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Clinical Trial Note

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# A randomized, open-label, Phase III trial of pertuzumab retreatment in HER2-positive locally advanced/metastatic breast cancer patients previously treated with pertuzumab, trastuzumab and chemotherapy: the Japan Breast Cancer Research Group-M05 PRECIOUS study

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## Abstract

The PRECIOUS study (UMIN000018202) is being conducted as a multicenter, randomized, open-label Phase III study to determine if retreatment with pertuzumab is more effective than conventional treatment in HER2-positive locally advanced (LA)/metastatic breast cancer (MBC) patients

previously treated with pertuzumab, trastuzumab and chemotherapy. Patients are randomized 1:1 into chemotherapy plus trastuzumab with or without pertuzumab groups. The latest regimen before enrollment did not include pertuzumab, and the number of previous chemotherapy regimens for LA/MBC did not exceed three. The primary endpoint is investigator-assessed progression-free survival. Secondary endpoints include independent reviewer-assessed progression-free survival, progression-free survival in patients treated with trastuzumab emtansine as the latest regimen, response rate, response duration, overall survival, safety and health-related quality of life. Target accrual is 370 patients, allowing the observation of 325 events, yielding an 80% power for detection of a hazard ratio of 0.739 with a one-sided 5% level of significance.

**Key words:** breast cancer, pertuzumab, retreatment

## Introduction

### Study background

Advanced/recurrent breast cancer is rarely cured even with combined modality therapy, and has a 10-year survival rate of ~5% (1). Currently, therapy for advanced/recurrent breast cancer focuses on ameliorating symptoms, improving quality of life (QoL), and prolonging survival time, rather than curing the disease. For breast cancer cases that are human epidermal growth factor receptor 2 (HER-2)-positive, a combination of anti-HER2 therapy and chemotherapy is recommended.

Pertuzumab, a recombinant humanized immunoglobulin G1 monoclonal antibody, specifically binds to the extracellular domain of HER2 and inhibits dimerization of HER2 with other HER family members (epidermal growth factor receptor/HER1, HER3 and HER4), mainly HER3. Like trastuzumab, the first anti-HER2 antibody for clinical use, pertuzumab can induce growth suppression and apoptosis of tumor cells by blocking intracellular HER2 signaling. Pertuzumab also mediates antibody-dependent cellular cytotoxicity. Among the various combinations of dimerization between HER2 and HER family members, ligand-induced HER2–HER3 signaling has the most potent proliferation stimulating activity in HER2-amplified cancer cells. Pertuzumab binds to the extracellular dimerization domain II of HER2, which is a different binding epitope from that for trastuzumab. Trastuzumab binds to the extracellular dimerization domain IV of HER2 and inhibits ligand-independent HER2–HER3 heterodimerization, but not ligand-dependent HER2–HER3 heterodimerization. In contrast, pertuzumab inhibits ligand-dependent HER2–HER3 heterodimerization and blocks HER2–HER3 intracellular signaling (2).

The clinical utility of pertuzumab in combination with trastuzumab and chemotherapy has been reported in several trials. The CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) study (3) was a randomized double-blind placebo-controlled Phase III trial in patients with untreated HER2-positive metastatic breast cancer (MBC). Patients were randomized 1:1 to receive either pertuzumab and trastuzumab plus docetaxel or placebo and trastuzumab plus docetaxel. The addition of pertuzumab to trastuzumab in combination with docetaxel resulted in a statistically significant improvement in progression-free survival (PFS; median PFS, 18.5 months vs. 12.4 months, respectively; hazard ratio, 0.62 95% confidential interval (CI), 0.51–0.75; objective response rate (ORR), 80.2% vs. 69.3%; $P = 0.001$) and overall survival (OS; median OS: 56.5 months vs. 40.8 months, respectively; hazard ratio, 0.68; 95% CI, 0.56–0.84). Adverse events (AEs) ≥ Grade 3 that occurred significantly more frequently in the pertuzumab arm than in the placebo arm were febrile neutropenia (13.8% vs. 7.6%, respectively), and diarrhea (7.9% vs. 5.0%, respectively). However, no difference was found in the frequency of cardiac events between the two arms. The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (4) recommend the use of pertuzumab, trastuzumab and taxane as first-line treatment for patients with MBC. As a second-line treatment, trastuzumab emtansine (T-DM1) is also recommended. After a pertuzumab-containing regimen and T-DM1, other HER2-targeted therapeutic regimens, including lapatinib-containing regimens and trastuzumab plus chemotherapy, are recommended as third-line treatments and beyond. However, continual pertuzumab use for progression after a pertuzumab-containing regimen and retreatment with pertuzumab are unclear based on evidence.

