced hypersensitivity/anaphylaxis as follows:
In the CLEOPATRA study, "Anaphylaxis and Hypersensitivity" in AEGT defined by Roche (hypersensitivity/anaphylaxis) occurred in 44 of 407 patients (10.8%) in the pertuzumab combination therapy group (breakdown by MedDRA PT [including patients with multiple events]: hypersensitivity [26], drug hypersensitivity [18], anaphylactic reaction [4]) and in 36 of 397 patients (9.1%) in the placebo combination therapy group (hypersensitivity [20], drug hypersensitivity [15], anaphylactic reaction [2]). Of these adverse events, Grade ≥3 events were observed in 8 of 407 patients (2.0%) in the pertuzumab combination therapy group (hypersensitivity [4], drug hypersensitivity [2], anaphylactic reaction [2]) and in 10 of 397 patients (2.5%) in the placebo combination therapy group (hypersensitivity [3], drug hypersensitivity [6], anaphylactic reaction [1]). Treatment was discontinued in 4 of 407 patients (1.0%) and in 6 of 397 patients (1.5%), respectively.

The median time to the onset of hypersensitivity/anaphylaxis was 2.0 days both in the pertuzumab combination therapy group and in the placebo combination therapy group.

*: Hypersensitivity/anaphylaxis in AEGT defined by Roche include the following MedDRA PTs: anaphylactic reaction, anaphylactic shock, anaphylactic transfusion reaction, anaphylactoid reaction, anaphylactoid shock, application site hypersensitivity, circulatory collapse, documented hypersensitivity to administered drug, drug hypersensitivity, first use syndrome, human seminal plasma hypersensitivity, hypersensitivity, implant site hypersensitivity, infusion site hypersensitivity, injection site hypersensitivity, kounis syndrome, shock, type I hypersensitivity, type II hypersensitivity, type IV hypersensitivity reaction, vaccination site hypersensitivity.

PMDA considers as follows:
The incidence of Grade ≥3 hypersensitivity/anaphylaxis did not tend to be higher in pertuzumab

combination therapy group compared with the placebo combination therapy group. However, there were patients, albeit in small numbers, who experienced serious adverse events (hypersensitivity [3], drug hypersensitivity [3], and anaphylactic reaction [1] in pertuzumab combination therapy group) or who were withdrawn from the treatment. Since prompt and appropriate treatment is critical for hypersensitivity/amaphylaxis, it is necessary to raise caution against these adverse events in an appropriate manner.

4.(iii).B.(3).9) Rash

The applicant explained pertuzumab-induced rash as follows:

In the CLEOPATRA study, "EGFR-Associated Rash"* in AEGT defined by Roche (rash) occurred in 184 of 407 patients (45.2%) in the pertuzumab combination therapy group and in 143 of 397 patients (36.0%) in the placebo combination therapy group. Of these patients, 11 of 407 patients (2.7%) and 5 of 397 patients (1.3%), respectively, had Grade ≥3 events. Treatment was discontinued in 10 of 407 patients (2.5%) and 1 of 397 patients (0.3%), respectively.

*: Rash in AEGT defined by Roche include the following MedDRA PTs: acne, acne cystic, acne fulminans, acne pustular, acute generalized exanthematous pustulosis, butterfly rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis infected, drug eruption, drug rash with eosinophilia and systemic symptoms, eczema, eczema infected, eczema vesicular, erythema, erythema multiforme, erythema of eyelid, exfoliative rash, eyelid folliculitis, folliculitis, furuncle, generalised erythema, ucocutaneous rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash rubelliform, rash scarlatiniform, rash vesicular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic skin eruption, vasculitic rash.

PMDA considers as follows:

Although rash resulted in treatment discontinuation in only a small number of patients, suggesting the tolerability of pertuzumab, the incidence of rash tended to be higher in the pertuzumab combination therapy group compared with the placebo combination therapy group. Therefore, due attention should be paid to rash.

4.(iii).B.(4) Clinical positioning

PMDA has confirmed that the description on pertuzumab in the Japanese and overseas guidelines for the diagnosis and treatment of patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy is as follows. At the current moment, there is no description on pertuzumab in guidelines such as *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 9th edition (PA, USA: Lippincott Williams & Wilkins; 2011), which is one of the international textbook of clinical oncology, or in *Evidence-based Clinical Practice Guideline of Breast Cancer I. Treatment Methods*, 2011 (the Japanese Breast Cancer Society ed. Kanehara & Co., Ltd; 2011).

Clinical practice guidelines

- U.S. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer (v.3.2012):
  Combination therapy with pertuzumab/trastuzumab/taxane antineoplastic drug is recommended for treating patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy, and as taxane antineoplastic drugs, DTX is recommend for category 1 and PTX for category 2A.

  Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
  Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Based on the results of the review of sections "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," PMDA considers clinical usefulness of pertuzumab as follows:
The CLEOPATRA study failed to confirm the consistency of PFS between the Japanese population and the total population. On the other hand, the total population of the CLEOPATRA study showed prolongation of not only PFS assessed by IRF, the primary endpoint, but also OS (the true endpoint) defined as the secondary endpoint in the study. This result suggests that, both in and outside of Japan, pertuzumab will tremendously affect the treatment of patients with HER2-positive inoperable or recurrent breast cancer who have not received chemotherapy. In addition to the above-mentioned situations, PMDA has concluded that pertuzumab is positioned as a treatment option for Japanese patients, based on the comprehensive review of the following findings: (a) the second interim analysis of OS in the Japanese population showed no concern for detecting any adverse effect of concomitant use of trastuzumab/DTX with pertuzumab on OS, (b) the medical environment in the breast cancer field is similar among the countries or regions that participated in the CLEOPATRA study, (c) no clear difference in PK of pertuzumab was observed between Japanese and foreign patients [see "4.(ii).B.(1) PK of pertuzumab in Japanese and foreign populations"], and (d) concomitant use of pertuzumab/trastuzumab/DTX was tolerated in the Japanese population.

However, since limited information is currently available on the efficacy of pertuzumab in Japanese patients, and since efficacy information in Japanese patients is important in weighing the benefits and risks of treatment methods in routine clinical practice in Japan, it is necessary to continue to collect the relevant information after the market launch [see "4.(iii).B.(7) Post-marketing investigations"]. Also, efficacy information in Japanese patients obtained in the CLEOPATRA study should be provided appropriately in the package insert and other materials.

4.(iii).B.(5) Indication
The proposed indication for pertuzumab was "HER2-positive inoperable or recurrent breast cancer." Also, at the time of regulatory submission, the applicant explained that the Precautions for Indications section would include the following: (a) as is the case with trastuzumab, test for HER2 should be performed by pathologists or laboratories with sufficient experience, and (b) the efficacy and safety of pertuzumab in adjuvant chemotherapy have not been established.

Upon reviewing "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," "4.(iii).B.(4) Clinical positioning," and the following in this section, PMDA has concluded that the indication should be "HER2-positive inoperable or recurrent breast cancer" and that caution should be provided in Precautions for Indications section that the efficacy and safety of pertuzumab in neo-adjuvant chemotherapy have not been established, in addition to the description proposed by the applicant as above. Therefore, the Precautions for Indications section should include the following statement.

- Testing for HER2 should be performed by an experienced pathologist or in a laboratory with demonstrated expertise in such testing.
- The efficacy and safety of pertuzumab in neo-adjuvant or adjuvant chemotherapy have not been established.

4.(iii).B.(5).1) Selection of patients based on HER2 expression level
PMDA asked the applicant to explain the background/reason for setting the inclusion criterion related to HER2 expression level in the CLEOPATRA study (patients with inoperable or recurrent breast cancer of IHC 0/1+ could also be enrolled if FISH-positive) and the efficacy for each HER2 level.

The applicant responded as follows:
At the initiation of the CLEOPATRA study (February 2008), patients were screened for HER2 expression level first by IHC. If IHC 3+, patients were determined to be eligible without

undergoing FISH test. If IHC2+, patinets underwent FISH test, and they were eligible if FISH positive. In IHC staining, cases of HER2 protein overexpression (IHC 3+/2+) can be detected if test specimens are handled appropriately. However, such specimens may be judged as IHC 0/1+ as a result of the degradation of HER2 protein due to inappropriate specimen handling. In contrast, the clinical usefulness of FISH test had been established. With these situations taken into consideration and in order to screen patients more rapidly, the new screening method was employed from August 2008 in which IHC and FISH tests were performed simultaneously, and patients with IHC 3+ (regardless of the results of FISH test) and patients positive for FISH (regardless of the results of IHC staining) were defined as eligible.

In the CLEOPATRA study, HER2 expression levels and the efficacy by HER2 expression level were as shown in the table below. Results of PFS (IRF assessment) and of OS (at the final analysis of PFS) suggest that in the IHC 3+ subpopulation, the efficacy is expected regardless of the results of FISH test; and in the IHC 2+ subpopulation, the efficacy is expected only in FISH-positive patients, judging from the finding that all patients in this subpopulation were FISH-positive except 1 patient in the placebo combination therapy group (protocol deviation). In the subpopulation of IHC unknown/0/1+, all patients were FISH-positive, and PFS (IRF assessment) and OS (at final analysis of PFS) were 4.3 to 31.1 months and 23.0 to 32.2 months, respectively, in the pertuzumab combination therapy group (5 patients) and 2.0 to 8.3 months and 6.9 to 14.0 months, respectively, in the placebo combination therapy group (3 patients). Thus, the results, albeit obtained from a limited number of patients, at least did not negate the efficacy of pertuzumab.

Based on the above, the applicant considered that pertuzumab is recommendable for patients who are IHC 3+ or FISH-positive but not for other patients.

HER2 expression level and efficacy (the CLEOPATRA study)

HER2 expression level		Pertuzumab combination therapy group (N = 402) No. of patients (%)	Placebo combination therapy group (N = 406) No. of patients (%)	Hazard ratio [95% CI] of PFS (IRF assessment) in pertuzumab combination therapy group to placebo combination therapy group	Hazard ratio [95% CI] of OS (at final analysis of PFS) in pertuzumab combination therapy group to placebo combination therapy group
IHC	FISH				
Unknown	Unknown	0	0	–*2	–*2
	Negative	0	0		
	Positive	1 (0.2)	1 (0.2)		
0	Unknown	0	0	–*2	–*2
	Negative	0	0		
	Positive	2 (0.5)	0		
1+	Unknown	0	0	–*2	–*2
	Negative	0	0		
	Positive	2 (0.5)	2 (0.5)		
2+	Unknown	0	0	0.90 [0.53, 1.54]	0.54 [0.24, 1.26]
	Negative	0	1 (0.2)		
	Positive	47 (11.7)	31 (7.6)		
3+	Unknown	17 (4.2)	19 (4.7)	0.60 [0.49, 0.74]	0.66 [0.47, 0.93]
	Negative	1 (0.2)	3 (0.7)		
	Positive	332 (82.6)	349 (86.0)		

*1: Mistakenly enrolled patient (protocol deviation), *2: Not calculated because of a small number of patients.

Herceptin for Injection 60 and 150, which contains the active ingredient trastuzumab that targets HER2, is indicated for breast cancer in which “HER2 overexpression is confirmed,” whereas the proposed indication of pertuzumab is “HER2-positive” breast cancer. Therefore, PMDA asked the applicant to explain whether or not the target patient population of pertuzumab is different from that of trastuzumab.

The applicant responded as follows:
At the time when trastuzumab was approved, the drug was targeted at patients in whom HER2 protein measured by IHC staining was overexpressed above a certain level. Therefore, the indication was "HER2 overexpressed" breast cancer. However, FISH has come to be widely used as a method for testing HER2 expression and, currently, trastuzumab is used in patients who are IHC 3+ or FISH-positive, namely "HER2-positive" patients, as is the case with pertuzumab.

