Chinese Society of Clinical Oncology (CSCO) Breast Cancer guidelines 2024

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Background: Developing guidelines for the diagnosis and treatment of common cancers in China based on the evidence-based practice, the availability of diagnosis and treatment products, and the up-to-date advances in precision medicine is one of the basic tasks of the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) Committee.

Methods: Protocols with high evidence level and good availability are used as the Level I recommendations; protocols with relatively high evidence level but slightly lower expert consensus or with poor availability are used as the Level II recommendations; and protocols that are clinically applicable but with low evidence level are regarded as the Level III recommendations. Based on the findings of clinical research at home and abroad and the opinions of CSCO BC experts, the CSCO BC guidelines determine the levels of recommendations for clinical application.

Results: For human epidermal growth factor receptor 2 (HER2)-positive breast cancer, a combination of trastuzumab and pertuzumab regimen were recommended as Level I recommendation for neoadjuvant and first line metastatic breast cancer. Pyrotinib is also recommended as Level I recommendation in first line and second line therapy according to the latest studies conducted in China. Antibody drug conjugates was also recommended for patients with trastuzumab progression. For triple negative breast cancer, immunotherapy in early and metastatic breast cancer was highlighted and listed as new chapters in this version of guideline. For hormone receptor (HR)-positive breast cancer, cyclin dependent kinase 4/6 (CDK4/6) was recommended in different stages, especially in adjuvant therapy. There was also a new chapter for HER2-low breast cancer stratified by HR status.

Conclusions: We firmly believe that evidence-based, availability-concerned, and consensus-based guidelines will be more feasible for clinical practice in China and in other countries with similar situations.

Keywords: Breast cancer; Chinese Society of Clinical Oncology (CSCO); stages; subtypes; recommendation

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Introduction

Breast cancer has been one of the most common diagnosed cancers both in China and worldwide. In recent years, the availability of medical resources has become a major concern in clinical guidelines, which is particularly important for developing countries or socioeconomically diverse countries and territories. China is the world's largest developing country, with a large territory and uneven economic and academic developments. Guidelines for breast cancer must take into account the differences in regional development, the availability of medicines and diagnostic methods, and the social value of cancer treatment. Therefore, for each clinical problem and intervention, the levels of evidence should be graded according to the currently available evidences and expert consensuses, and the grades of recommendations should be based on the availability and cost-effectiveness of the products.

Here in this article, we would like to report the latest version and updates in Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guideline in 2024 so as to maintain the accuracy, fairness, and timeliness of this guideline. Due to the space limitations, some chapters were not included in this article.

Highlight box

Key recommendations

- For human epidermal growth factor receptor 2 (HER2)-positive, trastuzumab, pertuzumab, pyrotinib and trastuzumab deruxtecan are recommended in different lines of therapy. For hormone receptor (HR)-positive, CDK4/6 inhibitors are preferred. For triple-negative breast cancer, immunotherapies are highlighted.

What was recommended and what is new?

- We updated several chapters such as ADCs for HER2-positive, CDK4/6 inhibitors for HR-positive and immunotherapy for triple negative breast cancer. We also added a new chapter of HER2 low according to the latest studies.

What is the implication, and what should change now?

- This evidence-based, availability-concerned, and consensus-based guidelines will be more feasible for clinical practice in China. Objective indicators would be used in the future.

Methods

The CSCO BC guideline has taken all the differences in regional development, the availability of medicines, and the social value of cancer treatment into account since its first publication in 2017. In this guideline, 5 levels of evidence were defined. Two dimensional indicators are used to define the level of evidence (Table S1). The guideline working group determine the levels of recommendations for clinical application according to the currently evidences, expert consensuses, and the availability as well as cost-effectiveness in China. For example, in CSCO BC guideline, regimens with high evidence level and good availability are regarded as the Level I recommendations; for these with relatively high evidence level but slightly lower expert consensus or poor availability are used as the Level II recommendations; and protocols with low evidence level while are clinically applicable are regarded as the Level III recommendations.

Preoperative neoadjuvant treatment of breast cancer

Neoadjuvant drug treatments include chemotherapy, targeted therapy, and endocrine therapy (ET). Patients who meet one of the following conditions may choose preoperative neoadjuvant treatment: (I) large tumor size; (II) positive axillary lymph nodes; (III) human epidermal growth factor receptor 2 (HER2)-positive; (IV) triple-negative; (V) a desire for breast-conserving surgery (BCS), which, however, cannot be achieved due to the large proportion of tumor in the breast.

Neoadjuvant treatment can be considered for primary breast masses sized >5 cm. For primary breast masses sized 2–5 cm, other biological indicators should be considered. When only "HER2-positive" or "triple negative" is used as the criterion for neoadjuvant treatment of breast cancer, the tumor diameter should be larger than 2 cm; otherwise, the

Table 1 Recommendation of neoadjuvant for HER2 positive breast cancer

Level I recommendations	Level II recommendations
(I) TCbHP (1A)	(I) THP×4 (1B)
(II) THP×6 (2A)	(II) TH + pyrotinib (1B)
	(III) Anti-HER2 therapy combined with taxane-based regimens (2B), such as AC-THP (2B)
	(IV) Scientifically and rationally designed clinical trials, such as anti-HER2 ADC

T, taxanes, including docetaxel, albumin-bound paclitaxel, and paclitaxel; A, anthracyclines, including epirubicin, pirarubicin, and doxorubicin; C, cyclophosphamide; Cb, carboplatin; H/P, approved trastuzumab, pertuzumab, and their subcutaneous preparations; HER2, human epidermal growth factor receptor 2; ADC, antibody drug conjugate.

patient may participate in a rigorously-designed clinical trial.

Neoadjuvant treatment for HER2-positive breast cancer

Neoadjuvant treatment

Patients with HER2-positive breast cancer were recommended to receive neoadjuvant therapy whether they had tumor lesions larger than 2 cm, positive lymph node or inflammatory breast cancer. Clinical studies have demonstrated that neoadjuvant treatment with trastuzumab in combination with chemotherapy significantly increases the pathological complete response (pCR) rate in patients with HER2-positive breast cancer, establishing trastuzumab as a standard agent in the neoadjuvant treatment of HER2-positive breast cancer. In an era of dual-targeted therapy, the expert group generally acknowledges that dual-targeted therapy may be considered during neoadjuvant treatment in all patients who qualify for single-targeted therapy (*Table 1*).

The NeoSphere study confirmed that adding pertuzumab to TH could further increase the pCR rate in HER2-positive patients (1). The PEONY study confirmed the efficacy and safety of the THP regime in Asian populations (2). Therefore, THP can be considered as a neoadjuvant treatment option for HER2-positive patients. However, surgery was conducted after 4 cycles of neoadjuvant treatment with THP, which raised concerns.

The KRISTINE study demonstrated the efficacy and safety of the paclitaxel with carboplatin combined with trastuzumab + pertuzumab (TCbHP) regimen in neoadjuvant settings (3). The TRAIN-2 study showed that the TCbHP regimen could achieve the same pCR rate as an anthracycline-based regimen, while exhibiting significantly lower toxicities such as neutropenia (4). Therefore, TCbHP is the preferred regime in preoperative treatment. However, 6 cycles of THP therapy may also be considered for some patients, such as those aged >60 years with a small tumor load and generally intolerant to platinum-based combination regimens.

The PHEDRA study was conducted to investigate the efficacy and safety of pyrotinib combined with trastuzumab and docetaxel, compared to placebo in combination with trastuzumab and docetaxel, for the neoadjuvant treatment of HER2-positive early or locally advanced breast cancer (5). The results revealed that the total pCR was 41% among participants receiving pyrotinib in combination with trastuzumab and docetaxel, which was significantly superior to that (22%) in the control group. However, the use of pyrotinib in the neoadjuvant setting has led to debates on postoperative adjuvant targeted therapy.

