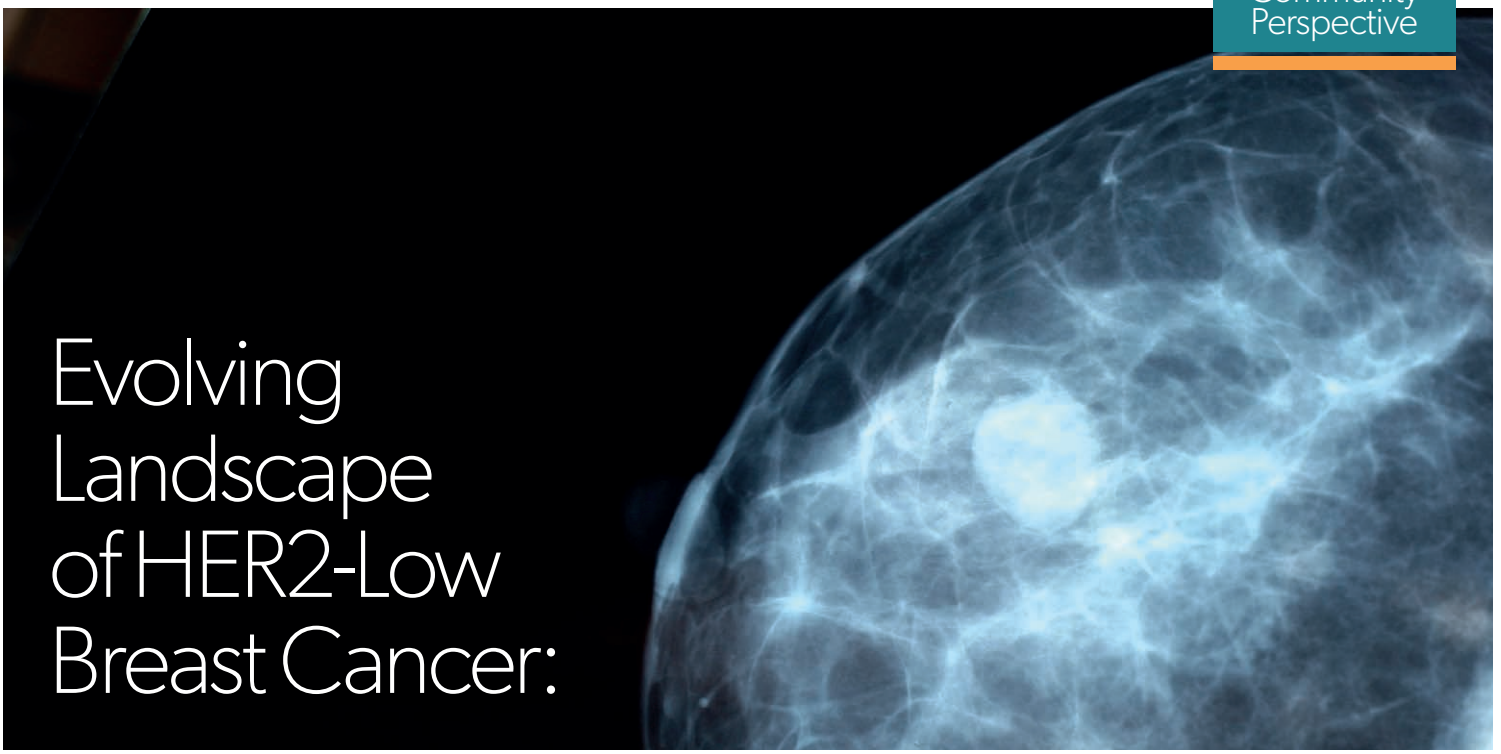

Evolving Landscape of HER2-Low Breast Cancer:

New Diagnosis and Treatment Paradigm Shift

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IN THE US, breast cancer is the most common cancer and the second most common cause of cancer death among women.[1] Like other cancers, breast cancer is a heterogeneous disease with various oncogenic drivers. Treatment decisions rely on evaluating the intrinsic biological factors that distinguish the four primary clinical subtypes, which are then further differentiated based on receptor status: luminal-A like (estrogen receptor (ER) and progesterone receptor (PR)-positive, human epidermal growth factors receptor 2 (HER2)-negative with low proliferative rate), luminal B-like (ER/PR positive, HER2-negative with high proliferative rate), HER2-enriched, and triple-negative or basal-like breast cancer.[2]

