Guideline

Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2022

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Abstract: 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 (CSCO). 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. The CSCO guidelines 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 in the CSCO guidelines, 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. 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 experts, the CSCO guidelines determine the levels of recommendations for clinical application. The CSCO Guidance Working Group firmly believes that evidence-based, availability-concerned, and consensus-based guidelines will be more feasible for clinical practice. Again, any comments from our readers are greatly appreciated and will be considered in updates of these guidelines, so as to maintain the accuracy, fairness, and timeliness of the CSCO guidelines.

Keywords: Chinese Society of Clinical Oncology Breast Cancer (CSCO BC); guideline; accessibility; recommendation

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Introduction

Breast cancer has been one of the most common diagnosed cancers both in China and worldwide. Choosing an optimal guideline for breast cancer in China based on the clinical practice, the availability of treatment products, and the up-to-date evidences has become a major concern for Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) committee.

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, 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. We firmly believe that will be more feasible for clinical practice in China.

Here in this article, we would like to report the latest version and updates in CSCO BC guideline so as to maintain the accuracy, fairness, and timeliness of this guideline.

Preoperative neoadjuvant treatment of breast cancer

Patients who meet one of the following conditions may choose preoperative neoadjuvant treatment: (I) large tumor size; (II) positive axillary lymph nodes; (III) HER2-positive; (IV) triple-negative; and (V) with a desire of breast-conserving surgery, which, however, cannot be achieved due to the large proportion of tumor among breast.

Neoadjuvant treatment can be considered for primary breast masses sized >5 cm; for primary breast masses sized 2–5 cm, other biological markers should be detected before a decision of neoadjuvant treatment is made.

Neoadjuvant treatment of HER2-positive breast cancer

Clinical studies have proved that neoadjuvant treatment with trastuzumab plus chemotherapy significantly increase the pathologic complete response (pCR) rate in HER2-positive breast cancer patients, laying a foundation for 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 recognizes that dual-targeted therapy can be considered during the neoadjuvant treatment in all patients who qualify for single-targeted therapy.

The NeoSphere study (1) showed that adding pertuzumab to trastuzumab and chemotherapy (TH) could further increase the pCR rate in HER2-positive patients. The PEONY study (2) confirmed the effectiveness and safety of the THP (paclitaxel + trastuzumab + pertuzumab) regime in Asian populations. Therefore, THP can be used as a neoadjuvant treatment in HER2-positive patients. However, in the above study, surgery was performed after 4 cycles of neoadjuvant treatment with THP, and the dual-targeted therapy was suspended after surgery and then continued after 3 cycles of FEC therapy. Thus, the clinical feasibility of this protocol was quite questionable. The KRISTINE study (3) confirmed the effectiveness and safety of TCbHP regimen in neoadjuvant treatment. The TRAIN-2 study (4) showed that the TCbHP regimen could achieve the same pCR rate compared to an anthracycline-based regimen, but with significantly lower toxicities such as neutropenia. Therefore, TCbHP can be the preferred regimen 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 burden and generally intolerant to platinum-based combination regimens. Based on the findings of research on AC→TH (anthracycline combined with cyclophosphamide followed by sequential taxanes combined with trastuzumab)regimen in the single-targeted era, some experts agree that AC→THP can be used as an optional regimen for neoadjuvant therapy, which, however, has not been validated in well-designed clinical studies.

Trastuzumab combined with taxane-based chemotherapy has become the basic regimen in neoadjuvant chemotherapy for HER2-positive breast cancer. The TCbH (docetaxel, carboplatin combined with trastuzumab) regimen has been demonstrated to be effective and safe in preoperative neoadjuvant therapy and postoperative adjuvant therapy and thus can be recommended for neoadjuvant therapy.

The PHEDRA study was designed to explore the efficacy and safety of pyrotinib in combination with trastuzumab and docetaxel (pyrotinib group) versus placebo in combination with trastuzumab and docetaxel (control group) in the neoadjuvant treatment of HER2-

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Table 1 Recommendations of neoadjuvant therapy for HER2-positive breast cancer

Level I recommendations	Level II recommendations
(I) TCbHP (1A)	(I) Anti-HER2 monoclonal antibody combined with taxane-based regimens (2B)
(II) THP ×4 (1B)	• Such as TCbH (2B) and AC→THP (2B)
(III) THP ×6 (2A)	(II) Scientific and rationally designed clinical trials
	• Such as H + TKI and anti-HER2 ADC

T, taxene; A, anthracycline; C, cyclophosphamide; Cb, carboplatin; H, trastuzumab; P, pertuzumab; TKI, tyrosine kinase inhibitor; ADC, antibody drug conjugate.

positive early or locally advanced breast cancer. The results showed that the pCR rate was 41% in the pyrotinib group, compared with 22% in the control group, demonstrating a statistically significant difference (superiority) and confirming that the neoadjuvant regimen of "pyrotinib + trastuzumab", a combination of large and small molecules, can provide a clear benefit for patients with HER2-positive early-stage breast cancer (*Table 1*).

The pre-planned treatment cycles must be completed during the neoadjuvant therapy for HER2-positive breast cancer. Surgery is performed only after the full course of neoadjuvant therapy is completed. The postoperative adjuvant treatment is performed (or not) based on the implementation of neoadjuvant therapy and the achievement of postoperative pCR. Pathological evaluation is an important tool for evaluating the efficacy of preoperative neoadjuvant chemotherapy and the pCR achieved after surgery. It is valuable for evaluating the effectiveness of neoadjuvant therapy and determining postoperative adjuvant treatment options. There are two definitions of pCR: (I) generally, it means the achievement of no residual histological evidence of malignant tumor in the primary breast cancer, with or without the presence of carcinoma *in situ*; and (II) more strictly, it means the achievement of no histological evidence of malignant tumors in the primary breast lesion or in metastatic regional lymph nodes, with or without the presence of carcinoma *in situ*.

For patients who have reached pCR after a full course of neoadjuvant therapy, the initial targeted therapy may continue in the postoperative adjuvant therapy. For patients who only use trastuzumab for neoadjuvant therapy, dual-targeted therapy can also be considered based on the outcomes of postoperative adjuvant therapy. Clinical studies have shown that the dual-targeted therapy with trastuzumab and pertuzumab is superior to trastuzumab alone. In the KATHERINE study (5), for patients who failed to achieve pCR after preoperative treatment with trastuzumab, adjuvant therapy with T-DM1 further improved the prognosis. However, so far there is no definite evidence that T-DM1 is superior to HP therapy; thus, subsequent treatments should be rationally selected in patients who fail to achieve pCR after dual-targeted neoadjuvant therapy: (I) if the tumor regression is obvious after a full course of treatment (e.g., Miller & Payne grades 3 and 4), continuing the use of dual-targeted therapy is preferred; and (II) if the tumor regression is not obvious (e.g., Miller & Payne grades 1 and 2), switching to T-DM1 may be a more feasible option.

