A fixed-dose combination of pertuzumab, trastuzumab and hyaluronidase-zzxf (Phesgo™) for the treatment of early and metastatic breast cancer

General information

Drug description [1, 2]	Indication [1]
Phesgo™ is a fixed-dose combination of pertuzumab, trastuzumab, and hyaluronidase–zzxf for subcutaneous injection. Pertuzumab and Trastuzumab are monoclonal antibodies targeting the HER2, disrupting HER2 signaling, and also mediating antibody-dependent cell-mediated cytotoxicity.	Phesgo™ is indicated for the treatment of early breast cancer (EBC) and metastatic breast cancer (MBC).

Current treatment [3, 4]

- ❖ According to NICE, the following are recommended in the treatment of **EBC:**
  - Adjuvant chemotherapy
    - A regimen which contains both a taxane and anthracyclin is recommended for people of sufficient risk that chemotherapy is indicated.
  - Biological therapy
    - Adjuvant trastuzumab is recommended for people with T1a/T1b, T1c and above HER2-positive in combination with surgery, chemotherapy and radiotherapy as appropriate
    - Adjuvant bisphosphonate therapy (zoledronic acid or sodium clodronate) is also recommended for postmenopausal women.
    - Pertuzumab, with intravenous trastuzumab and chemotherapy is recommended in patients with HER2-positive and lymph-node-positive disease.
- ❖ Therapeutic approaches for the treatment of **advanced HER2-positive breast cancer** include:
  - First-line treatment:
    - Pertuzumab, in combination with trastuzumab and docetaxel
    - Trastuzumab in combination with paclitaxel
    - Trastuzumab monotherapy for people who have received at least two chemotherapy regimens for MBC
  - Second-line treatment
    - Trastuzumab emtansine is recommended, as an option for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.
  - Third-line treatment
    - Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).

Regulatory status

EMA	FDA [5]
Approval status for this indication: On 12 November 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Phesgo™, intended for the treatment of early and metastatic breast cancer. Date of issue of marketing authorisation valid throughout the European Union: **21/12/2020** -Therapeutic indication: ❖ EBC: Phesgo™ is indicated for use in combination with chemotherapy in: • the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence ❖ MBC:	**Approval status for this indication**: On 29 June 2020, the FDA approved a new fixed-dose combination of pertuzumab, trastuzumab, and hyaluronidase–zzxf for subcutaneous injection for the following indications: ❖ 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 EBC; • 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 MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease **Other indications**: none

- Phesgo™ is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Other indications: none

✓ **Medicine under additional monitoring**

Costs

Currently no cost information available.

Warnings and precautions [6]

- ❖ **Cardiomyopathy**: Phesgo™ administration can result in subclinical and clinical cardiac failure manifesting as congestive heart failure (CHF), and decreased left ventricular ejection fraction (LVEF), with greatest risk when administered concurrently with anthracyclines. Cardiac function should be evaluated prior to and during treatment and discontinued for cardiomyopathy.
- ❖ **Embryo-fetal toxicity**: Exposure to Phesgo™ can result in embryo-fetal death and birth defects (need for effective contraception).
- ❖ **Pulmonary toxicity**: Discontinuation of Phesgo™ for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
FeDeriCa WO40324 NCT03493854	500	Arm A: 8 cycles of CT in the neoadjuvant setting with H IV (loading dose 8 mg/kg, maintenance 6 mg/kg) + P IV (loading dose 840 mg, maintenance 420 mg) (Arm A)	Arm B: CT per Arm A + pertuzumab-trastuzumab fixed-dose combination (loading dose 1200 mg P SC/600 mg H SC, maintenance 600 mg each)	Noninferiority of the pre-dose cycle 8 pertuzumab serum (Ctrough) within the pertuzumab-trastuzumab fixed-dose combination versus pertuzumab	open-label, multicenter, randomized, two-arm, phase III trial	HER2	Hoffmann – La Roche	Link (Abstract only)

Efficacy (I vs. C)[1]

The study met its **PE**: **Pertuzumab GMR** was 1.22 (90% CI 1.14-1.31) with the lower limit of the 90% CI being above the pre-specified non-inferiority margin of 0.8. **Trastuzumab GMR** was 1.33 (90% CI 1.24-1.43), meeting the non-inferiority criteria.

tpCR rates were comparable between arms: 59.5%; 95% CI 53.2-65.6 in Arm A vs. 59.7%; 95% CI 53.3-65.8 in Arm B

Safety (I vs. C)[2]

Any grade 3 AE: n=87/252 (34.5%) vs. n=79/248 (31.9%)
Any grade 4 AE: n=45/252 (17.9%) vs. n=41/248 (16.5%)
Any grade 5 AE: n=1/252 (0.4%) vs. n=1/248 (0.4%)
Any serious AE: n=45/252 (17.9%) vs. n=40/248 (16.1%)
The percentage of patients with at least one cardiac disorder was 22% in arm A; the most frequent cardiac adverse reaction in arm A was ejection fraction decreased.

ESMO-MCBS version 1.1

The available study endpoints are not assessable via the ESMO-MCBS.

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	unclear	no, open-label	unclear	yes[3]	unclear[4]

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[1] Primary analysis data; FeDeriCa trial is ongoing until 05/2023
[2] Primary analysis data; FeDeriCa trial is ongoing until 05/2023
[3] Industry-funded
[4] Currently only study abstract available

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHF= congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=chemotherapy, Ctrough=trough concentration, EBC=early breast cancer, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FDC=fixed-dose combination, FM=final magnitude of clinical benefit grade, GMR=geometric mean ratio, HER2= human epidermal growth factor receptor 2, H IV=intravenous trastuzumab, HR=hazard ratio, I=intervention, Int.=intention, MBC=metastatic breast cancer, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health and Care Excellence, LVEF=left ventricular ejection fraction, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, P IV=intravenous pertuzumab, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, tpCR=total pathologic complete response

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8. U.S. National Library of Medicine, ClinicalTrials.gov. A Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Combination With Chemotherapy in Participants With HER2-Positive Early Breast Cancer (FeDeriCa) [Available from: https://clinicaltrials.gov/ct2/show/study/NCT03493854.