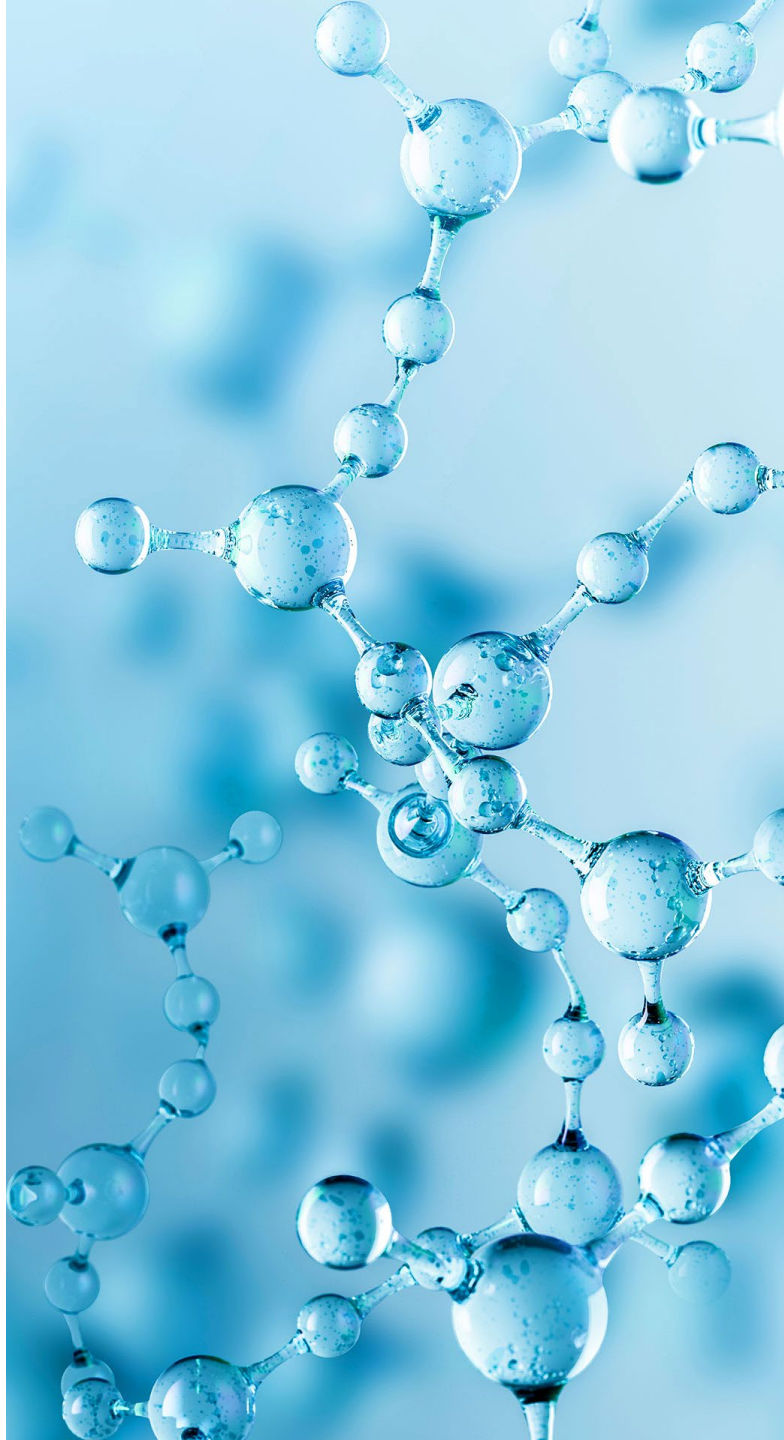
**Antineoplastic agent/Anti-HER2 combination humanized monoclonal antibody/hyaluronan-degradation enzyme combination drug**

# Information Meeting on “PHESGO® combination for subcutaneous injection MA / IN”

## Chugai Pharmaceutical Co., Ltd.

November 30, 2023



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Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

# Agenda

01 **Overview of PHESGO® Combination for Subcutaneous Injection MA/IN**

HER2 Franchise Lifecycle Leader,
Chugai Pharmaceutical Co., Ltd.
**Yuji Habara**

02 **Clinical Significance of PHESGO® in the Treatment of HER2-Positive Breast Cancer**

Professor and Chairman, Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine
**Naoki Hayashi, M.D., Ph.D.**

03 **Q&A session**

# Overview of PHESGO® Combination for Subcutaneous Injection MA/IN

Standard Commodity Classification No. of Japan (SCCJ): 874291

Antineoplastic agent/Anti-HER2[Note1)] humanized monoclonal antibody/hyaluronic acid-degrading enzyme combination drug

Biological product, powerful drug, prescription drug[Note2)]

Listed on the NHI Drug Price List

**PHESGO® combination for subcutaneous injection MA/IN**


pertuzumab (genetical recombination), trastuzumab (genetical recombination), and vorhyaluronidase alfa (genetical recombination) injection

Note 1) Human Epidermal Growth Factor Receptor Type 2 (also known as c-*erb*B-2)
Note 2) Caution - Use only pursuant to the prescription of a physician, etc.

**Yuji Habara**
**HER2 Franchise Lifecycle Leader**
**Chugai Pharmaceutical Co., Ltd.**

# Today's Agenda

- **Product summary of PHESGO® combination for subcutaneous injection MA/IN**
- **Clinical study results, etc.**
- **Description in the guidelines, clinical positioning, etc.**

# Basic Information on PHESGO®

[Brand name]
PHESGO® combination for subcutaneous injection MA
PHESGO® combination for subcutaneous injection IN

IN: Initial dose, MA: Maintenance dose

[Non-proprietary name]
pertuzumab (genetical recombination)/trastuzumab (genetical recombination)/vorhyaluronidase alfa (genetical recombination) injection

[Origin of product name]
English name: PHESGO → **P**erjeta **H**erceptin **E**a**S**y to **GO**

- Herceptin (trastuzumab)
- Perjeta (pertuzumab)

PHESGO® is a combination for subcutaneous injection consisting of pertuzumab and trastuzumab, anti-HER2 humanized monoclonal antibodies, at a fixed dose of each, which is further combined with vorhyaluronidase alfa to promote penetration and absorption of the drug solution.

# History of Development of PHESGO

**[Conventional treatment]**
- Combination therapy with pertuzumab and trastuzumab is the standard treatment for HER2-positive breast cancer
- The time required for administration is approximately 150 minutes for the initial dose, and 60 to 150 minutes for the second and subsequent doses*

* If the initial dose is well-tolerated, the duration can be shortened to 30 minutes for both drugs

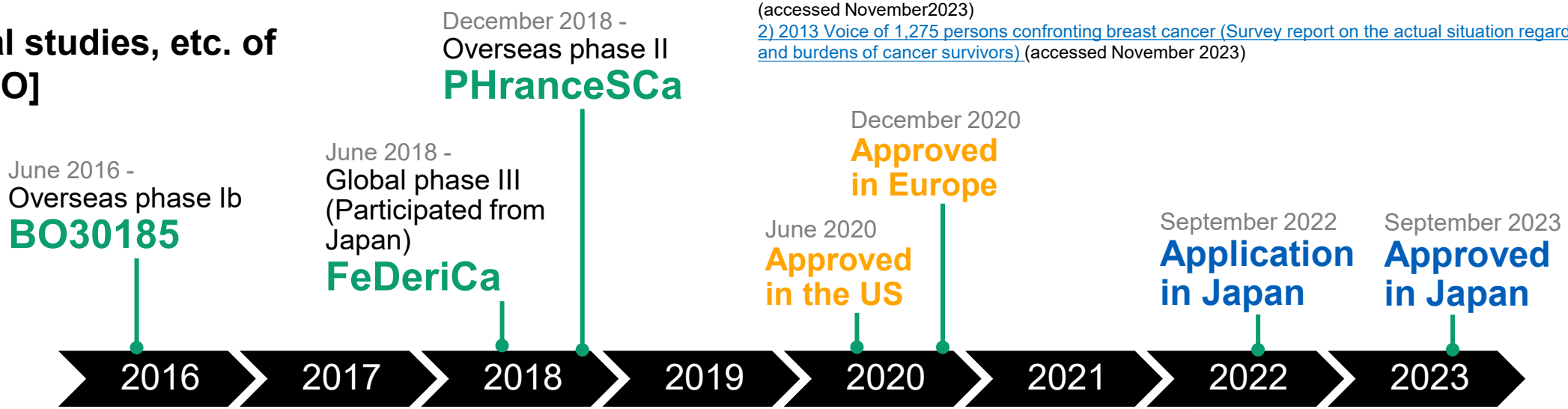
**[Patient's perspective (needs)]**
- Breast cancer is common among working-age women, so balancing work with childcare, nursing care, etc. is important[1)]
- The most common "work-related concern from diagnosis to the present" was "adjusting work schedules and securing time off for hospital visits and treatment"[2)]

**[Medical institution's perspective (needs)]**
- Efficient management of time is important as new drugs are introduced, treatment regimens increase, and chemotherapy rooms, etc. are crowded

**PHESGO contributes to improved patient convenience and the efficiency of medical resources**

1) National Cancer Center Cancer Information Service "Cancer Statistics" (National Cancer Registry) (accessed November2023)
2) 2013 Voice of 1,275 persons confronting breast cancer (Survey report on the actual situation regarding the concerns and burdens of cancer survivors) (accessed November 2023)

**[Clinical studies, etc. of PHESGO]**



# Active Pharmaceutical Ingredients of PHESGO

**Inhibitory effect on HER2 signaling**
**ADCC (antibody-dependent cellular cytotoxicity)**

**pertuzumab (genetical recombination)**

**trastuzumab (genetical recombination)**

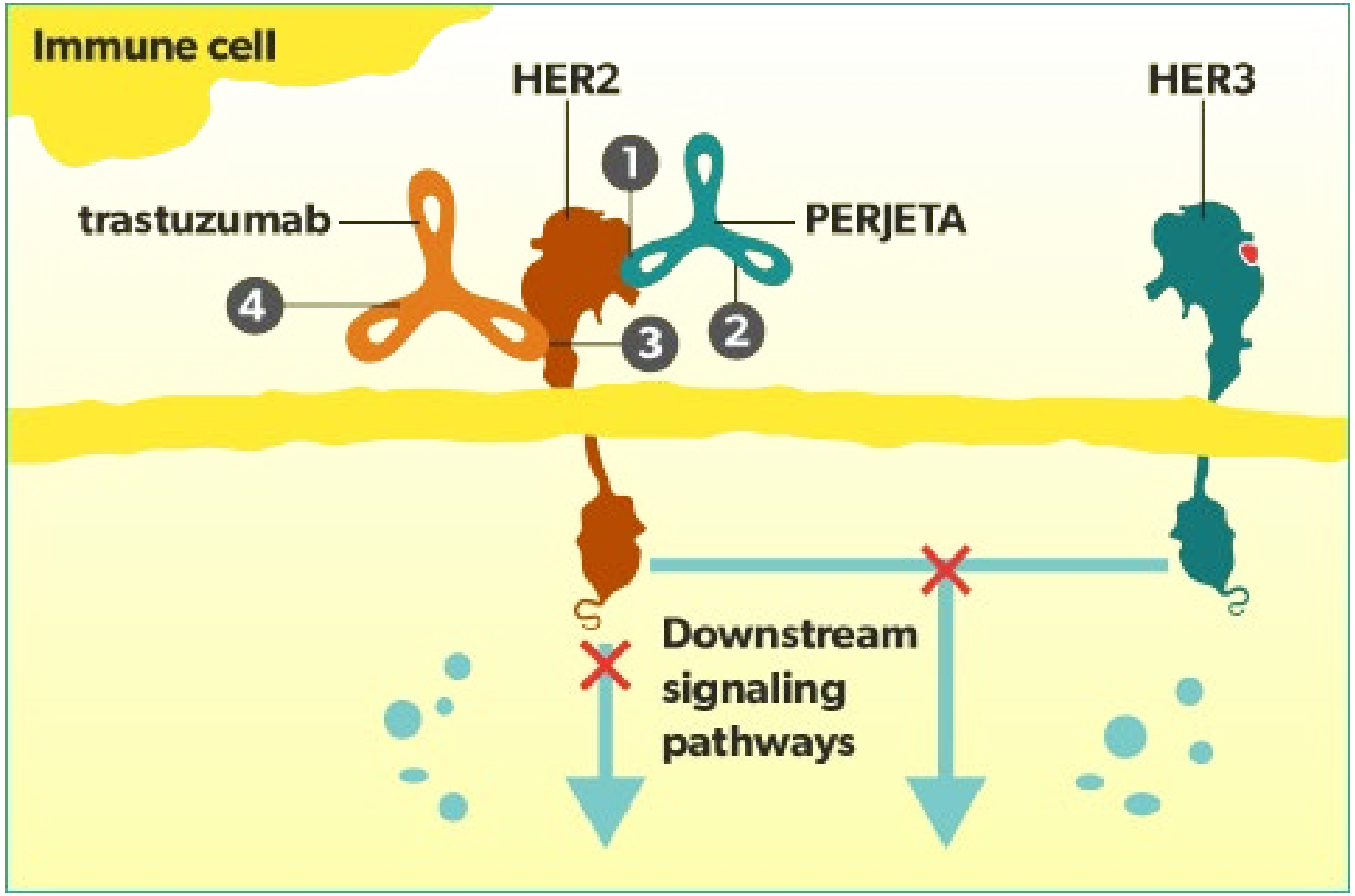
**Tissue permeability-increasing action**

**vorhyaluronidase alfa (genetical recombination)**

conceptual illustration

# Mechanism of Action

Because pertuzumab and trastuzumab bind to different HER2 sites, the combination of these two components is considered to comprehensively block HER2 signals, suppress cell proliferation, and induce apoptosis.[1)]




pertuzumab (Perjeta):

(1) Binds to domain II of the extracellular domain of HER2

(2) to inhibit HER2 dimerization and inhibit the activation of downstream signaling pathways, and to induce ADCC activity[2)]

trastuzumab (Herceptin):

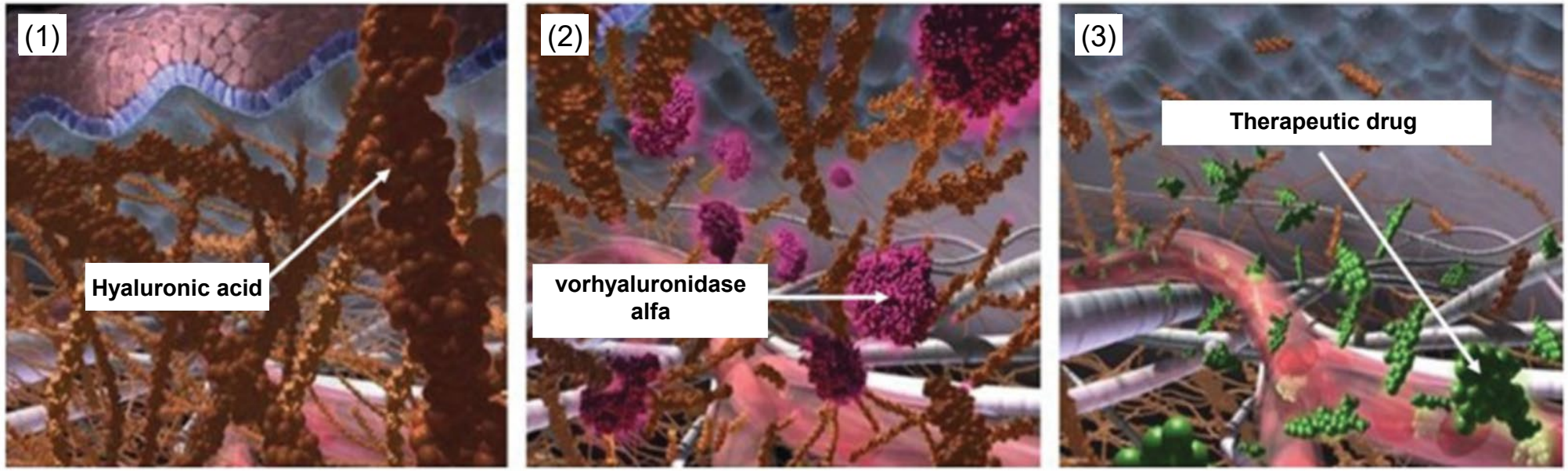
(3) Binds to domain IV of the proximal part of the HER2 cell membrane

(4) to inhibit tumor growth by inducing ADCC activity[2)]

1) Diermeier-Daucher S, *et al.* Ann N Y Acad Sci. 2008; 1130: 280-286.
2) Scheuer W, *et al.* Cancer Res. 2009; 69(24): 9330-9336.

# Mechanism of Action (vorhyaluronidase alfa)

- ✓ Vorhyaluronidase alfa depolymerizes hyaluronic acid by hydrolyzing the bond between D-glucuronic acid and N-acetylglucosamine, which constitutes hyaluronic acid, a substrate for skin, and transiently reduces the viscosity of hyaluronic acid in the extracellular matrix.
- ✓ Vorhyaluronidase alfa is thought to decrease resistance during drug infusion and to have a local, transient, permeability-increasing action.




Locke KW, *et al.* Drug Deliv. 2019; 26(1): 98-106.

(1) The viscosity of hyaluronic acid limits the penetration and diffusion of therapeutic drugs.

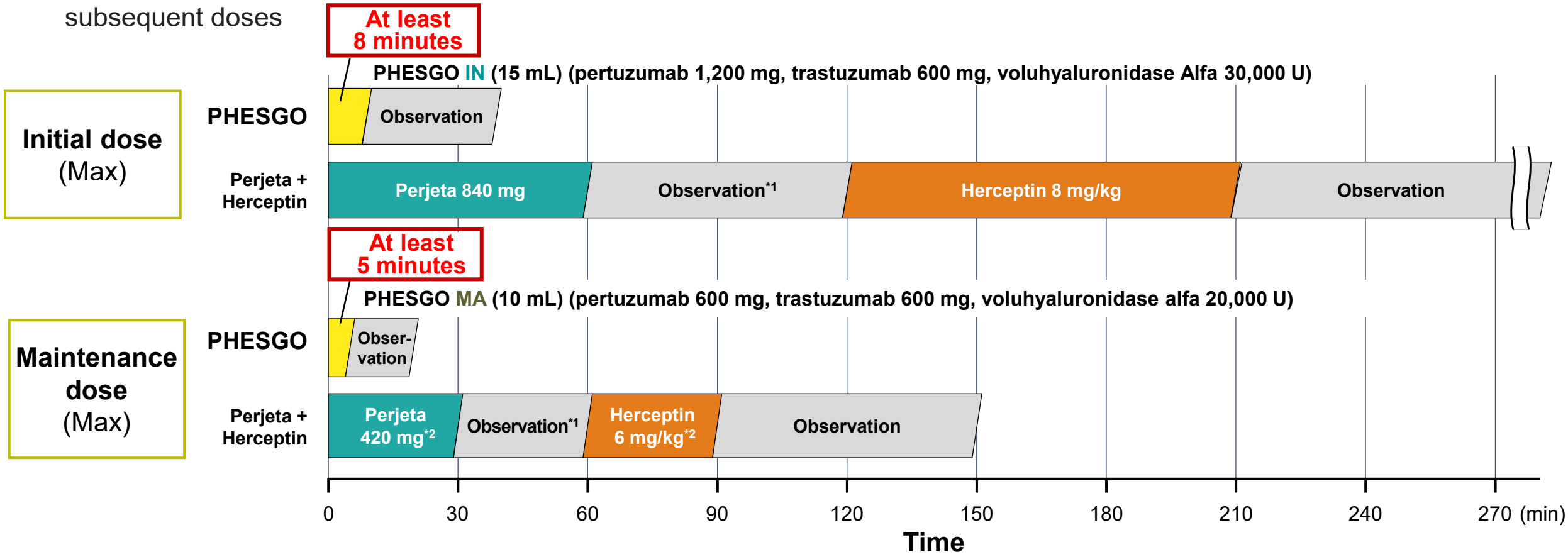
(2) Vorhyaluronidase alfa depolymerizes hyaluronic acid.

(3) Locally and transiently increases the permeability of the drug, and promotes drug penetration and diffusion.

Fessler JH. Biochem J. 1960; 76(1): 132-135.
Hechter O. J Exp Med. 1947; 85(1): 77-97.
Bookbinder LH, *et al.* J Control Release. 2006; 114(2): 230-241.

