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Submitted by:
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NCCN Guidelines Panel: Breast Cancer

On behalf of Genentech, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel to review the following key online publication for:

- **Perjeta® (pertuzumab) and Herceptin® (trastuzumab)**: Adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC)

  von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer [supplementary appendix appears online]. N Engl J Med. E-pub Date: [published online ahead of print June 5, 2017] 2017.
  http://www.nejm.org/doi/pdf/10.1056/NEJMoa1703643

Specific Changes:

- Please consider the Phase 3 APHINITY trial results for your evaluation of adjuvant Perjeta, trastuzumab and chemotherapy in patients with operable HER2-positive EBC.

FDA Clearance:

- Perjeta is not FDA-approved for treatment of patients with HER2-positive breast cancer in the adjuvant setting.
- Perjeta is FDA-approved for use in combination with trastuzumab and docetaxel for the 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. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival.

  Limitations of Use:
  - The safety of Perjeta as part of a doxorubicin-containing regimen has not been established.
  - The safety of Perjeta administered for greater than 6 cycles for early breast cancer has not been established.

- Herceptin is FDA-approved for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer:
  - As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
  - As a part of a treatment regimen with docetaxel and carboplatin
  - As a single agent following multi-modality anthracycline based therapy

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

Please refer to the product prescribing information for the full FDA-approved indications and safety information.

- Full Perjeta® prescribing information available at: http://www.gene.com/download/pdf/perjeta_prescribing.pdf
- Full Herceptin® prescribing information available at: https://www.gene.com/download/pdf/herceptin_prescribing.pdf

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Rationale:
APHINITY is a Phase 3, randomized, multicenter, double-blind, placebo-controlled study conducted to evaluate the efficacy of chemotherapy and 1 year of Perjeta plus trastuzumab compared to chemotherapy and 1 year of placebo plus trastuzumab in adjuvant HER2-positive EBC. The study met its primary end point of invasive disease-free survival (iDFS), which was defined as time from randomization to recurrence of invasive breast cancer or death.

- At a median follow up of 45.4 months, patients in the Perjeta arm had a statistically significant improvement in iDFS vs. the control arm (hazard ratio=0.81; 95% CI, 0.66-1.00; p=0.045). The 3-year rate of iDFS was 94.1% in Perjeta-treated patients and 93.2% in placebo-treated patients.
- The safety profile of the Perjeta-based regimen was consistent with previous clinical studies and no new safety signals were identified. Adverse events $\geq$ Grade 3 were reported in 64.2% of Perjeta-treated patients and 57.3% of placebo-treated patients, with diarrhea being more common in Perjeta-treated patients than placebo (9.8% vs 3.7%, respectively) during the chemotherapy phase of the study.

Currently, APHINITY is the only Phase 3 trial with published results that has been conducted to evaluate Perjeta in the adjuvant treatment of HER2-positive EBC.

Respectfully submitted,

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