PHESGO®

pertuzumab/trastuzumab/hyaluronidase-zzxf

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

COMBINING THE ANTIBODIES YOU KNOW IN ONE FASTER MODE OF ADMINISTRATION[1,2]

PHESGO—a fixed-dose subcutaneous formulation with PERJETA® (pertuzumab) and trastuzumab that's administered in **~5 minutes.***[1]

*Refers to actual PHESGO injection time of ~5 minutes for the maintenance dose. **The loading dose is ~8 minutes.** This does not account for observation time and other aspects of treatment. Actual clinic time may vary.[1]

PHESGO is FDA approved for all the same HER2+ breast cancer indications as PERJETA.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) state that pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use **(PHESGO) may be substituted anywhere that IV pertuzumab (PERJETA) + trastuzumab are given** as part of systemic therapy for HER2+ breast cancer.†[3]

Indications

Early Breast Cancer

PHESGO® (pertuzumab, trastuzumab, and hyaluronidase-zzxf) is indicated for use in combination with chemotherapy for

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer (EBC)
- the adjuvant treatment of adult patients with HER2-positive EBC at high risk of recurrence

Select patients for therapy based on an FDA-approved companion diagnostic test.

Metastatic Breast Cancer

PHESGO is indicated for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic test.

†Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use (PHESGO) has different dosing and administration instructions compared to the intravenous products.

HER2=human epidermal growth factor receptor 2.

Important Safety Information

BOXED WARNINGS: Cardiomyopathy, Embryo-Fetal Toxicity, and Pulmonary Toxicity

- **PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment with PHESGO. Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function**
- **Exposure to PHESGO can result in embryo-fetal death and birth defects, including oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- **PHESGO administration can result in serious and fatal pulmonary toxicity. Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve**

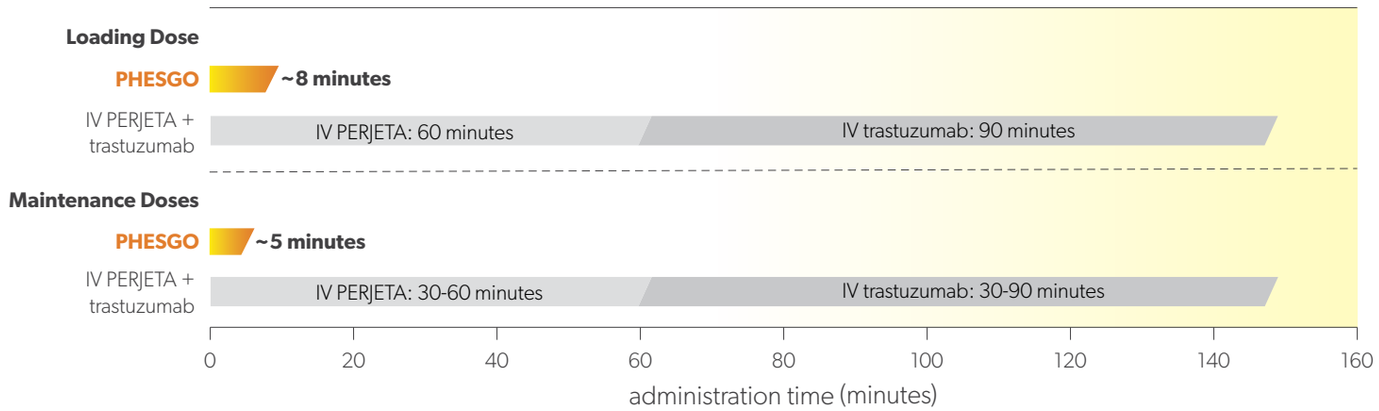
Please see Important Safety Information throughout, and click here for full Prescribing Information, including BOXED WARNINGS.

PHESGO can be given to eligible patients, such as those[1]:

- With HER2+ EBC or MBC
- Who already started IV PERJETA® (pertuzumab) + trastuzumab and would like to switch
- Who have not started any HER2+ breast cancer treatment yet
- Who have or haven't completed chemotherapy as part of their complete treatment regimen

PHESGO is a faster treatment option for your patients and practice[1,2]

Faster administration with PHESGO vs IV PERJETA + trastuzumab*[1,2]



- Patients should be observed for a minimum of 30 minutes after initial dose of PHESGO and 15 minutes after each maintenance dose of PHESGO for signs of hypersensitivity symptoms or administration-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use
- An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or chemotherapy

*Refers to actual injection time of PHESGO vs infusion time of IV PERJETA + trastuzumab and does not account for all aspects of treatment. Actual clinic time may vary. PERJETA and trastuzumab can be given in any order.[1,2] Please see the PERJETA full Prescribing Information for additional dosing information for PERJETA + trastuzumab.

Fixed-dose PHESGO requires[1]:

NO reconstitution
NO dilution
NO weight adjustments
NO IV loading dose
NO port access with a subcutaneous injection

Eligible patients currently receiving IV PERJETA + trastuzumab can be transitioned to PHESGO at the next scheduled dose of treatment.[1]

The same indications and treatment schedule you're used to with PERJETA + trastuzumab-based therapy[1,2]

In early breast cancer,

- Eligible patients should receive PHESGO as part of a complete treatment regimen, every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first†

In metastatic breast cancer,

- Eligible patients should receive PHESGO alongside docetaxel as first-line treatment, every 3 weeks until disease progression or unmanageable toxicity, whichever occurs first