ER, PR, and HER2 drive tumorigenesis of most breast cancers, and their expression signifies a dependence on these hormones or growth factors that further suggests targeted therapies may be effective. ER and PR are cytoplasmic hormone receptors (HR) that translocate to the nucleus upon binding their respective ligands, and most breast cancer patients, about 84 percent, will have tumors that express HR. In contrast to ER and PR, HER2 is a membranous cell surface receptor that activates upon dimerization, causing a signaling cascade that promotes cancer growth. ERBB2, the gene that encodes the HER2 protein, is amplified in about 15 percent of breast cancers, resulting in its overexpression. HER2-positive tumors display a more aggressive behavior than HER2-negative tumors, but the development of HER2-directed therapies has changed the trajectory of HER2-positive breast cancer.[3]

In clinical practice, testing for ER, PR, and HER2 is generally performed at the time of initial diagnosis due to the prognostic and therapeutic importance of these biomarkers. Immunohistochemical evaluation alone is adequate for evaluation of ER and PR but a combination of immunohistochemistry (IHC) and *in situ* hybridization (ISH) is utilized for HER2 analysis.[2] In this paper, we discuss the use of a complex testing algorithm for HER2 that has historically been used to standardize test results and select for patients who might benefit the most from HER2-targeting therapies.

Evaluation of HER2 expression status

Several institutions have endorsed specific algorithms for defining the spectrum of HER2 expression by immunohistochemistry and *in situ* hybridization. In the US, the Food and Drug Administration (FDA) oversees and approves companion diagnostics associated with approved therapies, and professional organizations such as the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) provide evidence-based guidance within those testing guidelines.[4]

At many institutions, the initial evaluation of HER2 expression is assessed on a four-point scale (0, 1+, 2+, 3+) using an IHC staining assay. For patients with breast cancer with a HER2 score of 0, fewer than 10 percent of tumor cells will have no staining or an incomplete membrane staining

that is faint or barely perceptible. A score of 1+ is defined as faint or barely perceptible incomplete membrane staining in more than 10 percent of tumor cells. Tumors with weak-moderate complete membrane staining in greater than 10 percent of tumor cells are scored as 2+. Tumors with complete, intense membrane staining involving more than 10 percent 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 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. For these HER2-positive tumor types, clinical guidelines recommend therapy with anti-HER2 targeted agents.

We depict the process for sample collecting, testing, and reporting results in **Figure 1**.

For many years, tumors with HER2 IHC scores of 0, 1+, or 2+ with negative ISH have been considered HER2-negative. However, recent research and clinical trial results have challenged this paradigm and tumors with HER2 IHC scores of +1 or +2 with negative ISH have now been termed HER2-low (**Figure 2**). The therapeutic significance of this subset of tumors was demonstrated by the DESTINY-Breast04 clinical trial, which showed impressive response rates and survival advantage from a novel anti-HER2 antibody-drug conjugate (ADC), trastuzumab deruxtecan (T-DXd).[5-7]

Key results from the DESTINY-Breast04 clinical trial

T-DXd is composed of an antigen-specific antibody backbone linked to a potent chemotherapy payload.[8] T-DXd has a multi-modal mechanism of action. First, trastuzumab, the antibody backbone of T-DXd, targets the HER2 receptor on the surface of a tumor cell and prevents its dimerization and activation. At the same time, each antibody is conjugated to about eight molecules of chemotherapy payload – in this case, deruxtecan, a topoisomerase-I inhibitor – via a cleavable peptide-based linker. Once bound to the HER2 receptor, the cell internalizes the HER2-bound ADC. The peptide linker is stable within the plasma but cleaved by lysosomal enzymes as the trastuzumab-deruxtecan conjugate is processed for degradation by the cell. Once cleaved, the chemotherapy payload is released and prevents replication by inhibiting DNA uncoiling.
The payload is membrane permeable and creates a bystander effect, as the released molecules diffuse to nearby tumor cells and exert cytotoxic effects independent of cellular HER2 expression status.[8-11]

