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Practice Guidelines

Consensus on clinical diagnosis and medical treatment of HER2-low breast cancer (2022 edition)

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ABSTRACT

Treatment of breast cancer with low expression of human epidermal growth factor receptor 2 (HER2; HER2-low) has drawn much attention in recent years. With the proven therapeutic effect of trastuzumab deruxtecan (T-DXd) in patients with HER2-low (immunohistochemistry [IHC] 1+, or IHC2+/in situ hybridization [ISH]-) breast cancer, HER2-low may become a new subtype of targeted therapy for breast cancer. The expert committee formulated this consensus based on the current clinical studies and clinical medication experience. The current

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consensus is the collaborative work of an interdisciplinary working group, including experts in the fields of pathology and oncology. The purpose of this consensus was to guide the clinical diagnosis and treatment of HER2-low breast cancer, thereby prolonging the overall survival of patients.

1. Background

In 2020, a total of 19.3 million cases were newly diagnosed with malignant tumors worldwide, of which 2.3 million (11.7%) were females with newly identified breast cancer, making breast cancer the most common malignant tumor.[1] The therapeutic regimen for breast cancer is often decided based on traditional biological subtypes, and breast cancer has been primarily classified into four subtypes: Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative breast cancer (TNBC).[2-5] HER2 is an important driver gene and prognostic indicator for breast cancer and is a key indicator to predicting the efficacy of anti-HER2 medications. In HER2-positive breast cancer, *erb-B2* gene amplification leads to overexpression of HER2 protein, and patients have stronger tumor invasiveness and poorer prognoses.[6,7] Currently, multiple target drugs specific to HER2 have significantly improved the clinical prognoses of early and advanced HER2-positive breast cancers.[8] However, approximately 45% to 55% of breast cancers show low HER2 expression marked by immunohistochemistry (IHC)-positive (1+) or IHC-positive (2+) without in situ hybridization (ISH) HER2 gene amplification.[9,10] With confirmed efficacy of antibody-drug conjugates (ADCs) in patients with HER2-low breast cancer, novel ADCs have become a new option for patients with HER2-low advanced breast cancer.

Although the European Society for Medical Oncology (ESMO) has released consensus statements on HER2-low breast cancer,[11] we still have some different views on the treatment compared with ESMO statements. To guide the clinical diagnosis and treatment of HER2-low breast cancer in China, the Chinese Anticancer Association and Chinese Medical Doctor Association gathered multidisciplinary experts and scholars in relevant fields to formulate the consensus on clinical diagnosis and treatment of HER2-low breast cancer (2022 edition) based on current clinical studies and clinical medication experience. All recommendations are accompanied by a level of evidence based on the Infectious Diseases Society of America-United States Public Health Service Grading System (Table 1).[12]

2. Definition and evaluation of HER2-low breast cancer

The IHC staining requirements and interpretation of IHC and ISH results were specified in the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines and the 2019 Chinese guidelines for HER2 detection in breast cancer.[13,14] In this consensus, HER2 IHC-positive (3+) or IHC 2+/ISH-positive (+) is defined as HER2-positive, while HER2 IHC 1+ or IHC 2+/ISH-negative (-) is defined as HER2-low, and HER2 IHC-negative (0) as HER2-negative (Fig. 1).

For the cases around the IHC 0/IHC 1+ threshold, pathologists are recommended to follow the 2023 ASCO-CAP guideline,[15] and make best practice efforts to distinguish IHC 1+ results from 0 by the following practices:

1) Examining HER2 IHC-stained slides using standardized ASCO-CAP guidelines scoring criteria;
2) Examining HER2 IHC at high power when discriminating 0 from 1 staining;
3) Considering second pathologist review when results are close to the 0 versus 1+ interpretive threshold (10% of cells with incomplete membrane staining that is faint/barely perceptible);
4) Using controls with a range of protein expression (including 1+) to help ensure the assay has an appropriate limit of detection; and
5) Careful attention to preanalytic conditions of breast cancer tissue samples from both primary and metastatic sites.