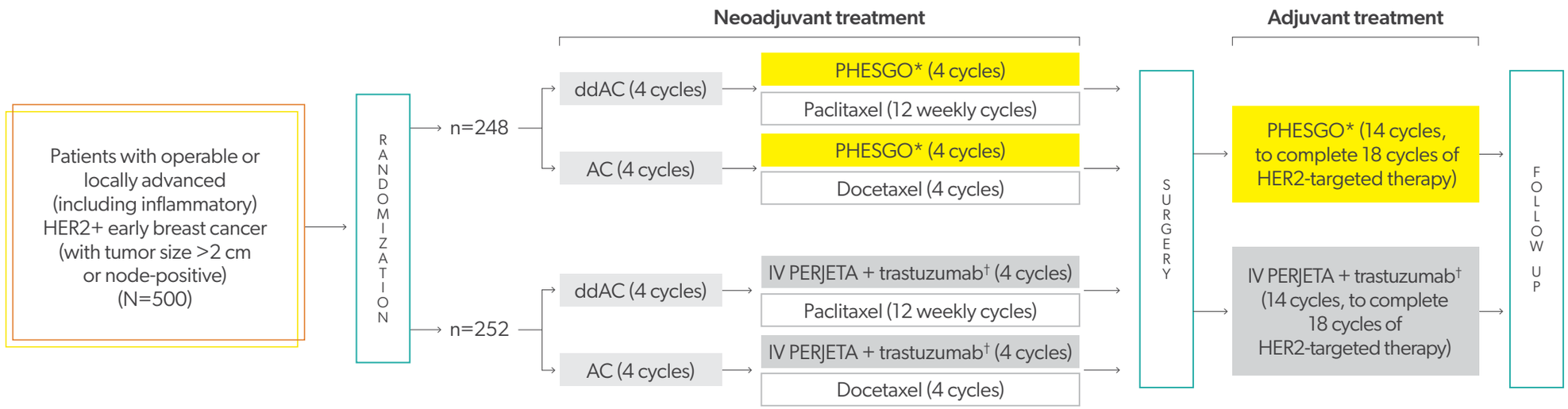
†In early breast cancer, patients who begin PHESGO-based therapy in the neoadjuvant setting should receive 3-6 cycles before surgery and should continue treatment after surgery, every 3 weeks, to complete 1 year (up to 18 cycles). Patients who begin treatment in the adjuvant setting should receive a total of 1 year (up to 18 cycles) of PHESGO-based therapy, every 3 weeks, starting on Day 1 of the first taxane-containing cycle.[1]

See full PHESGO dosing and administration information on page 11

FeDeriCa evaluated the pharmacokinetics (PK), efficacy, and safety of PHESGO vs IV PERJETA® (pertuzumab) + trastuzumab[1]

FeDeriCa trial design[1,4,5]

Phase III, randomized, open-label trial designed to demonstrate non-inferiority of PHESGO compared to intravenous PERJETA and trastuzumab.



Treatment cycles with PHESGO or IV PERJETA + trastuzumab were received every 3 weeks. Patients received adjuvant radiotherapy and endocrine therapy as per investigator's discretion.

Primary endpoint: Non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum C_{trough}.

Secondary endpoints: Non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) trastuzumab C_{trough}, efficacy (pCR),‡ and safety.

Stratification factors: Hormone receptor status; clinical stage at presentation (Stage II-IIIA or IIIB-IIIC); type of chemotherapy.

*__PHESGO dosing:__ 1200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase loading dose, followed by 600 mg pertuzumab/600 mg trastuzumab/20,000 units hyaluronidase maintenance dose.

†__IV PERJETA dosing:__ 840 mg loading dose, 420 mg for subsequent cycles; __IV trastuzumab dosing:__ 8 mg/kg loading dose, 6 mg/kg for subsequent cycles. In adjuvant period, substitution of IV trastuzumab for subcutaneous trastuzumab (trastuzumab-oysk) was permitted at investigator discretion. Trastuzumab-oysk was given as a fixed dose of 600 mg. 61 patients received trastuzumab-oysk.

‡pCR=pathological complete response (ypT0/is, ypN0, defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes).

__Chemotherapy regimens: ddAC dosing:__ doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks; __AC dosing:__ doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks; __paclitaxel dosing:__ 80 mg/m^2 weekly; __docetaxel dosing:__ 75 mg/m^2 every 3 weeks. Docetaxel dose could be escalated to 100 mg/m^2 at subsequent cycles at investigator's discretion.

AC=doxorubicin + cyclophosphamide; ddAC=dose-dense doxorubicin-cyclophosphamide.

Important Safety Information (cont'd)

Contraindications

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients.

Please see Important Safety Information throughout, and click here for full Prescribing Information, including BOXED WARNINGS.

Patient demographics and disease characteristics were well balanced between both arms of the study[4,5]

Select patient baseline characteristics[5]

	PHESGO (n=248)	**IV PERJETA® (pertuzumab) + trastuzumab** (n=252)
Median age, years (range)	52 (25-81)	49 (27-76)
Race, n (%)		
American Indian or Alaska Native	10 (4.0)	10 (4.0)
Asian	51 (20.6)	54 (21.4)
Black or African American	3 (1.2)	3 (1.2)
Native Hawaiian or Other Pacific Islander	0	0
White	165 (66.5)	164 (65.1)
Multiple	3 (1.2)	2 (0.8)
Unknown	16 (6.5)	19 (7.5)
Clinical stage at presentation, n (%)		
II-IIIA	198 (79.8)	201 (79.8)
IIIB-IIIC	50 (20.2)	51 (20.2)
Hormone receptor status, n (%)		
ER- and PgR-negative	96 (38.7)	97 (38.5)
ER- or PgR-positive	151 (60.9)	155 (61.5)
Unknown*	1 (0.4)	0
Nodal status, n (%)		
Node-negative	101 (40.7)	109 (43.3)
Node-positive	147 (59.3)	141 (56.0)
Unknown†	0	2 (0.8)
Type of chemotherapy, n (%)		
ddAC → paclitaxel	120 (48.4)	120 (47.6)
AC → docetaxel	128 (51.6)	132 (52.4)

*Status is considered unknown if either ER or PgR status is unknown.[4]
†Regional lymph nodes could not be assessed (e.g., previously removed or not removed at all).[5]

- Clinical stage at presentation, hormone receptor status, and type of chemotherapy were stratification factors[5]

ER=estrogen receptor; PgR=progesterone receptor.

