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Congress Abstract

HER2-Ultralow in Invasive Breast Cancer: Frequency, Reclassification and Concordance of HER2 Status Assessment

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Introduction: The expansion of indications for trastuzumab deruxtecan following the DESTINY-Breast06 trial has increased the clinical relevance of minimal HER2 membrane staining that was previously included within the HER2 0 category. In the current CAP protocol, HER2 0 is further subdivided into 0 with no membrane staining and 0+ with membrane staining, corresponding to the HER2-ultralow phenotype. Conventional HER2 immunohistochemistry (IHC) has historically been focused on identifying HER2 overexpression, whereas assessment of very low levels of HER2 staining is less reproducible. This places greater emphasis on the distinction between HER2 0 with no detectable expression (HER2-null), HER2-ultralow, and HER2 IHC 1+.

Objective: To determine the frequency of HER2-ultralow expression among invasive breast carcinomas initially classified as HER2 0, to assess patterns of reclassification on repeat review, and to evaluate concordance between the initial and repeat standard HER2 status.

Materials and Methods: A retrospective single-center study included 241 cases of invasive breast carcinoma without prior neoadjuvant therapy diagnosed between January and July 2026. Initial HER2 status was assessed by IHC in routine clinical practice according to the 2023 ASCO/CAP recommendations, and all slides were subsequently reviewed by a second pathologist. IHC was performed using the HER2 antibody clone 4B5 (Ventana). During repeat assessment, HER2 0 cases were further subclassified as HER2-null or HER2-ultralow. For concordance analysis, both subcategories were combined within the conventional HER2 0 category. Overall percent agreement and Cohen's κ coefficient were calculated. Clinicopathological associations were evaluated in an exploratory analysis.

Results: The initial HER2 distribution was as follows: 0 in 112/241 cases (46.5%), 1+ in 66 (27.4%), 2+ in 24 (10.0%), and 3+ in 39 (16.2%). Following repeat review, HER2-ultralow expression was identified in 55/241 cases (22.8%). Among the 112 tumors initially classified as HER2 0, 61 (54.5%) were categorized as HER2-null, 44 (39.3%; 95% CI, 30.7–48.5%) as HER2-ultralow, and 7 (6.2%) were reclassified as HER2 1+. Standard HER2 status changed in 22/241 cases (9.1%), with 20/22 discrepancies (90.9%) occurring at the HER2 0↔1+ boundary. Overall agreement was 90.9%, with a Cohen's κ of 0.864. Among tumors initially classified as HER2 0 with known hormone receptor (HR) status, HER2-ultralow expression was identified in 35/80 (43.8%) HR-positive tumors and 2/16 (12.5%) HR-negative tumors (OR, 5.44; 95% CI, 1.16–25.55; p=0.024). No statistically significant differences were observed according to histologic grade or Ki-67 proliferation index.

Discussion and Conclusions. HER2-ultralow expression was identified in 39.3% of tumors initially classified as HER2 0, a proportion comparable with that reported in recent retrospective studies. Changes in HER2 classification occurred predominantly at the HER2 0↔1+ boundary, highlighting the diagnostic vulnerability of the lower

range of HER2 expression. Although concordance for conventional HER2 categories was high (κ=0.864), this analysis does not assess the reproducibility of distinguishing HER2-null from HER2-ultralow because interobserver agreement specifically at this boundary was not evaluated. These findings emphasize the heterogeneity of the HER2 0 category and support the importance of standardized assessment and explicit reporting of minimal HER2 membrane staining in routine pathologic practice.

Keywords: Breast Cancer; HER2-Ultralow; Immunohistochemistry