In the ExteNET study (6), patients with stage II–III HER2-positive breast cancer started adjuvant treatment with oral neratinib for 1 year within 2 years of completing adjuvant trastuzumab. Compared with the placebo group, the neratinib group had significantly increased invasive disease-free survival (iDFS) rate. For patients who do not achieve pCR after neoadjuvant therapy, HP or T-DM1 is preferred in adjuvant targeted therapy. Sequential neratinib can be considered after the completion of adjuvant targeted therapy with HP; however, there is still a lack of direct data on whether sequential neratinib is feasible in patients who choose T-DM1 (*Table 2*).

Neoadjuvant treatment for triple-negative breast cancer (TNBC)

The treatment regimen and cycles are decided before neoadjuvant chemotherapy according to different treatment aims. In principle, in patients who respond to the combination of anthracycline and taxanes, the neoadjuvant chemotherapy should be completed as planned, and the timing and procedure of surgery should be discussed timely. However, the chemotherapy regimen may be changed for those operable patients who respond poorly to the neoadjuvant chemotherapy. For instance, some patients may respond poorly to AT, in whom NP may be applied

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Table 2 Recommendations of adjuvant therapy after neoadjuvant therapy

	Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Preoperative anti-HER2 treatment with trastuzumab alone	pCR	HP (2A)	Trastuzumab (1B)	–
	NonpCR	(I) T-DM1 (1B) (II) HP (2A)	–	Sequential neratinib after HP (2A)
Preoperative anti-HER2 treatment with trastuzumab and pertuzumab	pCR	HP (1A)	Trastuzumab (2B)	–
	NonpCR	(I) T-DM1 (1B) (II) HP (2A)	–	Sequential neratinib after HP (2A)

H, trastuzumab; P, pertuzumab; pCR, pathological complete response; nonpCR, non-pathological complete response.

Table 3 Recommendations of neoadjuvant therapy for triple negative breast cancer

Level I recommendations	Level II recommendations	Level III recommendations
(I) Combination of anthracycline and taxanes: (i) TAC (1A) (ii) AT (2A) (II) TP (2A)	(I) AC→T (2A) (II) AC→TP (2A) (III) Participates in rigorously-designed clinical trial	Chemotherapy combined with PD-1 inhibitors

T, taxene; A, anthracycline; C, cyclophosphamide; P, platinum.

instead. If the response to sequential treatment is still poor, the treatment strategy should be adjusted to seek surgical opportunities. For patients who do not reach pCR after completing neoadjuvant treatment, 6 to 8 cycles of capecitabine may be given after surgery.

The results of the neoCART study (7) showed that a 6-cycle TP regimen can further improve the pCR rate of neoadjuvant therapy in TNBC patients compared with an 8-cycle AC→T regimen; however, platinum-containing regimens are not routinely recommended due to the lack of data from phase III clinical trials. Nevertheless, platinum-containing regimens may be considered for young TNBC cancer patients with a family history of breast cancer, especially when there is a *BRCA* mutation.

The KEYNOTE 522 study (8) suggested that, in TNBC patients, the addition of PD-1 inhibitors on the basis of TP-AC in neoadjuvant therapy significantly increased the pCR rate, and the continued use of PD-1 inhibitors after surgery further improved the event-free survival (EFS) (*Table 3*).

In TNBC patients, subsequent therapy should be selected according to whether pCR is achieved after neoadjuvant therapy. According to the CREATE-X study, if pCR is not achieved after a full course of neoadjuvant chemotherapy, 6–8 cycles of capecitabine can be given after surgery; for patients with a *BRCA* mutation, treatment with olaparib can also be considered after neoadjuvant therapy (9).

PD-1 inhibitors are considered for adjuvant therapy only in patients who were treated with PD-1 inhibitors in neoadjuvant therapy. TNBC patients who have been treated with PD-1 inhibitors in neoadjuvant therapy can continue to use PD-1 inhibitors for a full year after surgery, regardless of whether they achieve pCR after surgery. Patients should be strictly monitored for adverse effects during the use of PD-1 inhibitors (*Table 4*).

Neoadjuvant endocrine therapy for hormone receptor-positive breast cancer

Preoperative endocrine therapy is feasible for the following populations: (I) patients who require preoperative treatment but are not suitable for chemotherapy; (II) patients who are temporarily unsuitable for surgery; and (III) hormone-dependent patients who do not need immediate surgery.

For postmenopausal hormone receptor-positive patients, the third-generation aromatase inhibitors (including anastrozole, letrozole, and exemestane) are recommended for neoadjuvant endocrine therapy; fulvestrant may be considered in some patients who are not suitable for aromatase inhibitors (e.g., with a bone density T-score

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Table 4 Recommendations of adjuvant therapy after neoadjuvant therapy

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
pCR	–	–	Continue the use of PD-1 inhibitors for a full year in patients who have been treated with PD-1 inhibitors during neoadjuvant therapy (2B)
nonpCR	Capecitabine (1A)	Olaparib (in the presence of a *BRCA* mutation) (1B)	Continue the use of PD-1 inhibitors for a full year in patients who have been treated with PD-1 inhibitors during neoadjuvant therapy (2B)

PCR, pathological complete response; nonpCR, non-pathological complete response.

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

Stratification	Level I recommendations	Level II recommendations
Postmenopausal	• AI (1A) • AI + CDK4/6 inhibitors (2A)	Fulvestrant (2B) (participates in rigorously-designed clinical trials)
Premenopausal	–	• OFS + AI (1A) • OFS + AI + CDK4/6 inhibitors (2B)

AI, aromatase inhibitor; OFS, ovarian function suppression.

of <–2.5). For premenopausal hormone receptor-positive patients, ovarian function suppression plus aromatase inhibitors may be applied. Some patients with locally advanced breast cancer requiring neoadjuvant endocrine therapy may be treated with endocrine therapy combined with CDK4/6 inhibitors or participate in clinical trials.

Generally, the response to preoperative endocrine therapy should be evaluated every 2 months. If the treatment is effective and tolerable, it can last for up to 6 months. Patients will undergo surgical treatment after the preoperative endocrine therapy is completed. Postoperative treatments are then chosen based on the postoperative pathology.

Few clinical studies have compared the values of preoperative endocrine therapy versus preoperative chemotherapy in premenopausal patients. In principle, preoperative endocrine therapy is not recommended for premenopausal patients (except for clinical studies) (*Table 5*).

