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CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on Phesgo

November 30, 2023

Event Summary

[Company Name]	CHUGAI PHARMACEUTICAL CO., LTD.
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[Date]	November 30, 2023
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[Time]	13:30 – 14:34 (Total: 64 minutes, Presentation: 40 minutes, Q&A: 24 minutes)
[Venue]	Webcast
[Venue Size]	
[Participants]	

[Number of Speakers]	3	
	Yuji Habara	Phesgo Lifecycle Leader
	Naoki Hayashi	M.D. Professor and Chairman, Division of Breast Surgical Oncology Department of Surgery, Showa University School of Medicine
	Kae Miyata	Head of Corporate Communications Dept.
[Analyst Names]*	Fumiyoshi Sakai	UBS Securities
	Kazuaki Hashiguchi	Daiwa Securities
	Hidemaru Yamaguchi	Citigroup Global Markets
	Koichi Mamegano	BofA Securities

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

Presentation

Miyata: Thank you very much for attending today's Information Meeting on PHESGO of CHUGAI PHARMACEUTICAL CO., LTD.

I'm Miyata from the corporate communications department, and I will be your facilitator today. Thank you.

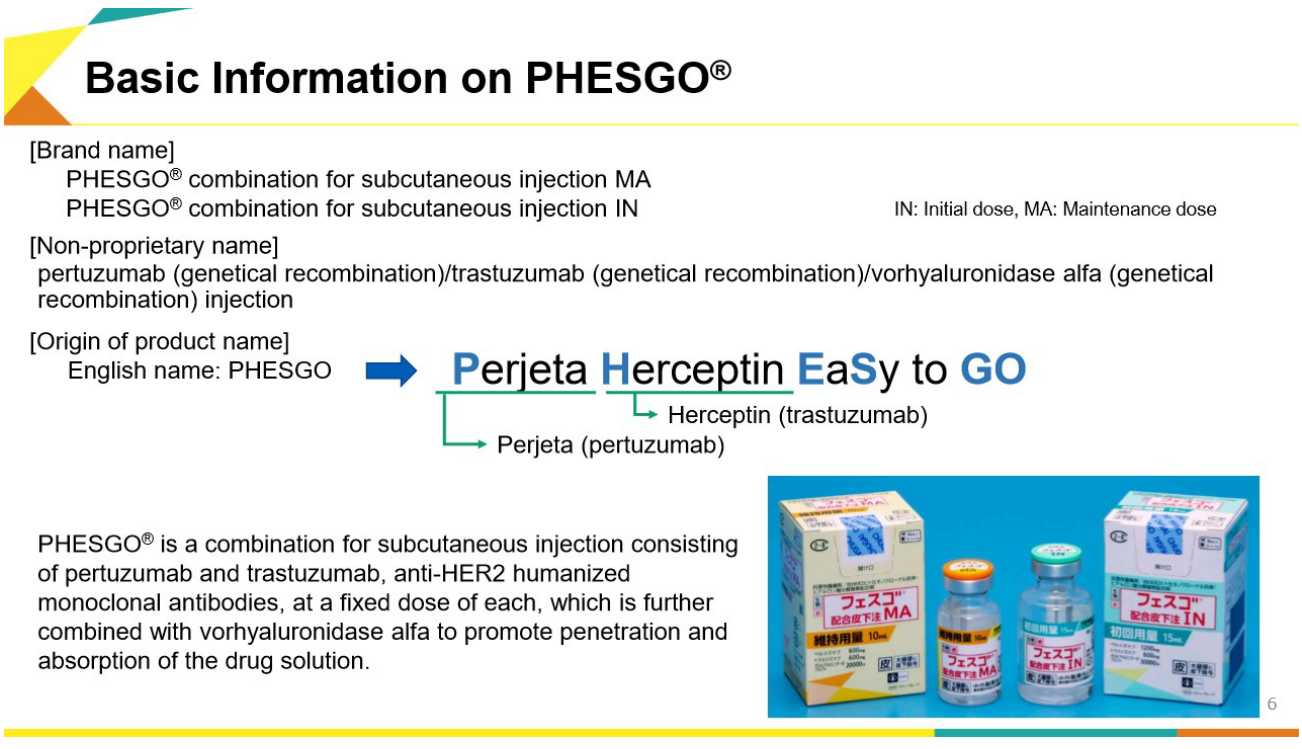
Today's event is held on an on-site basis and also distributed on a Zoom webinar basis at the same time. The agenda for today's meeting is shown on the venue screen, on the web screen and on the third page of the presentation materials. I will explain the contents accordingly.

Today, we have invited as a special lecturer, Dr. Naoki Hayashi, M.D. Professor and Chairman, Division of Breast Surgical Oncology, Showa University School of Medicine.

Please note that there will be time for screen capture before each presentation.

Questions will be taken after all presentations have been completed. The Q&A session is expected to last 30 minutes, so we hope you will be proactive and ask questions. Please note that your audio will be muted during the presentation.

Habara, PHESGO Lifecycle Leader, CHUGAI PHARMACEUTICAL, will now give an overview of PHESGO. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Thank you.

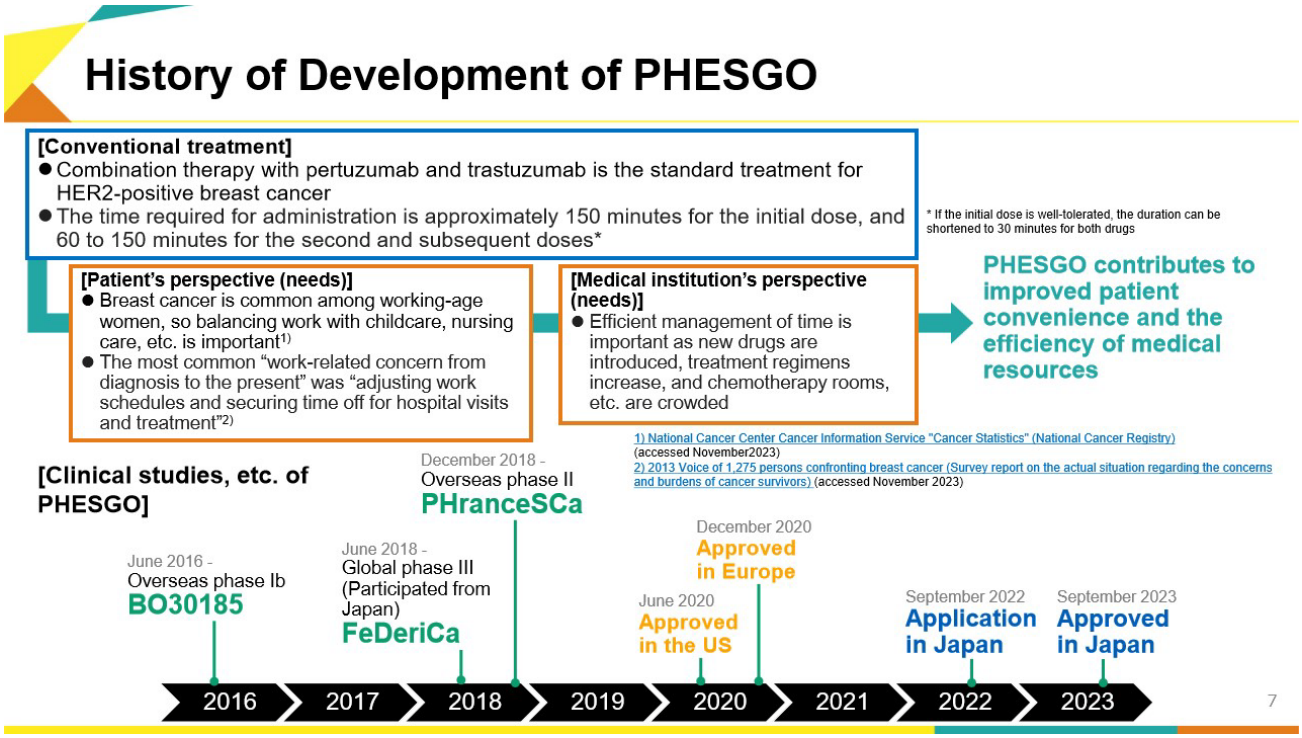


Habara: My name is Habara, and I am responsible for the product. I would like to give an overview of the product PHESGO, with three divided parts.

First, here is some basic information. There are two trade names, MA and IN, for PHESGO combination for subcutaneous injection. IN refers to the initial dose and MA refers to the maintenance dose.

PHESGO is a subcutaneous injection formulation containing fixed doses of pertuzumab and trastuzumab, anti-HER2 humanized monoclonal antibodies, respectively, plus vorhyaluronidase alfa to promote drug penetration and absorption.

The product name is derived from Perjeta, the product name of pertuzumab, and Herceptin, the product name of trastuzumab, combined with "easy to go," meaning easy to administer and shortening the time spent at the medical institution, to form Perjeta Herceptin EaSy to GO. Taking these key alphabets, the product was named PHESGO.



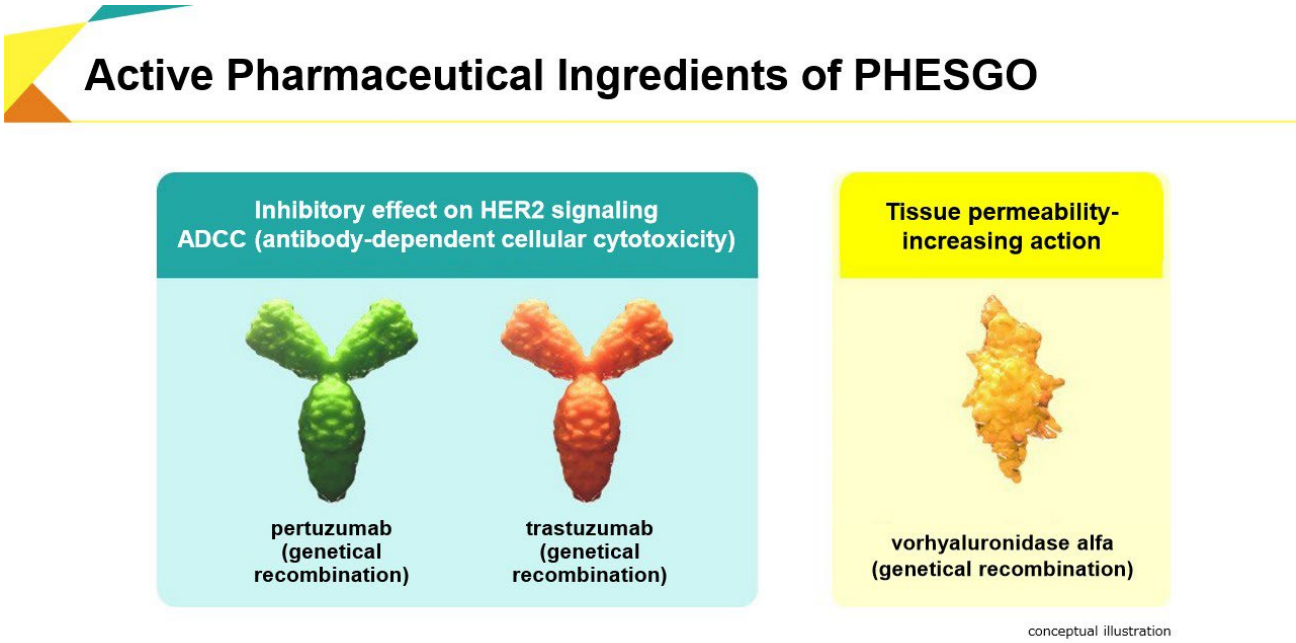
This is the development process. This is a combination therapy with pertuzumab and trastuzumab. Both are monoclonal antibodies and are used as standard treatment for HER2-positive breast cancer. The first dose of these two drugs takes about 150 minutes, and the second and subsequent doses take from 60 to 150 minutes with some ranges of time, although the time required varies.

We thought that patients and medical institutions have time needs of their own. As lifestyles and living environments change dramatically, many breast cancer patients are women of working age, and we recognize the importance of balancing work with caregiving and childcare. For this reason, the time spent at the medical institution and the time required for administration were the significant key for these patients, and we considered there were high needs.

On the other hand, from the viewpoint of medical institutions, with the advent of new drugs, treatment regimens becoming more and more complex, and the chemotherapy rooms becoming very crowded, we hear that time management and efficient management are important.

We hope that PHESGO will contribute to the improvement of patient convenience and the efficiency of medical resources.

These are the clinical trials. A Phase I trial started overseas in June 2016, followed by a global Phase III trial in which the patients from Japan participated, the FeDeriCa trial, and, although those of Japan did not participate, the PHranceSCa trial, and then the application was submitted in Japan last September and approval was obtainned this September.

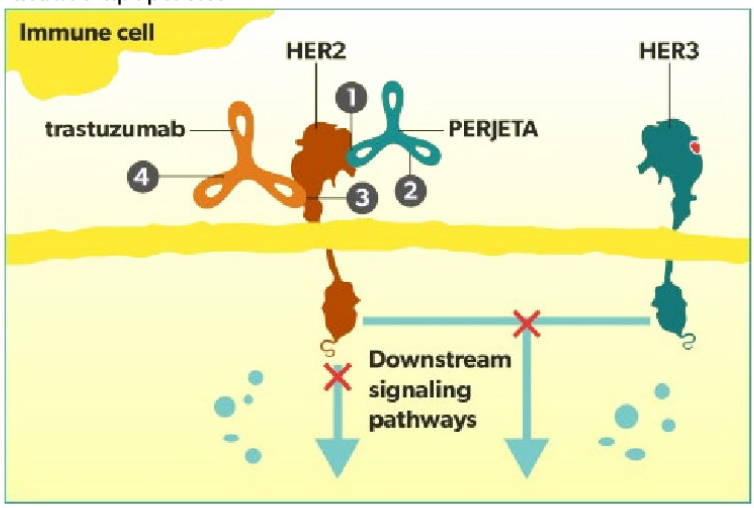


These are the active pharmaceutical ingredients.

As I mentioned, PHESGO is a combination product of three recombinant drugs. Pertuzumab and trastuzumab have two effects of inhibiting HER2 signaling as well as antibody-dependent cytotoxicity, while volhyaluronidase alfa has the effect of increasing tissue penetration. These three agents are combined in this product.

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.