Taking account of these situations, the indication has been set as "HER2-positive" breast cancer, as a more appropriate description at the current moment, although it is different from that used for trastuzumab which is intended for the same patient population. In the United States, trastuzumab is approved for the indication for "HER2-overexpressing" breast cancer. In contrast, the proposed indication in the application of pertuzumab in the United States and the EU is "HER2-positive" breast cancer, and the product was approved as submitted in the United States [see "1.(2) Development history etc."].

PMDA considers as follows:
Among IHC 3+ or FISH-positive patients, the population for whom pertuzumab is recommended, the subpopulation who are IHC unknown/0/1+ and FISH-positive have produced only a small amount of study data, thus, it is not possible to come to a conclusion on the efficacy in this subpopulation. However, PMDA accepted the applicant's response that pertuzumab is recommended for IHC 3+ or FISH-positive patients, for the following reasons:

- In the CLEOPATRA study, results obtained from the subpopulation who were IHC unknown/0/1+ and FISH-positive at least did not negate the efficacy of pertuzumab.
- The Japanese clinical practice guidelines define IHC staining as the first choice for HER2 test for reasons of health insurance coverage, but also state that it is appropriate to perform a FISH test first and, if IHC 2+, repeat the FISH test, by citing the guideline of the American Society of Clinical Oncology (*J Clin Oncol*. 2007;25:118-45) and other guidelines (*Evidence-based Clinical Practice Guideline of Breast Cancer 2. Epidemiology and Diagnosis*, 2011, the Japanese Breast Cancer Society ed. Kanehara & Co., Ltd., 2011).

Also, by taking into account the intended patient population of trastuzumab in the current routine clinical practice, PMDA accepted the response of the applicant, and regarding the indication, concluded that it is acceptable to use the expression "HER2-positive" which is different from the description of the indication of trastuzumab. However, it is necessary to provide information, using materials, etc., to facilitate understanding of the target patients of pertuzumab and trastuzumab selected based on HER2 expression level (including IHC 3+ or FISH positive).

4.(iii).B.(5).2) Efficacy and safety of pertuzumab in neo-adjuvant or adjuvant chemotherapy

In the proposed indication in the draft package insert at the time of regulatory submission, a caution was provided in the Precautions for Indications section that the efficacy and safety of pertuzumab in adjuvant chemotherapy have not been established, whereas no caution was provided for neo-adjuvant chemotherapy. Therefore, PMDA asked the applicant to explain the necessity of providing such caution.

The applicant responded as follows:
The efficacy and safety of pertuzumab in adjuvant chemotherapy are currently being evaluated in the global phase III study (Study BO25126 [Study APHINITY]). The efficacy and safety of pertuzumab in neo-adjuvant chemotherapy were evaluated in the foreign phase II study (Study WO20697 [Study NEOSPHERE]) involving 417 patients with HER2-positive early breast cancer. Study results showed that concomitant use of pertuzumab/trastuzumab/DTX significantly

increased the pathological complete response rate, which was the primary endpoint, and that there were no additional safety concerns. Therefore, neo-adjuvant chemotherapy was not included in the Precautions for Indications section of the draft package insert submitted in the application. However, in view of the fact that the results of confirmatory studies have not been obtained on the efficacy of the combination of pertuzumab/trastuzumab/DTX in neo-adjuvant chemotherapy, caution will be provided regarding this proviso in the Precautions for Indications section.

PMDA accepted the response of the applicant.

4.(iii).B.(6) Dosage and administration

The proposed dosage and administration was as follows: "The usual loading dose for adults is 840 mg of pertuzumab administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab as 60-minute infusions every 3 weeks, in combination with other antineoplastic drugs. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated."

As a result of the following review, PMDA has concluded that, since pertuzumab is administered at least in combination with trastuzumab, the description of concomitant drugs, "in concomitant use with other antineoplastic drugs," should not be used and "in concomitant use with trastuzumab and other antineoplastic drugs" should be included in the Dosage and Administration section. PMDA has also concluded that it is appropriate to include the following cautions in the Precautions for Dosage and Administration section.

- Treatment with pertuzumab should be started in combination with other antineoplastic drugs and continued in combination with trastuzumab.
- Antineoplastic drugs other than trastuzumab to be concomitantly administered with pertuzumab should be selected by a physician with a thorough understanding of the "Clinical Studies" section.
- The efficacy and safety of pertuzumab monotherapy have not been established.
- If administration delays for any reason, it is advisable to administer pertuzumab according to the following procedure:
  - If 6 weeks have not passed since the previous administration, administer 420 mg.
  - 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.

4.(iii).B.(6).1) Dose and dosing intervals

The applicant explained the rationale for the dose, dosing intervals, and dose adjustment, as follows:

In the foreign phase I study (Study TOC2297g) in which pertuzumab alone was administered up to the dose of 15 mg/kg, MTD was not reached. In the Japanese phase I study (Study JO17076) in which pertuzumab was administered up to the dose of 25 mg/kg, MTD was not reached. From these results and from the results of pertuzumab 420 mg administration, it was predicted that the target trough serum concentration of 20 μg/mL could be reached in a majority of patients. Therefore, in the CLEOPATRA study, the dose and dosing intervals were set as a loading dose of 840 mg followed by 420 mg every 3 weeks, so that pertuzumab concentration could reach steady state rapidly [see "4.(ii).B.(2) Determination of dosage and administration"]. Since the study results confirmed the efficacy and safety of pertuzumab, this dose and dosing interval were set as the proposed dosage and administration.

In the CLEOPATRA study, when pertuzumab administration was deferred, the procedures were taken as shown in the table below. Therefore, this will be included in the Precautions for Dosage and Administration section to provide caution.

Procedure taken when pertuzumab was not administered as scheduled (the CLEOPATRA study)

Time of delay in pertuzumab administration	Procedure
<6 weeks	Administer 420 mg of pertuzumab every 3 weeks
≥6 weeks	Administer the re-loading dose of 840 mg. For the subsequent doses, administer 420 mg every 3 weeks.

PMDA considers as follows:
PMDA accepted the response of the applicant. However, the CLEOPATRA study specified a procedure to be taken in case of delays in trastuzumab administration that is different from that stipulated in the Precautions for Dosage and Administration section of the current package insert for trastuzumab, using the same rule as that for pertuzumab (in case of ≥6 week delay, 8 mg/kg, which is the initial loading dose, should be given). This information should be provided appropriately.

4.(iii).B.(6).2) Administration method
The applicant explained pertuzumab monotherapy and concomitant use with antineoplastic drugs other than DTX, as follows:
(a) Monotherapy:
Since the clinical usefulness of pertuzumab monotherapy has not been established, pertuzumab monotherapy is not recommended.

(b) Concomitant use with antineoplastic drugs other than DTX:
From the mechanism of action of pertuzumab and from the results of nonclinical and clinical studies conducted, pertuzumab is expected to exhibit clinical usefulness when used as an add-on drug to concomitant use of trastuzumab with other antineoplastic drugs.

Currently, a pertuzumab/trastuzumab/PTX concomitant therapy study (Study US IST MSKCC [investigator-initiated foreign phase II study]) and a pertuzumab/trastuzumab emtansine (genetical recombination) (T-DM1, which have not been approved in Japan) concomitant therapy study (global phase III study [Study BO22589, (MARIANNE study)]) are being conducted to evaluate the efficacy and safety. In future, pertuzumab may possibly be used also in combination with antineoplastic drugs other than trastuzumab and DTX.

At the current moment, however, it is not recommended to concomitantly administer pertuzumab with antineoplastic drugs other than trastuzumab/DTX, the combination evaluated in the CLEOPATRA study.

For reasons described in (a) and (b) above, it will be specified in the Dosage and Administration section that pertuzumab be administered in combination with other antineoplastic drugs and the following cautions will be included in the Precautions for Dosage and Administration section.

- The efficacy and safety of pertuzumab monotherapy have not been established.
- Treatment with pertuzumab should be started in combination with other antineoplastic drugs including trastuzumab and continued in combination with trastuzumab.
- Other antineoplastic drugs to be concomitantly administered with pertuzumab should be selected by a physician with a thorough understanding of the “Clinical Studies” section.

PMDA considers as follows:
The applicant’s response generally acceptable. However, given that pertuzumab is expected to exhibit efficacy in combination use with other antineoplastic drugs including at least trastuzumab, and that the efficacy and safety of pertuzumab were, and are being, evaluated in concomitant use

with other antineoplastic drugs including trastuzumab, PMDA has concluded that in order to clarify the necessity of combination use of pertuzumab at least with trastuzumab, the dosage and administration should be set as follows.

[Dosage and Administration]
The usual loading dose for adults is 840 mg of pertuzumab administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab as 60-minute infusions every 3 weeks, in combination with other antineoplastic drugs including trastuzumab. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

4.(iii).B.(7) Post-marketing investigations
The applicant explained the items to be investigated in the post-marketing surveillance at the time of application, as follows:
The applicant plans to conduct a post-marketing surveillance of breast cancer patients treated with pertuzumab using the central registration system in order to evaluate items such as the safety of pertuzumab in routine use.

The priority item of the post-marketing surveillance will be febrile neutropenia. The adverse event was one of the Grade ≥3 adverse events with an incidence of ≥5% observed in the pertuzumab combination therapy group in the CLEOPATRA study (neutropenia, febrile neutropenia, leukopenia, diarrhoea), and it occurred with a particularly higher incidence in the pertuzumab combination therapy group compared with the placebo combination therapy group. In addition, the event was considered to affect continued administration of pertuzumab. Detailed information, such as the incidence, time of onset, and seriousness of febrile neutropenia in clinical practice will be collected, and whether it may be a factor affecting continued treatment will be investigated. Infusion reaction and hypersensitivity/anaphylaxis, which are the adverse events considered to be characteristic to antibody drugs, will not be handled as priority items because, in the CLEOPATRA study, they did not show any clear increase in the incidence in the pertuzumab combination therapy group compared with the placebo combination therapy group.

The planned sample size for analysis in this post-marketing surveillance is 300 patients, the number that allows estimating the incidence of febrile neutropenia in routine clinical use of pertuzumab and at the same time provides a ≥95% probability of detecting a minimum of one case of unknown adverse drug reaction with an incidence of 1%. The post-marketing surveillance will be conducted at approximately 200 centers, and the recruitment period required will be 2 years.

As regards the observation period for each patient in this post-marketing surveillance, since the incidence of adverse events observed in the CLEOPATRA study tended to decrease with increasing treatment cycle, it is expected that information on most of adverse events, including febrile neutropenia which is the priority item of this post-marketing surveillance, can be collected by observation up to Cycle 8 (6 months) of administration of pertuzumab. Therefore, from the aspect of safety evaluation, it will be sufficient to observe each patient up to Cycle 8 (6 months). However, since information on efficacy such as PFS will be collected in the post-marketing surveillance for reference purposes as well, the observation period for each patient will be set at 2 years, taking account of the treatment duration in Japanese patients in the CLEOPATRA study (median, 17.5 cycles; range, 3-30 cycles).

PMDA considers as follows:
Concomitant use of pertuzumab caused no additional safety problems other than those observed with administration of trastuzumab, an antibody that targets HER2, as is the case with pertuzumab. However, given the limited number of patients treated with pertuzumab before the submission of

the application, there is no sufficient information accumulated on the safety of pertuzumab in Japanese patients. Also, taking into account the review in "4.(iii).B.(4) Clinical positioning" section, it is necessary to continue to collect information on the efficacy of pertuzumab in Japanese patients after the market launch. Therefore, the post-marketing surveillance should be performed to collect information not only on the safety but also on the efficacy of pertuzumab in Japanese patients with breast cancer.

In collecting safety information, the priority items should include not only febrile neutropenia selected by the applicant, but also interstitial lung disease, the event that occurred with a higher incidence in Japanese patients than in foreign patients in the CLEOPATRA study. The planned sample size for analysis and the observation period should be reviewed according to the change of the priority items, etc.

