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REVIEW

Open questions, current challenges, and future perspectives in targeting human epidermal growth factor receptor 2-low breast cancer

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Approximately 60% of traditionally defined human epidermal growth factor receptor 2 (HER2)-negative breast cancers express low levels of HER2 [HER2-low; defined as immunohistochemistry (IHC) 1+ or IHC 2+/*in situ* hybridization (ISH)−]. HER2-low breast cancers encompass a large percentage of both hormone receptor-positive (up to 85%) and triple-negative (up to 63%) breast cancers. The DESTINY-Breast04 trial established that HER2-low tumors are targetable, leading to the approval of trastuzumab deruxtecan (T-DXd) as the first HER2-directed therapy for the treatment of HER2-low breast cancer in the United States and Europe. This change in the clinical landscape results in a number of questions and challenges—including those related to HER2 assessment and patient identification—and highlights the need for careful assessment of HER2 expression to identify patients eligible for T-DXd. This review provides context for understanding how to identify patients with HER2-low breast cancer with respect to sample types, scoring and reporting HER2 status, and testing methods and assays. It also discusses management of important T-DXd-related adverse events. Available evidence supports the efficacy of T-DXd in patients with any history of IHC 1+ or IHC 2+/ISH− scores; however, future research may further refine the population who could benefit from T-DXd or other HER2-directed therapies and identify novel methods for patient identification. Because HER2 expression can change with disease progression or treatment, and variability exists in scoring and interpretation of HER2 status, careful re-evaluation in certain scenarios may help to identify more patients who may benefit from T-DXd.

Key words: breast cancer, human epidermal growth factor receptor 2, HER2-low, trastuzumab deruxtecan

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a biomarker that drives treatment decisions in breast cancer.[1-3] HER2 status has been categorized as either HER2+ [immunohistochemistry (IHC) 3+ or IHC 2+/*in situ* hybridization (ISH)+] or HER2− (IHC 0, IHC 1+, or IHC 2+/ISH−)[2-4] (Figure 1). These definitions of HER2+ and HER2− breast cancer are based on response to trastuzumab.[5,6] However, this classification system does not reflect the full range of the HER2 expression continuum. Tumors with low levels of HER2 expression (HER2-low; IHC 1+ or IHC 2+/ISH−), along with those that have no detectable HER2 expression, are deemed HER2−.[4] Approximately 60% of HER2− breast cancers [including hormone receptor (HR)+ and HR− disease] may be classified as HER2-low.[7-10]

Until recently, only patients with HER2+ tumors were eligible for HER2-directed treatments.[11] However, the results of the DESTINY-Breast04 trial (NCT03734029) established that HER2-low status in breast cancer was clinically actionable,[12] leading to the approval of the antibody–drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) as the first HER2-directed therapy for HER2-low breast cancer.[13-16] T-DXd is also approved for the treatment of HER2+ breast cancer.[2,15,17-21] Using T-DXd in HER2-low tumors changes the clinical landscape and is accompanied by questions and challenges, including how to assess HER2-low expression and identify patients who may benefit from treatment in the HER2-low setting. Here, we summarize existing evidence for the assessment and treatment of HER2-low breast cancer and provide guidance for patient identification and management strategies for important T-DXd-related adverse events (AEs). We also describe the evolution of HER2 classification and perspectives on the future, including

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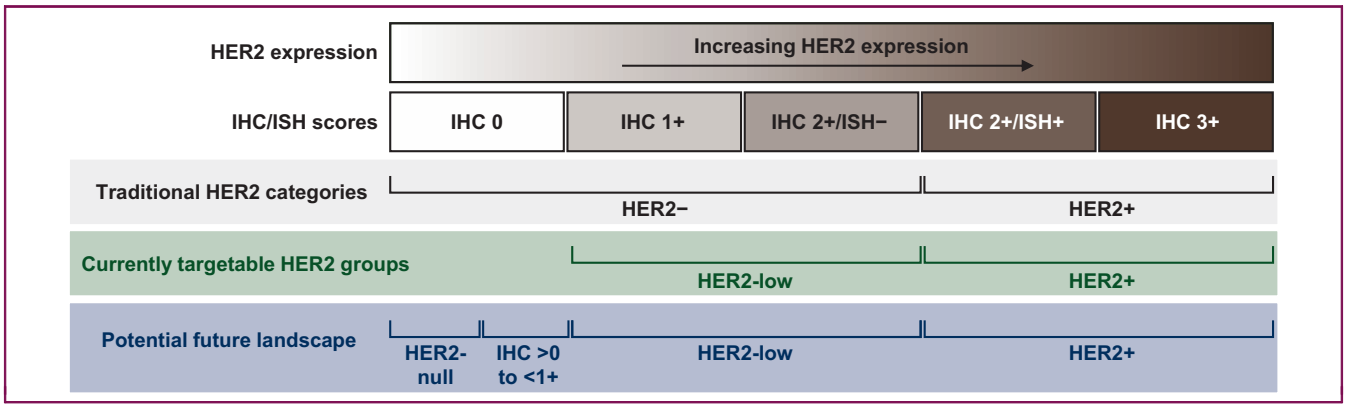

Figure 1. Evolution of HER2 classification and current categories.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization.

evaluation of other therapies for HER2-low breast cancer and technologies that may improve assessment of HER2 status.

CLINICOPATHOLOGIC FEATURES AND THE PROGNOSTIC ROLE OF HER2-LOW STATUS IN BREAST CANCER

HER2-low status is more common among HR+ breast cancer. Approximately 46%-85% of HR+/HER2− breast cancers and 32%-63% of triple-negative breast cancers (TNBCs) are classified as HER2-low.[7,9,10,22-30] A higher proportion of HER2-low (55%-91%) versus HER2 IHC 0 (34%-82%) tumors are HR+.[9,22,23,28-36] Additionally, a continuous association exists between higher estrogen receptor expression and higher prevalence of HER2-low expression.[32]

Robust differences in other clinicopathologic features have not been identified between HER2-low and HER2 IHC 0 breast cancer. Differences in tumor size, tumor grading, Ki-67 proliferation rate, or nodal status between HER2-low and HER2 IHC 0 breast cancer exist[9,22,26,28-30,34-44]; however, they are not consistent across studies[9,23,26,27,37,41,45-47] and may depend on HR status.[9,22,40,48] Genomic alteration and prediction analysis of microarray 50 (PAM50) intrinsic subtype differences between HER2-low and HER2 IHC 0 tumors have been observed,[9,22,48,49] but these were largely dependent on HR status.[9,22,48] HER2-low tumors were more likely to have *PIK3CA* mutations and less likely to have *TP53* mutations when HR subsets were combined; however, no differences in *PIK3CA* mutation prevalence were observed when HR subsets were analyzed separately, and differences in *TP53* mutation prevalence were observed only among HR+ tumors.[22] Additionally, among HR+ breast cancers, HER2-low tumors were less likely than HER2 IHC 0 tumors to have *TP53* mutations, while no difference was observed among HR− breast cancers.[50] Small but statistically significant differences in PAM50 intrinsic subtype prevalence between HER2-low and HER2 IHC 0 breast cancers were observed among HR+ tumors.[9] HR+/HER2-low tumors had higher luminal-related and lower proliferation-related gene expression than HR+/HER2 IHC 0 tumors.[9] No differences in PAM50 subtypes or gene expression were observed among HR− tumors.[9]

While prognostic differences between HER2-low and HER2 IHC 0 breast cancers have been reported,[7,22,25,29,35,39,42,45,46,51-55] most studies found small or no differences in prognosis after adjusting for HR status[9,10,26,28,31,32,34,37,40,43,47,48,54,56-62] (Table 1). Taken together, the evidence does not support HER2-low as a biologically distinct breast cancer subtype. Nonetheless, HER2-low expression provides a therapeutic target.

