Genentech
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Submitted by:
Ellen Yang, PharmD
Managed Care Medical Communications, Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: (800) 821-8590
Email: genentechmedinfo-d@gene.com
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NCCN Guidelines Panel: Breast Cancer

Dear NCCN Breast Panel,

Please find enclosed information for your review regarding Phesgo™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf) subcutaneous (SC) injection. This submission also references Perjeta® (pertuzumab), Herceptin® (trastuzumab), and Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk).

Request:
Consider the recent Food and Drug Administration (FDA) approval of Phesgo in HER2-positive neoadjuvant, adjuvant and metastatic breast cancer on June 29, 2020 and the pivotal and supportive trial publications for inclusion into the guidelines.[1-6]

Rationale:
The FDA approval is based on data from the pivotal FeDeriCA and supportive PHranceSCa studies, which are enclosed for your reference and summarized below:[2]

FeDeriCa was a Phase III, randomized, open-label trial conducted to compare the pharmacokinetic (PK) profile, efficacy, and safety of Phesgo versus intravenous Perjeta and Herceptin in patients with HER2-positive (neo) adjuvant breast cancer.[3,4] Patients receiving intravenous Perjeta and Herceptin could switch to subcutaneous Herceptin Hylecta only in the adjuvant phase while continuing Perjeta. Phesgo demonstrated non-inferiority compared with intravenous Perjeta and Herceptin based on the primary PK (pre-dose Cycle 8 pertuzumab serum trough concentration [C_{trough}]) and secondary PK (pre-dose Cycle 8 trastuzumab serum trough concentration [C_{trough}]) endpoints. Total pathological complete response (tpCR) rates, a key secondary clinical endpoint, were also similar between the two arms. For safety, there were more patients with Grade ≥3 adverse events (AE) in the Perjeta and Herceptin arm vs Phesgo arm (52.8% vs 48.8%, respectively). There were two primary and four secondary cardiac events in the Phesgo arm, and nine secondary cardiac events in the Perjeta and Herceptin arm.

PHranceSCa was a Phase 2, open-label, randomized, multi-center, two-arm, cross-over trial conducted in patients with HER2-positive early breast cancer who completed neoadjuvant treatment.[5,6] Patients received either Phesgo followed by intravenous Perjeta and Herceptin or both IV formulations first followed by Phesgo. Patients then received either Phesgo or both IV formulations for a total of 18 cycles. The primary endpoint of this study was the proportion of patients who preferred Phesgo. At an interim analysis (n=51), 82% of patients preferred Phesgo regulardless of sequencing. The U.S. Prescribing Information (PI) reports the primary analysis (n=160), which states that 85% of patients preferred subcutaneous administration of Phesgo over intravenous Perjeta and Herceptin.[1] The most common adverse events (>5%) were local injection site reaction, radiation skin injury, diarrhea, and hot flush.[5,6]

FDA Clearance:

- Phesgo is FDA-approved for neoadjuvant, adjuvant and metastatic breast cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/phesgo_prescribing.pdf
    - The loading dose of Phesgo™ is 1200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed by a

maintenance dose of 600 mg pertuzumab/600 mg trastuzumab/20,000 units hyaluronidase administered subcutaneously over approximately 5 minutes every 3 weeks.
    - The USPI reports that patients currently receiving intravenous pertuzumab and trastuzumab can transition to Phesgo.
- Perjeta, Herceptin, and Herceptin Hylecta are also FDA-approved for breast cancer. Please refer to the respective product prescribing information for the full FDA-approved indications and safety information, available at:
    - https://www.gene.com/download/pdf/perjeta_prescribing.pdf
    - https://www.gene.com/download/pdf/herceptin_prescribing.pdf
    - https://www.gene.com/download/pdf/herceptin_hylecta_prescribing.pdf

Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Ellen Yang, PharmD

References

1. Phesgo™ [package insert]. Genentech; South San Francisco, CA. 2020.
2. FDA Approves Genentech's Phesgo (Fixed-Dose Combination of Perjeta and Herceptin for Subcutaneous Injection) for HER2-Positive Breast Cancer [Press Release]. South San Francisco, CA; Genentech, Inc. June 29, 2020. Accessed from: https://www.gene.com/media/press-releases/14859/2020-06-29/fda-approves-genentechs-phesgo-fixed-dos
3. Tan A, Im SA, 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 [abstract]. In: Proceedings of the 2019 San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2020;80(4 Suppl):Abstract nr PD4-07. https://cancerres.aacrjournals.org/content/80/4_Supplement/PD4-07
4. Tan A, Im SA, 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.
5. O'Shaughnessy J. 80O- Patient (pt) preference and satisfaction with the subcutaneous fixed-dose combination of pertuzumab (P) and trastuzumab (H) in pts with HER2-positive early breast cancer (HER2+ eBC): Interim analysis of the open-label, randomised cross-over PHranceSCa study [abstract]. In: Proceedings of the European Society for Medical Oncology Breast Cancer Virtual Meeting; 2020 May 23–24: Annals of Oncology 2020; Volume 31 (2 Suppl): Abstract 800. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2820%2936099-3
6. O'Shaughnessy J, Sousa S, Cruz J, et al. 80O: Patient (pt) preference and satisfaction with the subcutaneous fixed-dose combination of pertuzumab (P) and trastuzumab (H) in pts with HER2-positive early breast cancer (HER2+ eBC): Interim analysis of the open-label, randomised cross-over PHranceSCa study. Presented at the European Society for Medical Oncology Breast Cancer Virtual Meeting May 23–24, 2020. ESMO Oral Presentation.