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REVIEW ARTICLE

Diagnosis and management of *HER2*-low breast cancer

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Abstract

HER2 acts as a prognostic and predictive biomarker in early and metastatic breast cancer (BrCa). A HER2-positive tumor has an IHC score of 3+ or 2+ with confirmed HER2 amplification by in situ hybridization (ISH). HER2-low breast cancer has a score of 1+ or 2+ without gene amplification. In Mexico, 47.3% of patients with metastatic breast cancer are HER2-low. Antibody-drug conjugates have demonstrated efficacy in patients with HER2-positive and HER2-low disease.

Keywords: *HER2-low. Breast cancer. Treatment. Diagnosis. Review.*

Diagnóstico y tratamiento del cáncer de mama HER2-bajo

Resumen

HER2 actúa como biomarcador pronóstico y predictivo en cáncer de mama (CaMama) temprano metastásico. Un tumor HER2-positivo tiene IHQ de 3+ o 2+ con amplificación confirmada de HER2 mediante hibridación in situ (ISH). El CaMama HER2-bajo tiene puntuación de 1+ o 2+ sin amplificación génica. En México, el 47.3% de los pacientes con CaMama metastásico es HER2-bajo. Los conjugados anticuerpo-fármaco han demostrado eficacia en pacientes con HER2 positivo y HER2 bajo.

Palabras clave: *HER2-bajo. Cáncer de mama. Tratamiento. Diagnóstico. Revisión.*

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Introduction

The human epidermal growth factor receptor 2 gene (*HER2*/neu or *HER2*) is located on the long arm of chromosome 17 and encodes the *HER2* transmembrane receptor protein, which possesses tyrosine kinase activity[1].

HER2 belongs to the epidermal growth factor receptor (EGFR) family, also known as the ErbB family[1]. This family includes four components (HER1 to HER4) and is involved in intercellular communication, as well as communication between cells and stroma[2]. Therefore, receptors within the HER family exhibit abnormal signaling activity in a wide variety of tumors[1].

Dimerization of *HER2* with other receptors in the ErbB family leads to autophosphorylation of tyrosine residues in its cytoplasmic domain. This phosphorylation promotes different intracellular signaling pathways and cellular proliferation.

HER2 is an oncogene considered a therapeutic target because alterations in the *HER2* gene induce a phenotype in breast cancer (BC) known as *HER2*-positive[1,3], which represents 15-25% of BC cases. It is associated with higher histological grade and advanced stages at diagnosis, greater metastatic potential, and lower overall survival (OS)[3-5].

HER2 is also a prognostic and predictive biomarker in early or metastatic BC[6,7]. Patients with invasive BC should be evaluated by immunohistochemistry (IHC) to detect *HER2* expression[8].

IHC determines *HER2* expression using scores of 0, 1+, 2+, or 3+. A tumor is *HER2*-positive if it has IHC 3+ or 2+ with gene amplification by in situ hybridization (ISH). Tumors with IHC 2+ without evidence of amplification by ISH are considered *HER2*-negative, as are those with IHC 1+ or 0[7].

This study adheres to the PRISMA guidelines.

Definition

For more than two decades, BC and its expression of the *HER2* protein have been classified in a binary manner: positive, if *HER2* protein overexpression is detected by IHC or gene amplification (ISH positive), and negative in the absence of these characteristics[7]. Under this concept, 80–85% of BC cases have been defined as *HER2*-negative, although up to 50% of them may present detectable concentrations of the *HER2* protein by IHC, identified as 1+ or 2+[9].

In routine clinical practice, IHC is used to determine the level of *HER2* protein expression[10-13]. According to the IHC result, a score of 0, 1+, 2+, or 3+ is assigned to the level of *HER2* protein expression.

Table 1. Definition of *HER2*-low

HER2 status	Criteria
HER2-negative	IHC 0
HER2-low	IHC 1+or IHC 2 + (ISH-negative)
HER2-positive	IHC 2+(ISH-positive) or IHC 3+

IHC: immunohistochemistry; ISH: *in situ* hybridization.

Based on the criteria of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for *HER2* evaluation, a tumor is considered *HER2*-positive if the IHC score is 3+ or if it is 2+ with evidence of *HER2* gene amplification by FISH (fluorescence in situ hybridization) or ISH[11]. Tumors with an IHC score of 2+ but without evidence of *HER2* gene amplification are classified as *HER2*-negative, along with those with IHC scores of 1+ or 0.