### Study rationale

Several randomized trials in metastatic and neoadjuvant settings have revealed that trastuzumab plus pertuzumab is more effective than trastuzumab alone. Trastuzumab plus pertuzumab is also better tolerated than lapatinib-containing regimens, although a direct comparison between pertuzumab-containing regimens and lapatinib-containing regimens has not been reported. Thus, trastuzumab plus pertuzumab offers several advantages over other HER2-targeted therapies such as trastuzumab, lapatinib, trastuzumab plus lapatinib, and trastuzumab plus pertuzumab, making it an attractive option for clinicians. The efficacy and the safety of two distinct modalities of a trastuzumab plus pertuzumab-containing regimen after pertuzumab use should be assessed in MBC: continual treatment and retreatment. However, it is clinically difficult to examine the efficacy of continual treatment with a trastuzumab plus pertuzumab-containing regimen because the ASCO Clinical Practice Guidelines (4) recommend the use of trastuzumab, pertuzumab and taxane as first-line treatment and T-DM1 as second-line treatment. When the efficacy of trastuzumab, pertuzumab and other chemotherapies is compared with that of trastuzumab plus chemotherapy, T-DM1 is generally selected as the agent for trastuzumab plus chemotherapy as a second-line treatment. However, the addition of pertuzumab to T-DM1 did not improve PFS in the MARIANNE study (5), which was a randomized, three-arm, multicenter, placebo-control Phase III study that evaluated the efficacy and the safety of T-DM1 plus pertuzumab or T-DM1 versus trastuzumab plus taxane as first-line treatment in patients with HER2-positive locally advanced (LA)/MBC.

In addition, it is also important to evaluate the usefulness of retreatment with a pertuzumab-containing regimen. Continual pertuzumab treatment for progression after pertuzumab treatment is not the same as pertuzumab retreatment. In the pertuzumab retreatment, pertuzumab-containing regimen is previously used for LA/MBC, but pertuzumab is not included in the last treatment before re-administration of pertuzumab-containing regimen. If HER2–HER3-signaling suppressed

by pertuzumab-containing regimens may be restored by anti-HER2 therapy without pertuzumab, pertuzumab retreatment might potentially re-suppress HER2–HER3-signaling.

If the efficacy of pertuzumab retreatment would be demonstrated in this study, pertuzumab retreatment becomes one of standard treatment as a third and subsequent therapy for HER2-positive LA/MBC. On the other hand, when the efficacy of pertuzumab retreatment would not be showed in this study, it is proved that pertuzumab treatment should not be used as subsequent treatment for that.

## Protocol digest of the precious study

### Purpose

This study is being conducted to confirm the superiority, in terms of improvement in PFS, of pertuzumab retreatment in patients with HER2-positive LA/MBC who were previously treated with pertuzumab, trastuzumab and chemotherapy.

### Study setting

This study is a multicenter, randomized, open-label, Phase III study in which HER2-positive LA/MBC patients pretreated with pertuzumab, trastuzumab and chemotherapy will be enrolled. Patients are randomized 1:1 into two groups: one that will receive chemotherapy based on the physician's choice (docetaxel, paclitaxel, nab-paclitaxel, vinorelbine, eribulin, capecitabine and gemecitabine) plus trastuzumab with pertuzumab and the other that will receive chemotherapy plus trastuzumab without pertuzumab (Fig. 1).

### Endpoints

The primary endpoint is investigator-assessed PFS.

Secondary endpoints include independent reviewer-assessed PFS, PFS in patients treated with T-DM1 as the latest regimen, response rate, duration of response, overall survival (OS), safety, and health-related (HR) QoL. Translational research studies using blood samples are also planned to identify prognostic and predictive markers for patients receiving anti-HER2 treatment.