Meanwhile, clinical studies have demonstrated that the trough serum drug concentration following subcutaneous injection of trastuzumab is non-inferior to that achieved with intravenous injection by the 7th cycle, and there is no significant difference in pCR between these 2 administration methods. Subcutaneous formulations may be used in place of single- or dual-target intravenous injections at any stage of treatment, upon approval. However, it is crucial to consider that subcutaneous formulations may have varying dosages and administration methods compared to intravenous treatments. The recommended dosing regimen for the subcutaneous formulation of trastuzumab involves administering 600 mg of trastuzumab and 1,200 mg of pertuzumab, and then repeating the doses of both drugs at 600 mg each.

Adjuvant treatment for HER2-positive breast cancer after neoadjuvant therapy

Pathological examination serves as a critical component for assessing the effectiveness of pre-operative neoadjuvant chemotherapy and the achievement of pCR post-surgery. This evaluation is instrumental in gauging the success of neoadjuvant therapy and informs decisions regarding

Table 2 Recommendation of adjuvant treatment for HER2-positive patients after neoadjuvant therapy

Condition	Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Trastuzumab alone in neoadjuvant	pCR	Trastuzumab + pertuzumab (2A)	Trastuzumab (1B)	
	Non-pCR	(I) T-DM1 (1A)		Extended adjuvant therapy with neratinib (2B)
		(II) Trastuzumab + pertuzumab (2A)		
Trastuzumab and pertuzumab in neoadjuvant	pCR	Trastuzumab + pertuzumab (1A)	Trastuzumab (2B)	
	Non-pCR	(I) T-DM1 (2A)		Extended adjuvant therapy with neratinib (2B)
		(II) Trastuzumab + pertuzumab (2A)		

pCR, pathological complete response; T-DM1, trastuzumab emtansine.

postoperative adjuvant treatment (*Table 2*).

For patients who have reached pCR after a full course of neoadjuvant therapy, the primary targeted therapy may be continued as part of the postoperative adjuvant treatment regimen. For patients who have undergone neoadjuvant therapy with only trastuzumab, experts believed the option of dual-targeted therapy could be explored based on the results of the postoperative adjuvant treatment.

Clinical research has demonstrated that dual-targeted therapy, which combines trastuzumab and pertuzumab, is more effective than trastuzumab monotherapy. In the KATHERINE study, patients who did not achieve pCR after preoperative treatment with trastuzumab saw their prognosis further improved with postoperative adjuvant therapy using trastuzumab emtansine (T-DM1) (6). Thus, T-DM1 is recommended for patients who do not achieve pCR after preoperative anti-HER2 treatment with trastuzumab alone. However, so far there is no definite evidence that T-DM1 is superior toHP therapy; thus, HP may also be considered for some patients with significant tumor regression after neoadjuvant therapy. T-DM1 can be considered for patients who fail to achieve pCR after preoperative anti-HER2 treatment with dual-targeted therapy.

In the ExteNET study, patients with stage II–III HER2-positive breast cancer received initiated adjuvant treatment with oral neratinib for 1 year, beginning within 2 years of completing adjuvant trastuzumab therapy (7). Compared to the placebo group, the neratinib group demonstrated a significantly improved invasive disease-free survival (iDFS) rate. The benefit in iDFS was driven by the hormone receptor (HR)-positive subgroup. Thus, for patients who do not achieve pCR after neoadjuvant therapy, HP or T-DM1 is preferred for the adjuvant targeted therapy. Consideration may also be given to sequential neratinib treatment after the completion of adjuvant targeted therapy.

Neoadjuvant treatment for triple-negative breast cancer (TNBC)

Neoadjuvant therapy

Similar with HER2-positive, patients with triple breast cancer were recommended to receive neoadjuvant therapy whether they had tumor lesions larger than 2 cm, positive lymph node or inflammatory breast cancer. The treatment regimens typically involve the use of taxanes in combination with either anthracyclines or platinum. In principle, for patients who respond well to taxanes and anthracyclines, it is crucial to proceed with the neoadjuvant chemotherapy as planned. Additionally, timely discussions regarding the timing and procedures of the surgical intervention are essential. However, for operable patients who do not respond adequately to neoadjuvant chemotherapy, it may be necessary to alter the chemotherapy regimen (*Table 3*).

The results of the neoCART study showed that a 6-cycle TP regimen can further raise the pCR rate of neoadjuvant therapy in TNBC patients compared with an 8-cycle AC→T regimen (8). In the initial phase of neoadjuvant therapy for TNBC, the addition of platinum-based drugs has been shown to increase pCR rate and potentially improve event-free survival (EFS) or DFS. However, whether this approach translates to an overall survival (OS) benefit remains controversial due to the insufficient follow-up time in clinical studies. Platinum-containing regimens may be preferred in young TNBC patients with a family history of breast cancer, especially those with *BRCA* mutations.

The KEYNOTE-522 study found that incorporating programmed cell death protein 1 (PD-1) inhibitors into the TP→AC regimen for neoadjuvant therapy significantly

Table 3 Recommendation of neoadjuvant for triple negative breast cancer

Condition	Level I recommendations	Level II recommendations
Neoadjuvant chemotherapy	(I) Taxanes with anthracycline	(I) AC→T (1B)
	• TAC (1A)	(II) AC→TP (2A)
	• AT (2A)	
	(II) Taxanes with platinum	
	• TP (2A)	
Neoadjuvant chemotherapy with immunotherapy	(I) TP→AC with pembrolizumab (1A)	Clinical study
	(II) TP + PD-1 inhibitors (1A)	

T, taxanes, including docetaxel, albumin-bound paclitaxel, and paclitaxel; A, anthracyclines, including epirubicin, pirarubicin, and doxorubicin; C, cyclophosphamide; P, platinum; PD-1, programmed cell death protein 1.

enhanced the pCR rate in patients with TNBC. Moreover, continuing to use PD-1 inhibitors following surgery had a beneficial effect on EFS (9). The cTRIO trial, which was a multi-center clinical study conducted in China, demonstrated that administering 6 cycles of TP + PD-1 inhibitors yielded a high pCR rate, thereby providing additional treatment options for TNBC patients. Programmed cell death ligand 1 (PD-L1) expression serves as a biomarker for predicting the response to neoadjuvant immunotherapy, yet there is a consensus among the panel members that treatment decisions involving the use of immunotherapy should not be predicated solely on the combined positive score (CPS) scores.

Adjuvant treatment for TNBC patients after neoadjuvant therapy

In TNBC patients, subsequent treatments after neoadjuvant therapy should be tailored based on the pCR outcome. According to the CREATE-X study, if a pCR is not achieved following a complete course of neoadjuvant chemotherapy, postoperative treatment with 6–8 cycles of capecitabine may be considered (*Table 4*). The selection of capecitabine should be tailored to the patient's overall health status, treatment response, and prior treatments. The utilization of olaparib therapy may also be contemplated for patients with TNBC harboring *BRCA* mutations, following neoadjuvant treatment (10).

Patients with TNBC who have received PD-1 inhibitors as part of neoadjuvant therapy may continue to receive these inhibitors with a total time of a full year following surgery, irrespective of whether they achieve a pCR after the operation. It is imperative that these patients be closely monitored for potential adverse effects like severe skin reaction, adrenal insufficiency, throughout the course of PD-1 inhibitor treatment.