Expert recommendation 1: HER2-low is defined as HER2 IHC 1+ or IHC 2+/ISH−, according to the definition used in the DESTINY-Breast04 study. (I, A)

Expert recommendation 2: Either primary tumor or metastatic tissue can be used to determine HER2 expression status. Re-interpretation, testing, or biopsy can be considered for patients previously evaluated as HER2 IHC 0 if there is any possibility of anti-HER2 therapy. (III, A)

3. Clinical implications and prognosis of HER2-low breast cancer

Based on hormone receptor (HR) expression, epidemiological data have suggested that 80% of HER2-low breast cancers are luminal subtypes, while 15%–20% are TNBC subtype.[9,10] Generally, no HER2 protein overexpression is observed in the absence of gene amplification; however, translational studies have demonstrated that there may be differences in gene expression between HER2-low and HER2 IHC 0 tumors,[16,17] indicating that HER2-low breast cancer may have unique molecular characteristics, which can be the potential target of the treatment.

The prognostic value of HER2-low is still controversial. Multiple retrospective analyses have also explored the prognoses of HER2-low patients, but the results have been inconsistent, indicating that HER2-low is not an independent prognostic factor.[18-24] Given the benefits of novel anti-HER2 ADC drugs in patients with HER2-low breast cancer, the target population has been expanded from patients with HER2-positive to patients with HER2-low breast cancer.[25,26] Moreover, HER2-low is currently expected to be a new breast cancer treatment type, but it has not yet been considered a new biological subtype.

Expert recommendation 3: HER2-low is a drug selection indicator that predicts clinical efficacy in advanced breast cancer. (III, A)

4. Treatment on HER2-low advanced breast cancer

The new-generation anti-HER2 ADC drugs have shown anticancer activity in HER2-low breast cancer, providing more options for these patients. ADCs are an evolving class of anticancer agents that exploit monoclonal antibodies to selectively deliver small cytotoxic molecules

Table 1
Quality of evidence and grading of expert recommendations.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