Postoperative adjuvant treatment for breast cancer

Adjuvant treatment for HER2-positive breast cancer

As shown in the APHINITY study (10), compared with the trastuzumab-containing regimen, the dual-targeted therapy containing pertuzumab and trastuzumab reduced the risk of recurrence, especially in lymph node-positive patients. Therefore, for patients at high risk of recurrence, especially for patients with positive axillary lymph nodes, dual-targeted therapy with pertuzumab and trastuzumab is recommended. However, experts disagree that dual-targeted therapy should be considered in all patients who are suitable for single-targeted adjuvant therapy. For patients with negative axillary lymph nodes, other risk factors (e.g., large tumor size, negative ER status, histological grade 3, and high Ki-67 expression) should also be considered before an optimal treatment protocol is made. The NSABP B-31/-N9831 study (11) demonstrated that AC→TH was superior to conventional AC→T. The BCIRG006 study demonstrated that TCbH was also superior to AC→T and thus could be used as another option for adjuvant treatment. After a 10-year long-term follow-up, the study showed TCbH and AC→TH had similar long-term efficacy; however, the incidence of cardiac insufficiency was lower in the TCbH group. Therefore, TCbH may be selected for patients with higher requirement on cardiac safety.

Studies have shown that the 5-year risk of recurrence/metastasis in HER2-positive T1abN0M0 patients is more than 5 times that of HER2-negative patients. Therefore, 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 group of patients, chemotherapy can be further reduced on

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Table 6 Recommendations of initial adjuvant therapy for HER2 positive breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Positive axillary lymph nodes	• AC→THP (1A) • TCbHP (1A)	• AC→TH (2A) • TCbH (2A)	TC + H (2B)
Negative axillary lymph nodes, tumor sized >2 cm, and with high risk factors such as: (I) ER-negative; (II) high Ki67 expression	• AC→TH (2A) • TCbH (2A)	• AC→THP (2A) • TCbHP (2A)	TC + H (2B)
Negative axillary lymph nodes: tumor sized >2 cm but without other risk factors; or, tumor sized ≤2 cm	TC + H (2A)	TH (2B)	–
Positive hormone receptors and no chemotherapy is required; or, cannot tolerate chemotherapy	–	H + endocrine therapy (2A)	–

T, taxene; A, anthracycline; C, cyclophosphamide; Cb, carboplatin; H, trastuzumab; P, pertuzumab.

Table 7 Recommendations of intensive adjuvant therapy for HER2 positive breast cancer

Stratification	Level I recommendations	Level II recommendations
Positive lymph nodes and after adjuvant therapy with H	Sequential neratinib (1A)	–
Positive lymph nodes and after adjuvant therapy with HP	–	Sequential neratinib (2A)

H, trastuzumab; P, pertuzumab.

top of trastuzumab. Previous studies suggest that patients with early-stage breast cancer treated with TC + H had 2-year DFS and 2-year OS rates as high as 97.8% and 99.2% (12), and the APT study (13) suggested that patients with HER2-positive small tumors (≤3 cm) had a 3-year iDFS rate of 98.7% with the wTH regimen. Therefore, TC + H or wTH regimens may be considered for low-risk patients with T1N0 HER2-positive tumors (*Table 6*).

The ExteNET study (6) explored another anti-HER2 dual-targeted treatment strategy in patients with stage II–III HER2-positive breast cancer started adjuvant treatment with oral neratinib for 1 year within 2 years of completing adjuvant trastuzumab. Compared with the placebo group, the neratinib group had significantly increased iDFS rate. When intensive targeted therapy is required in HER2-positive patients, the indication for dual-targeted therapy should be considered first. For patients who have completed trastuzumab-based adjuvant therapy and whose disease has not progressed but have high-risk factors, sequential neratinib may be considered (*Table 7*).

As drugs such as trastuzumab and pertuzumab may increase cardiotoxicity, its concurrent use with anthracyclines is not recommended; however, these drugs can be used concurrently with adjuvant radiotherapy and adjuvant endocrine therapy. For hormone receptor-positive patients, endocrine therapy combined targeted therapy can be considered in low-risk patients who do not need chemotherapy or in patients who need chemotherapy but cannot tolerate it.

Adjuvant treatment for TNBC

Principles of adjuvant chemotherapy include: (I) 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 regimen. drugs, dosages, treatment cycles, and courses. (II) The selection, dosing, and application of chemotherapy drugs and the management of chemotherapy-associated toxicities are particularly complicated. Factors such as toxicity, individual differences, and comorbidities must be considered. A chemotherapy regimen may be selected according to the patient's risk, tolerance, and personal wishes as well as the background of a clinical trial. Meanwhile, a protocol for preventing nausea/vomiting and bone marrow suppression should be established. (III) Special attention should be paid to the order of administration, infusion time, and dose intensity of

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Table 8 Recommendations of initial adjuvant therapy for triple negative breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
In the presence of any of the following conditions: positive lymph nodes; tumor sized >2 cm	• AC→T 3 (1A) • ddAC-ddT (1A)	• TAC (1B) • TP (2A)	• FEC→T (2B) • AC→TP (2B)
Patients at low risk of recurrence: tumor sized ≤2 cm and with negative lymph nodes	• AC (1A) • TC ×4 (1A)	• AC→T (2A) • TC ×6 (2A)	–

T, taxene; A, anthracycline; C, cyclophosphamide; P, platinum; E, epirubicin; F, fluorouracil.

chemotherapy drugs during chemotherapy. The drug instructions and the incompatibility of drugs must be strictly followed. In general, do not reduce the number cycles in a standard chemotherapy regimen unless there are special circumstances.

For some patients with TNBC, if there are known *BRCA* mutations, platinum (e.g., cisplatin and carboplatin) may be added on top of anthracyclines and taxanes. Most experts believe that platinum should be considered in advance in neoadjuvant therapy for these patients. In the HR-negative subgroup, the AC→paclitaxel 3-week regimen achieved better DFS than AC adjuvant chemotherapy. Therefore, AC→T chemotherapy is currently recommended for patients at relatively high risk of recurrence.

The role of platinums in the adjuvant treatment of TNBC remains controversial. The PATTERN study (14) showed that platinum-containing regimens improved 5-year DFS by 6.2% (86.5% *vs.* 80.3%) and reduced the risk of recurrence by 35% compared with FEC→T regimens, and those with younger age and higher tumor grade were found to benefit more from platinum-based therapy in an exploratory subgroup analysis.

Some clinical studies have revealed that 4-cycle AC regimen, as a shorter and simpler treatment, was equivalent to CMF regimen in terms of efficacy; in addition, the toxicities were not significantly different between these two regimens. Thus, AC can be used as a basic regimen for some intermediate- and low-risk patients who require adjuvant chemotherapy.