Targeting HER2-low expression with novel ADCs

The actionability of HER2-low expression in breast cancer has been confirmed in recent trials of novel ADCs,[12,63-66] with the most conclusive data observed with T-DXd.[12] T-DXd was approved [United States: August 2022; European Union (EU): January 2023] for the treatment of patients with unresectable or metastatic HER2-low breast cancer who received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of adjuvant chemotherapy.[13,14,67] The phase III DESTINY-Breast04 trial evaluated the safety and efficacy of T-DXd in patients with HER2-low metastatic breast cancer who previously received chemotherapy (one or two lines) and in patients who also received prior endocrine therapy for HR+ disease.[12] T-DXd reduced the risk of disease progression or death versus chemotherapy, with a median progression-free survival (mPFS) of 9.9 versus 5.1 months [hazard ratio 0.50, 95% confidence interval (CI) 0.40-0.63, $P < 0.001$] and median overall survival (OS) of 22.9 versus 16.8 months (hazard ratio 0.69, 95% CI 0.55-0.86, $P = 0.001$) in patients with HR+ or HR−/HER2-low metastatic breast cancer.[12,68] The safety profile of T-DXd was consistent with the safety profile in the HER2+ setting.[12] The results of this trial established patients with HER2-low breast cancer as a targetable population, demonstrating that low levels of HER2 expression on tumor cells can provide a target for HER2-directed ADCs.

Results from DESTINY-Breast04 also support the observation that the benefit of T-DXd in the HER2-low setting is similar between patients with IHC 1+ tumors and those with IHC 2+/ISH− tumors and is not dependent on HR status.[12] Patients with IHC 1+ disease and those with IHC

Table 1. Summary of studies evaluating the prognostic significance of HER2-low breast cancer

Reference	Population	Outcome assessed	Difference found between HER2-low versus HER2 IHC 0?[a]	Comment(s)
Agostinetto et al. 2021[56]	Primary BC ($n = 671$)[b]	PFI DFI OS	X X X	No differences when stratified by HR status
Almstedt et al. 2022[42]	Consecutive node-negative BC ($n = 351$)	OS DFS	— ✓	Longer OS in HER2-low for the overall population and HR+ subgroup; no difference in HR− Longer DFS in HER2-low
Alves et al. 2022[30]	eBC ($n = 72$)	pCR DFS OS	X X X	—
Baez-Navarro et al. 2023[43]	Primary invasive BC ($n = 53\,833$)	OS	—	Longer OS in HER2-low for the overall population; no difference when adjusted for HR status
Bao et al. 2021[51]	HR+ mBC ($n = 106$)	PFS	✓	Shorter PFS in HER2-low
Carlino et al. 2022[47]	HR+ mBC ($n = 165$)	PFS OS	X X	—
Chen et al. 2022[58]	HR+ primary BC ($n = 2099$)	DFS	X	—
Denkert et al. 2021[22]	Primary BC ($n = 2310$)	pCR DFS	— —	Lower pCR in HER2-low for HR+ only Shorter DFS in HER2-low for HR− only
de Moura Leite et al. 2021[37]	eBC ($n = 855$)	pCR RFS OS	X X X	— No difference after adjusting for other factors[c]
de Nonneville et al. 2022[28]	Invasive eBC ($n = 1111$)	pCR DFS	— X	Lower pCR in HER2-low for HR+ only —
Di Cosimo et al. 2022[26]	Newly diagnosed, nonmetastatic BC ($n = 444$)	pCR DFS	— X	Lower pCR in HER2-low for the overall population; no difference when stratified by HR status —
Domergue et al. 2022[44]	eBC ($n = 437$)	pCR DFS OS	X X X	—
Douganiotis et al. 2022[27]	HR+ eBC ($n = 949$)	RFS	X	—
Douganiotis et al. 2022[61]	HR+ mBC ($n = 191$)	PFS	—	Worse PFS in HER2-low for the subgroup of patients treated with fulvestrant only; no difference in the overall population or other evaluated subgroups
Gampenrieder et al. 2022[60]	HR− BC ($n = 691$)	OS	X	—
Guven et al. 2022[53]	Not specified ($n = 2013$)[b]	OS DFS Risk of brain metastases	X — ✓	— Lower DFS in HER2-low for the overall population and HR+ subgroup; no difference for the HR− subgroup Higher risk of brain metastases in HER2-low
Holthius et al. 2022[57]	mBC ($n = 1261$)[b]	OS	X	—
Jiang et al. 2022[7]	*De novo* mBC ($n = 30\,929$)	OS	✓	Longer OS in HER2-low, regardless of HR status
Kang et al. 2022[54]	Stage 1-3 BC ($n = 1572$)	pCR OS DFS	— — —	Lower pCR in HER2-low for the overall population; no difference when stratified by HR status Longer OS in HER2-low for the overall population; no difference when stratified by HR status Longer DFS in HER2-low for the overall population and HR− subgroup; no difference in the HR+ subgroup
Li et al. 2022[25]	mBC ($n = 1433$)	OS	—	Longer OS in HER2-low for the overall population and HR+ subgroup; no difference in the HR− subgroup
Mutai et al. 2021[45]	ER+ eBC ($n = 608$)	OS DDFS DFS	— — —	Longer OS, DFS, and DDFS in HER2-low for high genomic risk only
Omar and Darwish 2021[31]	Not specified ($n = 500$)	DFS OS	X X	—
Qiao et al. 2023[35]	Not specified ($n = 132$)	pCR OS	— —	Lower pCR in HER2-low for the overall population; no difference when stratified by HR status