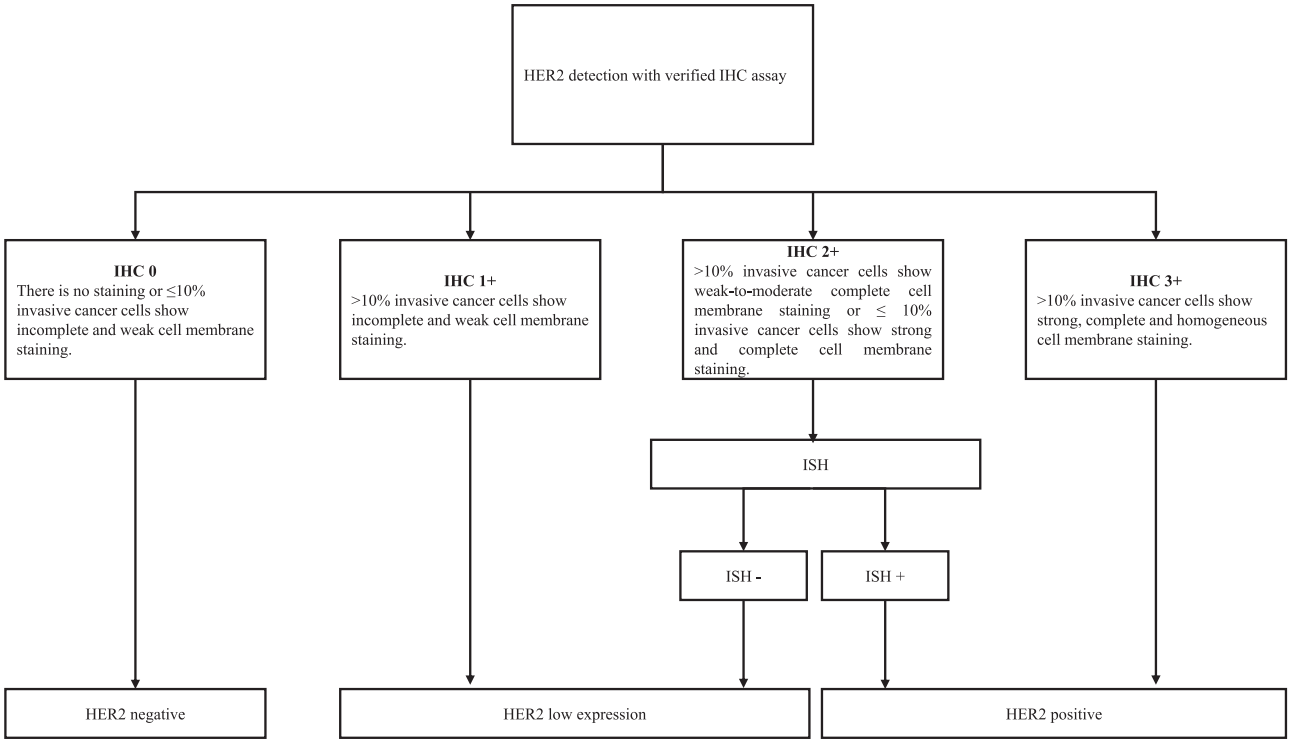

Fig. 1. Flowchart of HER2-low breast cancer evaluation. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybrization.

Table 2
Summary of clinical studies on ADC drugs for HER2-low breast cancer.

Drug name	NCT registration No.	Study phase	Study state	Sample size	Patient type
T-DXd	NCT03734029 (DESTINY-Breast04)[25]	Phase III	Completed	557	HER2 low expression advanced breast cancer (IHC 1+ or IHC 2+/ISH-) progressed in the first-to-second-line chemotherapy
SG	NCT03901339 (TROPiCS-02)[28]	Phase III	Completed	283	HR + and HER2 - (including HER2 low expression and HER2 IHC 0) advanced breast cancer after the second-to-fourth chemotherapy
T-DXd	NCT04494425 (DESTINY-Breast06)	Phase III	Ongoing	About 850	Endocrine refractory and advanced chemotherapy-naïve HER2-low HR+ breast cancer patients (0 < IHC < 1+, or IHC 1+ or IHC 2+/ISH-)
Disitamab Vedotin	NCT04400695 (C012)	Phase III	Ongoing	About 366	HER2-low advanced breast cancer (IHC 2+/ISH-) progressed in the first-to-second-line chemotherapy

Drug name	Dose regimen			mPFS, months		mOS, months		ORR,%	
	Trial group	Control group	Patient ratio	Trial group	Control group	Trial group	Control group	Trial group	Control group
T-DXd	T-DXd	TPC	2:1	9.9	5.1	23.4	16.8	52.3	16.3
SG	SG	TPC	1:1	6.4	4.2	–	–	38	16
T-DXd	T-DXd	TPC	1:1	–	–	–	–	–	–
Disitamab Vedotin	RC48	TPC	1:1	–	–	–	–	–	–

Abbreviations: ADC, antibody-drug conjugate; HER-2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan; SG, Sacituzumab Govitecan; IHC, immunohistochemistry; ISH, in situ hybrization; HR, hormone receptor; TPC, treatment of physician's choice; mPFS, median progression-free survival; mOS, median overall survival; ORR, objective response rate; -: not issued.

to the target cancer cells. ADCs consist of three primary components: a monoclonal antibody (vehicle) with high specificity and affinity, an efficient small-molecule cytotoxic agent (payload), and a synthetic linker.[27] The ongoing phase III clinical studies of ADC treatment on HER2-low breast cancer are shown in Table 2.