# PHESGO is Expected to Shorten the Duration of Administration and Improve Convenience, Compared to the Conventional Intravenous Drip Infusion

When the intravenous formulations of Perjeta and Herceptin are administered continuously, the duration of administration is approximately 150 minutes for the initial dose and 60 to 150 minutes for the second and subsequent doses, while the duration of administration of PHESGO is at least 8 minutes for the initial dose and at least 5 minutes for the second and subsequent doses



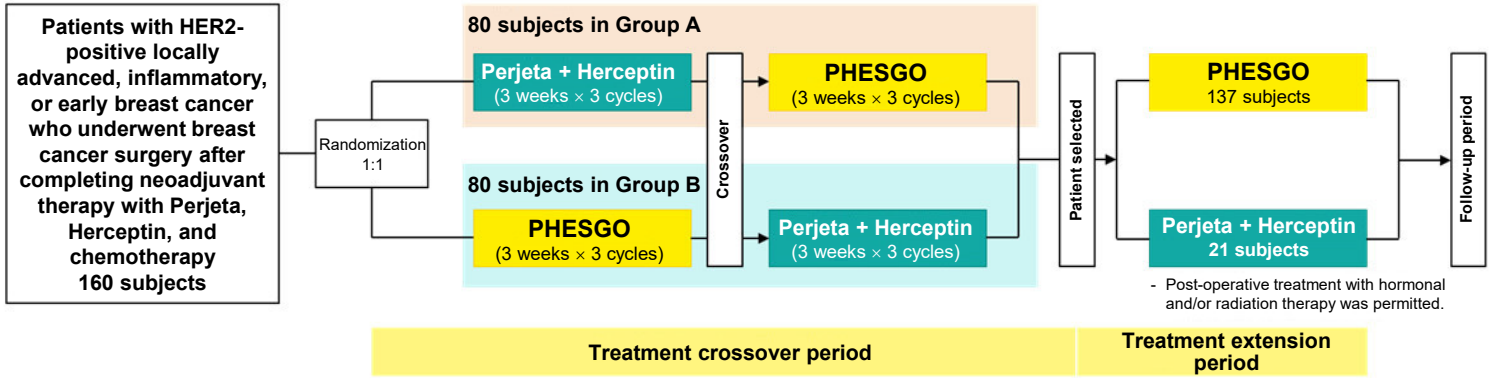

*1: After the completion of administration, the patient should be observed, and the next drug should be administered after confirming that no infusion reaction symptoms are observed. In clinical studies, subjects were observed for 60 minutes at the initial administration, and if there were no problems such as infusion reaction and the drug was well-tolerated in Cycle 2 and subsequent cycles, the monitoring period could be shortened to 30 minutes.

*2: If the initial dose is well-tolerated, the duration of the second and subsequent doses can be shortened to 30 minutes.

# 85% of Patients Preferred PHESGO

## (Overseas phase II clinical study [PHranceSCa Study])

[Objective] To evaluate patient preference and satisfaction for treatment, by intravenously administering PHESGO or Perjeta and Herceptin (Perjeta + Herceptin [IV]) as a postoperative therapy in patients with HER2-positive early breast cancer.




**Stratification factor**

- Type of neoadjuvant chemotherapy (anthracycline + taxane, carboplatin + taxane, or taxane only)
- Response to preoperative therapy: pCR or non-pCR
- Hormone receptor expression status (ER and/or PgR positive, or ER and PgR negative)

pCR: pathological complete response
ER, estrogen receptor; PgR, progesterone receptor

**[Endpoints]**

**Primary endpoint:** Patient preference for PHESGO (based on responses to PPQ Question 1) [reference information]

**Secondary endpoints:** The strength of preference for the method of administration preferred in PPQ Question 1 and main reasons for the preference (PPQ Questions 2 and 3) [reference information], patient satisfaction with PHESGO and Perjeta + Herceptin (IV) (based on responses to TASQ-SC and TASQ-IV Question 1) [reference information], selection rate of PHESGO for the treatment extension period [reference information], and healthcare professional perception of time/resource use and convenience with PHESGO (based on healthcare professional's responses to HCPQ) [reference information], etc.

**Patient preference for PHESGO (based on responses to PPQ Question 1) [reference information]**

85.0% of patients (95% CI: 78.5 - 90.2) preferred PHESGO, while 13.8% of patients preferred Perjeta + Herceptin (IV).

| Number of patients (%) | Group A (n = 80) Perjeta + Herceptin (IV) → PHESGO | Group B (n = 80) PHESGO → Perjeta + Herceptin (IV) | All patients (n = 160) |
|---|---|---|---|
| PHESGO | 70 (87.5%) | 66 (82.5%) | 136 (85.0%) |
| Perjeta + Herceptin (IV) | 10 (12.5%) | 12 (15.0%) | 22 (13.8%) |
| No particular preference | 0 | 2 ( 2.5%) | 2 ( 1.3%) |

Data cutoff date for the primary analysis: February 24, 2020

Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa Study), O'Shaughnessy J, *et al.* Eur J Cancer. 2021; 152: 223 -232.
This publication includes employees of F. Hoffmann-La Roche and Genentech, as well as authors funded by F. Hoffmann-La Roche and Genentech.

Overseas phase II clinical study: MO 40628 Study (PHranceSCa Study) (overseas data)

# Common Adverse Events During the Treatment Crossover Period (≥ 5 Patients in any)

The major adverse events during the treatment crossover period included radiation skin injury [Group A: at the time of administration of Perjeta + Herceptin (IV) (Cycle 1-3) 21.3%, Group A: at the time of administration of PHESGO (Cycle 4-6) 8.8%, Group B: at the time of administration of PHESGO (Cycle 1-3) 12.5%, Group B: at the time of administration of Perjeta + Herceptin (IV) (Cycle 4-6) 12.5%; the same order, hereinafter], injection site reaction (Group A: 0%, 15.0%, Group B: 30.0%, 0%), and diarrhea (Group A: 15.0%, 8.8%, Group B: 7.5%, 5.0%).

| n (%) | Group A (n = 80) Perjeta + Herceptin (IV) → PHESGO | | Group B (n = 80): PHESGO → Perjeta + Herceptin (IV) | |
|---|---|---|---|---|
| | At the time of administration of Perjeta + Herceptin (IV) Cycle 1-3 | At the time of administration of PHESGO Cycle 4-6 | At the time of administration of PHESGO Cycle 1-3 | At the time of administration of Perjeta + Herceptin (IV) Cycle 4-6 |
| All adverse events | 62 (77.5%) | 58 (72.5%) | 62 (77.5%) | 51 (63.8%) |
| Radiation skin injury* | 17 (21.3%) | 7 ( 8.8%) | 10 (12.5%) | 10 (12.5%) |
| Injection site reactions | 0 | 12 (15.0%) | 24 (30.0%) | 0 |
| Diarrhoea | 12 (15.0%) | 7 ( 8.8%) | 6 ( 7.5%) | 4 ( 5.0%) |
| Hot flush | 6 ( 7.5%) | 4 ( 5.0%) | 5 ( 6.3%) | 0 |
| Pruritus | 6 ( 7.5%) | 3 ( 3.8%) | 0 | 1 ( 1.3%) |
| Erythema | 6 ( 7.5%) | 1 ( 1.3%) | 1 ( 1.3%) | 1 ( 1.3%) |
| Fatigue | 5 ( 6.3%) | 4 ( 5.0%) | 5 ( 6.3%) | 4 ( 5.0%) |
| Infusion reaction | 5 ( 6.3%) | 0 | 0 | 1 ( 1.3%) |
| Arthralgia | 4 ( 5.0%) | 3 ( 3.8%) | 5 ( 6.3%) | 2 ( 2.5%) |
| Upper respiratory infection | 1 ( 1.3%) | 2 ( 2.5%) | 5 ( 6.3%) | 4 ( 5.0%) |

* During the treatment crossover period in this study, concomitant radiotherapy was used in 23 patients (28.8%) in Group A and 21 patients (26.3%) in Group B.

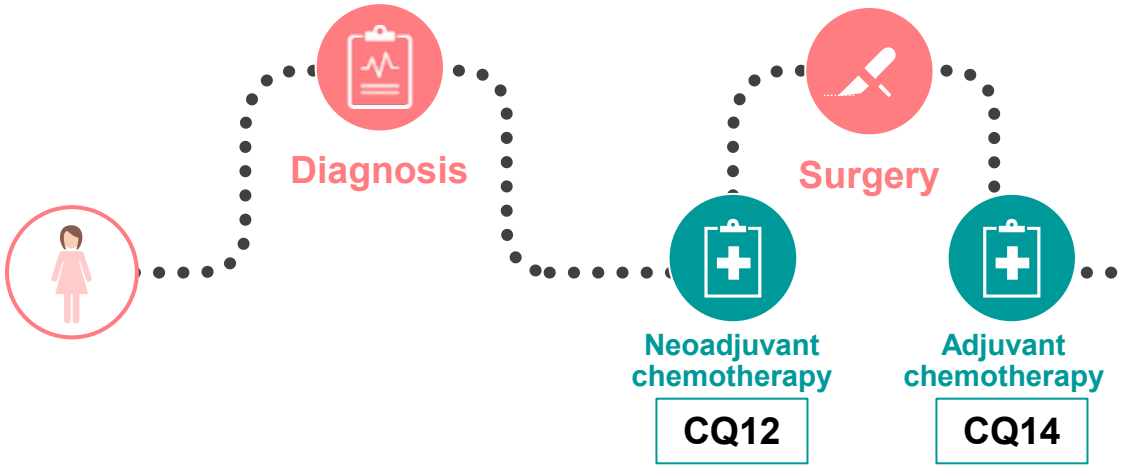
MedDRA ver.22.1

Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa Study), O'Shaughnessy J, *et al.* Eur J Cancer. 2021; 152: 223 -232.
This publication includes employees of F. Hoffmann-La Roche and Genentech, as well as authors funded by F. Hoffmann-La Roche and Genentech.

# Overview of HER2-Positive Breast Cancer Treatment (PHESGO Prescription Segment)

The segments for which Herceptin + Perjeta combination therapy is recommended in the Japanese guidelines are preoperative/postoperative therapy and first-line therapy for advanced/recurrent breast cancer. These are expected to be replaced by PHESGO

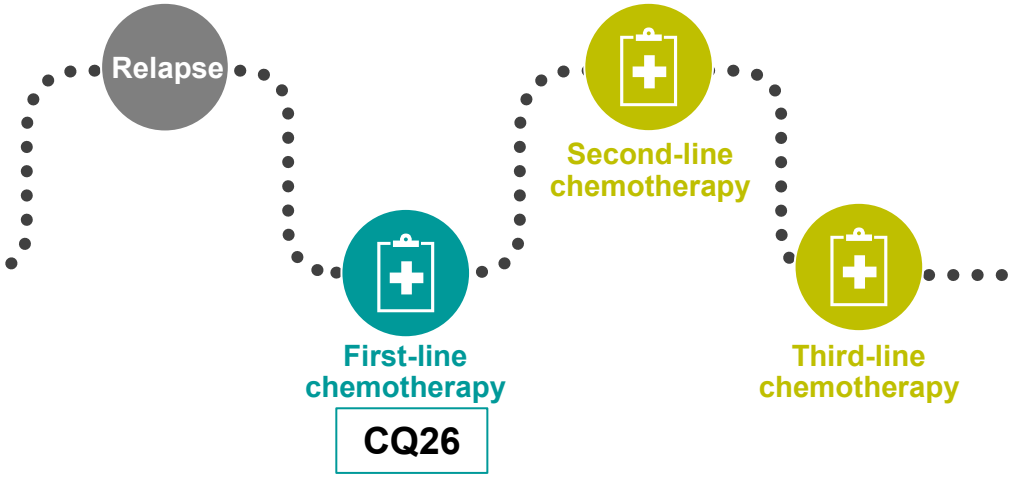
## Early breast cancer




**CQ12: Is it recommended to add pertuzumab to trastuzumab in patients with HER2-positive early breast cancer receiving neoadjuvant chemotherapy?**
**The addition of pertuzumab to trastuzumab is strongly recommended.**

**CQ14: Is it recommended to add pertuzumab to trastuzumab in patients with HER2-positive early breast cancer receiving adjuvant chemotherapy?**
**Adding pertuzumab to trastuzumab is strongly recommended in patients at a high risk of recurrence.**

## Advanced/recurrent breast cancer



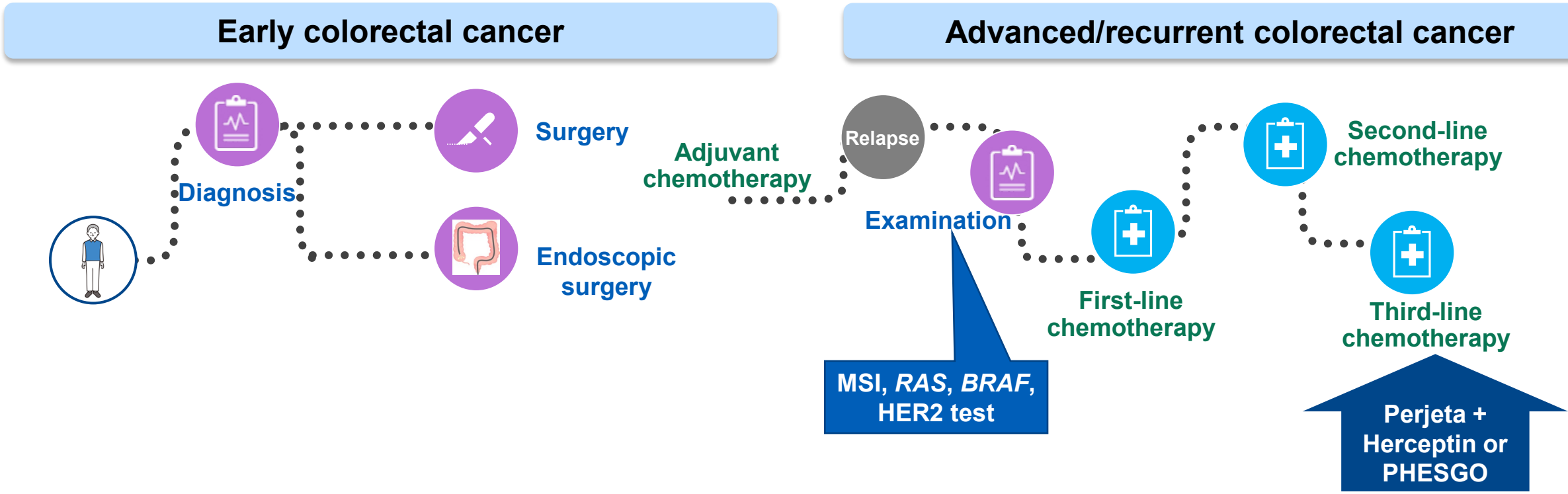

**CQ26: Is trastuzumab + pertuzumab + taxane combination therapy recommended as a first-line therapy for HER2-positive metastatic/recurrent breast cancer?**
**The combination of trastuzumab + pertuzumab + docetaxel is strongly recommended.**
**Combination therapy with trastuzumab + pertuzumab + paclitaxel is weakly recommended.**



Breast Cancer Treatment Guidelines https://jbcs.xsrv.jp/guideline/2022/y_index/ (Japanese only) (accessed November 2023)

# Overview of HER2-Positive Colorectal Cancer Treatment (PHESGO Prescription Segment)

The segment for which Herceptin + Perjeta combination therapy is recommended in the Japanese guidelines is HER2-positive unresectable advanced/recurrent colorectal cancer that has progressed after cancer chemotherapy. This is expected to be replaced by PHESGO




Colorectal Cancer Treatment Guidelines https://www.jsccr.jp/guideline/2022/particular.html (Japanese only) (accessed November 2023)
Guidelines-related updates: https://www.jsccr.jp/guideline/news/202203_01.html (Japanese only) (accessed November 2023)

# Indications/Dosage and Administration

[Indications]

- ○ HER2-positive breast cancer
- ○ Advanced or recurrent HER2-positive colorectal cancer that has progressed following cancer chemotherapy and is not amenable to curative resection

[Dosage and administration]

< HER2-positive breast cancer >

The usual adult dosage is an initial dose of 1200 mg, 600 mg, and 30000 U of pertuzumab (genetical recombination), trastuzumab (genetical recombination), and vorhyaluronidase alfa (genetical recombination), respectively, administered subcutaneously over 8 minutes, followed by 600 mg, 600 mg, and 20000 U of the second and subsequent doses over 5 minutes every 3 weeks thereafter, in combination with other antineoplastic agents. For neoadjuvant or adjuvant therapy, the duration of treatment should be up to 12 months.

< Advanced or recurrent HER2-positive colorectal cancer that has progressed following cancer chemotherapy and is not amenable to curative resection>

The usual adult dosage is an initial dose of 1200 mg, 600 mg, and 30000 U of pertuzumab (genetical recombination), trastuzumab (genetical recombination), and vorhyaluronidase alfa (genetical recombination), respectively, administered subcutaneously over 8 minutes, followed by 600 mg, 600 mg, and 20000 U of the second and subsequent doses over 5 minutes every 3 weeks thereafter.

# Summary of PHESGO

1. PHESGO is a combination for subcutaneous injection consisting of pertuzumab and trastuzumab (monoclonal antibody in Perjeta and Herceptin), the standard of care drugs for the treatment of HER2-positive breast cancer, and voluhyaluronidase alfa, which can be administered at fixed doses, without the need for reconstitution.

2. When the conventional intravenous formulation is administered continuously*, the duration of administration is approximately 150 minutes for the initial dose and 60 to 150 minutes** for the second and subsequent doses, while the duration of administration of PHESGO is at least 8 minutes for the initial dose and at least 5 minutes for the second and subsequent doses, which is expected to improve convenience by shortening the administration time.