Recently, the term *HER2*-low has been introduced, which includes cases of BC showing *HER2* scores of 1+ or 2+ by IHC without *HER2* gene amplification by ISH. Therefore, we now have tumors that do not have sufficient protein expression to be classified as *HER2*-positive (*HER2*+), but are not completely negative for *HER2*[14]. (Table 1).

The inclusion of this term arises from the development of antibody-drug conjugates (ADC), which represent a technological advance in the application of systemic therapy in this group of patients with lower *HER2* expression[9].

Similarly, it is important to mention another relevant concept for understanding *HER2*: *HER2* microheterogeneity. *HER2* microheterogeneity refers to variability in *HER2* protein expression within different areas of the same tumor or among different tumor cells in the same patient. This means that not all tumor cells express *HER2* uniformly. This variability may complicate diagnostic evaluation, as some cells may respond to *HER2*-targeted therapies while others may not[12].

Diagnosis

Accurate identification of *HER2* expression is important for developing appropriate treatment regimens and establishing prognosis in patients with BC[15].

The French clinical guidelines (2021 edition) for *HER2* detection recommend that *HER2* IHC results be

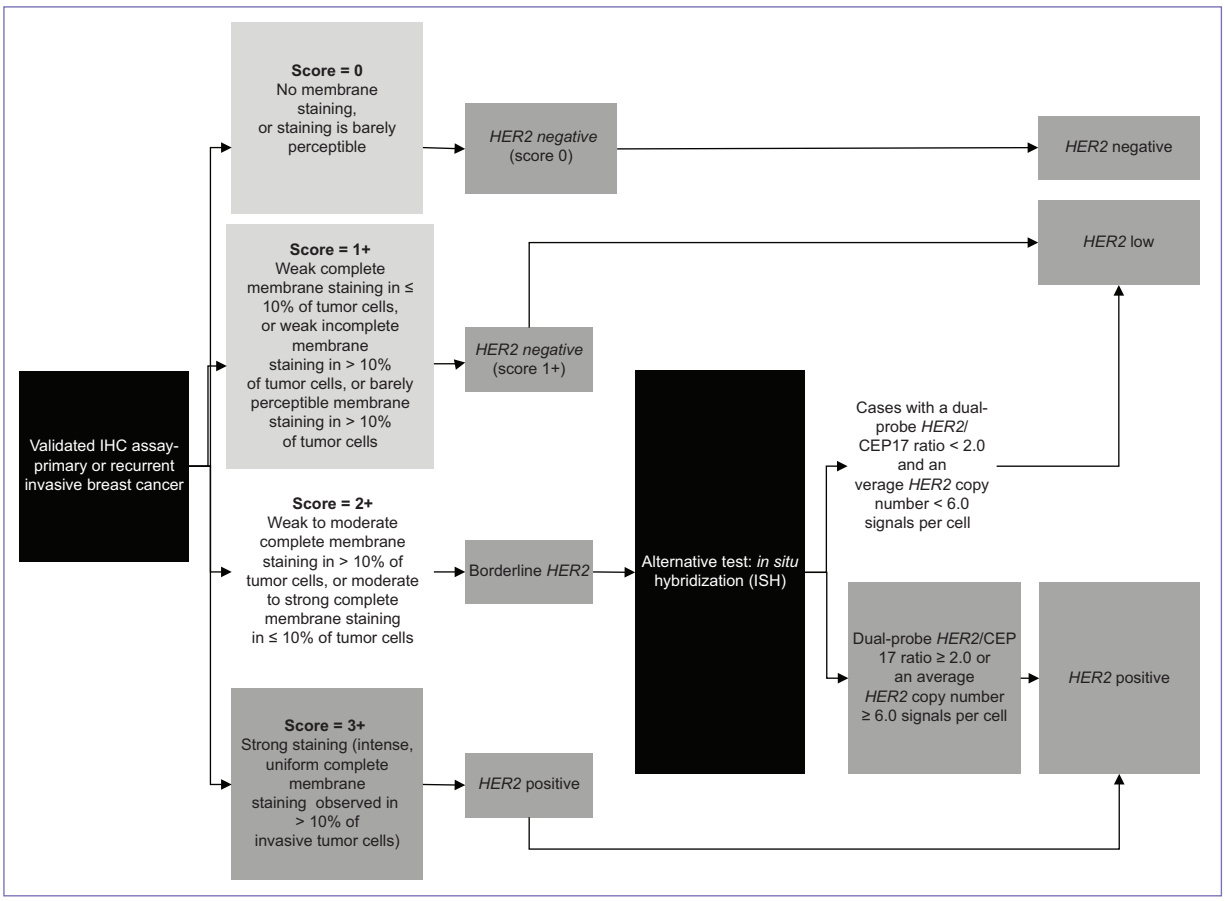


Figure 1. Diagnostic process of *HER2*-low and *HER2*+. IHC: immunohistochemistry.

clearly reported in three components used to assess *HER2* scores. These include intact or incomplete *HER2* tumor cell membranes, staining intensity (which requires careful observation at high magnification), and the percentage of infiltrating tumor cells positive for staining[16].

The diagnostic process for *HER2*-low BC (Fig. 1) involves several critical steps to determine the *HER2* status of neoplastic cells and guide appropriate treatment.

Biopsy of tissue

Diagnosis begins with a breast tissue biopsy, where a sample of the tumor is obtained. This is analyzed in a pathology laboratory to determine the presence and degree of *HER2* expression.

It is recommended that the time from tissue collection to fixation be as short as possible, that samples be fixed in 10% neutral buffered formalin for a period of 6 to 72 hours, and that they be sectioned at intervals of 5 to 10 mm after adequate macroscopic inspection and placed in a sufficient volume of neutral buffered formalin[7].

According to ASCO/CAP (2023) recommendations, oncologists may consider *HER2* IHC results obtained from primary samples or simultaneous samples from other metastatic sites. This is because variability in *HER2* expression may occur between different samples[17].