PHESGO demonstrated non-inferior PK vs IV PERJETA® (pertuzumab) + trastuzumab[1]

PK results for pertuzumab and trastuzumab within PHESGO vs IV PERJETA and trastuzumab[1,5]

	PHESGO (n=206)	**IV PERJETA + trastuzumab** (n=203)
Primary endpoint: pertuzumab Cycle 7 C_{trough}	88.7 mcg/mL	72.4 mcg/mL
Geometric mean ratio	1.22 (90% CI: 1.14-1.31)	
Secondary endpoint: trastuzumab Cycle 7 C_{trough}	58.7 mcg/mL	44.1 mcg/mL
Geometric mean ratio	1.33 (90% CI: 1.24-1.43)	

- Non-inferiority was concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥0.8[4,5]

Secondary endpoint: efficacy (pCR)*[1]

PHESGO (n=248)	**IV PERJETA + trastuzumab** (n=252)
59.7% (95% CI: 53.3-65.8)	59.5% (95% CI: 53.2-65.6)

*pCR=pathological complete response (ypT0/is, ypN0, defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes).

Important Safety Information (cont'd)

Cardiomyopathy

- PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. An increased incidence of left ventricular ejection fraction (LVEF) decline has been observed in patients treated with intravenous pertuzumab, intravenous trastuzumab, and docetaxel
- PHESGO can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death
- PHESGO can also cause asymptomatic decline in LVEF
- Patients who receive anthracycline after stopping PHESGO may also be at increased risk of cardiac dysfunction
- Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function

Comparable safety was observed in FeDeriCa between both arms[1]

Summary of adverse reactions (ARs) occurring in ≥15% of patients who received PHESGO[1]

	All Grades (%)		Grades 3-4 (%)	
	PHESGO (n=248)	**IV PERJETA® (pertuzumab) + IV/SC trastuzumab** (n=252)	**PHESGO** (n=248)	**IV PERJETA + IV/SC trastuzumab** (n=252)
Alopecia	77	71	0	0.4
Nausea	60	61	2	1.6
Diarrhea	60	57	7	4.8
Anemia	36	43	1.6	4.4
Asthenia	31	32	0.4	2.4
Fatigue	29	24	2	2
Stomatitis	25	24	0.8	0.8
Myalgia	25	19	0.4	0.4
Arthralgia	24	28	0	0.4
Constipation	22	21	0	0
Neutropenia	22	27	14	14
Vomiting	20	19	0.8	1.2
Radiation skin injury	19	19	0.4	0.4
Dysgeusia	17	14	0	0
Headache	17	25	0	0.8
Decreased appetite	17	19	0.8	0.4
Insomnia	17	13	0	0.4
Peripheral sensory neuropathy	16	14	0.8	0.4

SC=subcutaneous.

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Summary of adverse reactions (ARs) occurring in ≥15% of patients who received PHESGO (cont'd)[1]

	All Grades (%)		Grades 3-4 (%)	
	PHESGO (n=248)	**IV PERJETA® (pertuzumab) + IV/SC trastuzumab** (n=252)	**PHESGO** (n=248)	**IV PERJETA + IV/SC trastuzumab** (n=252)
Rash	16	21	0.4	0
Dry skin	15	13	0.4	0
Mucosal inflammation	15	20	0.8	1.2
Injection site reaction*	15	0.8	0	0
Cough	15	13	0.4	0

*An injection site reaction was defined as a local reaction.[5]

Understanding injection site reactions (ISRs) from both arms in the FeDeriCa trial[1,5,6]

- ISRs in FeDeriCa were all mild to moderate (Grades 1-2)
- Mild ISRs were characterized by tenderness with or without associated symptoms like warmth, erythema, or itching
- Moderate ISRs were characterized by pain, lipodystrophy, edema, or phlebitis

Serious ARs occurring in patients receiving PHESGO[1]

- Serious ARs occurred in 16% of patients who received PHESGO
- Serious ARs in >1% of patients included febrile neutropenia (4%), neutropenic sepsis (1%), and neutrophil count decreased (1%)
- One fatal adverse reaction occurred in 1/248 (0.4%) of patients, which was due to acute myocardial infarction, and occurred prior to the start of HER2-targeted treatment with PHESGO

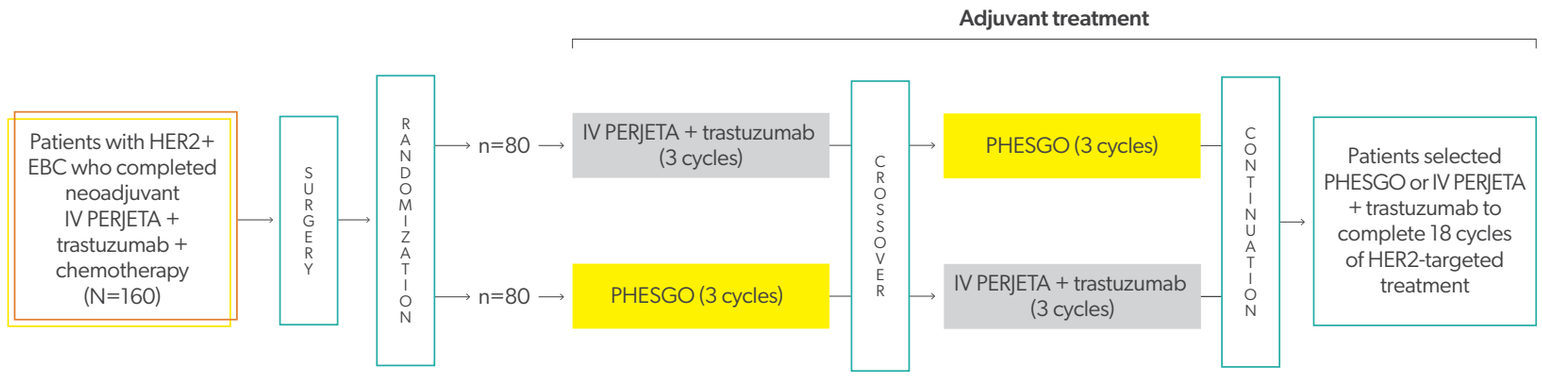
Adverse reactions resulting in permanent discontinuation of any study drug occurred in 8% of patients in the PHESGO arm. Adverse reactions which resulted in permanent discontinuation of PHESGO were ejection fraction decreased (1.2%), cardiac failure (0.8%), and pneumonitis/pulmonary fibrosis (0.8%).[1]