Continued

Table 1. Continued

Reference	Population	Outcome assessed	Difference found between HER2-low versus HER2 IHC 0?[a]	Comment(s)
		DFS	—	Longer OS and DFS in HER2-low for the overall population and HR+ subgroup; no difference for the HR− subgroup
Russo et al. 2022[39]	Not specified ($n = 391$)	OS	✓	Longer OS in HER2-low for the overall population and ER+ subgroup
		PFS	X	—
Schettini et al. 2021[9]	Not specified ($n = 3689$)	OS	X	—
Shao et al. 2022[62]	Not specified ($n = 314$)	pCR	—	Lower pCR in HER2-low for the overall population and HR+ subgroup[d]; no difference for the HR− subgroup
		DFS	X	—
		OS	X	—
Shi et al. 2023[36]	Primary unilateral BC ($n = 436$)	Total pCR	X	—
		Breast pCR	X	—
		Axillary pCR	—	Higher pCR in HER2-low for the HR− subgroup among patients with high Ki67 expression only; no differences for overall population or HR+ subgroup among those with high Ki67 expression; no differences among patients without high Ki67 expression
Shi et al. 2023[138]	Recurrent BC ($n = 180$)[b]	BCSS	—	Marginally longer BCSS in HER2-low for the overall population; longer BCSS in HER2-low for the HR− subgroup; no difference for the HR+ subgroup
Tan et al. 2022[52]	Nonmetastatic BC ($n = 28\,280$)	RFS	—	Longer DFS in HER2-low for the overall population and HR+ subgroup; no difference for the HR− subgroup
		OS	✓	Longer OS in HER2-low
Tarantino et al. 2022[32]	eBC ($n = 5235$)	pCR	X	No differences when stratified by HR status
		DFS	X	
		DDFS	X	
		OS	X	
van den Ende et al. 2022[48]	Primary BC ($n = 318$)	OS	X	No differences when stratified by HR status
		DFS	X	
		DDFS	X	
Viale et al. 2022[10]	Unresectable or mBC ($n = 789$)	TFST	X	No differences when stratified by HR status
		OS	X	
Wang et al. 2023[46]	Invasive BC ($n = 148$)	DFS	✓	Longer DFS in HER2-low
Won et al. 2022[40]	Stage 1-3 BC ($n = 30\,491$)	OS	X	No difference when stratified by HR status
		BCSS	✓	Longer BCSS in HER2-low for both HR+ and HR−
Xu et al. 2022[41]	eBC ($n = 777$)	OS	—	Longer OS in HER2-low for HR− only
		DFS	X	—
Xu et al. 2023[59]	Nonmetastatic BC ($n = 2605$)	DFS	X	—
		OS	—	Longer OS in HER2-low for the HR− subgroup; no difference in the overall population or HR+ subgroup
Xu et al. 2023[55]	Primary invasive BC ($n = 429$)	pCR	✓	Lower pCR in HER2-low in the overall population and HR− subgroup
		DFS	X	—
Zhang et al. 2022[34]	Not specified ($n = 149$)	pCR	—	Lower pCR in HER2-low for the overall population; no difference when stratified by HR status
		DFS	X	—
Zhou et al. 2023[29]	eBC ($n = 325$)	pCR	X	—
		OS	✓	Longer OS in HER2-low
		DFS	X	—

BC, breast cancer; BCSS, breast cancer-specific survival; DDFS, distant disease-free survival; DFI, disease-free interval; DFS, disease-free survival; eBC, early breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; OS, overall survival; pCR, pathological complete response; PFI, progression-free interval; PFS, progression-free survival; RFS, recurrence-free survival; TFST, time to first subsequent treatment.

[a]✓ Indicates that a statistically significant difference was observed. X indicates no difference was observed. — indicates that observations were mixed (e.g. differences were observed for some, but not all groups, evaluated).

[b]Reflects the number of patients with HER2-low and HER2 IHC 0 disease; additional patients were included in the study.

[c]No difference in OS was observed after adjusting for pCR, stage, clinical node positivity, and subtype (luminal versus triple-negative breast cancer).

[d]When pCR was defined as the absence of invasive or noninvasive cancer in the breast and axillary lymph nodes. No differences were observed when pCR was defined as the absence of invasive cancer in the breast, regardless of ductal carcinoma *in situ* and axillary lymph nodes.

2+/ISH− disease had a similar hazard ratio for disease progression or death with T-DXd versus chemotherapy (IHC 1+: 0.48; 95% CI 0.35-0.65; IHC 2+/ISH−: 0.55; 95% CI 0.38-0.80).[12] Despite the relatively small proportion of patients with HR−/HER2-low breast cancer ($n = 40/373$), the similar overall response rate and mPFS in patients with HR+ and those with HR− tumors support the observation that the benefit is not limited to HR+ disease.[12] The mPFS with T-DXd was 10.1 months (95% CI 9.5-11.5 months) in patients with HR+ tumors and 8.5 months (95% CI 4.3-11.7 months) in those with HR− tumors, and the overall response rate was 52.6% (95% CI 47.0% to 58.0%) and 50.0% (95% CI 33.8% to 66.2%), respectively.[12]

DESTINY-Breast04 subgroup analyses demonstrated the benefit of T-DXd regarding treatment history. The hazard ratio for disease progression or death with T-DXd versus chemotherapy was 0.55 (95% CI 0.42-0.73) in patients with prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor treatment versus 0.42 (95% CI 0.28-0.64) in those without.[12] These data support the benefit of T-DXd regardless of previous CDK4/6 inhibitor use; therefore, CDK4/6 inhibitor treatment when indicated is recommended before T-DXd treatment. The hazard ratio for disease progression or death with T-DXd versus chemotherapy was also similar in patients who had received one (0.54, 95% CI 0.40-0.73) or at least two (0.47, 95% CI 0.33-0.68) prior lines of chemotherapy.[12] Therefore, patients should receive at least one line of chemotherapy in the metastatic setting before T-DXd, except in cases of disease progression within 6 months of receiving (neo)adjuvant chemotherapy.

MECHANISM OF ACTION OF T-DXD IN HER2-LOW BREAST CANCER

The efficacy of T-DXd in the HER2-low setting is unlikely to be related to HER2 pathway blockade, as HER2-directed monoclonal antibodies (mAbs) did not exert meaningful clinical activity in HER2-low breast cancer.[69,70] Instead, low levels of HER2 expression provide a target for T-DXd binding, enabling the delivery of a potent cytotoxic agent (Figure 2). T-DXd is an ADC composed of an anti-HER2 antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload.[71,72] The mAb component of T-DXd selectively binds to HER2 on the tumor surface.[73] After binding, T-DXd is internalized and the tetrapeptide-based linker is cleaved by lysosomal enzymes in the tumor cell.[73,74] The topoisomerase I inhibitor payload is released and enters the cell nucleus, resulting in cell death.[73] The released membrane-permeable payload may enter neighboring cells, regardless of HER2 expression, extending cytotoxicity to these surrounding tumor cells[73,74]; this is known as a bystander antitumor effect. The increased activity of T-DXd compared with the ADC trastuzumab emtansine (T-DM1), which did not demonstrate substantial activity in HER2-low breast cancer,[75,76] may be explained by the structural characteristics of T-DXd. These characteristics include the plasma-stable cleavable linker (versus the noncleavable linker in T-DM1),[74] greater potency of the topoisomerase I payload,[74] higher drug-to-antibody ratio (≈8 versus ≈3.5 for T-DM1),[72,77] and greater lipophilicity and membrane permeability of the payload compared with that of T-DM1.[74]

HER2 classification

With the approval of T-DXd, HER2-low status has become clinically actionable. Accordingly, the need to identify patients who may be eligible for T-DXd based on current HER2 score definitions—as well as more precise assessment of HER2 levels—has gained attention. In particular, the recent ability to treat based on HER2-low status requires a broader understanding of HER2 expression beyond the categories of HER2+ and HER2−. This binary classification does not capture the full breadth of HER2 expression, which exists not only on a continuum of low to high but can also be heterogeneous within a tumor or patient[38,78,79] since both HER2-low and HER2 IHC 0 lesions have been identified in many patients.[79] Currently, pathologists should score HER2-low expression using the American Society of Clinical Oncology—College of American Pathologists (ASCO/CAP) 2018 algorithm,[4,80] but it is recommended that the term 'faint' be used rather than 'faint/barely perceptible' for the definition of IHC 0 and IHC 1+—a simplification used in the DESTINY-Breast04 trial.[12,81]