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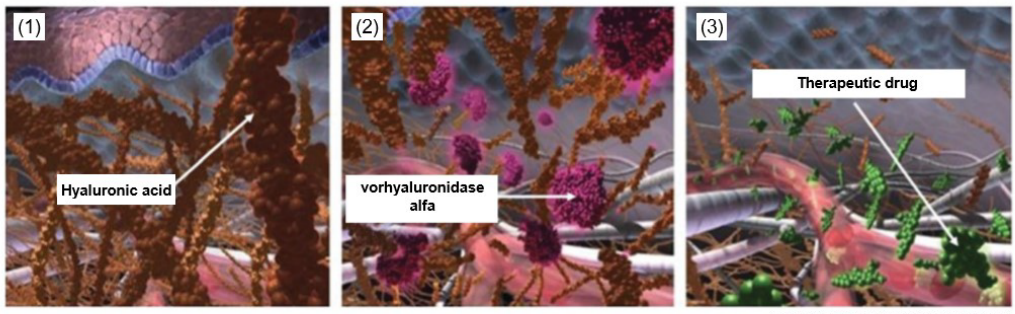
This is the mechanism of action.

For the extracellular region of HER2, domain II, which pertuzumab binds to. Trastuzumab binds to domain IV of the HER2 membrane proximal domain, and we believe that the combination of these two antibodies comprehensively blocks HER2 signaling, suppresses cell proliferation, and induces apoptosis.

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.

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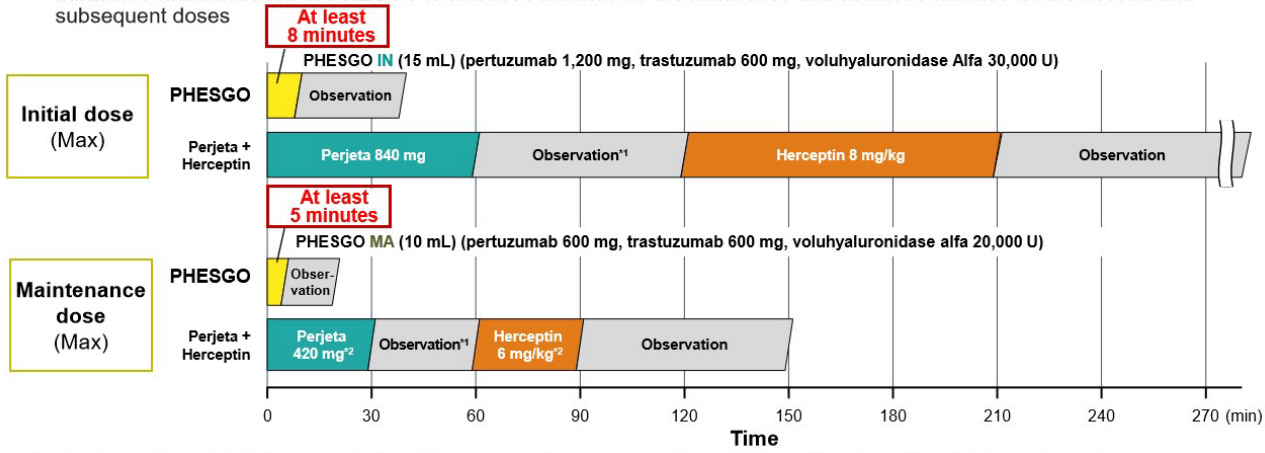
Hyaluronidase alfa depolymerizes hyaluronic acid, a skin matrix, and transiently decreases the viscosity of hyaluronic acid in the extracellular matrix, thereby increasing drug absorption by increasing penetration.

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.

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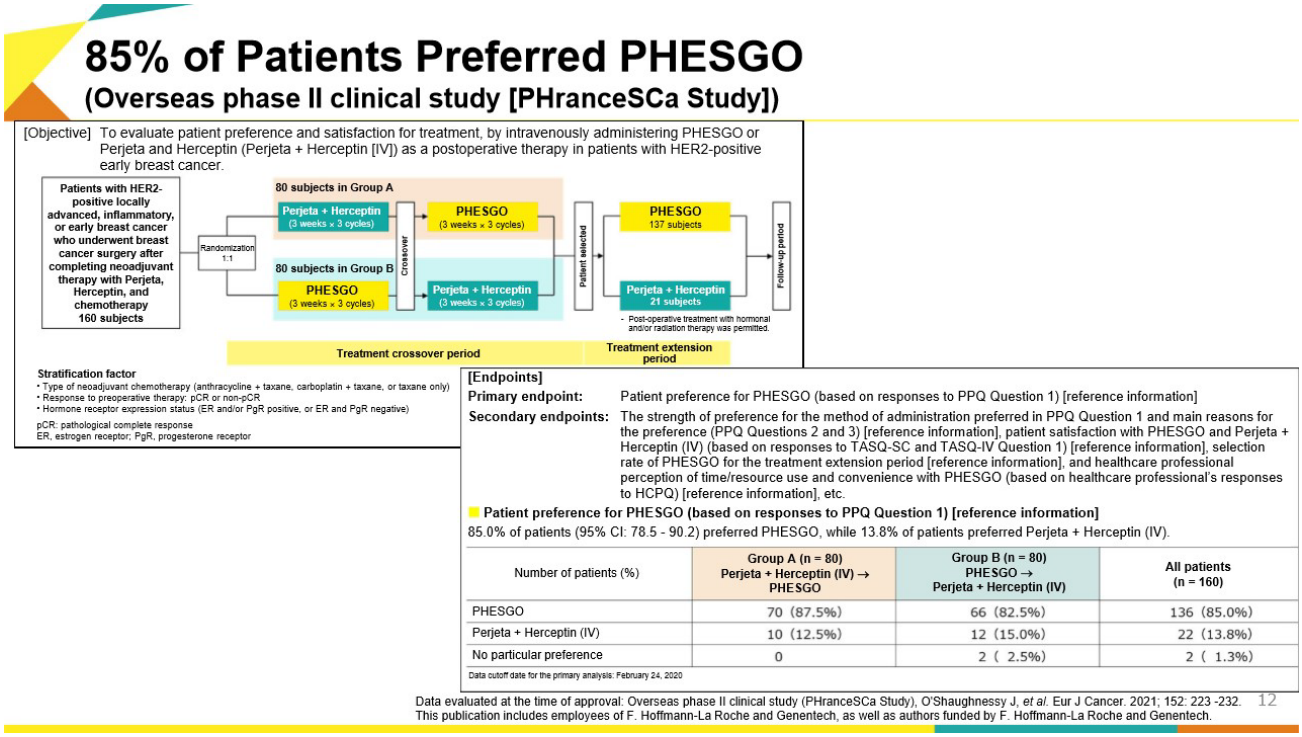
By combining these three drugs, antibody products, and genetic recombinants, we expect to shorten the administration time and greatly improve the convenience of PHESGO compared to conventional intravenous infusion.

As I mentioned, as for the conventional intravenous infusion combination therapy, the time required for the first dose is 150 minutes, but with PHESGO, the time is more than eight minutes. The second and subsequent maintenance doses require 60 to 150 minutes, but with PHESGO, the time can be shortened to five minutes or more.



For the overseas Phase II trial, the PHranceSCa trial, the primary endpoint is the preference of the patient, which treatment they prefer. As a result, 85% of patients preferred PHESGO.

Dr. Hayashi, who will be speaking later, will give you more details about the design of this clinical trial, so I'll leave this part to him.

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.

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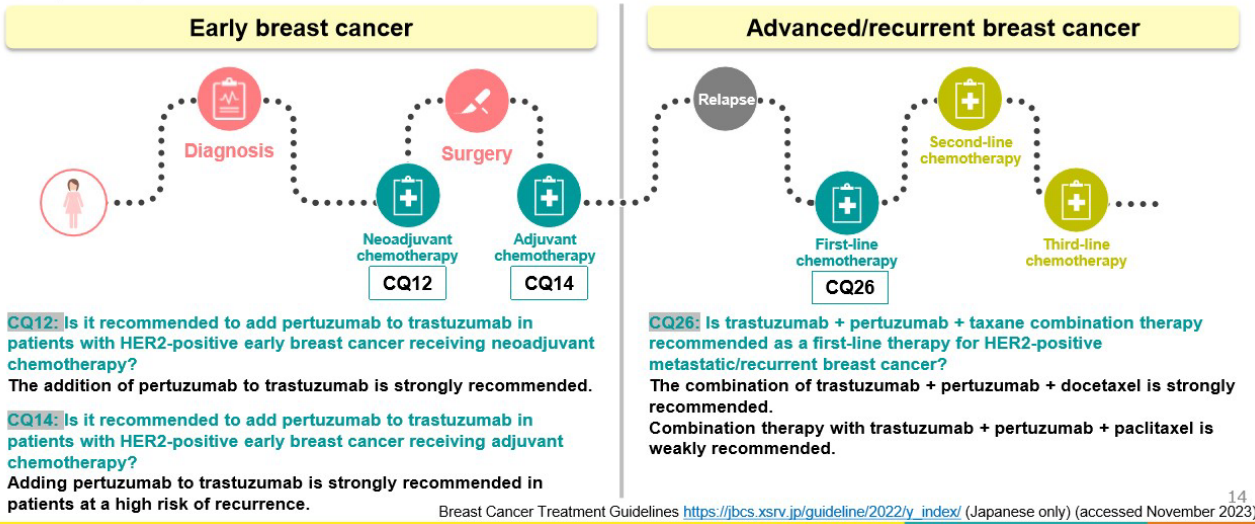
I would also like to mention safety, and I believe that the combination of the intravenous formulation and this PHESGO was well tolerated and had the same safety profile.

The characteristic feature of this product is that it is a subcutaneous injection formulation, so the injection site reaction is higher than that of intravenous infusion in comparison. On the other hand, the frequency of infusion reactions, such as fever, dyspnea, and other common symptoms, was zero in this study. As for IV, there is a little bit of it. Dr. Hayashi will explain this in detail later.

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



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

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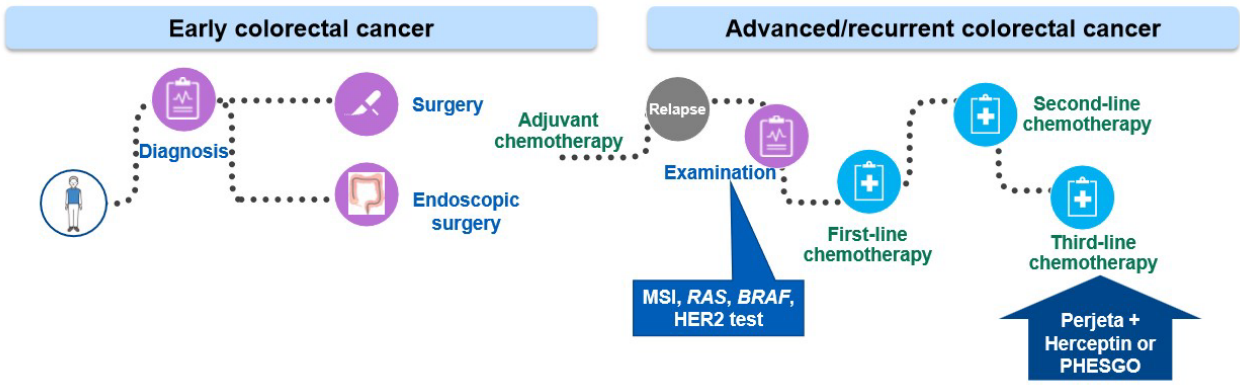
HER2-positive breast cancer, this is the segment that we expect PHESGO to be prescribed for in the overall treatment of this disease. Currently, the combination therapy of HERCEPTIN and PERJETA is widely used in Japan as a first-line therapy for breast cancer, including neoadjuvant and adjuvant setting of early-stage breast cancer, and advanced or recurrent breast cancer, according to domestic guidelines. We are hopeful that these will be replaced by PHESGO.

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)

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Similarly, as for colorectal cancer, PHESGO has been used in the treatment of HER2-positive advanced or recurrent unresectable colorectal cancer that has worsened after current cancer chemotherapy. We expect PHESGO will replace the conventional combination use of intravenous formulations.

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.

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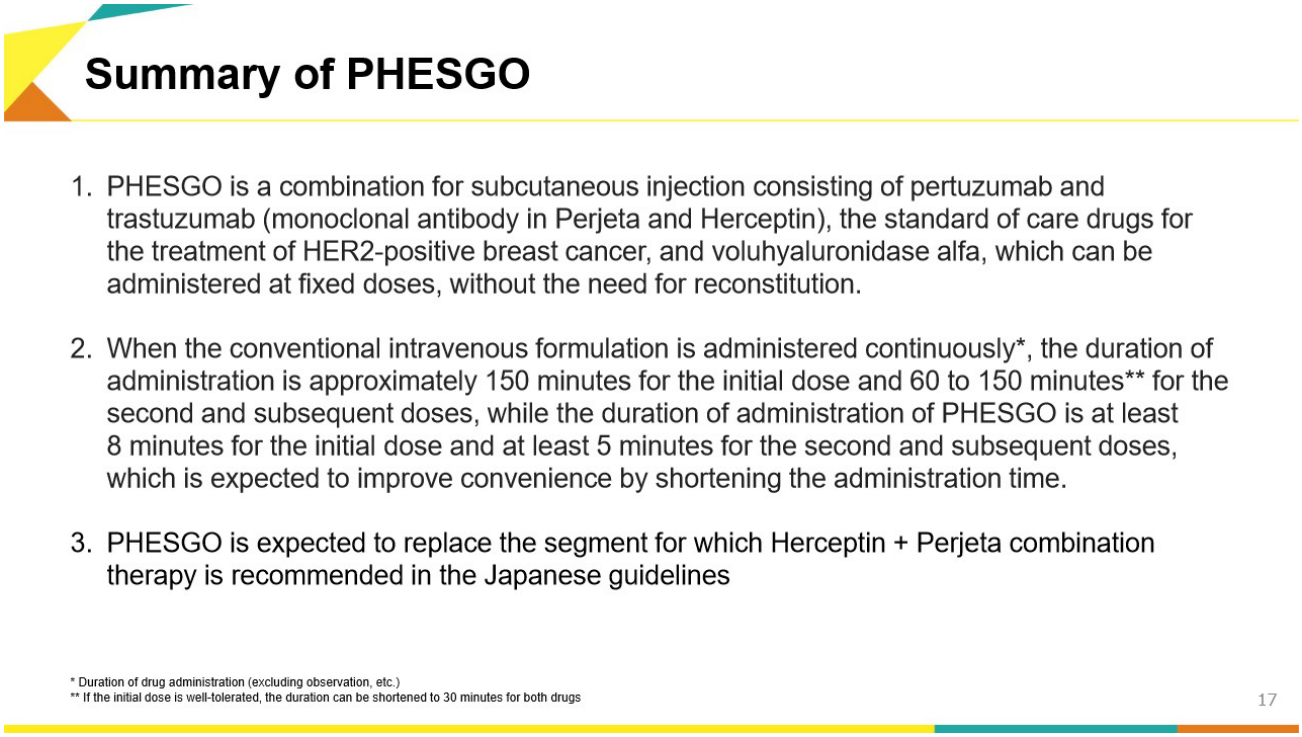
PHESGO combination for subcutaneous injection MA/IN, electronic package insert prepared in December 2023 (2nd Edition)

In addition to HER2-positive breast cancer, which I explained earlier, the indication is for HER2-positive advanced or recurrent unresectable colorectal cancer that has worsened after cancer chemotherapy.

