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Review

Taiwan Expert Consensus on the appropriate treatment strategies for HER2-low breast cancer

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ABSTRACT

Background: Breast cancer (BC) is one of the most common cancers among women in Taiwan, with an increasing incidence rate. Advancements in treatment, particularly new-generation antibody-drug conjugates (ADCs), have shown promise for HER2-low BC. This consensus aims to help clinicians formulate treatment guidelines for HER2-low patients.

Methods: The Taiwan Breast Cancer Society convened a multidisciplinary panel to conduct a systematic literature review and discuss nine key topics. The panel utilized the US Preventive Services Task Force and GRADE approach for evidence grading and employed the modified Delphi technique to achieve expert consensus.

Results: The panel developed 25 consensus statements regarding ADCs and HER2 status. Key findings include that HER2 expression is necessary for trastuzumab-DM1 (T-DM1) and trastuzumab deruxtecan (T-DXd), while TROP2 testing is not required for sacituzumab govitecan (SG). T-DXd is the preferred second-line treatment for HER2-positive metastatic breast cancer and is effective in HER2-low disease and brain metastases. For HR-positive/HER2-negative metastatic breast cancer, both T-DXd and SG improve outcomes after endocrine therapy and CDK4/6 inhibitors. In triple-negative breast cancer, SG offers significant benefits in refractory cases. For HER2-low breast cancer, T-DXd is considered first in HR-positive cases, and SG in HR-negative cases. The routine sequential use of multiple ADCs is not currently supported by evidence

Conclusion: This consensus provides essential insights into HER2-low BC, highlighting its characteristics and evolving treatment options, serving as a practical reference for clinicians.

Introduction

Breast cancer (BC) is one of the most prevalent cancers worldwide and has become a leading cause of mortality, posing a significant challenge for global health systems. According to World Health Organization (WHO) statistics, an estimated 2.3 million people were affected by breast cancer in 2022, resulting in 670,000 deaths. The incidence and mortality rates for breast cancer in that year were 58.7 and 17.0 per 100,000, respectively[1]. In Taiwan, breast cancer has been the most common cancer among women for 18 consecutive years, with

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its incidence rate steadily increasing. Currently, there are over 15,000 new cases diagnosed each year, and about 3000 women die from breast cancer annually.[2]

As breast cancer treatment continues to advance, there is growing interest in developing specific treatment strategies for different subtypes of the disease. A simplified categorization based on the expression levels of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) has been widely adopted in clinical practice.[3,4] This method allows breast cancers to be classified into three distinct subtypes: 1) Luminal-like tumors (ER-positive and/or PR-positive and HER2-negative); 2) HER2-positive tumors (HER2-positive, regardless of their ER and PR status); and 3) Triple-negative tumors (ER-negative, PR-negative, and HER2-negative). While the proportions of each subtype vary across studies, Luminal-like tumors are generally the most common, accounting for about 70 % of all cases. HER2-positive and Triple-negative tumors each make up approximately 10–20 %. This classification system assists in tailoring treatment strategies for breast cancer patients.[5,6]

Anti-HER2 therapies have demonstrated promising effectiveness in treating HER2-positive breast cancers. However, these benefits have not traditionally extended to tumors that do not show HER2 overexpression. Recent clinical trials, particularly with new-generation antibody-drug conjugate (ADC) therapies, have indicated significant clinical improvements for metastatic breast cancer patients with a newly recognized subgroup: HER2-low breast cancer[7,8]

This HER2-low subgroup is characterized by an immunohistochemistry (IHC) score of 1 + , or an IHC score of 2 + with a negative fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) test result. This emerging category encompasses a substantial portion of breast cancer patients previously classified as HER2-negative and has been shown to respond to novel ADCs.[8,9]

In order to provide a comprehensive and systematic reference to assist physicians in proposing appropriate treatment strategies for HER2-low patients, the Taiwan Breast Cancer Society (TBCS) convened a consensus meeting working group in October 2023 to discuss important issues in the clinical treatment of HER2-low breast cancer.

Methods

Expert panel composition

The Taiwan Breast Cancer Society (TBCS) convened a multidisciplinary expert panel consisting of 47 members who specialize in breast cancer. Panel members were chosen based on their clinical expertise and research experience with breast cancer therapeutics, particularly antibody-drug conjugates (ADCs). The panel's objective was to develop consensus statements regarding the use of ADCs in advanced breast cancer. Their focus included the integration of ADCs into current treatment strategies, addressing biomarker issues, managing toxicity, and tackling emerging challenges.

Literature searching strategies

The panel subgroups conducted a literature search in PubMed, concluding in March 2023. They used the keywords “ADC,” “HER2-low,” “HER2-ultralow,” and “breast cancer”. Studies published in 2011–2023 and written in English were selected, and only full-text articles were reviewed. The panel also included existing guidelines, such as those from ASCO, NCCN, and ESMO, except for clinical trial publications and conference proceedings. After completing the systematic literature search, the panel reviewed the literature pertaining to their assigned topics. In total, over 30 publications were considered as the evidentiary basis for the consensus.

Evidence grading

The quality of supporting evidence for each statement was graded as Level I, II, or III, using criteria adapted from the US Preventive Services Task Force and the GRADE approach[10]. Level I was defined as evidence from at least one well-conducted randomized controlled trial (or meta-analysis of RCTs). Level II evidence included data from well-designed non-randomized studies, cohort or case-control studies, or large series. Level III evidence was based on expert opinion, case reports, or descriptive studies. Concurrently, we also followed the NCCN Development and Update of Guidelines to categorize the strength of each recommendation, which were: A (strong recommendation), B (moderate recommendation), C (weak), or D (recommendation against use). By predefined voting rules, a statement required ≥ 85 % agreement to be assigned a strength of A or B, ≥ 50 % (but < 85 %) for C, and ≥ 25 % for D.[11] Statements not achieving consensus were to be revised or discarded.