According to the recommendations of the Sociedad Europea de Oncología Médica (ESMO, European Society for Medical Oncology) consensus on *HER2*-low, in cases where *HER2*-0 has been recorded throughout the course of the disease, it is suggested to perform a biopsy (if possible) to reassess *HER2* status [I, B][18].

IHC results should be reported according to the scoring system: score 0 (no staining or incomplete and faint/barely perceptible membrane staining in ≤ 10% of tumor cells), score 1+ (incomplete and faint/barely perceptible membrane staining in > 10% of tumor cells), score 2+ (complete weak/moderate membrane staining in > 10% of tumor cells or complete and intense membrane staining in ≤ 10% of tumor cells), and score 3+

Table 2. Definition of *HER2* IHC staining patterns, proposed by ASCO/CAP and ESMO

Staining description	ASCO/CAP 2018 designation	ASCO/CAP 2018 conclusion	ESMO 2023 conclusion
No staining Incomplete or weak staining in ≤ 10% of invasive tumor cells	*HER2* 0 *HER2* 0	*HER2*-negative *HER2*-negative	*HER2*-0 *HER2*-null *HER2*-ultralow
Incomplete or weak staining in > 10% of invasive tumor cells	*HER2* 1 +	*HER2*-negative	*HER2*-low
Complete membrane staining, weak to moderate, in > 10% of invasive tumor cells (ISH-negative)	*HER2* 2 + non-amplified	*HER2*-negative	*HER2*-low
Complete membrane staining, weak to moderate, in > 10% of invasive tumor cells (ISH-positive)	*HER2* 2 + amplified	*HER2*-positive	*HER2*-positive
Intense complete membrane staining in > 10% of invasive tumor cells	*HER2* 3 +	*HER2*-positive	*HER2*-positive

ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; ESMO: European Society for Medical Oncology; IHC: immunohistochemistry; ISH: *in situ* hybridization.

(complete and intense membrane staining in > 10% of tumor cells)[16].

Table 2 summarizes the conclusions related to each *HER2* IHC staining pattern proposed by the ASCO and CAP 2018 guidelines, as well as the ESMO 2023 consensus recommendations[7,14,19].

Of note, the evaluation of *HER2* expression must be a standardized process, as over time an evolution in measurement methods has been observed, aiming to achieve a balance between precision and reproducibility.

The first commercial method developed was the IHC HercepTest, which maintained the scoring of the original method used during the preclinical phases of trastuzumab development: 0, 1+, 2+, 3+. The HercepTest demonstrated 79% concordance with preclinical methods and 86% with FISH[20].