Dosage interruptions (of any study drug) due to an adverse reaction occurred in 40% of patients who received PHESGO. Adverse reactions which required dosage interruption (of any study drug) in >1% of patients who received PHESGO included neutropenia (8%), neutrophil count decreased (4%), and diarrhea (7%).[1]

More patients preferred subcutaneous administration with PHESGO over IV administration with PERJETA® (pertuzumab) + trastuzumab[1]

PHranceSCa trial design[1,7,8]

Phase II, randomized, open-label, crossover trial of patients with HER2+ early breast cancer. The primary objective of the study was to evaluate patient preference for PHESGO.



Primary endpoint: Percentage of patients who preferred PHESGO over IV PERJETA + trastuzumab when surveyed after Cycle 6 of adjuvant treatment.

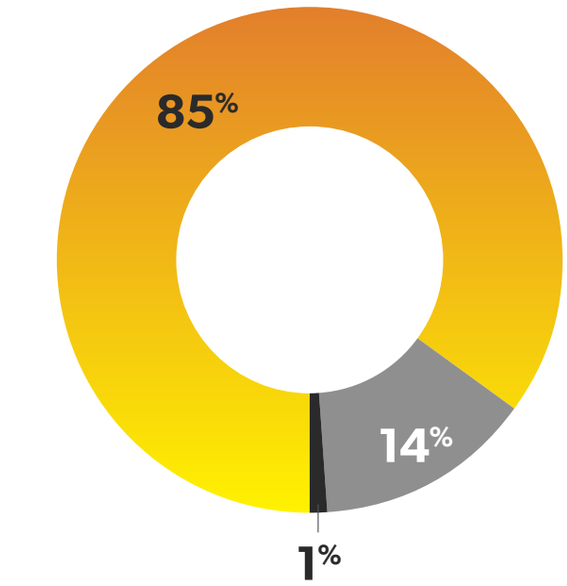
EBC=early breast cancer.

Important Safety Information (cont'd)

Cardiac Monitoring

- Evaluate cardiac function prior to and during treatment. For adjuvant breast cancer therapy, also evaluate cardiac function after completion of PHESGO
- Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Monitor frequently for decreased left ventricular function during and after PHESGO treatment
- Monitor more frequently if PHESGO is withheld for significant left ventricular cardiac dysfunction

85% of patients preferred using PHESGO over IV PERJETA + trastuzumab, citing **less time in the clinic** as the most common reason*[1]



14% of patients preferred using IV PERJETA + trastuzumab, citing more comfort during administration as the most common reason.*[1]

*When surveyed after Cycle 6 of adjuvant treatment. Data are based on the primary analysis with a clinical cut-off date (CCOD) of February 24, 2020. As of the CCOD, all 160 patients had completed all 6 cycles of the crossover period.[1,8]

Safety data from the PHranceSCa trial*[5,7]

	IV PERJETA® (pertuzumab) + trastuzumab → PHESGO		**PHESGO → IV PERJETA + trastuzumab**		
Five most common ARs (in ≥5% of patients), n (%)	Cycles 1-3 (n=80)	Cycles 4-6 (n=80)	Cycles 1-3 (n=80)	Cycles 4-6 (n=80)	All patients (n=160)
Radiation skin injury	17 (21.3%)	7 (8.8%)	10 (12.5%)	10 (12.5%)	43 (26.9%)
Injection site reaction	0	12 (15.0%)	24 (30.0%)	0	36 (22.5%)
Diarrhea	12 (15.0%)	7 (8.8%)	6 (7.5%)	4 (5.0%)	25 (15.6%)
Fatigue	5 (6.3%)	4 (5.0%)	5 (6.3%)	4 (5.0%)	15 (9.4%)
Hot flush	6 (7.5%)	4 (5.0%)	5 (6.3%)	0	15 (9.4%)
Total # of patients with ≥1 AR (%)	62 (77.5%)	58 (72.5%)	62 (77.5%)	51 (63.8%)	140 (87.5%)

AR rates before and after switching treatment[5,7]:

- From IV PERJETA + trastuzumab to PHESGO: 78% → 73%
- From PHESGO to IV PERJETA + trastuzumab: 78% → 64%