Regarding dosage and administration, for HER2-positive breast cancer, in combination with other anti-cancer agents, the initial dose, IN, should be administered first, followed by a maintenance dose of MA for at least eight minutes and five minutes, respectively. The maintenance dose is to be administered at 3-week intervals.

For colorectal cancer, there is no indication for concomitant use with other agents for malignant cancer, but the administration of IN and MA at three-week intervals is the same as for breast cancer.



Summary. PHESGO is a subcutaneous formulation of pertuzumab and trastuzumab, the standard drugs for the treatment of HER2 breast cancer, in combination with vorhyaluronidase alfa, and can be administered in fixed doses without the need for adjustment.

When following a conventional intravenous formulation, the initial administration time is reduced from 150 minutes to more than eight minutes, and the second and subsequent administrations from 60 to 150 minutes to more than five minutes, which is expected to improve convenience. It is expected that PHESGO will replace HERCEPTIN and PERJETA in the segment where the combination therapy is recommended on the domestic guidelines.

That is all.

Miyata: Thank you very much. Dr. Naoki Hayashi will continue with an explanation of the clinical positioning of PHESGO in the treatment of HER2-positive breast cancer. There will be a short pause at the beginning, so if you would like to take a screen capture, please use this opportunity. Doctor, please go ahead.

About Breast Cancer

Hayashi: Hello, everyone. I am Hayashi of Showa University, Division of Breast Surgical Oncology. Today, I would like to talk about the clinical position of PHESGO in the treatment of HER2-positive breast cancer.

First of all, I would like to talk about breast cancer in general, from a basic point of view.

Probability of Getting Breast Cancer during Your Lifetime

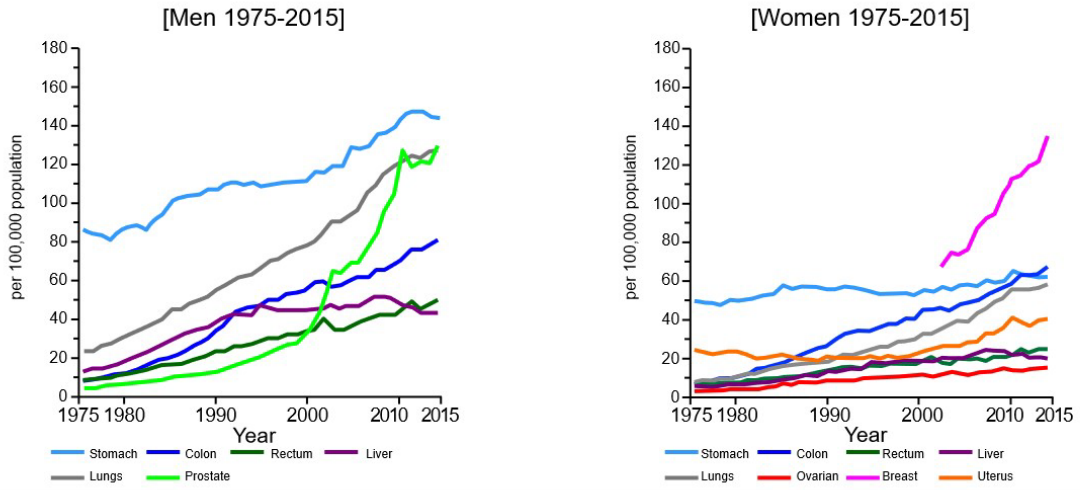
1/9 persons

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

National Cancer Center Japan, Cancer Information Service
"Cancer statistics" (National Cancer Registry) 21

It is said that the lifetime probability of developing breast cancer in Japan is one in nine. Roughly, more than 95,000 new breast cancer patients are diagnosed annually. More than 20 years ago, it was said that breast cancer was 1 in 25 to 26 people, and even 5 to 6 years ago, it was 1 in 11 to 12 people. The number of breast cancer patients has been increasing every year in Japan. It has become a very familiar disease in this way.

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

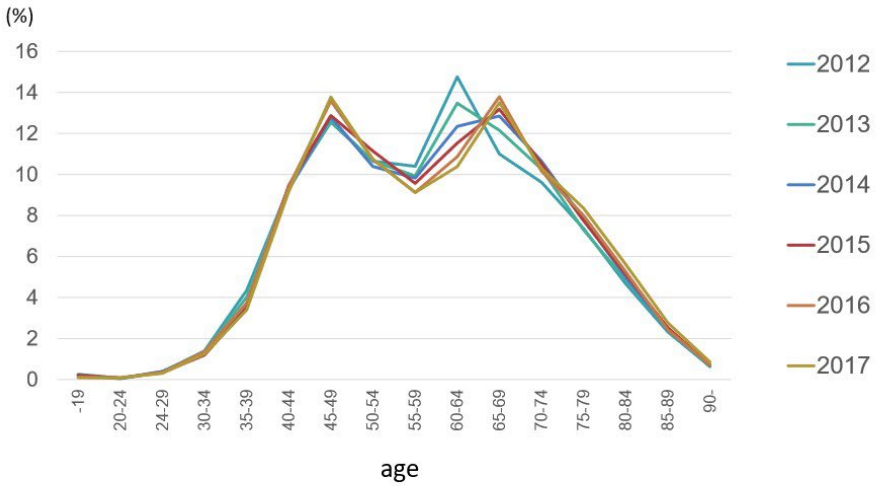


Summary of cancer registry/statistics: "population-based cancer registry " is a system that started in January 2016. It is a new system to aggregate, analyze, and manage data of all patients diagnosed with cancer in Japan. Data collected from throughout Japan is put together in a national database, and 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 22

The right graph shows women cancer patients, and the pink line represents breast cancer. This record has been available since 2000, and as can be seen from the trends in incidence rates by major cancer site and per 100,000 population, breast cancer is increasing every year.

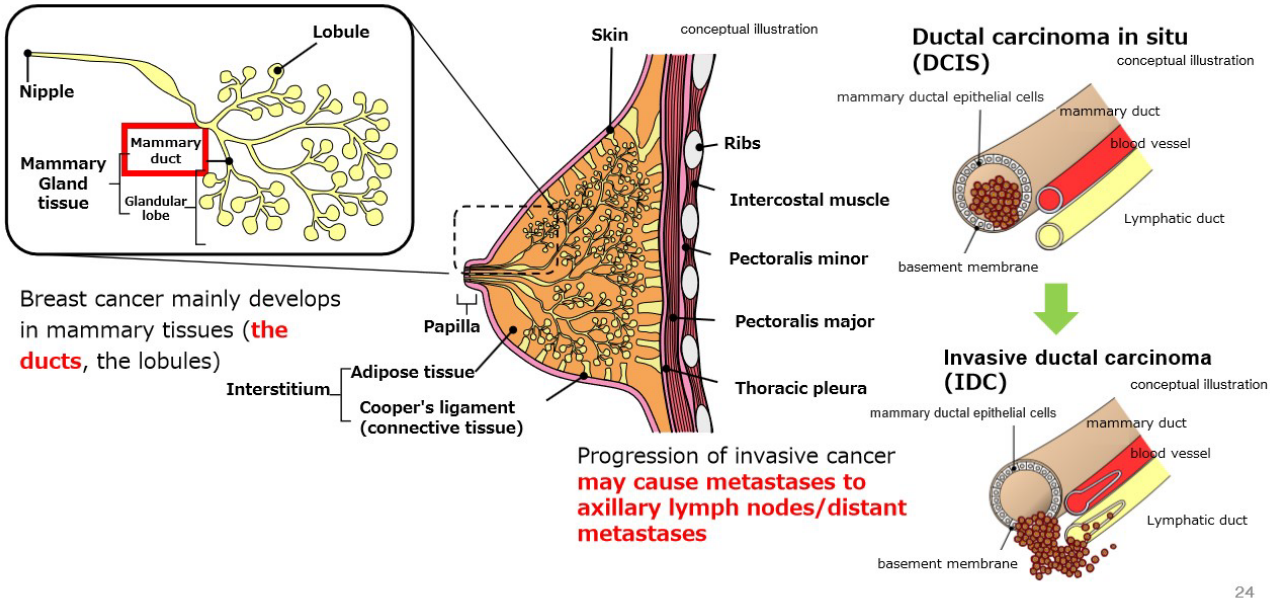
Figure 1 Number of Japanese Breast Cancer Patients by Age



Naoki Hayashi et al. Breast Cancer. 2020 Sep;27(5):803-809. [23]

According to the data from the national breast cancer registry, which is also available here, breast cancer in Japan is characterized by a bimodal pattern, with breast cancer in the 40s and 60s, as shown here. We have recently learned that the number has been gradually increasing from the latter half of the 30s, then 40s, and in recent years the line has been shifting gradually toward the 70s as the population ages.

Invasive and Non-invasive Cancers

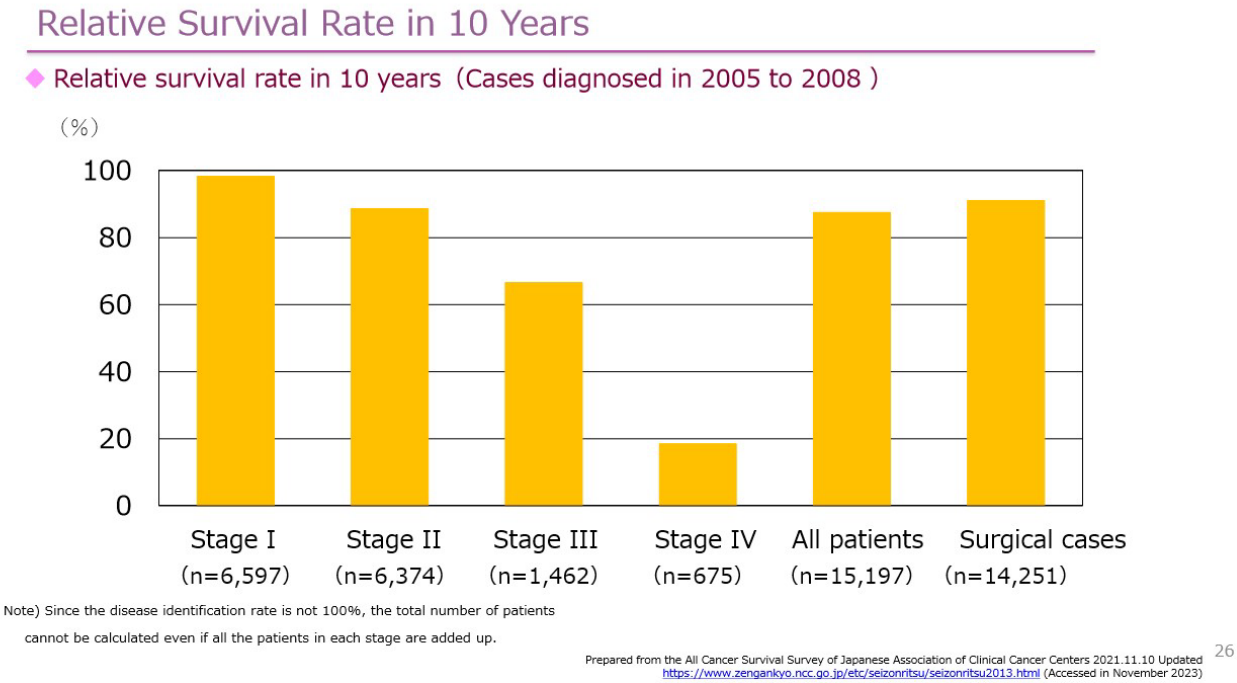


Breast cancer mainly develops in mammary tissues. The lobule is where milk is produced, and from there to the nipple, there are 15 to 20 ducts called milk ducts through which milk flows throughout the mammary gland. These ducts come together at the nipple and secrete milk.

More than 85% of breast cancers emerge from these ducts. As shown in the figure on the right, as long as it remains in the duct, no matter how large it is, this breast cancer is a non-invasive cancer, meaning that it is not invasive, so it is a so-called very early stage 0 cancer. It will be something that can be cured if the surgery is done properly.

If the ducts are breached even slightly, it becomes invasive ductal carcinoma, and as the disease progresses, there is a possibility of metastasis to the axillary lymph nodes or distant metastasis, for example.

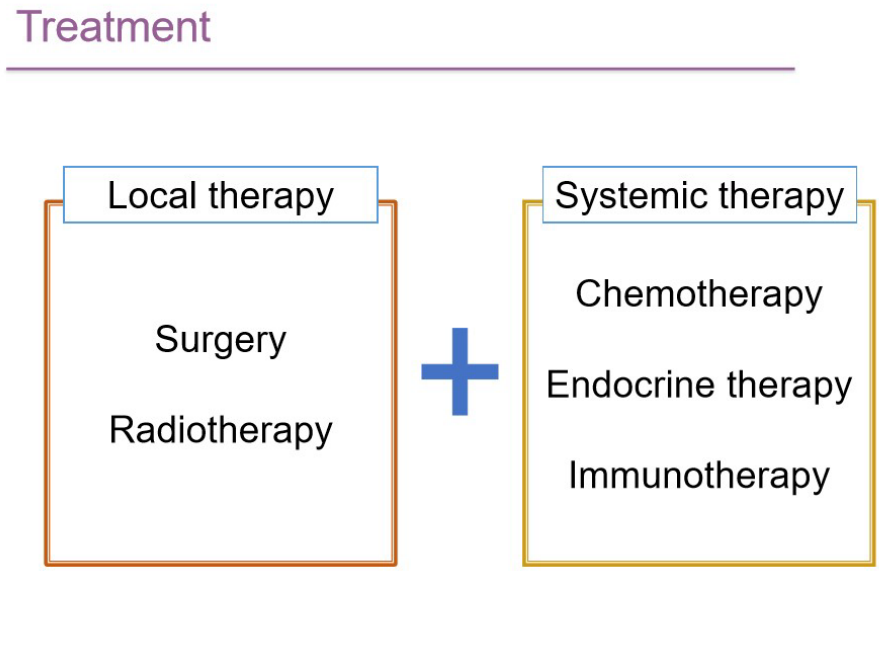
In Japan, data shows that at the time of diagnosis, more than 85% of the patients have invasive cancer. The prognosis of breast cancer varies depending on the subtype, which I will discuss in the next section, as well as the extent, stage, and stage of the disease at the time of diagnosis.