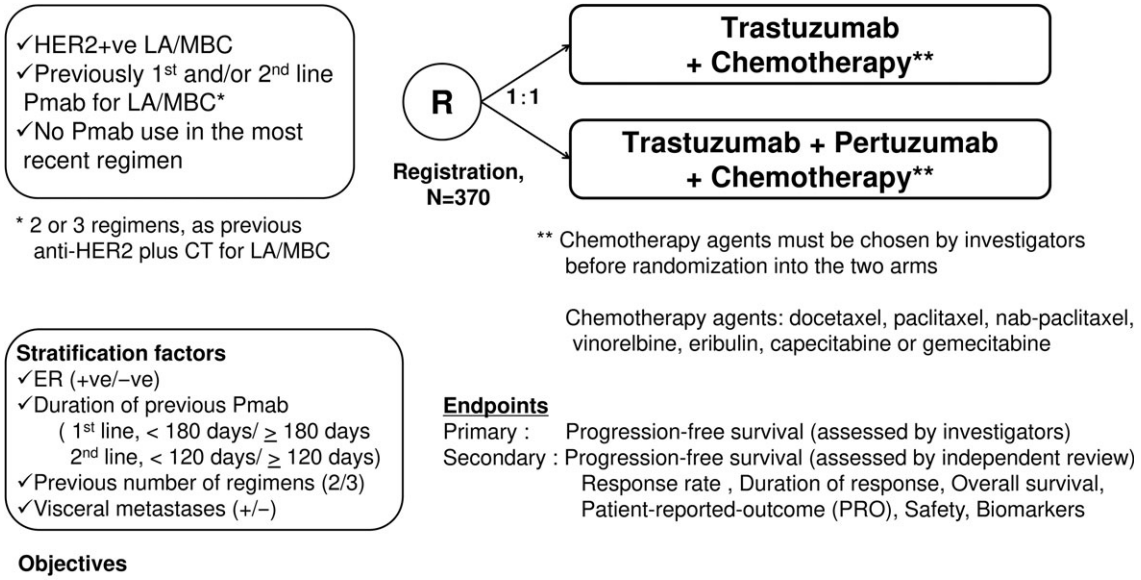
### Eligibility criteria

**Inclusion criteria**

Patients received pertuzumab, trastuzumab and chemotherapy for HER2-positive LA/MBC as first-line and/or second-line anti-HER2-containing chemotherapy. The latest regimen before enrollment did not include pertuzumab, and the number of previous chemotherapy regimens for LA/MBC did not exceed three.

*Inclusion criteria:*

1. Histologically or cytologically confirmed invasive breast cancer.
2. A HER2-positive status confirmed at each institute by means of immunohistochemical analysis (with 3+ indicating positive status) and/or *in situ* hybridization (with an amplification ratio ≥2.0 indicating positive).
3. History of pertuzumab and trastuzumab-containing chemotherapy for locally advanced/metastatic breast cancer (two or three regimens, as previous chemotherapy regimens for LA/MBC). The latest regimen before enrollment must not include pertuzumab.
4. Patients must have measurable and/or non-measurable disease, according to RECIST Version 1.1.
5. Female patients aged ≥20 years.




**Main enrollment pattern**

| Pattern | 1st line | 2nd line | 3rd line | 4th line |
|---|---|---|---|---|
| 1 | Pmab + Tmab + CT1 | T-DM1 | Enrollment | |
| 2 | Pmab + Tmab + CT1 | T-DM1 | LAP + CAPE | Enrollment |
| 3 | Tmab + CT1 | Pmab + Tmab + CT2 | T-DM1 | Enrollment |

**Figure 1.** The schema of the PRECIOUS study. Definition of abbreviations as follows: CAPE: capecitabine, CT: chemotherapy, ER: estrogen receptor, HER2: human epidermal growth factor receptor-2, LA: locally advanced, LAP: lapatinib, MBC: metastatic breast cancer, T-DM1: trastuzumab emtansin, Tmab: trastuzumab, Pmab: pertuzumab, +ve: positive, –ve: negative.

6. Left Ventricular Ejection Fraction ≥50% at baseline (within 28 days before enrollment) as determined by either echocardiography or a multigated acquisition scan.
7. Eastern Cooperative Oncology Group performance status of 0, 1 or 2.
8. Patient life expectancy of at least 3 months.
9. Signed and written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) must be obtained, prior to any study procedure.