3. PHESGO is expected to replace the segment for which Herceptin + Perjeta combination therapy is recommended in the Japanese guidelines

* Duration of drug administration (excluding observation, etc.)
** If the initial dose is well-tolerated, the duration can be shortened to 30 minutes for both drugs

SHOWA UNIVERSITY HOSPITAL
BREAST CENTER

# Clinical Significance of PHESGO®
# in the Treatment of HER2-Positive Breast Cancer

Naoki Hayashi, M.D., Ph.D.
Chief Professor, Division of Chest Surgery, Department of Surgery,
Showa University School of Medicine
/Department Chair, Department of Breast Surgical Oncology,
Showa University Hospital

# COI

| | | | |
|---|---|---|---|
| Research fund | ◆Scientific research fund | Sponsor | MSD, Chugai, and Konica Minolta Japan |

| | | | |
|---|---|---|---|
| **Name of lead presenter** | **Naoki Hayashi** | **Institution or company/position** | **Professor, Division of Breast Surgical Oncology<br>Department of Surgery<br>Showa University School of Medicine** |

| | No | If yes, please specify the name of company and/or organization, your status. |
|---|---|---|
| Employee of company and/or profit-making organization | ☑ | |
| Adviser of company and/or profit-making organization | ☑ | |
| Profit of stock | ☑ | |
| Lecturer fees | ☐ | Eli Lilly, Astrazeneca, taiho, Eizai, ExactScience,Daiichi-Sankyo Novartis, Pfizer, and Chugai |
| Manuscript fees | ☑ | |
| Research expenses | ☑ | |
| Contributions | ☑ | |
| Fees of testimony, judgment, comment, etc. | ☑ | |
| Representative of organization for clinical study receiving research expenses from company | ☑ | |
| Presents or any payment | ☑ | |

# About Breast Cancer

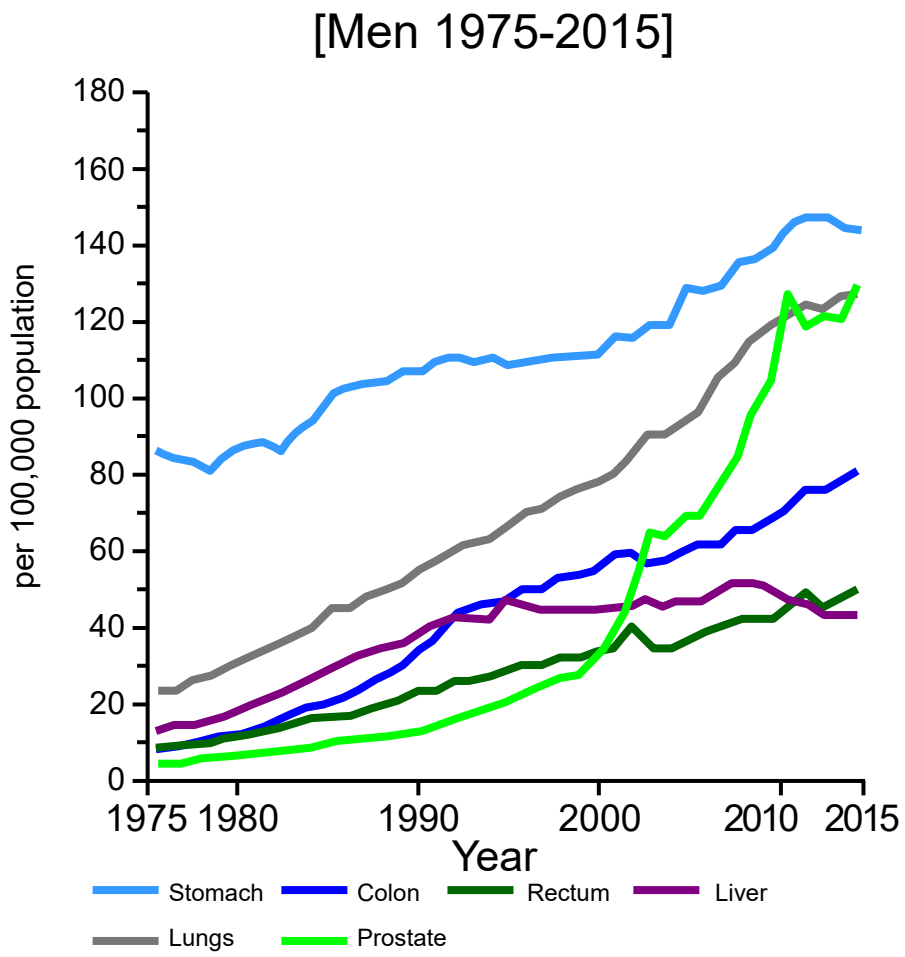
# Probability of Getting Breast Cancer during Your Lifetime

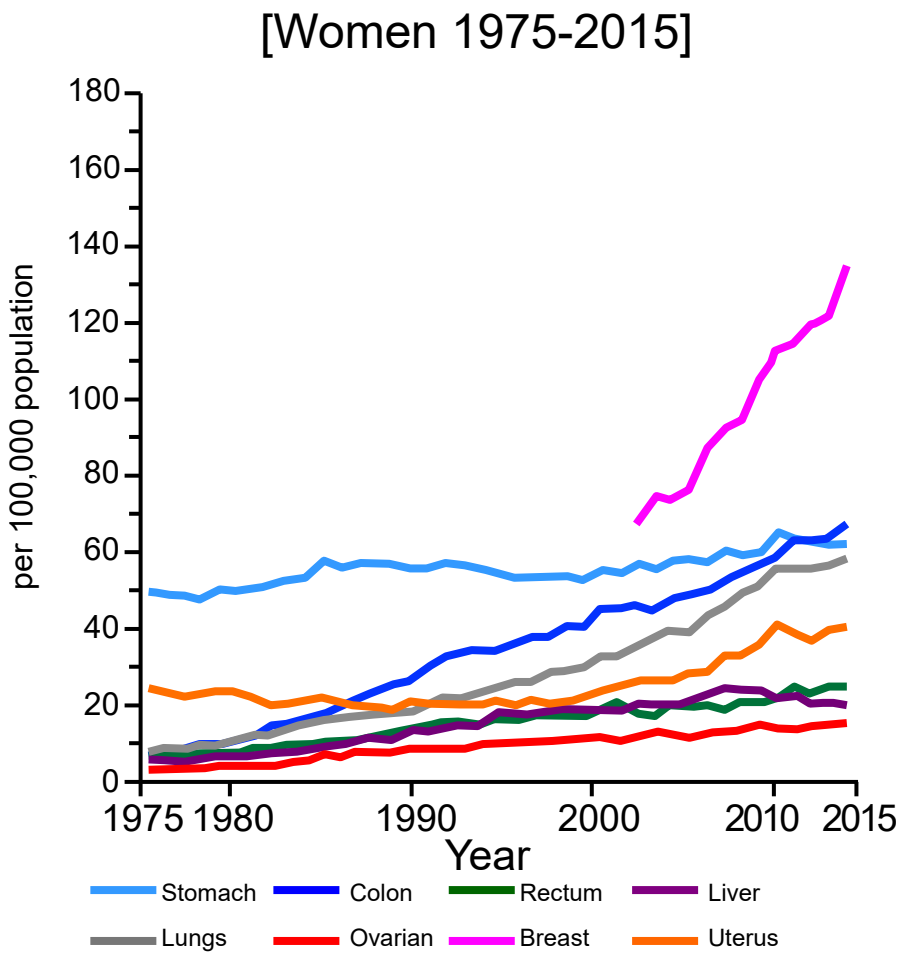
1/9 persons

Approximately 95,000 or more annually
(2016～2019)

National Cancer Center Japan, Cancer Information Service
“Cancer statistics”（National Cancer Registry）

# Annual Change of Crude Incidence by Major Cancer Sites (Japan, by gender, per 100,000 population)



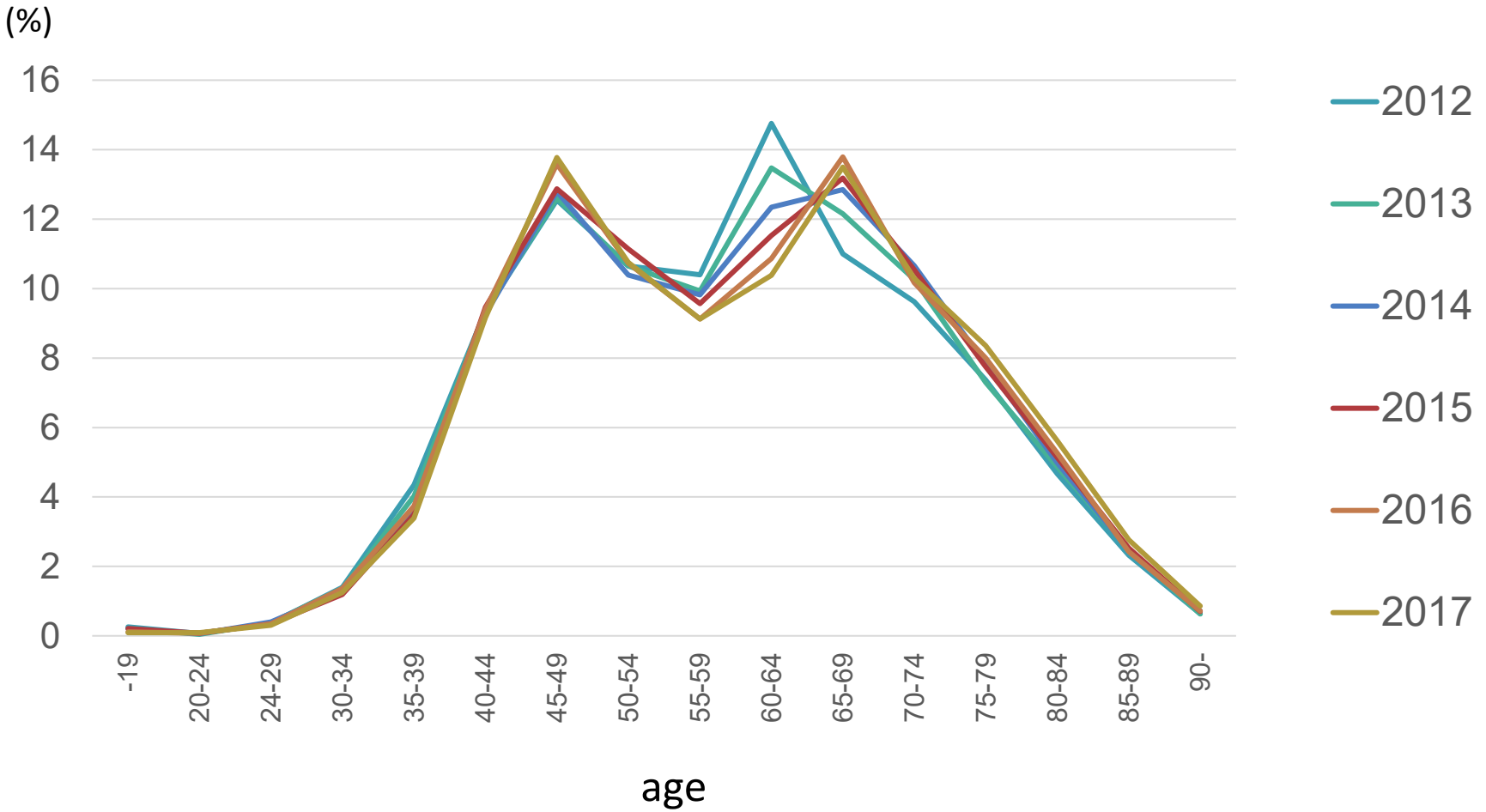




Summary of cancer registry/statistics: “population-based cancer registry ” is a system that started in January 2016. It is a new system to aggregate, analyze, and manage data of all patients diagnosed with cancer in Japan. Data collected from throughout Japan is put together in a national database, and the latest statistical information obtained from analysis is published on the "Cancer Registry and Statistics" section of the website of National Cancer Center's Center for Cancer Control and Information Services (http://ganjoho.jp/reg_stat/).

Prepared from the website of Center for Cancer Control and Information Services, National Cancer Center
http://gdb.ganjoho.jp/graph_db/index Accessed in November 2023

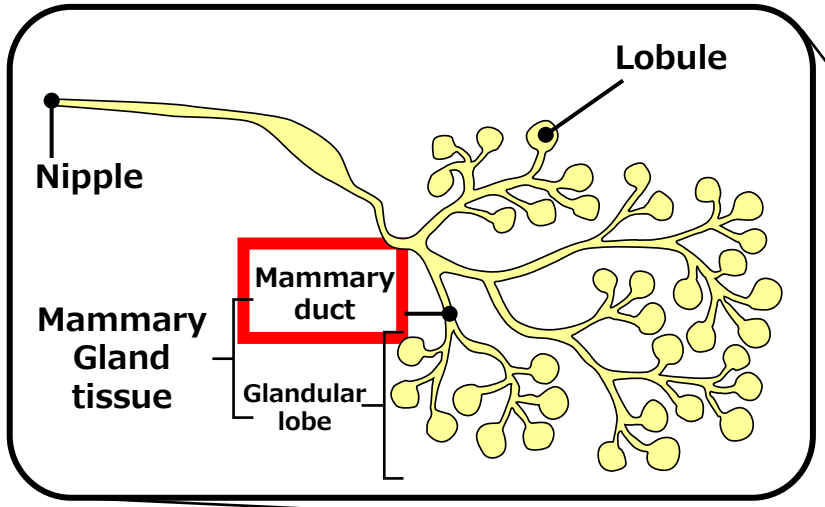
# Annual Report of the Japanese Breast Cancer Registry for 2017

Figure 1　Number of Japanese Breast Cancer Patients by Age

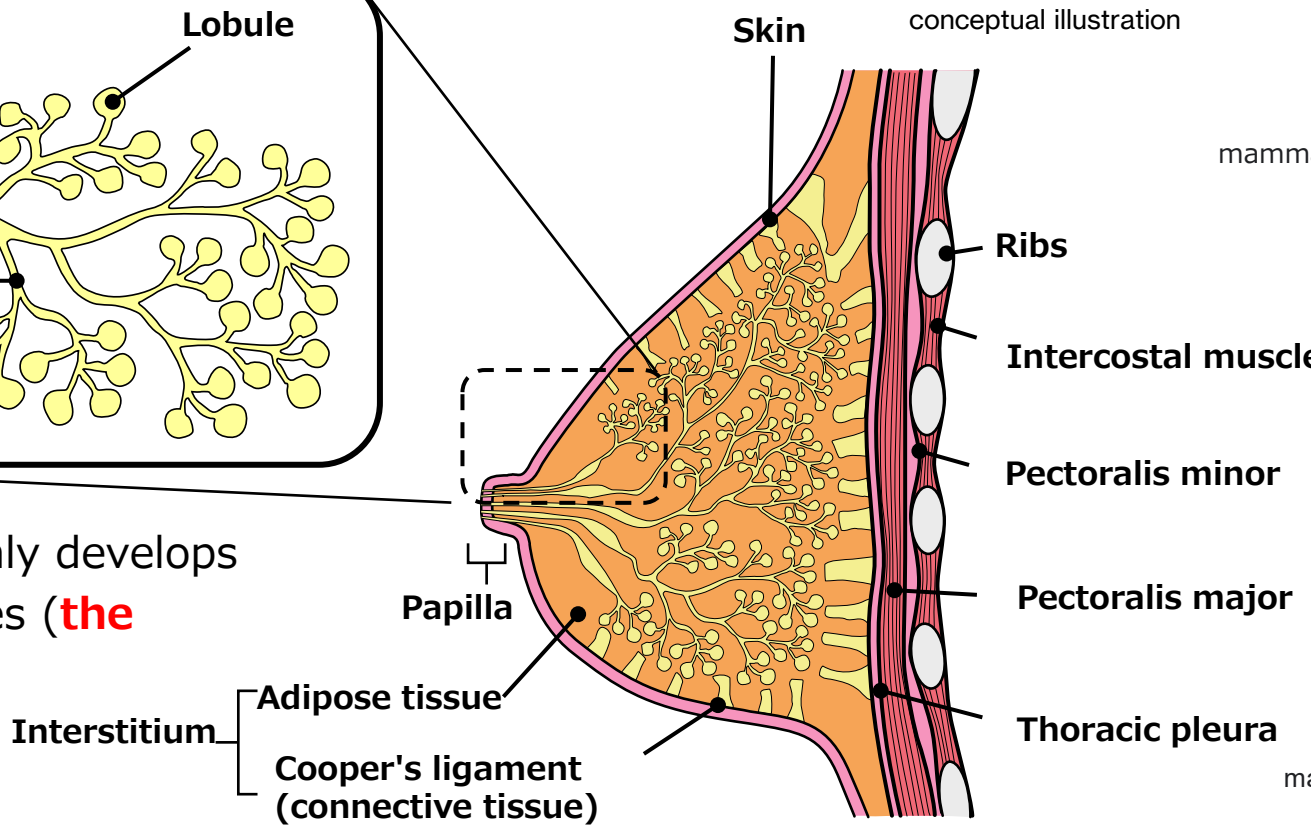



Naoki Hayashi et al. Breast Cancer. 2020 Sep;27(5):803-809.

# Invasive and Non-invasive Cancers

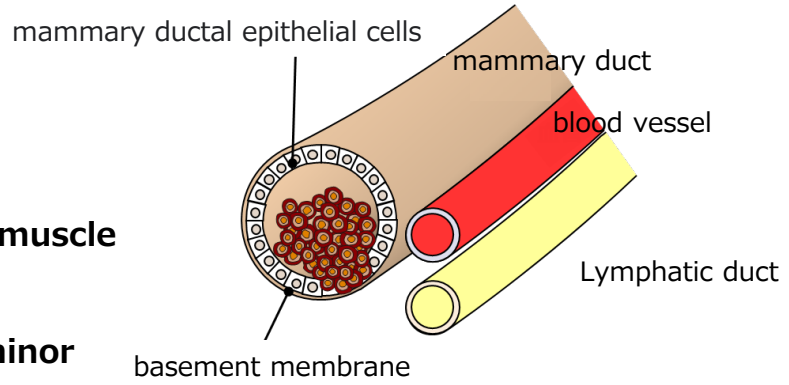



Breast cancer mainly develops in mammary tissues (**the ducts**, the lobules)

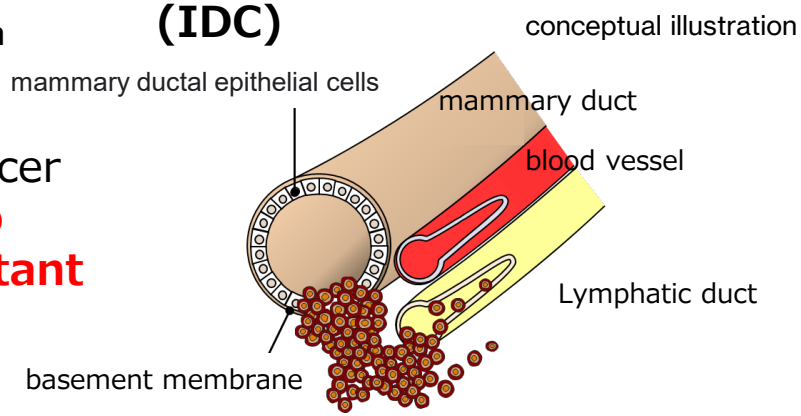



Progression of invasive cancer **may cause metastases to axillary lymph nodes/distant metastases**

## Ductal carcinoma in situ (DCIS)




## Invasive ductal carcinoma (IDC)

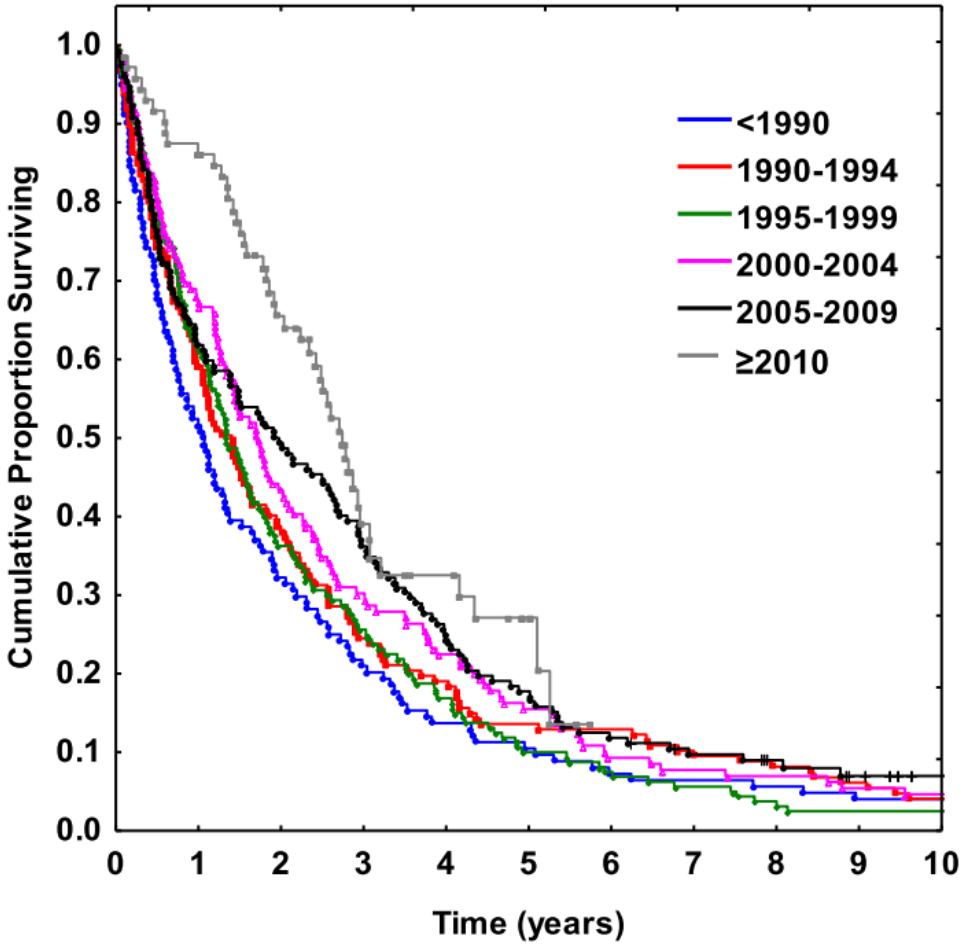





Prepared from National Hospital Organization Shikoku Cancer Center, Total Guide to Breast Cancer Nursing, Shorin-Sha 2008

# Improvement Survival of Breast Cancer

Fig. 1. Cumulative survival of 784 patients diagnosed with metastatic breast cancer by successive time periods




Survey method

Patients diagnosed with disseminated breast cancer in Sweden between 1985 and 2014 were identified and followed until 2016.