Now, if it is found at stage I, it will be almost 100% if it is stage zero non-invasive cancer, but if we look at it over 10 years, stage I will be over 95%. Stage II, III, and IV are the types where the prognosis becomes worse and worse.

What I am going to talk about today is HER2 positive breast cancer. PERJETA and HERCEPTIN, drugs that can be used only for this HER2 positive breast cancer, have come out and dramatically improved its prognosis.

This is the prognosis for breast cancer as a whole, and the current principle is that stage IV breast cancer is basically incurable, but recent clinical trials have shown that nearly 10% of HER2-positive breast cancers disappear completely with the use of PERJETA and HERCEPTIN. It is said that these new drugs are highly effective in treating breast cancer, especially HER2-positive breast cancer.

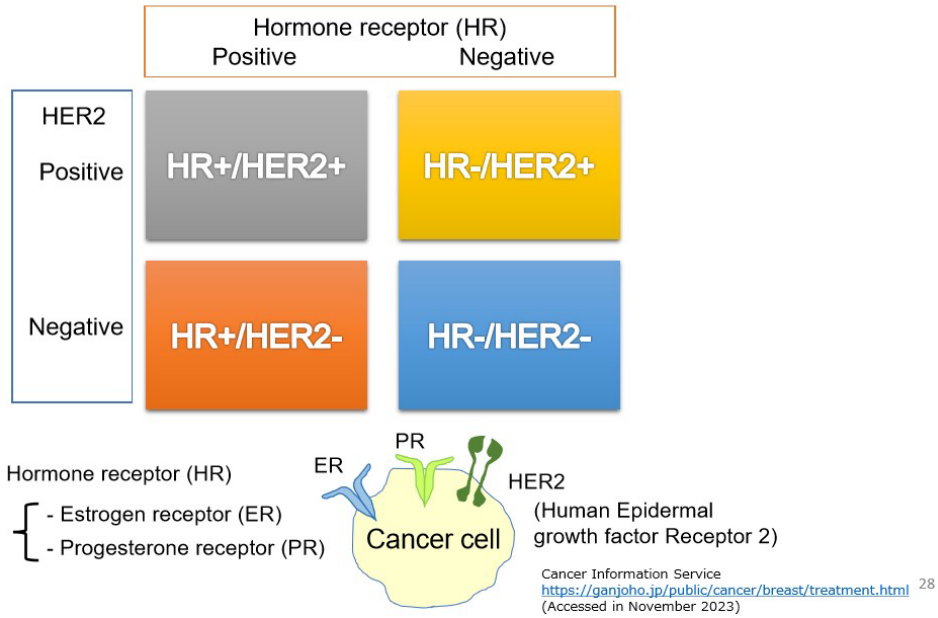


First of all, when considering treatment, breast cancer is treated in two ways: local therapy and systemic therapy. One of the goals of local therapy is to control the local area, first by surgery and then, if partial resection has progressed, by radiation therapy.

Systemic treatments include chemotherapy, endocrine therapy, so-called hormone-suppressing drugs, and the recently introduced immunotherapy, which is a drug that affects the entire body. This is a double feature.

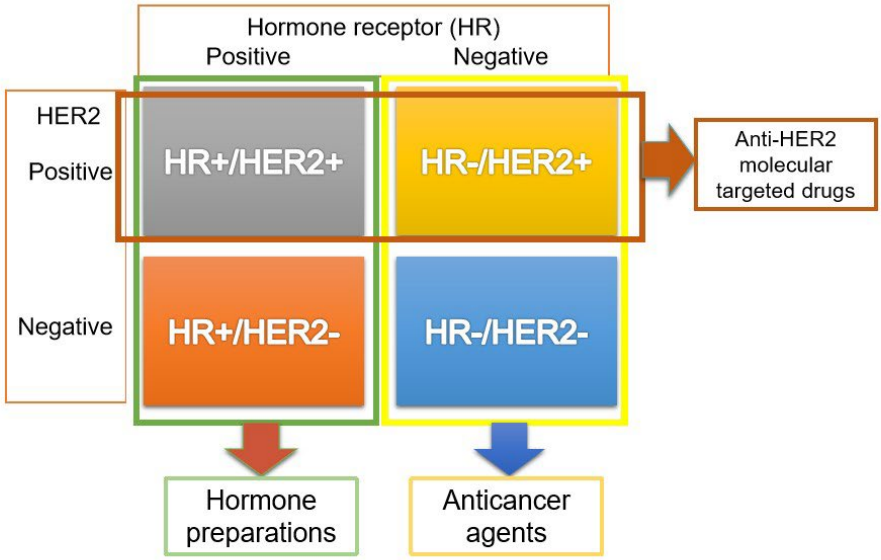
The reason why we take double approach is that some people basically have had the whole thing surgically removed with local therapy, but it still recurs later. It is possible that small micrometastases, which do not show up on images, CT scans, or blood samples, are circulating throughout the body at the time of diagnosis. If it later gets bad and takes root in the whole body, it will recur and cannot be cured. For this reason, we try to nip the buds before they take root, which is why we use systemic treatment and medications.

Four Subtypes of Breast Cancer



We divide breast cancer into four major subtypes, and the treatment plan is changed according to the subtype. We classify the disease in terms of hormone receptors and the marker called HER2. When we consider two-by-two, we divide them according to whether they are hormone receptor positive, HER2 positive, or hormone negative or positive. Think of this hormone receptor or HER2 as the markers of cancer cells, as you can see in the picture below.

Basic Treatment Concept According to the Subtype



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

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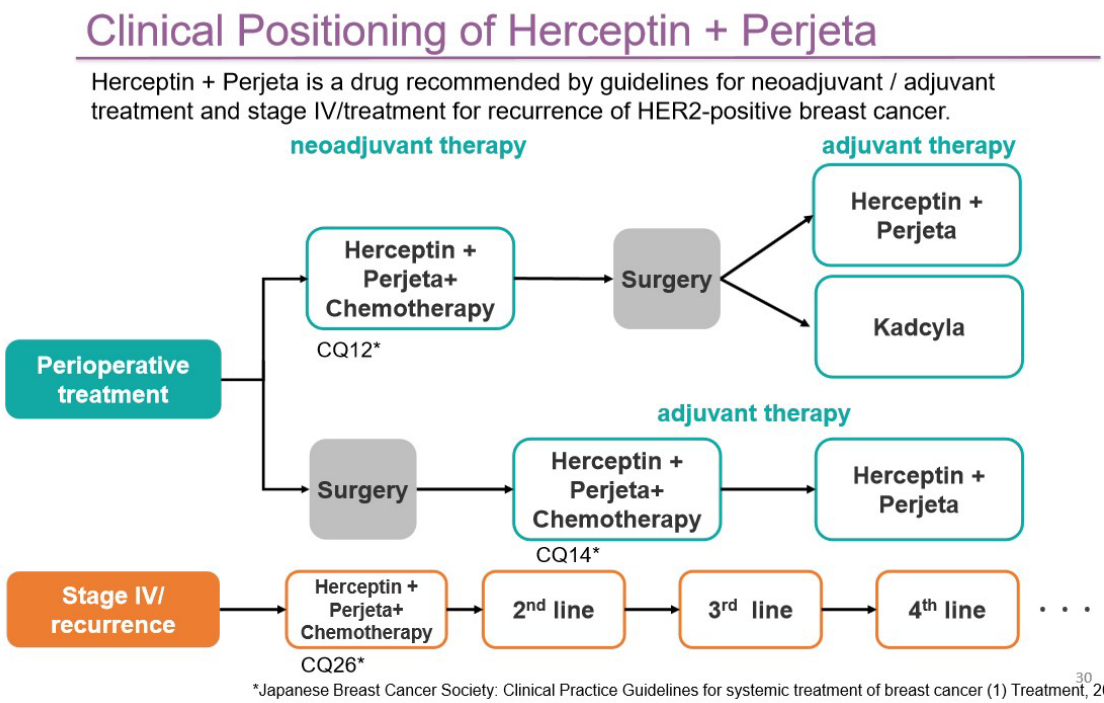
The treatment plan will be changed according to this result. If the hormonal status is positive, then hormone-suppressing drugs or hormones drugs are used. On the other hand, if hormones are ineffective, we use anticancer drugs because there is nothing more we can do.

Also, now when we look at HER2, if HER2 is positive, we will start using anti-HER2drugs, molecular targeted drugs, which will be PERJETA and HERCEPTIN.



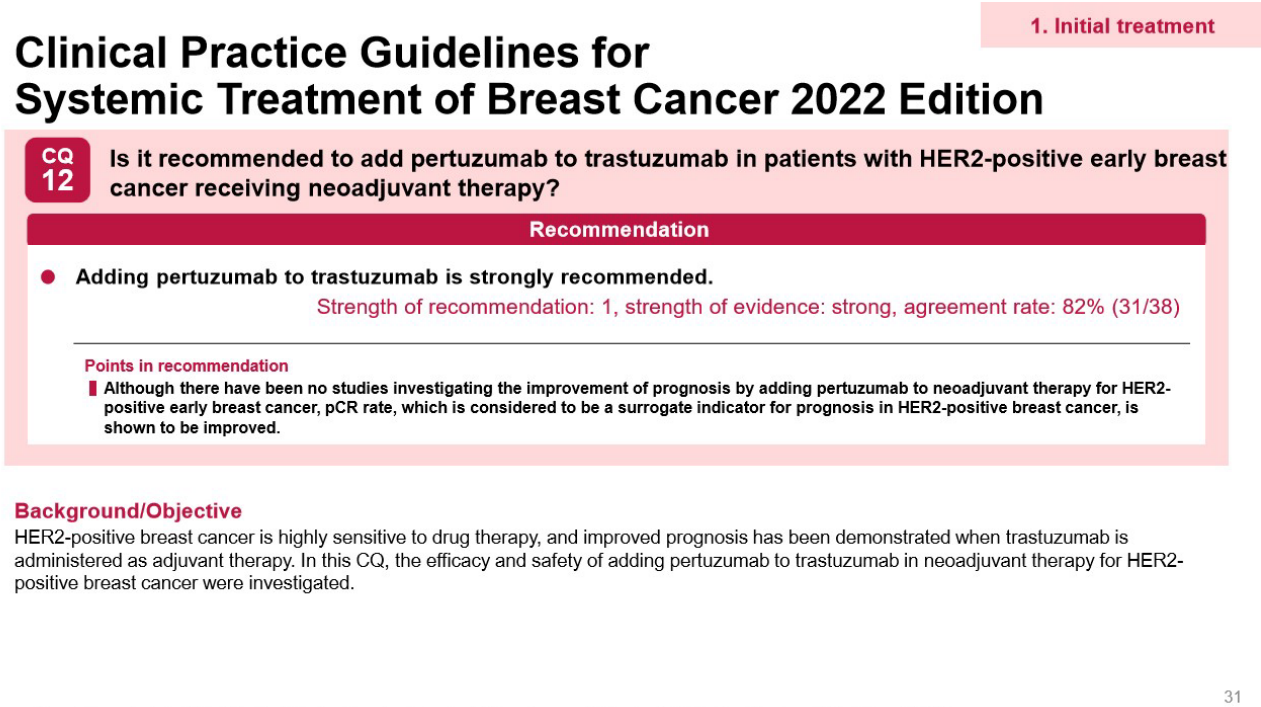
HER2-positive breast cancer, the subject of today's discussion. The upper group is the perioperative treatment, that is, those who are willing to do surgery and anticancer drugs because they have a high chance of being cured.

The orange shows the stage IV, so-called metastasis or recurrence. Basically, these are people who are difficult to cure, so for them, the standard of care is HERCEPTIN, PERJETA, and chemotherapy, and these three drugs are always used. If it stops working, it will be changed to other drugs.

Next is perioperative treatment for so-called early-stage breast cancer. If the patient can be operated on, surgery is performed first, or as neoadjuvant therapy, HERCEPTIN, PERJETA, and chemotherapy is given before surgery.

During neoadjuvant therapy, all patients with HER2-positive breast cancer are basically treated with HERCEPTIN and PERJETA. After surgery, patients continue to use Herceptin and Perjeta for nine months, once every three weeks. If a lot of cancer remained, the treatment of choice was to switch to a different drug, Kadcyla, to further improve the prognosis for those who had originally seemed to have a poor prognosis.