Trastuzumab deruxtecan (T-DXd) is a new-generation ADC drug with potential therapeutic efficacy against HER2-low cancers in preclinical studies. The DESTINY-Breast04 study was the first phase III clinical trial to verify the efficacy of T-DXd in patients with HER2-low breast cancer. In this trial, 557 patients with HER2-low unresectable and/or metastatic breast cancer who had received one or two previous lines of chemotherapy were randomized into the T-DXd group or the treatment of physician's choice (TPC) group (e.g., Capecitabine, Eribulin, Gemcitabine, Paclitaxel, or Albumin Paclitaxel). The results suggested that regardless of the HR states, patients in the T-DXd group benefited from the T-DXd treatment, with a median progression-free survival (mPFS) of 9.9 months (vs. 5.1 months in the TPC group) and a median overall survival (mOS) of 23.4 months (vs. 16.9 months in TPC group) in the whole population (HR=0.64).[25,29] Based on the results of this study, the Food and Drug Administration (FDA) approved T-DXd for adult patients with

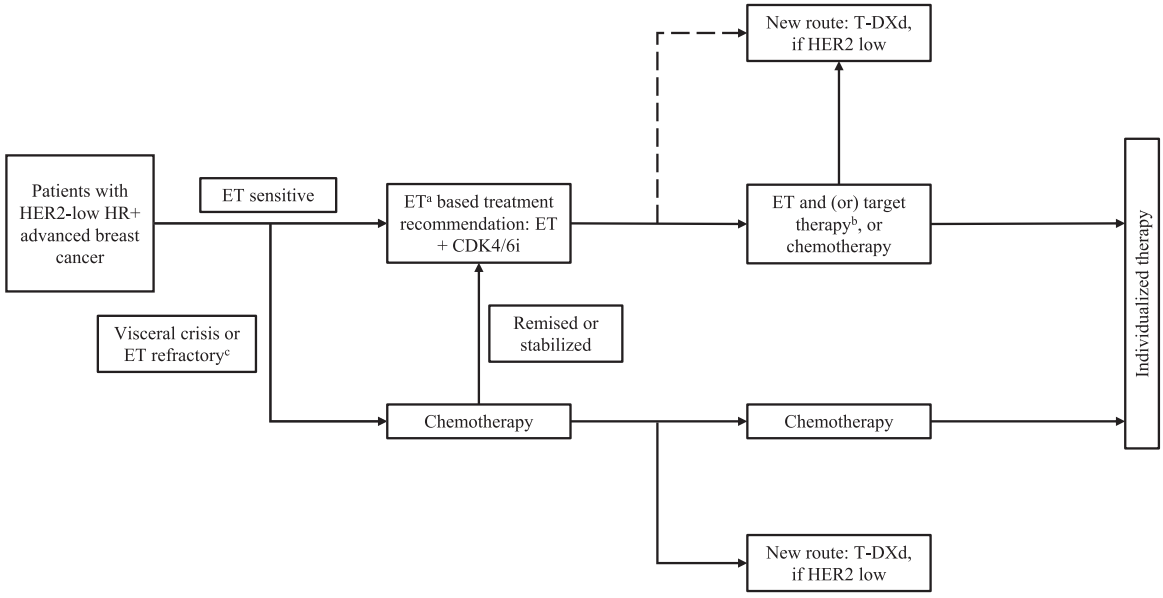

Fig. 2. Treatment routines for patients with HER2-low HR+ advanced breast cancer. The full lines represent recommended treatments, while the dotted line represents optional treatment. [a] Endocrine therapy, including aromatizing enzyme inhibitors, estrogen receptor modulator, and tamoxifen. [b] Target therapy, including HDAC inhibitors, mTOR inhibitors, PI3K inhibitors (PIK3CA mutation), CDK4/6 inhibitors, and PARP inhibitors (e.g. gBRCA mutation). [c] Endocrine refractory populations, including populations with endocrine primary drug resistance, and advanced populations in whom two consecutive lines of endocrine therapy failed. CDK4/6i, CDK4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; T-DXd, trastuzumab deruxtecan.

unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who had received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

In addition, a phase I clinical study on anti-HER2 ADC disitamab vedotin (RC48) revealed potential effectiveness in HER2-low patients.[30] A phase III clinical trial of RC48 in HER2-low (HER2 IHC 2+/ISH-) advanced breast cancer patients is undergoing, and we hope that this study will provide more clinical data.