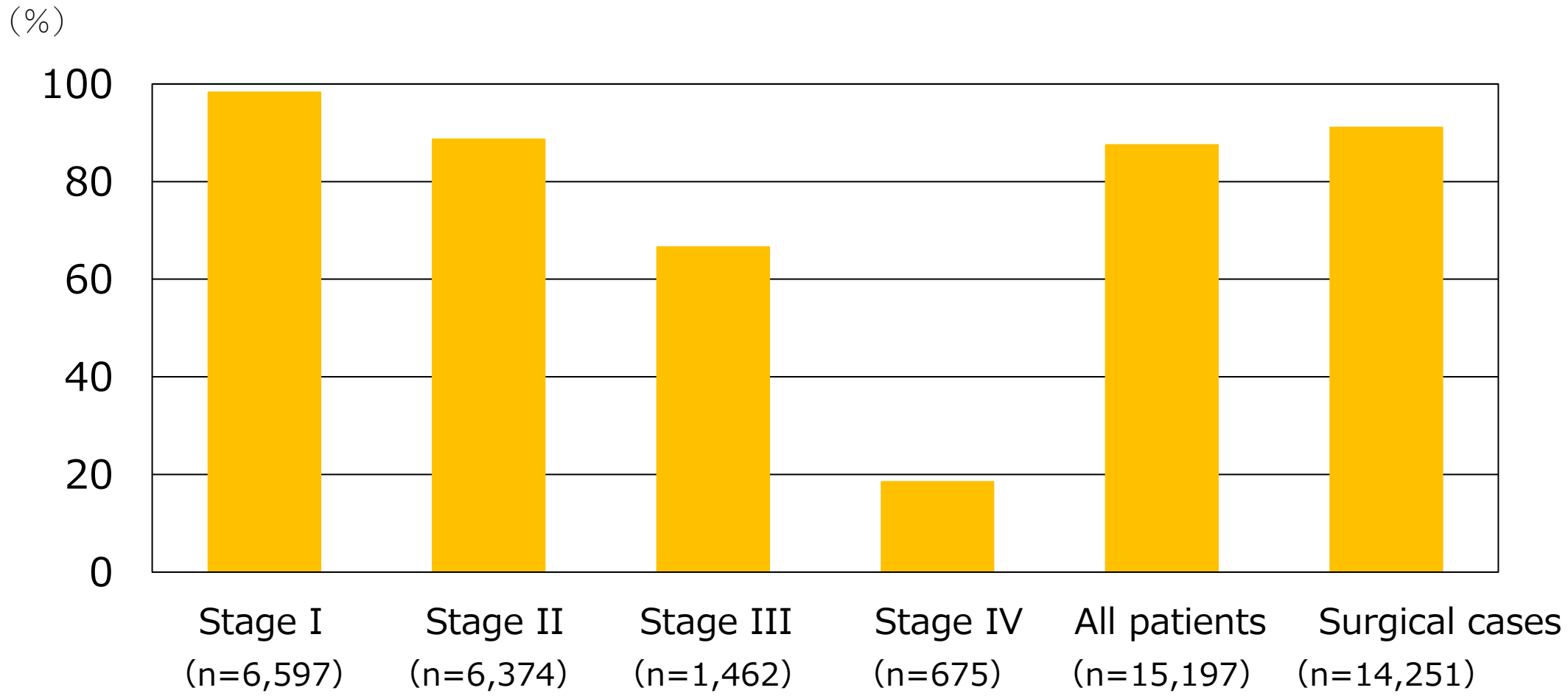
Survival rates were calculated at each consecutive 5-year interval.

Patients with ER and/or PR and HER2 positivity were analyzed separately.

Sundquist M et al The Breast 31:46-50,2017

# Relative Survival Rate in 10 Years

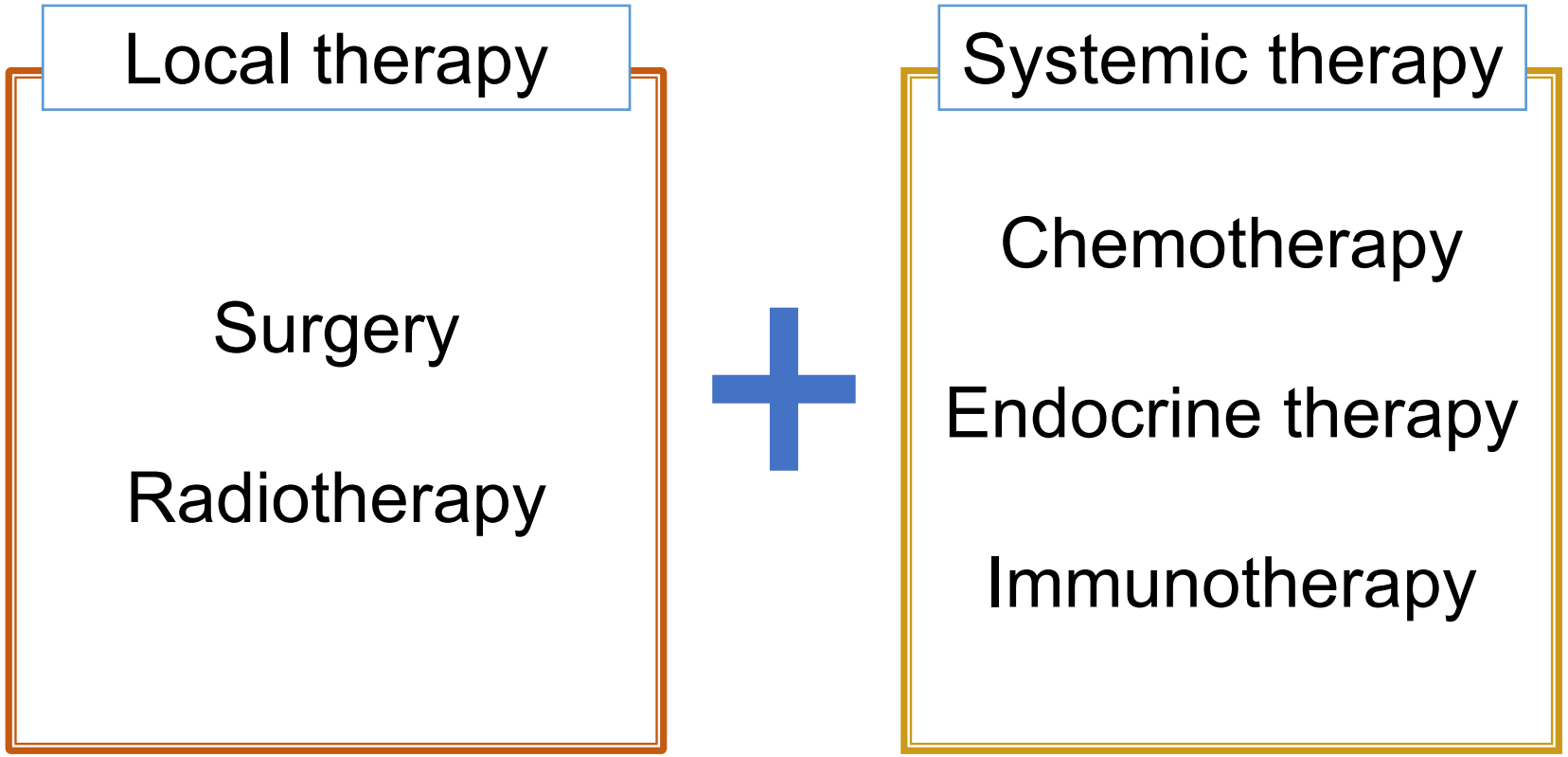
◆ Relative survival rate in 10 years（Cases diagnosed in 2005 to 2008 ）




Note) Since the disease identification rate is not 100%, the total number of patients cannot be calculated even if all the patients in each stage are added up.

Prepared from the All Cancer Survival Survey of Japanese Association of Clinical Cancer Centers 2021.11.10 Updated
https://www.zengankyo.ncc.go.jp/etc/seizonritsu/seizonritsu2013.html (Accessed in November 2023)

# Treatment

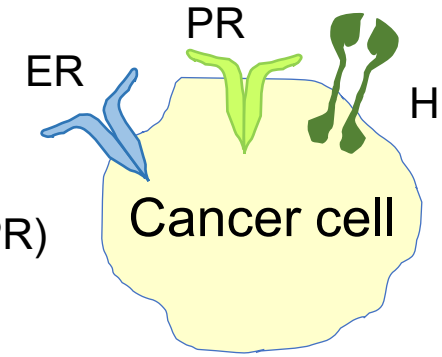

Local therapy
Surgery
Radiotherapy
Systemic therapy
Chemotherapy
Endocrine therapy
Immunotherapy

# Four Subtypes of Breast Cancer

| | Hormone receptor (HR) Positive | Hormone receptor (HR) Negative |
|---|---|---|
| HER2 Positive | HR+/HER2+ | HR-/HER2+ |
| HER2 Negative | HR+/HER2- | HR-/HER2- |

Hormone receptor (HR)

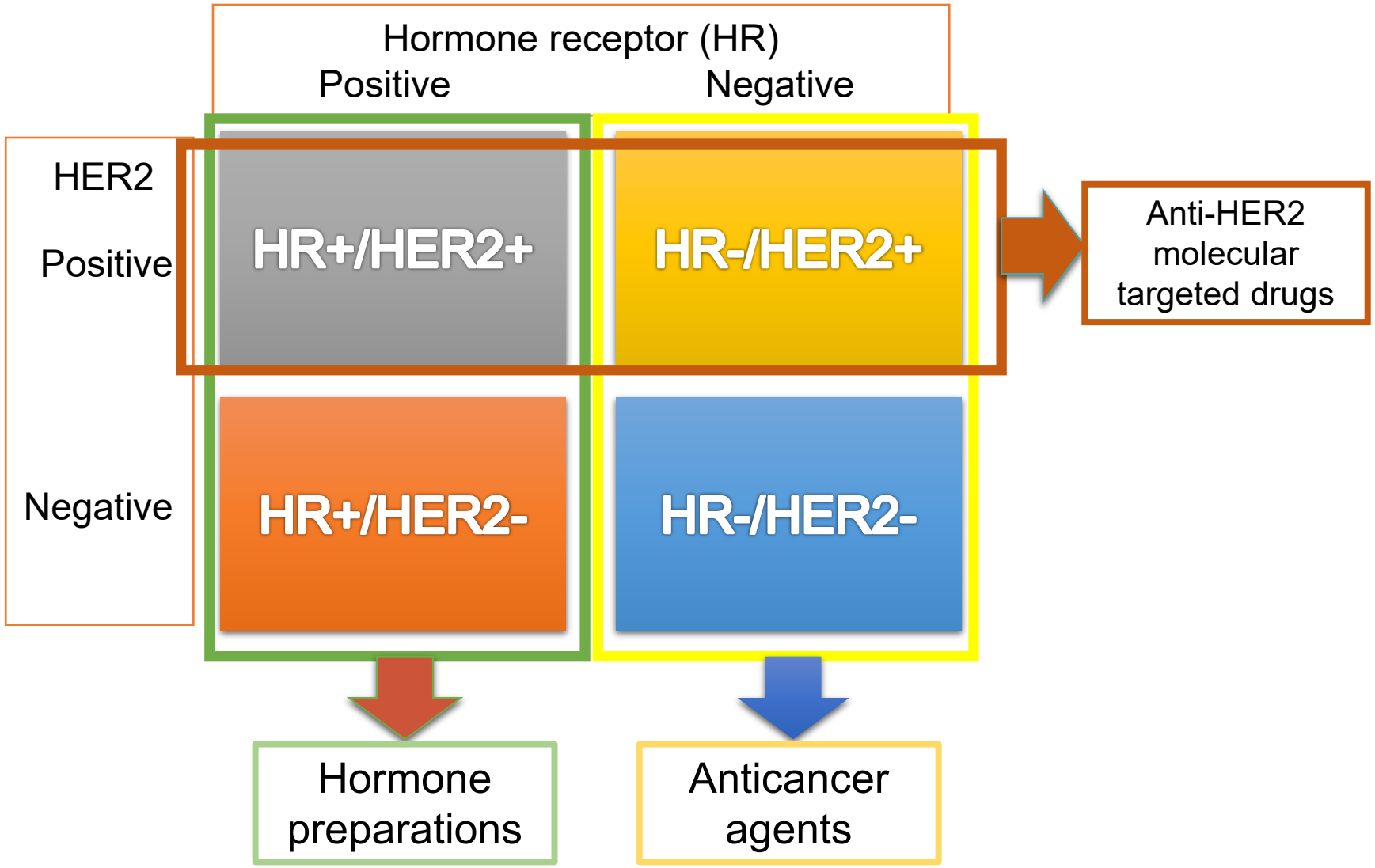
- Estrogen receptor (ER)
- Progesterone receptor (PR)




(Human Epidermal growth factor Receptor 2)

Cancer Information Service
https://ganjoho.jp/public/cancer/breast/treatment.html
(Accessed in November 2023)

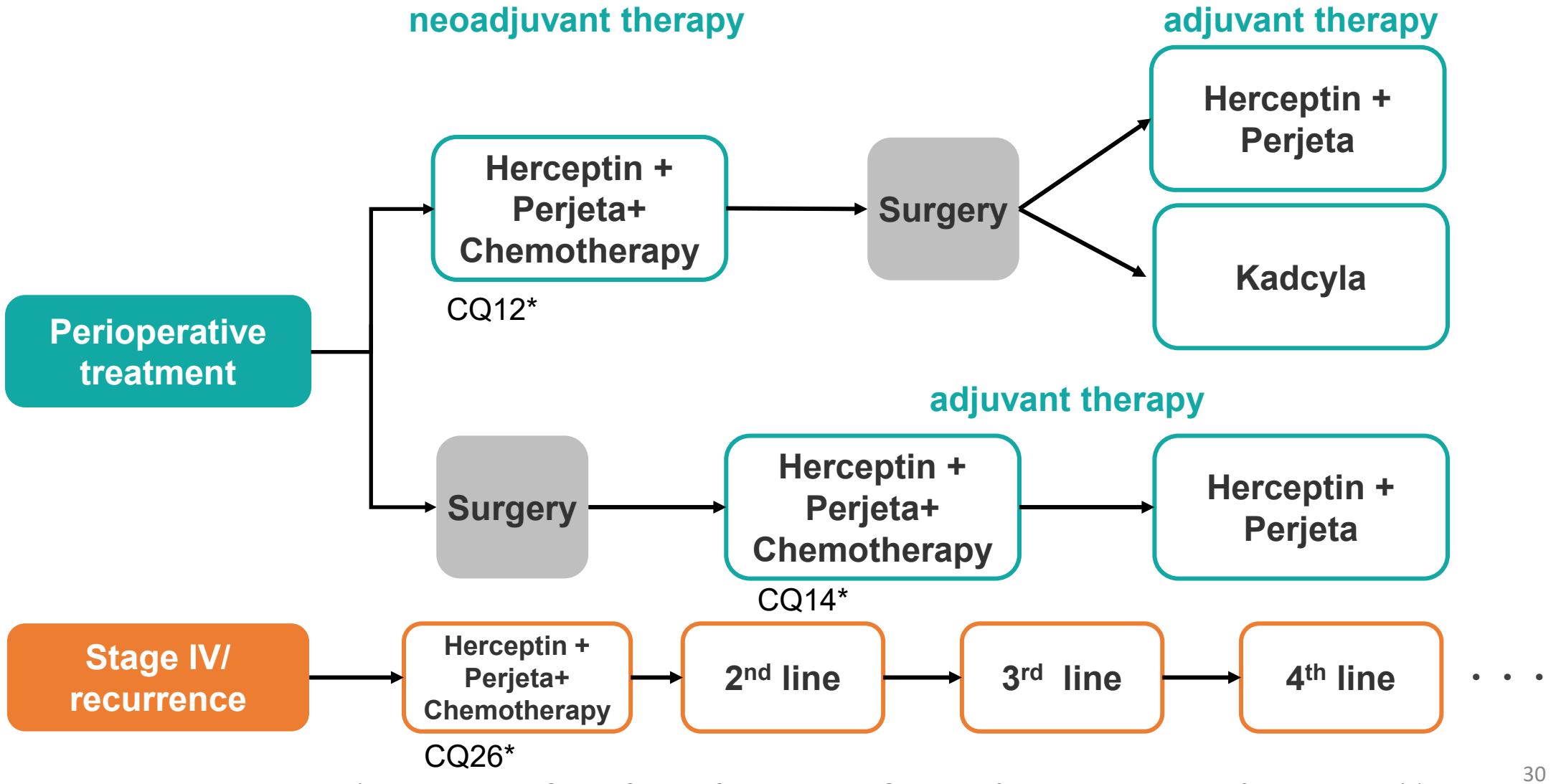
# Basic Treatment Concept According to the Subtype




Cancer Information Service
https://ganjoho.jp/public/cancer/breast/treatment.html
(Accessed in November 2023)

# Clinical Positioning of Herceptin + Perjeta

Herceptin + Perjeta is a drug recommended by guidelines for neoadjuvant / adjuvant treatment and stage IV/treatment for recurrence of HER2-positive breast cancer.






*Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition

# Clinical Practice Guidelines for Systemic Treatment of Breast Cancer 2022 Edition

**CQ 12** **Is it recommended to add pertuzumab to trastuzumab in patients with HER2-positive early breast cancer receiving neoadjuvant therapy?**

## Recommendation

- **Adding pertuzumab to trastuzumab is strongly recommended.**

  Strength of recommendation: 1, strength of evidence: strong, agreement rate: 82% (31/38)

---

**Points in recommendation**

- **Although there have been no studies investigating the improvement of prognosis by adding pertuzumab to neoadjuvant therapy for HER2-positive early breast cancer, pCR rate, which is considered to be a surrogate indicator for prognosis in HER2-positive breast cancer, is shown to be improved.**

## Background/Objective

HER2-positive breast cancer is highly sensitive to drug therapy, and improved prognosis has been demonstrated when trastuzumab is administered as adjuvant therapy. In this CQ, the efficacy and safety of adding pertuzumab to trastuzumab in neoadjuvant therapy for HER2-positive breast cancer were investigated.



Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition, Kanehara & Co., Ltd., pp105-107

# Clinical Practice Guidelines for Systemic Treatment of Breast Cancer 2022 Edition

**CQ 14** **Is it recommended to add pertuzumab to trastuzumab in patients with HER2-positive early breast cancer receiving adjuvant therapy?**

## Recommendation

- **For patients with high risk of recurrence, adding pertuzumab to trastuzumab is strongly recommended.**

  Strength of recommendation: 1, strength of evidence: strong, agreement rate: 89% (34/38)

---

**Points in recommendation**

- **Stratified analysis in the APHINITY study has demonstrated an improvement in invasive disease-free survival (IDFS) by adding pertuzumab in patients with positive lymph node metastases. Adding pertuzumab to trastuzumab is a recommended treatment for patients with high risk of recurrence, such as those with positive lymph node metastases.**

## Background/Objective

HER2-positive breast cancer is highly sensitive to drug therapy, and improved prognosis has been demonstrated when trastuzumab is administered as adjuvant therapy [→ See Treatment Review. III.4.b.7) (3)]. In this CQ, the efficacy and safety of adding pertuzumab to trastuzumab in adjuvant therapy for HER2-positive breast cancer were investigated.



Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition, Kanehara & Co., Ltd., pp110 -111

# Clinical Practice Guidelines for Systemic Treatment of Breast Cancer 2022 Edition

**CQ 26** **Is trastuzumab + pertuzumab + taxane combination therapy recommended as first-line therapy for HER2-positive metastatic/recurrent breast cancer?**

## Recommendation

- **The combination therapy of trastuzumab + pertuzumab + docetaxel is strongly recommended.**
  Strength of recommendation: 1, strength of evidence: strong, agreement rate: 100% (35/35)
- **The combination therapy of trastuzumab + pertuzumab + paclitaxel is weakly recommended.**
  Strength of recommendation: 2, strength of evidence: moderate, agreement rate: 97% (33/34)

---

**Points in recommendation**

- **In first-line treatment of HER2-positive metastatic/recurrent breast cancer, docetaxel is strongly and paclitaxel is weakly recommended as combination chemotherapy with trastuzumab and pertuzumab.**

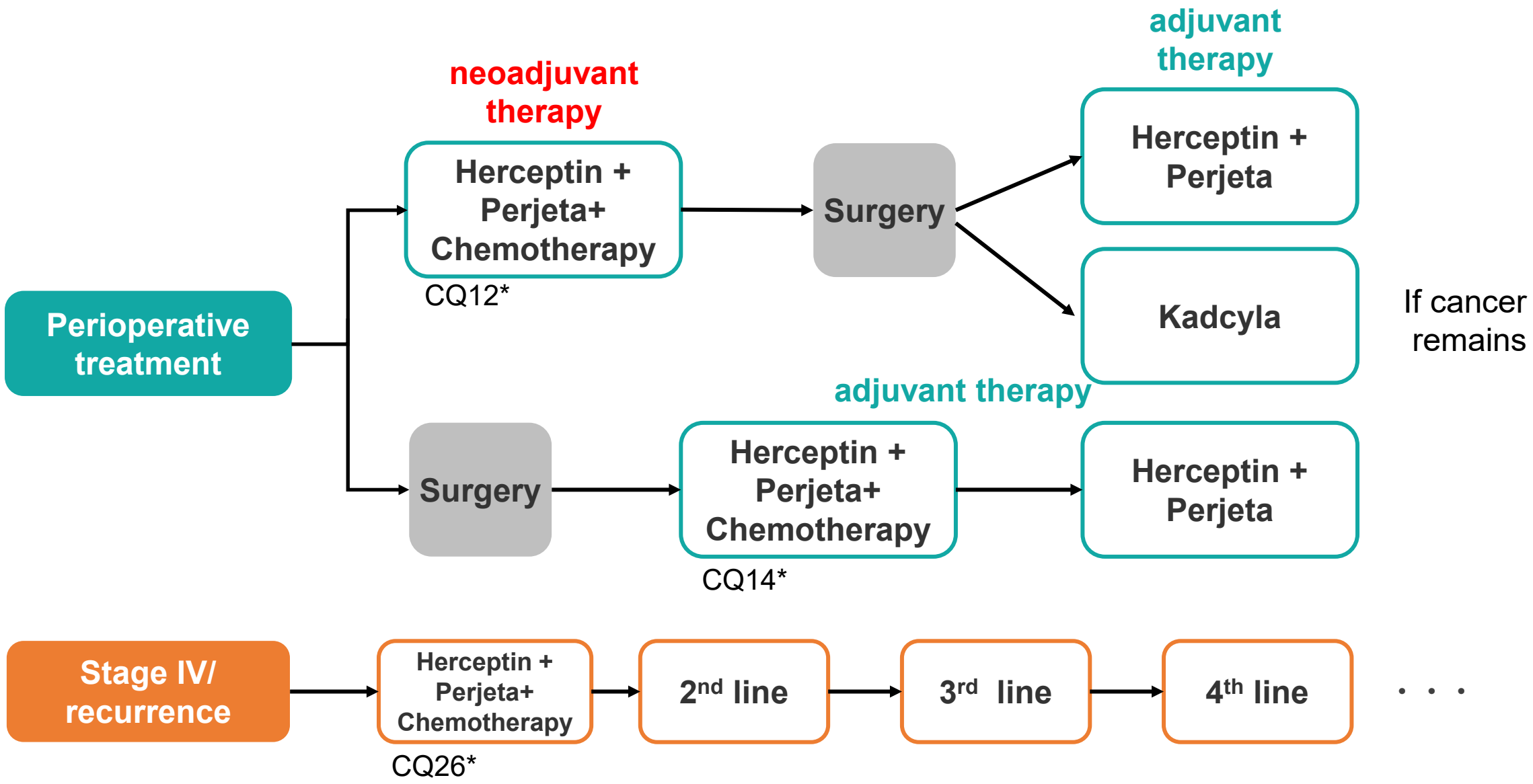
## Background/Objective

In this CQ, first-line therapy for HER2-positive metastatic/recurrent breast cancer was examined.
In this guideline, "first-line therapy" for HER2-positive metastatic/recurrent breast cancer is defined as "the first treatment" after metastasis/recurrence, regardless of the timing of recurrence.
The next line therapy is defined as "second-line therapy" [See Treatment Review. V.4.a.a-1.1)].
Factors to determine the recommended regimen for "first-line therapy (first anti-HER2 therapy after metastasis/recurrence)" include "details of perioperative therapy" and "treatment-free interval."



Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition, Kanehara & Co., Ltd., pp204 -208

# Clinical Positioning of Herceptin + Perjeta

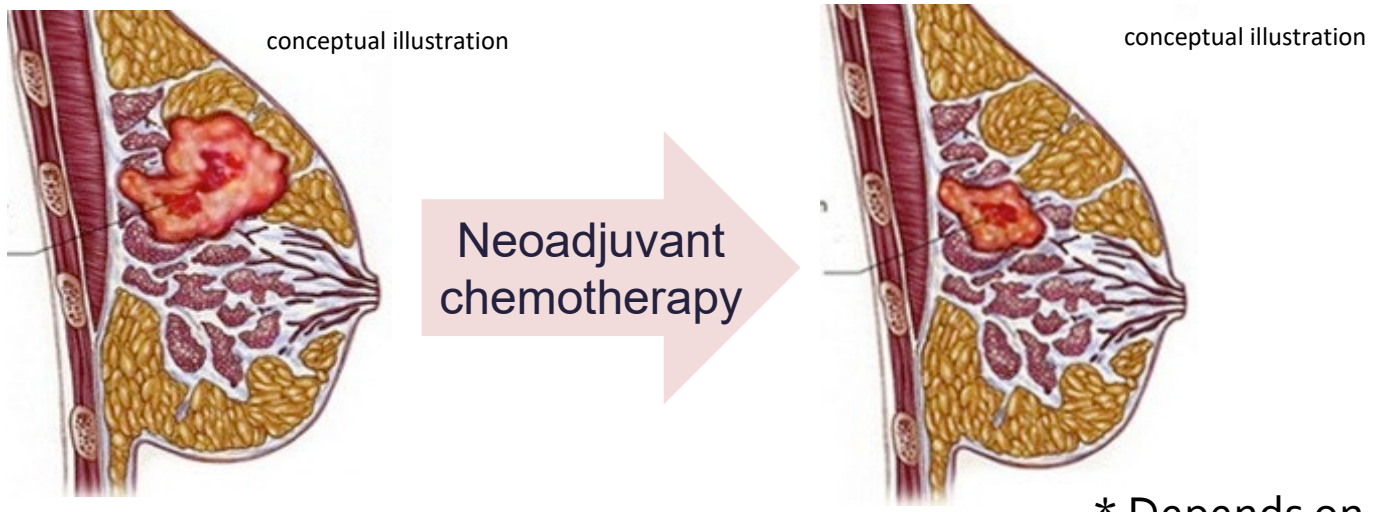



*Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition

# Advantages of Neoadjuvant Chemotherapy

- Downstaging
  Reduce the disease stage by making the tumor smaller or eliminating any of the lymph node metastases
- Increase in the partial resection rate
- Early evaluation of individual therapeutic effects

**Pathologic complete response = favorable prognosis***

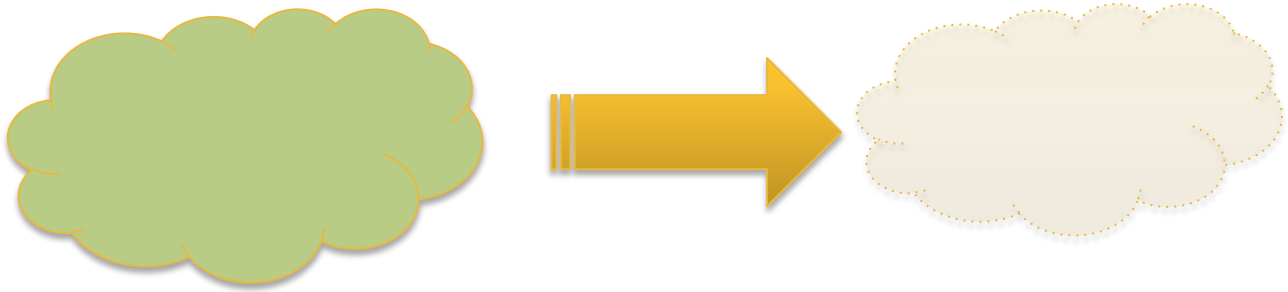



* Depends on breast cancer subtype

Reference: Prepared from Breast Cancer Clinical Practice Guidelines for Patients 2019 edited by the Japanese Breast Cancer Society, Kanehara & Co., Ltd., 2019, page 84-85

# Early Assessment of Individual Response (HER2-Positive Breast Cancer)

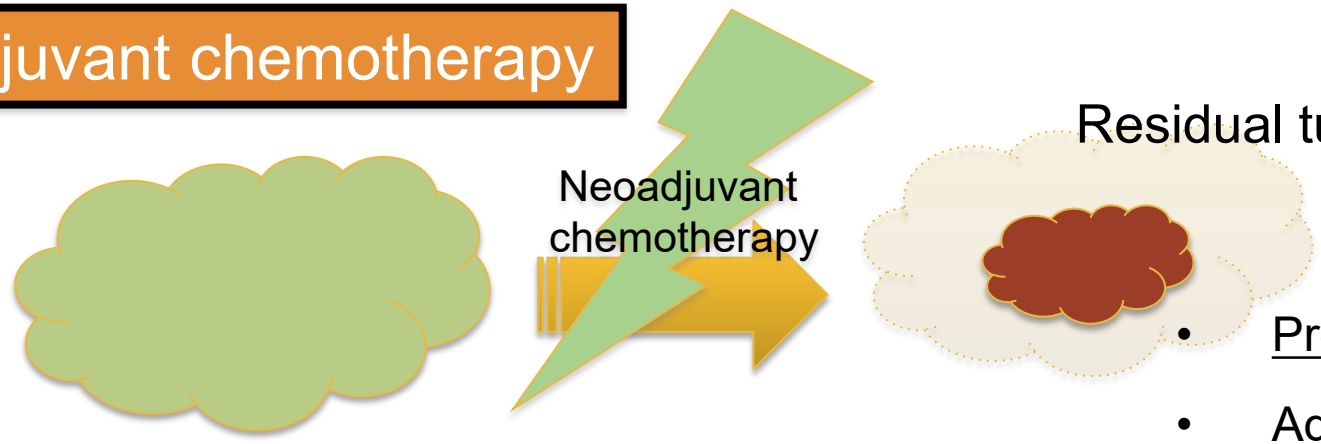
## Adjuvant chemotherapy



Conventional postoperative treatment

It is not tailor-made therapy

## Neoadjuvant chemotherapy




Residual tumor

- Prognosis information
- Additional treatment information
  T-DM1 for HER2 (KATHERINE)

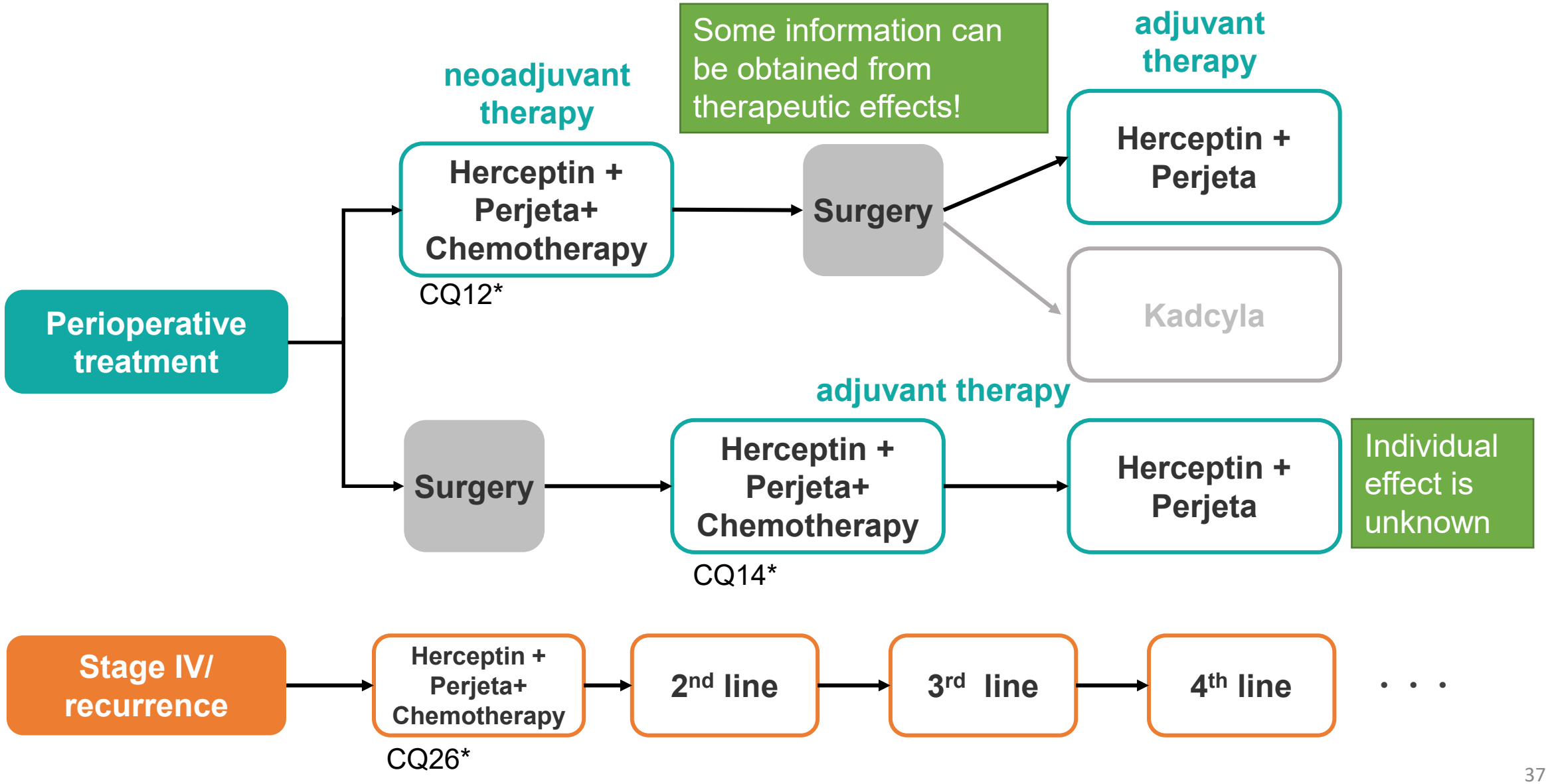
➡ Improvement of prognosis

Speaker preparation

* von Minckwitz G, et al. N Engl J Med 2019; 380: 617-628

This study was supported by F. Hoffmann-La Roche and Genentech.

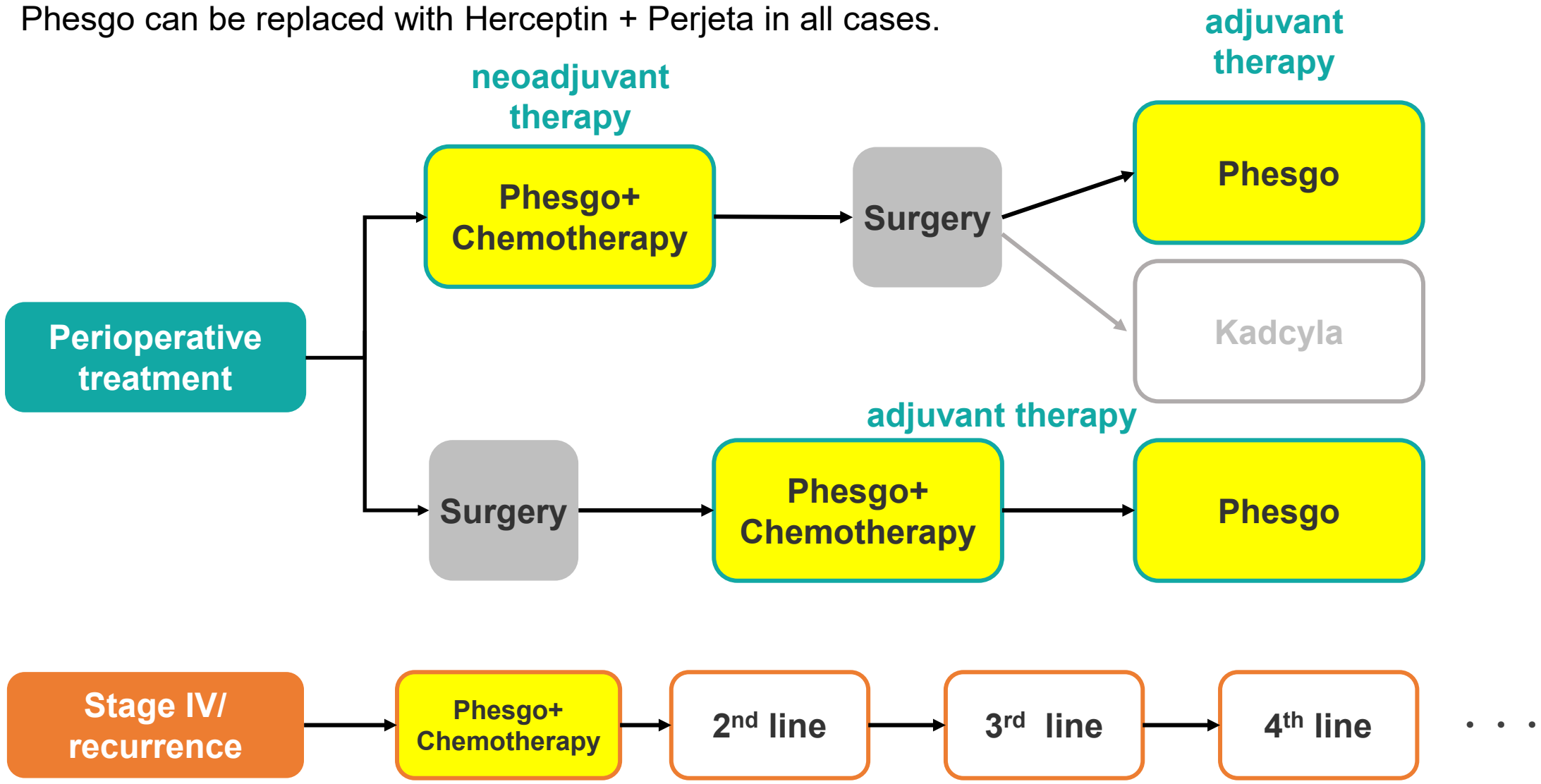
# Clinical Positioning of Herceptin + Perjeta




*Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition

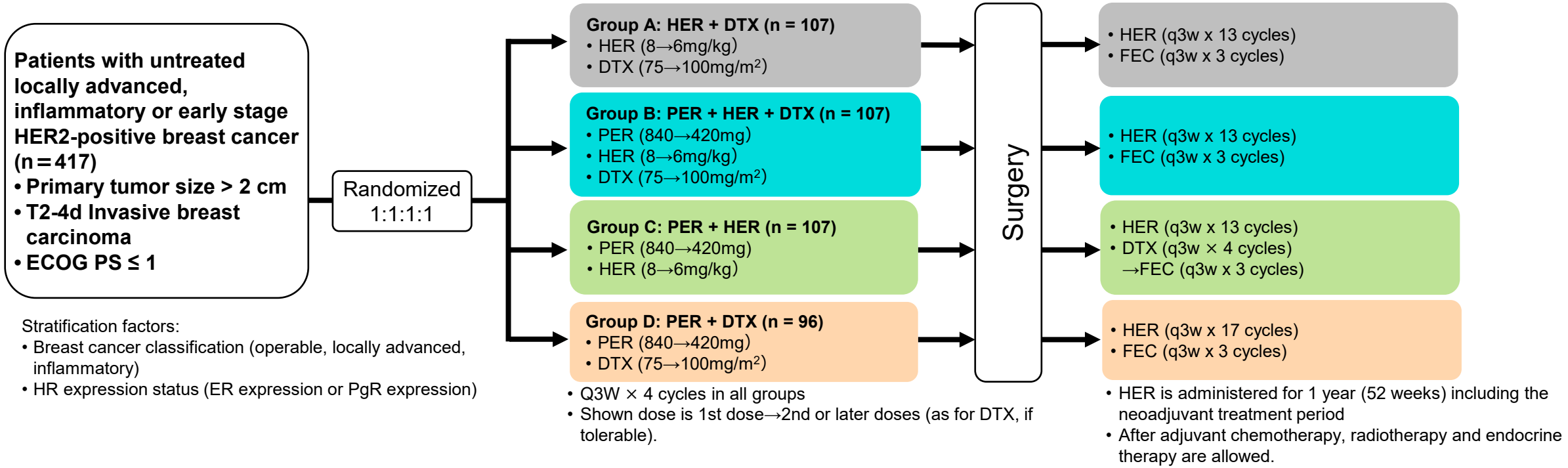
# Clinical Positioning of Phesgo (Breast Cancer)

Phesgo can be replaced with Herceptin + Perjeta in all cases.