Taking account of the review in "4.(iii).B.(4) Clinical positioning" section, PMDA considered it necessary to continue to collect efficacy information in Japanese patients after the market launch, and asked the applicant to explain the plan for collecting efficacy information.

The applicant responded as follows:
Efficacy information in Japanese patients will continue to be collected (a) from the following 2 currently ongoing Japanese phase III randomized comparative studies involving patients with HER2-positive breast cancer and (b) from such as the scheduled investigator-initiated Japanese randomized comparative study in patients with HER2-positive operable early breast cancer to evaluate the efficacy of concomitant use of pertuzumab/trastuzumab/chemotherapy as neo-adjuvant chemotherapy.

- MARIANNE study: Study to evaluate the efficacy and safety of combination therapy of pertuzumab/trastuzumab emtansine (genetical recombination) (which have not been approved in Japan) in patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy
- APHINITY study: Study to evaluate the efficacy and safety of concomitant use of pertuzumab/trastuzumab/chemotherapy as adjuvant chemotherapy in patients with HER2-positive operable early breast cancer

PMDA accepted the response of the applicant.

4.(iv) Adverse events observed in clinical studies

Deaths reported in the clinical studies submitted as the safety evaluation data were described in "4.(iii) Summary of clinical efficacy and safety." Other main adverse events were shown below.

4.(iv).(1) Japanese phase I study (Study JO17076)

Adverse events were observed in all patients (100%) in the 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, and 25 mg/kg groups, and those for which a causal relationship with pertuzumab could not be ruled out were also observed in all patients. Adverse events reported by ≥2 patients in any group were as shown in the following table.

Adverse events reported by ≥2 patients in any group

Event	Number of patients (%)									
	5 mg/kg group N = 3		10 mg/kg group N = 3		15 mg/kg group N = 3		20 mg/kg group N = 3		25 mg/kg group N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	0	3 (100)	0	3 (100)	1 (33)	3 (100)	0	6 (100)	1 (17)
Diarrhoea	2 (67)	0	3 (100)	0	3 (100)	0	2 (67)	0	1 (17)	0
Brain natriuretic peptide increased	2 (67)	0	0	0	2 (67)	0	1 (33)	0	4 (67)	0
Rash	3 (100)	0	2 (67)	0	1 (33)	0	0	0	3 (50)	0
Lymphocyte count decreased	1 (33)	0	1 (33)	0	2 (67)	1 (33)	2 (67)	0	2 (33)	1 (17)
White blood cell count increased	2 (67)	0	2 (67)	0	2 (67)	0	2 (67)	0	0	0
Haemoglobin decreased	1 (33)	0	1 (33)	0	0	0	2 (67)	0	3 (50)	0
Hyperglycaemia	1 (33)	0	2 (67)	0	2 (67)	0	1 (33)	0	1 (17)	0
Blood albumin decreased	1 (33)	0	2 (67)	0	0	0	2 (67)	0	1 (17)	0
AST increased	0	0	0	0	1 (33)	1 (33)	2 (67)	0	2 (33)	0
Blood ALP increased	1 (33)	0	0	0	2 (67)	0	1 (33)	0	1 (17)	0
Neutrophil count increased	2 (67)	0	1 (33)	0	2 (67)	0	0	0	0	0
Urinary occult blood positive	2 (67)	0	0	0	0	0	1 (33)	0	2 (33)	0
Nausea	2 (67)	0	0	0	1 (33)	0	1 (33)	0	1 (17)	0
INR increased	0	0	0	0	2 (67)	0	0	0	2 (33)	0
ALT increased	0	0	0	0	2 (67)	0	1 (33)	0	1 (17)	0
Blood LDH increased	1 (33)	0	0	0	2 (67)	0	1 (33)	0	0	0
White blood cell count decreased	1 (33)	0	0	0	0	0	2 (67)	0	1 (17)	0
Vomiting	2 (67)	0	0	0	1 (33)	0	1 (33)	0	0	0

AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

The serious adverse event observed was intestinal obstruction in 1 of 3 patients (33%) in the 20 mg/kg group. A causal relationship of the serious adverse event with pertuzumab was ruled out. There were no adverse events leading to pertuzumab discontinuation.

4.(iv).(2) Global phase III study (Study WO20698 [CLEOPATRA study])

Adverse events were observed in 406 of 407 patients (100%) in the pertuzumab combination therapy group and in 391 of 397 patients (98%) in the placebo combination therapy group. Adverse events for which a causal relationship with pertuzumab or placebo could not be ruled out were observed in 396 of 407 patients (97%) in the pertuzumab combination therapy group and in 382 of 397 patients (96%) in the placebo combination therapy group. Adverse events with an incidence of ≥10% in either group were as shown in the table below.

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

Event	Number of patients (%)			
	Pertuzumab combination therapy group N = 407		Placebo combination therapy group N = 397	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	406 (100)	302 (74)	391 (98)	289 (73)
Alopecia	248 (61)	0	240 (60)	1 (<1)
Diarrhoea	272 (67)	32 (8)	184 (46)	20 (5)
Neutropenia	215 (53)	199 (49)	197 (50)	182 (46)
Nausea	172 (42)	5 (1)	165 (42)	2 (1)
Fatigue	153 (38)	9 (2)	146 (37)	13 (3)
Rash	137 (34)	3 (1)	96 (24)	3 (1)
Asthenia	106 (26)	10 (2)	120 (30)	6 (2)
Decreased appetite	119 (29)	7 (2)	105 (26)	6 (2)
Oedema peripheral	94 (23)	2 (<1)	119 (30)	3 (1)
Vomiting	98 (24)	6 (1)	95 (24)	6 (2)
Mucosal inflammation	113 (28)	6 (1)	79 (20)	4 (1)
Myalgia	93 (23)	4 (1)	95 (24)	3 (1)
Nail disorder	93 (23)	5 (1)	91 (23)	1 (<1)
Anaemia	94 (23)	10 (2)	75 (19)	14 (4)
Neuropathy peripheral	86 (21)	11 (3)	80 (20)	7 (2)
Cough	87 (21)	2 (<1)	74 (19)	1 (<1)
Constipation	61 (15)	0	99 (25)	4 (1)
Leukopenia	74 (18)	50 (12)	81 (20)	58 (15)
Headache	85 (21)	5 (1)	67 (17)	2 (1)
Pyrexia	76 (19)	5 (1)	71 (18)	2 (1)
Stomatitis	77 (19)	2 (<1)	61 (15)	1 (<1)
Dysgeusia	75 (18)	0	62 (16)	0
Arthralgia	63 (15)	1 (<1)	64 (16)	3 (1)
Upper respiratory tract infection	68 (17)	3 (1)	53 (13)	0
Dyspnoea	57 (14)	4 (1)	62 (16)	8 (2)
Lacrimation increased	57 (14)	0	55 (14)	0
Pain in extremity	62 (15)	2 (<1)	47 (12)	1 (<1)
Insomnia	54 (13)	0	53 (13)	0
Abdominal pain	57 (14)	0	49 (12)	3 (1)
Peripheral sensory neuropathy	49 (12)	2 (<1)	56 (14)	1 (<1)
Back pain	55 (14)	6 (1)	46 (12)	4 (1)
Nasopharyngitis	48 (12)	0	51 (13)	1 (<1)
Dizziness	51 (13)	2 (<1)	48 (12)	0
Pruritus	57 (14)	0	40 (10)	0
Dyspepsia	49 (12)	0	48 (12)	0
Oedema	46 (11)	2 (<1)	50 (13)	4 (1)
Febrile neutropenia	56 (14)	56 (14)	30 (8)	30 (8)
Paraesthesia	37 (9)	1 (<1)	40 (10)	3 (1)
Dry skin	43 (11)	0	17 (4)	0

Serious adverse events were observed in 140 of 407 patients (34%) in the pertuzumab combination therapy group and in 104 of 397 patients (26%) in the placebo combination therapy group. Serious adverse events reported by ≥2 patients include febrile neutropenia (46 patients), neutropenia (18 patients), diarrhoea (11 patients), cellulitis (7 patients), pyrexia (6 patients), pneumonia (5 patients), neutropenic infection, pulmonary embolism, and left ventricular dysfunction (4 patients each), anaemia, urinary tract infection, lower respiratory tract infection, drug hypersensitivity, hypersensitivity, and deep vein thrombosis (3 patients each), gastroenteritis, pharyngitis, upper respiratory tract infection, urosepsis, vomiting, oesophagitis, fatigue, asthenia, influenza like illness, pleural effusion, dyspnoea, interstitial lung disease, back pain, and femur fracture (2 patients each) in the pertuzumab combination therapy group; and febrile neutropenia (20 patients), neutropenia (19 patients), pneumonia and left ventricular dysfunction (7 patients each), diarrhoea (5 patients), pleural effusion (4 patients), anaemia, herpes zoster, sepsis, pyrexia,

and drug hypersensitivity (3 patients each), cellulitis, neutropenic sepsis, viral infection, intestinal perforation, constipation, chest pain, general physical health deterioration, dyspnoea, atrial fibrillation, myocardial infarction, dehydration, and renal failure acute (2 patients each) in the placebo combination therapy group. Of these, a causal relationship with pertuzumab or placebo could not be ruled out for febrile neutropenia (46 patients), neutropenia (18 patients), diarrhoea (10 patients), cellulitis and left ventricular dysfunction (4 patients each), neutropenic infection, urinary tract infection, lower respiratory tract infection, drug hypersensitivity, and hypersensitivity (3 patients each), pyrexia, pneumonia, anaemia, vomiting, and interstitial lung disease (2 patients each), urosepsis, oesophagitis, fatigue, asthenia, back pain, pleural effusion, and pulmonary embolism (1 patient each) in the pertuzumab combination therapy group; and febrile neutropenia and neutropenia (19 patients each), left ventricular dysfunction (7 patients), diarrhoea, anaemia, herpes zoster, and drug hypersensitivity (3 patients each), pneumonia, pyrexia, neutropenic sepsis, intestinal perforation, and dehydration (2 patients each), sepsis, viral infection, atrial fibrillation, and myocardial infarction (1 patient each) in the placebo combination therapy group.

Adverse events leading to discontinuation of pertuzumab, placebo, or trastuzumab (those leading to discontinuation of only DTX were excluded) were observed in 25 of 407 patients (6%) in the pertuzumab combination therapy group and in 21 of 397 patients (5%) in the placebo combination therapy group. These adverse events observed in the pertuzumab combination therapy group were left ventricular dysfunction (6 patients), hypersensitivity, diarrhoea, and rash (2 patients each), cardiovascular insufficiency, ventricular fibrillation, drug hypersensitivity, anaphylactic reaction, urinary tract infection, sepsis, dermatitis allergic, fatigue, interstitial lung disease, neuropathy peripheral, cerebrovascular accident, back pain, febrile neutropenia, and haematoma (1 patient each); and those observed in the placebo combination therapy group were left ventricular dysfunction (8 patients), myocardial ischaemia, pericardial effusion, hypersensitivity, drug hypersensitivity, diarrhoea, intestinal perforation, herpes simplex, post operative wound infection, rash erythematous, fatigue, asthenia, dyspnoea, pleural effusion, and fluid retention (1 patient each). Of these, a causal relationship with pertuzumab, placebo, or trastuzumab could not be ruled out for left ventricular dysfunction (6 patients), hypersensitivity and diarrhoea (2 patients each), cardiovascular insufficiency, ventricular fibrillation, drug hypersensitivity, anaphylactic reaction, urinary tract infection, rash, dermatitis allergic, fatigue, interstitial lung disease, neuropathy peripheral, back pain, and febrile neutropenia (1 patient each) in the pertuzumab combination therapy group; and left ventricular dysfunction (8 patients), myocardial ischaemia, pericardial effusion, hypersensitivity, drug hypersensitivity, diarrhoea, intestinal perforation, herpes simplex, rash erythematous, fatigue, asthenia, dyspnoea, and pleural effusion (1 patient each) in the placebo combination therapy group.