Previous HER2-low studies focused on patients with advanced breast cancer who failed standard treatments, and the initial treatment for patients with HER2-low advanced cancer still needs to be conducted based on biological subtypes. After progression to initial treatment, subsequent therapy should be administered based on clinical evidence.

4.1. Treatment for patients with HER2-low HR+ advanced breast cancer

In HR+ breast cancer, HER2-low accounts for 55–65% of cases.[16,31] CDK4/6 inhibitors combined with endocrine therapy (ET) are the standard first-line treatment for patients with HER2-low HR+ advanced breast cancer. If CDK4/6 inhibitors are not used in the first-line setting, it is clinically acceptable to use ET plus CDK4/6 inhibitors as a subsequent therapy. In patients who relapse after ET plus CDK4/6 inhibitor, there is no standard therapeutic regimen until now. The selection of subsequent lines of treatment should be based on previous treatments, tumor burden, and biological markers. In second-line and subsequent lines of treatment, ET with or without targeted therapy can be considered, such as ET plus everolimus (mammalian target of rapamycin (mTOR) inhibitor), chidamide (histone deacetylase (HDAC) inhibitor), or alpelisib (phosphatidylinositol 3-kinase (PI3K) inhibitor). Olaparib (a polyadenosine diphosphate-ribose polymerase (PARP) inhibitor) monotherapy should be considered for patients with germline pathogenic *BRCA1/2* mutations and as an option for patients with somatic pathogenic or likely pathogenic *BRCA1/2* or germline *PALB2* mutations. In addition, clinical studies should be considered for these patients. However, there is limited stratification analysis of HER2-low in the reported studies of ET combined targeted therapy.

In the DESTINY-Breast04 study, patients with HER2-low HR+ endocrine refractory advanced breast cancer who had received one or two previous lines of chemotherapy were enrolled, and the results revealed that T-DXd significantly prolonged PFS and OS compared with chemotherapy (mPFS: 10.1 vs. 5.4 months; mOS: 23.9 vs. 17.5 months).[25] Therefore, T-DXd has become the recommended treatment for patients with HER2-low HR-positive (+) endocrine-refractory advanced breast cancer (Fig. 2).

Since the definition of “endocrine refractory” is still controversial, the following populations are considered endocrine-refractory based on consistent suggestions from experts in the consensus group after voting: (1) patients with primary endocrine resistance (who relapsed during the first 2 years of adjuvant ET or progression of disease [PD] within the first 6 months of first-line ET for metastatic breast cancer); and (2) patients who failed after two consecutive lines of ET based therapy in the metastatic setting (generally indicating endocrine drug resistance).[32]

Expert recommendation 4: For patients with HER2-low HR+ advanced breast cancer without visceral crisis* and disease progression after first-line ET plus a CDK4/6 inhibitor, the selection of subsequent lines of treatment should be based on previous treatments, tumor burden, and biological markers. (III, A)

Expert recommendation 5: T-DXd is recommended as a treatment option for HER2-low advanced breast cancer with remarkable efficacy. In HER2-low HR+ patients, T-DXd is preferred for endocrine-refractory advanced breast cancer (defined as having progressed to at least one ET and having been determined by the clinician to no longer benefit from further ET) who have received at least one prior line of chemotherapy. (I, A)

4.2. Treatment for HER2-low HR- advanced breast cancer

In HR- breast cancer, HER2-low accounts for approximately 35% of cases.[16,31] At present, the treatment for HER2-low HR- advanced breast

* According to the 5th ESO-ESMO international consensus guidelines[4] for advanced breast cancer, a visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid disease progression. A visceral crisis is not the mere presence of visceral metastases, but implies important organ compromise, leading to a clinical indication for the most rapidly efficacious therapy.