Neoadjuvant therapy for HR-positive breast cancer

Patient with HR-positive breast cancer was recommended to receive neoadjuvant therapy only if they had tumor lesions larger than 5 cm, positive lymph node or inflammatory breast cancer. Chemotherapy is recommended first. Neoadjuvant endocrine treatment (NET) can be considered in: (I) patients who require preoperative neoadjuvant therapy but are not fit for chemotherapy; (II) patients who are temporarily unsuitable for surgery or do not require immediate surgery; and (III) hormone-dependent patients who are insensitive to neoadjuvant chemotherapy or have an inadequate response to chemotherapy.

For postmenopausal patients with HR-positive, aromatase inhibitors (AIs) (including anastrozole, letrozole, and exemestane) are recommended for NET. However, in certain cases where AIs are not appropriate (e.g., with a bone density T-score of <–2.5), fulvestrant may be an option. For premenopausal patients with HR-positive, OFS plus AIs may be applied in preoperative ET. Some patients with locally advanced breast cancer who are in need of NET may be treated with ET combined with CDK4/6 inhibitors or participate in clinical trials (*Table 5*).

Generally, the response to NET should be evaluated every 2 months. If the treatment is effective and well-tolerated, it may continue for up to 6 months. After completion of NET, patients will proceed to surgical treatment. The choice of postoperative treatments is then determined based on the results of the postoperative pathology report. Regimens for adjuvant therapy should be

Table 4 Recommendation of adjuvant therapy for triple negative breast cancer after neoadjuvant

Stratification	Level I recommendations	Level II recommendations
pCR		Neoadjuvant regimen with PD-1 inhibitor continued for 1 year (1A)
Non-pCR	Capecitabine 1 (1A)	(I) Neoadjuvant regimen with PD-1 inhibitor continued for 1 year (1A)
		(II) Olaparib (*BRCA* mutation) (1B)

Capecitabine: 1,250 mg/m^2 bid, 2 weeks on/1 week off for a total of 6–8 cycles; or 650 mg/m^2 bid, orally for 1 year. Olaparib, 300 mg bid, orally for 1 year. pCR, pathological complete response; PD-1, programmed cell death protein 1.

Table 5 Recommendation of neoadjuvant endocrine therapy for HR positive breast cancer

Condition	Level I recommendations	Level II recommendations
Postmenopausal	AI (1A)	Fulvestrant (2B)
	AI + CDK4/6 inhibitor (2A)	Participates in rigorously designed clinical trials
Premenopausal		OFS + AI (1A)
		OFS + AI + CDK4/6 inhibitor (2B)

CDK4/6 inhibitor, including CDK4/6 inhibitors that have been marketed in China, but the indications of adjuvant therapy should be considered. AI, aromatase inhibitor; OFS, ovarian function suppression; HR, hormone receptor.

recommended according to postoperative pathology.

Postoperative adjuvant treatment of breast cancer

Adjuvant treatment for HER2-positive breast cancer

The APHINITY study demonstrated that compared to a regimen containing trastuzumab alone, a dual-targeted therapy incorporating both pertuzumab and trastuzumab decreased the risk of recurrence, particularly in patients with positive lymph nodes (11). Accordingly, for patients who are at a high risk of breast cancer recurrence, especially those with positive axillary lymph nodes, the use of dual-targeted therapy with pertuzumab and trastuzumab is recommended (12) (*Table 6*).

However, there is a lack of consensus among experts regarding the universal application of dual-targeted therapy for all patients who are candidates for single-targeted therapy. In cases where patients have negative axillary lymph nodes, it is crucial to consider additional risk factors such as tumor size, estrogen receptor (ER) negativity, histological grade 3, and elevated Ki-67 expression before establishing an optimal treatment protocol. The NSABP B-31/-N9831 study and BCIRG006 study has demonstrated that AC→T or TCbH (docetaxel, carboplatin combined with trastuzumab) were superior to AC→T and thus could be used as options for adjuvant treatment. After a 10-year long-term follow-up, the study showed that TCbH and AC→TH had similar long-term efficacy outcomes. However, the incidence of cardiac insufficiency was lower in the TCbH group. Therefore, TCbH may be preferred for patients who require a higher level of cardiac safety.

Patients with HER2-positive and lymph node-negative small tumors are still at high risk of recurrence compared with those with HER2-negative small tumors. For this patient group, the regimen can be further simplified by reducing the chemotherapy component in addition to incorporating trastuzumab. TC + H or weekly TH regimens may be considered as treatment options for low-risk patients with T1N0 HER2-positive tumors.

Given that drugs such as trastuzumab and pertuzumab may potentiate cardiotoxicity, their co-administration with anthracycline chemotherapy is generally not recommended. However, these medications can be used in conjunction with adjuvant radiotherapy (RT) and adjuvant ET. For HR-positive patients, expert agreed ET plus targeted therapy can be considered in low-risk patients who do not need chemotherapy or in patients who need chemotherapy but cannot tolerate it.

In instances where intensive targeted therapy is necessitated in patients with HER2-positive cancer, it is initially advisable to evaluate the potential for dual-targeted therapy. According to ExteNet study, for individuals with

Table 6 Recommendation of adjuvant therapy for HER2 positive breast cancer without neoadjuvant therapy

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Primary treatment			
Positive axillary lymph nodes	(I) AC→THP (1A)	(I) AC→TH (2A)	
	(II) TCbHP (1A)	(II) TCbH (2A)	
Negative axillary lymph nodes, tumor sized >2 cm, and with high risk factors such as: (I) ER-negative; (II) high Ki-67 expression	(I) AC→TH (2A)	(I) AC→THP (2A)	TC + H (2B)
	(II) TCbH (2A)	(II) TCbHP (2A)	
(I) Negative axillary lymph nodes, tumor sized >2 cm, and without other risk factors; (II) negative axillary lymph nodes and tumor sized ≤2 cm	TC + H (2A)	TH (2A)	
HR positive and no chemotherapy is required; or, can not tolerate chemotherapy		H + ET (2A)	
Extended therapy			
Positive lymph nodes and after adjuvant therapy with H	Sequential neratinib (1A)		
Positive lymph nodes and after adjuvant therapy with HP		Sequential neratinib (2A)	

A, anthracyclines, including epirubicin, pirarubicin, and doxorubicin; T, taxanes, including docetaxel and paclitaxel; C, cyclophosphamide; Cb, carboplatin; ET, endocrine therapy; H and P, approved trastuzumab, pertuzumab, and their subcutaneous preparations; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor.

HR-positive HER2-positive who have already undergone trastuzumab-based adjuvant treatment and remain progression-free but possess significant risk factors for recurrence, the sequential use of neratinib may be an option

Adjuvant treatment for TNBC

The role of platinums in the adjuvant treatment of TNBC remains controversial. The PATTERN study (13) showed that platinum-containing regimens resulted in a 5-year DFS improvement of 6.2 percentage points (86.5% *vs.* 80.3%) and a 35% reduction in the risk of recurrence when compared to the 5-FU, epirubicin, and cyclophosphamide followed by taxanes (FEC→T) regimen. Additionally, an exploratory subgroup analysis revealed that patients who were younger and had higher tumor grades appeared to benefit more from platinum-based therapy. For patients with TNBC who have known *BRCA* mutations, adjuvant therapy may consider the addition of platinum agents (such as cisplatin and carboplatin) on top of anthracyclines and taxanes. Most of experts advocate for the preemptive use of platinum in neoadjuvant therapy for these patients (*Table* 7).

The PLAN B study evaluated the role of an doxorubicin-free TC regimen versus the standard A→T sequential therapy for the treatment of clinically high-risk or genomically intermediate-to-high-risk HER2-negative early breast cancer, and the results showed that both TC and EC→T regimens achieved a 5-year DFS rate of 90%, meeting the expected non-inferiority criteria (14). TC has a similar survival outcome with EC→T, and the 6-cycle TC regimen can be used as one of the adjuvant treatment options for HER2-negative early-stage breast cancer.

