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NCCN Guidelines Panel: Breast Cancer

Dear NCCN Guidelines Breast Panel:

Please find references for your review regarding Tecentriq® (atezolizumab), Perjeta® (pertuzumab) and Kadcyla® (ado-trastuzumab emtansine). This submission also references Herceptin® (trastuzumab).

Requests:

1. Consider the enclosed IMpassion130 posters and presentation on the use of Tecentriq plus paclitaxel protein-bound for the treatment of patients with unresectable locally advanced or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 for your drug information updating needs. Primary efficacy and safety results were previously submitted.
2. Consider the enclosed CLEOPATRA poster of Perjeta plus Herceptin plus docetaxel in the first-line treatment of patients with metastatic breast cancer (MBC) for your drug information updating needs.
3. Consider the enclosed KATHERINE presentation on the use of Kadcyla in the adjuvant treatment of patients with HER2-positive early breast cancer who had had residual invasive disease after neoadjuvant systemic therapy for your drug information updating needs. Primary efficacy and safety results were previously submitted.
4. Consider the enclosed KRISTINE publication on the use of Kadcyla plus Perjeta in the adjuvant treatment of patients with HER2-positive early breast cancer (EBC).

Key Takeaways: Tecentriq

- The second interim analysis of the IMpassion130 trial maintained a numerical median overall survival (OS) improvement in the PD-L1+ population of patients receiving Tecentriq plus *nab*-paclitaxel in the first line metastatic TNBC setting.[1,2] These results were consistent with the first interim analysis.[2] An updated safety analysis reported no cumulative toxiciities and no new- or late-onset safety signals were observed.[3] There were no difference in time-to-deterioration in health-related quality of life, a pre-specified endpoint, between the treatment arms for the intent-to-treat or PD-L1-positive population.[4,5]

Key Takeaways: Perjeta

- The descriptive end-of-study analysis of the CLEOPATRA trial provided 8-year follow-up survival and safety data of Perjeta plus Herceptin plus docetaxel in patients with HER2-positive MBC.[6] The Perjeta plus Herceptin plus docetaxel arm reported a numerical OS benefit compared with the Herceptin plus docetaxel arm. The long-term overall safety and cardiac safety profiles for Perjeta plus Herceptin plus docetaxel also remained consistent with previous reports.

Key Takeaways: Kadcyla

- The pre-specified patient-reported outcomes (PRO) analysis of the KATHERINE study reported that at some point timepoints, patients in the Kadcyla arm showed deterioration in some symptoms compared with Herceptin; however, baseline global health status and functioning were generally maintained in both arms over the treatment course.[7,8]
- The final analysis of the KRISTINE study provided 3-year efficacy, safety, and PROs of neoadjuvant Kadcyla plus Perjeta vs. Herceptin plus Perjeta plus conventional systemic chemotherapy in Stage II-III HER2-positive breast cancer patients.[9] The primary endpoint of pathological complete response (pCR) was not met and results were previously published.[10] Secondary endpoints were not powered to detect statistically significant differences. Grade ≥3 adverse events (AE) were more common in

the Kadcyla plus Perjeta arm during the adjuvant treatment period, though Grade ≥3 AEs were less common in the Kadcyla plus Perjeta arm during the neoadjuvant treatment period.

FDA Clearance:

- Tecentriq is FDA-approved for use in the PD-L1 positive metastatic TNBC. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf
- Kadcyla is not FDA-approved for use in the early and metastatic HER2-positive 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/kadcyla_prescribing.pdf
- Perjeta is FDA-approved for use in the early and metastatic HER2-positive 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/perjeta_prescribing.pdf
- Herceptin is FDA-approved for use in the early and metastatic HER2-positive breast cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information of Herceptin, available at: https://www.gene.com/download/pdf/herceptin_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. Schmid P, Adams S, Rugo HS, et al. IMpassion130: updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + nab-paclitaxel in previously untreated locally advanced or metastatic TNBC. Presented at the American Society of Clinical Oncology Annual Meeting in Chicago, IL; May 31–June 4, 2019. ASCO Oral Presentation.
2. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer [supplementary appendix appears online]. N Engl J Med 2018;379:2108-2121. https://www.ncbi.nlm.nih.gov/pubmed/30345906
3. Schneeweiss A, Rugo H, Winer E, et al. IMpassion130: Expanded safety analysis from a P3 study of atezolizumab (A) + nab-paclitaxel (nP) in patients (pts) with treatment (tx)-naïve, locally advanced or metastatic triple negative breast cancer (mTNBC). Presented at the Annual Meeting of the American Society of Clinical Oncology in Chicago, IL; May 31–June 4, 2019. ASCO Poster.
4. Adams S, Dieras V, Barrios C, et al. Patient-reported outcomes (PROs) from the phase III IMpassion130 trial of atezolizumab (atezo) plus nabpaclitaxel (nP) in metastatic triple-negative breast cancer (mTNBC). Presented at the Annual Meeting of the American Society of Clinical Oncology in Chicago, IL; May 31–June 4, 2019. ASCO Poster.
5. Protocol for IMpassion130: A Phase III, Multicenter, Randomized, Placebo-Controlled Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination with NAB-Paclitaxel for Patients with Previously Untreated Metastatic Triple-Negative Breast Cancer. January 2015. Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1809615/suppl_file/nejmoa1809615_protocol.pdf. Accessed on July 23, 2019.
6. Swain SM, Miles D, Kim SB, et al. End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)-controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC).
7. Schneeweiss A, Loibl S, Mamounas E, et al. Patient-Reported Outcomes from KATHERINE: A Phase III Study of Adjuvant Trastuzumab Emtansine vs Trastuzumab in Patients with Residual Invasive Disease after Neoadjuvant Therapy for HER2-Positive Breast Cancer. Presented at the Annual Meeting of the American Society of Clinical Oncology in Chicago, IL; May 31–June 4, 2019. ASCO Poster.
8. Protocol for KATHERINE: Trastuzumab emtansine for residual invasive HER2-positive breast cancer June 2012. Available at

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1814017/suppl_file/nejmoa1814017_protocol.pdf Accessed on July 23, 2019.

9. Hurvitz S, Martin M, Jung K, et al. Neoadjuvant Trastuzumab Emtansine and Pertuzumab in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Three-Year Outcomes From the Phase III KRISTINE Study. J Clin Oncol 2019;1-17.
10. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;19:115-126.