Incidence and Management of Phesgo Administration-Related Reactions

This article responds to your request for information on the incidence and management of administration-related reactions associated with Phesgo® (pertuzumab, trastuzumab, and hyaluronidase). This response was developed according to the principles of evidence-based medicine and contains data from a Phase 3 study.

In brief

- Administration-related reactions (ARRs) include infusion-related reactions and local and systemic injection-related reactions.
- The FeDeriCa study evaluated the pharmacokinetics, efficacy, and safety of Phesgo in combination with chemotherapy in patients with Stage II-IIIC human epidermal growth factor receptor 2 (HER2)-positive early breast cancer.
    - ARRs within 24 hours of anti-HER2 therapy were reported in 22.2% of patients who received Phesgo and in 15.5% of patients who received intravenous (IV) Perjeta® (pertuzumab) + IV Herceptin® (trastuzumab). None of the patients who received Phesgo experienced a Grade ≥3 ARR compared to 1.2% of patients who received IV Perjeta + IV Herceptin.
    - Anaphylaxis and hypersensitivity reactions occurred at the same rate (1.6%) in patients who received Phesgo and in those who received IV Perjeta + IV Herceptin. None of the patients who received Phesgo experienced a Grade ≥3 anaphylactic or hypersensitivity reaction compared to 0.4% of patients who received IV Perjeta +IV Herceptin.
- ARRs following Phesgo administration should be managed according to local practice standards.
    - In FeDeriCa, patients who experienced ARRs following Phesgo administration were permitted to stop the Phesgo injections and to receive supportive care at the investigator's discretion, as per local practice.

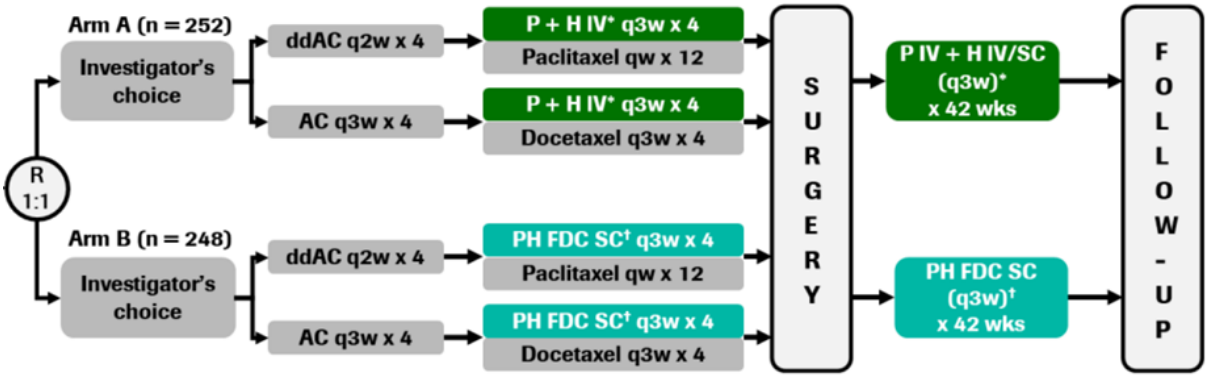
Overview of Phesgo

Phesgo is a ready-to-use fixed-dose combination of pertuzumab, trastuzumab and hyaluronidase (recombinant human) administered subcutaneously into the thigh over 5 to 8 minutes.[1] Hyaluronidase is a permeation enhancer that allows subcutaneous administration of larger drug volumes.

Phase 3 FeDerica study

FeDeriCa was a global, multicentre, Phase 3, open-label, randomized study, which evaluated the pharmacokinetics, efficacy, and safety of Phesgo once every 3 weeks in combination with chemotherapy in patients with Stage II-IIIC HER2-positive early breast cancer.[1] The study design is depicted in Figure 1.

Figure 1. FeDeriCa study design[1]



*IV Perjeta is given as a fixed dose of 840 mg (loading dose) and then 420 mg (maintenance doses); IV Herceptin is given as an 8 mg/kg (loading dose) and then 6 mg/kg (maintenance doses); SC trastuzumab is given as a fixed dose of 600 mg.

†PH FDC SC is given as a fixed dose (either 1,200 mg pertuzumab/600 trastuzumab loading dose; or 600 mg pertuzumab/600 mg trastuzumab maintenance dose).