The SYSUCC-001 study, a Chinese clinical study on the adjuvant treatment of early-stage TNBC, investigated the value of standard adjuvant chemotherapy followed by 1 year of capecitabine metronomic therapy (15). During a median follow-up of 56.5 months, the 5-year DFS rate was significantly higher in the capecitabine group than in the control group. Therefore, standard chemotherapy followed by capecitabine metronomic therapy for 1 year can lower the risk of recurrence in TNBC patients.

The OlympiA study enrolled high-risk patients with HER2-negative *BRCA1/2* mutations, and the results suggested that sequential olaparib reduced the risk of recurrence or death by 42% in patients after completion of neoadjuvant or adjuvant therapy, with an absolute benefit of 8.8%. The use of olaparib treatment may be considered for patients with TNBC with *BRCA1/2* mutations following

Table 7 Recommendation of adjuvant therapy for TNBC cancer without neoadjuvant therapy

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Primary treatment			
In the presence of any of the following conditions: positive lymph nodes, tumor sized >2 cm	(I) AC→T (1A) (II) ddAC-ddT (1A)	(I) TAC (1B) (II) TP (2A)	(I) AC→TP (2B) (II) FEC→T (2B)
Patients at low risk of recurrence: tumor sized ≤2 cm and with negative lymph nodes	(I) TC ×4 (1A) (II) AC (1A)	(I) AC→T (2A) (II) TC ×6 (2A)	
Extended therapy			
In the presence of any of the following conditions: (I) positive lymph nodes; (II) tumor sized >2 cm		Chemotherapy followed by capecitabine (2A) (*BRCA* wild-type) Chemotherapy followed by olaparib (1B) (with BRCA mutation type)	
Negative lymph nodes and tumor sized 1–2 cm		Chemotherapy followed by sequential capecitabine (2B) (*BRCA* wild-type)	

A, anthracyclines, including epirubicin, pirarubicin, and doxorubicin; T, taxanes, including docetaxel and paclitaxel; C, cyclophosphamide; Cb, carboplatin; E, eporubicin; F, fluorouracil; TNBC, triple-negative breast cancer.

the completion of adjuvant therapy (16).

The purpose of adjuvant chemotherapy for early breast cancer is to cure the disease; therefore, the chemotherapy should be performed in a standardized manner, including the standard protocols, drugs, dosages, treatment cycles, and courses. The selection, dosing, and application of chemotherapy drugs and the management of chemotherapy-associated toxicities are particularly complicated. Factors such as toxicity profiles, patient variations, and comorbidities require careful consideration. Chemotherapy regimens should be tailored to individual patient risks, tolerances, preferences, and clinical trial context. Additionally, protocols for preventing nausea, vomiting, and bone marrow suppression should be developed. Special attention should be paid to the order of administration, infusion time, and dose intensity of chemotherapy drugs during chemotherapy. The drug instructions and the incompatibility of drugs must be strictly followed. In general, it is advisable not to abbreviate the number of cycles in a standard chemotherapy regimen unless there are specific exceptional circumstances.

Adjuvant therapy for HR-positive breast cancer

Adjuvant chemotherapy

For HR-positive/HER2-negative patients, most experts believe that HR-positive breast cancer "responds poorly to chemotherapy". If there are indications for chemotherapy (e.g., 1–3 positive lymph nodes), an AC or TC regimen may be recommended; for high-risk patients with 4 or more positive lymph nodes, the AC→T regimen is typically recommended.

For patients with HR-positive/HER2-negative, pT1N0M0, it is recommended to receive gene test such as Oncotype, MammaPrint, etc. to decide whether to receive chemotherapy or not. However, due to the poor accessibility of gene test in China, Ki-67 is an important marker in the decision of adjuvant chemotherapy. For otherwise low-risk patients (e.g., HR-positive, HER2-negative, and T1N0), adjuvant chemotherapy is recommended if Ki-67 ≥30%; if Ki-67 ≤14%, adjuvant chemotherapy is not currently recommended because the benefit of such treatment is still uncertain; if Ki-67 is between 15% and 30%, the option of performing multi-gene testing should be considered. The decision about whether to proceed with adjuvant chemotherapy should be made following comprehensive discussions with the patient. These discussions should take into account the patient's individual preferences, their tolerance for chemotherapy, and the potential benefits and risks associated with the treatment.

Adjuvant endocrine treatment

Adjuvant endocrine therapy (AET) is essential for patients with HR [either ER or progesterone receptor (PR) s or

Table 8 Recommendation of adjuvant endocrine therapy for post-menopausal patients

Treatment phase	Level I recommendations	Level II recommendations	Level III recommendations
Primary therapy			
Patients at high risk of recurrence: (I) ≥4 positive lymph nodes; (II) 1–3 positive lymph nodes with other risk factors, such as G3, T ≥5 cm, or Ki-67 ≥20%	(I) AI + abemaciclib (1A) (II) AI (2A)	(I) TAM + abemaciclib (2A) (II) Sequential TAM→AI (2A)	TAM (2B)
Patients at low risk of recurrence: (I) negative lymph nodes; (II) 1–3 positive lymph nodes with G1–2, T <5 cm and Ki-67 <20%	AI (1A)	(I) Sequential TAM→AI (2A)	TAM (2B)
Extended therapy			
Extending the ET could be contemplated after 5 years of primary adjuvant AI treatment, provided the patient has tolerated the therapy well and fulfills any of the following criteria: (I) positive lymph nodes; (II) G3; (III) with other risk factors that require adjuvant chemotherapy	Continue the use of AI (2A)	(II) Switch to TAM (2B)	

AI, aromatase inhibitor; ET, endocrine therapy; TAM, tamoxifen.

both]-positive breast cancer. Breast cancers that are weakly ER-positive, with a positive rate ranging from 1% to 9%, exhibit biological behavior that closely mirrors that of ER-negative cancers. Consequently, adjuvant chemotherapy should not be omitted in these patients. Following the completion of adjuvant chemotherapy, the suitability of AET should be assessed. However, for premenopausal individuals with ER-positive breast cancer that has a weak positive rate of 1–9%, the combination of OFS with oral ET is generally not recommended. Tamoxifen might be considered for this kind of patinets. Concurrent adjuvant chemotherapy and ET is not recommended. ET may be initiated once chemotherapy cycles are completed. RT can be administered sequentially or concurrently with ET.

Strategies for AET in postmenopausal patients with HR-positive breast cancer

The MonarchE study included patients with ≥4 positive lymph nodes and patients with 1–3 positive lymph nodes but with high-risk factors such as histology grade 3, tumor size ≥5 cm, and/or Ki-67 ≥20%. The study found that after completion of neoadjuvant or adjuvant chemotherapy, the addition of abemaciclib for 2 years on top of ET further reduced the risk of recurrence, resulting in a 4-year absolute iDFS benefit of 6.4% (17). Therefore, for patients eligible for the MonarchE study, the combination of 2 years of abemaciclib on top of standard ET may be a feasible treatment option. The recommended dose of abemaciclib is 150 mg bid, although the actual dosage should be reasonably adjusted according to the patient's tolerance level. If abemaciclib is not tolerated due to adverse effects experienced during treatment, a switch to another CDK4/6 inhibitor, such as ribociclib, may be deemed appropriate. The NATALEE study enrolled patients with stage II or III disease, encompassing node-negative (T2N0) patients with histologic grade 3/2 and Ki-67 expression ≥20% or those with high-risk genetic profiles. It was found that the addition of 3 years of adjuvant ribociclib on top of ET reduced the recurrence risk by 25% (18). Therefore, for patients eligible for the NATALEE study, incorporating a 3-year regimen of ribociclib alongside non-steroidal aromatase inhibitors (NSAIs) may represent a viable treatment approach. The recommended dose of ribociclib is 400 mg qd, 21/28 d, although the actual dosage may be adjusted according to the patient's tolerance (*Table 8*). Attentionally, there are differences in inclusion criteria between NATALEE and monarchE, patients should choose the proper CDK4/6 inhibitor according to these criteria.