The US9735 study (15) compared the efficacy of TC versus AC in the adjuvant chemotherapy of breast cancer. The proportions of intermediate- and low-risk patients were high in this study. It was found that TC brought improvements in DFS and overall survival (OS). Therefore, for some intermediate- and low-risk patients who require adjuvant chemotherapy, especially when there is a hidden risk of anthracycline cardiotoxicity, adjuvant chemotherapy with TC is also preferred.

The PLAN B study (16), a clinical trial evaluating the role of an adriamycin-free TC regimen versus conventional 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 disease-free survival (DFS) rate of 90%, meeting the expected non-inferiority criteria. 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 (*Table 8*).

The SYSUCC-001 study (17), a Chinese clinical research on the adjuvant treatment of early-stage TNBC, investigated the value of standard adjuvant chemotherapy followed by 1 year of capecitabine metronomic therapy. 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 (18) 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%. However, there are no approved indications for olaparib use in China. Therefore, the use of olaparib treatment should be cautious for patients with TNBC with BRCA1/2 mutations after completion of adjuvant therapy (*Table 9*).

Adjuvant endocrine therapy for hormone receptor-positive breast cancer

Adjuvant endocrine therapy is particularly important for HR (ER/PR)-positive breast cancer patients. For the

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Table 9 Recommendations of intensive adjuvant therapy for triple negative breast cancer

Stratification	Level I recommendations	Level II recommendations
In the presence of any of the following conditions: (I) positive lymph nodes; (II) tumor sized >2 cm		
Without *BRCA* mutations	–	Chemotherapy followed by sequential capecitabine for 1 year (2A)
With *BRCA* mutations	–	Chemotherapy followed by sequential olaparib for 1 year (1B)
Negative lymph nodes and tumor sized 1–2 cm	–	Chemotherapy followed by sequential capecitabine for 1 year (2B)

criteria of hormone receptor positive, please refer to the "Molecular typing". The biological behavior of weakly ER-positive breast cancer (with a positive rate of 1–9%) is similar to that of ER-negative breast cancer. Therefore, adjuvant chemotherapy should not be abandoned in these patients. After adjuvant chemotherapy is completed, adjuvant endocrine therapy can be considered as appropriate (19). However, for premenopausal breast cancer patients with an ER positivity of 1–9%, ovarian function suppression combined with oral endocrine drugs is not recommended. Concurrent adjuvant chemo-endocrine therapy is not recommended. Endocrine therapy may be started after the chemotherapy cycle is over. Radiotherapy and endocrine therapy can be carried out either sequentially or concurrently.

Ovarian function is a key indicator in the selection of adjuvant endocrine therapy. No matter whether the patient is receiving chemotherapy or not, the patient's menstrual status must be inquired before the commencement of systemic treatment, which helps to determine the patient's ovarian function status and informs the development of all-course adjuvant treatment regimen(s). Definition of menopause: menopause can be divided into natural menopause and artificial menopause. Generally, it refers to the permanent cessation of menstruation, which indicates that the estrogen synthesized by the ovaries continuously decreases. Women will be considered menopausal if they meet any of the following criteria:

(I) Bilateral oophorectomy;
(II) Age ≥60 years;
(III) Age <60 years; amenorrhea for 12 or more months; having not received chemotherapy, tamoxifen, toremifene, or ovarian suppression within the past 12 months; follicle-stimulating hormone (FSH) and estradiol levels within the postmenopausal range;
(IV) If taking tamoxifen or toremifene and age <60 years, FSH and plasma estradiol levels should be in post-menopausal range in two consecutive measurements.

Adjuvant endocrine therapy strategies for postmenopausal breast cancer patients

The 10-year follow-up data from the ATAC study showed that 5-year AI treatment significantly improved DFS and lowered the risk of recurrence compared to 5-year TAM treatment, which confirmed the role of AI as a standard regimen for adjuvant treatment of early breast cancer in postmenopausal patients. The BIG-198 study (20) validated the above results and further demonstrated that there was no significant difference in treatment response between 5-year TAM/AI switching strategy and AI 5-year therapy. Therefore, the 5-year AI therapy is recommended as the initial adjuvant endocrine therapy for postmenopausal patients; for patients having medical contraindications to AI use, TAM may be considered for initial adjuvant endocrine therapy.

The MA17 study (21) included patients whose initial adjuvant endocrine therapy was TAM, which was switched to AI after 2–5 years, and the total duration of adjuvant endocrine therapy was at least 5 years. The results of these studies confirmed the feasibility and effectiveness of switching to AI for 2–5 years after initial adjuvant treatment with TAM (for patients who were pre-menopausal upon the commencement of initial treatment and were then confirmed as postmenopausal during treatment or for patients who initially chose TAM after menopause) (*Table 10*).

According to the results of the BIG1-98 study, the switching strategy was more suitable for patients who could not tolerate the initial regimen. During the treatment with AI or TAM, patients should be instructed to properly deal with adverse drug reactions. Switch between AI and TAM if either drug cannot be tolerated. For instance, if AI cannot be tolerated during the initial treatment, TAM can be used instead.

The MonarchE study (22) included patients with 4 or more positive lymph nodes and patients with 1–3 positive

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Table 10 Recommendations of initial adjuvant endocrine therapy for HR positive postmenopausal breast cancer patients

Treatment phase	Level I recommendations	Level II recommendations	Level III recommendations
Patients at low risk of recurrence: (I) ≥4 positive lymph nodes (II) 1–3 positive lymph nodes but with other risk factors including: (i) G3 (ii) Tumor sized ≥5 cm (iii) Ki-67 ≥20%	(I) AI for 5 years + Abemaciclib for 2 years (1A) (II) AI for 5 years (2A)	(I) TAM for 5 years + abemaciclib for 2 years (II) Sequential TAM for 2–3 years sequential AI for 2–3 years (2A)	TAM for 5 years (2B)
Patients at low risk of recurrence: (I) Negative lymph nodes (II) 1–3 positive lymph nodes and meeting any of the following conditions (i) G1–2 (ii) Tumor sized <5 cm (iii) Ki-67 <20%	(I) AI for 5 years (1A) (II) Patients who initially receive tamoxifen as adjuvant therapy may switch to AI 5-year treatment during the treatment course (1A)	TAM for 2–3 years, sequential AI for 2–3 years (2A)	TAM for 5 years (2B)

AI, aromatase inhibitor; TAM, tamoxifen.

lymph nodes but with high-risk factors (histology grade 3, tumor sized ≥5 cm, and/or Ki67 ≥20%) and found that after completion of (neo)adjuvant chemotherapy, the addition of abemaciclib for 2 years on top of endocrine therapy further decreased the risk of recurrence, with a 2-year absolute survival benefit of 3.5%. Therefore, for the patient population eligible for the MonarchE study, the combination of 2-year abemaciclib on top of standard endocrine therapy may be feasible.