# NEOSPHERE Study (WO20697)
# Neoadjuvant Treatment for Early Breast Cancer: Overseas Phase II Clinical Study

- **Objective: To evaluate the efficacy of Perjeta (PER) or Herceptin (HER) in combination with docetaxel (DTX) , both drugs in combination with DTX, and anti-HER2 drugs only, as a neoadjuvant treatment in patients with HER2-positive early breast cancer.**
- **Study design: A multicenter, open-label, randomized, 4- group comparison, multinational, phase II clinical study conducted in 16 countries and 59 centers overseas**
- **Subjects: 417 patients with locally advanced, inflammatory, or early stage HER2 positive breast cancer (3+ by IHC or 2+ by IHC and positive by FISH/CISH; central review)**
  **Efficacy analysis set: Intent-to-treat (ITT) population: 107 subjs in Group A, 107 subjs in Group B, 107 subjs in Group C, and 96 subjs in Group D**
  **Safety analysis set in the neoadjuvant treatment period: 107 subjs in Group A, 107 subjs in Group B, 108 subjs in Group C, and 94 subjs in Group D. Safety analysis set in the adjuvant treatment period: 103 subjs in Group A, 102 subjs in Group B, 94 subjs in Group C, and 88 subjs in Group D**




Stratification factors:
- Breast cancer classification (operable, locally advanced, inflammatory)
- HR expression status (ER expression or PgR expression)

- Q3W × 4 cycles in all groups
- Shown dose is 1st dose→2nd or later doses (as for DTX, if tolerable).

- HER is administered for 1 year (52 weeks) including the neoadjuvant treatment period
- After adjuvant chemotherapy, radiotherapy and endocrine therapy are allowed.

FEC, Fluorouracil 600 mg/m$^2$ + Epirubicin (EPI) 90 mg/m$^2$ + Cyclophosphamide (CPA) 600 mg/m$^2$ → administer every 3 weeks as standard adjuvant treatment; EGCO PS, Eastern Cooperative Oncology Group Performance Status; HR, hormone receptor; ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; CISH, chromogenic *in situ* hybridization

In this study, the administration method of Perjeta is partially different from the method approved in Japan. Refer to the package insert before using Perjeta .
The approved dosage and administration of Perjeta is "The usual adult dosage when used in combination with trastuzumab (genetical recombination) and other anticancer drugs is a loading dose of 840 mg of pertuzumab (genetical recombination) followed by 420 mg every three weeks given by intravenous infusion over 60 minutes. For neoadjuvant or adjuvant chemotherapy, however, treatment should be given for up to 12 months. The infusion time can be shortened to as little as 30 minutes from the second infusion onward if the first infusion is well tolerated. " (Package Insert Version 2) Therefore, the dosage and administration in the PER + HER group and the PER + DTX group is off-label use.

Data evaluated at the time of approval: Overseas phase II clinical study <NEOSPHERE Study>
1) Gianni L, et al. Lancet Oncol. 2012; 13(1): 25-32.
2) Gianni L, et al. Lancet Oncol. 2016; 17(6): 791-800.
Authors of literature 1, 2) includes Roche employees as well as those who were funded by Roche.
This study was supported by Roche.

## NEOSPHERE Study

# Study Summary

## Endpoints

- **Efficacy Endpoints**

  [Primary endpoint] Postoperative pathological complete response rate in the breast (bpCR rate, ypT0/is by TNM classification)[*1]

  [Secondary endpoints] Best overall response, response rate, time to response, breast conserving surgery rate, disease-free survival, progression-free survival, biomarker evaluation related to efficacy

- **Safety endpoints**

  Adverse events, hematology tests, blood biochemistry tests, vital signs, cardiac monitoring by ECHO or MUGA [left ventricular ejection fraction (LVEF)]

## Analysis Plan

- The Cochran Mantel-Haenszel test was used to calculate the bpCR (ypT0/is) rate and the 2-sided hypothesis testing (20% significance level) was performed against the null hypothesis that the bpCR rate was the same between groups for 3 pairwise comparison of HER+DTX group vs PER+HER+DTX group, HER+DTX vs PER+HER group, PER+DTX vs PER+HER+DTX group.
- A Simes multiplicity adjustment was applied to the individual p-values calculated to maintain the overall type I error rate at ≤ 20%.
- Subgroup analyses of the bpCR [ypT0/is] rate (by HR expression status, breast cancer classification) were planned at the start of the study.
- Time to response, disease-free survival, and progression-free survival were estimated using the Kaplan-Meier method, and the hazard ratio and 95% confidence interval (CI) were estimated using a stratified[*2] Cox proportional hazard model.

*1 bpCR [ypT0/is]: disappearance of invasive cancer in the breast (residual non-invasive cancer is acceptable)

*2 stratification factors: breast cancer classification (operable, locally advanced, inflammatory) and HR expression status (ER expression or PgR expression)

Data evaluated at the time of approval: Overseas phase II clinical study <NEOSPHERE Study>

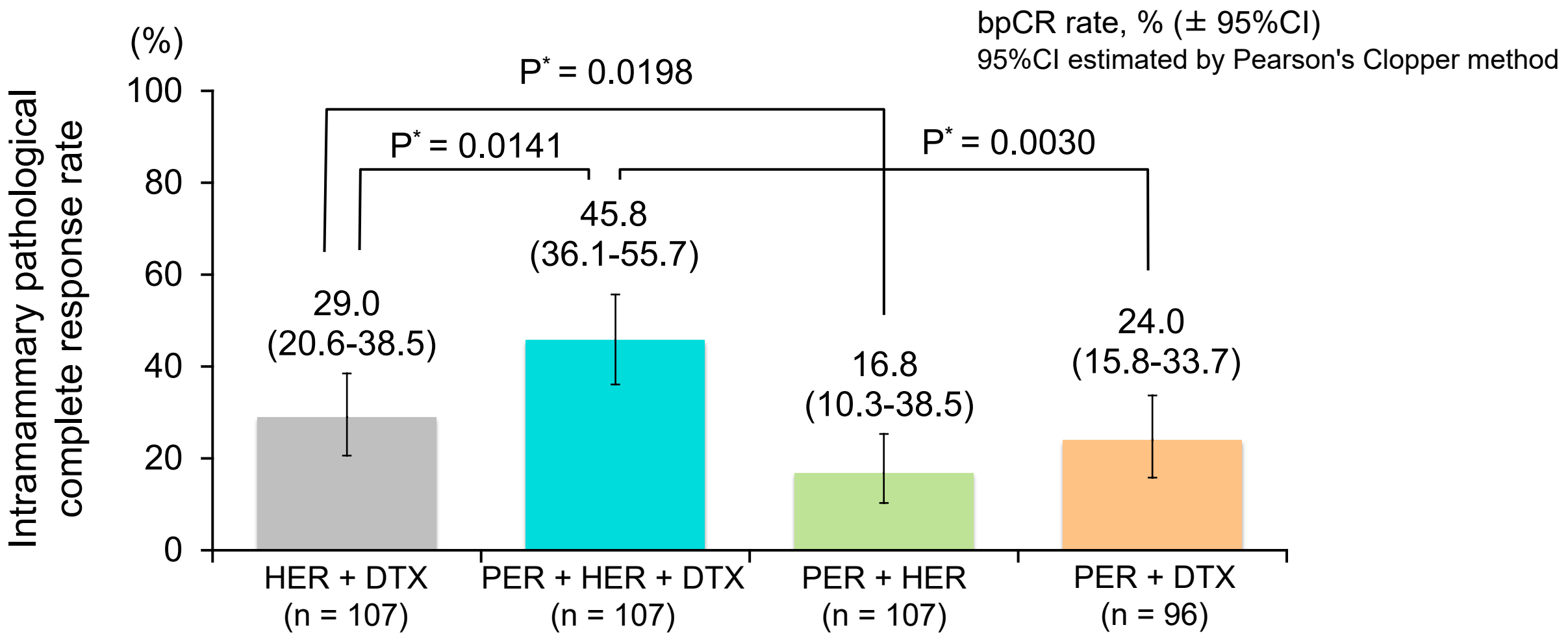
1) Gianni L, et al. Lancet Oncol. 2012; 13(1): 25-32.
2) Gianni L, et al. Lancet Oncol. 2016; 17(6): 791-800.

Authors of literature 1, 2) includes Roche employees as well as those who were funded by Roche.

This study was supported by Roche.

## NEOSPHERE Study: Primary Endpoint (ITT)

# bpCR rate: Intramammary Pathological Complete Response Rate [ypT0/is]



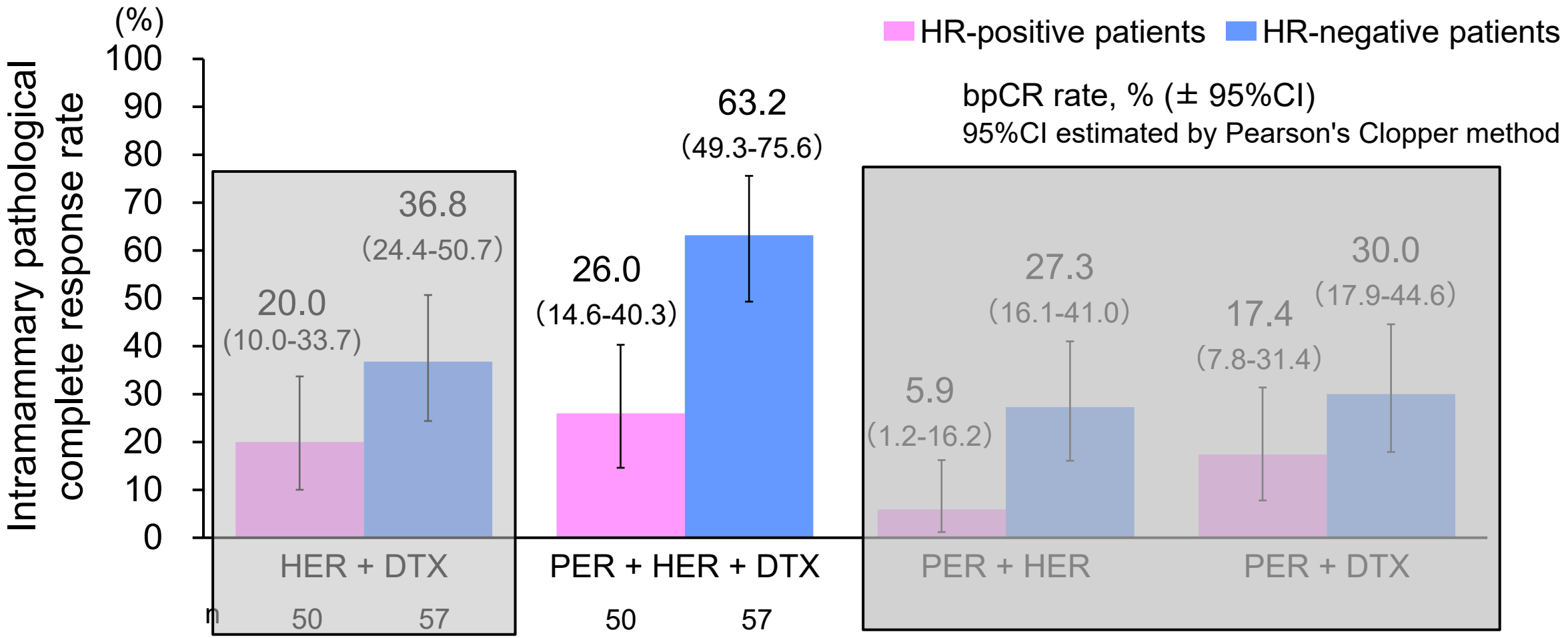

bpCR [ypT0/is]: disappearance of invasive cancer in the breast (residual non-invasive cancer is acceptable);
*p-value: Cochran Mantel-Haenszel test, multiplicity adjusted, two-sided significance level of 20%

In this study, the administration method of Perjeta is partially different from the method approved in Japan. Refer to the package insert before using Perjeta .
The approved dosage and administration of Perjeta is "The usual adult dosage when used in combination with trastuzumab (genetical recombination) and other anticancer drugs is a loading dose of 840 mg of pertuzumab (genetical recombination) followed by 420 mg every three weeks given by intravenous infusion over 60 minutes. For neoadjuvant or adjuvant chemotherapy, however, treatment should be given for up to 12 months. The infusion time can be shortened to as little as 30 minutes from the second infusion onward if the first infusion is well tolerated. " (Package Insert Version 2) Therefore, the dosage and administration in the PER + HER group and the PER + DTX group is off-label use.

Data evaluated at the time of approval: Overseas phase II clinical study <NEOSPHERE Study>
Gianni L, et al. Lancet Oncol. 2012; 13(1): 25-32.
Authors of this literature includes Roche employees as well as those who were funded by Roche.
This study was supported by Roche.

## NEOSPHERE study (ITT: subgroup analysis)

# bpCR [ypT0/is] Rate (by HR Expression Status)




bpCR [ypT0/is]: disappearance of invasive cancer in the breast (residual non-invasive cancer is acceptable)

In this study, the administration method of Perjeta is partially different from the method approved in Japan. Refer to the package insert before using Perjeta .
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Data evaluated at the time of approval: Overseas phase II clinical study <NEOSPHERE Study>
Gianni L, et al. Lancet Oncol. 2012; 13(1): 25-32.
Authors of this literature includes Roche employees as well as those who were funded by Roche.
This study was supported by Roche.

## NEOSPHERE Study (safety analysis set)

# Common Adverse Events* (Neoadjuvant Treatment Period, All Grades/Grade≥3)

| Number of subjects (%) | Group A: HER + DTX (n = 107) | | Group B: PER + HER + DTX (n = 107) | | Group C: PER + HER (n = 108) | | Group D: PER + DTX (n = 94) | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 |
| All adverse events | 105 (98.1%) | 78 (72.9%) | 105 (98.1%) | 67 (62.6%) | 78 (72.2%) | 7 (6.5%) | 93 (98.9%) | 66 (70.2%) |
| Alopecia | 70 (65.4%) | 1 (0.9%) | 68 (63.6%) | 5 (4.7%) | 1 (0.9%) | 0 | 63 (67.0%) | 4 (4.3%) |
| Neutropenia | 67 (62.6%) | 61 (57.0%) | 54 (50.5%) | 48 (44.9%) | 1 (0.9%) | 1 (0.9%) | 59 (62.8%) | 52 (55.3%) |
| Nausea | 39 (36.4%) | 0 | 41 (38.3%) | 0 | 15 (13.9%) | 0 | 34 (36.2%) | 1 (1.1%) |
| Diarrhea | 36 (33.6%) | 4 (3.7%) | 49 (45.8%) | 6 (5.6%) | 30 (27.8%) | 0 | 51 (54.3%) | 4 (4.3%) |
| Fatigue | 29 (27.1%) | 0 | 28 (26.2%) | 1 (0.9%) | 13 (12.0%) | 0 | 24 (25.5%) | 1 (1.1%) |
| Myalgia | 24 (22.4%) | 0 | 24 (22.4%) | 0 | 10 (9.3%) | 0 | 19 (20.2%) | 0 |
| Leukopenia | 23 (21.5%) | 13 (12.1%) | 10 (9.3%) | 5 (4.7%) | 0 | 0 | 12 (12.8%) | 7 (7.4%) |
| Rash | 23 (21.5%) | 2 (1.9%) | 28 (26.2%) | 2 (1.9%) | 12 (11.1%) | 0 | 27 (28.7%) | 1 (1.1%) |
| Mucosal inflammation | 23 (21.5%) | 0 | 28 (26.2%) | 2 (1.9%) | 3 (2.8%) | 0 | 24 (25.5%) | 0 |
| Asthenia | 19 (17.8%) | 0 | 22 (20.6%) | 2 (1.9%) | 3 (2.8%) | 0 | 15 (16.0%) | 2 (2.1%) |
| Peripheral sensory neuropathy | 13 (12.1%) | 1 (0.9%) | 9 (8.4%) | 1 (0.9%) | 2 (1.9%) | 0 | 10 (10.6%) | 0 |
| Vomiting | 13 (12.1%) | 0 | 14 (13.1%) | 0 | 5 (4.6%) | 0 | 15 (16.0%) | 1 (1.1%) |
| Headache | 12 (11.2%) | 0 | 12 (11.2%) | 0 | 15 (13.9%) | 0 | 12 (12.8%) | 0 |
| Insomnia | 12 (11.2%) | 0 | 9 (8.4%) | 0 | 4 (3.7%) | 0 | 8 (8.5%) | 0 |
| Pyrexia | 11 (10.3%) | 0 | 18 (16.8%) | 0 | 9 (8.3%) | 0 | 8 (8.5%) | 0 |
| Dysgeusia | 11 (10.3%) | 0 | 16 (15.0%) | 0 | 5 (4.6%) | 0 | 7 (7.4%) | 0 |
| Bone pain | 11 (10.3%) | 0 | 10 (9.3%) | 1 (0.9%) | 0 | 0 | 4 (4.3%) | 0 |
| Oedema peripheral | 11 (10.3%) | 0 | 3 (2.8%) | 0 | 1 (0.9%) | 0 | 5 (5.3%) | 0 |
| Arthralgia | 9 (8.4%) | 0 | 11 (10.3%) | 0 | 5 (4.6%) | 0 | 9 (9.6%) | 0 |
| Stomatitis | 8 (7.5%) | 0 | 19 (17.8%) | 0 | 5 (4.6%) | 0 | 9 (9.6%) | 0 |
| Decreased appetite | 7 (6.5%) | 0 | 15 (14.0%) | 0 | 2 (1.9%) | 0 | 14 (14.9%) | 0 |

*items 10% or higher in all grades in either group

MedDRA ver.12.1,CTCAE ver.3.0



Data evaluated at the time of approval: Overseas phase II clinical study <NEOSPHERE Study>

# The Importance of Considering Time Toxicity

# Problems with the Healthcare Situation in Japan

The impact of the long time it takes to wait for a medical consultation, to visit the hospital and to receive treatment

- Burden on breast cancer patients
  - Work
  - Childcare
  - Nursing care
  - Physical exhaustion

- Burden on healthcare professionals
  - Securing an outpatient chemotherapy room
  - Manpower (physician, nurse, pharmacist; The amount of infusion is dependent on the body weight ⇨ Preparation also takes a certain amount of time)
  - Personnel expenses

The shorter administration time of each dose of Phesgo may contribute to improve the quality of life of patients and the burden on medical care.