Following the use of HercepTest, other assays for *HER2* evaluation were developed, including VENTANA 4B5, which is currently the most widely used test.

For the determination of *HER2*-low expression, ASCO/CAP guidelines have not introduced changes in the official recommendations for *HER2* evaluation, nor have they established a superior evaluation method for *HER2*-low[17].

Thus, HercepTest and VENTANA 4B5 are 2 types of antibodies that have been approved by the US Food and Drug Administration (FDA) for detecting *HER2* status by IHC. Despite this, research has revealed significant differences in low *HER2* detection rates between these tests. HercepTest and VENTANA 4B5 differed in their detection of low *HER2* expression. The FDA approved the VENTANA PATHWAY anti-*HER2* (4B5) antibody as a companion diagnostic in 2022 for detecting *HER2*-low expression[21].

Among the ASCO/CAP recommendations for distinguishing between IHC 0 and 1+ are the following[7]:

- Examine *HER2* IHC slides at 40× magnification.
- Perform a second pathology review when results approach the threshold between 0 and 1+ (> 10% of cells with incomplete, faint, or barely perceptible membrane staining).

More precise future methods for measuring *HER2* have been proposed, including quantitative immunofluorescence and messenger RNA evaluation[19].

If the IHC score is 2+, a FISH or ISH test should be performed. This test measures the number of copies of the *HER2* gene in tumor cells. A positive ISH result confirms *HER2* gene amplification.

Results from a retrospective study on prevalence, clinicopathological characteristics, treatments, and outcomes of *HER2*-low indicated that reconsidering a new *HER2* assessment in patients initially scored as IHC 0 may be useful to improve treatment selection in subsequent lines[22].

A relevant diagnostic challenge is distinguishing between IHC 1+ (incomplete membrane staining that is faint or barely perceptible and present in > 10% of invasive tumor cells) and IHC 0 (no staining or incomplete, weak, or barely perceptible membrane staining in > 10% of invasive tumor cells)[23]. The term *HER2*-ultralow is used to describe BC tumors with very low *HER2* protein expression. These are tumors with IHC scores of 0, but with very weak or barely detectable *HER2* expression in > 10% of tumor cells. This finding distinguishes them from *HER2*-negative cancers, which completely lack this protein.

Recognizing *HER2*-ultralow as a separate category is crucial, as it could increase the number of patients who may benefit from therapies previously reserved only for *HER2*-low tumors[24].

Distribution of *HER2*-low according to molecular surrogate subtypes by immunohistochemistry

The distribution of *HER2*-low across different BC subtypes based on IHC is as follows[25]:

- Approximately 60% of breast tumors with positive hormone receptors (HR+) and *HER2*-negative status show *HER2* expression classified as 1+ or 2+ without gene amplification.
- Around 40% of BC classified as triple-negative breast cancer (TNBC), meaning no expression of estrogen receptor, progesterone receptor, or *HER2* by IHC, also exhibit *HER2* expression classified as 1+ or 2+ without gene amplification.

Epidemiology

In retrospective cohort studies, the clinicopathological and molecular characteristics of patients with BC and *HER2*-low were analyzed. It was identified that between 55% and 60% were classified as *HER2*-low. Of these, approximately 80% were tumors associated with hormone receptor expression and between 15% and 20% were triple-negative tumors[19].

The ESME cohort (Epidemiological Strategy and Medical Economics) recently provided epidemiological data on incidence and oncological outcomes in patients with *HER2*-low metastatic BC (MBC) compared with *HER2*-negative and *HER2*-positive patients[26]. The study showed the following:

- Of the 19,585 patients with MBC included in the study, 6,118 (31.2%) were *HER2*-low, 50.8% *HER2*-negative, and 18% *HER2*-positive.
- The median follow-up was 48.6 months.
- The cumulative incidence rate of brain and/or leptomeningeal metastases (BLM) was similar between *HER2*-negative and *HER2*-low patients, but higher in *HER2*-positive patients.
- The prevalence of BLM at metastatic diagnosis was 4.5% in *HER2*-low, 5.4% in *HER2*-negative, and 10.6% in *HER2*-positive.
- The cumulative incidence of BLM at 5 years during the disease course was 18.9% for *HER2*-low, 21.0% for *HER2*-negative, and 33.7% for *HER2*-positive.
- The median OS after BLM diagnosis was 6.6 months for *HER2*-low (HR, 0.39 *HER2*-positive vs. *HER2*-low; $p < 0.001$), 5.5 months for *HER2*-negative (HR, 1.08 *HER2*-negative vs. *HER2*-low; $p = 0.06$), and 24.4 months for *HER2*-positive.