The initial adjuvant endocrine therapy with AI can be discontinued after 5 years of use in postmenopausal low-risk breast cancer patients. "Low risk" is defined as patients who meet all of the following conditions: postoperative pT ≤2 cm; G1; negative lymph nodes; without peritumoral vascular invasion; ER- and/or PR-positive; and HER2-negative. After initial 5 years of adjuvant AI therapy, if the patient tolerates it well and meets any of the following conditions, extending the endocrine therapy may be considered: (I) positive lymph nodes; (II) G3; (III) with other risk factors (e.g., Ki67 >30%) that require adjuvant chemotherapy.

As found in the MA17R study, patients received 5 additional years of AI after initial treatment with TAM for 3–5 years followed by 5 years of AI treatment (i.e., the duration of AI treatment reached 10 years), the risk of recurrence was further reduced compared to the placebo group. In the NSABP-B42 trial, it was found that in patients who had received 5 years of AI or in patients who had received 2.5 years of TAM and then switched to AI for 2.5 years, an additional 5 years of AI treatment significantly lowered the risk of breast cancer recurrence. These evidences supported the clinical application of extended AI therapy.

No randomized controlled trial has explored the role of 5 years of AI followed by 5 years of TAM or AI in postmenopausal patients. However, since some previous studies have demonstrated that switching to AI for another 5 years after 5 years of TAM treatment can be beneficial, switching to 5-year TAM treatment may be feasible in patients who require extended therapy but cannot tolerate AI treatment (*Table 11*).

Adjuvant endocrine therapy strategies for premenopausal breast cancer patients

The NATO and Stockholm studies have confirmed that, for patients who were HR-positive after surgery, adjuvant treatment with TAM for 5 years significantly prolonged DFS and OS compared with no endocrine therapy or TAM for 2 years. On the basis of the standard postoperative adjuvant treatment, the SOFT study (23) compared the efficacies between OFS + TAM and TAM alone for 5 years. During

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Table 11 Recommendations of intensive adjuvant endocrine therapy for HR positive postmenopausal breast cancer patients

Treatment phase	Level I recommendations	Level II recommendations
After initial 5 years of adjuvant AI therapy, if the patient tolerates it well and meets any of the following conditions, extending the endocrine therapy may be considered: (I) positive lymph nodes; (II) G3; (III) with other risk factors that require adjuvant chemotherapy	Continue the use of AI (2A)	Switch to TAM (2B)

AI, aromatase inhibitor; TAM, tamoxifen.

Table 12 Recommendations of initial adjuvant endocrine therapy for HR positive premenopausal breast cancer patients

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
≥4 positive lymph nodes	(I) OFS + AI for 5 years + abemaciclib for 2 years (1A)	(I) OFS + TAM + abemaciclib for 2 years (1B)	TAM for 5 years (2B)
	(II) OFS + AI for 5 years (2A)	(II) OFS + TAM for 5 years (2A)	
1–3 positive lymph nodes, along with one of the following risk factors: (I) G3; (II) Ki-67 ≥20%; (III) tumor sized ≥5 cm	(I) OFS + TAM for 5 years + abemaciclib for 2 years (1A)	(I) OFS + AI for 5 years + abemaciclib for 2 years (1B)	TAM for 5 years (2B)
	(II) OFS + TAM (2A)	(II) OFS + AI for 5 years (2A)	
1–3 positive lymph nodes but without other risk factors; or, negative lymph node but with one of the following risk factors: (I) G2 or G3; (II) tumor sized >2 cm; (III) high Ki-67 expression	OFS + TAM for 5 years (1A)	OFS + AI for 5 years (2A)	TAM (2B)
Negative lymph nodes and meeting any of the following conditions: (I) G1; (II) tumor sized ≤2 cm; (III) low Ki-67 expression	TAM for 5 years (1A)	–	–

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

the 8-year follow-up, the OFS combinations significantly prolonged the DFS of premenopausal patients, with the DFS benefit increased by 7% in the OFS + AI subgroup; compared with the TAM monotherapy group, the 8-year distant recurrence-free interval (DRFI) increased by 2.8% in the OFS + AI group. Most of the patients in the pre-designated postoperative non-adjuvant chemotherapy subgroup were lymph node negative, G1, and T <2 cm, and subgroup analysis showed that there was limited benefit from OFS plus endocrine therapy. Therefore, it is recommended that the basic strategy of postoperative adjuvant endocrine therapy for these patients is 5-year TAM treatment (*Table 12*).

Strategies used for ovarian suppression include drug-induced ovarian function suppression [e.g., GnRH agonists (GnRHa) such as goserelin and leuprolide] and surgery. Ovarian radiotherapy has been available but it is not routinely recommended. Be wary of the possibility of incomplete drug-induced ovarian function suppression; however, it is not recommended to routinely monitor hormone levels during the use of GnRHa.

The pre-set chemotherapy subgroup in the SOFT study and the analysis of the clinical characteristics of patients benefiting from chemotherapy combined with OFS in the 2007 meta-analysis of OFS showed that patients with positive lymph nodes, higher tumor grade [2–3] and large size (>2 cm) were more likely to benefit from the OFS combinations. 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 (24) 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.

No relevant research has been carried out in patients who are pre-menopausal at the time of initial treatment but will enter menopause within 2 to 3 years. The expert group proposes the following options for this population:

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Table 13 Recommendations of intensive adjuvant endocrine therapy for HR positive premenopausal breast cancer patients

Stratification	Level I recommendations	Level II recommendations
Patients who have completed the initial 5-year TAM treatment and require extended therapy	(I) Extended adjuvant TAM for up to 10 years in premenopausal patients (1A) (II) AI can be used sequentially for 5 years in patients whose menopause is confirmed (1A)	–
Patients who have completed the initial 5 years of OFS + TAM, and the therapy is well tolerated	Sequential AI treatment for menopausal patients for 5 years (2A)	Premenopausal patients treated with TAM for 5 years (2B)
Patients who have completed the initial 5 years of OFS + AI, and the therapy is well tolerated	3–5-year AI treatment for menopausal patients (2A)	Premenopausal patients treated with TAM for 5 years (2B) or OFS + AI for 5 years (2B)

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

(I) For patients with 4 or more positive lymph nodes or had a histological grade 3 tumor, ovariectomy followed by AI may be considered.
(II) For G2 patients with 1–3 positive lymph nodes, TAM can be selected as the initial adjuvant treatment, and 5-year AI can be used instead after menopause.