Results from future and ongoing clinical trials may further evolve this scoring algorithm and the classification of HER2, as studies refine the population expected to benefit from HER2-directed therapies. In preliminary results from patients with HER2 IHC 0 advanced breast cancer in the ongoing phase II DAISY trial ($n = 36$), a confirmed response to T-DXd was observed in 11 patients (30.6%).[82] This suggests that the lower bound of targetable HER2 expression with T-DXd could be further extended. According to the ASCO/CAP 2018 definition,[4] IHC 0 includes tumors with no HER2 membrane staining (HER2-null) and tumors with faint or barely perceptible HER2 staining in ≤10% of cells (HER2 IHC >0 to <1+). The efficacy and safety of T-DXd are being explored in patients with HER2-low and HER2 IHC >0 to <1+ tumors in the ongoing phase III DESTINY-Breast06 trial (NCT04494425).[22,83] If a benefit in HER2 IHC >0 to <1+ breast cancer is demonstrated, HER2 IHC 0 tumors may be subdivided into two groups: HER2 IHC >0 to <1+ and HER2-null (Figure 1). Activity of T-DXd in HER2-null tumors should be assessed in future studies, and lack of activity in this subgroup should not be assumed.

IDENTIFYING PATIENTS WITH HER2-LOW BREAST CANCER: EXPERT OPINION AND RECOMMENDATIONS

Biopsy types and rescoring samples

Best practices for identifying HER2-low disease are outlined subsequently and summarized in Figure 3. Results from any sample that was previously scored as HER2-low (IHC 1+ or IHC 2+/ISH−) can be used to identify patients who could

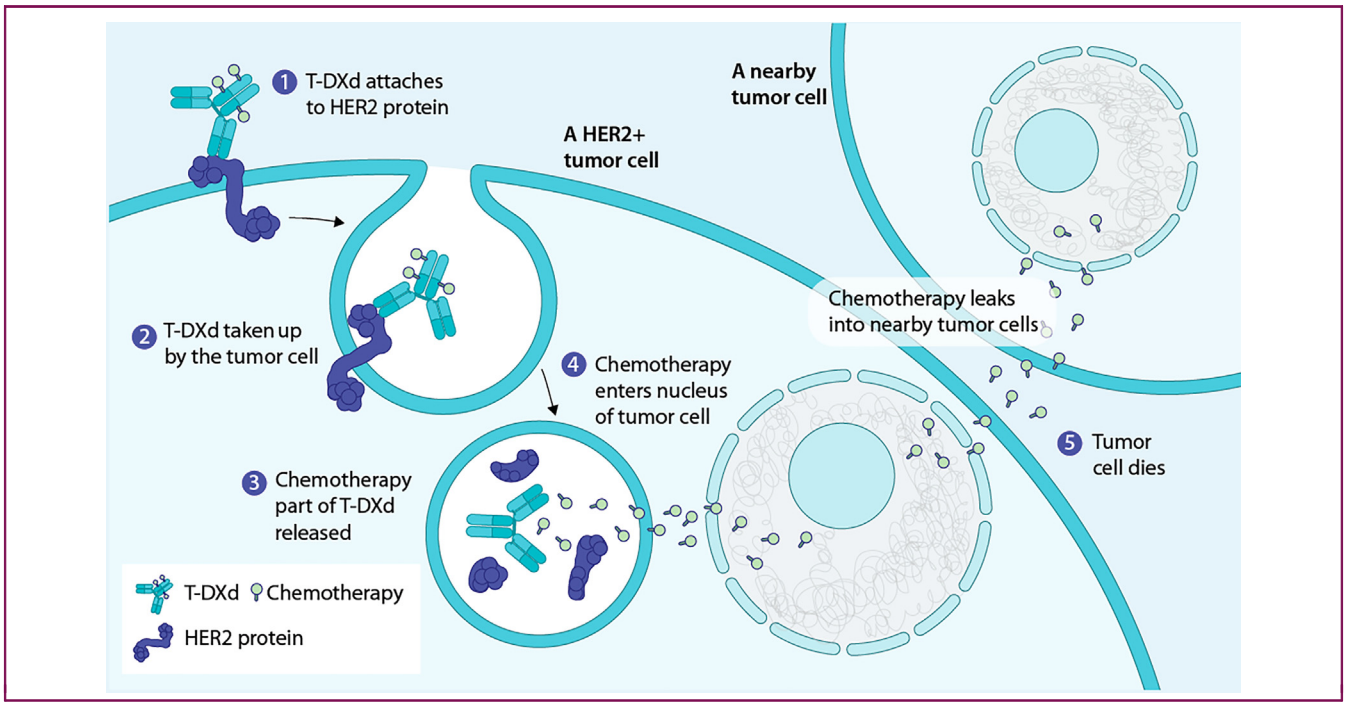

Figure 2. Mechanism of action of T-DXd.
HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan. Reproduced with permission. Creative Commons license and disclaimer available from https://creativecommons.org/licenses/by-nc-nd/4.0/.

be eligible for T-DXd. There is no strong rationale to rescore samples previously identified as HER2 IHC 1+ or 2+, as patients with any history of either score, regardless of sample type, may benefit from T-DXd.[84] Furthermore, most samples (>87%) that were historically identified as HER2-low (IHC 1+ or IHC 2+/ISH−) were rescored as HER2-low by pathologists who received training on low-end HER2 expression scoring.

In contrast, rescoring of samples previously identified as IHC 0 may be warranted in the absence of any previous HER2-low samples. Previously, the distinction between IHC 0 and IHC 1+ was not clinically meaningful. Therefore, pathologists likely did not strive to distinguish between these two categories, and variability in scoring or interpretation of IHC results between pathologists or laboratories occurred[9,10,85-90]—with the worst agreement observed between IHC 0 and 1+ scores.[9,88,90] One study reported concordance of 26% between IHC 0 and 1+,[88] while others have reported concordance rates ranging from 15% for IHC 0 to 71%-73% for IHC 1+ tumors.[86,89] Furthermore, ∼30% of samples historically scored as IHC 0 were rescored as HER2-low after training was provided on low-end HER2 expression scoring, suggesting that a proportion of historical HER2 IHC 0 samples might be classified as HER2-low. Now that differentiation between IHC 0 and IHC 1+ is clinically important because patients with IHC 1+ tumors may be eligible for T-DXd and could benefit from its use, careful re-evaluation of IHC 0 samples is prudent. If a primary tumor is scored as IHC 0, we recommend that metastases be evaluated; if a metastatic sample is not available or is scored as IHC 0, we recommend that previous biopsy specimens be re-evaluated. This is consistent with current ASCO/CAP recommendations that HER2 IHC results on prior or concurrent primary samples or other metastases can be considered.[80]