The 10-year follow-up data from the ATAC study demonstrated that in comparison to 5 years of treatment with TAM, 5 years of treatment with AI significantly extended DFS and diminished the risk of recurrence, thereby affirming the position of AI as a standard treatment option for the adjuvant management of early breast cancer in postmenopausal women.

The primary AET with AI may be considered for discontinuation after 5 years for postmenopausal patients

Table 9 Recommendation of adjuvant endocrine therapy for pre-menopausal patients

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Primary therapy			
≥4 positive lymph nodes	(I) OFS + AI + abemaciclib (1A)	(I) OFS + TAM + abemaciclib (1B)	TAM (2B)
	(II) OFS + AI (2A)	(II) OFS + TAM (2A)	
1–3 positive lymph nodes with other risk factors, such as G3, T ≥5 cm, or Ki-67 ≥20%	(I) OFS + TAM + abemaciclib (1A)	(I) OFS + AI + abemaciclib (1B)	TAM (2B)
	(II) OFS + TAM (2A)	(II) OFS + AI (2A)	
(I) 1–3 positive lymph nodes without any other risk factor; (II) negative lymph nodes but with risk factors G2–3, T >2 cm, or high Ki-67	OFS + TAM (1A)	(I) OFS+AI (2A)	TAM (2B)
Negative lymph nodes without any risk factor	TAM (1A)		
Extended therapy			
Patients who have completed the primary 5-year TAM treatment and require extended therapy	(I) Extended TAM in premenopausal patients (1A)		
	(II) Sequential AI in patients with confirmed menopause (1A)		
Patients who have completed the initial 5 years of OFS + TAM and tolerate the treatments well	Sequential AI for menopausal patients (2A)	TAM for premenopausal patients (2B)	
Patients who have completed the initial 5 years of OFS + AI and tolerate the treatments well	AI for postmenopausal patients (2A)	TAM (2B) or OFS + AI (2B) for premenopausal patients	

OFS, ovarian function suppression; AI, aromatase inhibitor; TAM, tamoxifen.

with low-risk breast cancer. Following the initial 5 years of adjuvant AI therapy, continuation of ET may be considered for patients who have tolerated the treatment well and meet any of the following criteria: (I) positive lymph nodes; (II) G3; (III) additional risk factors, such as a Ki-67 >30%, that necessitate adjuvant chemotherapy.

AET strategies for premenopausal breast cancer patients

The TEXT&SOFT joint analysis (19) compared the efficacy of 5-year postoperative AET (with OFS) with 5-year TAM or 5-year AI. For patients receiving chemotherapy, the distant recurrence rate was reduced by 2.6% in the TEXT study and by 3.4% in the SOFT study, which confirmed the benefit of 5-year OFS + AI treatment. Further comprehensive quantitative analysis (20) revealed that factors associated with the absolute benefit of OFS + AI included age <35 years, ≥4 positive lymph nodes, and histological grade 3. Thus, patients with these factors are more likely to benefit from OFS + AI treatment (*Table 9*).

In the context of standard postoperative adjuvant therapy, the SOFT study evaluated the relative efficacy of adjuvant therapy combining OFS with TAM compared to TAM alone for a 5-year duration. The 8-year follow-up of this study revealed that OFS plus TAM significantly extended the DFS in premenopausal patients. Specifically, the definite DFS benefit was augmented by 7% in the subgroup receiving OFS plus AI; when compared to the TAM monotherapy group, the 8-year distant recurrence-free interval (DRFI) benefit was increased by 2.8% in the OFS + AI group. The majority of patients in the pre-defined subgroup that did not receive postoperative adjuvant chemotherapy were characterized by lymph node-negative status, G1, and T <2 cm, and patients in this subgroup had minimal benefit from OFS plus ET. Consequently, it is recommended that the foundational strategy for postoperative adjuvant ET in these patients involves a 5-year course of TAM treatment.

The risk of long-term recurrence remains a concern even after 5 years of adjuvant OFS combined with oral

Table 10 Recommendation of adjuvant RT after BCS

Condition	Level I recommendations	Level II recommendations	Level III recommendations
DCIS	WBRT (1A) ± boost to tumor bed (2A)	APBI/PBI (2A)	Omit RT for low-risk patients (2B)
Invasive carcinoma with negative lymph node (ALN)	WBRT (1A) ± boost to tumor bed (1B)	(I) APBI/PBI (2A) (II) One-week ultra-hypofractionated WBRT (2A) (III) Omit RT for low-risk patients (2A)	WBRT + RNI ± boost to tumor bed for high-risk patients (2B)
1–2 positive SLNs without ALND	WBRT ± boost to tumor bed + comprehensive RNI including the undissected axilla (1B)	High tangential field WBRT (1B) ± boost to tumor bed (1B) for low-risk patients	
1–3 positive lymph node after ALND	WBRT ± boost to tumor bed + comprehensive RNI (1B)	WBRT ± boost to tumor bed for low-risk patients (2B)	
≥4 positive ALNs after ALND	WBRT ± boost + comprehensive RNI (1A)		
With neoadjuvant therapy			
cN_0, ypN_0, BCS	WBRT ± boost to tumor bed (2A)		WBRT ± boost to tumor bed + comprehensive RNI for high-risk patients (2B)
cN_+, ypN_0, BCS	WBRT ± boost to tumor bed + comprehensive RNI (2A)	WBRT ± boost to tumor bed for cN1 patients (2A)	
$cN_{0–3}$, ypN+, BCS	WBRT ± boost to tumor bed + comprehensive RNI (1B)		

BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; WBRT, whole breast radiotherapy; APBI, accelerated partial breast irradiation; PBI, partial breast irradiation; RT, radiotherapy; ALN, axillary lymph nodes; RNI, regional nodal irradiation; SLN, sentinel lymph node; ALND, axillary lymph node dissection.

ET. To date, no study has investigated the outcomes of prolonged ET in these patients. Furthermore, there is a lack of randomized controlled trials that compare the efficacy of extending ET following 5 years of OFS plus endocrine drugs with that of 10-year TAM. Nevertheless, in light of the evidence supporting the benefit of extended ET, this strategy can be recommended for patients who can tolerate it.

Adjuvant RT for breast cancer

The results of the BIG 3-07/TROG 07.01 trial reveal that there is no significant difference in outcomes and adverse effects between the moderate hypofractionated and conventional whole breast radiotherapy (WBRT) (21). This guideline recommends an equivalent use of both conventional and hypofractionated schemes for WBRT in DCIS. Accelerated partial breast irradiation (APBI)/partial breast irradiation (PBI): suitable candidates were selected by the recommendations of the American Society for Radiation Oncology (ASTRO) (22) or the inclusion criteria of RAPID/NSABP B-39, APBI-IMRT-Florence, GEC-ESTRO, IMPORT LOW, DBCG PBI studies (23,24). The recommended external beam APBI fractionation is 30 Gy/5 fractions (QOD). 40 Gy/15 fractions may also be considered (*Tables 10,11*).

The long-term follow-up of the CALGB 9343 study demonstrated that, in patients aged ≥70 years, T1N0M0, HR-positive, HER2-negative, RT still showed a significant benefit on local control, while no significant benefit on DFS and OS, which was also confirmed by the updated 10-year follow-up results of the PRIME II study (19). Low-risk DCIS or invasive cancer patients who meet the criteria of PRECISION, LUMINA, IDEA, and PROSPECT trials may be considered for omitting RT (25,26).