In the NSABP B-14 study, for ER-positive and lymph node-negative breast cancer patients, the 5-year TAM group showed no survival superiority over the 10-year TAM group. Two large randomized controlled trials [ATLAS (25) and aTTom] demonstrated that 10-year TAM was superior to 5-year TAM in lowering breast cancer recurrence rate. For patients who have already selected TAM for the initial treatment and have not yet entered menopause after 5 years of TAM treatment, it is recommended to extend the TAM treatment for another 5 years (up to 10 years) if such extension is required.

The risk of long-term recurrence persists even after 5 years of OFS combined with oral endocrine drugs. No study has explored the results of extended endocrine therapy in these patients, and no randomized controlled trial has compared the efficacies of the extended endocrine therapy following 5 years of OFS + endocrine drugs versus 10-year TAM treatment. Nevertheless, based on the evidence for the benefit of extended endocrine therapy, extended endocrine therapy can be recommended for patients who can tolerate it (*Table 13*).

Adjuvant radiotherapy after breast cancer surgery

According to BIG 3-07/TROG 07.01 study, the hypofractionated schedule and the conventional fractionated schedule were equivalent in terms of local-regional recurrence and DFS, and they had similar side effects of radiotherapy. The study defined intermediate-high risk as <50 or ≥50 years with one of the following conditions: palpable mass, multifocal, sized ≥1.5 cm, intermediate-high-grade lesions, central necrosis, comedo necrosis, and <10 mm from the cutting edge. Considering that the long-term efficacy and safety of hypofractionated radiotherapy regimen in invasive carcinomas have been widely recognized and from the perspective of saving medical resources and increasing the affordability, the experts make equal recommendations for the conventional fractionated radiotherapy regimen and the hypofractionated radiotherapy regimen for WBI of ductal carcinoma in situ (DCIS).

Postoperative WBI can reduce the risk of recurrence of DCIS and invasive carcinoma by about 50% in DCIS patients. In addition, retrospective studies have confirmed that many polygenic models including DCISionRT, Rst, and DCIS Score can accurately distinguish the risk of local recurrence after breast-conserving surgery for DCIS, and patients with a low polygenic risk score have limited benefits from radiotherapy. However, there is still a lack of high-level evidence to guide radiotherapy decisions based on polygenic scores. We encourage DCIS patients to receive assessment using polygenic risk score models on top of a variety of clinicopathological prognostic factors including age, histological grade, and resection margins. Among estrogen receptor-positive intraductal carcinoma patients who are receiving endocrine therapy, postoperative radiotherapy may be omitted in DCIS patients with low risk of recurrence or in patients with contraindications to radiotherapy after a thorough consideration of the risks and benefits of radiotherapy and adequate communication with the patients or their

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Table 14 Recommendations of adjuvant radiotherapy for patients after breast-conserving surgery

Stratification	Level I recommendations	Level II recommendations
DCIS	WBI ± tumor bed boost (2B)	APBI (2A)
Invasive carcinoma (negative axillary lymph nodes)	WBI (1A) ± tumor bed boost (1B)	(I) APBI (2A) (II) Whole-breast one-week hyperfractionated schedule (2A) (III) WBI ± tumor bed boost + regional lymph node radiotherapy (2B)
Positive axillary lymph nodes, with axillary lymph node dissection	WBI ± tumor bed boost + regional lymph node radiotherapy (1B)	WBI ± tumor bed boost (2B)
1–2 positive sentinel lymph nodes, without axillary lymph node dissection	WBI + tumor bed boost (1A)	WBI + tumor bed boost + regional lymph node radiotherapy (including axilla) (2B)
≥3 positive sentinel lymph nodes, without axillary lymph node dissection	–	WBI + tumor bed boost + regional lymph node radiotherapy (including axilla) (2B)

DCIS, ductal carcinoma in situ; WBI, whole breast irradiation; APBI, accelerated partial breast irradiation.

families (*Table 14*).

The long-term follow-up in clinical studies have confirmed that postoperative radiotherapy still has the advantage of higher local control rate over endocrine therapy alone in elderly patients who are ≥70 years, with a stage of T1N0M0, and being HR-positive and HER2-negative, although it did not affect OS and DFS in these patients. With the availability of more novel polygenic prediction models, radiotherapy regimens for patients with early-stage low-risk breast cancer can be selected in a more precise manner. For patients meeting the inclusion criteria in the above study, postoperative radiotherapy may be avoided or reduced on top of endocrine therapy after a thorough consideration of the risks and benefits of radiotherapy and adequate communication with the patients or their families.

For patients who only require WBI on the affected breast, the recommended WBI radiotherapy includes: conventional fractionation: 6 Gy/8 fractions; or, hypofractionation: 40–42.5 Gy/15–16 fractions. While these two schedules are equally effective and have comparable cosmetic effects and side effects, the hypofractionated radiotherapy can save medical resources and lower the medical expenditure. Thus, the hypofractionated radiotherapy is recommended as the preferred schedule.

Accelerated partial breast irradiation (APBI): patients may be selected according to the American Society for Radiation Oncology (ASTRO) recommendations (26). IMRT or interstitial brachytherapy may be applied for APBI, with IMRT being the preferred technique for external irradiation. The recommended fractionation regimens include: 38.5 Gy/10 fractions, twice daily; or, 30 Gy/(5 fractions × 2 weeks). However, the minimum and most effective doses for APBI need to be further investigated. APBI-OPAR, the first published head-to-head comparison of two dose gradients of ABPI, enrolled patients with either DCIS or invasive breast cancer; during the 4-year follow-up, the cosmetic effect of the 5.5 or 6.0 Gy/fraction, qd ×5 treatment modality was significantly better than that in the RAPID study but inferior to that in the APBI-IMRT-Florence study. However, the prognostic efficacy of this modality needs to be further explored in long-term follow-up. We encourage eligible patients to actively participate in prospective clinical studies exploring the APBI fractionation modalities in China and abroad.

Regional lymph node radiation: in patients who have received complete axillary lymph node dissection (basically defined as axillary lymph node dissection at stations 1 and 2), the regional lymph node dissection typically includes the supraclavicular/subclavian areas on the affected side and the Internal mammary lymph nodes (between the first and the third intercostal spaces).