Abbreviations:AC=doxorubicin + cyclophosphamide; ddAC=dose-dense doxorubicin + cyclophosphamide; H=trastuzumab; IV=intravenous; P=pertuzumab; PH FDC SC=subcutaneous fixed-dose combination of pertuzumab and trastuzumab (Phesgo); qw=every week; qxw=every x weeks; R=randomized; SC=subcutaneous.

Notes:Chemotherapy regimens= dose-dense doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) q2w for 4 cycles followed by weekly paclitaxel (80 mg/m^2) for 12 weeks, or doxorubicin and cyclophosphamide q2w for 4 cycles followed by docetaxel (75 mg/m^2, escalating to 100 mg/m^2 if tolerated) q3w for 4 cycles.

Administration-related reactions in the Phase 3 FeDeriCa study

Administration-related reactions (ARRs), as defined in the Phase 3 FeDeriCa study protocol, comprised of:[2]

- Infusion-related reactions — A systemic reaction with symptoms such as chills, diarrhoea, fatigue, headache, nausea, and pyrexia
- Injection-related reactions — Either a systemic reaction, similar to an infusion-related reaction, or a local injection-site reaction with signs and symptoms such as erythema, induration, swelling, pain, hypoesthesia and discomfort

Incidence of ARRs and hypersensitivity reactions in the Phase 3 FeDeriCa study

ARRs

In the FeDeriCa study, an injection- or infusion-related reaction was defined as any systemic reaction reported within 24 hours of Phesgo or IV Perjeta and Herceptin administration.[3] Injection-related reactions were reported in 1.2% of Phesgo-treated patients and infusion-related reactions were reported in 10.3% of IV Perjeta and Herceptin-treated patients.

Injection-site reactions were defined as any local reaction reported within 24 hours of Phesgo administration.[3] Injection-site reactions were reported in 12.9% of Phesgo-treated patients; all events were of grade 1 or 2 severity.

Hypersensitivity and anaphylaxis reactions

In the FeDeriCa study, the overall frequency of hypersensitivity and anaphylaxis events related to HER2-targeted therapy was 1.6% in both the Phesgo-treated patients and IV Perjeta and Herceptin-treated patients; no events were of grade 3 or 4 severity.[3]

Table 1 summarises ARRs and hypersensitivity and anaphylaxis reactions reported in the overall FeDeriCa safety population.[4] The table includes all reported events, regardless of whether considered to be related to study treatment or not.

Table 1. Summary of ARRs and hypersensitivity reactions in FeDeriCa (safety population)[4]

n (%)	Perjeta IV + Herceptin IV (*n*=252)	Phesgo (*n*=248)
ARR within 24 hours Grade ≥3	39 (15.5) 3 (1.2)	55 (22.2) 0
Anaphylaxis and hypersensitivity Grade ≥3	4 (1.6) 1 (0.4)	4 (1.6) 0

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Recommendation on the management of ARRs

Roche does not have recommendations on the management of ARRs. ARRs following Phesgo administration should be managed according to local practice standards.

Clinical management guidelines from the FeDeriCa study

In the FeDeriCa trial, patients who experienced ARRs were permitted to be managed several ways:[2,5]

- Slow or stop the IV Perjeta or IV Herceptin infusion
- Stop the Phesgo injection
- Provide supportive care in line with local practice, at the investigator's discretion. This could include, but was not limited to
    - analgesics/antipyretics, such as meperidine or paracetamol
    - antihistamines, such as diphenhydramine
    - beta agonists
    - oxygen, or
    - corticosteroids.
- Pre-medicate subsequent doses with analgesia and antihistamines as per local practice.

References

1. Tan A, Im S, Mattar A, 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. Presented at the San Antonio Breast Cancer Symposium in San Antonio, TX; December 10-14, 2019. SABCS Poster #PD4-07. www.sabcs.org

2. Roche Internal Clinical Report (Protocol WO40324). Accessed 2 August 2023.

3. Roche Internal Regulatory Report (Phesgo CDS 3.0). Accessed 21 June 2023.

4. Im S, Tan A, Mattar A, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) plus chemotherapy in HER2-positive early breast cancer (EBC): Safety results from the adjuvant phase of the randomised, open-label, multicentre phase 3 (neo)adjuvant FeDeriCa study. Presented at the European Society for Medical Oncology Breast Cancer 2021 Virtual Congress May 5-8, 2021. ESMO Poster #476. www.esmo.org

5. Roche Internal Clinical Report (Phesgo IB). Accessed 03 August 2023.