HER2 expression may change with disease progression or treatment[8,23,24,46,91-94] and can vary between metastases in the same patient.[95] HER2 expression can increase over time, with more HER2-low tumors identified with each consecutive biopsy in TNBC.[96] Repeating biopsies after disease progression may identify patients with HER2-low breast cancer who are eligible for T-DXd. If other metastases are not available, bone biopsies may be considered for the identification of HER2-low expression, although they are not recommended, as decalcification can decrease HER2 staining.[97] Surgical excision specimens may be preferable when available, as HER2-low status may be harder to detect in core-needle biopsies.[98,99]

Scoring and reporting of HER2 expression

IHC results can vary[9,10,85-90]; therefore, training on low-end HER2 expression scoring can improve identification of HER2 IHC 0 and HER2-low tumors and lead to appropriate scoring of HER2-low breast cancer.[100] Because the term 'HER2-low' is not routinely used clinically, reporting IHC scores along with HER2− status will help identify patients who may be eligible for treatment in the HER2-low setting. In reporting HER2 testing results, pathologists should maintain a nomenclature consistent with the ASCO/CAP 2018 algorithm.[4,80,81] The HER2 IHC score (0, 1+, 2+, or 3+) should always be included in the report to assist in determining eligibility for T-DXd.[81]

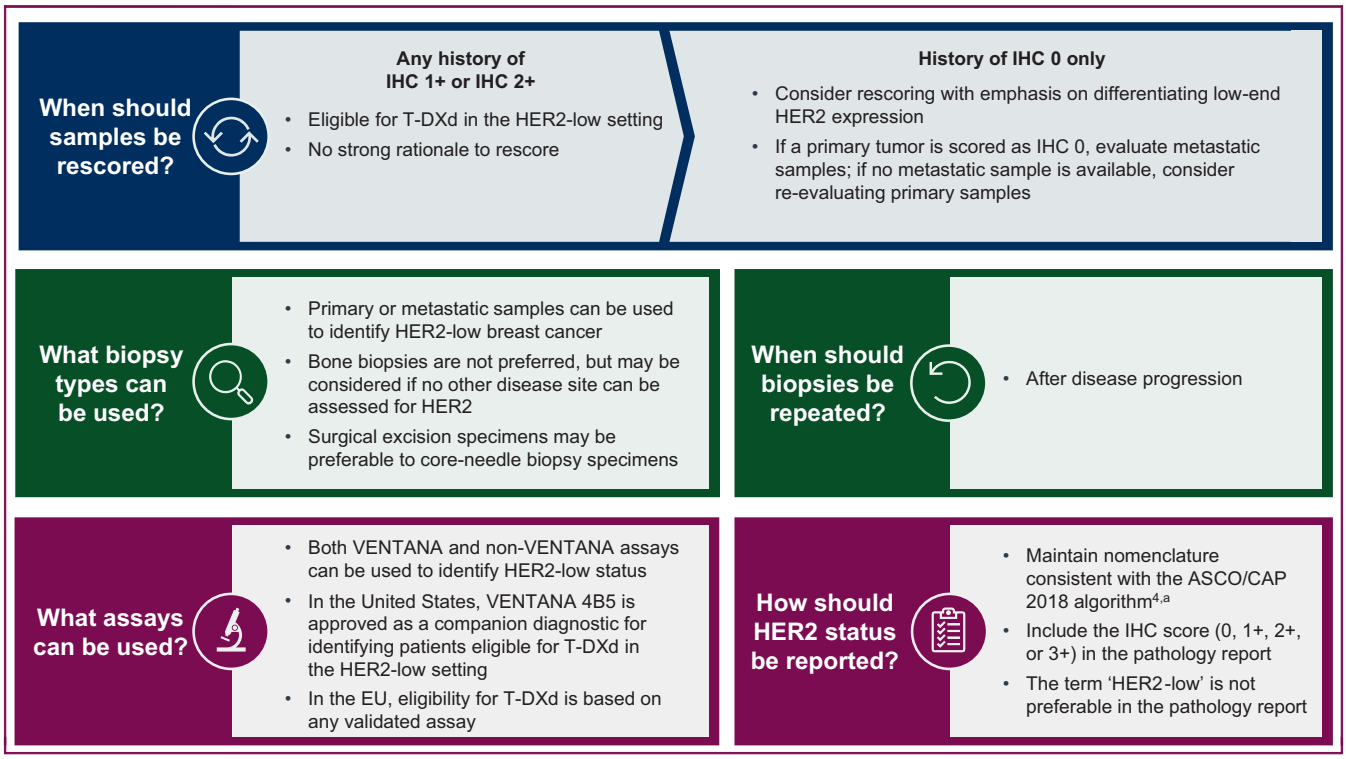

Figure 3. Best practices for identifying patients with HER2-low breast cancer.
ASCO/CAP, American Society of Clinical Oncology—College of American Pathologists; EU, European Union; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DXd, trastuzumab deruxtecan.
[a]It is recommended that pathologists use the term 'faint' rather than 'faint/barely perceptible' for the definition of IHC 0 and IHC 1+, as in the DESTINY-Breast04 trial.[12]

Assays and testing methods

With many HER2 assays available, it is important to understand whether any offer an advantage in identifying HER2-low breast cancer. The VENTANA 4B5 assay (Roche Diagnostics) is approved in the United States as a companion diagnostic for identifying patients with HER2-low breast cancer who are eligible for T-DXd.[61,101] However, T-DXd eligibility in the EU is based on any validated assay.[11,15] Similar prevalence of HER2-low breast cancer has been seen with the VENTANA 4B5 and non-VENTANA assays. Additionally, concordance between historical HER2 scores and rescores after low-end HER2 expression scoring training was similar between VENTANA (81.8%) and non-VENTANA (80.0%) assays. Therefore, both VENTANA and non-VENTANA assays can be used to detect HER2-low breast cancer. The new monoclonal HercepTest (Agilent Technologies, Inc, Santa Clara, CA) has higher sensitivity to detect low levels of HER2 expression than the VENTANA 4B5 assay[102]; however, higher sensitivity does not invariably translate to stronger predictive value. Thus, studies are needed to compare and establish the predictive value of different assays.

SAFETY AND MANAGEMENT OF AES OF INTEREST IN HER2-LOW BREAST CANCER

The ability to target HER2-low breast cancer with T-DXd necessitates an understanding of its safety profile. The safety profile of T-DXd in patients with HER2-low breast cancer is consistent with that in patients with HER2+ disease.[12,89] Monitoring and management of nausea and vomiting, interstitial lung disease (ILD)/pneumonitis, and cardiovascular AEs are particularly important in patients receiving T-DXd (Figure 4).[73,103]

Nausea and vomiting

Gastrointestinal AEs are among the most common in patients with HER2-low breast cancer receiving T-DXd,[12,89] consistent with the HER2+ setting.[104,105] In the DESTINY-Breast04 trial, any-grade and grade ≥3 nausea was reported in 73% and 4.6% of patients, and any-grade and grade ≥3 vomiting was reported in 34% and 1.3%, respectively.[12] Similar rates are observed in HER2+ disease.[104,105]

Because T-DXd is considered highly emetogenic per the National Comprehensive Cancer Network guidelines,[106] prophylactic treatment with antiemetic medications is recommended.[103,106,107] The medications can be adjusted based on individual tolerances and emetic risk factors.[103,106,107]