WBRT dosing: the conventional dose of 50 Gy/25 fractions or the hypofractionated dose of 40–42.5 Gy/15–16 fractions (recommended). The sequential tumor

Table 11 Recommendation of adjuvant RT after mastectomy

Condition	Level I recommendations	Level II recommendations	Level III recommendations
Negative ALN, T ≤5 cm, margin ≥1 mm	No RT (1B)		RT for high-risk patients (2B)
Negative ALN, T >5 cm or margin <1 mm	RT to chest wall ± comprehensive RNI (2A)	Omit RT for low-risk patients (2B)	
1–3 positive ALN(s)	RT to chest wall + comprehensive RNI (1B)	Omit RT for low-risk patients (2B)	
≥4 positive ALNs	RT to chest wall + comprehensive RNI (1A)		
With neoadjuvant therapy			
cN_0, ypN_0, mastectomy	No RT (2A)		Chest wall ± RNI for high-risk patients (2B)
cN_1, ypN_0, mastectomy	Chest wall ± comprehensive RNI (2A)	Omit RT (2B)	
cN_{2-3}, ypN_0, mastectomy	Chest wall + comprehensive RNI (2A)		
cN_{0-3}, ypN+, mastectomy	Chest wall + comprehensive RNI (1B)		

ALN, axillary lymph nodes; RT, radiotherapy; RNI, regional nodal irradiation.

bed boosts dosing: the conventional dose of 10–16 Gy/5–8 fractions or the hypofractionated dose of 8.7–10 Gy/3–4 fractions (27). The IMPORT HIGH study indicates that simultaneous integrated boost (SIB) can reduce the duration of RT without increasing adverse effects, so SIB of 48 Gy/15 fractions may be considered (28).

The FAST-FORWARD trial demonstrates that there is no statistically significant difference in efficacy and toxicity between the 26 Gy/5 fractions/1 week and 40 Gy/15 fractions/3 weeks (29). The 1-week regimen could be considered for patients who meet the criteria of the FAST-FORWARD trial. However, the radiation dose to the target and OARs should be carefully evaluated. Patients are encouraged to participate in clinical trials of 1-week WBRT with proton therapy (30).

For patients who received axillary lymph node dissection (ALND), comprehensive regional nodal irradiation (RNI) includes supra/infraclavicular and internal mammary lymph nodes (IMN). Most of clinical trials and meta-analyses support the IMN irradiation. For patients with positive sentinel lymph nodes (SLNs) without ALND, high tangential field RT is recommended for patients eligible for the Z0011 study. If the predicted probability of non-SLN metastasis exceeds 25% to 30% using an SLN prediction nomogram, axillary RT is recommended. The AMAROS study shows that for patients with limited positive SLNs, axillary RT is as effective as ALND in controlling the disease and reduces lymphedema. Most studies indicate that N1 patients benefit from RNI. According to the EORTC 22922-10925 and MA20 trials, RNI is recommended for "high risk" N0 patients with tumors in the central/medial quadrant, pT2, and one of the following risk factors: histological grade III, HR-negative, lymphovascular invasion (LVI), or with pT3 after BCS. The hypofractionated RNI regimen should be considered, concerning the protocols of the HARVEST trial (31) and the POTENTIAL trial (32) in clinical practice.

For patients with neoadjuvant therapy, RT is based on clinical staging and pathological staging. The RAPCHEM study (33) indicates that in patients with cT1–2, good local control could be achieved by stratifying the risk of recurrence and making individualized RT decisions, according to ypN stage, axillary surgery, and risk factors (including grade III, LVI, and tumor >3 cm). The NSABP B51 trial reveals that RNI does not significantly improve the Invasive breast cancer recurrence-free interval. When considering the de-escalation of RNI in clinical practice, it is essential to base it on the cT, cN, and ypN stages together.

The indications for postoperative RT in patients post-breast reconstruction should follow the same criteria as those in post-mastectomy. Postoperative RT should start 2–8 weeks after chemotherapy or within 8 weeks after surgery if no chemotherapy is given. Avoid starting RT within 4 weeks after BCS. Endocrine and anti-HER2 therapies can be given concurrently with RT, focusing on cardiac safety. CDK4/6 inhibitors, PARP inhibitors, ICIs, and capecitabine should be used after RT.

Table 12 Recommendation of salvage therapy for HER2 positive advanced breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Trastuzumab-sensitive	(I) THP (1A)	(I) TXH (2A)	(I) Pyrotinib + capecitabine (2A)
	(II) TH + pyrotinib (1A)	(II) H + chemotherapy (2A) (chemotherapy includes: taxanes, vinorelbine, and capecitabine)	(II) HP + chemotherapy (2B)
Trastuzumab-resistant	(I) Pyrotinib + capecitabine (1A)	T-DM1 (1A)	(I) Neratinib + capecitabine (2A)
	(II) T-Dxd (1A)		(II) Margetuximab + chemotherapy (2B)
			(III) Lapatinib + capecitabine (2B)
			(IV) TKI + other chemotherapy (2B)
			(V) HP + other chemotherapy (2B)
TKI-resistant		(I) T-Dxd (1A)	Another TKI + chemotherapy (2A)
		(II) HP + other chemotherapy (2A)	
		(III) T-DM1 (2A)	
		(IV) Rigorously-designed clinical trial	

HER2, human epidermal growth factor receptor 2; H/P including trastuzumab, pertuzumab and their subcutaneous preparations, biosimilar medications, and inetetamab, which have been launched in China; TKIs, tyrosine kinase inhibitors, include pyrotinib, lapatinib, neratinib, and tucatinib; P, pertuzumab; X, capecitabine; T, taxanes, including docetaxel, paclitaxel and nab-paclitaxel; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.

Salvage treatment for advanced breast cancer

Salvage treatment for HER2-positive advanced breast cancer

All patients diagnosed with HER2-positive recurrent or metastatic breast cancer should be fully informed of the importance and benefits of timely HER2-targeted therapy.

Trastuzumab-sensitive populations are defined as: (I) trastuzumab-naïve; (II) responsive to neoadjuvant therapy; (III) with recurrence within 1-year post-adjuvant treatment; and (IV) having undergone drug withdrawal after successful salvage therapy. For such patients, trastuzumab-based therapy is the treatment of choice. The selection of a rational combination treatment regimen should be based on the patient's HR status and history of neoadjuvant/adjuvant therapies.

The CLEOPATRA study confirmed that the combination of docetaxel with dual-targeted therapy, which incorporates pertuzumab and trastuzumab, was more effective than the combination of docetaxel with single-targeted trastuzumab therapy in prolonging progression-free survival (PFS) and OS. Consequently, this combination has emerged as the preferred treatment option for HER2-positive patients who have not responded to trastuzumab and taxanes (34). The PHILA study demonstrated that the median progression-free survival (mPFS) of patients receiving first-line treatment with TH + pyrotinib for HER2-positive advanced breast cancer reached 24.3 months, which was significantly superior to that observed with TH therapy alone, offering a novel treatment option for trastuzumab-sensitive patients (35) (*Table 12*).

For patients resistant to trastuzumab, according to the PHENIX study, in patients who failed the treatment with taxanes and trastuzumab, pyrotinib combined with capecitabine was more effective than capecitabine monotherapy in increasing overall response rate (ORR) and PFS (36). Similarly, the PHOEBE study showed that in advanced breast cancer patients who have previously received trastuzumab, taxanes, and/or anthracyclines, pyrotinib combined with capecitabine achieved better PFS than lapatinib combined with capecitabine (37). Therefore, the experts recommend pyrotinib combined with capecitabine for the treatment of patients who have failed to respond to trastuzumab and taxanes.