4.(iv).(3) Foreign phase I study (Study TOC2297g)

Adverse events were observed in all patients (100%) in the 0.5 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg, and 15 mg/kg groups, and those for which a causal relationship with pertuzumab could not be ruled out were observed in 16 of 21 patients (76%). Adverse events reported by ≥2 patients in any group were as shown in the table below.

Adverse events reported by ≥2 patients in any group

Event	Number of patients (%)									
	0.5 mg/kg group N = 3		2 mg/kg group N = 3		5 mg/kg group N = 4		10 mg/kg group N = 3		15 mg/kg group N = 8	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	3 (100)	1 (33)	4 (100)	2 (50)	3 (100)	0	8 (100)	6 (75)
Fatigue	3 (100)	0	1 (33)	0	1 (25)	0	1 (33)	0	5 (63)	0
Vomiting	3 (100)	0	1 (33)	0	4 (100)	0	0	0	3 (38)	1 (13)
Nausea	3 (100)	1 (33)	1 (33)	0	2 (50)	0	2 (67)	0	2 (25)	0
Anaemia	2 (67)	0	0	0	0	0	2 (67)	0	3 (38)	0
Diarrhoea	0	0	1 (33)	0	1 (25)	0	1 (33)	0	3 (38)	1 (13)
Dyspepsia	1 (33)	0	0	0	1 (25)	0	1 (33)	0	3 (38)	0
Pyrexia	2 (67)	0	1 (33)	0	1 (25)	0	0	0	2 (25)	0
Rash	0	0	2 (67)	0	1 (25)	0	2 (67)	0	1 (13)	0
Blood ALP increased	1 (33)	0	1 (33)	0	0	0	1 (33)	0	2 (25)	0
Constipation	2 (67)	0	0	0	1 (25)	0	0	0	2 (25)	0

ALP: Alkaline phosphatase

Serious adverse events were observed in a total of 11 of 21 patients (52%) in the 0.5 mg/kg, 2 mg/kg, 5 mg/kg, and 15 mg/kg groups combined. Serious adverse events observed were pleural effusion, pleuritic pain, jugular vein thrombosis, metastatic breast cancer, and ureteric stenosis (1 patient each) in the 0.5 mg/kg group; supraventricular tachycardia (1 patient) in the 2 mg/kg group; mental status changes and depression (1 patient each) in the 5 mg/kg group; and pleural effusion, gastric varices haemorrhage, gastric haemorrhage, diarrhoea, anaemia, myocardial infarction, pain, chest pain, drug hypersensitivity, and abdominal pain (1 patient each) in the 15 mg/kg group. Of these, a causal relationship to pertuzumab could not be ruled out for gastric varices haemorrhage, gastric haemorrhage, diarrhoea, and anaemia (1 patient each) in the 15 mg/kg group.

There were no adverse events leading to pertuzumab discontinuation.

4.(iv).(4) Foreign phase II study (Study BO17929)

Adverse events were observed in 64 of 66 patients (97%) in cohorts 1 and 2 combined and in 28 of 29 patients (97%) in cohort 3 and those for which a causal relationship with pertuzumab could not be ruled out were observed in 54 of 66 patients (82%) and 23 of 29 patients (79%), respectively. Adverse events with an incidence of ≥10% in cohorts 1 and 2 combined and in cohort 3 were as shown in the table below.

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

Event	Number of patients (%)			
	Cohorts 1 and 2 N = 66		Cohort 3 N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	64 (97)	10 (15)	28 (97)	7 (24)
Diarrhoea	42 (64)	2 (3)	16 (55)	2 (7)
Fatigue	24 (36)	0	8 (28)	2 (7)
Nausea	19 (29)	0	12 (41)	0
Rash	18 (27)	1 (2)	5 (17)	0
Headache	15 (23)	0	4 (14)	0
Vomiting	8 (12)	0	10 (34)	0
Arthralgia	12 (18)	0	4 (14)	0
Decreased appetite	11 (17)	0	5 (17)	0
Asthenia	9 (14)	1 (2)	6 (21)	0
Cough	11 (17)	0	3 (10)	0
Pruritus	9 (14)	0	4 (14)	0
Myalgia	12 (18)	0	0	0
Constipation	9 (14)	0	3 (10)	0
Back pain	5 (8)	1 (2)	6 (21)	1 (3)
Dizziness	9 (14)	1 (2)	2 (7)	0
Muscle spasms	9 (14)	0	1 (3)	0
Dyspepsia	8 (12)	0	2 (7)	0
Dyspnoea	6 (9)	0	3 (10)	0
Pain in extremity	6 (9)	0	3 (10)	0
Abdominal pain upper	5 (8)	0	4 (14)	0
Nail disorder	7 (11)	0	2 (7)	0
Musculoskeletal chest pain	5 (8)	0	3 (10)	0
Paraesthesia	8 (12)	0	0	0
Nasopharyngitis	7 (11)	0	1 (3)	0
Chills	4 (6)	0	3 (10)	0
Oropharyngeal pain	3 (5)	0	3 (10)	1 (3)
Upper respiratory tract infection	3 (5)	0	3 (10)	0
Abdominal distension	3 (5)	0	3 (10)	0
Weight decreased	0	0	3 (10)	0

Serious adverse events were observed in 10 of 66 patients (15%) in cohorts 1 and 2 and in 1 of 29 patients (3%) in cohort 3. Serious adverse events observed in cohorts 1 and 2 were back pain (2 patients), cellulitis, central line infection, pneumonia, palpitations, haematemesis, performance status decreased, hepatic failure, hypokalaemia, loss of consciousness, toe amputation, and deep vein thrombosis (1 patient each), and those observed in cohort 3 were femur fracture and osmotic demyelination syndrome (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for central line infection and palpitations (1 patient each) in cohorts 1 and 2 and osmotic demyelination syndrome (1 patient) in cohort 3.

Adverse events leading to pertuzumab discontinuation were reported by 2 of 66 patients (3%) in cohorts 1 and 2 and 1 of 29 patients (3%) in cohort 3. These adverse events include somnolence and diplopia (1 patient each) in cohorts 1 and 2 and osmotic demyelination syndrome (1 patient) in cohort 3. Of these, a causal relationship to pertuzumab could not be ruled out for osmotic demyelination syndrome (1 patient) in cohort 3.

4.(iv).(5) Foreign phase I study (Study BO17003)

Adverse events were observed in all patients (100%) of each dose level, and those for which a causal relationship with pertuzumab could not be ruled out were also observed in all the patients. Adverse events reported by ≥2 patients in any group were as shown in the table below.

Adverse events reported by ≥2 patients in any group

Event	Number of patients (%)					
	Dose level 1 N = 5		Dose level 2 N = 6		Dose level 3 N = 7	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	5 (100)	1 (20)	6 (100)	1 (17)	7 (100)	1 (14)
Diarrhoea	3 (60)	0	3 (50)	0	7 (100)	0
Nausea	4 (80)	0	4 (67)	0	4 (57)	0
Inappetence	2 (40)	0	3 (50)	0	4 (57)	0
Asthenia	1 (20)	0	3 (50)	0	4 (57)	0
Vomiting	2 (40)	0	3 (50)	0	2 (29)	0
Mucosal inflammation	0	0	2 (33)	0	4 (57)	0
Lethargy	2 (40)	1 (20)	2 (33)	1 (17)	2 (29)	0
Abdominal pain upper	0	0	2 (33)	0	2 (29)	0
Pyrexia	0	0	2 (33)	0	2 (29)	0
Skin reaction	2 (40)	0	0	0	2 (29)	0
Keratoconjunctivitis sicca	0	0	0	0	4 (57)	0

Dose level 1: Cape 825 mg/m^2 + pertuzumab 1050 mg
Dose level 2: Cape 1000 mg/m^2 + pertuzumab 1050 mg
Dose level 3: Cape 1250 mg/m^2 + pertuzumab 1050 mg

Serious adverse events were observed in 1 of 6 patients (17%) at dose level 2 and in 1 of 7 patients (14%) at dose level 3. These serious adverse events include intestinal obstruction at dose level 2 and pulmonary embolism at dose level 3, both observed in 1 patient each. Of these, a causal relationship to pertuzumab could not be ruled out for pulmonary embolism observed (1 patient) at dose level 3.

Adverse events leading to pertuzumab discontinuation were reported by 1 of 6 patients (17%) at dose level 2 and by 1 of 7 patients (14%) at dose level 3. These adverse events include intestinal obstruction (1 patient) at dose level 2 and pulmonary embolism (1 patient) at dose level 3. Of these, a causal relationship to pertuzumab could not be ruled out for pulmonary embolism observed (1 patient) at dose level 3.

4.(iv).(6) Foreign phase I study (Study BO17021)

Adverse events were observed in all patients (100%) at each dose level, and those for which a causal relationship with pertuzumab could not be ruled out were also observed in all the patients. Adverse events reported by ≥2 patients in any group were as shown in the table below.

Adverse events reported by ≥2 patients in any group

Event	Number of patients (%)							
	Dose level 1 N = 6		Dose level 2 N = 2		Dose level 2A N = 6		Dose level 3A N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	3 (50)	2 (100)	2 (100)	6 (100)	2 (33)	5 (100)	4 (80)
Fatigue	5 (83)	1 (17)	2 (100)	1 (50)	6 (100)	1 (17)	5 (100)	1 (20)
Diarrhoea	5 (83)	0	2 (100)	2 (100)	5 (83)	2 (33)	4 (80)	0
Nausea	4 (67)	0	1 (50)	0	2 (33)	0	4 (80)	1 (20)
Dysgeusia	4 (67)	0	1 (50)	0	4 (67)	0	0	0

Event	Number of patients (%)							
	Dose level 1 N = 6		Dose level 2 N = 2		Dose level 2A N = 6		Dose level 3A N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Alopecia	0	0	0	0	5 (83)	0	4 (80)	0
Rash	4 (67)	0	0	0	2 (33)	0	2 (40)	0
Epistaxis	1 (17)	0	0	0	5 (83)	0	1 (20)	0
Arthralgia	2 (33)	0	0	0	4 (67)	0	1 (20)	0
Abdominal pain	4 (67)	0	0	0	0	0	2 (40)	1 (20)
Dyspepsia	2 (33)	0	0	0	2 (33)	0	2 (40)	0
Mouth ulceration	2 (33)	0	0	0	3 (50)	0	0	0
Vomiting	1 (17)	0	0	0	1 (17)	0	3 (60)	1 (20)
Mucosal inflammation	2 (33)	0	0	0	2 (33)	0	1 (20)	0
Headache	1 (17)	0	0	0	2 (33)	0	2 (40)	0
Inappetence	2 (33)	0	0	0	2 (33)	0	1 (20)	0
Stomatitis	1 (17)	0	0	0	0	0	3 (60)	1 (20)
Malaise	2 (33)	0	0	0	1 (17)	0	1 (20)	0
Nail disorder	1 (17)	0	0	0	2 (33)	0	1 (20)	0
Lower respiratory tract infection	1 (17)	1 (17)	1 (50)	0	0	0	2 (40)	0
Cough	2 (33)	0	0	0	1 (17)	0	1 (20)	0
Lacrimation increased	1 (17)	0	0	0	2 (33)	0	1 (20)	0

Dose level 1: DTX 60 mg/m^2 + pertuzumab 1050 mg
Dose level 2: DTX 75 mg/m^2 + pertuzumab 1050 mg
Dose level 2A: DTX 75 mg/m^2 + pertuzumab 420 mg
Dose level 3A: DTX 100 mg/m^2 + pertuzumab 420 mg

Serious adverse events were observed in 3 of 6 patients (50%) at dose level 1, in 2 of 2 patients (100%) at dose level 2, and in 2 of 5 patients (40%) at dose level 3A. Serious adverse events observed include lower respiratory tract infection, urinary tract infection, hypertension, pyrexia, and paralysis (1 patient each) at dose level 1; febrile neutropenia, diarrhoea, and fatigue (1 patient each) at dose level 2; and nausea, vomiting, and febrile neutropenia (1 patient each) at dose level 3A. Of these, a causal relationship to pertuzumab could not be ruled out for hypertension (1 patient) at dose level 1, febrile neutropenia and diarrhea (1 patient each) at dose level 2, and febrile neutropenia(1 patient) at dose level 3A.