ILD/pneumonitis

ILD/pneumonitis is an important identified risk with T-DXd, and patients receiving T-DXd should be proactively monitored for and advised of the risk of ILD/pneumonitis.[73] In the DESTINY-Breast04 trial, independently adjudicated drug-related ILD/pneumonitis occurred in 12.1% of patients with HER2-low breast cancer receiving T-DXd; 1.3% had grade 3 events and 0.8% had grade 5 events.[12] The rate of ILD/

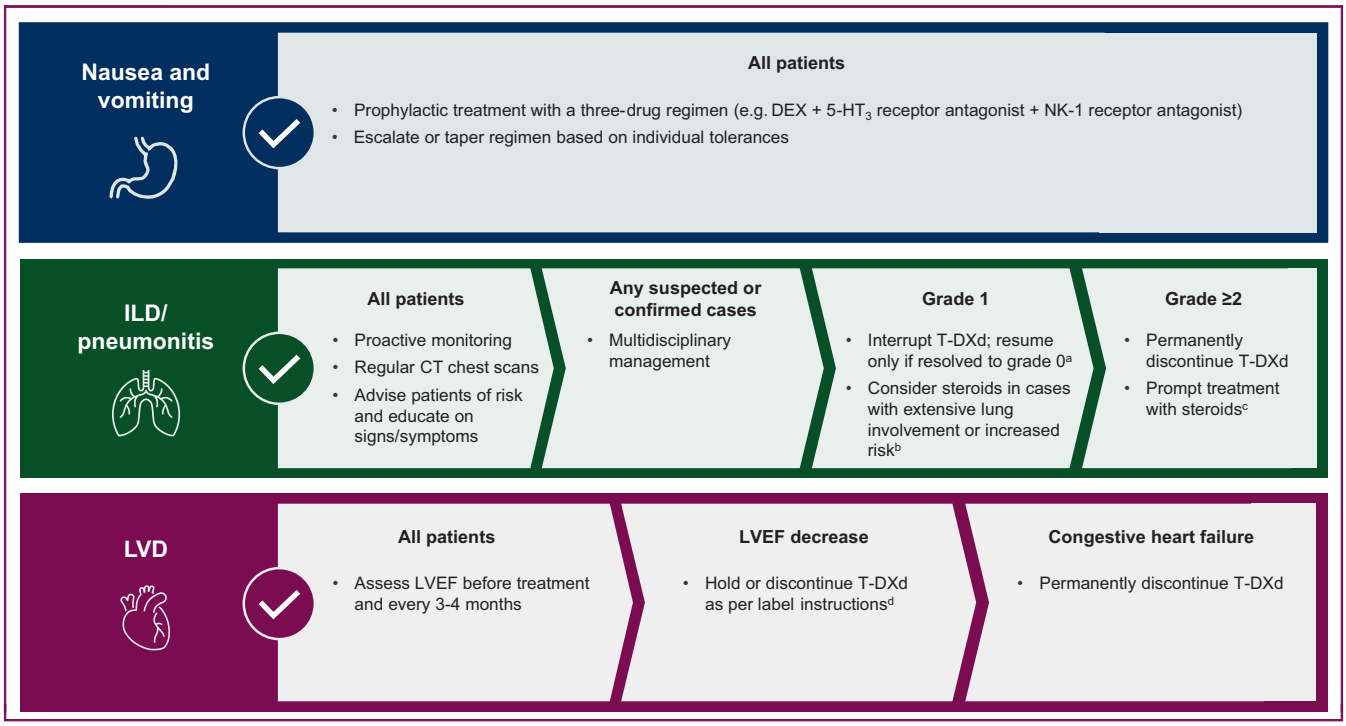

Figure 4. Overview of strategies for managing adverse events of interest with T-DXd.[2,15,73,81,103]
CT, computed tomography; DEX, dexamethasone; ILD, interstitial lung disease; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; NK-1, neurokinin-1; T-DXd, trastuzumab deruxtecan.
[a]If resolved in ≤28 days from the date of onset, maintain dose. If resolved in >28 days from the date of onset, reduce dose one level according to the label.[2,15] If not resolved within 18 weeks (126 days) from the last infusion, discontinue T-DXd.
[b]For asymptomatic (grade 1) ILD/pneumonitis, consider treatment with corticosteroids (e.g. ≥0.5 mg/kg/day prednisolone or equivalent). If diagnostic observations worsen despite corticosteroid treatment, follow grade 2 guidelines.[2,15,73]
[c]For symptomatic (grade 2 or higher) ILD/pneumonitis, promptly initiate systemic corticosteroid treatment. For grade 2 cases, systemic corticosteroid treatment (e.g. ≥1.0 mg/kg/day prednisolone or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings followed by gradual taper for ≥4 weeks is recommended. Symptoms should be monitored closely and imaging should be repeated as clinically indicated; if worsening or no improvement is observed in 5 days, (i) consider increasing dose of steroids, (ii) consider switching steroid to intravenous administration, (iii) escalate care as clinically indicated, and (iv) consider additional work-up for alternative etiologies. For grade 3 or 4 cases, hospitalization is required. Empirical high-dose methylprednisolone intravenous treatment (e.g. 500-1000 mg/day for 3 days) is recommended followed by ≥1.0 mg/kg/day prednisone or equivalent for ≥14 days or until complete resolution of clinical and chest CT findings followed by gradual taper for ≥4 weeks. Imaging should be repeated as clinically indicated; if no improvement is observed within 3-5 days, consider treatment with other immunosuppressants and consider additional work-up for alternative etiologies.[2,15,73]
[d]If LVEF is >45% and the absolute decrease from baseline is 10%-20%, continue treatment with T-DXd. If LVEF is 40%-45% and the absolute decrease from baseline is <10%, continue treatment with T-DXd and repeat LVEF assessment within 3 weeks. If LVEF is 40%-45% and the absolute decrease from baseline is 10%-20%, interrupt treatment with T-DXd and repeat LVEF assessment within 3 weeks: if LVEF has not recovered to within 10% from baseline, permanently discontinue T-DXd; if LVEF recovers to within 10% from baseline, resume treatment at the same dose. If LVEF is <40% or the absolute decrease from baseline is >20%, interrupt treatment with T-DXd and repeat LVEF assessment within 3 weeks: if LVEF is <40% or absolute decrease from baseline >20% is confirmed, permanently discontinue T-DXd.

pneumonitis observed in HER2-low breast cancer was consistent with prior experience with T-DXd.[108] In a pooled analysis of T-DXd monotherapy in patients with HER2-expressing or HER2-mutant solid tumors, the incidence of adjudicated drug-related ILD/pneumonitis was 15.4%; among patients with HER2+ breast cancer, it was 16.3%.[108]

