RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	PHESGO™
Generic Name	pertuzumab, trastuzumab, and hyaluronidase-zzxf
Drug Manufacturer	Genentech, Inc.

New Drug Approval

PHESGO™ is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for:

- Use in combination with chemotherapy as:
  - neoadjuvant treatment of 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.
  - Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.
- Use in combination with docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

FDA Approval Date: 06/29/2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Breast cancer is the second most common cancer among women in the United States. Black women and white women get breast cancer at about the same rate, but black women die from breast cancer at a higher rate than white women.

In 2020, an estimated 276,480 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 48,530 new cases of non-invasive (in situ) breast cancer.

About 1 in 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime.

In women under 45, breast cancer is more common in Black women than white women. Overall, Black women are more likely to die of breast cancer. For Asian, Hispanic, and Native-American women, the risk of developing and dying from breast cancer is lower. Ashkenazi Jewish women have a higher risk of breast cancer because of a higher rate of BRCA mutations.

About 42,170 women in the U.S. are expected to die in 2020 from breast cancer. Death rates have been steady in women under 50 since 2007, but have continued to drop in women over 50. The overall death rate from breast cancer decreased by 1.3% per year from 2013 to 2017. These decreases are thought to be the result of treatment advances and earlier detection through screening.

For women in the U.S., breast cancer death rates are higher than those for any other cancer, besides lung cancer.

Efficacy

Neoadjuvant and Adjuvant Treatment of Breast Cancer:

Effectiveness of PHESGO™ for use in combination with chemotherapy has been established for the treatment of patients with HER2-positive early breast cancer. This use is supported by evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab administered in

combination with chemotherapy in adults with HER2-overexpressing early breast cancer (NCT00545688, NCT00976989, NCT02132949, NCT01358877) and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between PHESGO™ and intravenous pertuzumab and intravenous trastuzumab in FeDeriCa.

The FeDeriCa study (NCT03493854) was an open-label, multicenter, randomized study conducted in 500 patients with operable or locally advanced (including inflammatory) HER2- positive breast cancer with a tumor size > 2 cm or node-positive. Patients were randomized to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either PHESGO™ or intravenous pertuzumab and trastuzumab during cycles 5-8, followed by surgery.

Efficacy (pathological complete response [pCR], defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes), and safety. The median age was 51 years (range: 25-81), and the majority of patients were White (66%). The majority of patients had hormone receptor-positive disease (61%) or node-positive disease (58%).

The pCR rate was 59.7% (95% CI: 53.3, 65.8) in the PHESGO™ arm and 59.5% (95% CI: 53.2, 65.6) in the intravenous pertuzumab and trastuzumab arm.

Metastatic Breast Cancer:

The effectiveness of PHESGO™ for use in combination with docetaxel has been established for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Use of PHESGO™ for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab administered in combination with chemotherapy in adults with HER2-overexpressing metastatic breast cancer (NCT00567190).

Safety

ADVERSE EVENTS

Neoadjuvant and Adjuvant Treatment of Breast Cancer

- The most common adverse reactions (>30%) with PHESGO™ were alopecia, nausea, diarrhea, anemia, and asthenia.

Metastatic Breast Cancer (based on intravenous 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.

WARNINGS & PRECAUTIONS

- Warnings
  - Exacerbation of Chemotherapy-Induced Neutropenia.
  - Hypersensitivity and Administration-Related Reactions (ARRs): Monitor patients for systemic hypersensitivity reactions. Permanently discontinue PHESGO™ in patients who experience anaphylaxis or severe hypersensitivity reactions.
- Precautions
  - Administration-related reactions have been reported with an increased risk of severe or fatal events in patients experiencing dyspnea at rest. Monitoring required during and after injection. Dose interruption or permanent discontinuation may be necessary.

- Serious and fatal pulmonary toxicity may occur; discontinue for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome and monitor until symptoms completely resolve
- Can cause fetal harm; verify pregnancy status of females of reproductive potential prior to initiation. Advise females of reproductive potential to use effective contraception during therapy and for 7 months following last dose

CONTRAINDICATIONS

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

Clinical Pharmacology

MECHANISMS OF ACTION

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signaling pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively.

Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated cell proliferation and PI3K signaling pathway in human tumor cells that overexpress HER2.

Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase has been shown to increase the absorption rate of a trastuzumab product into the systemic circulation when given in the subcutis of Göttingen Minipigs

Dose & Administration

ADULTS

The initial dose

PHESGO™ is 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase administered subcutaneously over approximately 5 minutes.

Neoadjuvant Treatment of Breast Cancer

Administer PHESGO™ every 3 weeks for 3 to 6 cycles as part of a treatment regimen for early breast cancer.

Adjuvant Treatment of Breast Cancer

Administer PHESGO™ every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. Start PHESGO™ on Day 1 of the first taxane-containing cycle.

Metastatic Breast Cancer (MBC)

When administered with PHESGO™, the recommended initial dose of docetaxel is 75 mg/m2 administered as an intravenous infusion. The dose may be escalated to 100 mg/m2 administered every 3 weeks if the initial dose is well tolerated

PEDIATRICS

None.

GERIATRICS

None.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15 mL (80 mg, 40 mg, and 2,000 units/mL) of solution in a single-dose vial.
- 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL (60 mg, 60 mg, and and 2,000units/mL) of solution in a single-dose vial