Eligibility criteria

The DESTINY-Breast04 clinical trial was a Phase III, open-label, randomized clinical trial that evaluated the activity of T-DXd compared to physician's choice of chemotherapy in patients with HER2-low, locally advanced, unresectable, or metastatic breast cancer.[6] Eligible patients must have received chemotherapy for metastatic disease or have had recurrence within six months of completing adjuvant chemotherapy. Patients with HR-positive disease must have received at least one line of endocrine therapy. Patients with treated and stable brain metastases were eligible, and patients with a history of interstitial lung disease were excluded.

HER2 status assessment

HER2 expression status was determined through central testing using Roche's Ventana HER2/neu (4B5) investigation use only (IUO) assay. This assay was performed on archived or recent tumor-biopsy specimens and the results were reported in accordance with an algorithm based on the 2018 ASCO/CAP testing guidelines.[4] Specimens that had IHC scores of HER2 2+ were reflexed to ISH testing using Ventana's IUO Inform HER2 Dual ISH DNA Probe Cocktail assay system.

Trial design

Randomization was stratified according to HER2-low status, number of previous lines of chemotherapy, and HR status. A total of 557 patients (494 HR-positive and 58 triple-negative) were randomly assigned in a 2:1 ratio to receive T-DXd or physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel,

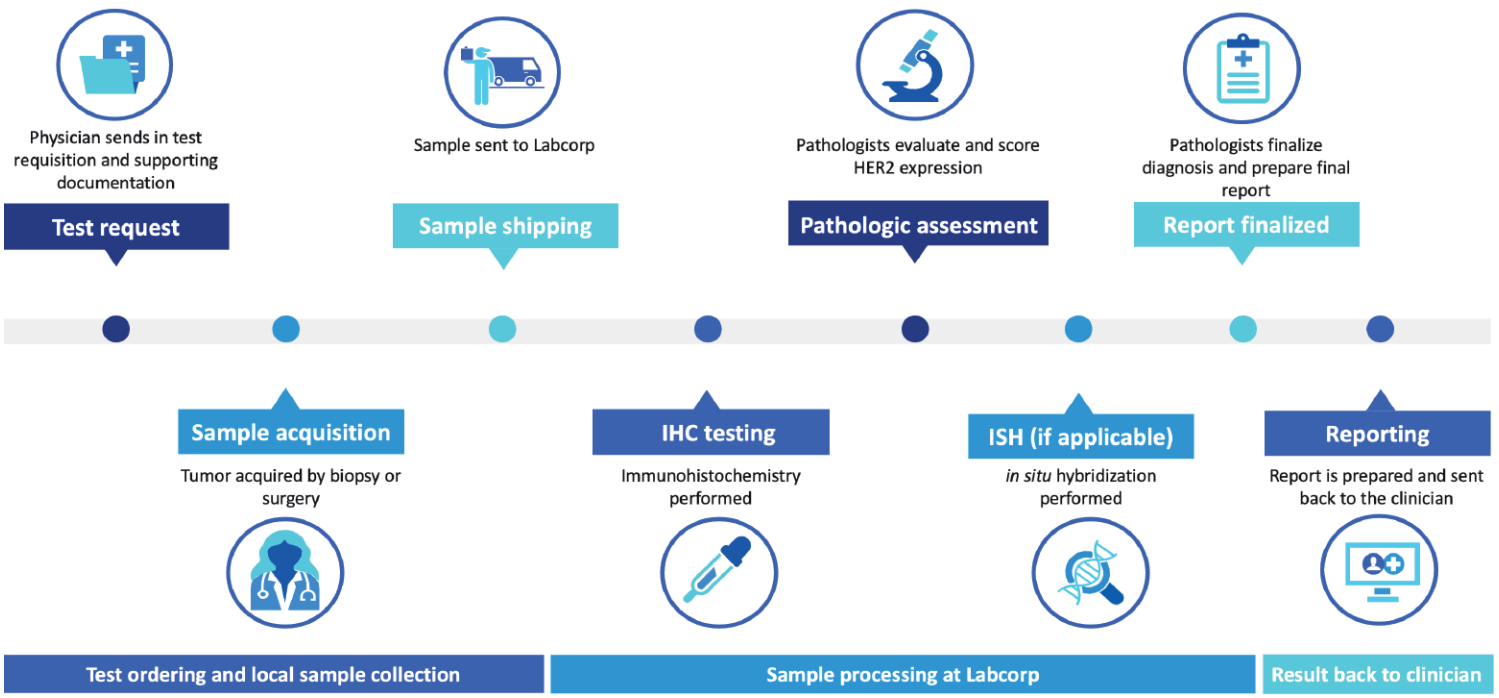