The DESTINY-Breast03 trial demonstrated that T-Dxd significantly improved PFS and decreased the risk of disease progression or death by 72% compared to T-DM1 in the setting of trastuzumab failure. This finding confirmed the efficacy of T-Dxd as a second- and later-line treatment option for patients following the failure of

trastuzumab therapy (38). Considering the accessibility of T-Dxd, the expert group encourages the inclusion of this drug in the medical insurance plans; meanwhile, patients are encouraged to actively participate in clinical research related to ADC drugs at home and abroad.

The selection of targeted drugs after ADC failure is an important and challenging clinical issue. T-Dxd is preferred after the failure of T-DM1, yet there remains a paucity of high-quality clinical research guiding the selection of therapies following T-Dxd resistance. Incorporating real-world evidence and expert opinions, current recommendations suggest that the decision should be tailored to the patient's treatment history. T-Dxd is also preferred after tyrosine kinase inhibitor (TKI) failure compared with T-DM1 (39). In addition, dual-target (H + P) therapy combined with other chemotherapy or T-DM1 can also be considered.

Furthermore, HER2-targeted therapy combined with ET + CDK4/6 inhibitors have certain efficacy. Targeted therapy combined with 'endocrine +' therapy may be applied in some patients. In patients who have achieved stable disease (SD) after HER2-targeted therapy plus chemotherapy, maintenance therapy with HER2-targeted therapy plus ET may be considered after the chemotherapy is stopped.

Salvage treatment for triple-negative advanced breast cancer

The preferred chemotherapy regimens include single-agent chemotherapy and combination chemotherapy. Compared with the single-agent chemotherapy, the combination chemotherapy usually has a higher ORR and longer DFS. However, combination chemotherapy is more toxic and has limited survival benefits. Therefore, combination chemotherapy is only feasible for patients who need to shrink the tumor or relieve symptoms within a short period of time. In contrast, single-agent chemotherapy is preferred for patients in whom drug tolerability and quality of life are the top concerns.

For recurrent/metastatic breast cancer patients who have failed prior anthracycline-containing preoperative/adjuvant therapy, taxane-based regimens are typically preferred, and both single-agent and combination regimens can be selected for the first-line treatment. Other optional drugs may include capecitabine, gemcitabine, and vinorelbine.

In the ASCENT study, patients with advanced TNBC who had received prior second- or later-line chemotherapy were randomized to receive sacituzumab govitecan or single-agent chemotherapy (including capecitabine, eribulin, vinorelbine, or gemcitabine, upon the investigator's choice), respectively (40). It was found that sacituzumab govitecan reduced the risk of disease progression by 59% and the risk of death by 52% in patients with refractory TNBC that was resistant to multi-line treatments. Thus, the new anti-Trop-2 ADC brings additional treatment options to patients with advanced TNBC (*Table 13*).

In the KEYNOTE-355 study, chemotherapy combined with a PD-1 inhibitor significantly improved PFS compared with chemotherapy alone in patients whose tumors expressed PD-L1 and had a CPS of ≥10 (41), suggesting the potential role of immune checkpoint inhibitors (ICIs) in the treatment of TNBC. In the TORCHLIGHT study (42), toripalimab in combination with chemotherapy significantly improved PFS in PD-L1-positive (CPS ≥1) populations, with a clear trend towards OS benefit regardless of PD-L1 expression. Thus, the panel agrees that in clinical practice, there is no longer a need to make a decision about whether to use immunotherapy based on CPS scores.

Available data from treatment courses suggest that, compared to short-course chemotherapy, continuous chemotherapy can result in longer PFS and, potentially, OS. Nevertheless, the choice between long-course chemotherapy and short-course chemotherapy (consisting of 6–8 cycles) followed by drug withdrawal or maintenance treatment should be based on a careful consideration of efficacy, adverse drug reactions, and the patient's quality of life.

Salvage therapy for HR-positive advanced breast cancer

Chemotherapy or ET is preferred in the salvage therapy for HR-positive patients. The RIGHT Choice study found that ET plus ribociclib improved PFS significantly over chemotherapy, with similar ORR and time to response (43). Thus, CDK4/6 inhibitors combined with ET can be considered a first-line treatment option for HR-positive/HER2-negative advanced breast cancer patients. For patients with visceral metastases, prior resistance to ET, or no optimal ET option, salvage chemotherapy is often preferred.

Selection of first-line ET for recurrent or metastatic breast cancer should consider prior treatments, DFI, and disease burden. ET should be continued where possible in patients who have benefited from the treatment until disease progresses; however, the tolerance to long-term drug use should also be assessed. Combining ET with chemotherapy is generally not advised. For HR-positive/HER2-positive patients ineligible for salvage chemotherapy, a first-line treatment approach involving ET combined with HER2-

Table 13 Recommendation of salvage therapy for triple negative advanced breast cancer

Condition	Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Chemotherapy	Taxanes-sensitive	(I) Taxane monotherapy	(I) Monotherapy	Olaparib# (2A)
		• Albumin-bound paclitaxel (1A)	• Capecitabine (2A)	Liposomal paclitaxel (2A)
		• Docetaxel (2A)	• Vinorelbine (2A)	Liposomal doxorubicin (2B)
		• Paclitaxel (2A)	• Gemcitabine (2A)	
		(II) Combination therapy	• Etoposide (2B)	
		• TX (1A)	(II) Combination therapy	
		• GT (1A)	• Taxanes + bevacizumab (2B)	
		• TP (2A)		
	Taxanes-resistant	(I) Monotherapy	(I) Monotherapy	Olaparib# (2A)
		• Eribulin (1A)	• Albumin-bound paclitaxel* (2A)	Liposomal doxorubicin (2B)
		• Vinorelbine (2A)	• Sacituzumab govitecan (SG) (2A)	Liposomal paclitaxel (2B)
		• Capecitabine (2A)	• Etoposide (2B)	
		• Gemcitabine (2A)	(II) Combination therapy	
		(II) Combination therapy	• Capecitabine + bevacizumab (2B)	
		• NP (1A)	• Albumin-bound paclitaxel* + other chemotherapy drugs (2B)	
		• GP (1A)		
		• Utidelone + capecitabine (1A)		
		• NX (2A)		
Chemotherapy with immunotherapy	Taxanes-sensitive	Albumin-bound paclitaxel + PD-1 inhibitors	(I) Paclitaxel + PD-1 inhibitors (1B)	Clinical study
			(II) GP + PD-1 inhibitors (1B)	
			(III) Other chemotherapy + PD-1 inhibitors (2A)	
	Taxanes-resistant	GP + PD-1 inhibitors	Other chemotherapy + PD-1 inhibitors (2A)	Clinical study

*, consider switching to albumin-bound paclitaxel if progressed to docetaxel or paclitaxel; #, recommended in the presence of BRCA mutation. T, taxanes, including docetaxel paclitaxel and nab-paclitaxel; X, capecitabine; G, gemcitabine; N, vinorelbine; PD-1, programmed cell death protein 1.

targeted therapy may be considered. The second-line ET for advanced breast cancer should be chosen based on prior treatment history and response, avoiding reused adjuvant therapies or previously resistant drugs (*Table 14*).

Clinical studies have demonstrated the efficacy of CDK4/6 inhibitors plus ET for HR-positive advanced breast cancer, but differences exist in the mechanisms of action, dosages, indications, and toxicities among different CDK4/6 inhibitors (44-47). Therefore, CDK4/6 inhibitors and their combinations should be chosen based on the populations studied in clinical trials and the individual patient's circumstances.

