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Submitted by:
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Date of request: June 29, 2015
NCCN Guidelines Panel: Breast Cancer

On behalf of Genentech, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed recent presentations for:

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

  Gianni L, Pienkowski T, Im Y-M, et al. Five-year analysis of the Phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, Illinois; May 29–June 2, 2015. ASCO Abstract #505.

  Gianni L, Pienkowski T, Im YM, et al. Five-year analysis of the Phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, Illinois; May 29–June 2, 2015. ASCO Oral presentation #505.

  Abstract can be found at: http://meetinglibrary.asco.org/content/147709-156

- **Perjeta® (pertuzumab) and Kadcyla® (ado-trastuzumab emtansine):** First-line treatment of HER2-positive metastatic breast cancer (MBC)

  Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine ± pertuzumab vs trastuzumab + taxane for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, Illinois; May 29–June 2, 2015. ASCO Oral Presentation #507.

  Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. Presented at the American Society of Clinical Oncology 2015 Annual Meeting in Chicago, IL; May 29–June 2, 2015. ASCO Abstract #507.

  Abstract can be found at: http://meetinglibrary.asco.org/content/147990-156

Specific Changes:

Please consider the Gianni et al. and Ellis et al. presentations for your updating purposes.

FDA Clearance:

- Perjeta®: is FDA-approved for use in combination with Herceptin and docetaxel 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.
- The combination of Perjeta® and Kadcyla® is not FDA approved for the treatment of metastatic breast cancer.

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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 Kadcyla® prescribing information avaialbe at: http://www.gene.com/download/pdf/kadcyla_prescribing.pdf

Rationale:

- **Gianni et al.**: Efficacy and safety results were previously submitted for the randomized, multicenter, international, open-label, Phase 2 neoadjuvant study of Perjeta and Herceptin (NeoSphere) in patients with locally advanced, inflammatory, or early HER2-positive breast cancer.[1] Disease-free survival (DFS) and progression-free survival (PFS) were secondary endpoints in the study. Pre-planned, follow-up analyses of DFS and PFS rates were conducted in the intent-to-treat population 5 years following randomization of the last patient. Results were descriptive and not statistically powered. Five-year DFS rate in patients treated with Perjeta, trastuzumab and docetaxel (PTD) was 84% compared with 81% in patients treated with trastuzumab, docetaxel (TD) [hazard ratio (HR)=0.60, 95% CI 0.28-1.27] and 80% and 75% in those treated with Perjeta + trastuzumab (PT) and Perjeta + docetaxel (PD), respectively. Five-year PFS rate in patients treated with PTD was 86% compared with 81% in patients treated with TD (HR=0.69, 95% CI 0.34-1.4) and 73% and 73% in patients treated with PT and PD, respectively.. No changes in the overall safety profile were noted from previous publication.[1] Additional data on the use of Perjeta and Herceptin in the neoadjuvant setting has been reported.[2]

- **Ellis et al.**: In a Phase III, randomized, controlled trial of 1,095 patients with locally advanced or metastatic breast cancer, Kadcyla with or without Perjeta was compared with Herceptin plus a taxane as first-line therapy. The primary endpoints were PFS assessed by independent review and safety. Secondary endpoints included overall response rate (ORR), overall survival (OS), duration of response (DOR), time to treatment failure (TTF), quality of life (QOL) and investigator-assessed PFS. To control the overall type I error, the MARIANNE study was designed to test the primary efficacy endpoint and key secondary efficacy and safety endpoints in a hierarchical sequence. Progression-free survival was tested first for non-inferiority for each of the Kadcyla-containing treatment arms versus Herceptin and a taxane at a 2-sided alpha of 2.5%. Subsequently, PFS superiority was tested at the same level of alpha for the comparison groups which achieved non-inferiority. A formal PFS superiority of Kadcyla and Perjeta versus Kadcyla alone could have been tested if Kadcyla and Perjeta achieved PFS superiority over Herceptin and a taxane. The HR for PFS for Kadcyla with Perjeta was non-inferior (stratified HR=0.87; 97.5% CI 0.69-1.08; p=0.14) to Herceptin and a taxane. The HR for PFS for Kadcyla alone was non-inferior (stratified HR=0.91; 97.5% CI 0.73-1.13; p=0.31) to Herceptin plus a taxane. The HR for PFS for Kadcyla and Perjeta was not statistically superior compared with Kadcyla alone (stratified HR=0.91; 97.5% CI 0.73-1.13; p=0.31). The incidence of Grade 3-5 adverse events was 54.1%, 45.4%, and 46.2% in the Herceptin plus a taxane arm, the Kadcyla alone arm, and the Kadcyla plus Perjeta arm, respectively. Health-related quality of life was maintained for a longer duration with a median of 7.7 months for Kadcyla alone (HR=0.70; 95% CI 0.57-0.86) and a median of 9 months for Kadcyla with Perjeta (HR=0.68; 95% CI 0.55-0.84) compared with a median of 3.9 months for Herceptin and a taxane. Additional data on the use of Kadcyla in combination with Perjeta in patients with MBC have been reported.[3-5]

Respectfully submitted,

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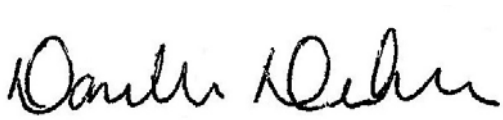

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Supplemental References

1. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, Phase 2 trial. Lancet Oncol 2012;13:25-32. http://www.ncbi.nlm.nih.gov/pubmed/22153890.
2. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized Phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-2284. http://www.ncbi.nlm.nih.gov/pubmed/23704196.
3. Miller KD, Dieras V, Harbeck N, et al. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2-positive, locally advanced, or metastatic breast cancer. J Clin Oncol 2014;32:1437-1444.
4. Elias A, Modi S, Krop IE, et al. Results from a Phase 2a study of trastuzumab emtansine (T-DM1), paclitaxel, and pertuzumab in patients with human epidermal growth factor receptor-positive metastatic breast cancer. Presented at the San Antonio Breast Cancer Symposium in San Antonio, TX; December 10–13, 2013. SABCS Poster #P4-12-09.
5. Martin M, Garcia-Sáenz J, Dewar JA, et al. Interim results from a Phase 1b/2a study of trastuzumab emtansine and docetaxel, with and without pertuzumab, in patients with HER2-positive locally advanced or metastatic breast cancer. Presented at the San Antonio Breast Cancer Symposium in San Antonio, TX; December 4–8, 2012. SABCS Poster #P5-18-O5.

C#15-M0083