Figure 1: Example workflow for HER2 testing. A physician orders testing for a patient whose tumor requires HER2 evaluation. Tissue for testing is acquired from biopsy or surgery and shipped to Labcorp for further testing. Immunohistochemistry (IHC) is performed using the FDA-approved PATHWAY anti-Her2/neu (4B5) assay and in situ hybridization (ISH) is performed using the FDA-approved HER2 FISH pharmDx assay following the products' package inserts. A report is finalized by a Labcorp pathologist and sent back to the clinician for treatment planning.

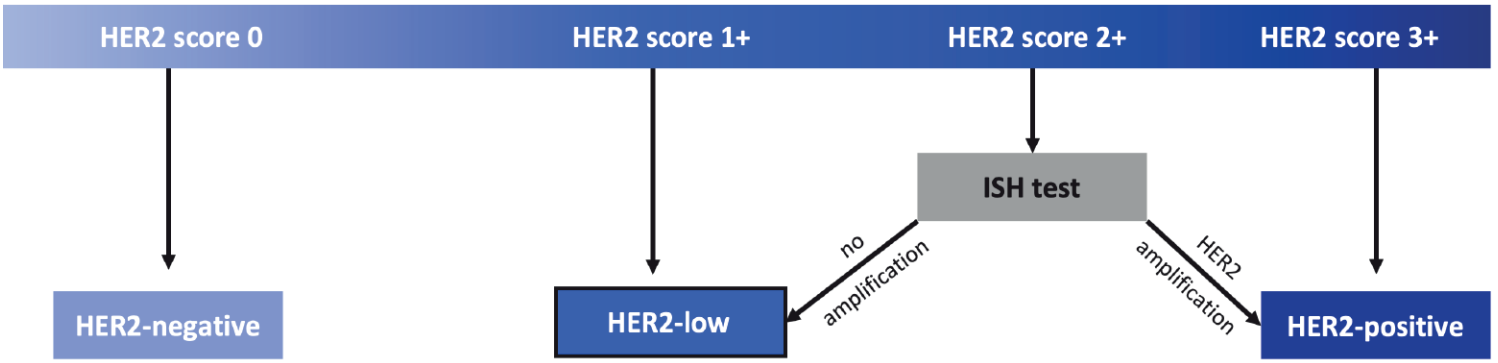


Figure 2: Revised categories of HER2 receptor expression in patients with breast cancer.

or nab-paclitaxel). The groups were well-matched with regard to HER2 IHC expression: 57.6 percent of patients in each group had 1+ expression of HER2 on IHC and 42.4 percent had 2+ HER2 expression and were ISH-negative. Patients in both groups had metastatic disease involving the brain, liver, and lungs, and both groups had a median of three lines of therapy for their metastatic disease. About three-quarters of the population in each group received prior targeted therapies including CDK4/6 inhibitors, immunotherapy, or other targeted agents.

Trial endpoints

The primary endpoint was progression-free survival (PFS) in patients with HR-positive cancers. Secondary endpoints included PFS, overall survival (OS), response, duration of response, and efficacy in patients with HR-negative disease. The median duration of follow-up for survival was 18.4 months.