A retrospective study analyzed data from 3,547 women aged < 40 years with *HER2*-negative BC and pathogenic variants in *BRCA1* and *BRCA2*[27]. Results showed that 32.3% of all cases were *HER2*-low; in these patients, pathogenic variants were more common in the BRCA2 gene than in *BRCA1* ($p = 0.001$). Patients with *HER2*-low had longer disease-free survival than *HER2*-zero patients (HR, 0.86; 95% CI, 0.76-0.97).

Regarding genomic characteristics of *HER2*-low disease, greater expression of genes related to the luminal subfamily has been demonstrated, including BCL2, *BAG1, FOXA1*, and *ESR1*, whereas genes associated with proliferation (*CCNE1, CCNB1, MYBL2, MKI67*, and *MELK*) and tyrosine kinase receptors (*EGFR, FGFR4*) showed lower expression[28].

In a systematic review of *HER2*-low prevalence in Hispanic or Latina women, a *HER2*-low prevalence of 32% was reported, and among patients initially reported as negative (0, 1+, and 2+ with FISH negative), *HER2*-low prevalence was 53% and 47%, respectively[29].

Data on HER2-low epidemiology in Mexico

Data on *HER2*-low epidemiology in Mexican patients with metastatic breast cancer (MBC) are limited. A cohort treated between 2017 and 2020 evaluated the frequency and prognosis of *HER2*-low[30].

- Of the 55 patients with MBC included in the study, 26 (47.3%) had *HER2*-low tumors.
- The median age at diagnosis was 51 years.
- The prevalence of *HER2*-low was higher in patients with positive hormone receptor expression (HR+) (51.3%) than in those with negative hormone receptors (HR–) (31.3%). This difference was not statistically significant ($p = 0.11$).
- In the subgroup of patients with *HER2*-low and HR+, the median OS was 36.6 months, whereas in those with *HER2*-low and HR– it was 15.8 months ($p = 0.009$).

In another study conducted at Hospital de Oncología del Centro Médico Nacional Siglo XXI, 213 patients diagnosed with advanced BC between 2018 and 2022 were analyzed, with a median age of 57 years. 44.6% had *HER2*-low tumors, while 55.4% were *HER2*-negative. There were no statistically significant differences in OS at 48 months of follow-up between the *HER2*-low and

HER2-negative groups (87.1 and 70%, respectively). However, among patients with *HER2*-low tumors, those with HR+ had a significantly higher survival rate (98.31%) compared with HR– (49.17%)[31].

In Mexico, accurate identification of the *HER2*-low subtype faces multiple technical and structural barriers:

- Variability in IHC testing makes it difficult to differentiate between IHC 0, 1+, and 2+ and requires high standardization, quality control, and pathologist expertise.
- Many laboratories have not yet adopted uniform or updated protocols in accordance with international guidelines (ASCO/CAP), and there are significant differences in the quality of reagents, equipment, and interpretation criteria between public and private institutions.
- Limitations in diagnostic infrastructure and unequal distribution of specialized services.
- In several states, the lack of accredited laboratories or personnel trained in *HER2* techniques reduces the reliability of results and delays diagnostic confirmation.
- The absence of national quality assurance and external control programs prevents consistency across centers.
- High cost and restricted access to targeted therapies, such as ADCs, discourage in some settings the implementation of more refined testing or *HER2*-low categorization in routine clinical practice.
- Lack of diagnostic uniformity also limits the generation of local data on prevalence and therapeutic response, hindering informed public policy decisions and access strategies.

Therefore, overcoming these obstacles is essential. Improving *HER2*-low identification would optimize oncologic treatment, as it would enable more precise selection of patients eligible for ADCs, prolong survival, and improve quality of life.

To achieve this, Mexico needs to strengthen quality control programs and laboratory reaccreditation processes, ensure continuous and systematic training for pathologists and technicians in *HER2* evaluation, and establish centralized referral pathways to guarantee consistent diagnoses nationwide.