Adverse events leading to pertuzumab discontinuation were reported by 2 of 6 patients (33%) at dose level 1, 1 of 2 patients (50%) at dose level 2, 1 of 6 patients (17%) at dose level 2A, and 1 of 5 patients (20%) at dose level 3A. These adverse events include fatigue and paralysis (1 patient each) at dose level 1, fatigue (1 patient) at dose level 2, ventricular dysfunction (1 patient) at dose level 2A, and vomiting (1 patient) at dose level 3A. Of these, a causal relationship to pertuzumab could not be ruled out for fatigue (1 patient) at dose level 1 and ventricular dysfunction (1 patient) at dose level 2A.

4.(iv).(7) Foreign phase II study (Study WO20697)

Adverse events were observed in 105 of 107 patients (98%) in group A, in 104 of 107 patients (97%) in group B, in 76 of 108 patients (70%) in group C, and in 93 of 94 patients (99%) in group D, and those for which a causal relationship with the study drug could not be ruled out were observed in 104 of 107 patients (97%), 102 of 107 patients (95%), 71 of 108 patients (66%), and 92 of 94 patients (98%), respectively. Adverse events with an incidence of ≥20% in any group were as shown in the table below.

Adverse events with an incidence of ≥20% in any group

Event	Number of patients (%)							
	Group A N = 107		Group B N = 107		Group C N = 108		Group D N = 94	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	105 (98)	78 (73)	104 (97)	67 (63)	76 (70)	7 (6)	93 (99)	66 (70)
Alopecia	70 (65)	1 (1)	68 (64)	5 (5)	1 (1)	0	63 (67)	4 (4)
Neutropenia	67 (63)	61 (57)	54 (50)	48 (45)	1 (1)	1 (1)	59 (63)	52 (55)
Diarrhoea	36 (34)	4 (4)	49 (46)	6 (6)	30 (28)	0	51 (54)	4 (4)
Nausea	39 (36)	0	41 (38)	0	15 (14)	0	34 (36)	1 (1)
Fatigue	29 (27)	0	28 (26)	1 (1)	13 (12)	0	24 (26)	1 (1)
Rash	23 (21)	2 (2)	28 (26)	2 (2)	12 (11)	0	27 (29)	1 (1)
Mucosal inflammation	23 (21)	0	28 (26)	2 (2)	3 (3)	0	24 (26)	0
Myalgia	24 (22)	0	24 (22)	0	10 (9)	0	19 (20)	0
Asthenia	19 (18)	0	22 (21)	2 (2)	3 (3)	0	15 (16)	2 (2)
Leukopenia	23 (21)	13 (12)	10 (9)	5 (5)	0	0	12 (13)	7 (7)

Serious adverse events were observed in 18 of 107 patients (17%) in group A, in 11 of 107 patients (10%) in group B, in 4 of 108 patients (4%) in group C, and in 16 of 94 patients (17%) in group D. Serious adverse events observed include febrile neutropenia (7 patients), diarrhoea (2 patients), neutropenia, neutropenic sepsis, wound infection, appendicitis, breast abscess, urinary tract infection, metrorrhagia, ovarian disorder, pyrexia, epistaxis, and tumour haemorrhage (1 patient each) in group A; febrile neutropenia (6 patients), neutropenia (4 patients), pyelonephritis acute, neutropenic infection, pyrexia, hepatitis fulminant, and upper limb fracture (1 patient each) in group B; infection, impaired healing, cardiac failure congestive, and drug hypersensitivity (1 patient each) in group C; and febrile neutropenia and neutropenia (6 patients each), staphylococcal sepsis, cellulitis, diarrhoea and uterine haemorrhage (1 patient each) in group D. Of these, a causal relationship to the study drug could not be ruled out for febrile neutropenia (7 patients), diarrhoea (2 patients), neutropenia, neutropenic sepsis, appendicitis, urinary tract infection, and pyrexia (1 patient each) in group A; febrile neutropenia (6 patients), neutropenia (4 patients), pyelonephritis acute, neutropenic infection, pyrexia, and hepatitis fulminant (1 patient each) in group B; cardiac failure congestive and drug hypersensitivity (1 patient each) in group C; and febrile neutropenia and neutropenia (6 patients each), staphylococcal sepsis, cellulitis, and diarrhoea (1 patient each) in group D.

Adverse events leading to the study drug discontinuation were reported by 1 of 107 patients (1%) in group B, by 2 of 108 patients (2%) in group C, and by 2 of 94 patients (2%) in group D. These adverse events include drug hypersensitivity (1 patient) in group B, drug hypersensitivity and cardiac failure congestive (1 patient each) in group C, and colitis ulcerative and neutropenia (1 patient each) in group D. Of these, a causal relationship to the study drug was ruled out for colitis ulcerative observed in group D.

4.(iv).(8) Foreign phase II study (Study BO16934)

Adverse events were observed in 36 of 41 patients (88%) in group A and in 37 of 37 patients (100%) in group B and those for which a causal relationship with pertuzumab could not be ruled out were observed in 6 of 41 patients (15%) and in 5 of 37 patients (14%), respectively. Adverse events with an incidence of ≥20% include diarrhoea (24 of 41 patients [59%]), nausea (12 of 41 patients [29%]), asthenia and vomiting (10 of 41 patients [24%] each) in group A; and diarrhoea (22 of 37 patients [59%]), nausea (13 of 37 patients [35%]), asthenia (9 of 37 patients [24%]), vomiting and inappetence (8 of 37 patients [22%] each) in group B. Of these, Grade ≥3 adverse events were diarrhoea (3 patients) and vomiting (1 patient) in group A and diarrhoea (2 patients) in group B.

Serious adverse events were observed in 10 of 41 patients (24%) in group A and in 8 of 37 patients (22%) in group B. Serious adverse events observed include ejection fraction decreased (2 patients), ascites, lung infection, pneumonia, sepsis, pleural effusion, cardiac failure, pericardial effusion, neck pain and headache (1 patient each) in group A; and ascites, diarrhoea, dysphagia, large intestinal obstruction, pleural effusion, epistaxis, palmar-plantar erythrodysaesthesia syndrome, and urticaria (1 patient each) in group B. Of these, a causal relationship to pertuzumab could not be ruled out for ejection fraction decreased (2 patients), sepsis and cardiac failure (1 patient each) in group A; and diarrhoea and urticaria (1 patient each) in group B.

Adverse events leading to pertuzumab discontinuation were reported by 1 of 41 patients (2%) in group A and by 1 of 37 patients (3%) in group B. These adverse events include cardiac failure (1 patient) in group A and diarrhoea (1 patient) in group B, for both of which, a causal relationship to pertuzumab could not be ruled out.

4.(iv).(9) Foreign phase II study (Study TOC2689g)

Adverse events were observed in 61 of 61 patients (100%) in cohort 1 and in 61 of 62 patients (98%) in cohort 2, and those for which a causal relationship with pertuzumab could not be ruled out were observed in 44 of 61 patients (72%) and in 52 of 62 patients (84%), respectively. Adverse events with an incidence of ≥20% in either group were as shown in the table below.

Adverse events with an incidence of ≥20% in either group

Event	Number of patients (%)			
	Cohort 1 N = 61		Cohort 2 N = 62	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	61 (100)	35 (57)	61 (98)	35 (57)
Diarrhoea	40 (66)	7 (12)	45 (72)	7 (11)
Fatigue	21 (34)	2 (3)	34 (55)	2 (3)
Abdominal pain	26 (43)	4 (7)	21 (34)	3 (5)
Nausea	25 (41)	6 (10)	22 (36)	4 (7)
Vomiting	25 (41)	11 (18)	17 (27)	3 (5)
Rash	14 (23)	0	16 (26)	0
Constipation	17 (28)	4 (7)	11 (18)	1 (2)
Inappetence	15 (25)	2 (3)	12 (19)	2 (3)
Oedema peripheral	13 (21)	0	14 (23)	0
Ejection fraction decreased	11 (18)	0	14 (23)	0
Abdominal distension	13 (21)	0	8 (13)	0
Dehydration	13 (21)	4 (7)	8 (13)	2 (3)
Dyspepsia	6 (10)	0	13 (21)	0

Serious adverse events were observed in 26 of 61 patients (43%) in cohort 1 and in 18 of 62 patients (29%) in cohort 2. Serious adverse events observed include small intestinal obstruction (8 patients), intestinal obstruction, abdominal pain, aspiration, ascites, diarrhoea, and vomiting (2 patients each), dehydration, pleural effusion, atrial fibrillation, endocarditis noninfective, nausea, asthenia, hepatic function abnormal, abdominal abscess, influenza, pneumonia, intestinal stoma complication, malignant ascites, malignant pleural effusion, obstructive uropathy, and thrombosis (1 patient each) in cohort 1; and small intestinal obstruction (6 patients), intestinal obstruction, dehydration, and pleural effusion (2 patients each), abdominal pain, cardiac tamponade, pericardial effusion, ejection fraction decreased, hypercalcaemia, ovarian cancer, bladder pain, bladder spasm, renal failure acute, ureteric obstruction, and pulmonary embolism (1 patient each) in cohort 2. Of these, a causal relationship to pertuzumab could not be ruled out for atrial fibrillation, abdominal pain, diarrhoea, and pneumonia (1 patient each) in cohort 1; and pericardial effusion and ejection fraction decreased (1 patient each) in cohort 2.

Adverse events leading to pertuzumab discontinuation were reported by 9 of 61 patients (15%) in

cohort 1 and 4 of 62 patients (6%) in cohort 2. These adverse events include small intestinal obstruction (2 patients), endocarditis noninfective, vomiting, abdominal pain, abnormal faeces, diarrhoea, asthenia, fatigue, oedema, dehydration, malignant ascites, malignant pleural effusion, and pleural effusion (1 patient each) in cohort 1; and small intestinal obstruction (2 patients), abdominal pain, nausea, vomiting, blood creatinine increased, and pruritus (1 patient each) in cohort 2. Of these, a causal relationship to pertuzumab could not be ruled out for abdominal pain, abnormal faeces, diarrhoea, fatigue, oedema, and dehydration (1 patient each) in cohort 1 and pruritus (1 patient) in cohort 2.

4.(iv).(10) Foreign phase II study (Study TOC2572g)

Adverse events were observed in 42 of 43 patients (98%), and those for which a causal relationship with pertuzumab could not be ruled out were observed in 27 of 43 patients (63%). Adverse events with an incidence of ≥20% include fatigue (16 of 43 patients [37%]) and diarrhoea (15 of 43 patients [35%]). Of these, fatigue and diarrhoea (1 patient each) were Grade ≥3 adverse events.

Serious adverse events were observed in 15 of 43 patients (35%). Serious adverse events observed include pneumonia (7 patients), pericardial effusion, nausea, pain, hypersensitivity, cellulitis, sepsis, hypercalcaemia, non-small cell lung cancer, spinal cord compression, acute respiratory distress syndrome, dyspnoea, hypoxia, pleural effusion, pulmonary embolism, and deep vein thrombosis (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for acute respiratory distress syndrome and hypersensitivity (1 patient each).

Adverse events leading to pertuzumab discontinuation were reported by 4 of 43 patients (9%). These adverse events include spinal cord compression, hypersensitivity, pneumonia, and oedema peripheral (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for hypersensitivity (1 patient).