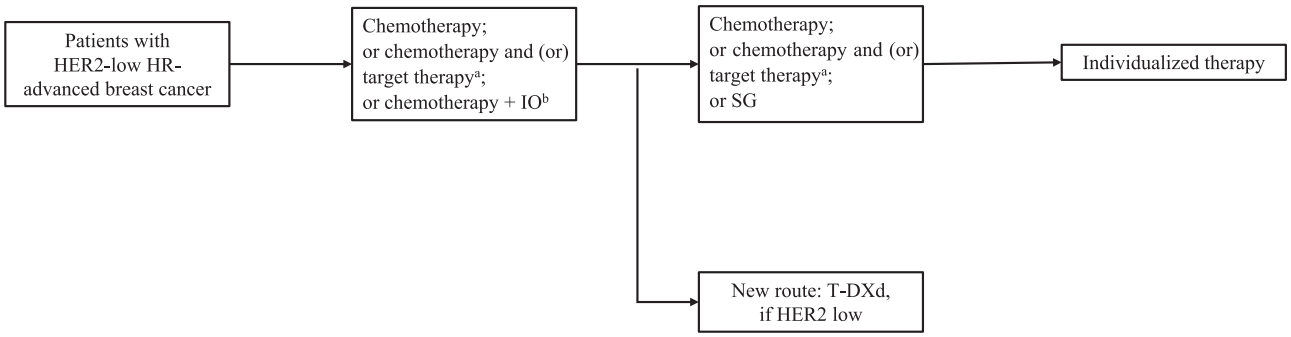

Fig. 3. Treatment routines for patients with HER2-low HR- advanced breast cancer. [a] Target therapy, including VEGF inhibitors and PARP inhibitors (gBRCA mutation); [b] For PD-L1-positive patients, anti-neoplastic immunotherapy concomitant with chemotherapy is available as the first-line treatment. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IO, tumor immunotherapy; PD-L1, programmed death ligand 1; T-DXd, trastuzumab deruxtecan; VEGF, vascular endothelial growth factor.

Table 3
Recommendation list.

No.	Recommendation	Quality of evidence	Grade of recommendation
1	HER2-low is defined as HER2 IHC 1+ or IHC 2+/ISH −, according to the definition used in the DESTINY-Breast04 study.	I	A
2	Either primary tumor or metastatic tissue can be used to determine HER2 expression status. Re-interpretation, testing, or biopsy can be considered for patients previously evaluated as HER2 IHC 0 if there is any possibility of anti-HER2 therapy.	III	A
3	HER2-low is a drug selection indicator that predicts clinical efficacy in advanced breast cancer.	III	A
4	For patients with HER2-low HR+ advanced breast cancer without visceral crisis and disease progression after first-line ET plus a CDK4/6 inhibitor, the selection of subsequent lines of treatment should be based on previous treatments, tumor burden, and biological markers.	III	A
5	T-DXd is recommended as a treatment option for HER2-low advanced breast cancer with remarkable efficacy. In HER2-low HR+ patients, T-DXd is preferred for endocrine-refractory advanced breast cancer (defined as having progressed to at least one ET and having been determined by the clinician to no longer benefit from further ET) who have received at least one prior line of chemotherapy.	I	A
6	The initial treatment of HER2-low HR- advanced breast cancer refers to that of TNBC, including chemotherapy, immunotherapy, targeted therapy, and so on. T-DXd is recommended as a second-line treatment after first-line chemotherapy.	III	A

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybrization; HR, hormone receptor; ET, endocrine therapy; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer.

cancer refers to that for TNBC, with chemotherapy in the majority. For patients in whom previous neoadjuvant or adjuvant anthracycline therapy has failed, taxane-based monotherapy or concomitant therapy is recommended as the first-line treatment. At the same time, other optional drugs include capecitabine, vinorelbine, gemcitabine, and etoposide, whereas patients with *gBRCA* mutations are advised to use platinum or PARP inhibitors.[33] In the KEYNOTE-355 study, pembrolizumab combined with chemotherapy significantly improved the PFS and OS of patients with programmed cell death-ligand 1 (PD-L1) positivity (combined positive score [CPS] ≥10 points) compared with chemotherapy alone.[34,35] Therefore, for TNBC patients with PD-L1 CPS ≥10 points, immune checkpoint inhibitors concomitant with chemotherapy can be recommended as the first-line treatment.