Consensus development

The panel employed a modified Delphi process: initial statements were circulated via email for feedback and then discussed in a series of virtual meetings that took place from September 2023 to March 2024. Statements were revised for clarity and accuracy based on iterative feedback until a preliminary consensus was reached.

The final consensus meeting was held in person on January 6 and 7, 2024, during the “2024 ADC Consensus Symposium” in Taipei. Panel members reviewed the collated evidence and voted anonymously on each statement’s acceptance and recommendation grade. All 25 statements met the consensus threshold for acceptance; none required further modification after this meeting. The entire consensus document was reviewed and officially endorsed by the TBCS Board in March 2024.

Results

Q1: Should breast cancer be reclassified based on trial results

The first question we need to consider is whether breast cancer should be reclassified based on the results of clinical trials. As previously mentioned, the effects of antibody-drug conjugates (ADCs) on HER2-positive breast cancer patients have been positive. Additionally, the DESTINY-Breast04 study has shown beneficial effects on patients classified as HER2-low.[8] The expert panel referenced the article by Wolff et al., which proposed that “the HER2-low classification now falls within the specified criteria for HER2-negative classification.”[12] Therefore, we recommend that **the HER2-low classification encompasses HER2 testing results that exhibit IHC 1 + or IHC 2 + / ISH- as determined by validated methods.** (Quality of Evidence (QoE): I; Strength of Recommendation(SoR): A)

Next, five papers were reviewed to discuss whether the definition of HER2 low classification needs to be revised for the usage of the HER2-directed antibody-drug conjugate. (see Table 2) Mass *et al.* investigated the impact of HER2 gene amplification on the outcomes of women with metastatic breast cancer who were treated with trastuzumab. They used fluorescence in situ hybridization (FISH) to analyze breast cancer tissue samples. A HER2:CEP17 ratio of 2.0 or higher indicated a positive result for gene amplification. All the samples had already shown high levels of HER2 protein. The researchers compared response rates, time until disease progression, and survival between FISH-positive and FISH-negative patients across three clinical trials. They obtained valid FISH results from 765 out of 799 patients (96 %); 596 patients (78 %) were FISH-positive, while 169 patients (22 %) were FISH-negative, with similar rates observed across all trials.[13]

Table 1
Strength of the recommendation and quality of evidence.

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use
Quality	Evidence
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Fehrenbacher *et al.* investigated whether adding trastuzumab to adjuvant chemotherapy (CRx) would enhance invasive disease-free survival (IDFS) in patients with HER2-negative breast cancer. They randomly assigned 3270 women with high-risk primary invasive breast cancer to receive CRx with or without one year of trastuzumab. The results showed that the addition of trastuzumab to CRx did not improve IDFS, the distant recurrence-free interval, or overall survival in women with non-HER2-overexpressing invasive breast cancer. Therefore, trastuzumab does not provide benefits for women without IHC 3 + or FISH ratio-amplified breast cancer.[14] Burris *et al.* conducted a Phase II study on the antibody-drug conjugate trastuzumab-DM1 for the treatment of HER2-positive breast cancer in patients who had previously received HER2-directed therapy. They found that trastuzumab-DM1 (T-DM1) demonstrates strong single-agent activity in heavily pretreated patients with HER2-positive metastatic breast cancer and is well tolerated at the recommended Phase II dose.[15] The phase II study conducted by Krop et al. assessed the efficacy of trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer who had previously been treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. The study found that T-DM1 is well tolerated and demonstrates single-agent activity in this patient population. This suggests that T-DM1 could be an effective new treatment option for individuals with HER2-positive metastatic breast cancer who have already received both approved HER2-targeted therapies and several chemotherapy agents[16]. Modi *et al.* found that Trastuzumab deruxtecan (T-DXd, formerly known as DS-8201a) demonstrated promising preliminary antitumor activity in patients with HER2-low breast cancer. Most side effects were related to the gastrointestinal (GI) system or hematologic in nature. Notably, interstitial lung disease has been identified as a significant risk and should be monitored closely and managed proactively.[17] Another study revealed that trastuzumab deruxtecan resulted in significantly longer progression-free and overall survival for patients with HER2-low metastatic breast cancer compared to chemotherapy.[8] Based on these findings, we recommended that **the HER2-low classification is specifically designated for but not limited to usage of the HER2-directed antibody-drug conjugate such as trastuzumab deruxtecan.** (QoE: I; SoR: A)

Q2: How to identify HER2-low breast cancer consistently and reproducibly

Six papers were selected to address this question. The expert panel first reviewed studies by Wolff *et al.* and Ivanova *et al.*'s studies[18,19], which updated the ASCO-College of American Pathologists guidelines and incorporated the 2023 ASCO/CAP updates, as well as the 2023 ESMO consensus statements on HER2-low breast cancer. After examining these articles, the expert panel recommended to **follow 2023 ASCO/CAP guidelines to control pre-analytic factors, validate staining, follow scoring criteria, and report with HER2 IHC scores (3 + / 2 + / 1 + / 0).** (QoE: II; SoR: A)

Table 2
HER2-low classification for HER2-directed antibody-drug conjugate usage.