Similarly, it is necessary to promote the generation of local data and clinical registries on *HER2*-low prevalence and response to ADCs in order to guide clinical decisions, optimize resources, and support the incorporation of innovative therapies into the health care system.

Treatment of *HER2*-low

The term *HER2*-low represents between 45 and 64% of BC cases[32]. Its identification is essential to recognize patients eligible for ADCs[9].

In patients with MBC and progression after multiple lines of treatment, the trastuzumab-deruxtecan (T-Dxd) combination may be a treatment option, as it is a *HER2*-targeted ADC that links a humanized anti-*HER2* antibody to a topoisomerase I inhibitor via a cleavable peptide linker. After binding to *HER2* and internalization, the linker is cleaved in lysosomes and releases Dxd, which induces DNA damage. Its high drug-to-antibody ratio (~8) and the lipophilicity of Dxd allow a bystander effect (diffusion to neighboring cells), explaining its activity in tumors with *HER2*-low expression[33].

In a phase III study involving patients with *HER2*-low MBC who had received at least one prior line of chemotherapy, patients were randomly assigned in a 2:1 ratio to receive T-Dxd at a dose of 5.4 mg/kg every 3 weeks or physician's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel[32].

A total of 88.7% had HR+ disease, 11.3% had HR– disease, and 70% of patients had received a CDK4/6 inhibitor[32].

Patients in both groups had a median of three prior lines of treatment for metastatic disease. In the control group, patients received eribulin (51.1%), capecitabine (20.1%), nab-paclitaxel (10.3%), gemcitabine (10.3%), or paclitaxel (8.2%)[32].

In the HR+ cohort, the median OS was 23.9 months in the T-Dxd group and 17.5 months in the physician's choice group, with a 46% reduction in the risk of death (HR, 0.64; $p = 0.003$). Progression-free survival (PFS) was 10.1 months for patients receiving T-Dxd vs. 5.4 months in the control arm (HR, 0.50; $p \leq 0.0001$), which is why T-Dxd is considered an option for patients with *HER2*-low who have progressed after 1 or 2 lines of chemotherapy[34]

Regarding adverse events (AEs) with T-Dxd, the most common and particularly relevant are shown in table 3[33].

Several clinical trials have shown that patients may experience sustained emesis for several days during the treatment cycle[32,35,36]. Therefore, a triple antiemetic regimen is necessary, including a 5-HT3 receptor antagonist (preferably palonosetron), dexamethasone, and a neurokinin-1 receptor antagonist, a combination required for effective management[37]. Patients with persistent nausea or vomiting despite triple therapy may be candidates for olanzapine.

The most serious AE is pneumonitis/interstitial lung disease. The incidence rate in BC patients treated with the ADC was 11.7% across all grades, of which 80.2% (174/217) were grade 1/2.

When patients develop interstitial lung disease (ILD)/symptomatic pneumonitis (grade > 2), T-Dxd should be permanently discontinued, corticosteroid treatment should be initiated promptly and continued for at least 14 days or until complete resolution of clinical and chest CT findings. Subsequently, the dose should be gradually tapered over at least 4 weeks[38,39].

It is essential that health care personnel (nurses, primary care physicians, oncologists) are aware of signs and symptoms suggestive of pneumonitis in patients receiving T-Dxd. Similarly, patient education regarding warning signs, such as cough, dyspnea, and desaturation, is necessary to ensure early detection of AEs.

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To reduce complications associated with T-Dxd-related pneumonitis, key recommendations have been established[40].

- Educate patients about early signs and symptoms of pneumonitis (cough, dyspnea, fever, and decreased capillary oxygen saturation).
- Advise patients to report any occurrence of these signs and symptoms to their physician.
- Provide training to nurses to deliver patient care and education.
- Perform periodic evaluations with standard or high-resolution chest CT every 9-12 weeks.
- Assess capillary oxygen saturation at each visit and inquire about respiratory symptoms.
- A multidisciplinary team should manage patients with pneumonitis, including a pulmonology specialist[40].

T-Dxd has become an important therapeutic agent not only in the treatment of *HER2*-positive MBC but also in tumors with *HER2*-low expression[34,41].

Understanding resistance mechanisms is crucial to improve therapeutic strategies and subsequent patient outcomes.

