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EDITORIAL

Is HER2-Low a New Clinical Entity or Merely a Biomarker for an Antibody Drug Conjugate?

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Key Summary Points

Since the U.S. Food and Drug Administration (FDA) approval of trastuzumab deruxtecan (T-DXd) for advanced HER2-low breast cancer, researchers and clinicians have raised an important question of whether HER2-low should be considered as a separate clinical entity with distinct molecular and clinicopathological features, or solely a biomarker for a HER2-directed antibody–drug conjugate.

If HER2-low is considered as a separate clinical subtype, this may require updating the clinical guidelines on human epidermal growth factor receptor 2 (HER2) scoring and testing in breast cancer along with its therapeutic indication.

This editorial provides current available data on characteristics of HER2-low breast cancer, and most importantly, addresses the recent timely updates from the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines on reporting terminology for HER2-low versus HER2-negative breast cancer.

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Human epidermal growth factor receptor 2 (HER2) expression has historically been scored on a continuous scale from very low/absent to very high (0 to 3+) using an immunohistochemistry (IHC) staining assay. A HER2 IHC score of 0 represents a staining pattern where there is no staining or incomplete membrane staining that is faint or barely perceptible in less than 10% of tumor cells. A score of 1+ is defined as faint or barely perceptible incomplete membrane staining in more than 10% of tumor cells. Tumors with weak–moderate complete membrane staining in more than 10% of tumor cells are scored as 2+. Lastly, tumors with complete, intense membrane staining involving more than 10% of tumor cells receive a 3+ expression score. Historically, breast cancer has been classified as HER2-positive when the expression is scored as 3+ or 2+ by IHC—if gene amplification is further confirmed in the latter by in situ hybridization (ISH), which is defined by a HER2/CEP17 ratio of less than 2.0, with an average HER2 copy number of 4.0 to 5.9 per cell [1]. HER2-directed therapies, including naked antibodies such as trastuzumab [2] and pertuzumab [3] and small-molecule inhibitors such as lapatinib [4], were indicated for patients with HER2-positive breast cancer. However, this paradigm shifted in 2022 when the results of the DESTINY-Breast04 clinical trial [5] not only unlocked a new unique treatment option of a HER2-directed antibody–drug conjugate (ADC) but also supported a newly described category called HER2-low, tumors with HER2 IHC scores of 1+ or 2+ with negative ISH [6, 7]. This trial found that targeting low levels of HER2 expression with trastuzumab deruxtecan (T-DXd) in patients with metastatic breast cancer resulted in better outcomes than those treated with chemotherapy. The risk of disease progression or death was about 50% lower and the risk of death was 36% lower with T-DXd than with chemotherapy, regardless of hormone receptor status [5]. These results led to the U.S. Food and Drug Administration (FDA) approval of T-DXd for the treatment of advanced HER2-low breast cancer. As a result, clinical guidelines have been updated to recommend this new standard-of-care therapy in advanced HER2-low breast cancer [8].

While the results of DESTINY-Breast04 are practice-changing, this newly identified category of HER2-low breast cancer has raised several questions and challenges among researchers and clinicians. One of the questions is whether HER2-low breast cancer should be classified as a separate clinical entity [9]. To be considered as an independent breast cancer subtype, a few key questions need to be addressed: (1) Do HER2-low tumors display molecular and clinical characteristics distinct from other subtypes of breast cancer? (2) How does HER2-low status affect prognosis and survival outcomes in breast cancer? Understanding whether HER2-low tumors exhibit different behaviors that translate into better survival outcomes as compared to HER2-negative will be necessary before classifying it as a new category of breast cancer. However, these questions remain under investigation.

Experts continued to debate whether HER2-low should be considered a separate clinical entity or solely a biomarker for targeted therapy at the 2022 San Antonio Breast Cancer Symposium [10]. Several studies have also shown contradictory results in addressing this question [11]. A few studies have shown that there were differences in gene expression profiles between HER2-low and HER2-negative breast cancer; however, this was largely driven by the hormone receptor (HR) status [12, 13]. A pooled analysis of four prospective neoadjuvant clinical trials showed that patients with HER2-low tumors had significantly longer survival but lower pathological complete response (pCR) rates than HER2-negative tumors, suggesting that HER2-low breast cancer should be considered a different subtype [14].