Study (Reference)	Study Purpose	HER2 Detection Method	HER2 Definition (Positive/Negative)	Key Findings
Mass et al.	Evaluate the impact of HER2 gene amplification on prognosis in metastatic breast cancer patients treated with trastuzumab	FISH	HER2:CEP17 ratio ≥ 2.0 positive	78 % of patients were FISH-positive, consistent with high protein expression; compared response rates, time to progression, and survival between FISH-positive and -negative patients.
Fehrenbacher et al.	Evaluate whether adjuvant trastuzumab plus chemotherapy improves invasive disease-free survival in HER2-negative breast cancer patients	Specific detection method not provided, emphasized IHC 3 + or FISH amplification negative	Non-HER2 overexpression (IHC 3 + or FISH amplification negative)	Trastuzumab did not improve invasive disease-free survival, distant recurrence-free interval, or overall survival in patients with non-HER2 overexpressing invasive breast cancer.
Burris et al.	Phase II study of T-DM1 in HER2-positive breast cancer patients	Not explicitly stated, but for HER2-positive patients	HER2-positive (previously treated with HER2-targeted therapy)	T-DM1 demonstrated potent single-agent activity and was well-tolerated in heavily pretreated HER2-positive metastatic breast cancer patients.
Krop et al.	Phase II study of T-DM1 in HER2-positive metastatic breast cancer patients (heavily pretreated)	Not explicitly stated, but for HER2-positive patients	HER2-positive (previously treated with trastuzumab, lapatinib, anthracyclines, taxanes, and capecitabine)	T-DM1 was well-tolerated and showed single-agent activity in this patient population, suggesting it could be a new treatment option.
Modi et al. (Phase Ib) / Modi et al. (DESTINY-Breast04)	Evaluate the antitumor activity and safety of T-DXd in HER2-low breast cancer patients	IHC 1 + or IHC 2 + /ISH-	HER2-low	T-DXd showed promising preliminary antitumor activity in HER2-low breast cancer patients; significantly prolonged progression-free survival and overall survival compared to chemotherapy.

The expert panel also recommended that **using the 4B5 kit with its validated staining protocol as a companion test might be considered, due to notable inter-assay variabilities in the HER2 test.** (QoE: II; SoR: B) They referred to the work of Modi et al.[2] and Ruschoff et al.[13]. Both studies identified that variability existed among assays; therefore, the 4B5 kit might be considered to be used as a companion test to validate the staining protocol.

Geukens et al. investigated the intra-patient and inter-metastasis heterogeneity of HER2-low status in HER2-negative metastatic breast cancer. They discovered variability in HER2-low status within individual patients and between different metastases.[20] Tarantino et al. reviewed data from patients with HER2-negative breast cancer to understand how HER2 expression (specifically HER2-zero and HER2-low) may change between the initial tumor and later biopsies in advanced stages of the disease[21]. The study also compared disease-free survival, overall survival, and progression-free survival among patients with HER2-zero and HER2-low expression in their primary tumors. The findings indicated that HER2-low expression is dynamic in breast cancer and may become more prevalent in advanced stages. However, no prognostic significance was found for HER2-low expression. Based on these findings, the expert panel recommended that **HER2-low status may be heterogeneous and subject to dynamic changes. Recommend re-biopsy in case of recurrence or metastasis.** (QoE: II; SoR: B)

Q3: What are the differences in the transcriptomic profiles between HER2-low and HER2-negative breast cancer (BC)?

The expert panel chose to review the works of Dai *et al.*[22] and Atallah *et al.*[23] to address this question.

Dai et al. studied a cohort of 434 Chinese patients with HER2-low breast cancer, integrating various profiling data. They discovered that HER2-low tumors differ significantly from HER2-zero tumors, especially within the hormone receptor-negative subgroup. In this subgroup, basal-like tumors are more similar to HER2-zero disease, while non-basal-like HER2-low tumors align more closely with HER2-positive disease. Non-basal-like tumors are often classified within the HER2-enriched and luminal androgen receptor subtypes. These tumors exhibit PIK3CA mutations, overexpression of FGFR4, PTK6, and ERBB4, as well as increased lipid metabolism. Among hormone receptor-positive tumors, HER2-low tumors show fewer deletions in the 17q peaks compared to HER2-zero tumors. These findings underscore the heterogeneity of HER2-low breast cancers and the necessity for precise stratification based on hormone receptor status and molecular subtype.

Atallah et al. compared two cohorts to examine the clinico-pathological and molecular profiles of HER2-low breast cancer, focusing on responses to therapy and patient outcomes. Their results indicated that 90 % of HER2-low tumors were hormone receptor positive (HR +), primarily belonging to the luminal intrinsic molecular subtype. These tumors exhibited low HER2 signaling gene expression and demonstrated favorable clinical behavior compared to HER2-negative breast cancers. In hormone receptor-positive breast cancer, no significant prognostic differences were found between HER2-low and HER2-negative tumors. However, in hormone receptor-negative breast cancer, HER2-low tumors were less aggressive and associated with longer patient survival. Most HR-/HER2-low tumors were classified as the luminal androgen receptor (LAR) subtype, enriched with T-helper lymphocytes and activated dendritic cells, while HR-/HER2-negative tumors were predominantly basal-like and associated with tumor-associated macrophages. Based on these findings, the expert panel recommended that **the biology of HER2-low breast cancer is not driven by the HER2 oncogenic signaling pathway.** (QoE: N/A; SoR: N/A) **Differences between HER2-low and HER2-zero breast cancer are mainly attributed to the differences in hormone receptor status.** (QoE: N/A; SoR: N/A) **Only minor differences were found comparing the transcriptomic profiles of HR-positive, HER2-low breast cancer to HR-positive, HER2-zero cancer.** (QoE: N/A; SoR: N/A) **An increased proportion of non-basal-like tumors was found in HR-negative, HER2-low breast cancer, compared to HR-negative, HER2-zero breast cancer.** (QoE: N/A; SoR: N/A) **These non-basal-like tumors are enriched with tumors of the luminal AR subtype, characterized by the increased expression of lipid metabolism-related genes and up-regulation of fatty acid and steroid hormone metabolism pathways.** (QoE: N/A; SoR: N/A) This question is to evaluate the transcriptomic discrepancy between HER2-low and HER2-negative breast cancer, which is currently not relevant to clinical practice, consequently no direct impact on decision making and treatment outcomes. No recommendation and evidence level can be made.

