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NCCN Guidelines Panel: Breast Cancer

Dear NCCN Breast Panel,

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

Requests:

1. Consider the recent Phase 3 KATHERINE publication on the adjuvant use of Kadcyla in patients with HER2-positive early breast cancer (eBC) who have residual disease following neoadjuvant chemotherapy and HER2-targeted therapy for inclusion into the guidelines.
2. Consider the recently presented IMpassion130 biomarker analysis as additional support for the inclusion of the following into the guidelines:
    - Tecentriq + nab-paclitaxel in PD-L1+ patients with first-line metastatic triple-negative breast cancer (TNBC).
    - PD-L1 testing on immune cells as part of the workup for Recurrent/Stage IV breast cancer. (BINV-18)

Rationale-Kadcyla:

KATHERINE is a Phase 3, randomized, open-label trial conducted to evaluate the efficacy and safety of adjuvant treatment with Kadcyla vs. Herceptin in patients with HER2-positive eBC who had residual invasive disease after neoadjuvant systemic therapy.[1] The trial met its primary endpoint of invasive disease-free survival (IDFS). The safety profile was consistent with previously reported safety risks of Kadcyla.

- KATHERINE randomized 1,486 patients with HER2-positive early breast cancer who had pathologic residual invasive tumor in the breast and/or axilla following neoadjuvant treatment with taxane- and Herceptin-containing therapy to receive 14 cycles of Kadcyla or Herceptin.[1] Patients who received neoadjuvant dual HER2-targeted therapy were also included in the study.
- At this pre-specified interim analysis, IDFS results crossed the early reporting efficacy boundary which triggered a full study analysis for Kadcyla.[1] Patients treated in the adjuvant setting with Kadcyla experienced significant improvement in IDFS compared to patients treated with Herceptin (Hazard ratio [HR]: 0.50; 95% CI: 0.39-0.64; p<0.001).[1] The 3-year IDFS rates were 88.3% and 77.0% for Kadcyla and Herceptin, respectively. Consistent IDFS results were seen across stratification cohorts and other subgroups, including patients treated irrespective of neoadjuvant HER2-targeted therapy and patients with small residual primary disease.
- Overall survival is a secondary endpoint of KATHERINE. At the time of data-cut off, the OS analysis did not cross the early reporting boundary (HR: 0.70; 95% CI: 0.47-1.05) with 98 deaths reported.[1]
- The following adverse events (AE) rates were observed for Kadcyla and Herceptin:
    - Serious AEs occurred in 12.7% and 8.1%, respectively.[1] Overall Grade ≥3 AEs occurred in 25.7% and 15.4%, respectively. For Grade ≥3 AEs, decreased platelet count and hypertension were the most common for Kadcyla, and hypertension and radiation-related skin injury for Herceptin.

- The AE profile of Kadcyla was consistent with prior studies, with an expected higher rate of AEs for Kadcyla compared with adjuvant Herceptin alone.

Rationale-Tecentriq:

The IMpassion130 study met its co-primary endpoints of progression-free survival (PFS) in the intent-to-treat (ITT) and PD-L1-positive (PD-L1+) population for Tecentriq + nab-paclitaxel versus placebo + nab-paclitaxel.[2] OS in the ITT and PD-L1+ populations were also co-primary endpoints and were previously submitted. The safety profile was consistent with previously reported safety risks of the individual medicines. Pre-specified biomarker subgroup analyses were recently presented.[3,4]

- Both PFS and OS benefit were observed in PD-L1 immune cell (IC)-positive patients, defined as PD-L1 expression of ≥ 1% on immune cells, for Tecentriq + nab-paclitaxel compared with placebo + nab-paclitaxel.[3] However, PFS and OS benefit were not seen for Tecentriq + nab-paclitaxel compared with placebo + nab-paclitaxel in the PD-L1 IC-negative subgroup.
- No additional safety results were reported.[3]

FDA Clearance:

- Kadcyla is not FDA-approved for early breast cancer.[5] Please refer to the product prescribing information for the full FDA-approved indications and safety information of Kadcyla, available at:
  - https://www.gene.com/download/pdf/kadcyla_prescribing.pdf
- Herceptin is FDA-approved for early breast cancer.[6] 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
- Tecentriq is not FDA-approved for triple-negative breast cancer.[7] Please refer to the product prescribing information for the full FDA-approved indications and safety information of Tecentriq, available at:
  - https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

Additional studies have been conducted to evaluate Kadcyla in early breast cancer[8-13] and Tecentriq in triple-negative breast cancer.[14-15]

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,
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