Trial execution and results

For patients with hormone-receptor positive cancer, treatment with T-DXd resulted in a median PFS of 10.1 (9.5 to 11.5) months, almost double the 5.4 (4.4 to 7.1) months (hazard ratio 0.51, p<0.001) seen in those who received chemotherapy. Similarly, improved OS (23.9 months for T-DXd versus 17.5 months for chemotherapy, HR 0.64, p= 0.003) was seen in patients with HR-positive cancer. Regardless of hormonal receptor status, patients receiving T-DXd had a median overall survival of 23.4 months (95 percent CI, 20.0 to 24.8) compared to 16.8 months (95 percent CI, 14.5 to 20.0) for patients receiving chemotherapy. These consistent results of improved PFS and OS were also seen in an exploratory analysis of patients with TNBC treated with T-DXd. The percentage of all patients with a confirmed objective response was 52.3 percent for those treated with T-DXd compared to 16.3 percent with chemotherapy. This included 12 complete responses in the T-DXd group and only one complete response in the chemotherapy group.

Adverse events and side effects

The side effect profiles of T-DXd and chemotherapy were comparable; the most common toxicities included gastrointestinal symptoms, myelotoxicity, fatigue, and alopecia. Of the patients in the T-DXd treated cohort, 52.6 percent experienced a grade 3 or higher adverse event compared to 67.4 percent of patients treated with chemotherapy. The most common grade 3 event was neutropenia. In addition, 12 percent of the patients receiving T-DXd developed interstitial lung disease (1.3 percent grade 3 and 0.8 percent grade 5 events). This remains a main side effect of concern from T-DXd, warranting careful monitoring for symptoms while on treatment.

> Until recently, tumors with HER2 IHC scores of 0, 1+, or 2+ with negative ISH have been considered HER2-negative. However, recent research and clinical trial results have challenged this paradigm.

Conclusions from DESTINY-Breast04

This trial found that targeting low levels of HER2 expression with 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 percent lower and the risk of death was 36 percent lower with T-DXd than with chemotherapy regardless of hormonal receptor status.[6]

Integrating a new standard of care, challenges for clinical practice

The results of the DESTINY-Breast04 clinical trial have led to updated ASCO and National Comprehensive Cancer Network recommendations and created a new standard of care. Going forward, patients with HER2-low metastatic breast cancer who meet treatment criteria should be offered treatment with T-DXd. HER2-low cases include those patients with tumors with a HER2 IHC score of 1+ or 2+ non-amplified on ISH performed on "either fresh or archival biopsies" as defined by DESTINY-Breast04.[12,13]

Addressing challenges in the implementation into clinical practice

While the results of DESTINY-Breast04 are practice changing, significant obstacles are anticipated for widespread implementation of the resulting treatment recommendations. These challenges include raising clinician awareness through education, updating practice guidelines, managing increasing treatment complexity, and addressing a lack of data surrounding the complex characteristics and temporal heterogeneity of HER-low tumors.

First, clinicians must become better informed of the clinical significance and complex characteristics of HER2-low breast cancers, even as our current understanding of HER2-low expression evolves. For instance, HER2-low expression status may be subject to temporal fluctuations, and their 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.[14,15]

Given that DESTINY-Breast04 enrollment criteria allowed testing for HER2-low status from both fresh and archival biopsies, clinicians should offer T-DXd to patients with HER2-low breast cancer diagnosed at any time during their cancer journey. Still, more data are necessary,

including on the optimal tumor samples to test (i.e., initial diagnostic tissue versus fresh biopsy of metastases) and whether complete loss of HER2 expression during the course of treatment has clinical implications.

Another challenge is the sequencing of treatments in patients with HER2-low advanced breast cancer. In patients with HR-positive, HER2-negative metastatic breast cancer, combinations of endocrine therapy and cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors are used in the first-line setting, resulting in a median PFS of approximately two years after which treatment resistance develops.[16] DESTINY-Breast04 required that patients receive at least one prior line of systemic chemotherapy for their metastatic disease in addition to one line of endocrine therapy. However, given the robust and long-lasting activity seen with T-DXd compared to chemotherapy, sequencing after chemotherapy may not be optimal. The ongoing phase III DESTINY-Breast06 clinical trial will help answer the question of how T-DXd will perform compared to chemotherapy in chemotherapy-naïve patients.[6]