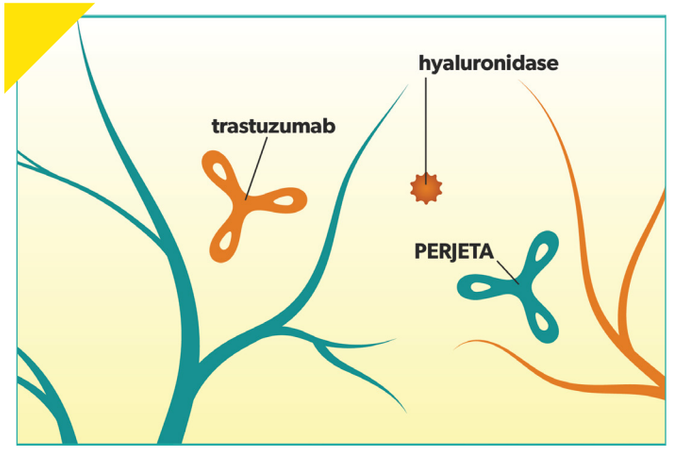
During the crossover period, serious ARs were reported in 2 patients (1.3%) receiving PHESGO and in 6 patients (3.8%) receiving IV PERJETA + trastuzumab; Grade ≥3 ARs were reported in 4 patients (2.5%) receiving PHESGO and in 6 patients (3.8%) receiving IV PERJETA + trastuzumab. There were no Grade 4 or 5 ARs reported during the study at the clinical cut-off date. More injection site reactions were observed with PHESGO (all Grade 1 or 2). There were no discontinuations due to local injection site reactions with PHESGO.[5,7]

* Data are based on the primary analysis with a CCOD of February 24, 2020. As of the CCOD, all 160 patients had completed all 6 cycles of the crossover period.[1,8]

Limitations of data: These safety analyses are descriptive only.

Proposed mechanism of action for the PHESGO subcutaneous injection

Specially formulated with hyaluronidase[1,9,10]



- PHESGO combines PERJETA® (pertuzumab) and trastuzumab, 2 monoclonal antibodies, with recombinant human hyaluronidase

- Hyaluronidase is an endoglycosidase used to increase dispersion and absorption of co-administered drugs when administered subcutaneously

How hyaluronidase is thought to work[1]

- Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan, based on preclinical studies
- In the doses administered, hyaluronidase in PHESGO acts transiently and locally
- The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours

Important Safety Information (cont'd)

Embryo-Fetal Toxicity

- PHESGO can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of intravenous trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of intravenous pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}
- Verify the pregnancy status of females of reproductive potential prior to the initiation of PHESGO. Advise pregnant women and females of reproductive potential that exposure to PHESGO during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PHESGO
- There is a pregnancy pharmacovigilance program for PHESGO. If PHESGO is administered during pregnancy, or if a patient becomes pregnant while receiving PHESGO or within 7 months following the last dose of PHESGO, health care providers and patients should immediately report PHESGO exposure to Genentech at 1-888-835-2555

Recommended dosing and administration for PHESGO

Important: PHESGO has different dosage and administration instructions than IV pertuzumab, IV trastuzumab, and subcutaneous trastuzumab when administered alone. Do not substitute PHESGO for or with PERJETA® (pertuzumab), trastuzumab, ado-trastuzumab emtansine, or fam-trastuzumab deruxtecan.[1]

PHESGO should be administered every 3 weeks[1,5]

Loading (initial) dose

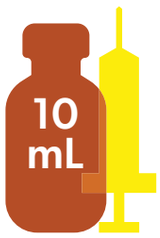
1200 mg pertuzumab, 600 mg trastuzumab, 30,000 units hyaluronidase per 15 mL supplied in a **single-dose, ready-to-use vial**

Administer subcutaneously over approximately **8 minutes** at a rate of no more than 2 mL/min

Observe for hypersensitivity or administration-related reactions: **minimum of 30 minutes***

NDC: 50242-245-01

Maintenance dose



600 mg pertuzumab, 600 mg trastuzumab, 20,000 units hyaluronidase per 10 mL supplied in a **single-dose, ready-to-use vial**

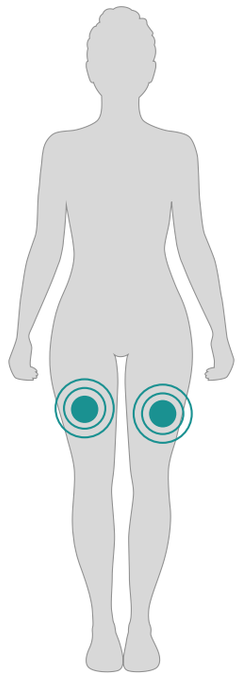
Administer subcutaneously over approximately **5 minutes** at a rate of no more than 2 mL/min

Observe for hypersensitivity or administration-related reactions: **minimum of 15 minutes***

NDC: 50242-260-01

*Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Administration instructions[1]



PHESGO must always be administered by a healthcare professional.

PHESGO is for subcutaneous use **ONLY in the thigh. Do NOT administer intravenously.**

- **Do not split the dose** between 2 syringes or between 2 sites of administration
- Injection site should be alternated between the left and right thigh only
- New injections should be given at least 1 inch from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard
- During the treatment course with PHESGO, other subcutaneous medications should preferably be injected at different sites

Eligible patients currently receiving IV PERJETA + trastuzumab can be transitioned to PHESGO at the next scheduled dose of treatment.[1]

Watch a video for detailed instructions on how to administer PHESGO and download the Dosing & Administration Guide →

Additional dosing considerations and dose modifications

Patient selection[1]

Assessment of HER2 protein overexpression and/or HER2 gene amplification should be performed using FDA-approved tests specific for breast cancers by laboratories with demonstrated proficiency.