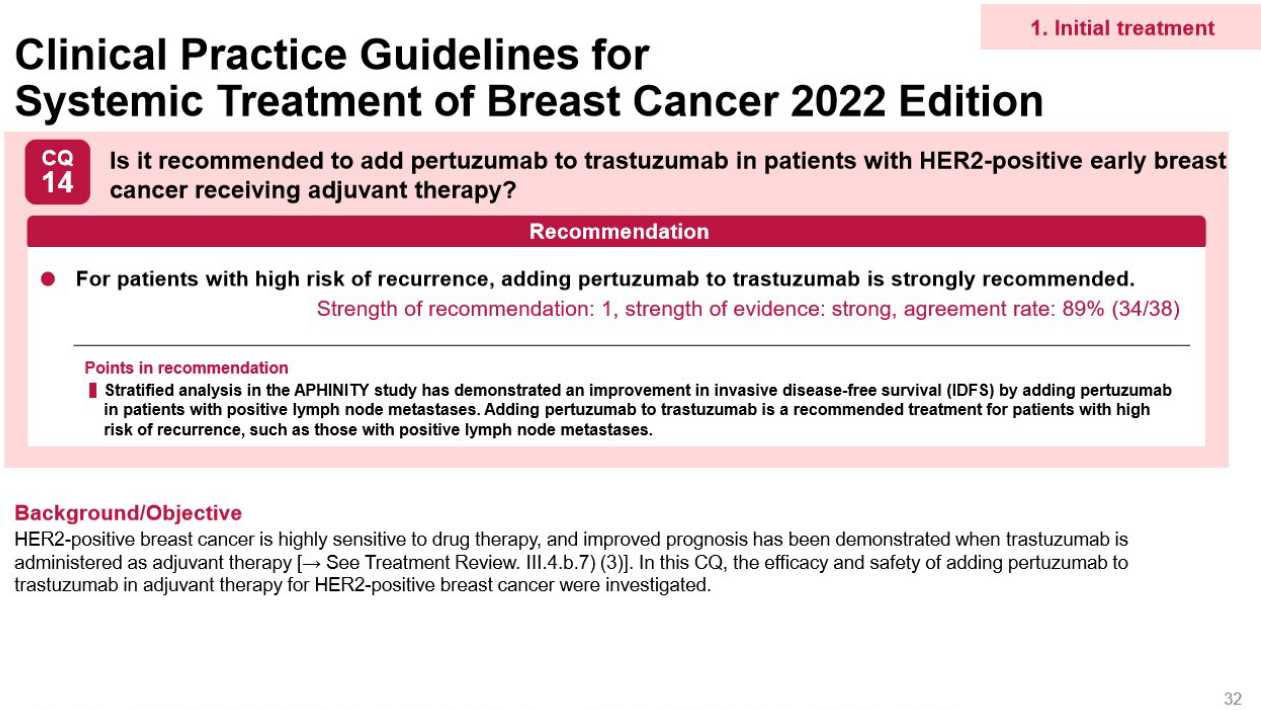
If surgery is done first, then Herceptin and Perjeta and chemotherapy is used. In any case, HER2-positive breast cancer, as I mentioned earlier, the anti-HER2drugs are very effective, and if that is the case, the principle is to do a combination of anticancer drugs. After that, Herceptin and Perjeta will be used.



Treatment is based on evidence-based guidelines, and we basically follow them. There is CQ12, clinical question, number 12, in the most recent breast cancer treatment guideline.

This is a question as to whether the addition of trastuzumab and pertuzumab, or HERCEPTIN and PERJETA, to HER2-positive early-stage breast cancer with neoadjuvant therapy is recommended. Basically, the addition of trastuzumab-pertuzumab is strongly recommended in the guideline. Recommendation is determined based on the strength of the evidence, but the strength of the recommendation is also consistent and the strength of the evidence is also strong.

In the past, there was a time when trastuzumab was used alone, but there is now clear evidence from clinical trials that it is more effective than trastuzumab alone, so basically, both are used.



Another question is about neoadjuvant therapy, for those who had surgery first. It says whether it is recommended to add pertuzumab to trastuzumab for these people, but if the risk of recurrence is high, there are firm guidelines recommending the use of both for these people.

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."

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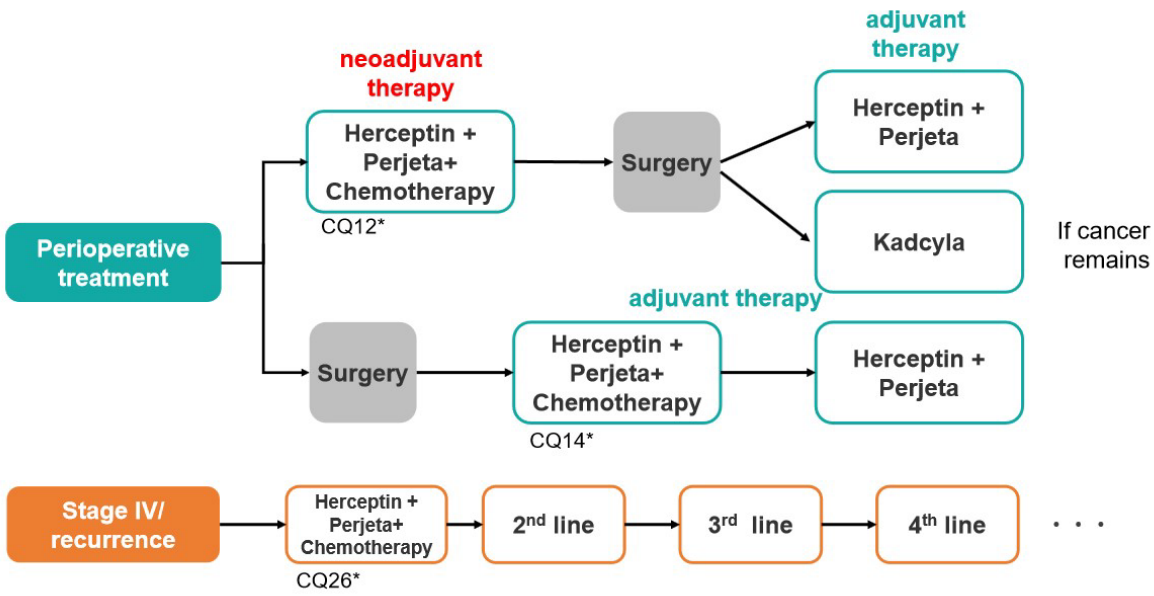
Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition, Kanehara & Co., Ltd., pp204 -208

Another one, this one is metastatic or recurrent breast cancer. For this group, the purpose of treatment changes a bit. As I mentioned earlier, the possibility of cure is very low, so the principle of treatment for metastatic and recurrent breast cancer is to control the disease, minimize progress, and improve the quality of life.

The evidence is strong that the combination of trastuzumab, pertuzumab, and taxane should be used as the first choice.

Clinical Positioning of Herceptin + Perjeta



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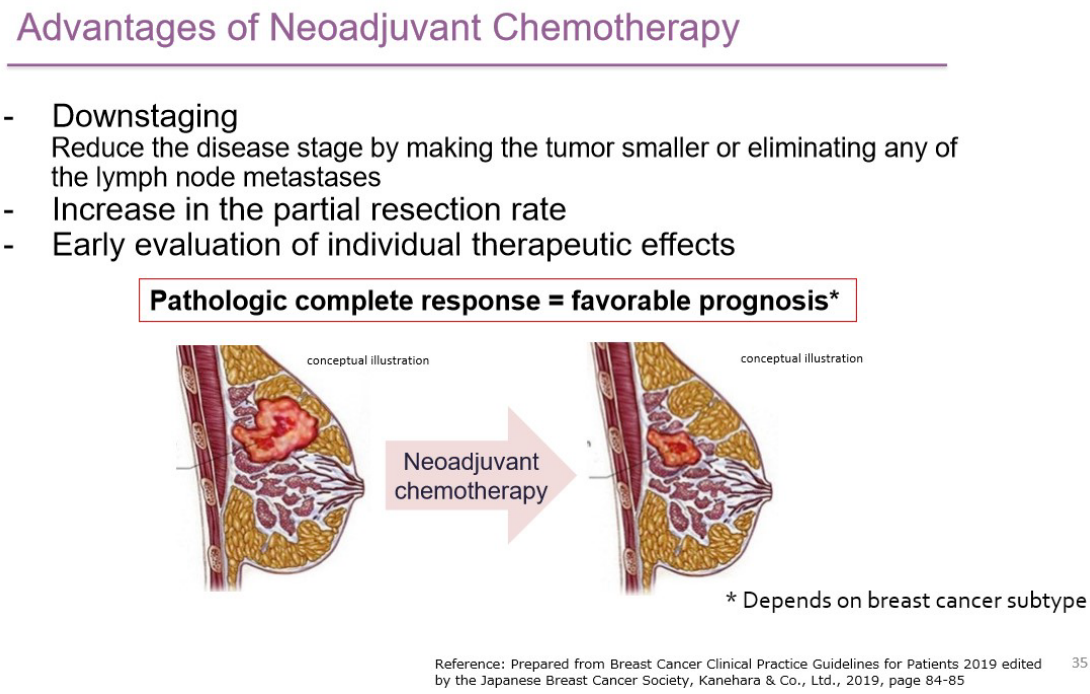
*Japanese Breast Cancer Society: Clinical Practice Guidelines for systemic treatment of breast cancer (1) Treatment, 2022 edition

This is the table we saw previously. Thus, as I mentioned, neoadjuvant therapy is often the first choice for HER2-positive breast cancer, especially if the cancer is a little advanced or of a certain size.

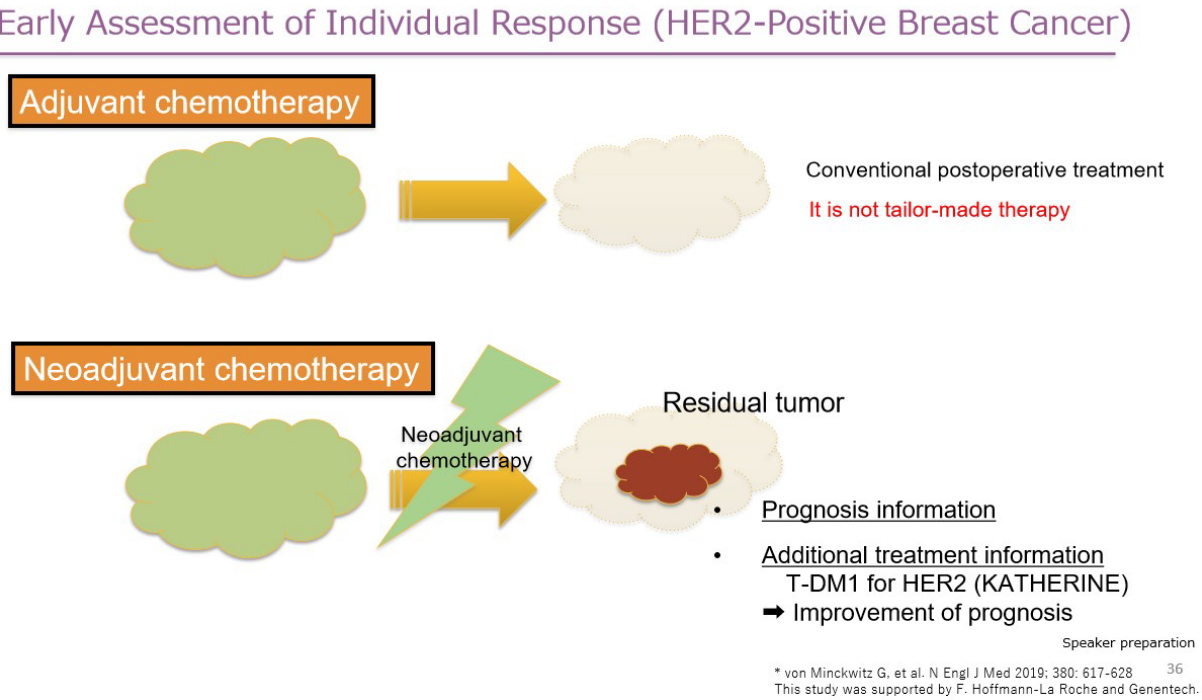


The reason for this is that neoadjuvant therapy and adjuvant therapy had been said to have the same prognosis in the past, but now, if neoadjuvant therapy is given first, it is possible to downstage the tumor to make it smaller and to eliminate lymph node metastasis once it is smaller. Not all cases, but it is more likely. This will still improve the prognosis. If it disappears completely, it is a sign that the prognosis is already good.

In addition, the smaller size means that there is a greater chance that what was originally told to perform a total resection can be reduced to a partial resection. The most major advantage of neoadjuvant therapy recently is that it allows early evaluation of individual treatment effects.

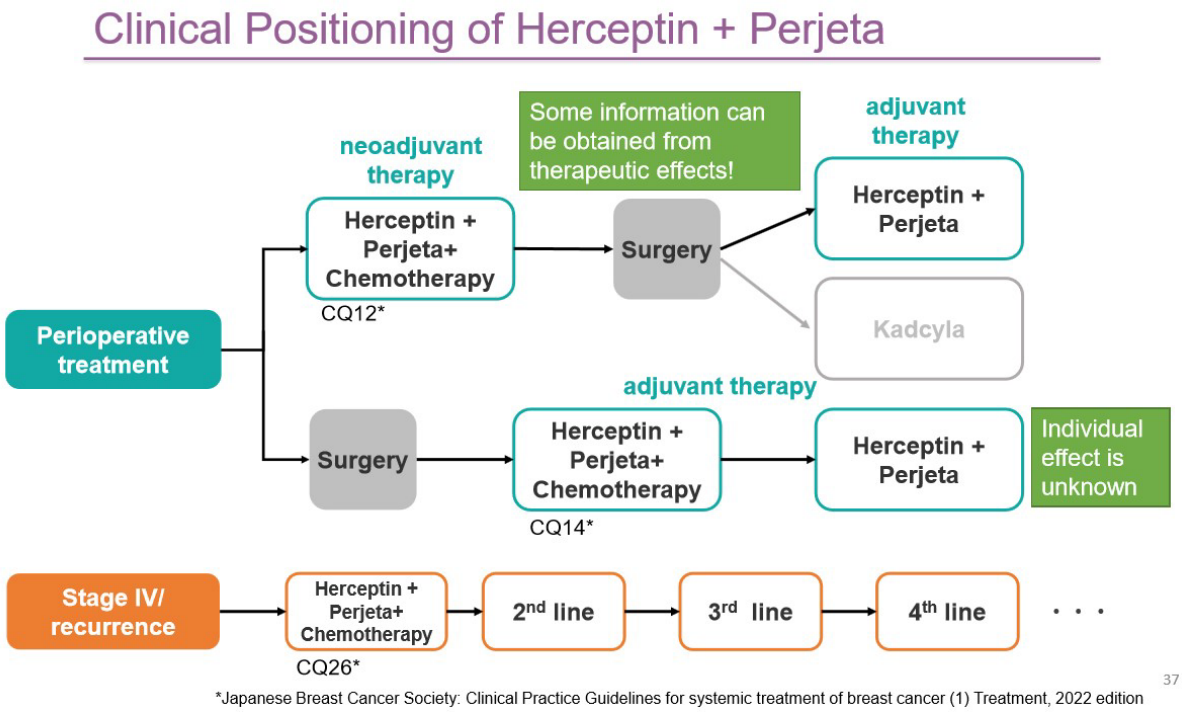
As I mentioned earlier, if you use it after surgery we say we should do it because the people who did it have a better chance of coming in healthy than those who didn't, but you don't know which group the patient belongs to.