There is also an increasing number of therapeutic options, which raises additional questions regarding sequencing treatments. In particular, sacituzumab govitecan (Gilead's Trodelvy), ADC directed against trophoblast cell-surface antigen 2 (TROP2), has been approved for use in patients with pre-treated metastatic TNBC and, more recently, in HR-positive breast cancers. Sacituzumab govitecan (SG) has been shown to improve both PFS and OS significantly with remarkable activity in pre-treated metastatic TNBC in the ASCENT clinical trial.[17] But SG and T-DXd have potential risks of cross-resistance with sequential use as they both carry a topoisomerase-1 chemotherapy payload. There are no direct studies comparing SG and T-DXd in pretreated metastatic TNBC, therefore, leaving the decision on which ADC to prioritize to the treating physician.

Some clinicians may prioritize SG over T-DXd given that the ASCENT study evaluating SG in advanced TNBC was a higher-powered study than the subgroup analysis of 58 patients with TNBC in DESTINY-Breast04 for T-DXd.[6,17] Similarly, SG now has been recommended as a treatment option for HR-positive metastatic breast cancer based on the positive results from the TROPICS-02 trial.[18] Of note, patients in the TROPICS-02 trial were more heavily pretreated than those enrolled in DESTINY-Breast04; therefore, clinicians should consider using SG more in later lines of treatment in HR-positive metastatic breast cancer. Continued research and discussions on how HER2-low breast cancer should be clinically defined and how treatments should be sequenced with T-DXd among other ADCs and systemic therapy in metastatic breast cancer are ongoing.

Pathologic evaluation, laboratory considerations

With the introduction of T-DXd to treat HER2-low breast cancers, a number of changes to laboratory workflows will be necessary to distinguish reliably between 0 and 1+ HER2 staining. These modifications may include revision of technical procedures and validation steps, continuing education of anatomic pathologists, modification of reporting standards, modernizing proficiency tests, and updating digital image analysis algorithms.

> While the results of DESTINY-Breast04 are practice changing, significant obstacles are anticipated for widespread implementation of the resulting treatment recommendations.

Consistency in staining and interpretation of results

One of the expected challenges to accommodating the new treatment paradigm of HER2-low targeted therapies will be the accurate staining of HER2 samples and subsequent interpretation of the test results. In the context of testing to identify HER2-amplified tumors, the distinction between 0 and 1+ scores have held no clinical significance up to now. As we have discussed, however, some workflows may require adjustments and training to reliably distinguish between them to identify HER2-low tumors.

The interpretation of 1+ scores may be viewed as subjective; a staining some laboratories may interpret as 1+, others may interpret as a negative. Interobserver variability can be expected in cases of tumors that display "faint or barely perceptible" HER2 expression in small proportion of cells (i.e., tumors with staining in close to 10 percent of cells). Staining intensity may depend upon a number of laboratory parameters, such as sample storage, tissue section thickness, buffer solutions, incubation times, antibody dilution, control tissues, and quality control standards. In the past, these parameters may have been determined and validated by individual laboratories but standardizing such values may reduce interobserver variability and improve the reliability of HER2-low assessment. Vendors of FDA-approved HER2 companion diagnostics (i.e., Roche/Ventana, Agilent/Dako, and Leica) can help in this regard by releasing strict protocol recommendations.

Improving standardized training and education within and across laboratories

Other interventions may help pathologists more reliably distinguish between 0 and 1+ HER2 staining and reduce interobserver variability. Pathologists may benefit from improved education, and vendors can potentially provide informative instructional materials, including real world examples, to provide guidance on how to interpret low-level HER2 expression. Testing for HER2 expression has been incorporated into a variety of other solid tumor types including colorectal, non-small cell lung, gastroesophageal, gastric, and endometrial cancer for evaluation of patients for targeted therapy. However, there are limited data to guide oncologists about whether HER2-low results can be applied to these other tumor types.