4.(iv).(11) Foreign phase II study (Study BO17004)

Adverse events were observed in 30 of 35 patients (86%) in cohort A and in 27 of 33 patients (82%) in cohort B, and those for which a causal relationship with pertuzumab could not be ruled out were observed in 26 of 35 patients (74%) and 22 of 33 patients (67%), respectively. Adverse events with an incidence of ≥20% include diarrhoea (18 of 35 patients [51%]), fatigue (15 of 35 patients [43%]), nausea (11 of 35 patients [31%]), and inappetence (8 of 35 patients [23%]) in cohort A, and diarrhoea (17 of 33 patients [52%]) in cohort B. Of these, diarrhoea and fatigue (1 patient each) in cohort A and diarrhoea (1 patient) in cohort B were Grade ≥3 adverse events.

Serious adverse events were observed in 9 of 35 patients (26%) in cohort A and in 6 of 33 patients (18%) in cohort B. Serious adverse events observed include urinary retention (3 patients), renal insufficiency, anaemia, haemolytic uraemic syndrome, atrial fibrillation, oedema peripheral, electrocardiogram T wave inversion, hypoglycaemia, cauda equina syndrome, and epistaxis (1 patient each) in cohort A; and abdominal pain, haematemesis, ileus paralytic, nausea, central line infection, sepsis, metastatic pain, and deep vein thrombosis (1 patient each) in cohort B. Of these, a causal relationship to pertuzumab could not be ruled out for haemolytic uraemic syndrome, atrial fibrillation, electrocardiogram T wave inversion, and hypoglycaemia (1 patient each) in cohort A, and abdominal pain (1 patient) in cohort B.

Adverse events leading to pertuzumab discontinuation were reported by 3 of 35 patients (9%) in cohort A and 1 of 33 patients (3%) in cohort B. These adverse events include atrial fibrillation, electrocardiogram T wave inversion, and cauda equina syndrome (1 patient each) in cohort A; and sepsis (1 patient) in cohort B. Of these, a causal relationship to pertuzumab could not be ruled out for atrial fibrillation and electrocardiogram T wave inversion (1 patient each) in cohort A.

4.(iv).(12) Foreign phase II study (Study TOC2682g)

Adverse events were observed in 40 of 41 patients (98%), and those for which a causal relationship with pertuzumab could not be ruled out were observed in 36 of 41 patients (88%). Adverse events with an incidence of ≥20% include diarrhoea (25 of 41 patients [61%]), nausea and fatigue (14 of 41 patients [34%] each), arthralgia (13 of 41 patients [32%]), ejection fraction decreased (12 of 41 patients [29%]), inappetence (11 of 41 patients [27%]), constipation, vomiting, and oedema peripheral (8 of 41 patients [20%] each). Of these, Grade ≥3 adverse events were diarrhoea and arthralgia (2 patients each), fatigue, constipation, vomiting, and oedema peripheral (1 patient each).

Serious adverse events were observed in 11 of 41 patients (27%). Serious adverse events observed include bone pain and ureteric obstruction (2 patient each), tachycardia, constipation, duodenal ulcer haemorrhage, ileus, pain, cellulitis, pneumonia, stent occlusion, troponin T increased, metastatic pain, neuropathy, bilateral hydronephrosis, pleural effusion, and deep vein thrombosis (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for duodenal ulcer haemorrhage and troponin T increased (1 patient each).

Adverse events leading to pertuzumab discontinuation were reported by 5 of 41 patients (12%). These adverse events include bone pain (2 patients), ileus, oedema peripheral, pneumonia, troponin T increased, bilateral hydronephrosis, ureteric obstruction, and pleural effusion (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for troponin T increased (1 patient).

4.(iv).(13) Foreign phase II study (Study BO17931)

By the end of Cycle 6, adverse events were observed in 73 of 75 patients (97%) in the pertuzumab/chemotherapy* group and in 70 of 74 patients (95%) in the chemotherapy group, and those for which a causal relationship with the study drug could not be ruled out were observed in 71 of 75 patients (95%) and in 64 of 74 patients (86%), respectively. Adverse events with an incidence of ≥20% in either group were as shown in the table below. After Cycle 6, treatment with pertuzumab alone was continued for 11 cycles in the pertuzumab/chemotherapy group. During these treatment cycles, adverse events were observed in 37 of 75 patients (49%), and those for which a causal relationship with the study drug could not be ruled out were observed in 26 of 75 patients (35%), but none of them with an incidence of ≥20%.

*: Carboplatin/PTX or carboplatin/GEM

Adverse events with an incidence of ≥20% in either group

Events	Number of patients (%)			
	Pertuzumab/chemotherapy group N = 75		Chemotherapy group N = 74	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	73 (97)	47 (63)	70 (95)	52 (70)
Neutropenia	36 (48)	25 (33)	43 (58)	35 (47)
Nausea	44 (59)	1 (1)	33 (45)	3 (4)
Diarrhoea	43 (57)	5 (7)	14 (19)	1 (1)
Fatigue	29 (39)	4 (5)	27 (36)	4 (5)
Alopecia	21 (28)	0	25 (34)	1 (1)
Vomiting	23 (31)	3 (4)	22 (30)	2 (3)
Constipation	18 (24)	0	23 (31)	0
Anaemia	19 (25)	2 (3)	21 (28)	6 (8)
Abdominal pain	17 (23)	2 (3)	15 (20)	3 (4)
Thrombocytopenia	10 (13)	6 (8)	18 (24)	12 (16)
Rash	15 (20)	1 (1)	7 (9)	0

By the end of Cycle 6, serious adverse events were observed in 15 of 75 patients (20%) in the pertuzumab/chemotherapy group and in 12 of 74 patients (16%) in the chemotherapy group. Serious adverse events reported by ≥2 patients were drug hypersensitivity (4 patients), diarrhoea, vomiting, and pyrexia (2 patients each) in the pertuzumab/chemotherapy group and febrile neutropenia (3 patients) in the chemotherapy group. Of these, a causal relationship with the study drug could not be ruled out for drug hypersensitivity (3 patients), diarrhoea (2 patients), and vomiting (1 patient) in the pertuzumab/chemotherapy group and febrile neutropenia (3 patients) in the chemotherapy group. During the pertuzumab monotherapy period after Cycle 6, serious adverse events were observed in the 5 of 75 patients (7%) in the pertuzumab/chemotherapy group. Serious adverse events observed include abdominal pain, intestinal obstruction, diaphragmatic hernia, epistaxis, and cardiac failure congestive (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for cardiac failure congestive (1 patient).

By the end of Cycle 6, adverse events leading to the study drug discontinuation were reported by 4 of 75 patients (5%) in the pertuzumab/chemotherapy group and 6 of 74 patients (8%) in the chemotherapy group. These adverse events include diarrhoea, paronychia, drug hypersensitivity, and acute respiratory failure (1 patient each) in the pertuzumab/chemotherapy group and drug hypersensitivity (3 patients), thrombocytopenia, neutropenia, and large intestine perforation (1 patient each) in the chemotherapy group. Of these, a causal relationship with the study drug could not be ruled out for paronychia, drug hypersensitivity, and acute respiratory failure (1 patient each) in the pertuzumab/chemotherapy group and drug hypersensitivity (3 patients), thrombocytopenia and neutropenia (1 patient each) in the chemotherapy group. During the pertuzumab monotherapy period after Cycle 6, adverse events leading to pertuzumab discontinuation include intestinal obstruction and cardiac failure congestive (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for cardiac failure congestive (1 patient).

4.(iv).(14) Foreign phase II study (Study TOC3258g)

Adverse events were observed in 65 of 65 patients (100%) in the pertuzumab/GEM group and in 65 of 65 patients (100%) in the placebo/GEM group, and those for which a causal relationship with pertuzumab or placebo could not be ruled out were observed in 55 of 65 patients (85%) and in 51 of 65 patients (78%), respectively. Adverse events with an incidence of ≥30% in either group were as shown in the table below.

Adverse events with an incidence of ≥30% in either group

Event	Number of patients (%)			
	Pertuzumab/GEM group N = 65		Placebo/GEM group N = 65	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	65 (100)	49 (75)	65 (100)	52 (80)
Fatigue	51 (78)	14 (22)	44 (68)	11 (17)
Nausea	49 (75)	5 (8)	43 (66)	4 (6)
Diarrhoea	44 (68)	7 (11)	23 (35)	1 (2)
Anaemia	31 (48)	3 (5)	34 (52)	3 (5)
Vomiting	32 (49)	7 (11)	31 (48)	5 (8)
Neutropenia	32 (49)	23 (35)	28 (43)	14 (22)
Constipation	13 (20)	2 (3)	38 (58)	3 (5)
ALT increased	22 (34)	6 (9)	20 (31)	3 (5)
Back pain	27 (42)	6 (9)	15 (23)	1 (2)
Oedema peripheral	20 (31)	0	21 (32)	4 (6)
AST increased	21 (32)	1 (2)	20 (31)	2 (3)
Headache	24 (37)	1 (2)	17 (26)	1 (2)
Abdominal pain	22 (34)	7 (11)	18 (28)	4 (6)
Dyspnoea	20 (31)	8 (12)	15 (23)	5 (8)
Rash	26 (40)	0	9 (14)	0

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Serious adverse events were observed in 23 of 65 patients (35%) in the pertuzumab/GEM group and in 29 of 65 patients (45%) in the placebo/GEM group. Serious adverse events reported by ≥2 patients include pleural effusion (4 patients), thrombocytopenia, abdominal pain, small intestinal obstruction, dyspnoea, and deep vein thrombosis (2 patients each) in the pertuzumab/GEM group; and small intestinal obstruction (8 patients), vomiting (3 patients), febrile neutropenia, intestinal obstruction, nausea, infection, renal failure acute, pulmonary embolism, deep vein thrombosis, and hypotension (2 patients each) in the placebo/GEM group. Of these, a causal relationship to pertuzumab or placebo could not be ruled out for pleural effusion, thrombocytopenia, dyspnoea, and deep vein thrombosis (1 patient each) in the pertuzumab/GEM group, and febrile neutropenia (2 patients) and pulmonary embolism (1 patient) in the placebo/GEM group.

Adverse events leading to the study drug discontinuation were reported by 12 of 65 patients (18%) in the pertuzumab/GEM group and 7 of 65 patients (11%) in the placebo/GEM group. These adverse events include pneumonitis (2 patients), haemolytic uraemic syndrome, cardiac failure congestive, ileus, small intestinal obstruction, oedema peripheral, anaphylactic reaction, cellulitis, hyperglycaemia, hydronephrosis, renal failure acute, dyspnoea, interstitial lung disease, pleural effusion, pulmonary oedema, wheezing, erythema, and hypotension (1 patient each) in the pertuzumab/GEM group; and small intestinal obstruction (2 patients), tachycardia, nausea, cellulitis, hyperglycaemia, hypomagnesaemia, hyponatraemia, pulmonary fibrosis, respiratory failure, and hypotension (1 patient each) in the placebo/GEM group. Of these, a causal relationship to pertuzumab or placebo could not be ruled out for cardiac failure congestive, oedema peripheral, anaphylactic reaction, hyperglycaemia, hydronephrosis, interstitial lung disease, pulmonary oedema, wheezing, erythema, and hypotension (1 patient each) in the pertuzumab/GEM group and pulmonary fibrosis (1 patient) in the placebo/GEM group.

4.(iv).(15) Foreign phase I study (Study WO20024)

Adverse events were observed in 6 of 6 patients (100%) in cohort 1 and in 9 of 9 patients (100%) in cohort 2, and those for which a causal relationship with pertuzumab could not be ruled out were observed in 6 of 6 patients (100%) and in 7 of 9 patients (78%), respectively. Adverse events reported by ≥2 patients in either group were as shown in the table below.