If we give them neoadjuvant therapy, the cancer is there and we can see if it gets smaller or not. If it worked, then PERJETA and HERCEPTIN can be used as is after the surgery. If the drug was not very effective and the cancer remained, as I mentioned earlier, we can switch the adjuvant therapy to a drug called KADCYLA.

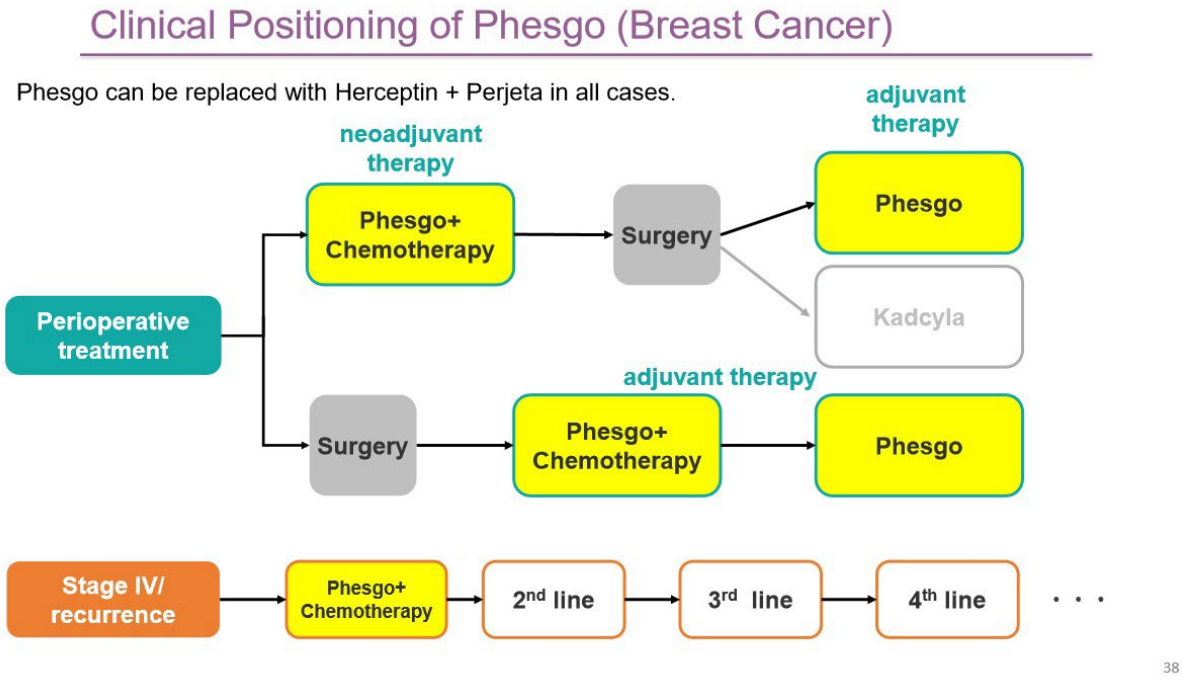


As you can see in the picture I have just described, the adjuvant therapy, the cancer indicated in green, is removed for the time being. Then, after that, we will try to do a certain standard medicine for the time being, and it will not be so-called tailor-made treatment.

In the case of neoadjuvant therapy, an anticancer drug is given and if the cancer is still there, there is information about it, so we can now offer options to further improve the prognosis of those who may have had a poor prognosis in the first place, such as switching the drug.



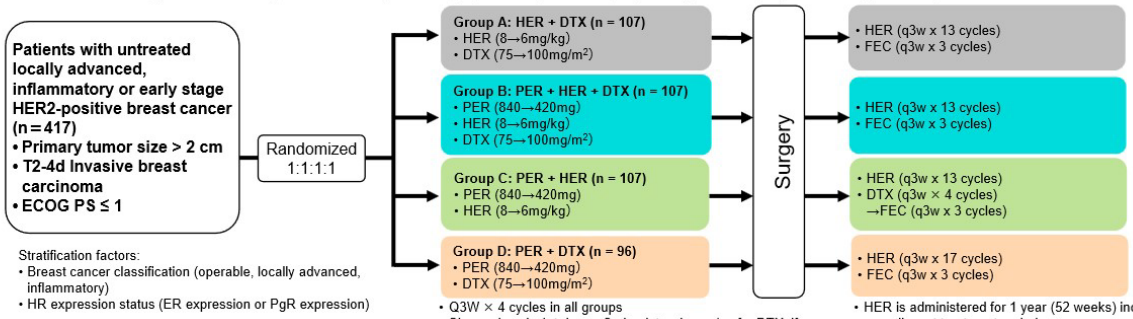
Today, we will leave aside KADCYLA for those who have this little bit of cancer left, HERCEPTIN and PERJETA, those who used it first before the surgery can basically use it after the surgery as well, and of course it can be used after the surgery. Also, in stage IV, of course, both drugs are always used in the first line, so HER2-positive breast cancer is basically based on the use of these two drugs.



Then, this time, it is PHESGO, and this clinical positioning, as we call it, means that everywhere, everything can be turned into PHESGO. It does not mean that it must be used only after surgery or only before surgery. We believe that all are likely to be replaced in the future.

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/m² + Epirubicin (EPI) 90 mg/m² + Cyclophosphamide (CPA) 600 mg/m² → 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.

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I have just said that this drug, PERJETA and HERCEPTIN, is very effective, very effective, but I am saying this based on clinical trials, not on my own experience.

There is a landmark study, the NEOSPHERE trial, in which HER2-positive breast cancer patients are divided into four groups and four drug combinations for surgery. We have solid data on how well it worked.

Group A is HERCEPTIN, the single agent we had been using for some time, and DTX is docetaxel, a taxane anticancer drug. This is what we used. Group B is now the standard therapy with all three drugs. And group C is PERJETA and HERCEPTIN without chemotherapy. Group D consists of only PERJETA and docetaxel. These are followed by surgery.

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)

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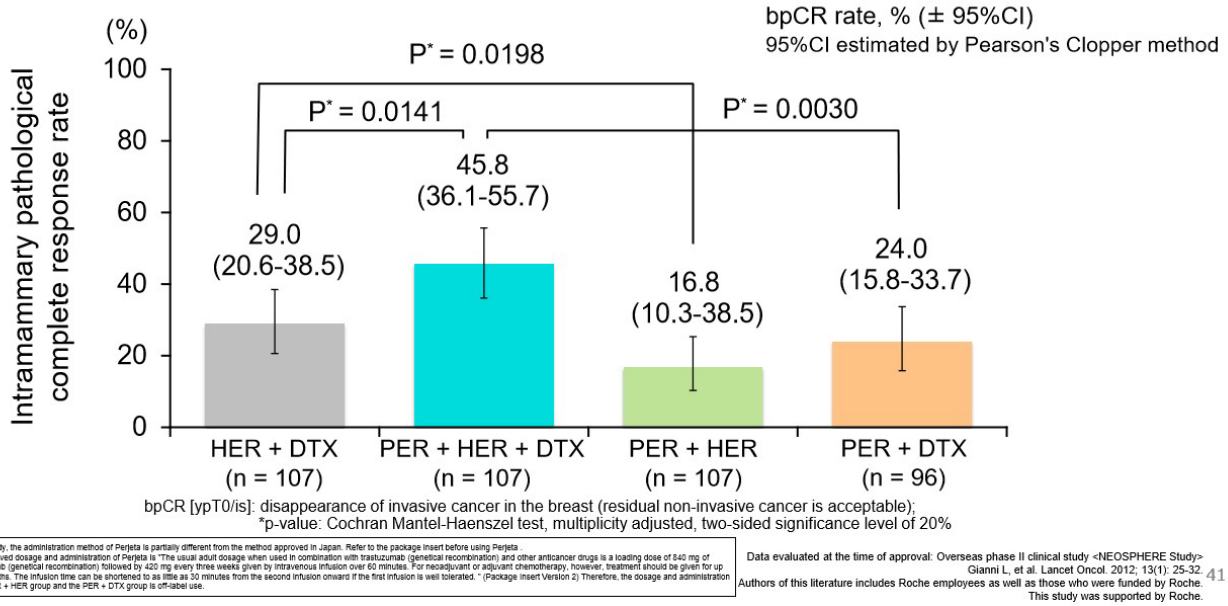
This is the primary endpoint of the study. A trial is designed first based on its primary endpoint, so this primary endpoint looks at the complete response rate of the breast cancer in terms of pathology after surgery, that is, how much of the tumors has completely disappeared.

The secondary evaluation is the best overall evaluation, such as the degree of effectiveness, the degree of preservation, the prognosis, and safety.

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%

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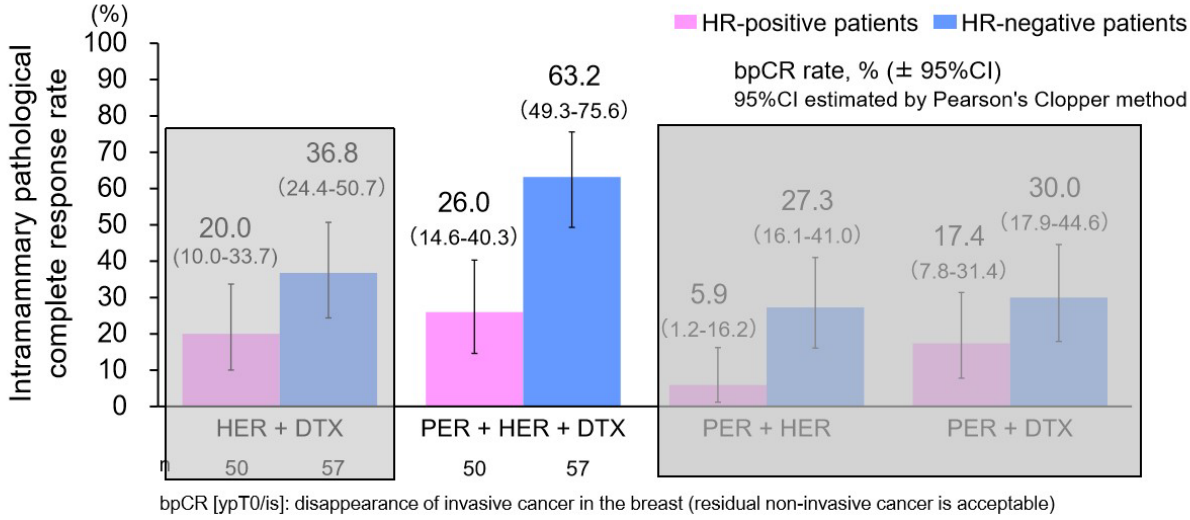
Then looking at the data for the three drugs group in the bar chart, second from the left. The rate of complete disappearance was clearly higher with docetaxel; PERJETA,HERCEPTIN and docetaxel. The results show that the number was statistically significantly higher. It was 45.8%.

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)

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As I mentioned earlier, as the analysis based on subtypes, subtypes are divided by hormone receptor-positive and hormone receptor-negative, and we know that the effectiveness of treatment differs depending on these subtypes. The blue bars are the types with negative hormone receptors. Everything is HER2 positive this time, so if the hormone receptor is negative and HER2 is positive, this is the second from the left, the graph without gray on it. Then, as far as that group is concerned, the percentage that cancers disappear completely is already 63%. The data is high, with 26% of hormone positives, cancer disappeared completely.

The other combinations are grayed out, but the data clearly show a higher probability of PCR, complete disappearance rate.

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

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

Talking about adverse events, these side effects were the highest.

We can see the data due to only with HERCEPTIN or PERJETA for HER2 positive breast cancer. Especially since diarrhea is a characteristic side effect of PERJETA, which is the fifth from the top. The group using PERJETA clearly showed an increase in diarrhea. Other than that, nothing is that remarkable.

The Importance of Considering Time Toxicity

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In this clinical trial, I was wondering what was important in introducing this PHESGO. As the previous speaker mentioned earlier, there is a concept of time toxicity recently. Cytotoxicity includes blood toxicity of blood cells and toxicity of the gastrointestinal tract, and treatment with anticancer drugs have been developed day by day to prevent such toxicities.

In terms of controlling various toxicities, I think it is a very important issue to consider time toxicity and to do it with the same effect, even if only a little better treatment.

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.

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These are the issues with the current medical situation here in Japan. This is not only true in Japan, but as shown in the previous graph, breast cancer rates increase dramatically from the late 30s, with the first peak occurring in the 40s. The fact that breast cancer is increasing among people in their 60s and 70s means that many breast cancer patients are in the working-hard generation, and the patients in the first peak, they are raising children, caring for their parents, going to the hospital, commuting to work, and all the other things that make up the physical strength of a person with breast cancer, which is a burden on them.

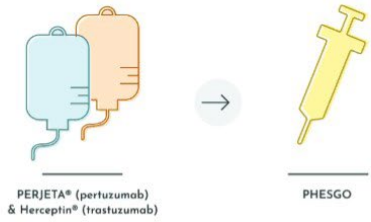
Waiting time for medical treatment, especially when treated in a large hospital. As we are also aware in our outpatient clinic, the patients have to wait for a long time before they meet doctors, and they also have to wait for the blood to be collected before consultation and for the results coming out. The time required to see the doctor, go to the infusion room, wait for the infusion, and then do the infusion, is really half a day to a full day, which is very burdensome for the patient. This also naturally increases the burden not only for patients, but also for medical professionals.

Nowadays, the outpatient chemotherapy room is like an infusion center or an oncology center, with a separate room for infusion, where anticancer drugs are often administered, but the number of breast cancer patients is increasing. Since anti-cancer drugs are being used more and more not only for breast cancer but also for other digestive organs, chemotherapy rooms in all large hospitals are really crowded.

Especially with this HER2-positive breast cancer, we use three drugs, the anticancer drug I mentioned earlier, PERJETA and HERCEPTIN, so we have to keep a very long time frame for the infusion. This also requires a lot of manpower, including doctors, nurses, and pharmacists, who mix the medicines in a highly blended manner, which takes a lot of time. That will still cost labor costs.

Therefore, PHESGO will shorten the administration time per dose, which may contribute to improving the quality of life of patients and the burden on healthcare professionals.