Dose sequencing[1]

- In patients receiving an anthracycline-based regimen for early breast cancer, administer PHESGO following completion of the anthracycline
- In patients receiving PHESGO for early breast cancer with docetaxel or paclitaxel, administer docetaxel or paclitaxel after PHESGO
- In patients receiving PHESGO for metastatic breast cancer with docetaxel, administer docetaxel after PHESGO

Transitioning from IV PERJETA® (pertuzumab) + trastuzumab to PHESGO[1,5]

- In patients receiving IV PERJETA + trastuzumab with <6 weeks since their last dose, administer PHESGO as a maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL and every 3 weeks for subsequent administrations
- In patients receiving IV PERJETA + trastuzumab with ≥6 weeks since their last dose, administer PHESGO as an initial dose of 1,200 mg, 600 mg, 30,000 units/15 mL, followed by a maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL every 3 weeks for subsequent administrations

Delayed or missed doses of PHESGO[1]

- If the time between 2 sequential injections **is less than 6 weeks, do not wait until the next planned dose.** The maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL should be administered
- If the time between 2 sequential injections is **6 weeks or more, readminister the initial dose** of 1,200 mg, 600 mg, 30,000 units/15 mL followed every 3 weeks thereafter by maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL

Dosing adjustments[1]

- No dose adjustments for PHESGO are required for patient body weight or for concomitant chemotherapy regimen
- For chemotherapy dose modification, see relevant prescribing information
- **If patient experiences a significant injection-related reaction, slow down or pause the injection** and administer appropriate medical therapies. Evaluate and carefully monitor patients until complete resolution of signs and symptoms
- **If patient experiences a serious hypersensitivity reaction (e.g., anaphylaxis), discontinue injection immediately**

Dose modification and monitoring for left ventricular dysfunction[1]

Assess left ventricular ejection fraction (LVEF) prior to initiation of PHESGO and at regular intervals during treatment.

Pre-treatment LVEF:		Withhold PHESGO for at least 3 weeks for an LVEF decrease to:	Resume PHESGO after 3 weeks if LVEF has recovered to:	
Early Breast Cancer (EBC)	≥55%*	<50% with a fall of ≥10%-points below pre-treatment value	Either ≥50%	Either <10% points below pre-treatment value
Metastatic Breast Cancer (MBC)	≥50%	<40%	40%-45% with a fall of ≥10%-points below pre-treatment value	>45%	40%-45% with a fall of <10%-points below pre-treatment value

*For patients receiving anthracycline-based chemotherapy, an LVEF of ≥50% is required after completion of anthracyclines before starting PHESGO.

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Monitor LVEF prior to initiation and then every ~12 weeks in MBC and EBC (once during neoadjuvant therapy).[1]

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, has declined further, and/or the patient is symptomatic, permanently discontinue PHESGO.

Treatment regimens for EBC and MBC, based on pertuzumab studies and FeDeriCa

Early breast cancer treatment regimen[1,2]

Eligible patients with HER2+ EBC should receive PHESGO every 3 weeks to complete 1 year of treatment (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete treatment regimen including anthracycline- and/or taxane-based chemotherapy.

Neoadjuvant chemotherapy regimens

Neoadjuvant Setting →	→ Adjuvant Setting
4 cycles of **PHESGO** + docetaxel* (based on pertuzumab studies)	**3 postoperative cycles** of FEC† and ***continue PHESGO*** *to complete 1 year (up to 18 cycles) of treatment* ***per full Prescribing Information***
3 or 4 cycles of FEC,† followed by **3 or 4 cycles** of **PHESGO** + docetaxel* (based on pertuzumab studies)	
6 cycles of **PHESGO** + docetaxel* + carboplatin‡ (based on pertuzumab studies)	*Continue* ***PHESGO*** *to complete 1 year (up to 18 cycles) of treatment* ***per full Prescribing Information***
4 cycles of ddAC,§ followed by **4 cycles** of **PHESGO** + paclitaxel‖ or docetaxel* (based on a pertuzumab study and FeDeriCa)	
4 cycles of AC,¶ followed by **4 cycles** of **PHESGO** + docetaxel* (based on FeDeriCa)	

SURGERY

Adjuvant chemotherapy regimens

PHESGO should start on Day 1 of the first taxane-containing cycle.

Non-anthracycline-based chemotherapy regimen

6 cycles of docetaxel** + carboplatin††

Anthracycline-based regimens

3 or 4 cycles of FEC‡‡ or FAC§§, followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel‖‖

4 cycles of AC¶¶ or EC***, followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel‖‖

Metastatic breast cancer treatment regimen[1,11]

Eligible patients with HER2+ MBC should receive PHESGO every 3 weeks until disease progression or unmanageable toxicity, whichever occurs first, alongside at least 6 cycles of docetaxel.

- In CLEOPATRA (NCT00567190), it was recommended that docetaxel be administered for a minimum of 6 cycles
  - The docetaxel dose could be decreased by 25% due to toxicity or increased to 100 mg/m^2 in those patients who could tolerate this dose
  - Fewer than 6 cycles were allowed for unmanageable toxicity
  - Comparable docetaxel exposure between the 2 treatment arms in CLEOPATRA
    - Docetaxel was administered for a median of 8 cycles in both treatment arms
- PHESGO should be continued until disease progression or unmanageable toxicity
- If docetaxel is discontinued, PHESGO may be continued on its own

*Docetaxel dosing: 75 mg/m^2, which could be escalated to 100 mg/m^2 if initial dose was well tolerated (escalation of docetaxel above 75 mg/m^2 is not recommended when administered with carboplatin as in TRYPHAENA [NCT00976989]).
†FEC dosing in NeoSphere (NCT00545688): 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2); FEC dosing in TRYPHAENA and BERENICE (NCT02132949): 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2).
‡Carboplatin dosing: AUC 6.
§ddAC dosing: doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks for 4 cycles with GCSF support.
‖Paclitaxel dosing: 80 mg/m^2.
¶AC dosing: 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks.
**Docetaxel dosing: 75 mg/m^2, which could be escalated to 100 mg/m^2 if initial dose was well tolerated (not escalated in non–anthracycline-based regimens); docetaxel dosing following AC or EC administration: 100 mg/m^2 for 3 cycles or 75 mg/m^2 for first cycle and 100 mg/m^2 for subsequent 3 cycles, or 75 mg/m^2 for 4 cycles.
††Carboplatin dosing: AUC 6.
‡‡FEC dosing: 5-fluorouracil (500-600 mg/m^2), epirubicin (90-120 mg/m^2), and cyclophosphamide (500-600 mg/m^2).
§§FAC dosing: 5-fluorouracil (500-600 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500-600 mg/m^2).
‖‖Paclitaxel dosing: 80 mg/m^2.
¶¶AC dosing: doxorubicin (60 mg/m^2) and cyclophosphamide (500-600 mg/m^2) every 3 weeks or 2 weeks with GCSF support.
***EC dosing: epirubicin (90-120 mg/m^2) and cyclophosphamide (500-600 mg/m^2) every 3 weeks or 2 weeks with GCSF support.