Most ILD/pneumonitis events occur within the first 12 months of T-DXd treatment,[108] highlighting the need for careful monitoring during this time, although monitoring should be continued throughout treatment since cases of late-onset ILD/pneumonitis also arise.[108] T-DXd-related ILD/pneumonitis should be managed by a multidisciplinary team.[73] T-DXd treatment should be interrupted in the event of grade 1 (asymptomatic) ILD/pneumonitis, and the event must resolve before treatment is resumed.[73,103] T-DXd should be permanently discontinued in the event of grade ≥2 (symptomatic) ILD/pneumonitis.[73,103] Prompt treatment with steroids is recommended in all cases of grade ≥2 ILD/pneumonitis; steroids may also be considered in grade 1 cases with extensive lung involvement or in patients with increased risk.[73,103]

Left ventricular dysfunction

Left ventricular dysfunction (LVD) has been reported with T-DXd.[12,104,105] In DESTINY-Breast04, LVD occurred in 4.6% of patients with HER2-low breast cancer who received T-DXd; grade 2 or 3 decreased left ventricular ejection fraction (LVEF) occurred in 13.2%.[12] In patients with HER2+ breast cancer treated with T-DXd in the DESTINY-Breast03 trial, LVD occurred in one patient (0.4%), and decreased LVEF occurred in 2.3%.[105] However, rates were also higher in patients with HER2-low breast cancer who received chemotherapy in the DESTINY-Breast04 trial (grade 2 or 3 decreased LVEF occurred in 5.8%).[12] The increased prevalence of LVD in DESTINY-Breast04 may be attributed to a lack of prior cardiac screening. Namely, because patients with HER2-low disease had not previously received other

anti-HER2 agents, which have a known cardiotoxicity risk,[109] they may have been less likely to be excluded on the basis of prior cardiac screening.

LVEF should be assessed before beginning T-DXd treatment and at regular intervals during treatment (every 3-4 months).[2,15,103] If LVEF decrease is found, T-DXd should be held or discontinued according to the label instructions.[2,15] If congestive heart failure occurs, T-DXd should be permanently discontinued.[2,15,103]

FUTURE PERSPECTIVES

The future of HER2-low treatment

Ongoing studies may identify additional treatments for HER2-low breast cancer, including mAbs and other ADCs. The mAb margetuximab showed preclinical activity in the HER2-low setting[110] and is being investigated in a phase II clinical trial.[15,111] The ADC trastuzumab duocarmazine demonstrated efficacy in HER2-low metastatic breast cancer in a phase I trial[65] and is being investigated in combination with chemotherapy in an ongoing phase I trial.[112] The ADC disitamab vedotin demonstrated efficacy in HER2-low advanced breast cancer in a phase Ib trial[66] and is being investigated in combination with penpulimab in the neoadjuvant setting in an ongoing phase II trial.[113] The ADC SHR-A1811 has shown activity in HER2-low advanced breast cancer in a phase I trial[114] and is being investigated in HER2-low metastatic breast cancer in a phase III trial.[115]

Additional studies may identify tumors with even lower levels of HER2 expression as a targetable group. The phase III DESTINY-Breast06 study is evaluating T-DXd in advanced or metastatic HR+/HER2-low or HER2 IHC >0 to <1+ breast cancer.[22] Although efficacy in the HER2 IHC >0 to <1+ subgroup is not a primary objective, it will provide important insights into the lower bound of HER2 expression that could benefit from T-DXd.[22] If efficacy is shown among patients with HER2 IHC >0 to <1+ tumors, precise identification criteria for this group will become important because nearly all samples have at least one cell with HER2 staining.

While T-DXd demonstrated efficacy in HR−/HER2-low breast cancer in DESTINY-Breast04, the number of patients with HR− disease was relatively small ($n = 40$ randomized to T-DXd).[12] Future studies may provide a more thorough understanding of T-DXd in HR−/HER2-low breast cancer. Preliminary results from the ongoing phase Ib/II BEGONIA trial suggest efficacy of T-DXd combined with durvalumab in HR−/HER2-low advanced or metastatic breast cancer ($n = 46$), with confirmed responses in 57% of patients (95% CI 41% to 71%) and an mPFS of 12.6 months (95% CI 8 months to not reached).[116] Together with results from DESTINY-Breast04,[12] these preliminary results—albeit in a small number of patients and in combination with durvalumab—support the efficacy of T-DXd in the HR−/HER2-low population.

Understanding the optimal treatment sequence for patients with HER2-low breast cancer will be important, as patients may be eligible for multiple targeted treatments based on expression of HER2 and other biomarkers. While no data exist supporting the optimal sequence of T-DXd and the anti-TROP2-directed ADC sacituzumab govitecan (SG), this is an important consideration, as studies support the efficacy of both T-DXd and SG in pretreated HR+/HER2-low breast cancer.[12,63] DESTINY-Breast04 demonstrated the efficacy of T-DXd in pretreated (at least one prior line of chemotherapy) HER2-low metastatic breast cancer.[12] In the phase III TROPiCS-02 study (NCT03901339), SG demonstrated a survival benefit versus chemotherapy in pretreated (two to four prior lines of chemotherapy) HR+/HER2− metastatic breast cancer.[117] In a subgroup analysis, SG demonstrated a survival benefit in HR+/HER2-low and HR+/HER2 IHC 0 disease.[117] Although the patient populations differed between these two studies, similar hazard ratios for disease progression or death in HR+/HER2-low breast cancer were reported with T-DXd (0.51, 95% CI 0.40-0.64, $P < 0.001$)[12] and with SG (0.58, 95% CI 0.42-0.79, $P < 0.001$).[64] SG also demonstrated a survival benefit versus chemotherapy in metastatic TNBC in the phase III ASCENT trial (NCT02574455).[118] In a *post hoc* subgroup analysis, SG demonstrated a survival benefit versus chemotherapy in HR−/HER2-low (hazard ratio 0.43, 95% CI 0.28-0.67, $P < 0.001$) and HR−/HER2 IHC 0 (hazard ratio 0.51, 95% CI 0.39-0.66, $P < 0.001$) disease.[119] T-DXd is currently the standard of care for patients with HER2-low metastatic breast cancer, regardless of HR status, who received prior chemotherapy in the metastatic setting or developed disease recurrence within 6 months of adjuvant chemotherapy. However, SG is another treatment option for HER2-low disease after at least two prior systemic therapies.[120] Future studies may clarify the optimal sequence for these therapies and other emerging treatment options, including the anti-TROP2-directed ADC datopotamab deruxtecan, which demonstrated preliminary efficacy in HR+/HER2-low or HR+/HER2 IHC 0 metastatic breast cancer [objective response rate (ORR) 29%] in the phase I TROPION-PanTumor01 trial (NCT03401385)[121] and is being further evaluated in the ongoing phase III TROPION-Breast01 trial (NCT05104866).[122,123]

The efficacy of T-DXd in HER2-low breast cancer may inform the treatment of other tumor types. T-DXd is also approved in the United States for the treatment of locally advanced/metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) and unresectable/metastatic non-small-cell lung cancer with activating *ERBB2* mutations.[2] Preliminary results from the phase II DESTINY-PanTumor02 trial (NCT04482309) showed that T-DXd demonstrated durable responses in patients with multiple types of advanced, metastatic, or unresectable HER2-expressing solid tumors.[124-126] The finding that HER2-low expression is an actionable target in breast cancer raises the question of whether T-DXd may be effective in other tumor types with low HER2 expression. Exploratory results from a small number of patients with HER2-low GC/GEJC (IHC 2+/ISH−, $n = 21$; IHC 1+, $n = 24$) support the efficacy of T-DXd in this population, with a confirmed ORR of 26.3% (95% CI 9.1% to 51.2%) in patients with IHC 2+/ISH−

tumors and 9.5% (95% CI 1.2% to 30.4%) in patients with IHC 1+ tumors and median OS of 7.8 months (95% CI 4.7 months to nonevaluable) and 8.5 months (95% CI 4.3-10.9 months), respectively.[127] Future studies should further evaluate T-DXd in HER2-low GC and establish whether the activity of T-DXd in the HER2-low setting also extends to other tumor types.