Adverse events reported by ≥2 patients in either group

Event	Number of patients (%)			
	Cohort 1 N = 6		Cohort 2 N = 9	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	2 (33)	9 (100)	5 (56)
Rash	6 (100)	2 (33)	5 (56)	2 (22)
Diarrhoea	3 (50)	0	7 (78)	1 (11)
Pruritus	4 (67)	1 (17)	2 (22)	0
Asthenia	2 (33)	0	3 (33)	0
Headache	1 (17)	0	4 (44)	0
Inappetence	2 (33)	0	3 (33)	0
Vomiting	0	0	3 (33)	0
Dyspnoea	1 (17)	0	2 (22)	0

Serious adverse events were observed in 4 of 9 patients (44%) in cohort 2. Serious adverse events observed include myocardial infarction, diarrhoea, sudden death, renal failure acute, and thrombosis (1 patient each). Of these, a causal relationship to pertuzumab could not be ruled out for diarrhoea (1 patient).

Adverse events leading to pertuzumab discontinuation were reported by 1 of 9 patients (11%) in

cohort 2, which included myocardial infarction and renal failure acute (1 patient each). A causal relationship with the study drug was ruled out for both events.

4.(iv).(16) Foreign phase II study (Study TOC2664g)

An adverse event (ejection fraction decreased) was observed in 1 of 3 patients (33%), and a causal relationship with pertuzumab could not be ruled out.

There were no serious adverse events or adverse events leading to pertuzumab discontinuation.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2-3, 5.3.5.1-1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA concludes that the efficacy of the product in patients with HER2-positive inoperable or recurrent breast cancer has been demonstrated in the total population of the global phase III study (the CLEOPATRA study) and its safety is acceptable in view of its observed benefits. Pertuzumab is a drug with a new active ingredient which, unlike trastuzumab (genetical recombination) which binds to subdomain IV of HER2 located close to the cell membrane, is considered to bind to subdomain II, the region essential for HER2 dimer formation, thereby inhibiting heterodimer formation, resulting in suppression of tumor growth. PMDA considers that the product has a clinical significance as an option for the treatment of HER2-positive inoperable or recurrent breast cancer. Clinical positioning, indications, dosage and administration of pertuzumab, and post-marketing investigations will be further discussed at the Expert Discussion.

PMDA considers that pertuzumab may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

April 9, 2013

I. Product Submitted for Registration

[Brand name]	Perjeta Intravenous Infusion 420 mg/14 mL
[Non-proprietary name]	Pertuzumab (Genetical Recombination)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	May 25, 2012

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, 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) Efficacy

As a result of its review described in the "4.(iii).B.(2) Efficacy" section of the Review Report (1), PMDA concluded that the efficacy of pertuzumab in human epidermal growth factor receptor type 2 (HER2)-positive, inoperable or recurrent breast cancer was demonstrated based on the following findings in the global phase III study (Study WO20698 [CLEOPATRA study]) comparing the pertuzumab (genetical recombination) (pertuzumab)/trastuzumab (genetical recombination) (trastuzumab)/docetaxel hydrate (DTX) combination therapy (pertuzumab combination therapy group) with placebo/trastuzumab/DTX combination therapy (placebo combination therapy group) as the control group: (a) the superiority of pertuzumab combination therapy group was confirmed to the placebo combination therapy group in progression-free survival (PFS) (assessed by an independent review facility), and (b) the second interim analysis on the overall survival (OS) showed that OS increased in the pertuzumab combination therapy group compared with the placebo combination therapy group.

Clinical usefulness of pertuzumab in Japanese patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy is described in "(3) Clinical positioning."

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

(2) Safety

Based on the results of studies submitted, PMDA concluded that adverse events requiring caution in administering pertuzumab were neutropenia/leukopenia, diarrhoea/mucositis, cardiac disorders, infusion reaction, interstitial lung disease, rash, and hypersensitivity/anaphylaxis, and that caution should be exercised against the occurrence of these adverse events in administering pertuzumab. Although caution should be exercised against the occurrence of the above adverse events, PMDA concluded that pertuzumab is tolerable for Japanese patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy provided that monitoring and control of adverse events as well as the temporary withdrawal, dose reduction, or discontinuation of pertuzumab are performed in an appropriate manner by physicians with sufficient knowledge and experience of cancer chemotherapy.

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

(3) Clinical positioning

As a result of its review described in the "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Clinical positioning" sections of the Review Report (1), PMDA concluded that pertuzumab is positioned as a treatment option for Japanese patients with HER2-positive inoperable or recurrent breast cancer who had not received chemotherapy.

PMDA's conclusion that pertuzumab is positioned as a treatment option for the Japanese patients described above was supported by the expert advisors at the Expert Committee, with the following comments:

- It is appropriate to evaluate the efficacy of pertuzumab in the Japanese population based on the efficacy results in the total population in the CLEOPATRA study, in light of the findings that led PMDA to conclude that pertuzumab is positioned as a treatment option for Japanese patients (e.g., the finding that there is no apparent difference in the PK of pertuzumab between Japanese and foreign patients; [see Review Report (1) "II.4.(iii).B.(4) Clinical positioning"]), also taking account of the following:
  - No findings have so far been reported that suggest the ethnic difference in the efficacy of antineoplastic drugs in breast cancer field, including trastuzumab, an antibody that targets HER2, as is the case with pertuzumab.
  - There are no reports of somatic mutation or single nucleotide polymorphism in HER2 or its epitope characteristic to Japanese, nor are there any pharmacological findings reported that suggest the presence of ethnic difference in the efficacy of pertuzumab.
- The CLEOPATRA study showed interactions of treatment effect between Japanese and non-Japanese patient populations. Therefore, it is necessary to confirm whether or not efficacy results are consistent between the Japanese population and the total population. However, given the limited number of patients in the Japanese population and the limited number of events, the statistical model used may be inappropriate.

(4) Indications

As a result of the review described in the "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," "4.(iii).B.(4) Clinical positioning," and "4.(iii).B.(5) Indication" of the Review Report (1), PMDA concluded that pertuzumab should be indicated for "HER2-positive inoperable or recurrent breast cancer." PMDA also concluded that the following statements should be included in the Precautions for Indications section of the package insert; "(a) test for HER2 should be performed by pathologists or laboratories with sufficient experience and (b) the efficacy and safety of pertuzumab in neo-adjuvant or adjuvant chemotherapy have not been established." In addition, information should be provided using materials, etc., on the selection of patients to be treated with pertuzumab and trastuzumab based on HER2 expression level.

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

Based on the above, PMDA instructed the applicant to include the following statements in the Indications and Precautions for Indications sections of the package insert, and the applicant accepted it.

[Indication]

HER2-positive inoperable or recurrent breast cancer

[Precautions for Indications]

- Testing for HER2 should be performed by an experience pathologist or in a laboratory with demonstrated expertise in such testing

- The efficacy and safety of pertuzumab in neo-adjuvant or adjuvant chemotherapy have not been established.

(5) Dosage and Administration

As a result of the review described in the "4.(iii).B.(6) Dosage and administration" section of the Review report (1), PMDA concluded that the dosage and administration of pertuzumab should be stated as "The usual loading dose for adults is 840 mg of pertuzumab administered as a 60-minute intravenous infusion once daily, followed by subsequent doses of 420 mg of pertuzumab as 60-minute infusions every 3 weeks, in combination with other antineoplastic drugs including trastuzumab. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated". PMDA also concluded that information should be provided appropriately that the protocol of the CLEOPATRA study specified a procedure to be taken in case of delays in trastuzumab administration that is different from the procedure stipulated in the Precautions for Dosage and Administration section of the current package insert for trastuzumab, using the same rule as that for pertuzumab (in case of ≥6 week delay, 8 mg/kg, which is the initial loading dose, should be given).

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

Based on the above, PMDA instructed the applicant to include the following statements in the Dosage and Administration and in the Precautions for Dosage and Administration sections of the package insert, and that information should be provided in an appropriate manner on the above dosage regimen for trastuzumab, and the applicant accepted it.

[Dosage and Administration]

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 as 60-minute infusions every 3 weeks, in combination with trastuzumab (genetical recombination) and other antineoplastic drugs. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

[Precautions for Dosage and Administration]

- When pertuzumab is administered after discontinuation of antineoplastic agents other than trastuzumab, pertuzumab should be concomitantly administered with trastuzumab.
- Antineoplastic drugs other than trastuzumab to be concomitantly administered with pertuzumab should be selected by a physician with a thorough understanding of the "Clinical Studies" section.
- The efficacy and safety of pertuzumab monotherapy have not been established.
- If the scheduled dosing is delayed for some reason, it is advisable to administer pertuzumab according to the following procedure.
  - If 6 weeks have not passed since the previous administration, administer 420 mg.
  - 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.
- For the administration of pertuzumab, pertuzumab solution is withdrawn from the vial and added to 250 mL of Isotonic Sodium Chloride Solution (JP), and the entire volume of this solution is intravenously administered.

(6) Post-marketing investigations

The applicant plans to conduct a post-marketing surveillance involving breast cancer patients treated with pertuzumab (sample size for analysis of 300 patients; observation period, 2 years) to collect safety information in routine clinical use of pertuzumab.

In order to collect information on the efficacy of pertuzumab in Japanese patients with breast

cancer, the applicant plans to conduct this surveillance as a cohort study to estimate, in routine clinical use of the product, the efficacy of pertuzumab as a first-line treatment for patients with HER2-positive inoperable or recurrent breast cancer (control patients: all patients who are diagnosed with HER2-positive inoperable or recurrent breast cancer and undergo a first-line treatment within 14 months before market launch, in the medical institution where post-marketing surveillance will be conducted).

As a result of the review described in the "4.(iii).B.(4) Clinical positioning" and "4.(iii).B. (7) Post-marketing investigations" sections of the Review Report (1), PMDA concluded that a post-marketing study or surveillance should be conducted in Japanese patients with breast cancer to collect information on the efficacy, in addition to the safety of pertuzumab. PMDA also concluded, from the aspect of collecting safety information, that the priority items should include, not only febrile neutropenia proposed by the applicant but also interstitial lung disease, the adverse event observed in Japanese patients with a higher incidence than in foreign patients in the CLEOPATRA study. Thus, the sample size for analysis and observation period should be reconsidered according to the changes in the priority items, etc.

In addition to the opinion supporting the conclusion of PMDA, the following comments were raised from the expert advisors at the Expert Discussion:

- Since the results of the CLEOPATRA study have already been obtained, it is unreasonable, to perform, after market launch, a randomized comparable study involving the patient population similar to that investigated in the CLEOPATRA study.
- There is a certain clinical significance in obtaining the information on the efficacy of pertuzumab in Japanese patients in 2 phase III randomized comparative studies (MARIANNE and APHINITY studies) involving patients with HER2-positive breast cancer.
- As regards the information on the efficacy of pertuzumab in Japanese patients with breast cancer, it is not uncommon that CT imaging test is not performed periodically in clinical practice, and there is a limit to assess the PFS in post-marketing surveillance. Therefore, it is necessary to evaluate OS as well. In addition, the surveillance plan should be designed by taking account of the possibility of bias in efficacy evaluation.

PMDA, taking account of comments from the Expert Discussion and the review in "(3) Clinical positioning," concluded that a post-marketing study or surveillance should be conducted in Japanese patients with breast cancer to collect information on the efficacy of pertuzumab in addition to the safety of pertuzumab.

Based on the above, PMDA instructed the applicant to take appropriate actions accordingly.

The applicant responded as follows:
The appropriate actions will be taken according to the above instructions. The applicant plans to conduct, in the post-marketing surveillance for efficacy and safety assessment, a cohort study to estimate the efficacy of pertuzumab as a first-line treatment for HER2-positive inoperable or recurrent breast cancer. The study will be conducted appropriately upon discussion with PMDA, with consideration given to the following.

- For efficacy evaluation, study sites will be selected at which evaluation of the lesion is performed in clinical practice on a regular basis, and at the same time, information on the method of disease progression assessment will be collected to allow appropriate evaluation of PFS.
- Febrile neutropenia and interstitial lung disease will be selected as the priority items for safety evaluation. The sample size will be basically determined from the aspect of efficacy

evaluation, but a sufficient number of patients will be enrolled for detecting the occurrence of interstitial lung disease. In the CLEOPATRA study, the incidence of interstitial lung disease in pertuzumab combination therapy group was 2.2% (9 of 407 patients). Assuming that the incidence of interstitial lung disease in routine clinical use of pertuzumab is 2%, accumulation of data from 150 patients will allow identifying ≥1 case of the adverse event at the probability of 95%.