In the ACE study, for postmenopausal HR-positive/HER2-negative advanced breast cancer patients who had previously failed TAM and/or non-steroidal AI treatment, the combination of HDAC inhibitor chidamide with exemestane significantly prolonged PFS (7.4 *vs.* 3.8 months, *vs.* exemestane alone); also, it was superior to exemestane in terms of ORR and clinical benefit rate (48).

Treatments for HR-positive breast cancer patients after CDK4/6 inhibitor resistance are still under investigation. The BYLieve study suggests considering ET plus alpelisib

Table 14 Recommendation of salvage therapy for triple negative advanced breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
ET-naïve	AI + CDK4/6 inhibitors (1A)	(I) Fulvestrant + CDK4/6 inhibitors (2A)	TAM (2B)
		(II) AI (2A)	
		(III) Fulvestrant (2A)	
Failed to TAM	AI + CDK4/6 inhibitors (1A)	(I) AI + chidamide (1A)	(I) AI (2A)
		(II) AI + everolimus (IA)	(II) Fulvestrant (2A)
		(III) Fulvestrant + CDK4/6 inhibitors (1B)	
Failed to non-steroidal AIs	Fulvestrant + CDK4/6 inhibitors (1A)	(I) Steroidal AI + chidamide (1A)	(I) Fulvestrant (2A)
		(II) Steroid AI + everolimus (IB)	(II) Steroidal AI (2A)
			(III) TAM or toremifene (2B)
			(IV) Progesterone (2B)
Failed to steroidal AI	Fulvestrant + CDK4/6 inhibitors (1A)	(I) Fulvestrant + everolimus (2A)	(I) Fulvestrant (2A)
		(II) Non-steroid AI + CDK4/6 inhibitors (2A)	(II) Non-steroidal AI (2B)
			(III) TAM or toremifene (2B)
			(IV) Progesterone (2B)
Failed to CDK4/6 inhibitor		(I) A different class of CDK4/6 inhibitor + ET (2A)	(I) Progesterone (2B)
		(II) Other targeted drugs + endocrine drugs (2A)	(II) Toremifene (2B)
		(III) Clinical trials	(III) AKT inhibitors + endocrine drugs

CDK4/6 inhibitor, including palbociclib, abemaciclib, ribociclib and dalpiciclib that have been marketed in China. ET, endocrine therapy; AI, aromatase inhibitor; TAM, tamoxifen; AKT, serine/threonine kinase.

for *PIK3CA* mutation patients after CDK4/6 inhibitor resistance (49). The Destiny-Breast 04 study showed a greater survival advantage with T-Dxd over physician-chosen chemotherapy in patients with low HER2 expression (50). Real-world Chinese studies indicate that switching to a different CDK4/6 inhibitor can be effective for patients after initial inhibitor failure. The CAPItello-291 study demonstrated that the ATK inhibitor capivasertib plus fulvestrant prolonged PFS, with a notable improvement seen in patients who had previously received CDK4/6 inhibitors (approximately 70% of the total population) (51).

Salvage treatment for HER2-low advanced breast cancer

HER2 low is a special type of breast cancer with the definition of immunohistochemistry 1+ or 2+ fluorescence *in situ* hybridization negative. While the category for HER2 IHC 0 includes infiltrating cancer cells with a result of 0 and ≤10% showing incomplete and weak cell membrane staining.

HER2-low breast cancer represents about 44–57% of all breast cancer cases, with a higher prevalence in HR-positive patients. The treatment of HER2-low breast cancer may align with recommendations for triple-negative and HR-positive breast cancers in these Guidelines. Clinical focus on identifying HER2-low breast cancer is warranted due to its distinct survival prognosis from HER2-zero cases and varying response to therapies.

For HR-positive/HER2-low breast cancer, initial treatment aligns with the protocols for HR-positive breast cancer, including CDK4/6 inhibitor-based ET or taxane-based chemotherapy, with ADCs considered if a CDK4/6 inhibitor fails. The DESTINY-Breast 04 study compared the efficacy of T-Dxd with physician-chosen chemotherapy regimens and found that T-Dxd was significantly more effective for patients who had received 1–2 prior lines of therapy, particularly in the predefined subgroup of HR-positive patients. The TROPICs-02 study (52) investigated treatment options for HR-positive/HER2-negative breast cancer after the failure of taxanes and CDK4/6 inhibitors, demonstrating that SG could prolong PFS and OS compared to single-agent chemotherapy. SG significantly prolonged PFS in both HER2-low and HER2-zero

Table 15 Recommendation of salvage therapy for HR-positive/HER2-low advanced breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
CDK4/6 inhibitor naïve	Endocrine therapy + CDK4/6 inhibitors (1A)	Chemotherapy	
Treated with CDK4/6 inhibitor		(I) T-Dxd (1A)	Sacituzumab govitecan (SG) (2A)
		(II) Chemotherapy (2A)	
		(III) Other endocrine therapies (2A)	

CDK4/6 inhibitor, including palbociclib, abemaciclib, ribociclib and dalpiciclib that have been marketed in China. T-Dxd, trastuzumab deruxtecan; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

populations (*Table 15*).

Patients with HR-negative/HER2-low breast cancer should initially be treated with chemotherapy or a combination of chemotherapy and immunotherapy, as in TNBC patients. In the event of first-line treatment failure, ADC therapy is preferred, with options such as SG or T-Dxd. On a single-agent basis, multiple clinical studies have explored the feasibility of ADC in combination with other therapies. The BEGONIA Cohort 7 (53) trial found that combining Dato-Dxd with durvalumab achieved an ORR of up to 79%, indicating a good safety profile and high, lasting responses. A phase 2 study assessed the role of SKB264 in TNBC patients, many of whom (89.8%) had already received at least 3 lines of treatment for metastatic breast cancer. The study found that SKB264 prolonged mPFS to 5.7 months, showing promising potential for its use. Following ADC therapy, options such as *BRCA* inhibitors and anti-angiogenic inhibitors may be considered.

Conclusions

Here, we reported the main content of the CSCO BC guidelines in 2024, although there are still chapters on diagnosis, imaging, core biopsies, treatment safety management, clinical trials, artificial intelligence, liquid biopsy, etc., which were not included due to space limitations. Details about the frequency of drug administration, number of cycles, dosage were also excluded compared with the Chinese version. We hope to provide more insights through this guideline to help us and other countries with similar situations to develop guidelines that are tailored to their own conditions.

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Footnote

Peer Review File: Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-31/prf

Conflicts of Interest: All authors authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-31/coif). Z.J. serves as the Editor-in-Chief of *Translational Breast Cancer Research*. J.L. serves as an unpaid Managing Editor of *Translational Breast Cancer Research* from November 2019 to October 2024. E.S., Y.Y., J.C., Q.L., C.G., H.W., S.W., and J.W. serve as the unpaid editorial board members of *Translational Breast Cancer Research* from March 2024 to February 2026. C.H., K.W., Y.L., J.Z., J.N. serve as the unpaid editorial board members of *Translational Breast Cancer Research* from May 2023 to April 2025. X.W. serves as an unpaid editorial board member of *Translational Breast Cancer Research* from December 2022 to November 2024. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Category of evidence

Level	Evidence	Sources	Agreement from experts
1A	High	Rigorous randomized clinical trial or meta-analysis	With consensus (≥80% agreement)
1B	High	Rigorous randomized clinical trial or meta-analysis	With basic consensus (60–80% agreement)
2A	Moderate	General quality meta-analysis, small-scale randomized controlled trials, well-designed large-scale retrospective studies, case-control studies	With consensus (≥80% agreement)
2B	Moderate	General quality meta-analysis, small-scale randomized controlled trials, well-designed large-scale retrospective studies, case-control studies	With basic consensus (60–80% agreement)
3	Low	Non controlled single arm clinical study, case report expert opinion	No consensus while significant controversy (<60% agreement)

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