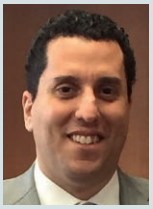
Additionally, current reporting standards may not reflect the new guidelines (e.g., if they contain outdated treatment recommendations or do not adequately report HER2 immunohistochemistry results), which may lead to confusion, treatment delays, and/or inconsistent treatment of patients, and may need to be updated. Laboratory reports will need to be reviewed and updated to ensure they accurately reflect the new therapy and test interpretations.

Proficiency testing will require updates as well, and it is worth noting that the semi-annual CAP proficiency testing does not currently address HER2-low assessments. Vendors and institutions with experience evaluating HER2 IHC could potentially provide recommendations to national organizations regarding proficiency testing, which should include an expanded assessment of 0 and 1+ staining interpretations. Lastly, vendors of digital pathology platforms can upgrade existing image analysis tools or develop new software to provide consistent interpretations of staining results. Such tools could facilitate education and allow for rapid confirmation and feedback of interpretation results, especially if they can utilize simple digital images.

Conclusion

The results of the DESTINY-Breast04 clinical trial have created a new standard-of-care treatment and classification category for HER2-low breast cancers. Implementation of this new treatment guideline will face obstacles including clinician awareness, complex treatment decision-making, new laboratory procedures, and the need for more data to refine our understanding of HER2-low

expressing breast tumors. We anticipate that laboratories will reach a consensus on staining protocols and the reporting and interpretation of results, which may then lead to standardizing the calls for this category of breast cancer assessment. PMQ



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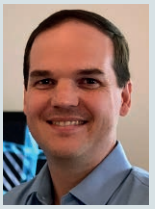

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References

1. Siegel, R.L., et al., Cancer statistics, 2022. CA Cancer J Clin, 2022. 72(1): p. 7-33.
2. Tarantino, P., et al., HER2-Low Breast Cancer: Pathological and Clinical Landscape. J Clin Oncol, 2020. 38(17): p. 1951-1962.
3. North American Association of Central Cancer Registries (NAACCR) 2019. American Cancer Society, Inc., Surveillance Research. . 2019 6 December, 2022]; Available from: https://www.naaccr.org/.
4. Wolff, A.C., et al., HER2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update Summary. J Oncol Pract, 2018. 14(7): p. 437-441.
5. Venetis, K., et al., HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer. Front Mol Biosci, 2022. 9: p. 834651.
6. Modi, S., et al., Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med, 2022. 387(1): p. 9-20.
7. Marchio, C., et al., Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. Semin Cancer Biol, 2021. 72: p. 123-135.
8. ENHERTU [prescribing information]. Daiichi Sankyo Inc., Basking Ridge, NJ and AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2022. 2022.
9. Nakada, T., et al., The Latest Research and Development into the Antibody-Drug Conjugate, [fam-] Trastuzumab Deruxtecan (DS-8201a), for HER2 Cancer Therapy. Chem Pharm Bull (Tokyo), 2019. 67(3): p. 173-185.
10. Ogitani, Y., et al., DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clin Cancer Res, 2016. 22(20): p. 5097-5108.
11. Ogitani, Y., et al., Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci, 2016. 107(7): p. 1039-46.
12. National Comprehensive Cancer Network. Breast Cancer (Version 4.2022). December 5, 2022]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
13. Giordano, S.H., et al., Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update. Journal of Clinical Oncology, 2022. 40(23): p. 2612-2635.
14. Miglietta, F., et al., Evolution of HER2-low expression from primary to recurrent breast cancer. NPJ Breast Cancer, 2021. 7(1): p. 137.
15. Tarantino, P., et al., Evolution of low HER2 expression between early and advanced-stage breast cancer. Eur J Cancer, 2022. 163: p. 35-43.
16. Martin, J.M. and L.J. Goldstein, In Support of CDK4/6 Inhibitors-A Meta-analysis of Available Randomized Data. JAMA Netw Open, 2020. 3(10): p. e2021062.
17. Bardia, A., et al., Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med, 2021. 384(16): p. 1529-1541.
18. Rugo, H.S., et al., Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer. Journal of Clinical Oncology, 2022. 40(17_suppl): p. LBA1001-LBA1001.