- Each patient will be observed for safety information for 2 years because in the CLEOPATRA study, all cases of interstitial lung disease occurred within 2 years after the initiation of pertuzumab administration, and because it is necessary to collect safety information during pertuzumab administration as much as possible.

PMDA accepted the response of the applicant.

(7) Risk management plan (RMP)

Based on the result of the review described in the "4.(iii).B.(3) Safety" and "4.(iii).B.(7) Post-marketing investigations" sections of the Review Report (1), PMDA concluded that the risk management plan for pertuzumab at present is outlined as follows:

- Among the elements of the safety specification, "important identified risks" include 'neutropenia,' 'infusion reaction,' 'hypersensitivity, anaphylaxis,' and 'interstitial lung disease," and "important potential risks" include 'cardiac disorders.'
- As additional pharmacovigilance activities, an early post-marketing phase vigilance and a post-marketing surveillance should be conducted.
- As additional risk minimization activities, the safety information based on the early post-marketing phase vigilance should be provided.

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

PMDA instructed the applicant to consider designing a risk management plan for pertuzumab based on the above, and the applicant responded that they would make the plan with the above contents.

(8) Others

Japanese patients participated in the CLEOPATRA study 1 year and 5 months after the initiation of the study and, as a result, there were only a limited number of events observed in Japanese patients at the time point of the final analysis. Therefore, PFS monitoring was continued, even after the final analysis, in Japanese patients only. The delay in the participation of Japanese patients appears to be due to the following reasons: In foreign countries, the CLEOPATRA study was initiated by F. Hoffmann-La Roche Ltd. based on the results of the phase II study (Study BO17929), whereas the applicant could not promptly obtain the results of Study BO17929, etc., that were conducted while the development of pertuzumab was being suspended in Japan. PMDA considers it essential that the developer carry out future clinical development in Japan simultaneously with the development in foreign countries by sharing the information on development in and outside Japan.

III. Additions to the Review Report (1)

The applicant's responses to the inquiries asked by PMDA at the time of preparation of the Review Report (1) are described below.

1. Data relating to quality

Outline of the review by PMDA

As a result of the following reviews including matters that had been under inquiry, PMDA concluded that the quality of pertuzumab is adequately controlled.

1) Quality by Design (QbD)

Pertuzumab was developed using the Quality by Design (QbD) approach, and a design space (DS) is proposed in the manufacturing process [see Review Report (1) "II.2.A.(4) Quality by Design (QbD)"].

(a) Identification of critical quality attributes (CQAs)

Critical quality attributes (CQAs) of pertuzumab was identified mainly according to the following process for each of [redacted], [redacted], components/contents, adventitious agents, [redacted], etc. In the course of the review, [redacted] was added to CQAs [see "II.2.A(4) Quality by Design (QbD)" and "II.2.B. Outline of the review by PMDA" in Review Report (1)].

- For [redacted] and [redacted], CQAs were identified using the risk ranking and filtering (RRF) method based on the combination of [redacted]* and [redacted]†.
- Since components/contents and adventitious substances must always be strictly controlled, all of these parameters were included in CQAs.
- For [redacted], no [redacted] were identified as CQAs as a result of evaluation of [redacted] ([redacted]), [redacted], and [redacted].

*: Indicates [redacted] that affects [redacted], [redacted], "immunogenicity," or "safety." [redacted] of [redacted] is used in identifying CQAs.
†: Indicates [redacted] that [redacted] [redacted] on each quality attribute.

PMDA considers that the criticality of each quality attribute should not vary depending on control elements, but should be evaluated based on the severity of harm inherent to the quality attribute itself. Therefore, the inclusion of [redacted] and [redacted] in CQAs by the applicant has the following problems:

- In the evaluation of a specific [redacted], based on the facts that the [redacted] was included in the batches (drug substance or drug product) used in clinical studies and that there were no immunogenicity or safety problems attributable to the [redacted] in clinical studies, low [redacted] were [redacted] to "immunogenicity" and "safety" and, as a result, the low [redacted] was stressed while due consideration was not given to the attributes of [redacted] itself.
- In the evaluation of [redacted], consideration was given to control elements for the manufacturing process performance, such as controllability during the manufacturing process.

Nevertheless, taking account of the following points, PMDA concluded that the proposed control strategy of pertuzumab is acceptable.

- Even in cases where [redacted] on "immunogenicity" and "safety" is considered low, CQAs were eventually identified, based on the evaluation of [redacted] or [redacted].
- For [redacted], it has been demonstrated that, during the manufacturing process of pertuzumab, it is sufficiently removed, or thought to be decreased to a level with no safety concern, based on its content, attributes, etc. [see "II.2.A.(1) Drug substance" in Review Report (1)]

(b) Identification of Critical Process Parameters (CPPs)

Critical process parameters (CPPs) were identified after evaluating the impact on CQA, according to the following procedures. Since [redacted] was added to CQAs in the course of the review, effect of each process parameter on [redacted] was evaluated and, as a result, an additional CPP was identified.

- The changes in CQAs observed by changing a process parameter from the target value to the limit value of [redacted] were [redacted] as [redacted]. If the change affected multiple CQAs, [redacted] was used.
- Parameters that were [redacted] to any of the CQAs were classified as [redacted] CPPs.
- Parameters that were [redacted] to any of the CQAs were classified as [redacted] CPPs or [redacted] CPPs, taking into account the further investigations based on the effect of other process parameters.
- Parameters that were [redacted] to all CQAs were classified as Non-CPPs.

Classification of process parameters based on [redacted] is dependent on their impact on the quality attributes. Therefore, the concept is consistent with that of determining whether relevant matters should be covered by a partial change application or a minor change notification. In Japan, such matters are classified according to the impact of the risk to the quality, efficacy, and safety of the product submitted in the application for marketing approval. [redacted] CPPs were handled as matters to be covered by a partial change application, and [redacted] CPPs as matters to be covered by a minor change notification. Process parameters classified as Non-CPPs, except [redacted], were handled as matters not required to be described in the application for marketing approval.

PMDA considers that it is not necessarily appropriate to handle a parameter as [redacted] because the parameter did not affect CQAs within the range studied, and that it is difficult to accept the applicant's intention on the description of parameters in the application for marketing approval. Therefore, PMDA instructed the applicant to include parameters related to viral safety, including those classified as Non-CPPs by the applicant, in the application for marketing approval.

The applicant agreed to take appropriate actions on the above, and PMDA accepted the response.

(c) Construction of design space (DS)

The application claims that the multi-dimensional space defined by the [redacted] of all CPPs of the manufacturing process corresponds to DS.

PMDA considers that, in order to ensure the product quality based on the construction of a DS, not only [redacted] of CPPs but also [redacted] of process parameters classified as Non-CPPs by the applicant should be included in the construction of the DS, for the following reasons. Therefore, PMDA instructed the applicant to reconsider the elements of DS.

- Based on the results of [redacted] conducted by the applicant, [redacted] was set not only for process parameters classified as CPPs but also for those classified as Non-CPPs.
- Process parameters classified as Non-CPPs by the applicant were not subjected to evaluation on the effect of the quality of the product manufactured using these parameters deviated from [redacted], which suggests that they may include important parameters in ensuring the quality of the product.

The applicant agreed to include process parameters classified as Non-CPP in the element of DS,

and PMDA accepted the applicant's response.

(d) Construction of strategy for tests for controlling quality attributes and evaluation of its robustness

The strategy for tests for controlling each quality attribute was classified into any of the following using the RRF method based on the combination of [redacted] and [redacted]* or [redacted]† employed in CQA identification. However, since the strategy solely based on this classification may fail to include tests useful for controlling the consistency of the product, the applicant has specified another measure to avoid this, and constructed the strategy for quality control tests by taking this measure into account. In the course of the review, PMDA instructed the applicant to control the antibody-dependent cellular cytotoxicity (ADCC). In response, the applicant included [redacted] in the specifications for the drug substance to ensure ADCC activity, thereby revising the strategy for quality control tests for pertuzumab [see Review Report (1) "II.2.B: ADCC activity"].

- Control system test (in-process control test, release test, or stability testing) required.
- Test for [redacted] or test in case of [redacted] of [redacted] of [redacted] required.
- Test not required.

*: Indicates [redacted] of [redacted].
†: Indicates [redacted] of [redacted].

The robustness of the strategy for quality control tests has been confirmed using the RRF method in which [redacted] with consideration to [redacted] of [redacted] and [redacted] were added to the above [redacted] and [redacted] or [redacted].

PMDA considers that the applicant's explanation is acceptable. In ensuring the quality of the product based on the DS, although there may be some risks remaining given that the product has not been manufactured at the commercial scale under all possible conditions within the DS, a sufficient level of the robustness of the control strategy has been demonstrated. Therefore, PMDA considers that the risks can be controlled by the combination of the DS with the strategy for quality control tests established and, thus the quality of the product can be controlled in an appropriate manner.

2) Shelf life of drug product

At the time of regulatory submission, the proposed shelf life of the drug product was "36 months" when stored at 5 ± 3°C protected from light, based on the results of the long-term testing on the drug product manufactured at [redacted] (plant A) ([redacted] batch) using the drug substance manufactured by the manufacturing process C [see "II.2.A.(2).5) Stability of the drug product" in Review Report (1)]. However, during the preparation of Review Report (1), foreign insoluble matter was found in the [redacted] batch which was stored for ≥[redacted] months after manufacturing. Therefore, the applicant submitted the request to change the shelf life of the drug product to "24 months," based on the results of the long-term testing on the drug product manufactured at [redacted] (plant B) (registration batch) using the drug substance manufactured by the manufacturing process D.

PMDA, after confirming the results of the long-term testing on the registration batch, accepted the applicant's proposal of a shelf life of 24 months when stored at 5 ± 3°C protected from light.

IV. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below, provided that appropriate cautions are included in the package insert and information concerning the proper use of pertuzumab is provided appropriately after the market launch, and that the proper use of pertuzumab is ensured under the supervision of physicians with a thorough knowledge of, and experience in, cancer chemotherapy in medical institutions that are fully capable of providing medical treatment in emergency situations. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication]	HER2-positive inoperable or recurrent breast cancer
[Dosage and administration]	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 as 60-minute infusions every 3 weeks, in concomitant use with trastuzumab (genetical recombination) and other antineoplastic drug. The infusion time for the subsequent doses may be reduced to 30 minutes if the loading dose is well tolerated.

[Warning]

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. Eligible patients should be carefully selected by referring to the package inserts of pertuzumab and concomitant drugs. Prior to the initiation of the therapy, consent must be obtained from the patient or his/her family member who are fully informed of the efficacy and risk of the therapy.

[Contraindications]

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 for Indications]

(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 in neo-adjuvant or adjuvant chemotherapy have not been established.

[Precautions for Dosage and Administration]

1. When pertuzumab is administered after discontinuation of antineoplastic drugs other than trastuzumab, pertuzumab should be concomitantly administered with trastuzumab.
2. Antineoplastic drugs other than trastuzumab to be concomitantly administered with pertuzumab should be selected by a physician with a thorough understanding of the “Clinical Studies” section.
3. The efficacy and safety of pertuzumab monotherapy have not been established.
4. If scheduled dosing is delayed for some reason, it is adivisable to administer pertuzumab according to the following procedure:
   (1) If 6 weeks have not passed since the previous administration, administer 420 mg.

(2) If ≥6 weeks have passed since the previous administration, administer the reloading dose of 840 mg. For the subsequent doses, administer 420 mg every 3 weeks.

5. For the administration of pertuzumab, pertuzumab solution is withdrawn from the vial and added to 250 mL of Isotonic Sodium Chloride Solution (JP), and the entire volume of this solution is intravenously administered.