Q4: What were the differences in mutational landscapes between HER2-low and HER2-zero BC

The next issue we were concerned about was the difference in mutational landscapes between HER2-low and HER2-zero BC. In addition to the works by Dai et al. and Atallah et al., the expert panel also selected four additional articles to compare the mutational landscapes between HER2-low and HER2-zero BC.(see Table 3)

Berrino *et al.* analyzed 99 HER2-low breast cancers (HLBCs), comparing their DNA and RNA profiles to MSKCC and internal breast cancer cohorts. They identified distinct genomic features in HLBCs compared to HER2-positive/negative cancers, revealing heterogeneity within HER2-low disease. HLBC-2E displayed the most unique features, while HLBC-1 resembled HER2-negative disease.[24] Jin *et al.* compared HER2-low and HER2-zero metastatic breast cancer. While prognosis was similar when HR status was matched, HER2-low HR + showed similar metastasis patterns to HER2-positive. HER2 status often changed between primary and metastatic tumors. Genomic analysis showed minor differences, suggesting HER2-low isn't a distinct entity but heterogeneous.[25] Tarantino *et al.* compared genomic profiles of 1039 HER2-negative metastatic breast cancers (487 HER2-low, 552 HER2-zero). HER2-low tumors showed significantly higher ERBB2 allele counts, while HER2-zero had more ERBB2 hemi-deletions (31.1 % vs. 14.5 %). No other genomic alterations or tumor mutational burden differed significantly between the groups, suggesting largely similar genomic landscapes.[26] Marra *et al.* analyzed clinicopathologic and genomic features of HER2-low breast cancers (BCs) compared to HER2-zero BCs using MSK-IMPACT sequencing data of 3608 HER2-negative samples. HER2-low tumors more frequently expressed hormone receptors and were more common in metastatic settings. While no major differences in subtype or mutation burden were found overall, HR-positive HER2-zero breast cancer showed more TP53 and CDKN1A alterations. Subdividing HER2-low into 1 + and 2 + revealed further genomic distinctions, particularly in HR-positive cases. The findings suggest HER2-low breast cancers aren't a distinct pathologic subtype, but exhibit some genomic variations.[27]. Based on these findings, we recommended that **According to currently available genomic and transcriptomic studies, HER2-low breast cancer is not considered as a biologically distinct entity.** (QoE: II; SoR: B)

Q5: What are the clinical presentations and prognostication of HER2-low BC from RWD?

HER2-low breast cancer represents a significant proportion of all breast cancer cases. Tarantino *et al.* indicated that more than half of breast cancers may be classified as HER2-low.[28] A systematic review conducted by Molinelli et al.[29] referenced a study by Peiffer et al.[30] that used the National Cancer Database. This study found that 65.5 % of non-HER2 amplified breast cancers were classified as ERBB2-low. This suggests that roughly 50–60 % of all breast cancers exhibit HER2-low expression, especially considering that HER2-positive (amplified) cases account for about 15 % of all breast cancers. Additionally, it appears that hormone receptor status influences the prevalence of HER2-low

Table 3
Comparison of mutational landscapes between HER2-low and HER2-zero breast.

Study (Reference)	Study Design/Patient Population	Comparison Groups	Key Findings (Mutational Landscape/Genomic Features)	Conclusion (Is HER2-low an independent entity?)
Berrino et al.	DNA and RNA profiling of 99 HER2-low breast cancers	HER2-low vs. HER2-positive/ negative; internal HER2-low subtypes	Identified unique genomic features of HER2-low, with internal heterogeneity (HLBC − 2E most distinct, HLBC − 1 similar to HER2-negative disease).	Emphasized internal heterogeneity within HER2-low.
Jin et al.	Comparison of HER2-low and HER2-zero metastatic breast cancer	HER2-low vs. HER2-zero (metastatic breast cancer)	Prognosis similar when HR-matched; HER2-low HR + metastasis patterns similar to HER2-positive; HER2 status often changes between primary and metastatic tumors; genomic analysis showed minimal differences.	Suggested HER2-low is not an independent entity, but heterogeneous.
Tarantino et al.	Genomic analysis of 1039 HER2-negative metastatic breast cancers	HER2-low (487 cases) vs. HER2-zero (552 cases)	HER2-low tumors had significantly higher ERBB2 allele copy numbers; HER2-zero had more ERBB2 hemizygous deletions (31.1 % vs. 14.5 %); no significant differences in other genomic alterations or tumor mutational burden.	Genomic profiles were largely similar.
Marra et al.	Clinicopathological and genomic characterization of 3608 HER2-negative samples (MSK-IMPACT)	HER2-low vs. HER2-zero	HER2-low tumors more frequently expressed hormone receptors, and were more common in the metastatic setting; HR-positive HER2-zero breast cancers showed more TP53 and CDKN1A alterations; HER2-low when categorized as 1 + and 2 + showed further genomic distinctions.	Suggested HER2-low breast cancer is not a unique pathological subtype but exhibits some genomic variations.

expression. The Peiffer *et al.* study demonstrated that higher estrogen receptor expression is associated with increased rates of ERBB2-low disease. This aligns with the general observation that HER2-low status is more frequent in hormone receptor-positive breast cancers compared to hormone receptor-negative ones, though precise percentages may vary across studies.[30]