*Exclusion criteria:*

1. History of ≥4 chemotherapy regimens for LA/MBC, except for treatment regimens that were free of cancer chemotherapeutic agents (e.g., hormonal therapy alone, a combination of hormonal therapy and trastuzumab, and anti-HER2 therapy alone).
2. Persistent non-hematologic toxicity ≥Grade 3, according to NCI-CTCAE v4.0-JCOG, resulting from previous therapy at the time of enrollment.
3. Symptomatic or uncontrolled central nervous system metastases.
4. Multiple malignancies without a history of breast cancer (within 10 years for invasive breast cancer, and within 5 years for malignancies other than invasive breast cancer).
5. History of exposure to the following cumulative doses of anthracyclines:
   - doxorubicin >360 mg/m$^2$
   - epirubicin >720 mg/m$^2$
   - mitoxantrone >100 mg/m$^2$
   - If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m$^2$ of doxorubicin.
6. Current uncontrolled hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) or unstable angina.
7. History of congestive heart failure of any New York Heart Association class (not less than class II), or serious cardiac arrhythmia requiring treatment (exceptions: atrial fibrillation and paroxysmal supraventricular tachycardia).
8. History of myocardial infarction within 6 months of enrollment.
9. Dyspnea at rest due to complications of advanced malignancy.
10. Inadequate organ function, as determined by the following laboratory results, within 28 days before enrollment:
    - Absolute neutrophil count <1500/mm$^3$
    - Platelet count <100,000/mm$^3$
    - Hemoglobin <8.0 g/dl
    - Total bilirubin >2.0 mg/dl, unless the patient has documented Gilbert's syndrome
    - Aspartate aminotransferase or alanine aminotransferase >100 IU/l with the following exception: if liver dysfunction is considered to be attributable to liver metastases, then aspartate aminotransferase or alanine aminotransferase >200 IU/l, or ≤200 and >100 IU/l with a serum albumin <2.5 g/dl)
    - Serum creatinine value >2.0 mg/dl or 177 μmol/l.
11. Current severe uncontrolled systemic diseases such as clinically significant cardiovascular, pulmonary, or metabolic disease, or a disorder related to wound healing, ulcer or fracture.
12. Uncontrolled malignancy-associated hypercalcemia syndrome being treated with bisphosphonates or denosumab.
13. A >Grade 2 radiation-related adverse event within 14 days before enrollment.
14. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of a need for major surgery during the course of study treatment.
15. Pregnant female patient or positive pregnancy test.
16. Nursing female patient.
17. History of receiving any investigational treatment within 28 days before enrollment.
18. Current known and active infection with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus.
19. Intravenous antibiotic treatment for infection within 14 days before enrollment.
20. Current chronic daily treatment (continuously for >3 months) with corticosteroids (dose equivalent to or greater than 10 mg/day of methylprednisolone), excluding inhaled steroids.
21. Known hypersensitivity to pertuzumab or trastuzumab without an infusion reaction related to these drugs (docetaxel, paclitaxel, nab-paclitaxel, vinorelbine, eribulin, capecitabine and gemecitabine).
22. Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

## Treatment

Control group: 3-weekly trastuzumab (8 mg/kg loading, 6 mg/kg maintenance doses) will be administered in combination with one of the following chemotherapeutic agents of each 3-weeks cycles: 75 or 60 mg/m$^2$ docetaxel intravenously on Day 1, 80 mg/m$^2$ paclitaxel intravenously on Day 1, 8, 15, 260 or 220 mg/m$^2$ nab-paclitaxel intravenously on Day 1, 25 mg/m$^2$ vinorelbine intravenously on Day 1 and 8, 1.4 mg/m$^2$ eribulin on Day 1 and 8, 2500 mg/m$^2$ capecitabine (1 250 mg/m$^2$ given twice daily) on Day 1–14 (6), and 1200 mg/m$^2$ gemcitabine intravenously on Day 1 and 8 (7).