# De-escalation for Time toxicity

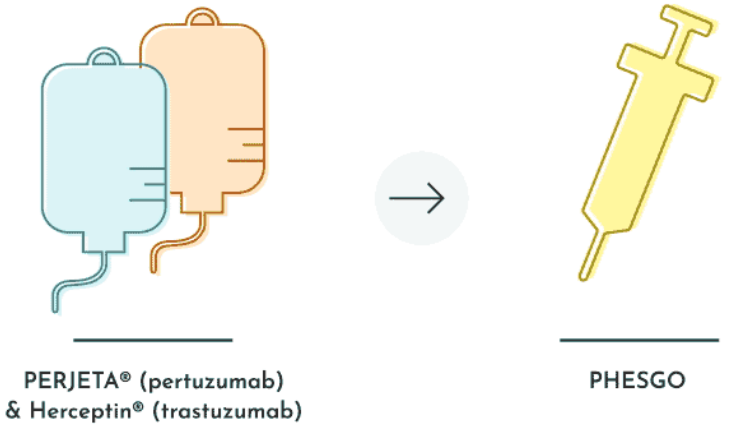
PHESGO®

pertuzumab/trastuzumab/hyaluronidase-zzxf

SUBCUTANEOUS INJECTION / 1,200 mg/600 mg/30,000 units
600 mg/600 mg/20,000 units


1st Injection


Other Injections



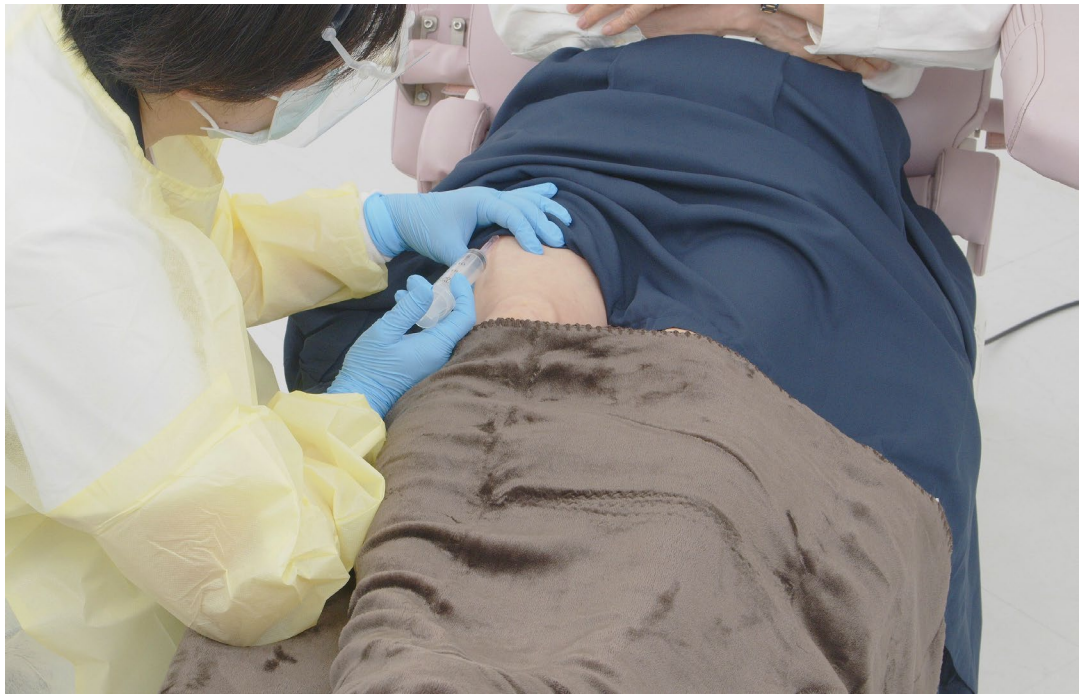

**In the clinical study,**
**no major difference** was seen in the amount of medicine that went into the bloodstream with PHESGO compared to PERJETA + Herceptin. The combined results of the study showed no major difference is expected in how it works.

https://www.phesgo.com
Accessed in November 2023

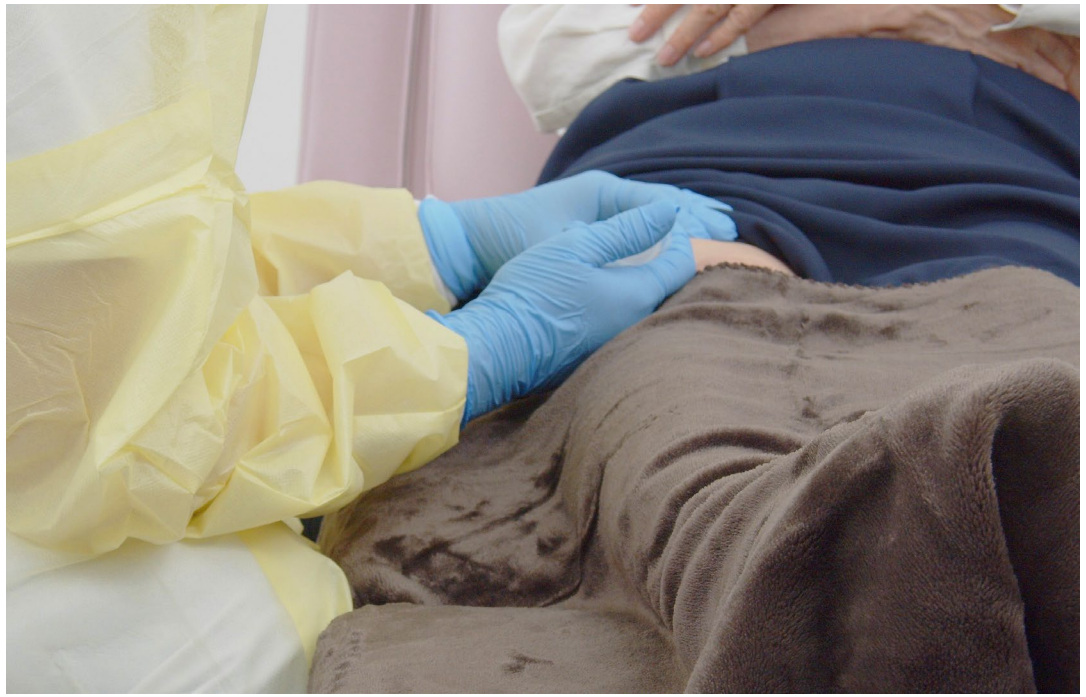
Administration method of PHESGO combination for SC injection

# Healthcare Professionals' Physical Position When Giving an SC Injection

SC injection requires over 5-8 minutes, so HCPs should continue administration in the same position. Find a comfortable position for administration in advance such as adjusting the height of the chair or the place to put the hand, so that the shot giver can maintain the same position.

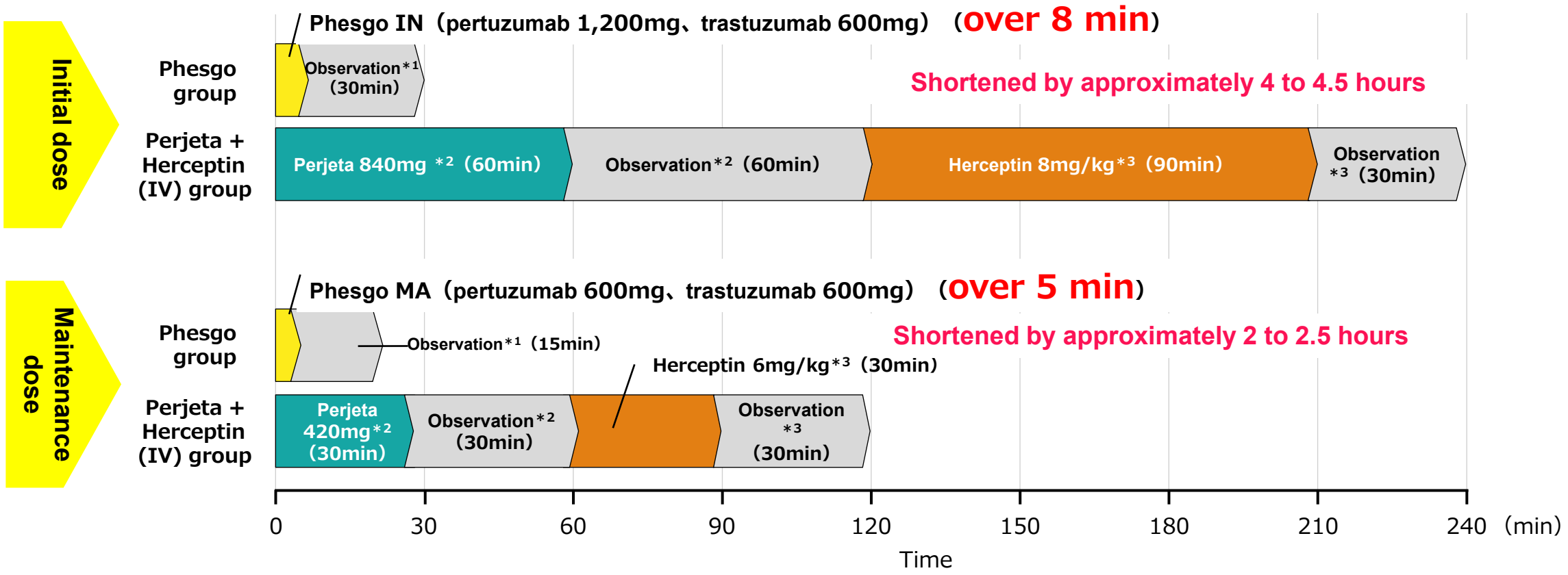


**Fix the shot giver's elbow to the reclining chair or bed**



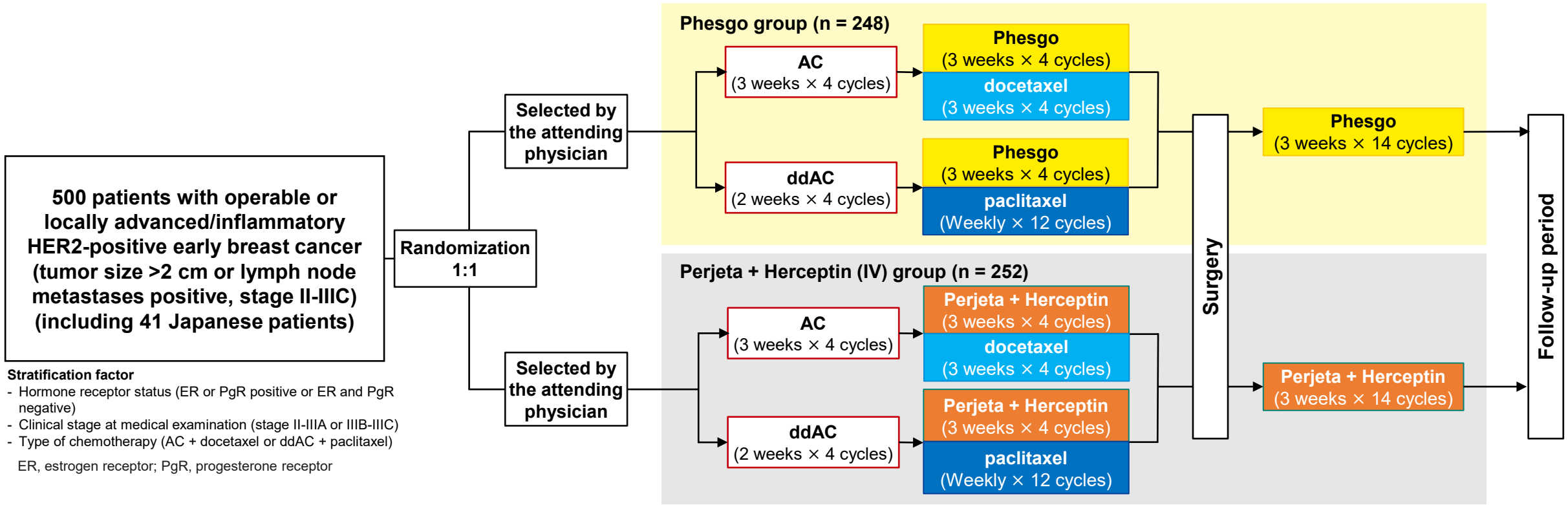
**Fix the shot giver's elbow to the knees**

# Shorter Administration Time of This Drug Than Conventional Intravenous Infusion




*1: Patients' progress should be observed after administration. After it has been confirmed that there are no symptoms of an infusion reaction, the next drug can be administered.
In clinical studies, patients were observed for 60 minutes after the initial dose, and if there were no problems such as infusion reactions and the drug was well tolerated in Cycle 2 and subsequent cycles, the observation time could be shortened to 30 minutes.
*2: If the first infusion is well tolerated, subsequent infusions may be administered over a shorter time of at least 30 minutes.

# A Phase 3, Multicenter, Randomized, : WO40324 Trial (FeDeriCa) Global Phase III Study




**Stratification factor**
- Hormone receptor status (ER or PgR positive or ER and PgR negative)
- Clinical stage at medical examination (stage II-IIIA or IIIB-IIIC)
- Type of chemotherapy (AC + docetaxel or ddAC + paclitaxel)

ER, estrogen receptor; PgR, progesterone receptor

- If hormone therapy and/or radiotherapy were indicated, they had to be concomitantly used as adjuvant chemotherapy.

**[Objectives]** To compare the pharmacokinetics, efficacy, and safety of Phesgo plus chemotherapy to those of intravenous Perjeta and Herceptin [Perjeta + Herceptin (IV)] as neoadjuvant/adjuvant chemotherapy in patients with HER2-positive early breast cancer.

**[Subjects]** 500 patients with operable or locally advanced/inflammatory HER2-positive early breast cancer of > 2 cm in tumor size or lymph node metastases positive (stage II-IIIC) (IHC 3+ and/or ISH positive, central evaluation), 409 patients (Phesgo, 206; Perjeta + Herceptin [IV], 203) in the pharmacokinetic analysis set (PPP, Per Protocol PK), 500 patients (Phesgo, 248; Perjeta + Herceptin [IV], 252) in the efficacy analysis set (ITT, intent-to-treat) and the safety analysis set

*1 The type of chemotherapy during the preoperative treatment period was selected by the attending physician.
*2 In the Perjeta + Herceptin (IV) group, switching from Herceptin IV to trastuzumab subcutaneous (SC) injection (not approved in Japan) was permitted during the postoperative treatment period at the discretion of the attending physician in countries where trastuzumab SC administration is routinely used.
*3 With ddAC (dose-dense doxorubicin + cyclophosphamide) therapy, granulocyte colony-stimulating factor (G-CSF) supporting therapy was added as necessary according to the local guidelines.
*4 ddAC therapy was not specified as the regimen used in Japan.

The approved dosage and administration of Herceptin are as follows:
**[DOSAGE AND ADMINISTRATION] (excerpted)** Use either Regimen A or Regimen B for breast cancer overexpressing HER2. Use Regimen B for advanced or recurrent gastric cancer overexpressing HER2 not amenable to curative resection, in combination with other antineoplastic agents. Regimen A: The usual adult dosage is a loading dose of 4 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 2 mg/kg once a week, each administered by intravenous infusion over at least 90 minutes. Regimen B: The usual adult dosage is a loading dose of 8 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 6 mg/kg every 3 weeks, each administered by intravenous infusion over at least 90 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a shorter time of at least 30 minutes.


1) Data evaluated at the time of approval: Global phase 3 clinical study (FeDeriCa study)
2) Tan AR, et al. Lancet Oncol. 2021; 22 (1): 85-97.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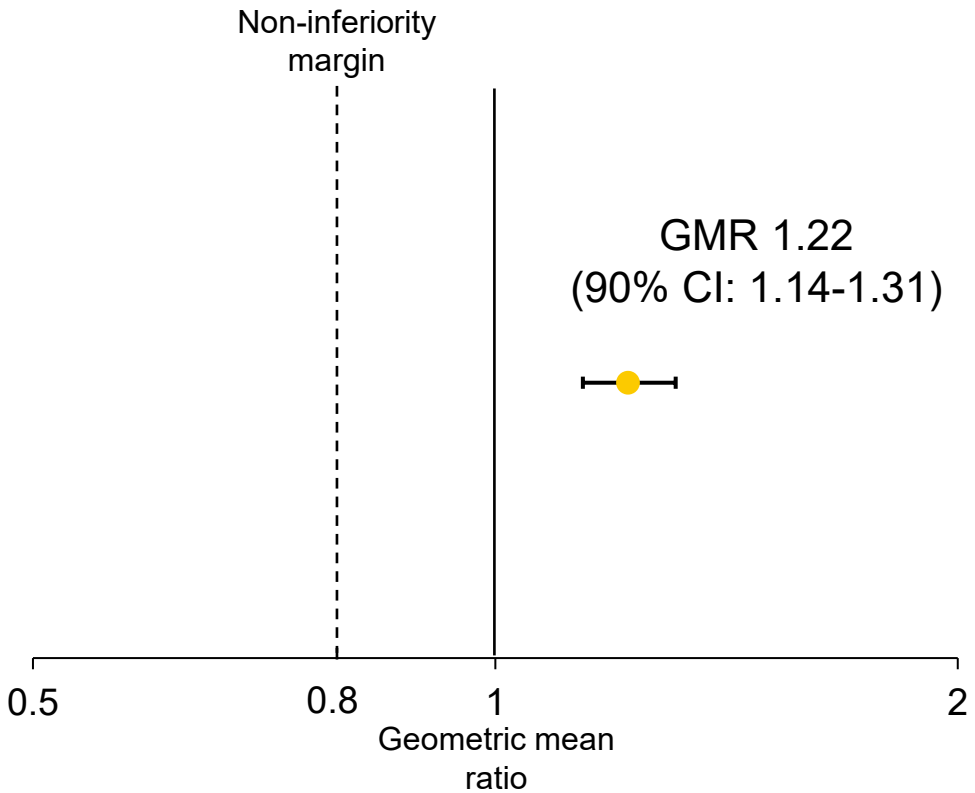
# Global Phase 3 Clinical Study: WO40324 Trial (FeDeriCa Study)
# Cycle 7 (Cycle 8 Predose) Pertuzumab Serum Trough Concentration ($C_{trough}$) [Primary Endpoint, PPP]

- The geometric mean ratio (GMR) of pertuzumab $C_{trough}$ in the Phesgo group compared to that in the Perjeta + Herceptin (IV) group was 1.22 (90% CI, 1.14-1.31). The non-inferiority of pertuzumab $C_{trough}$ in the Phesgo group that in the Perjeta + Herceptin (IV) group was verified as the lower limit of the confidence interval exceeded the non-inferiority margin of 0.8.

| | **Phesgo group (n = 206)** | **Perjeta + Herceptin (IV) group (n = 203)** |
|---|---|---|
| Mean (SD) (μg/mL) | 93.7 (31.5) | 78.5 (26.8) |
| Geometric mean (CV%) (μg/mL) | 88.7 (33.6) | 72.4 (34.1) |
| GMR (90% CI) | 1.22 (1.14-1.31) | |

Data cutoff date at primary analysis: July 4, 2019




The approved dosage and administration of Herceptin are as follows:
**[DOSAGE AND ADMINISTRATION] (excerpted)** Use either Regimen A or Regimen B for breast cancer overexpressing HER2. Use Regimen B for advanced or recurrent gastric cancer overexpressing HER2 not amenable to curative resection, in combination with other antineoplastic agents. Regimen A: The usual adult dosage is a loading dose of 4 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 2 mg/kg once a week, each administered by intravenous infusion over at least 90 minutes. Regimen B: The usual adult dosage is a loading dose of 8 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 6 mg/kg every 3 weeks, each administered by intravenous infusion over at least 90 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a shorter time of at least 30 minutes.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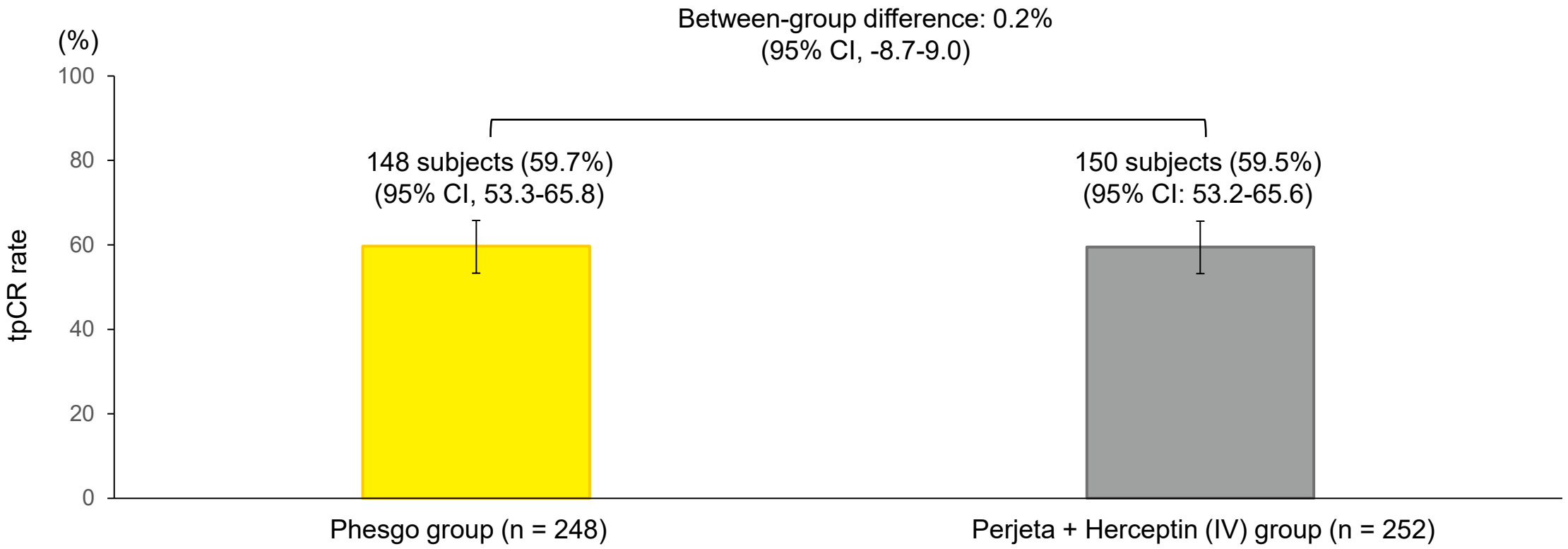
# Total Pathologic Complete Response Rate (tpCR Rate, ypT0/is ypN0)

