Letter to the Editor

Clinical Consequences of Altering the Definition of HER2-Positive Breast Cancer to Exclude Group 2, HER2-Negative Disease

Invasive breast cancers are classified as HER2-positive or HER2-negative. Essentially all of the pivotal adjuvant and metastatic breast cancer studies defined HER2-positive breast cancers as those tumors either with immunohistochemistry (IHC) assays demonstrating 3+ HER2 protein expression or fluorescence in situ hybridization (FISH) assays showing *HER2/CEP17* ratio ≥2.0 or, more recently, ≥6 *HER2* gene copies per cancer cell.

In 2018, an American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) expert panel recommended changing the breast cancer HER2 classification scheme. Among the changes, the panel recommended reclassifying cancers with FISH *HER2/CEP17* ratio ≥2 but with <4 *HER2* gene copies/cancer cell as HER2-negative (Group 2, HER2-negative). The panel suggested that pathology reports include the statement "evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with a *HER2/CEP17* ratio of ≥2 and an average *HER2* copy number of <4.0 per cell. In the first generation of adjuvant trials, patients in this subgroup who were randomly assigned to the trastuzumab arm did not seem to derive an improvement in disease-free or overall survival, but there were too few such cases to draw definitive conclusions."[1]

The NCCN Breast Cancer Panel endorsed the 2018 ASCO/CAP recommendations for reclassification. However, on the "Principles of Biomarker Testing: HER2 Testing" page in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer (page BINV-A; available at NCCN.org), the algorithm clearly defines FISH *HER2/CEP17* ratio ≥2 but with <4 *HER2* copies/cancer cell as HER2-negative (Group 2, HER2-negative), but with the exact same biomarker results, later in the guideline (page MS-4), the discussion states, "The rationale cited by the joint committee for including rare scenarios such as HER2 positivity when dual probe *HER2/CEP17* ratio is greater than or equal to 2.0 and average *HER2* copy number is less than 4 signals/cell is that … ."[2]

Based on the pre-2018 ASCO/CAP HER2 classification, whether being used as adjuvant therapy or therapy for metastatic HER2-positive disease, the FDA-approved anti-HER2 therapies offer truly remarkable benefits compared with treating patients with HER2-positive disease without those therapies. For example, as adjuvant therapy, anti-HER2 therapies reduce the relative risk of recurrence by >85% and for metastatic disease they prolong survival by years compared with not using anti-HER2 therapies.[2]

Although patients with Group 2, HER2-negative tumors are uncommon, the clinical consequences of the 2018 ASCO/CAP change and NCCN Breast Cancer Panel endorsement of the change are profound for these patients. For example, for years CDK4/6 inhibitors have been FDA approved as highly effective therapy for patients with hormone receptor (HR)–positive, HER2-negative metastatic breast cancers. Last year, the large monarchE adjuvant trial was reported to show an improvement in disease-free survival with CDK4/6 inhibitor use as adjuvant therapy for HR-positive, HER2-negative cancers.[3] Clinical trials of CDK4/6 inhibitors in metastatic breast cancer and the monarchE trial have excluded patients with Group 2, HER2-negative cancers, so it is unknown whether these patients would derive similar benefits.[3]

One of the investigators who reported the data used to justify the creation of Group 2, HER2-negative breast cancer responded to the suggestion that clinical trials be initiated to confirm the appropriateness of this creation, writing that "such clinical trials require patients to make commitments with their lives to these studies and are very expensive."[4] I agree.

However, there have now been many large adjuvant anti-HER2 therapy clinical trials and many large trials of anti-HER2 therapies for metastatic disease reported.[5,6] Particularly if the data from these trials are combined, I suspect that retrospective data could be generated from these trials to determine whether patients on these clinical trials with Group 2, HER2-negative tumors benefitted from anti-HER2 therapy. I believe most oncologists and their patients will appreciate further confirmation of the rationale for the creation of Group 2, HER2-negative breast cancer recommended by the 2018 ASCO/CAP expert panel, and endorsed by the NCCN Breast Cancer Panel.

As Heraclitus wrote, "no man ever steps in the same river twice," which has been interpreted to mean that an opportunity lost is lost forever. The opportunity to add to the level of evidence that was used by the NCCN Breast Cancer Panel to adopt the 2018 ASCO/CAP guideline is available. Oncologists and their patients will be much more comfortable choosing or not choosing anti-HER2 and CDK4/6 inhibitor therapy if the data from those many large trials are reported.

Steven Sorscher, MD[a]

[a]*Wake Forest School of Medicine, Winston-Salem, North Carolina*
Email: ssorsche@wakehealth.edu

doi: 10.6004/jnccn.2021.7053

References

1. Wolff AC, Hammond EH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol 2018;36:2105–2122.
2. Gradishar WJ, Anderson BO, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 6. 2020. Accessed September 8, 2020. To view the most recent version, visit NCCN.org
3. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38:3987–3998.
4. Press M, Slamon DJ. Controversies in HER2 oncogene testing: what constitutes a true positive result in patients with breast cancer? Letter to the editor: the authors respond. Accessed October 1, 2020. Available at: https://www.gotoper.com/publications/ajho/2017/2017october/controversies-in-her2-oncogene-testing-what-constitutes-a-true-positive-result-in-patients-with-breast-cancer
5. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617–628.
6. Johnston SDR, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal woman with HER2-positive, hormone receptor-positive metastatic breast cancer: updated results of ALTERNATIVE. J Clin Oncol 2021;39:79–89.