Mechanisms of resistance to T-Dxd may include modifications due to *HER2* receptor mutations; these may involve gene amplification or structural alterations that reduce receptor affinity for T-Dxd[34,42,43].

Additionally, activation of alternative signaling pathways, such as the PI3K/AKT/mTOR pathway, may contribute to sustained malignant cell proliferation, undermining the efficacy of T-Dxd. However, the introduction of new ADCs is expected in the coming years, and innovative approaches are being investigated to overcome resistance and improve treatment efficacy[18,44].

Currently, clinical trials are underway to evaluate ADC sequencing in patients with *HER2*-low, for example, the use of datopotamab-deruxtecan or sacituzumab-deruxtecan after progression on T-Dxd.

Other ADCs targeting 2 distinct epitopes of the *HER2* extracellular domain are under development, such as the conjugate TQB2102 for patients with *HER2*-positive and *HER2*-low disease[45].

Table 3. Adverse events of trastuzumab-deruxtecan

Adverse event	Any degree (%)	Grade 3 (%)
Neutropenia	33.2	13.7
Thrombocytopenia	23.7	5.1
Nausea	73.0	4.6
Vomiting	34.0	1.9
Diarrhea	22.4	1.1
Fatigue	47.7	7.5
Alopecia	37.7	0
Pneumonitis/ILD	12.1	0.5

ILD: Interstitial Lung Disease.
Adapted from Modi[34].

Discussion

Therefore, recognition of the *HER2*-low category has modified the traditional binary view of BC classification and has allowed identification of a subgroup of patients with biological and clinical characteristics intermediate between *HER2*-positive and *HER2*-negative tumors[19].

Findings from the ESME studies and national cohorts agree that in most cases *HER2*-low is associated with HR+ and luminal profiles[26].

Heterogeneity in *HER2* expression, as well as lack of standardization among antibodies and diagnostic platforms, remains a challenge for reproducibility and appropriate therapeutic selection[21].

The development of ADCs, especially T-Dxd, has transformed treatment in this population by demonstrating significant benefits in progression-free survival and OS in pretreated patients[34]. However, interstitial pulmonary toxicity and persistent emesis are relevant AEs that require monitoring and standardized management protocols[35].

In the near future, incorporation of new ADCs, evaluation of resistance mechanisms, and study of heterogeneity may further optimize clinical outcomes[18].

Conclusions

HER2-low has been identified as a category in BC classification, representing up to 50% of MBC cases. Its identification as a predictive biomarker has enabled benefit from ADCs. This treatment has demonstrated significant improvements in clinical outcomes, including increased OS and progression-free survival in patients with metastatic cancer who have progressed after chemotherapy and/or prior endocrine therapy.[32,43]

However, diagnosis of *HER2*-low presents challenges, particularly in the standardization and reproducibility of diagnostic tests such as IHC, FISH, and ISH. The need to precisely define the boundaries between *HER2*-low, negative, and ultralow underscores the importance of implementing robust and consistent diagnostic criteria globally to optimize patient selection and maximize the benefits of available therapies.

Additional efforts are required for proper management of AEs associated with T-Dxd. Furthermore, future research should focus on understanding the underlying biology of *HER2*-low, including its microheterogeneity and the impact of hormonal status, which may open new therapeutic opportunities for this patient population.

In conclusion, *HER2*-low status represents a significant advance in the personalization of BC treatment. However, its effective integration into clinical practice requires a multidisciplinary approach combining basic research, clinical management, and diagnostic standardization. This approach will expand access to targeted therapies and continue improving the quality of life of patients with *HER2*-low BC.

HER2-low represents a biological and clinical category with defined therapeutic implications. Its proper diagnostic characterization and precise identification through IHC and ISH are essential for selecting patients eligible for targeted therapies such as T-Dxd.[43]

Recent advances support the efficacy of ADCs in this subgroup, with significant improvements in survival, but also highlight the need for close AE monitoring and strategies to mitigate treatment resistance.[18] Consolidating global diagnostic criteria and promoting translational research will allow full exploitation of the potential of targeted therapy in *HER2*-low BC.

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Conflicts of interest

The authors declared no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, clinical records, or human biological samples; therefore, ethical approval is not required. SAGER guidelines do not apply.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of this manuscript.

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