## [Secondary endpoint, ITT]

- The tpCR rate was 59.7% (95% CI, 53.3-65.8) in the Phesgo group and 59.5% (95% CI, 53.2-65.6) in the Perjeta + Herceptin (IV) group, and therefore the difference in tpCR rate between the two groups was 0.2% (95% CI, -8.7-9.0).




tpCR: absence of invasive lesions in the breast and axilla
Data cutoff date at primary analysis: July 4, 2019

1) Data evaluated at the time of approval: Global phase 3 clinical study (FeDeriCa study)
2) Tan AR, et al. Lancet Oncol. 2021; 22 (1): 85-97.
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## Global Phase 3 Clinical Study: WO40324 Trial (FeDeriCa Study)

# Common Adverse Events (≥ 10% in Any Group)

| Number of patients (%) | **Phesgo group (n = 248)** | **Perjeta + Herceptin (IV) group (n = 252)** |
|---|---|---|
| All adverse events | 248(100%) | 251(99.6%) |
| Alopecia | 191(77.0%) | 177(70.2%) |
| Nausea | 146(58.9%) | 152(60.3%) |
| Diarrhea | 145(58.5%) | 139(55.2%) |
| Anemia | 84(33.9%) | 103(40.9%) |
| Asthenia | 70(28.2%) | 76(30.2%) |
| Fatigue | 69(27.8%) | 57(22.6%) |
| Stomatitis | 62(25.0%) | 60(23.8%) |
| Constipation | 54(21.8%) | 52(20.6%) |
| Myalgia | 53(21.4%) | 43(17.1%) |
| Neutropenia | 52(21.0%) | 64(25.4%) |
| Vomiting | 48(19.4%) | 45(17.9%) |
| Neutrophil count decreased | 42(16.9%) | 50(19.8%) |
| Dysgeusia | 41(16.5%) | 35(13.9%) |
| Decreased appetite | 40(16.1%) | 46(18.3%) |
| Arthralgia | 38(15.3%) | 45(17.9%) |
| Peripheral sensory neuropathy | 38(15.3%) | 34(13.5%) |
| Insomnia | 37(14.9%) | 28(11.1%) |
| Headache | 36(14.5%) | 50(19.8%) |

| Number of patients (%) | **Phesgo group (n = 248)** | **Perjeta + Herceptin (IV) group (n = 252)** |
|---|---|---|
| Mucosal inflammation | 36(14.5%) | 49(19.4%) |
| Alanine aminotransferase increased | 35(14.1%) | 48(19.0%) |
| Dry skin | 33(13.3%) | 31(12.3%) |
| Cough | 33(13.3%) | 30(11.9%) |
| Injection site reaction | 32(12.9%) | 2(0.8%) |
| Dyspepsia | 31(12.5%) | 26(10.3%) |
| Rash | 30(12.1%) | 44(17.5%) |
| Pyrexia | 30(12.1%) | 38(15.1%) |
| Procedural pain | 30(12.1%) | 23(9.1%) |
| Neuropathy peripheral | 28(11.3%) | 31(12.3%) |
| Epistaxis | 27(10.9%) | 34(13.5%) |
| Aspartate aminotransferase increased | 26(10.5%) | 37(14.7%) |
| Dyspnoea | 25(10.1%) | 11(4.4%) |
| Hot flush | 19(7.7%) | 26(10.3%) |
| Leukopenia | 18(7.3%) | 34(13.5%) |
| White blood cell count decreased | 17(6.9%) | 31(12.3%) |
| Infusion-related reaction | 9(3.6%) | 35(13.9%) |

MedDRA ver.22.0

The approved dosage and administration of Herceptin are as follows:
**[DOSAGE AND ADMINISTRATION] (excerpted)** Use either Regimen A or Regimen B for breast cancer overexpressing HER2. Use Regimen B for advanced or recurrent gastric cancer overexpressing HER2 not amenable to curative resection, in combination with other antineoplastic agents. Regimen A: The usual adult dosage is a loading dose of 4 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 2 mg/kg once a week, each administered by intravenous infusion over at least 90 minutes. Regimen B: The usual adult dosage is a loading dose of 8 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 6 mg/kg every 3 weeks, each administered by intravenous infusion over at least 90 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a shorter time of at least 30 minutes.


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# Any Adverse Events Leading to Discontinuation of Investigational Drug or Adverse Events Leading to Death

- **Adverse events leading to discontinuation of any investigational drug (≥ 2 patients in any group)**
  Adverse events leading to discontinuation of any investigational drug were observed in 6.9% (17/248 patients) in the Phesgo group and 10.3% (26/252 patients) in the Perjeta + Herceptin (IV) group. Major events were diarrhea [2 patients in the Phesgo group, 2 patients in the Perjeta + Herceptin (IV) group. The same applies hereinafter.], neutrophil count decreased (2 patients, 1 patient), pneumonitis (2 patients, 0 patient), ejection fraction decreased (1 patient, 3 patients), cardiac failure (1 patient, 2 patients), neuropathy peripheral (0 patient, 5 patients), peripheral sensory neuropathy (0 patient, 2 patients), etc.

- **Adverse events leading to death**
  Death due to an adverse event occurred in 1 patient (acute myocardial infarction) in the Phesgo group and 1 patient (urosepsis) in the Perjeta + Herceptin (IV) group.

The approved dosage and administration of Herceptin are as follows:
**[DOSAGE AND ADMINISTRATION] (excerpted)** Use either Regimen A or Regimen B for breast cancer overexpressing HER2. Use Regimen B for advanced or recurrent gastric cancer overexpressing HER2 not amenable to curative resection, in combination with other antineoplastic agents. Regimen A: The usual adult dosage is a loading dose of 4 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 2 mg/kg once a week, each administered by intravenous infusion over at least 90 minutes. Regimen B: The usual adult dosage is a loading dose of 8 mg/kg (body weight) trastuzumab (genetical recombination) once daily and subsequent doses of 6 mg/kg every 3 weeks, each administered by intravenous infusion over at least 90 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a shorter time of at least 30 minutes.

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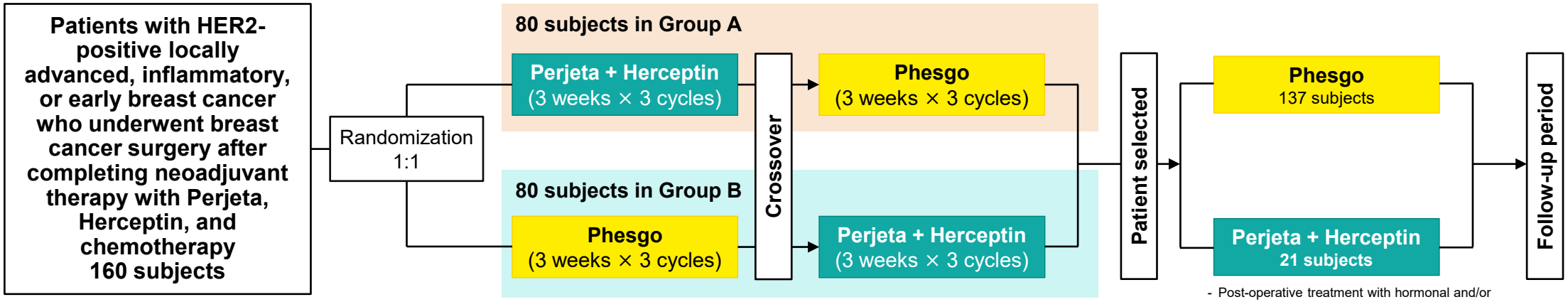
# Study Summary




**Stratification factors**
- Type of neoadjuvant chemotherapy (anthracycline + taxane, carboplatin + taxane, or taxane only)
- Response to preoperative therapy: pCR or non-pCR
- Hormone receptor expression status (ER and/or PgR positive, or ER and PgR negative)

pCR: pathological complete response
ER, estrogen receptor; PgR, progesterone receptor

**[Objectives]** To evaluate patient preference and satisfaction for treatment by intravenously administering Phesgo or Perjeta and Herceptin [Perjeta + Herceptin (IV)] as postoperative therapy in patients with HER2-positive early breast cancer.

**[Subjects]** 160 patients with HER2-positive locally advanced, inflammatory or early breast cancer who underwent breast cancer surgery after completing neoadjuvant therapy with Perjeta, Herceptin and chemotherapy (IHC 3+ and/or ISH positive, medical site evaluation)

Intent-to-treat (ITT) population: 160 subjs (80 subjs in Group A, 80 subjs in Group B); modified ITT (mITT): all 160 subjs who answered Patient Preference Questionnaire (PPQ) Question 1 (80 subjs in Group A, 80 subjs in Group B); Safety Analysis Set: 160 subjs (80 subjs in Group A, 80 subjs in Group B)

*Patients who started the study at least 6 weeks after the last administration of Perjeta and Herceptin in the preoperative therapy started the administration at the initial dose, and patients who started within 6 weeks after the last administration started at the maintenance dose.

1) Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa study)
2) O'Shaughnessy J, et al. Eur J Cancer. 2021; 152: 223-232.
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# Study Summary

**[Endpoints]**

**Primary endpoint**: Patient preference for Phesgo (based on responses to PPQ Question 1*1) [reference information]

*1 PPQ: Patient Preference Questionnaire
Question 1
Question: All things considered, which method of administration did you prepare?
Answer: SC [Phesgo], IV [Perjeta + Herceptin (IV)], No Preference

**Secondary endpoints:**

The strength of preference for the method of administration preferred in PPQ Question 1 and main reasons for the preference (PPQ Questions 2 and 3) [reference information], patient satisfaction with Phesgo and Perjeta + Herceptin (IV) (based on responses to TASQ*2-SC and TASQ-IV Question 1) [reference information], selection rate of Phesgo for the treatment continuation period [reference information], perception of time required for Phesgo/resource use and convenience with Phesgo (based on HCPs' responses to HCPQ*3) [reference information], etc. Phesgo

*2 TASQ: Therapy Administration Satisfaction Questionnaire
12-item questionnaire to assess the impact of treatment on five domains: physical impact, psychological impact, impact on daily living, convenience, and satisfaction. Physical impact was assessed in 3 items (Q2: experience of pain, Q3: experience of swelling, Q4: experience of redness), psychological impact was assessed in 1 item (Q5: restriction associated with SC injection/infusion), impact on daily living in 1 item (Q8: time lost/time achieved), convenience in 2 items (Q6: convenience for receiving SC injection/infusion; Q7: inconvenience for time required for SC injection/infusion), and satisfaction in 2 items (Q1: satisfaction with SC injection/infusion; Q12: desired treatment method).

*3 HCPQ: Healthcare Professional Questionnaire
A questionnaire for HCPs, consisting of questions regarding preparation of investigational product for HCPs in the dispensing room and questions related to preparation and administration for HCPs in the treatment room.

**Safety endpoints**: Adverse events, etc.

**[Analysis plan]**

Patient preference was assessed in all patients who answered PPQ question 1 (mITT: modified ITT).
Assuming that 70% of patients preferred Phesgo, a total of 140 patients were needed to estimate the 95%CI with an accuracy of ± 10%.
No formal hypothesis testing was planned for the primary or secondary endpoints.

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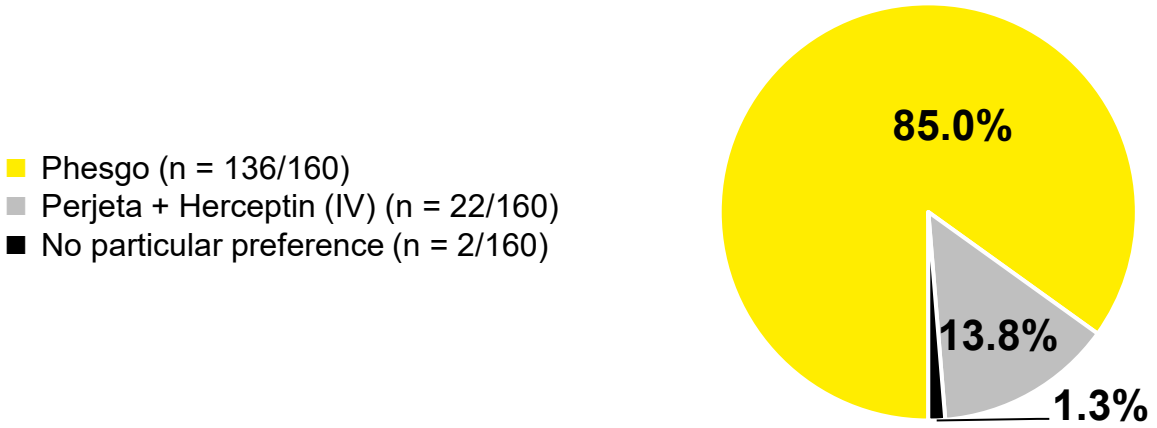
# Overseas phase II clinical study: MO40628 study (PHranceSCa study) (overseas data)
## Patient Preference for Phesgo (based on responses to PPQ Question 1[*1])
## [reference information, primary endpoint, mITT]

85.0% of patients (95%CI: 78.5 - 90.2) preferred Phesgo, and 13.8% of patients preferred Perjeta + Herceptin (IV).

| Number of subjects (%) | **Group A (n = 80) Perjeta + Herceptin (IV) → Phesgo** | **Group B (n = 80) Phesgo → Perjeta + Herceptin (IV)** | **All patients (n = 160)** |
|---|---|---|---|
| Phesgo | 70 (87.5%) | 66 (82.5%) | 136 (85.0%) |
| Perjeta + Herceptin (IV) | 10 (12.5%) | 12 (15.0%) | 22 (13.8%) |
| No particular preference | 0 | 2 ( 2.5%) | 2 ( 1.3%) |




*1 PPQ: Patient Preference Questionnaire
Question 1
Question: All things considered, which method of administration did you prepare?
Answer: SC [Phesgo], IV [Perjeta + Herceptin (IV)], No Preference
Data cutoff date for primary analysis: February 24, 2020

1) Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa study)
2) O'Shaughnessy J, et al. Eur J Cancer. 2021; 152: 223-232.
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# Overseas phase II clinical study: MO40628 study (PHranceSCa study) (overseas data) HCPs' Perception for Time Required for Phesgo/Resource Use and Convenience by Using Phesgo (based on HCPs' responses to HCPQ) [reference information, secondary endpoints, ITT]

## Time required for Phesgo

The median duration of preparation for administration in each cycle was 5 minutes for Phesgo and 15 to 20 minutes for Perjeta + Herceptin (IV). The median duration of administration in each cycle was 7 to 8 minutes for Phesgo and 60 to 150 minutes for Perjeta + Herceptin (IV). The median total time that a patient spent in the treatment room per cycle ranged from 33 to 50 mins with Phesgo and 130 to 300 mins with Perjeta + Herceptin (IV).

## HCPs' perception for resource use and convenience by using Phesgo

| Number of subjects (%) | **Group A (n = 80) Perjeta + Herceptin (IV) → Phesgo** | **Group B (n = 80) Phesgo → Perjeta + Herceptin (IV)** | **All patients (n = 160)** |
|---|---|---|---|
| HCPQ Dispensing Room Question 4: Which dosing regimen was the least resource required for drug preparation, nursing hours, facility costs, equipment, etc.? *1 | | | |
| Phesgo | 75 (93.8%) | 64 (80.0%) | 139 (86.9%) |
| Perjeta + Herceptin (IV) | 0 | 0 | 0 |
| Neither | 0 | 4 ( 5.0%) | 4 ( 2.5%) |
| No Answer | 5 ( 6.3%) | 12 (15.0%) | 17 (10.6%) |
| HCPQ Treatment Room Question 3: Which dosing regimen was most convenient for patients? *2 | | | |
| Phesgo | 70 (88.6%) | 68 (85.0%) | 138 (86.8%) |
| Perjeta + Herceptin (IV) | 5 ( 6.3%) | 1 ( 1.3%) | 6 ( 3.8%) |
| Neither | 2 ( 2.5%) | 4 ( 5.0%) | 6 ( 3.8%) |
| "I don't know" | 0 | 6 ( 7.5%) | 6 ( 3.8%) |
| No Answer | 2 ( 2.5%) | 1 ( 1.3%) | 3 ( 1.9%) |
| HCPQ Treatment Room Question 6: Which dosing regimen was the least resource required for dosing such as nursing hours, facility costs, equipment? *2 | | | |
| Phesgo | 66 (83.5%) | 71 (88.8%) | 137 (86.2%) |
| Perjeta + Herceptin (IV) | 0 | 1 ( 1.3%) | 1 ( 0.6%) |
| Neither | 11 (13.9%) | 7 ( 8.8%) | 18 (11.3%) |
| "I don't know" | 0 | 0 | 0 |
| No Answer | 2 ( 2.5%) | 1 ( 1.3%) | 3 ( 1.9%) |

*1 160 HCPs completed the questionnaire (50 nurses, 84 pharmacists, 23 pharmacy assistants, 3 others)
*2 159 HCPs completed the questionnaire (156 nurses, 3 oncologists)
Data cutoff date for primary analysis: February 24, 2020


1) Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa study)
2) O'Shaughnessy J, et al. Eur J Cancer. 2021; 152: 223-232.


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# Safety Summary of the Treatment Crossover Period

The adverse events were observed during the treatment crossover period as follows: Group A at Perjeta + Herceptin (IV) treatment (Cycles 1-3) 77.5% (62/80 patients), Group A at Phesgo treatment (Cycles 4-6) 72.5% (58/80 patients), Group B at Phesgo treatment (Cycles 1-3) 77.5% (62/80 patients), and Group B at Perjeta + Herceptin (IV) (Cycle 4-6) 63.8% (51/80 patients).

| Number of subjects (%) | Group A (n = 80) Perjeta + Herceptin (IV) → Phesgo | | Group B (n = 80) Phesgo → Perjeta + Herceptin (IV) | |
|---|---|---|---|---|
| | At the time of Perjeta + Herceptin (IV) administration Cycles 1-3 | At the time of Phesgo administration Cycles 4-6 | At the time of Phesgo administration Cycles 1-3 | At the time of Perjeta + Herceptin (IV) administration Cycles 4-6 |
| Number of subjects who experienced adverse events | 62 (77.5%) | 58 (72.5%) | 62 (77.5%) | 51 (63.8%) |
| Grade ≥ 3 adverse events | 2 ( 2.5%) | 1 ( 1.3%) | 3 ( 3.8%) | 4 ( 5.0%) |
| Serious Adverse Events | 1 ( 1.3%) | 1 ( 1.3%) | 1 ( 1.3%) | 5 ( 6.3%) |
| Adverse events leading to discontinuation of any investigational product | 0 | 1 ( 1.3%) | 0 | 0 |
| AEs leading to death | 0 | 0 | 0 | 0 |

CTCAE ver.4.0

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# Problems with the Healthcare Situation in Japan

The impact of the long time it takes to wait for a medical consultation, to visit the hospital and to receive treatment

- Burden on breast cancer patients
  - Work
  - Childcare
  - Nursing care
  - Physical exhaustion

- Burden on healthcare professionals
  - Securing an outpatient chemotherapy room
  - Manpower (doctor, nurse, pharmacist; The amount of infusion is dependent on the body weight ⇨ Preparation also takes a certain amount of time)
  - Personnel expenses

The shorter administration time of each dose of Phesgo may contribute to improve the quality of life of patients and the burden of the medical care.

# Take-home Message

Patients with early cancer can maintain QOL while aiming at cure

Patients with metastasis/recurrence can maintain QOL while aiming at a high therapeutic effects

Shorter administration time per dose with Phesgo may contribute to improving patients' QOL as well as
reducing the burden of medical care.

However, it is important to select the optimal dosage form individually according to the patient's condition and wishes, etc.

# Contacts

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# INNOVATION BEYOND IMAGINATION

Created in November 2023