De-escalation for Time toxicity



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

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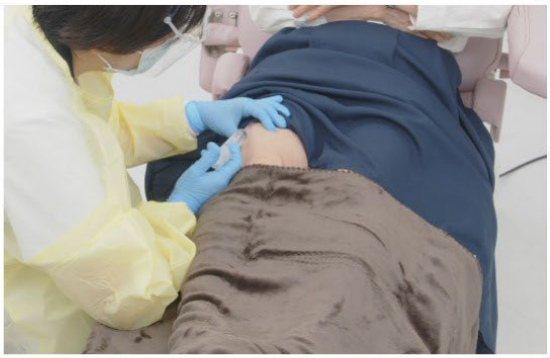
As the previous speaker mentioned earlier, the first injection takes eight minutes, and the second and subsequent infusions take five minutes, which is very short.

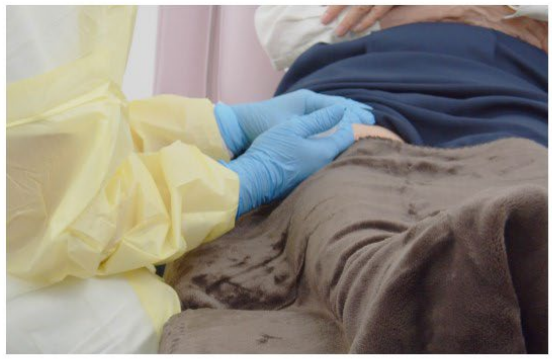
Administration method of PHESGO combination for SC injection

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

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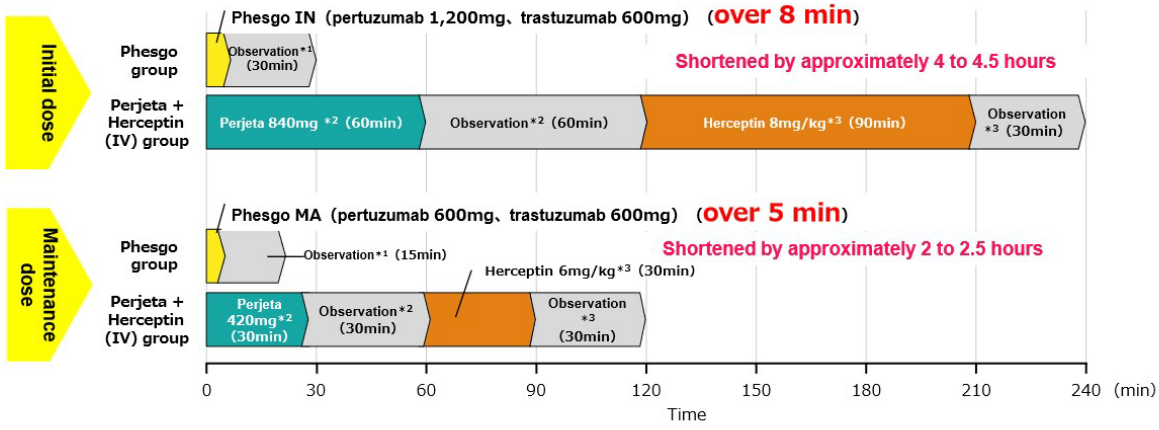
As an example, an injection should be administered for eight minutes, so we inject into the leg it is placed in the thigh for a while in the same posture. The injection site would be changed a little, slightly shifted.

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.

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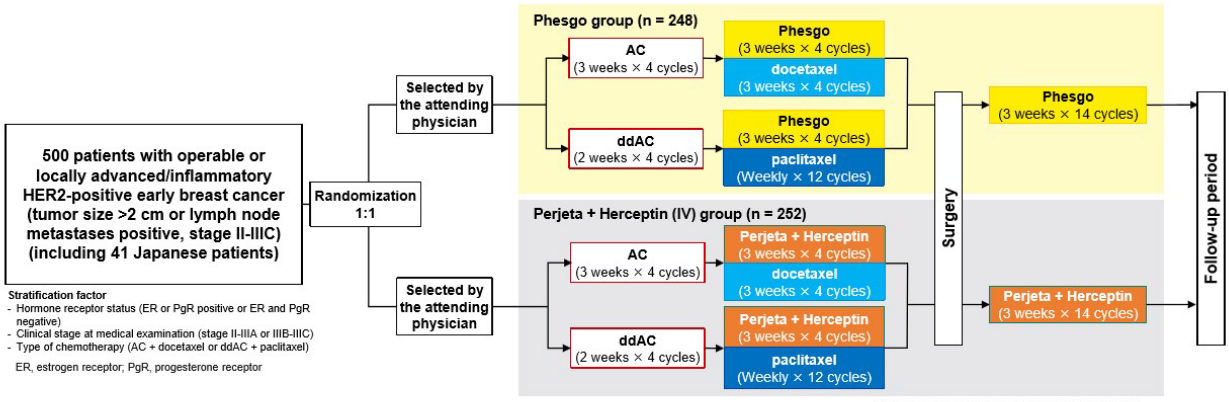
The first dose, the top figures, is PERJETA and HERCEPTIN, the IV group is the traditional infusion that we are using now.

This is the PERJETA, to be administrated for 60 minutes first and watch the progress for 60 minutes. HERCEPTIN treatment is given for 90 minutes and the follow-up observation, but if it turns to eight minutes of treatment and 30 minutes of observation, the time will be reduced by nearly four hours, which is a great advantage from both the patients and the medical professionals' point of view.

The second time, the infusion itself is already shorter, but the PHESGO takes still only five minutes, and the follow-up observation is even shorter this time, so the time required for the second infusion is reduced by almost two hours.

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



[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.
This study was supported by F. Hoffmann-La Roche and Genentech.
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This is not to say that it is good because injections have shortened the length of time, but evidence is still needed to change the standard of care, which is why we have this international phase III trial called FeDeriCa. For operable or locally advanced HER2-positive breast cancer, anthracycline and a combination of two anticancer drugs, docetaxel and paclitaxel, is used.

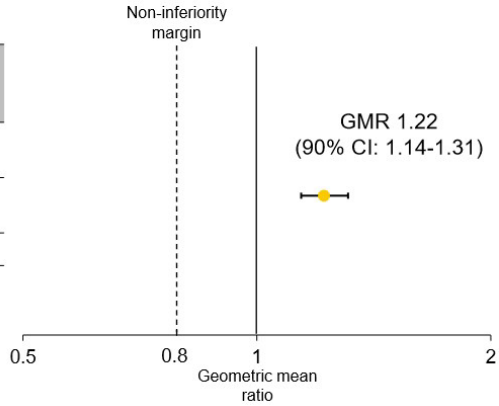
PERJETA and HERCEPTIN, the lower one, the one we usually do on the IV switched with PHESGO, the upper one. And after the surgery, we usually use PERJETA and HERCEPTIN for another nine months, so it is something where we will completely replace that with PHESGO and see which one is better.

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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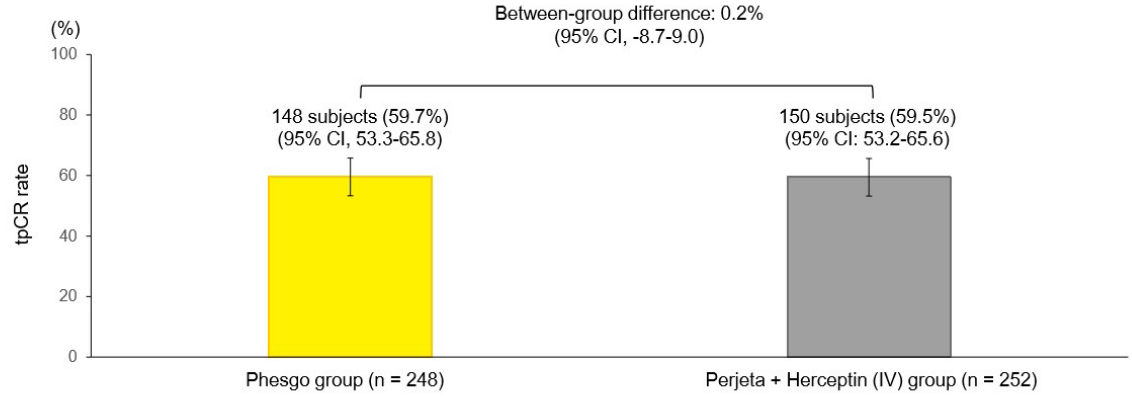
Since the blood concentration is important for how well the drug works, the blood concentration was measured at the point before seven or eight cycles of administration as the primary endpoint. The results showed that the blood levels of PERJETA and HERCEPTIN were similarly maintained in PHESGO, indicating non-inferiority.

Global Phase 3 Clinical Study: WO40324 Trial (FeDeriCa Study)

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

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Also, as a secondary endpoint, we are looking at the percentage of absence of invasive lesions in the breast and axilla.

The yellow on the left side is the PHESGO group, and the right side is the PERJETA and HERCEPTIN infusion group, and the results were comparable in that the same tpCR of just under 60% was obtained, and complete disappearance was obtained.

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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There is some data on adverse events.

As I said earlier, PERJETA is characterized by diarrhea, so it is the same, 58%, 55% respectively. There are other events that are out there, but these are used in conjunction with anti-cancer drugs.

The most characteristic adverse event is the one called infusion-related reaction at the bottom of the right-hand side. When PERJETA and HERCEPTIN are injected for the first time, the body is surprised and shows such a reaction. For example, there are some changes such as sweating or a drop in blood pressure, which are 13% or 14% with intravenous infusion, but with subcutaneous infusion, the sudden increase in blood concentration can be suppressed, and the PHESGO group came out at 3.6%, a lower value by comparison.

The fifth item from the top on the right shows the injection site reactions, which were almost none in the intravenous infusion group, but the same percentage of patients in the intravenous infusion group showed symptoms such as redness and swelling in 13% of the cases.

Global Phase 3 Clinical Study: WO40324 Trial (FeDeriCa Study)

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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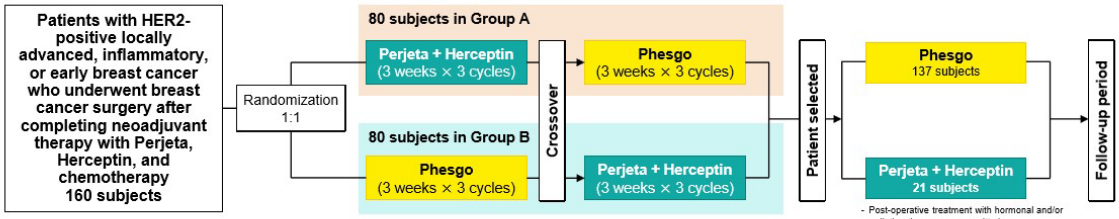
There are the adverse events leading to discontinuation of any investigational drug ordeath.

The discontinuations were 6.9% for PHESGO and 10.9% for infusion, and all of the events that came up were in one or two cases or so, but we believe that this was originally due to the drug, and there was no significant difference. Rather, the group of discontinuations was a bit small.

Overseas phase II clinical study: MO40628 study (PHranceSCa study) (overseas data)

Study Summary



[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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Another trial, the PHranceSCa trial, is also being conducted overseas to see how patients actually feel about it.

Likewise, the patients with PERJETA and HERCEPTIN in green is the intravenous drip. PHESGO, this subcutaneous injection, and they will experience both of them in a crossover. The trial is a very interesting design, in which patients are asked to choose which of the two they would like to use at the end.

Overseas phase II clinical study: MO40628 study (PHranceSCa study) (overseas data)

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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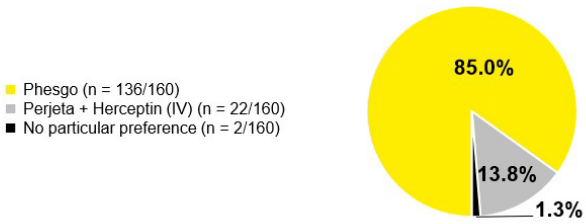
The primary endpoint is the patient's preference for PHESGO, the ratio of choosing PHESGO as a good choice, and so on.

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)
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Looking at this, first of all, the pie chart shows that 85% of the respondents chose that PHESGO was better. In fact, people may be surprised at first at the thought of injecting subcutaneously for five or eight minutes, but many patients who have actually tried it have also responded that they prefer PHESGO.

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)
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We are also looking at other surveys to see how healthcare professionals see the drug.

The data also showed that more than 85% of the respondents, such as nurses and pharmacists, said they would have preferred PHESGO even if they considered preparation, etc.

Overseas phase II clinical study: MO40628 study (PHranceSCa study) (overseas data)

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

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.
This study was supported by F. Hoffmann-La Roche. The literature includes authors who received funding from F. Hoffmann-La Roche or Genentech or employees of F. Hoffmann-La Roche or Genentech.

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Also, since we are doing both in crossover, we also see adverse events, Grade 3, which are side effects leading to further postponement of the drug. It also appears that neither of those percentages changed in either case.

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.

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To repeat what I said earlier, the fact that the time required for infusion and treatment can be shortened is a great benefit to the medical personnel, and the hospital, as well as to the burden on the patient. It's the patient's quality of life, collectively. It is expected to contribute to the improvement of the burden of 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.

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In any case, patients in this early stage must be treated to maintain their quality of life while aiming for proper radical cure. The metastatic-recurrent patients also need to maintain quality of life while aiming for high therapeutic efficacy.

The PHESGO may contribute to improving the quality of life of patients and the burden of medical care by shortening the duration of a single dose.

As the term "shared decision making" has recently become popular, patients are given a clear explanation based on their wishes and conditions, and then they choose what they prefer. This applies to all treatments, so we are treating patients based on this principle.

That is all for today. Thank you.

Miyata: Thank you very much.

Question & Answer

Miyata [M]: We will now move to the question-and-answer session.

We apologize for the inconvenience, but in order to encourage more people to ask questions, we would appreciate your cooperation in limiting the number of questions to two per person.

Please note that the audio of your questions, along with the presentation, will be posted on our website at a later date.

Sakai [Q]: Thank you for today. I'm Sakai from UBS Securities. I would like to ask one question each to Mr. Habara and one to the doctor.

The drug price for PHESGO this time has been decided, but basically in Japan, I don't know if we can call this a combination drug or not, but I think there was a rule of one plus one to be 1.8 in the process of deciding the price. First of all, I would like to know about the process of determining this price.

Naturally, with the release of this PHESGO, I think that the sales of PERJETA and HERCEPTIN will decrease by cannibalization, but what is the profitability for your Company, how should we think about this first of all?