The future of HER2 scoring and reporting

More quantitative measures for HER2 expression and an understanding of the impact of HER2 heterogeneity on responses to T-DXd or other HER2-directed therapies may help guide treatment decisions and refine best practices for HER2 scoring and reporting. Heterogeneity could influence the efficacy of HER2-directed therapies in the HER2-low setting and may contribute to efficacy in IHC 0 tumors. Because of T-DXd's proposed bystander antitumor effect—whereby after killing HER2-expressing tumor cells, the released topoisomerase I inhibitor payload can enter neighboring tumor cells regardless of HER2 expression[73,74]—understanding HER2 expression across a tumor may help predict susceptibility to T-DXd. Thus, while IHC scores are based on the highest level of IHC staining observed in >10% of cells, per current guidelines,[4] it may be necessary to report the intratumoral heterogeneity (the percentage of cells that are HER2 IHC 0, 1+, 2+, and 3+) and pattern of heterogeneity [clonal (two distinct clusters of positive and negative cells) versus mosaic (intermingling of positive and negative cells)], as these may indicate susceptibility to T-DXd. Additionally, if studies demonstrate the efficacy of T-DXd in HER2 IHC >0 to <1+ tumors, HER2 scoring and reporting guidelines may need to be further refined to ensure accurate identification of this group.

Novel methods for assessing HER2 may offer an advantage in identifying HER2-low breast cancer. More quantitative methods include those that analyze *HER2* messenger RNA levels[128] and those that assess HER2 protein using quantitative immunofluorescence or a reverse-phase protein array.[129-131] Additionally, digital pathology and computational methods[122,132-137] may help identify HER2-low breast cancer by removing subjectivity and variability and scoring all cells in a sample; they may also define signatures of HER2-low tumors susceptible to HER2-directed therapies.[133] Using samples from the phase I DS8201-A-J101 trial of T-DXd (NCT02564900), a deep learning-based image analysis that quantifies HER2 by generating a quantitative continuous score (QCS) was used to stratify HER2-low metastatic breast cancer into subgroups based on QCS cut-offs that correlated with ORR.[133] Overall, 42% of patients with HER2-low disease responded to T-DXd, with an mPFS of 11 months; the QCS-high subgroup had an ORR of 53% and an mPFS of 14.5 months, while the QCS-low subgroup had an ORR of 24% and an mPFS of 8.6 months.[133] These findings indicate that deep learning methods may identify patients expected to respond to T-DXd. Additionally, artificial intelligence-powered HER2 analysis may help achieve consistent HER2 IHC scoring by reducing interscorer variability in HER2-low cases.[138] Overall, the development of digital pathology and artificial intelligence-directed solutions should be considered a high priority. However, until the predictive value of novel assays is established, IHC remains the most appropriate tool for identifying HER2-low breast cancer.

PATIENT PERSPECTIVE

As described previously, the use of T-DXd in the HER2-low setting has opened another avenue of treatment for an additional subset of patients with metastatic breast cancer. As a patient with metastatic breast cancer, the approval of T-DXd for HER2-low breast cancer means one more treatment line that I can add to my list of options, and, in simpler terms, another opportunity to continue living a little longer. Living longer means getting to witness and be a part of more of the things that matter the most to me. One more treatment option means that I might surpass the average prognosis for metastatic breast cancer. For me, that is hope, and hope is not measurable in data and statistics.

I was diagnosed at age 31 with stage I invasive ductal carcinoma and at age 33 with metastatic breast cancer. I have no family history, genetic disposition, or major risk factors. My subtype is HER2−, but one of my biopsies indicated that my cancer was HER2-low (IHC 2+). This information was not useful when I was diagnosed, but it is today because of the data and studies that show that T-DXd is effective in the HER2-low population.

From a patient's perspective, to be effective, a treatment must also be tolerable and preserve a reasonable quality of life. I received T-DXd for 5 months, and during that time my most challenging side effects were brain fog that lasted for ∼4 days each treatment cycle, general fatigue, intermittent nausea, and bone pain that was most prominent on day 3 post-infusion. Usually, by day 5, I would emerge from my brain fog but would still experience fatigue and nausea intermittently during the 3-week treatment cycle. Around cycle 4, I began taking a very low dose of olanzapine, which helped me sleep better and reduced my nausea to almost nothing. With olanzapine, the disruptive nature of fatigue and nausea was controlled, making T-DXd more tolerable and giving me a better quality of life. During treatment, my oncologist recommended that I get scans every 6 weeks and an echocardiogram every 3 months to monitor for ILD and LVD. I did not experience ILD or LVD, but I had a heightened awareness of the seriousness of these issues that resulted in some anxiety.

Although the data quantify the spectrum of side effects and demonstrate the statistically significant improvements in PFS and OS with T-DXd, they do not capture what it means to be living with this disease. My experience is unique in some ways but average in others. Other patients living with metastatic breast cancer who have been treated with T-DXd have had similar experiences to mine and have wished that all treatments were as manageable as T-DXd, while others have had debilitating side effects. Although it is not yet possible to predict which side effects someone

will experience or to what extent they will experience them, having T-DXd as a treatment option is an overall positive outcome for patients with HER2-low metastatic breast cancer.

CONCLUSIONS

The approval of T-DXd for the treatment of HER2-low breast cancer established that low levels of HER2 expression, regardless of HR status, are targetable and suggests that potent HER2-directed ADCs can provide meaningful benefit even in the absence of canonical HER2 positivity. T-DXd has shown efficacy across subgroups of patients, regardless of HR expression, indicative of broad applicability in HER2-low breast cancer. As treatment based on HER2-low status represents a paradigm shift in the clinical landscape of breast cancer treatment, appropriate identification of HER2-low disease that may be eligible for treatment with T-DXd is required. Patients with any history of IHC 1+ or IHC 2+/ISH− samples may benefit from T-DXd, and data suggest that in the absence of prior evidence of HER2-low expression, re-evaluation of IHC 0 samples may help identify patients who are eligible for treatment. We need long-term follow-up studies to understand the prolonged effectiveness and safety of T-DXd. The long-term safety profile and potential adverse effects of T-DXd, particularly in a broader patient population, need to be collected in real-world studies. The results from the longer follow-up of DESTINY-Breast 04 continue to support the use of T-DXd as the new standard of care after one line of chemotherapy in patients with HER2-low metastatic breast cancer, confirming OS and mPFS benefit without affecting the safety profile.[139] Future research may refine best practices for assessing HER2 and expand the population of patients with breast or other cancers who may derive benefit from treatment with T-DXd or other HER2-directed therapies.

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