Experimental group: 3-weekly pertuzumb (840 mg loading, 420 mg maintenance doses) and trastuzumab (8 mg/kg loading, 6 mg/kg maintenance doses) will be administered in combination with one of the following chemotherapeutic agents: 75 or 60 mg/m$^2$ docetaxel intravenously on Day 1 every 3 weeks, 80 mg/m$^2$ paclitaxel intravenously on Day 1, 8, 15 every 3 weeks, 260 or 220 mg/m$^2$ nab-paclitaxel intravenously on Day 1 every 3 weeks, 25 mg/m$^2$ vinorelbine intravenously on Day 1 and 8 every 3 weeks, 1.4 mg/m$^2$ eribulin on Day 1 and 8 every 3 weeks, 2000 mg/m$^2$ capecitabine (1000 mg/m$^2$ given twice daily) on Day 1–14 every 3 weeks (6), and 1000 mg/m$^2$ gemcitabine intravenously on Day 1 and 8 every 3 weeks (8).

Dose of chemotherapy agents were decided based on results of previous clinical trials for HER2-positve metastatic breast cancer.

Chemotherapy agent must be chosen by investigators before randomization between both arms.

### Stratification factors

(i) Estrogen receptor status: positive/negative
(ii) Duration of previous pertuzumab treatment: more than/less than 180 days as first-line treatment, 120 days as second-line treatment
(iii) Number of previous chemotherapy regimens: 2/3
(iv) Site(s) of metastasis: visceral or non-visceral metastasis

## Statistical analysis

### Primary endpoint and sample size

The purpose of the primary analysis is to demonstrate the superiority of the test group relative to the control group, in terms of

investigator-assessed PFS, which is the primary variable of the study. The primary analysis set will be defined as the intention-to-treat population. Superiority will be tested using a stratified log-rank test that accounts for all stratification factors, and a one-sided *P* value of less than 0.05 will be considered an indicator of superiority. The distribution of PFS will be estimated using the Kaplan–Meier method. In addition, the hazard ratio and one-sided 95% CI of the therapeutic effect between the groups will be calculated using the Cox proportional hazard model. Three-hundred and seventy patients will be enrolled, which allows the observation of 325 events, yielding an 80% power to detect a hazard ratio of 0.739 at a one-sided 5% level of significance.

### HRQoL analysis

The primary HRQoL variable is the B-Trial Outcome Index (B-TOI). The B-TOI, which is the sum of the scores of Physical Well-Being, Functional Well-Being, and the Breast Cancer Subscale of the Functional Assessment of Cancer Therapy-Breast, has been widely used in clinical studies as a useful measure of QoL (9). The B-TOI scores in the test group and control group will be analyzed using a minimally important difference (MID) estimate. A clinically meaningful minimum difference in B-TOI, i.e. MID, has been reported to be 5 to 6 points (10). In this study, a clinically meaningful decrease in HRQoL is defined as a decrease of 5 points or more in the B-TOI score from the time of enrollment to the time at which a clinically meaningful decrease in B-TOI score, relative to the score at enrollment, was observed. This time to symptom progression (TTSP) for each patient will be calculated using the Kaplan–Meier method, and these values will be used to calculate the median TTSP value for each treatment group. TTSP will be compared between the groups by using a log rank test. In addition, the hazard ratio of TTSP and one-sided 95% CI between the groups will be calculated using the Cox proportional hazard model, with treatment as the stratification factor.

### Registration of the protocol

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000018202) on 6 July 2015 and at the ClinicalTrials.gov website, USA (protocol ID NCT02514681) on 28 July 2015.

## Accrual status

Recruitment began in August 2015 and is expected to be completed in July 2018, in Japan.

## Funding

This work is supported by Chugai Pharmaceutical Co., Ltd through a contract with the Japan Breast Cancer Research Group (JBCRG), which is the study operation organization. Each participating sites receives a research fund from the JBCRG. Chugai Pharmaceutical Co., Ltd is involved in the provision of information relating to the study, but not in the conduct of the study, or the analysis and interpretation of study results.

## Conflict of interest statement

The planning and conduct of this study, decision making regarding the presentation/publication of study results, and analysis of study results will be performed by the study operation organization, including the principal investigator. To ensure fairness and transparency, the study operation organization and the participating investigators should properly manage conflicts of interest according to the policies of the applicable academic societies as well as institutional policies, and should properly disclose potential conflicts of interest relevant to the study, upon the request of the academic societies or medical journals in which the study results will be presented. The funder of the study, Chugai Pharmaceutical Co., Ltd will not be involved in any of the planning and conduct of the study, decision making regarding the presentation/publication of study results, or analysis of study results, which will be independently performed by the study operation organization.

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