Habara [A]: Thank you for your question, Mr. Sakai. First, regarding the drug price process, in the drug price rules, in the article for the special calculation of new medical combination drugs, there is an exemption requirement for combination drugs that have demonstrated medical benefits to be exempt from the special calculation.

As you can see from the Chuikyo materials, the discussion at the Chuikyo, especially regarding PHESGO, was based on the combination with vorhyaluronidase and the fact that breast cancer patients, especially those with high medical needs, as Dr. Hayashi explained earlier, have high needs in terms of time. We recognized that this specific combination had been highly evaluated for its medical benefits.

As for cannibalization, as Dr. Hayashi explained, we are hoping to replace the intravenous formulation. From my perspective as a manager of lifecycle management, when we think about the lifecycle of this product as a franchise over the long term, we have decided to introduce it to the market not only for the benefit of patients, but also for the benefit of the Company. That is all.

Sakai [Q]: Thank you very much. Listening to Dr. Hayashi, I think this will be a pretty rapid switch in the medical field. In the U.S. and Europe, the switch has already been quite rapid, and I think this comes straight out when you look at Roche's sales. In your personal opinion, or in your thinking, do you have a timeline as to what percentage of the current use of PERJETA and HERCEPTIN would be switched over to the new use?

Hayashi [A]: Thank you. As I mentioned earlier in the first picture, I changed all the PERJETA and HERCEPTIN to yellow PHESGO in the picture, but theoretically I think we could change all the cases.

Rather, the fact that the probability of Infusion reaction is greatly reduced by subcutaneous infusion is very reassuring to healthcare professionals when they administer the infusion. So, we would rather use it in actual clinical practice to reduce adverse events and, as I said earlier, to reduce the infusion quota. This will have the advantage of allowing us to turn things over to other people more quickly, and also allow us to be a little more

flexible in areas such as the time when a patient could not get the time frame they wanted, since we will be holding back a lot of frames. So, everyone would like to introduce this as soon as possible.

As for the actual time frame, we are just now beginning to be able to use it. When I say as soon as possible, I mean that each hospital has a drug committee, which must first approve the drug, obtain approval, and then introduce it, although the speed varies from hospital to hospital. That's a lot of hospitals that are already starting to move, everywhere within a few months. The same is true of ours.

However, there is also the problem of manpower at the point of changing to something new. First of all, I think it will take a few months to change everything out of the blue, because there is still some familiarity, but I think that many and most things will really change in less than a year or so. Or rather, we hope to do so.

Sakai [M]: Thank you.

Kono [Q]: My name is Kono from Jihosha. Thank you very much for your presentation today.

I would like to ask Dr. Hayashi, what is the timeline for the HERCEPTIN and PERJETA in the current guidelines to be changed to PHESGO in the guidelines?

Hayashi [A]: The guidelines are basically revised every two years. It was 2022, right? However, we will continue to revise the newer ones that need to be revised little by little even within a year, so they may be reflected in next year's guidelines as soon as possible, but the wording in the PERJETA and HERCEPTIN sections is there and they are basically the same drug, we will have to discuss how to reflect that in the guidelines. We will consider them basically the same drug.

Kono [M]: I see. Thank you.

Takano [Q]: My name is Takano from Mainichi Newspapers. Thank you.

I would like to ask about the results of this clinical trial. In terms of patient preference, you said that 13% of the patients still chose PERJETA and HERCEPTIN. Did you also ask the reason for the choice?

Hayashi [A]: I think we can very much understand the psychology of a dozen percent of the patients, if the medicine is already working very well for them now with the first infusion, they don't want to change anymore. So, I think there are many such people, and although I do not have such detailed data, I think that is probably the situation. I assume that is the biggest reason.

Takano [Q]: What is the reason why some medical professionals, though only a few, still choose the traditional infusion?

Hayashi [A]: As I mentioned earlier, that a subcutaneous injection for a long time, well, five minutes is not a long time but a short time, but to sit still for five minutes, that is a lot of work, some people would think so.

Takano [M]: I see. Thank you.

Yoneyama [Q]: My name is Yoneyama from the Yomiuri Shimbun. Thank you for your presentation today.

I would like to ask the doctor two questions. The first question involves a survey of patients in the same clinical trial. Is there any data available as to why 85% preferred PHESGO?

Hayashi [A]: The time saved is still very significant.

Yoneyama [Q]: I understand. Thank you. In terms of reducing the time required for such improvements, are we seeing progress in this area of cancer drugs as a whole, or are we seeing more and more progress in the future? Would you tell us the trend?

Hayashi [A]: As I mentioned earlier, it would be better if you would move more and more in this direction, because it is a part that is quite burdensome for the hospital as well as for the patients, and we are also developing more and more. So, I think the world will flow in that direction.

There is also a drug called G-CSF, which is used to raise the white blood cell count, which drops dramatically with anticancer drugs, but there is also such a drug, so the world is now moving more and more in that direction.

Yoneyama [M]: I understand. Thank you.

Kondo [Q]: My name is Kondo from Yakuji News. Thank you very much for your presentation today.

I would like to confirm the dosage. It is 60 minutes for PERJETA and 90 minutes for HERCEPTIN, though that is to be reduced to more than eight minutes. Am I correct in understanding that this is the time chemotherapy is included?

Hayashi [A]: For chemotherapy, the chemotherapy time will be added to this time. So, the actual time spent being infused is much, much longer. This depends on the drug, for example, 30 minutes for paclitaxel, or a little longer for the Initial dose, 60 minutes, and so on. So, there is additional time to this, so from an overall perspective, it's quite a big advantage in that sense.

Also, as I mentioned earlier, those who have had surgery will really only be able to use PERJETA and HERCEPTIN, so they will really be able to get a lot of shortening in this area.

Kondo [M]: Thank you very much. **Miyata [M]:** Thank you. Do any of you have any questions? We will then take questions from those attending via Zoom webinar.

If you are participating in a Zoom webinar from a PC, tablet PC, or other device, please click the Raise Your Hand button at the bottom of the screen. We will call your name when it is your turn to ask a question. The office will send you a request to unmute. Please unmute your audio and tell your company name and your name followed by questions. If you wish to cancel to ask your question, please click on the "Hands Down" button.

Mr. Hashiguchi from Daiwa Securities, please go ahead.

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. Thank you. I have two questions. First, I believe HERCEPTIN is supposed to be administered in doses adjusted based on body weight. PHESGO has a fixed dosage as you mentioned today, but is there any possibility that the dosage may be too high for Japanese patients?

Habara [A]: Thank you for your question. The dosage of HERCEPTIN for PHESGO has not been approved in Japan, but a subcutaneous formulation of HERCEPTIN has been approved and launched overseas. The dosage is determined by confirming the PK from IV to SC, etc. set at that time. For PHESGO the dosage for both IN and MA is 600 mg, which is a fixed dosage.

Although a Phase I study for PHESGO has not been conducted in Japan, the IV to SC of HERCEPTIN data from overseas have been presented. Although the dosage of HERCEPTIN is IV in Japan, we do not think that PHESGO

will cause any particular symptoms. I explained such a reason to the health authorities, and they agreed with my explanation.

Hashiguchi [Q]: Generally, with other drugs in other disease areas, I think that if you use the same doses as in the overseas Phase III trials for Japanese patients, sometimes the doses are too high. I was asking if there are any such concerns about this drug.

Habara [A]: No, there is not. As you understand.

Hashiguchi [Q]: Thank you. The second question. If HERCEPTIN has already been converted to a biosimilar, due to the release of PHESGO, is it conceivable that it will also be converted to PHESGO?

Is there a case where a patient who is currently using a completely different therapy than the HERCEPTIN/PERJETA combination would choose PHESGO, or is it basically a replacement for the HERCEPTIN/PERJETA or Trastuzumab/PERJETA combination therapy?

Hayashi [A]: Basically, many hospitals are using biosimilar now, but if they are going to use 2 drugs together, they will replace them with PHESGO as well. Basically, I think it is a form of replacement for those who need to use two drugs now.

Hashiguchi [M]: Thank you very much. That's all.

Miyata [M]: Thank you. Next, Mr. Yamaguchi from Citigroup Global Markets, please go ahead.

Yamaguchi [Q]: Thank you very much. I'm Yamaguchi from Citigroup Global Markets.

I have one question, which is a little bit overlapping with the previous question. Time toxicity is exactly as you say. On the other hand, financial toxicity is also quite a hot topic. Just a minor point, but if a patient who is taking trastuzumab biosimilar and pertuzumab together switches to this one, will the medical costs go up a bit for that patient?

Habara [A]: Yes. As you understand. Currently, there is a price difference between the original HERCEPTIN and trastuzumab BS, and as you understand, that amount will be added to the patient's cost.

Yamaguchi [Q]: I understand. Still, since there is tremendous convenience to the field, or rather to the patients, do you feel that the reduction in time toxicity greatly outweighs the financial toxicity?

Hayashi [A]: I think the benefits are great.

Yamaguchi [Q]: I understand. Thank you. One more thing, you explained to us how to administer this. Currently, patients will be sent to infusion centers, or rather, the patient will be asked to go there. In this case, is it correct to say that the injection will be given by a nurse at the treatment site, and that the location where it is given will change?

Hayashi [A]: Basically, first of all, many hospitals will start doing it at the oncology center, the infusion center, where they do infusions.

Yamaguchi [Q]: So, you mean the patients are going over there to do it.

Hayashi [A]: Yes.

Yamaguchi [M]: I see. I understand.

Hayashi [A]: For example, in the case of Taxane and PERJETA and HERCEPTIN, two long frames had to be reserved, but now only one frame is needed, or a shorter frame will be newly created and used, this is what we are talking about.

Yamaguchi [Q]: So, it is naturally shorter and therefore more efficient?

Hayashi [A]: That's right.

Yamaguchi [M]: I understand. Thank you. That's all.

Miyata [M]: Thank you. Next, Mr. Idaka, please go ahead.

Idaka [Q]: This is Idaka from Yakushin Plaza. Thank you for your presentation today.

I listened to your presentation today, and I recognized that it is just a phenomenal reduction in the administration period. I am afraid I am confirming a basic point, but am I correct in understanding that the switch from intravenous infusion to subcutaneous infusion brought the most significant effect of this part of the changeover, and that this is the reason for this kind of breakthrough?

Hayashi [A]: That's right. I think that is the most significant key point. This is a molecular-targeted drug, which is a bit different from ordinary cytotoxic drugs, so I think it worked well in that sense.

Idaka [Q]: Thank you very much. And one more thing, and this is a bit of a big deal, but I'm sorry to ask about a cross-department question. The main topic of this session was HER2 positive breast cancer. In the case of colorectal cancer, the drug is supposed to be administered to patients who cannot be removed by surgery, but I am aware that the guidelines require drug treatment for breast cancer, whether or not surgery is performed.

In the layman's view, if the surgery is done well, then the subsequent drug treatment is not necessarily necessary, but is this part of the treatment inevitable in breast cancer?

Hayashi [A]: This is already past history, since there were data on the situation where only surgery was performed without anticancer drugs. Of course, the stage of the disease and the degree of progression will vary, but even if you think you have already taken care of the problem, the disease will still recur.

In particular, HER2-positive breast cancer was a cancer with a very poor prognosis before HERCEPTIN was introduced. At that point, at the time of diagnosis, we already knew that there were micrometastases, as I mentioned earlier, small portion of cancer cells buried in the blood or lymph, which eventually turned out to be a bad result later.

Therefore, even if we think that surgery has already removed the cancer at the time of diagnosis, there is solid evidence that the use of anticancer drugs and these anti-HER2 drugs together improves the prognosis, so we are performing both in this way for breast cancer. So systemic treatment, surgery, and local treatment.

Cancer behaves quite, if anything, totally differently depending on the types, and such a form of treatment is now the standard of care for breast cancer.

Idaka [Q]: I see. I think that surgical techniques vary considerably from doctor to doctor, although it would be a misnomer to say considerably, but is it correct to say that any doctor is now absolutely required by the guidelines to provide adjuvant treatment after performing surgery?

Hayashi [A]: You are quite right. For example, if the tumor is only 5 mm in diameter, the risk is very low, so of course, not even administering anticancer drugs is an option, but it's not easy to find cancer that small, so we do it in normal cases.

In terms of surgery, there may be a certain range, but there is a standardized procedure, plus systemic treatment, so that it can be used anywhere and the same therapeutic effect can be obtained anywhere. We are providing treatment based on such evidence and clinical trials.

Idaka [M]: Thank you very much.

Miyata [M]: Thank you. Next, Mr. Mamegano from BofA Securities, please go ahead.

Mamegano [Q]: My name is Mamegano from BofA Securities. Thank you.

I would like to ask the doctor one question. In the area of time toxicity, you mentioned that the time will be considerably shortened this time and that the replacement will proceed quickly. I wonder if there are people who do not want to administer PERJETA and HERCEPTIN with concomitant use so far because it takes a long time or something. Basically, looking at the evidence, I think we should use it in all cases. I would like to ask how many patients are not using it due to patient's intention or other reasons.

If there are such patients, I was wondering if there will be additional expansion with the release of PHESGO this time around, so let me ask a question. Thank you.

Hayashi [A]: Realistically, there is basically no patient not to use because of time as a reason. Conversely, we know that the prognosis will be considerably worse if it is not used, and we will use it after carefully discussing this with the patient.

However, if you ask me if there is someone or not, of course there may be such people in the world. Then there are those who are tremendously low-risk. There are some people who prefer to use HERCEPTIN alone, so a certain percentage of them continue to use HERCEPTIN or use biosimilar of HERCEPTIN that they are currently using.

Mamegano [Q]: I see. Thank you. I have one more question. If you have early-stage breast cancer and it recurs after using the combination of PERJETA and HERCEPTIN, I'm wondering if it might not work if you have already used it once. Am I correct in my understanding that it is normally used even in a case of progression and recurrence?

Hayashi [A]: This is still a very new area of evidence, but if PERJETA and HERCEPTIN no longer work, there are several other options that can be used. And then, if you are wondering whether you should use two drugs the next time you run out of hands again, new data from a Japanese clinical trial group recently showed that even if you use both drugs the second time, compared to a group that only uses HERCEPTIN , the data also show that it may be better to use two drugs.

Mamegano [M]: I see. Thank you.

Miyata [M]: Thank you. As there are no further questions, this concludes the question and answer session. If you have additional questions, please contact the public relations and investor relations department separately. The phone number and email address are provided on the last page of the presentation materials.

Thank you for joining us today despite your busy schedule. Thank you very much.

[END]

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