According to the FAST-FORWARD study (27), the hyperfractionated breast radiotherapy (26 Gy in 5 fractions over 1 week) was non-inferior to the hypofractionated regimen (40 Gy in 15 fractions over 3 weeks) in terms of the 5-year risk of ipsilateral intramammary recurrence and radiotherapy side effects. Since a shortened treatment course has many benefits including higher efficiency of medical resources utilization, increased accessibility of radiotherapy,

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Table 15 Recommendations of adjuvant radiotherapy for patients after mastectomy

Stratification	Level I recommendations	Level II recommendations
After axillary lymph node dissection, patients meet any of the following conditions: (I) T3–4; (II) positive axillary lymph nodes	Chest wall radiotherapy + regional lymph node radiotherapy (1–2A)	–
Positive sentinel lymph nodes, without axillary lymph node dissection	Chest wall radiotherapy + regional lymph node radiotherapy (including axilla) (2B)	–

and reduced patient burden, our current guidelines recommend that the hyperfractionated radiotherapy (26 Gy in 5 fractions over 1 week) be considered for patients who meet the enrollment criteria of the FAST-FORWARD study. The target dose should be carefully assessed and the organ-threatening dose strictly limited when using a one-week regimen, with reference to the FAST-FORWARD study protocol: PTV: D95% >95% of the prescribed dose, D5% <105% of the prescribed dose, D2% <107% of the prescribed dose, and maximum dose <110% of the prescribed dose; ipsilateral lung: V8Gy <15%; heart: V1.5Gy <30% and V7Gy <5%. Notably, this dosage covers only the whole breast and needs to be tailored based on individual risk of recurrence. For patients requiring a tumor bed boost, additional dose may be delivered according to the FAST-FORWARD study protocol.

The indications of postoperative radiotherapy after breast reconstruction should follow those after mastectomy for patients in the same stage. The complication rate after autologous reconstruction is lower than that after prosthetic reconstruction. For patients undergoing two-step tissue expander/implant (TE/I), whether the replacement of the tissue expander by a permanent breast implant should be done before or after postoperative radiotherapy remain controversial, depending on the skills and experience of the multidisciplinary team (*Table 15*).

In patients receiving combined regional lymph node radiotherapy, the recommended dose of the postoperative adjuvant radiotherapy for whole breast/chest wall irradiation at the affected and for irradiation of regional lymph node areas remains 50 Gy/25 fractions, and a tumor bed boost of 10–16 Gy/5–8 fractions is required for patients after breast-conserving surgery. A single-center prospective phase III trial in China has confirmed that postoperative hypofractionated radiotherapy (including supraclavicular lymph nodes and chest wall) can achieve similar efficacy as conventional fractionated radiotherapy in breast cancer patients after mastectomy (28). As more evidence has demonstrated the radiobiological equivalence of hypofractionated regimens to conventional fractionated regimens, our current guidelines recommend that combined regional lymph node hypofractionated radiotherapy regimens, preferably with precision radiotherapy techniques including IMRT, may be considered under the premise of strictly limiting the organ-threatening dose and ensuring dose coverage and dose uniformity in the target area. When the equivalent uniform dose (EUD) is calculated, tumor control probability (TCP) and normal tissue complication probability (NTCP, which is more complicated) should also be considered. This guideline also encourages patients to actively participate in prospective clinical studies on the regional lymph node hypofractionated radiotherapy on top of precision radiotherapy techniques.

Salvage treatment for advanced breast cancer

Salvage treatment for HER2-positive breast cancer

Trastuzumab-sensitive populations include: (I) trastuzumab-naïve; (II) showing response to neoadjuvant therapy; (II) having recurrence 1 year after the end of adjuvant therapy; and (IV) drug withdrawal after effective salvage treatment. For these patients, trastuzumab-based therapy is preferred. A reasonable combination treatment protocol should be selected according to the patient's HR status and the previous neoadjuvant/adjuvant therapies.

The CLEOPATRA study (29) confirmed that the combination of docetaxel with dual-targeted therapy with pertuzumab and trastuzumab was more effective than the combination of docetaxel with single-targeted therapy with trastuzumab in prolonging PFS And OS. Thus, the combination of docetaxel with dual-targeted therapy with pertuzumab and trastuzumab has become the preferred treatment for HER2 positive patients failing to respond to trastuzumab and taxanes. The CHAT study confirmed that, for patients who could tolerate dual-drug chemotherapy, trastuzumab combined with docetaxel

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Table 16 Recommendations of salvage treatment for HER2-positive breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Trastuzumab-sensitive	(I) THP (1A)	(I) H + chemotherapy (2A) (chemotherapy includes: taxanes, vinorelbine, and capecitabine)	H + P + other chemotherapy drugs (2B)
	(II) TXH (2A)	(II) Pyrotinib + capecitabine (2A)	
Trastuzumab-resistant	(I) Pyrotinib + capecitabine (1A)	(I) T-Dxd (1A)	(I) Neratinib + capecitabine (2A)
	(II) T-DM1 (1B)		(II) Lapatinib + capecitabine (2B)
			(III) TKI combined with other chemotherapy drugs (2B)
			(IV) HP combined with other chemotherapy drugs (2B)
			(V) Margetuximab + chemotherapy (2B)
TKI-resistant	–	(I) Anti-HER2 antibody-drug conjugates (ADCs) (e.g., T-Dxd and T-DM1) (2A)	Other unused anti-HER2-targeted agents
		(II) HP combined with other chemotherapy drugs (2A)	
		(III) Another TKI + chemotherapy (2A)	
		(IV) Rigorously-designed clinical trial	

T, taxene; X, capecitabine; H, trastuzumab; P, pertuzumab; TKI, tyrosine kinase inhibitor.

plus capecitabine was more efficient than trastuzumab combined with docetaxel, especially in patients requiring maintenance treatment (30). Trastuzumab may also be combined with capecitabine in patients who failed the taxane treatment (*Table 16*).

According to the PHENIX study (31), 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. Similarly, the PHOEBE study (32) showed that in MBC patients who have previously received trastuzumab, paclitaxel, and/or anthracycline, pyrotinib combined with capecitabine achieved better PFS than lapatinib combined with capecitabine. Therefore, the experts recommend pyrotinib combined with capecitabine for the treatment of patients who have failed to respond to trastuzumab and taxanes.

According to the NALA study (33), neratinib in combination with capecitabine significantly prolonged PFS compared with lapatinib in combination with capecitabine in patients with metastatic HER2-positive breast cancer who had received ≥2 prior targeted therapies, making it one of the current options after the failure of multiple lines of anti-HER2 therapy.