Based on these findings, we recommended that **About 50 % of all breast cancers are HER2-low disease. The percentage of HER2-low cases in HER2 non-amplification disease was higher in hormone receptor-positive breast cancer (around 60 %-65 %) compared to hormone receptor-negative breast cancer (around 35 %-40 %).** (QoE: N/A; SoR: N/A)

As for the pathological complete response rate between HER2-zero disease and HER2-low disease, the expert panel reviewed 4 studies. The summaries were bellowing: Petrelli *et al.*'s systematic review found that among 34,965 patients in 25 studies, the analysis revealed that HER2-low status was associated with improved overall survival (OS, HR = 0.83, 95 % CI: 0.76–0.9, $p < 0.01$) and disease-free survival (DFS) (HR = 0.89, 95 % CI: 0.84–0.94, $p < 0.01$) compared to HER2-negative disease. However, the pathological complete response (pCR) rate was significantly lower in HER2-low tumors (OR = 0.72, 95 % CI: 0.58–0.91; $p < 0.01$).[31] The results of Denkert *et al.*, pooled analysis revealed that a significantly higher proportion of HER2-low-positive tumors were hormone receptor-positive (64.0 % vs. 36.7 % in HER2-zero, $p < 0.0001$). HER2-low-positive tumors had a lower pCR rate compared to HER2-zero tumors (29.2 % vs. 39.0 %, $p = 0.0002$). However, patients with HER2-low-positive tumors showed significantly longer survival than those with HER2-zero tumors.[32] A study conducted by Tarantino *et al.* recruited 5235 patients with stage I-III, ERBB2-negative invasive breast cancer. They also classified patients into 5 groups, according to their ER expression, which was ER-negative, ER-low (ie, ER 1 %-9 %), ER-moderate (ie, ER 10 %-49 %), ER-high (ie, ER 50 %-95 %) and ER–very high (ie, > 95 %). The results indicated that most differences between ERBB2-low and ERBB2–0 tumors were linked to hormone receptor (HR) expression. ERBB2-low expression showed no prognostic significance when adjusted for HR status. Additionally, ERBB2-low expression was positively associated with estrogen receptor (ER) expression, with most ER-low (ER 1 %-9 %) tumors being ERBB2–0 and most ER-high (ER, 50 %-95 %) tumors being ERBB2-low. These findings indicate that ERBB2-low should not be considered a distinct biological subtype of breast cancer.[33]

Similar findings were existed in Molinelli *et al.*'s systematic review. A total of 1797,175 patients of 42 studies were identified. Their results showed that HER2-low status was associated with improved DFS and OS compared to HER2-zero status in the early setting. However, HER2-low status was also related to a lower pCR rate.[29] In Ergun *et al.*'s review, a total of 23 retrospective studies involving 636,535 patients were included. The HER2-low arm showed significantly improved results for DFS and OS. The hazard ratios for DFS and OS in the HR-positive group were 0.88 (95 % CI 0.83–0.94) and 0.87 (95 % CI 0.78–0.96), respectively. In the HR-negative group, the hazard ratios for DFS and OS were 0.87 (95 % CI 0.79–0.97) and 0.86 (95 % CI 0.84–0.89), respectively.[34]

Based on these findings, we recommended that **there was a trend of higher pathological complete response (pCR) rate in HER2-zero disease (around 22 %-24 %) versus HER2-low disease (around 15 %-18 %). The difference of pCR rate was mainly attributed to hormone receptor status.** (QoE: N/A; SoR: N/A)

In current real-world data with or without novel agents, it is still difficult to compare survival benefit in HER2-zero disease versus HER2-low disease directly even though there was slightly improved overall survival rate in HER2-low breast cancer compared to HER2-zero population regardless of hormone receptor expression in meta-analysis, but high heterogenicity in different setting of real-world clinical data was observed (QoE: N/A; SoR: N/A) This question only describe the clinical presentations and

prognostication of HER2-low breast cancer from RWD, which is not relevant to clinical decision making and no QoE and recommendation can be made.

Q6: Is HER2-low BC a good biomarker for the efficacy of Trastuzumab deruxtecan?

Modi *et al.*'s study[8] was chosen to address this question. The research included exploratory biomarker analyses to examine other potential predictive factors. While various biomarkers, such as PAM50, ESR1, and PIK3CA, were evaluated, the primary efficacy results were consistently linked to HER2-low status. The paper highlights the benefits of T-DXd specifically for the pre-specified subgroup of HER2-low patients. Consequently, the panel recommended that **HER2-low expression is currently the only biomarker capable of predicting the therapeutic efficacy of Trastuzumab Deruxtecan (T-DXd) in patients with HER2-low metastatic breast cancer.** (QoE: I; SoR: A)

Q7: What role does Anti-TROP2 ADC play in HER2-low BC?

The role of Anti-TROP2 ADC in HER2-low breast cancer is the next issue of concern. The expert panel selected two studies to review the treatment sequence of anti-TROP2 ADC for patients with HR-negative, HER2-low recurrent unresectable or metastatic disease. Carey *et al.* focused on patients with metastatic triple-negative breast cancer who have had relapsed or refractory disease after two or more prior chemotherapy regimens. They found that sacituzumab govitecan significantly benefits PFS and OS compared to standard chemotherapy in this patient population.[35] Bardia *et al.* recruited patients with relapsed or refractory metastatic triple-negative breast cancer (which was defined by the lack of expression of estrogen receptor, progesterone receptor, and HER2) who had received at least two prior chemotherapy regimens for unresectable, locally advanced or metastatic disease. The results showed that sacituzumab govitecan significantly benefit progression-free and overall survival compared to chemotherapy in this population.[36]