The ASCENT study revealed that in patients with advanced TNBC who progressed after two or more lines of treatment, compared with chemotherapy alone, sacituzumab govitecan (SG) significantly prolonged PFS and OS.[36] Therefore, ADC drugs targeting TROP-2 are one of the recommended regimens for treating advanced TNBC.

For HER2-low HR- patients, the subgroup analyses in the DESTINY-Breast04 study showed that T-DXd prolonged both PFS and OS (mPFS: 8.5 vs. 2.9 months; mOS:18.2 vs. 8.3 months),[25] therefore, T-DXd is one of the recommended regimens for disease progression after first-line treatment (Fig. 3).

Owing to the limited clinical data on HER2-low breast cancer at present, the expert committee selected highly controversial issues specific to HER2-low and obtained consistent clinical recommendations through expert group voting based on the present evidence, providing support for the decision-making of clinical physicians in the clinical diagnosis and treatment of HER2-low breast cancer (Table 3).

The interpretation of the lower limit of HER2-low is still controversial. The results of the DAISY study demonstrated that T-DXd showed anticancer activity in HER2 IHC 0 patients, with an objective response rate of 29.7%,[26] therefore, the IHC 0 populations were further classified into HER2 ultra-low (0< IHC <1+) and HER2 0. Furthermore, the ongoing phase III DESTINIT-Breast06 study aims to explore the efficacy and safety of T-DXd in patients with HER2-low and ultra-low HR+ advanced breast cancers, which will provide more data for the diagnosis and treatment of HER2-ultra-low breast cancers. Currently, T-DXd is not approved to treat HER2 ultra-low breast cancer.

The recently reported TROPiCS-02 study revealed that in patients with HR+/HER2- advanced breast cancer in whom ET and CDK4/6 inhibitors failed after 2–4 lines of chemotherapy, SG could significantly prolong the patients' PFS and OS compared with TPC. In contrast, the subgroup analysis revealed that SG could improve the efficacy outcomes in both HER2-low and HER2 IHC 0 subgroups, consistent with the intention-to-treat population.[29] Other anti-HER2 drugs, including ADC, monoclonal antibodies, vaccines, and double antibodies, have also been evaluated (Table 4) to provide more treatment options for patients with HER2-low breast cancer.

Table 4
Summary of studies on anti-HER2 drugs in the field of HER2-low breast cancer.