On the contrary, a more recent large-scale retrospective cohort study demonstrated that there were minimal prognostic differences between HER2-low and HER2-negative breast cancer. In a multivariable analysis, the investigators found that HER2-low status was associated with small improvements in overall survival (OS) and lower rates of pCR [15]. However, these differences were small in magnitude and were likely attributable to other factors such as HR-positive luminal versus triple-negative basal-like biology rather than the

low level of HER2 expression on the cell surface. These studies concluded that there were no statistically significant differences in survival outcomes between HER2-low and HER2-negative breast cancer, and therefore, HER2-low should not be considered a separate clinical entity.

There are clinical and pathological considerations that need to be considered for widespread implementation of therapeutic recommendations in advanced HER2-low breast cancer [9]. Clinicians need to be better informed of the clinical significance and complex characteristics of HER2-low breast cancers as our current understanding of HER2-low expression evolves. HER2-low expression status may be subject to temporal fluctuations, and its expression status may change during the course of a patient's therapy and/or disease progression. Thus, a tumor that expresses low levels of HER2 initially may lose all HER2 expression, or vice versa. This appears to be in direct contrast to HER2-overexpressing tumors, which tend to be more stable in their genomic aberration over time [16–18]. As a result, one could argue that HER2 expression itself is not consistent enough to define HER2-low as an independent subtype of breast cancer.

A major pathological challenge to accommodating the new treatment paradigm in advanced HER2-low breast cancer will be the accurate staining of HER2 samples and subsequent interpretation of the test results. The distinction between 0 and 1+ IHC scores has held no clinical significance up to now when testing for canonically defined HER2-positive tumors. The interpretation of the 1+ IHC score may be viewed as subjective, as some laboratories may interpret it as 1+ while others may interpret it as 0 or negative. Surveys from the College of American Pathologists showed that the concordance rate between 0 and 1+ interpretation among laboratories was only 26%, compared to 58% concordance between 2+ and 3+ scoring [19]. Standardizing techniques and laboratory parameters may reduce interobserver variability and improve the reliability of HER2-low assessment. In addition, strict protocol recommendations for HER2-low identification should be considered from vendors of FDA-approved HER2 companion diagnostics such as Roche/Venta and Agilent/Dako.

Current data are conflicting and insufficient to support a new classification of HER2 IHC 0 versus 1+ as prognostic or predictive threshold for therapy. Clinical trial data regarding HER2-directed ADC on HER2-negative tumors are limited. Patients with tumors with IHC scores of 0 were excluded from the DESTINY-Breast04 trial, and evidence is lacking that these tumors have distinct biology or that they respond differently to HER2-directed ADCs. The phase II DAISY trial demonstrated that the objective response rates (ORR) of HER2-low and HER2-negative breast cancers were similar when treated with T-DXd (37.5% vs. 29.7%, respectively), suggesting that HER2 expression may not be the sole determinant of T-DXd efficacy [20]. This may be due to the notion that HER2 expression varies on a continuous scale, and some tumors with HER2 IHC 0 (between 0 and 1) could have a degree of HER2 expression and may not be entirely HER2-negative. The DESTINY-Breast06 trial (NCT04494425), which is currently enrolling patients with tumors of IHC > 0 but $< 1+$, will provide more information [21]. Nevertheless, HER2-low is a clinically relevant biomarker for the treatment with T-DXd given the remarkable survival benefits seen with T-DXd over chemotherapy in patients with HER2 IHC 1+ or 2+/ISH-negative tumors. Pathologists and clinicians, therefore, should be aware that an IHC 0 versus IHC 1+ result has a new treatment implication in the metastatic setting.

Due to these aforementioned challenges, recent updates from American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines do not recommend changing the reporting terminology or designating a new classification for patients with a HER2 IHC score of 0 or 1+ at this time. HER2 IHC 0 or 1+ results should still be interpreted as HER2-negative using the previously recommended scoring algorithm; however, a quantitative IHC score (e.g., 1+ staining present) should be included on the report to identify those patients who may benefit from T-DXd [22].

The story is not over yet. We await the results from future studies to discern whether HER2-low tumors have distinct molecular and phenotypic features or whether HER2-low status remains a biomarker for HER2-directed ADCs.

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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