Based on these findings, we recommended that **Anti-TROP2 ADC may be used as later line of treatment for patients with HR-negative, HER2-low (IHC 1 + or 2 +/ISH negative) recurrent unresectable or metastatic disease, received at least 2 prior therapies.** (QoE: I; SoR: A)

Then, the expert panel concerned the role of anti-TROP2 ADC for patients with HR-positive, HER2-low metastatic/locally advanced unresectable breast cancer. The expert panel referred two phase III studies published by Rugo *et al.*[37,38]. Rugo *et al.* investigated sacituzumab govitecan in the treatment of HR + /HER2- metastatic breast cancer. They enrolled patients who had received prior systemic treatments, including endocrine therapy, a CDK4/6 inhibitor, and at least two, but no more than four, previous chemotherapy regimens for metastatic disease. The results demonstrated improved OS and a manageable safety profile with sacituzumab govitecan compared to chemotherapy in this heavily pretreated, endocrine-resistant population. These findings support the use of Anti-TROP2 ADC, specifically sacituzumab govitecan, in this setting after prior systemic treatments as specified. Based on these findings, we recommended that **Anti-TROP2 ADC may be used as later line of treatment for patients with HR-positive, HER2-low (IHC 1 + or 2 +/ISH negative) metastatic/locally advanced unresectable breast cancer after prior systemic treatment including endocrine therapy, a CDK4/6 inhibitor and at least 2 lines of chemotherapy.** (QoE: I; SoR: A)

Q8: Treatment sequence of novel ADCs for HER2-low BC for initial HR + BC

Then, the next question is what is the treatment sequence of novel ADCs for HER2-low BC for initial HR + BC? The expert panel selected three articles to answer this question. In Modi *et al.*,[8] they found that the effects of Trastuzumab Deruxtecan on PFS and OS were better among patients who had previously received at least one line of chemotherapy in the metastatic setting. **Therefore, the panel recommended that the current evidence support the use of Trastuzumab Deruxtecan (T-DXd) for patients who have progressed upon ≥ 1 lines of chemotherapy in the metastatic setting.** (QoE: I; SoR: A)

As for Sacituzumab Govitecan (SG), consistent with its established role as a later-line treatment for HR-positive, HER2-low metastatic breast cancer as discussed in Q7, the panel suggested that **In HER2-low, HR + metastatic breast cancer, current evidence support the use of Sacituzumab Govitecan (SG) for patients who have progressed upon ≥ 2 lines of chemotherapy in the metastatic setting.** (QoE: I; SoR: A)

The panel also recommended that **There is currently insufficient evidence to support using an antibody conjugate (ADC) after progression on prior ADC in HER2-low, HR + metastatic breast cancer**(QoE: II; SoR: B)**, and There is currently no evidence to support using an antibody drug conjugate (ADC) in chemotherapy naïve setting in HER2-low, HR + metastatic breast cancer**(QoE: III; SoR: A)**,** according to Abelman *et al.*[39] and Modi *et al.*[8] studies.

Last. the expert panel referred to the ESMO Metastatic Breast Cancer Living Guidelines[40], and recommended that **Both ADCs (T-DXd and SG) proved activity in patients with metastatic HER2-low, HR + BC** and **T-DXd could be considered before SG as the first ADC in this setting.** (QoE: II; SoR: B)

Q9: Treatment sequence of novel ADCs for HER2-low BC for initial triple-negative breast cancer

In the context of treatment sequences for novel antibody-drug conjugates (ADCs) targeting HER2-low breast cancer in patients with initial triple-negative breast cancer, what are the treatment outcomes of these novel ADCs? Bardia *et al.*[36] found that progression-free survival (PFS) and overall survival (OS) were significantly longer in patients who had progressed after receiving two or more prior therapies with sacituzumab govitecan compared to those treated with single-agent chemotherapy, among patients with metastatic triple-negative breast cancer. Based on these findings, we recommended that **In HER2-low, HR- metastatic breast cancer, current evidence support the use of Sacituzumab Govitecan (SG) for patients who have progressed after receiving ≥ 2 prior therapies (with at least 1 line in the metastatic setting).** (QoE: I; SoR: A)

In Modi *et al.*'s study[8], the DESTINY-Breast04 trial included patients with HER2-low metastatic breast cancer, both HR-positive and HR-negative, who had received one or two prior lines of chemotherapy. In the HR-negative cohort, trastuzumab deruxtecan demonstrated a significant improvement in PFS and OS compared to the physician's choice of chemotherapy. Based on these findings, we recommended that **In HER2-low, HR- metastatic breast cancer, current evidence support the use of Trastuzumab Deruxtecan (T-DXd) for patients who have progressed upon ≥ 1 lines of chemotherapy in the metastatic setting.** (QoE: I; SoR: A)

Abelman *et al.*[39] found that optimizing sequential use of Antibody Drug Conjugates is an area of unmet need and of rising clinical importance. It further suggests that optimal sequencing remains uncertain, highlighting the need for further research to guide optimal sequencing of ADC-based treatment options. Based on these findings, we recommended that **there is currently insufficient evidence to support using an antibody drug conjugate (ADC) after progression on prior ADC in HER2-low, HR- metastatic breast cancer.** (QoE: II; SoR: B) The expert panel also referred to the ESMO Metastatic Breast Cancer Living Guidelines[40] and recommended that **Both ADCs (T-DXd and SG) proved activity in patients with metastatic HER2-low, HR- BC. SG could be considered before T-DXd as the first ADC in this setting.** (QoE: II; SoR: B)

Table 4
The consensus treatment strategies for HER2-low breast cancer.