AUC=area under the curve; FAC=fluorouracil, doxorubicin, and cyclophosphamide; FEC=fluorouracil, epirubicin, and cyclophosphamide; GCSF=granulocyte colony–stimulating factor.

Please see the PERJETA® (pertuzumab) full Prescribing Information for additional dosing information for PERJETA + trastuzumab.

Preparation and storage

Vial storage[1]

PHESGO is supplied in sterile, preservative-free, single-dose vials for subcutaneous administration. Store PHESGO vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light, until time of use. Do not freeze.

Checking the vial[1]

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is PHESGO and not IV PERJETA® (pertuzumab), or IV or subcutaneous trastuzumab.

Inspect the vial for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. The solution should be clear to opalescent, colorless to slightly brownish. Do not shake.

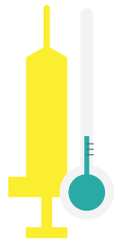
Preparing the injection[1]

A syringe, a transfer needle, and an injection needle are needed to withdraw PHESGO solution from the vial and inject it subcutaneously. PHESGO is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, and fluorinated ethylene polypropylene.

1 Do not dilute PHESGO. Use a syringe with a transfer needle to withdraw the PHESGO solution from the vial. Discard any unused portion remaining in the vial. Remove transfer needle.

2 Immediately prior to administration, attach a 25G-27G (3/8″–5/8″) hypodermic injection needle to the syringe. Check the syringe to ensure the right dose is being administered: initial dose (15 mL) or maintenance dose (10 mL).

3 Inject PHESGO into patient's thigh slowly and gently over about 8 minutes for the initial dose and about 5 minutes for the maintenance dose.



Syringe storage[1]

If the syringe containing PHESGO is not used immediately, it can be stored in the refrigerator for up to 24 hours (2°C to 8°C, 36°F to 46°F) and at room temperature for up to 4 hours (20°C to 25°C, 68°F to 77°F). Avoid unnecessary storage.

- If the dose is not to be administered immediately, and the solution of PHESGO has been withdrawn from the vial into the syringe, replace the transfer needle with a syringe closing cap
- Do not attach a hypodermic needle until time of administration to avoid needle clogging
- Label the syringe with the peel-off sticker

Financial Resources

ACCESS SOLUTIONS®

Helping patients access their Genentech medicines

- Genentech Access Solutions offers a range of access and reimbursement support for your patients and practice
- To learn more about Genentech Access Solutions programs and services, call **(888) 249-4918** or visit **genentech-access.com**

Oncology CO-PAY ASSISTANCE Program

1 co-pay card covers 2 antibodies.

Talk to eligible patients about enrolling today in the Genentech Oncology Co-pay Assistance Program

- Eligible patients pay as little as $5 per injection co-pay or co-insurance until the $25,000 annual limit is reached
- To learn more about the Genentech Oncology Co-pay Assistance Program or to get the full terms & conditions, call **(855) MY-COPAY (855-692-6729)** or visit **copayassistancenow.com**

The Genentech Oncology Co-pay Assistance Program is valid ONLY for patients with commercial insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medication. Patients using Medicare, Medicaid, or any other federal or state government program to pay for their medications are not eligible.

Under the Program, the patient will pay a co-pay. After reaching the maximum Program benefit, the patient will be responsible for all out-of-pocket costs.

All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. No party may seek reimbursement for all or any part of the benefit received through this Program. This Program is void where prohibited by law. Genentech reserves the right to rescind, revoke, or amend the Program without notice at any time. Additional eligibility criteria apply. See full terms and conditions at **copayassistancenow.com**.

Patient Coverage

Most commercially insured patients have favorable access to PHESGO[5]

- **Policies that cover at parity or better include United, Anthem, Aetna, Cigna, Humana, and HCSC***
- New and existing PHESGO patients have favorable coverage to PI on most commercial plans, without pertuzumab + biosimilar trastuzumab IV regimen required first†
- Less than 1% of patients do not have favorable coverage for PHESGO

Insurer/payer policies are subject to change. The completion and submission of coverage or reimbursement-related documentation are the responsibility of the patient and the healthcare provider. Genentech makes no representation or guarantee concerning coverage or reimbursement for any service or item. Inclusion of a plan or product is not intended to imply a recommendation or a particular plan or product.

*PHESGO is covered at parity or better compared with pertuzumab + biosimilar trastuzumab IV regimen.

†Percentages of commercially insured patients with favorable access to PHESGO is defined as coverage at parity or better compared with pertuzumab + biosimilar trastuzumab IV regimens. Calculation is based on data updated as of June 2021.[5]

Indications and Important Safety Information

Indications

Early Breast Cancer

PHESGO® (pertuzumab, trastuzumab, and hyaluronidase-zzxf) is indicated for use in combination with chemotherapy for

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer (EBC)
- the adjuvant treatment of adult patients with HER2-positive EBC at high risk of recurrence

Select patients for therapy based on an FDA-approved companion diagnostic test.

Metastatic Breast Cancer

PHESGO is indicated for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic test.

Important Safety Information

BOXED WARNINGS: Cardiomyopathy, Embryo-Fetal Toxicity, and Pulmonary Toxicity

- **PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment with PHESGO. Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function**
- **Exposure to PHESGO can result in embryo-fetal death and birth defects, including oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- **PHESGO administration can result in serious and fatal pulmonary toxicity. Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve**

Contraindications

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients.