Drugs	NCT registration No	Study phase	Sample size	Patient type	Drug Regimen	Study results
ADC						
RC48	NCT03052634 (C003)[30]	Phase Ib	48	HER2-low advanced breast cancer (IHC 1+ or 2+/ISH-) failed in standard treatment	RC48	ORR was 39.6% and mPFS was 5.7 months
MRG002	NCT04742153 (MRG002-005)[37]	Phase II	56	HER2-low advanced breast cancer (IHC 1+ or 2+/ISH-) failed in at least first-line standard treatment	MRG002	ORR was 33%, DCR was 75%, and mPFS was 5.6 months
ARX788	NCT03255070(ACE-Pan Tumor 01)[38]	Phase I	40	Treated HER2-low advanced breast cancer (IHC 1+/ISH-, or IHC 2+/ISH-)	ARX788	Not issued
PF-06804103	NCT03284723[39]	Phase I	35	Treated and locally assessed HER2-low advanced breast cancer (IHC 2+, without FISH validation)	PF-06804103	ORR was 52.4%
Monoclonal antibodies						
Pertuzumab	NCT02491892[40]	Phase II	78	Treated HER2-low metastatic breast cancer (IHC 1+ or 2+/ISH -) and HER2-(IHC 0) metastatic breast cancer (74 cases and 4 cases respectively)	Pertuzumab	ORR was 2.5%, and DCR was 43%
Trastuzumab	NCT01275677[41]	Phase III	3 270	Highly risky HER2-low early breast cancer (IHC 1+ or 2+/ISH-) that had been treated with adjuvant chemotherapy	Trastuzumab	The 5-year iDFSs were 89.6% and 89.2% in chemotherapy concomitant with Trastuzumab group and chemotherapy group, respectively
Margetuximab	NCT01828021[42]	Phase II	25	Treated, center assessed HER2-low advanced breast cancer (IHC 2+ or IHC 1+/ISH-)	Margetuximab	Not issued
Bispecific antibodies						
ZW25	NCT02892123[43]	Phase I	234	Treated HER2-expressed advanced breast cancer (IHC 1 to 3+)	ZW25	ORR was 46% in HER2 positive (+) population; HER2 low expression results were not issued
MCLA-128	NCT03321981[44]	Phase II	101	HR + and HER2-low (IHC 1+ or 2+) advanced breast cancer that progressed during endocrine therapy	MCLA-128+ endocrine therapy	DCR was 45%
Vaccine						
NeuVax	NCT01570036[45]	Phase IIb	275	HER2-low, lymph node positive and early breast cancer (IHC 1+ or 2+/ISH-)	NeuVax + Trastuzumab+ GM- CSF (VG group) and Trastuzumab+ GM-CSF (CG group)	ITT median follow-up was 25.7 months, and the DFS was 89.8% in VG group and 83.8% in CG group (HR = 0.62, P = 0.18); TNBC median follow-up was 25.7 months, and the DFS was 92.6% in VG group and 70.0% in CG group (HR = 0.26, P = 0.013).

Abbreviations: HER2, human epidermal growth factor receptor 2; ADC, antibody-drug conjugate; IHC, immunohistochemistry; ISH, in situ hybrization; HR, hormone receptor; CSF, granulocyte colony-stimulating factor; ORR, objective response rate; mPFS, median progress-free survival; DCR, disease control rate; iDFS, invasive disease free survival; ITT, intention-to-treat population; DFS, disease-free survival rate; VG, vaccine group; CG, control group; TNBC, triple-negative breast cancer.

Expert recommendation 6: The initial treatment of HER2-low HR-advanced breast cancer refers to that of TNBC, including chemotherapy, immunotherapy, targeted therapy, and so on. T-DXd is recommended as a second-line treatment after first-line chemotherapy. (III, A)

5. Conclusions

There is a lack of thorough recommendations for managing HER2-low breast cancer in China. In response, we compiled a consensus based on our current understanding and clinical experience from multiple Chinese hospitals. This consensus provides comprehensive and detailed practical recommendations for the diagnosis and treatment of HER2-low breast cancer. We hope this consensus will help clinicians effectively manage patients with HER2-low breast cancer.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Author contributions

P.Y. and B.X. provided the conception. Z.S. and H.B. were the consultants of the consensus. H.B., Y.F., Z.F., X.H., M.L., Q.L., N.L., T.L., J.N., Y.P., X.Q., Z.S., G.S., T.S., Y.T., Z.T., J.W., S.W., X.W., Y.W., Z.W., B.X., L.X., Y.X., W.Y., H.Y., J.Y., P.Y., J.Z., Q.Z., Y.Z. and J.Z. provided the study materials. X.W., P.Y., and B.X. collected and assembled the data. P.Y. and X.W. drafted this article. H.B., Y.F., Z.F., X.H., M.L., Q.L., N.L., T.L., J.N., Y.P., X.Q., Z.S., G.S., T.S., Y.T., Z.T., J.W., S.W., X.W., Y.W., Z.W., B.X., L.X., Y.X., W.Y., H.Y., J.Y., P.Y., J.Z., Q.Z., Y.Z. and J.Z. revised this article.

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