Consensus Statement	Quality of Evidence	Strength of Recommendation
Re-classification of breast cancer based on clinical trial results		
The HER2-low classification encompasses HER2 testing results that exhibit with IHC 1 + or IHC 2 + /ISH- as determined by validated methods.	I	A
The HER2-low classification is specifically designated for but not limited to usage of the HER2-directed anti-body drug conjugate such as trastuzumab deruxtecan.	I	A
How to identify HER2-low breast cancer consistently and reproducibly		
Follow 2023 [43] ASCO/CAP guidelines to control pre-analytic factors, validate staining, follow scoring criteria, and report with HER2 IHC scores (3 + / 2 + / 1 + / 0).	II	A
Due to notable inter-assay variabilities in the HER2 test, one may consider using the 4B5 kit (Roche) with its validated staining protocol as a companion test.	II	B
HER2-low status may be heterogeneous and subject to dynamic changes. Recommend re-biopsy in case of recurrence or metastasis.	II	B
Comparison of transcriptomic profiles between HER2-low and HER2-zero BC		
The biology of HER2-low breast cancer is not driven by the HER2 oncogenic signaling pathway	N/A	N/A
Differences between HER2-low and HER2-zero breast cancer are mainly attributed to the differences in hormone receptor status	N/A	N/A
Only minor differences were found comparing the transcriptomic profiles of HR-positive, HER2-low breast cancer to HR-positive, HER2-zero cancer1,2	N/A	N/A
An increased proportion of non-basal-like tumors was found in HR-negative, HER2-low breast cancer, compared to HR-negative, HER2-zero breast cancer. These non-basal-like tumors are enriched with tumors of the luminal AR subtype, characterized by the increased expression of lipid metabolism-related genes and up-regulation of fatty acid and steroid hormone metabolism pathways	N/A	N/A
Comparison of mutational landscapes between HER2-low and HER2-zero BC		
According to currently available genomic and transcriptomic studies, HER2-low breast cancer is not considered as a biologically distinct entity.	II	B
Clinical presentations and prognostication of HER2-low BC from RWD		
About 50 % of all breast cancers are HER2-low disease. The percentage of HER2-low cases in HER2 non-amplification disease was higher in hormone receptor-positive breast cancer (around 60 % − 65 %) compared to hormone receptor-negative breast cancer (around 35 % − 40 %)	N/A	N/A
In pooled analysis, there was a trend of higher pathological complete response (pCR) rate in HER2-zero disease (around 22 % − 24 %) versus HER2-low disease (around 15 % − 18 %). The difference of pCR rate was mainly attributed to hormone receptor status	N/A	N/A
In current real-world data with or without novel agents, it is still difficult to compare survival benefit in HER2-zero disease versus HER2-low disease directly even though there was slightly improved overall survival rate in HER2-low breast cancer compared to HER2-zero population regardless of hormone receptor expression in meta-analysis, but high heterogenicity in different setting of real-world clinical data was observed	N/A	N/A
Biomarkers for HER2-low BC		
HER2-low expression is currently the only biomarker capable of predicting the therapeutic efficacy of Trastuzumab Deruxtecan (T-DXd) in patients with HER2-low metastatic breast cancer.	I	A
Anti-TROP2 ADC in HER2-low BC		
Anti-TROP2 ADC may be used as later line of treatment for patients with HR-negative, HER2-low (IHC 1 + or 2 +/ ISH negative) recurrent unresectable or metastatic disease, received at least 2 prior therapies.	I	A
Anti-TROP2 ADC may be used as later line of treatment for patients with HR-positive, HER2-low (IHC 1 + or 2 +/ISH negative) metastatic/locally advanced unresectable breast cancer after prior systemic treatment including endocrine therapy, a CDK4/6 inhibitor and at least 2 lines of chemotherapy.	I	A
Treatment sequence of novel ADCs for HER2-low BC for initial HR + BC		
In HER2-low, HR + metastatic breast cancer, current evidence support the use of Trastuzumab Deruxtecan (T-DXd) for patients who have progressed upon ≥ 1 lines of chemotherapy in the metastatic setting.	I	A
In HER2-low, HR + metastatic breast cancer, current evidence support the use of Sacituzumab Govitecan (SG) for patients who have progressed upon ≥ 2 lines of chemotherapy in the metastatic setting.	I	A
There is currently insufficient evidence to support using an antibody drug conjugate (ADC) after progression on prior ADC in HER2-low, HR + metastatic breast cancer	II	B
There is currently no evidence to support using an antibody drug conjugate (ADC) in chemotherapy naïve setting in HER2-low, HR + metastatic breast cancer.	III	A
Both ADCs (T-DXd and SG) proved activity in patients with metastatic HER2-low, HR + BC. T-DXd could be considered before SG as the first ADC in this setting	II	B
Treatment sequence of novel ADCs for HER2-low BC for initial TNBC		
In HER2-low, HR- metastatic breast cancer, current evidence support the use of Sacituzumab Govitecan (SG) for patients who have progressed after receiving ≥ 2 prior therapies (with at least 1 line in the metastatic setting).	I	A
In HER2-low, HR- metastatic breast cancer, current evidence support the use of Trastuzumab Deruxtecan (T-DXd) for patients who have progressed upon ≥ 1 lines of chemotherapy in the metastatic setting.	I	A
There is currently insufficient evidence to support using an antibody drug conjugate (ADC) after progression on prior ADC in HER2-low, HR- metastatic breast cancer.	II	B
Both ADCs (T-DXd and SG) proved activity in patients with metastatic HER2-low, HR- BC. SG could be considered before T-DXd as the first ADC in this setting.	II	B

Discussion

Our panel reviewed 30 articles on the effects of new-generation antibody-drug conjugate on patients with HER2-low breast cancer. The final consensus on the treatment strategies for HER2-low breast cancer is presented in Table 4. This article provides a comprehensive review of current research and expert consensus on HER2-low breast cancer, a subtype that has gained increasing attention due to the development of new targeted therapies. The consensus spans several key areas, including:

1. **Reclassification of HER2-low breast cancer**
   The consensus begins by discussing whether HER2-low breast cancer should be reclassified. It highlights that the positive effects of antibody-drug conjugates (ADCs) in treating both HER2-positive and HER2-low breast cancer have prompted a reassessment of the current classification. The expert panel, referencing the article by Wolff *et al.*, suggests that the HER2-low classification should be integrated into the HER2-negative classification. This recommendation indicates a shift in how HER2-low breast cancer is viewed and categorized, which may impact clinical practice and future research.
2. **Identification of HER2-low breast cancer**
   Accurate and consistent identification of HER2-low breast cancer is essential for making appropriate treatment decisions. The article emphasizes the need for standardized testing and reporting procedures. It cites the 2023 ASCO/CAP guidelines and the 2023 ESMO consensus statements, advocating for careful control of pre-analytical factors, validation of staining techniques, adherence to scoring criteria, and detailed reporting of HER2 IHC scores. The use of the 4B5 kit with its validated staining protocol is recommended as a companion test to reduce inter-assay variability in HER2 testing. Furthermore, the article acknowledges the dynamic and heterogeneous nature of HER2-low status, recommending re-biopsy in cases of recurrence or metastasis to account for possible changes in HER2 expression.
3. **Biological characteristics of HER2-low breast cancer**
   The consensus explores the biological characteristics of HER2-low breast cancer, comparing it to HER2-zero disease. Transcriptomic profiling studies have revealed significant differences between these two subtypes, especially within the hormone receptor-negative subgroup. Importantly, HER2-low breast cancer does not appear to be driven by the HER2 oncogenic signaling pathway, and variations in hormone receptor status are crucial in distinguishing it from HER2-zero disease. Genomic analyses have also indicated that while HER2-low breast cancer is not considered a distinct biological entity, it displays some genomic variations.
4. **Clinical presentation and prognosis**
   The consensus provides an overview of the clinical presentation and prognosis of HER2-low breast cancer. It highlights that HER2-low breast cancer constitutes a significant portion of all breast cancer cases, with estimates suggesting that 50–60 % of all breast cancers fall into this category. Hormone receptor status influences the prevalence of HER2-low expression, with higher estrogen receptor expression associated with increased rates of HER2-low disease. In terms of prognosis, studies indicate that HER2-low status is linked to improved overall survival and disease-free survival compared to HER2-zero disease. However, HER2-low status is also associated with a lower pathological complete response (pCR) rate. This difference in pCR rates is mainly attributed to the higher proportion of hormone receptor-positive breast cancers within the HER2-low group, rather than an inherent biological distinction between HER2-low and HER2-zero subtypes
5. **Treatment strategies for HER2-low breast cancer**

The consensus dedicates considerable attention to treatment strategies for HER2-low breast cancer, particularly the use of novel ADCs. It identifies HER2-low expression as the sole biomarker currently capable of predicting the therapeutic efficacy of Trastuzumab Deruxtecan (T-DXd) in patients with HER2-low metastatic breast cancer. Notably, recent advancements, as highlighted by the DESTINY-Breast06 study, indicate that T-DXd may no longer require prior chemotherapy in certain settings for HER2-low breast cancer patients, expanding its utility earlier in the treatment paradigm.[41]

Anti-TROP2 ADCs are viewed as a later line of treatment for patients with hormone receptor-negative or hormone receptor-positive, HER2-low recurrent unresectable or metastatic disease after prior therapies. The sequence in which these novel ADCs are administered is a critical consideration, with factors such as prior chemotherapy lines, hormone receptor status, and disease progression influencing treatment decisions. The article also acknowledges the need for further research to optimize the sequencing of ADC-based treatment options.

The panel's deliberations on optimal ADC integration in HER2-low breast cancer acknowledge that both Trastuzumab Deruxtecan (T-DXd) and Sacituzumab Govitecan (SG) demonstrate significant activity in metastatic HR + and HR- subtypes. For HR + disease (Q8), T-DXd is generally considered as the initial ADC based on robust Level I evidence from trials like DESTINY-Breast04. Conversely, for HR-negative HER2-low metastatic breast cancer (Q9), SG is often prioritized as the first ADC, supported by strong Level I data from the ASCENT trial, though T-DXd also shows efficacy in this cohort (DESTINY-Breast04).

While current evidence remains insufficient to definitively guide optimal sequential ADC use after progression on a prior ADC, real-world data and clinical experience suggest that some patients may still derive modest or even durable benefit, particularly when a distinct antibody target is utilized. Despite the potential for cross-resistance, this observed benefit in selected cases underscores the critical need for further research to clarify sequencing strategies, refine personalized treatment approaches, and guide careful clinical consideration.[42]

Conclusion

In conclusion, this consensus provides a comprehensive overview of the current understanding of HER2-low breast cancer, highlighting its unique characteristics and the evolving treatment landscape. The ongoing research and expert discussions are shaping clinical practice and improving outcomes for patients with this subtype of breast cancer.

Ethics Statement

None

Author's Contribution

STC, and CCH contributed to organizing and implementing the process of consensus, serving as academic consultants and verifying the scientific accuracy of consensus statements.

STC, CCH, TCC, WPC, CYH, CPY, WLK, PHH, DYC, YFT, HHC, JPS, KTL, CYL, MYW, ACF, LCL, JIL, YCC, and GSL contributed to confirming the consensus framework, conducting the literature review, drafting the consensus statements and manuscript, and grading the quality of evidence and strength of recommendations. All authors contributed to reviewing the content of the statements and providing constructive feedback.

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Declaration of Competing Interests

The authors declare no conflicts of interest.

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