Additional Important Safety Information

Cardiomyopathy

- PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. An increased incidence of left ventricular ejection fraction (LVEF) decline has been observed in patients treated with intravenous pertuzumab, intravenous trastuzumab, and docetaxel
- PHESGO can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death
- PHESGO can also cause asymptomatic decline in LVEF
- Patients who receive anthracycline after stopping PHESGO may also be at increased risk of cardiac dysfunction
- Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function

Cardiac Monitoring

- Evaluate cardiac function prior to and during treatment. For adjuvant breast cancer therapy, also evaluate cardiac function after completion of PHESGO
- Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Monitor frequently for decreased left ventricular function during and after PHESGO treatment
- Monitor more frequently if PHESGO is withheld for significant left ventricular cardiac dysfunction

(cont'd next page)

Important Safety Information (cont'd)

Embryo-Fetal Toxicity
- PHESGO can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of intravenous trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of intravenous pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_{max}
- Verify the pregnancy status of females of reproductive potential prior to the initiation of PHESGO. Advise pregnant women and females of reproductive potential that exposure to PHESGO during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PHESGO
- There is a pregnancy pharmacovigilance program for PHESGO. If PHESGO is administered during pregnancy, or if a patient becomes pregnant while receiving PHESGO or within 7 months following the last dose of PHESGO, health care providers and patients should immediately report PHESGO exposure to Genentech at 1-888-835-2555

Pulmonary Toxicity
- PHESGO can cause serious and fatal pulmonary toxicity. These adverse reactions have been reported with intravenous trastuzumab
- Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity

Exacerbation of Chemotherapy-Induced Neutropenia
- PHESGO may exacerbate chemotherapy-induced neutropenia. In randomized controlled clinical trials with intravenous trastuzumab, Grade 3-4 neutropenia and febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not

Hypersensitivity and Administration-Related Reactions
- Severe administration-related reactions (ARRs), including hypersensitivity, anaphylaxis, and events with fatal outcomes, have been associated with intravenous pertuzumab and trastuzumab. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a severe or of a fatal ARR
- In the FeDeriCa study the incidence of hypersensitivity was 1.2% in the PHESGO arm. ARRs occurred in 21% of patients who received PHESGO. In the PHESGO arm, the most common ARRs were injection site reaction (15%) and injection site pain (2%)
- Closely monitor patients during and for 30 minutes after the injection of initial dose and during and for 15 minutes following subsequent injections of maintenance dose of PHESGO. If a significant injection-related reaction occurs, slow down or pause the injection and administer appropriate medical therapies. Evaluate and carefully monitor patients until complete resolution of signs and symptoms
- Permanently discontinue treatment with PHESGO in patients who experience anaphylaxis or severe injection-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to readministration of PHESGO

Most Common Adverse Reactions
Early Breast Cancer
The most common adverse reactions (>30%) with PHESGO were alopecia, nausea, diarrhea, anemia, and asthenia.

Metastatic Breast Cancer (based on IV pertuzumab)
The most common adverse reactions (>30%) with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.

You are encouraged to report side effects to Genentech and the FDA. You may report side effects to the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to Genentech at **1-888-835-2555**.

Please see full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.

PHESGO is a fixed-dose subcutaneous formulation with PERJETA® (pertuzumab) and trastuzumab that's administered in **~5 minutes***[1]

The same antibodies you know in one faster mode of administration[1,2]

PHESGO vs IV PERJETA:

- **SAME** indications
- **SAME** frequency†
- **SAME** number of cycles†

Does not require port access[1]

Fixed-dose PHESGO requires[1]**:**

- **NO** reconstitution
- **NO** dilution
- **NO** weight adjustments
- **NO** IV loading dose
- **NO** port access with a subcutaneous injection

*Refers to actual PHESGO injection time of ~5 minutes for the maintenance dose. **The loading dose is ~8 minutes.** This does not account for observation time and other aspects of treatment. Actual clinic time may vary.[1]

†See full PHESGO dosing guidelines on pages 11-14. See the PERJETA full Prescribing Information for additional dosing information for PERJETA + trastuzumab.

Consider starting or switching your eligible patients with HER2+ EBC or MBC to PHESGO today.

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Please see Important Safety Information throughout, and click here for full Prescribing Information, including BOXED WARNINGS.

References: 1. PHESGO Prescribing Information. Genentech, Inc. 2020. **2.** PERJETA Prescribing Information. Genentech, Inc. 2021. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed January 21, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Tan AR, et al. Subcutaneous administration of the fixed-dose combination of trastuzumab and pertuzumab in combination with chemotherapy in HER2-positive early breast cancer: primary analysis of the phase III, multicenter, randomized, open-label, two-arm FeDeriCa study. Poster presentation at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract PD4-07. **5.** Data on file. Genentech, Inc. **6.** National Cancer Institute. National Institutes of Health. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, June 14, 2010. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed October 28, 2021. **7.** O'Shaughnessy J, Sousa S, Cruz J, et al. Patient (pt) preference for the pertuzumab–trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) in HER2-positive early breast cancer (EBC): Primary analysis of the open-label, randomised crossover PHranceSCa study. https://medically.roche.com/global/en/asset-viewer.eeb4fcc7-b0b5-43d5-9b9a-8f4445f7424f.qr.html?cid=slpsxx2009onbresmo2020. Accessed October 28, 2021. **8.** ClinicalTrials.gov. A study to evaluate patient preference and satisfaction of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in participants with HER2-positive early breast cancer (PHranceSCa). https://clinicaltrials.gov/ct2/show/NCT03674112. Accessed October 28, 2021. **9.** Scheuer W, Friess T, Burtscher H, et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res.* 2009;69(24):9330-9336. **10.** Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. *Cancer Res*. 2008;68(14):5878-5887. **11.** Baselga J, Cortés J, Kim S-B, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119.

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