The SOPHIA study (34) included patients with advanced breast cancer who had received at least two prior lines of anti-HER2-targeted therapy but no more than three total lines. All subjects had previously received trastuzumab and pertuzumab, and approximately 90% had received prior T-DM1 therapy. The results showed that patients receiving margetuximab and chemotherapy had a median increase of 1.8 months in OS compared to those receiving trastuzumab and chemotherapy (21.6 *vs.* 19.8 months). Among the approximately 85% of patients carrying a CD16A 158F allele, the median OS was prolonged by 4.3 months in the margetuximab arm (23.7 *vs.* 19.4 months).

The results of the HER2CLIMB study (35) showed that in patients with locally advanced unresectable or metastatic HER2-positive breast cancer, the tucatinib plus X regimen demonstrated superior efficacy (a significant 46% reduction in the risk of disease progression or death and a 34% reduction in the risk of death) compared with the trastuzumab plus capecitabine (XH) regimen. In this trial, 47% of patients had brain metastases at study entry.

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For these patients, tucatinib further improved PFS and significantly reduced the risk of disease progression or death by 52%.

According to the DESTINY-Breast03 study (36), T-Dxd significantly improved PFS and reduced the risk of disease progression or death by 72% compared to T-DM1 after trastuzumab treatment failure; thus, T-Dxd has become a new standard second-line treatment after trastuzumab failure. Anti-HER2 ADCs have shown notable clinical benefits in MBC patients, especially in second-line or above settings. Although T-Dxd is not yet available in China, patients are encouraged to actively participate in domestic and international clinical trials of ADCs.

Subsequent targeted therapy after TKI failure still lacks the support of high-quality clinical trials. According to real-world data and expert opinions, it is recommended that the decision-making should be based on the previous treatments, with currently available options including T-DM1, H + P dual-targeted therapy plus other chemotherapy, T-Dxd, and switching to another TKI (37).

Anti-HER2 monoclonal antibodies (H) include trastuzumab, biosimilar medications, and inetetamab, which have been available in China.

TKIs include pyrotinib, lapatinib, neratinib, and tucatinib.

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 objective response rate 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, vinorelbine, liposomal doxorubicin, and liposomal paclitaxel.

There is currently no standard chemotherapy regimen for patients with recurrent/metastatic breast cancer who have failed preoperative/adjuvant treatments with anthracyclines and taxanes. The optional drugs may include capecitabine, vinorelbine, gemcitabine, platinum, eribulin, UTD1, another type of taxane (e.g., albumin paclitaxel), and liposomal doxorubicin. Either single-agent or combination regimens can be considered.

Taxanes (anthracyclines) failure is defined as disease progression during the salvage treatment with taxanes (anthracyclines) (after at least two cycles) or tumor recurrence/metastasis within 12 months after completing the adjuvant therapy. Patients who are feasible for re-treatment with taxanes include: (I) showing response to taxane-based neoadjuvant therapy; (II) experiencing recurrence one year after the end of taxane-based adjuvant therapy; and (III) drug withdrawal after effective salvage treatment with taxanes (*Table 17*).

In the KEYNOTE-355 study (38), chemotherapy combined with a PD-1 inhibitor significantly improved PFS compared with chemotherapy alone in patients whose tumors expressed PD-L1 and had a combined positive score (CPS) of ≥10, suggesting the potential role of immune checkpoint inhibitors in the treatment of TNBC. However, different studies had different drug combinations, target populations, and predictors, and immune checkpoint inhibitors are not currently approved to treat breast cancer in China. Therefore, the expert group encourages patients to actively participate in clinical studies but reminds that caution must be exercised when using these drugs in clinical settings.

The OlympiAD study (39) showed that, for patients with HER2-negative advanced breast cancer with *BRCA 1/2* germline mutations, olaparib significantly prolonged PFS (7 *vs.* 4.2 months, compared with chemotherapy). Therefore, the expert group generally agrees that patients with *BRCA1/2* germline mutations can receive treatment with olaparib or actively participate in relevant clinical trials.

The 304 study (24) showed that for patients with advanced breast cancer for whom anthracyclines and taxanes have failed, eribulin was superior to vinorelbine in prolonging PFS and increasing ORR, with similar incidence of adverse events. Thus, eribulin has become a new option after anthracycline and taxane failure in patients with advanced breast carcinoma.

The BG01-1312L study (40) showed that for patients with advanced breast cancer for whom anthracyclines and taxanes have failed, UTD1 combined with capecitabine was superior to capecitabine alone in prolonging PFS and OS,

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Table 17 Recommendations of salvage treatment for triple negative breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Taxanes-sensitive	(I) Taxane monotherapy	(I) Monotherapy	(I) Olaparib[#] (2A)
	• Albumin paclitaxel (1A)	• Capecitabine (2A)	(II) Liposomal paclitaxel (2A)
	• Docetaxel (2A)	• Vinorelbine (2A)	(III) Liposomal doxorubicin (2B)
	• Paclitaxel (2A)	• Gemcitabine (2A)	(IV) Chemotherapy + PD-1 inhibitors (2B)
	(II) Combination therapy	• Etoposide (2B)	
	• TX (1A)	(II) Combination therapy	
	• GT (1A)	• Albumin paclitaxel + PD-1 inhibitor (2A)	
	• TP (2A)	• Taxanes + bevacizumab (2B)	
Taxanes failure	(I) Monotherapy	(I) Monotherapy	(I) Olaparib[#] (2A)
	• Eribulin (1A)	• Albumin paclitaxel* (2A)	(II) Liposomal doxorubicin (2B)
	• Vinorelbine (2A)	• Sacituzumab govitecan (2A)	(III) Liposomal paclitaxel (2B)
	• Gemcitabine (2A)	• Etoposide (2B)	(IV) Chemotherapy + PD-1 inhibitors (2B)
	• Capecitabine (2A)	(II) Combination therapy	
	(II) Combination therapy	• Capecitabine + bevacizumab (2B)	
	• NP (1A)	• Albumin paclitaxel + other chemotherapy drugs (2B)	
	• GP (1A)		
	• NX (2A)		
	• Utidelone + capecitabine (2A)		

*, consider switching to albumin paclitaxel if docetaxel or paclitaxel fails; [#], recommended in the presence of BRCA1/2 mutations. T, taxene; G, gemcitabine; N, vinorelbine; X, capecitabine; P, platinum.

which offered a new treatment chance after anthracycline and taxane failure in patients with advanced breast carcinoma.

In the ASCENT study (41), patients with advanced TNBC who had received prior second- or later-line chemotherapy were randomized to receive sacituzumab govitecan-hziy or single-agent chemotherapy (including capecitabine, eribulin, vinorelbine, or gemcitabine, upon the investigator's choice), respectively. It was found that sacituzumab govitecan-hziy 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. In April 2020, the US Food and Drug Administration (FDA) granted accelerated approval to sacituzumab govitecan for adult patients with metastatic TNBC. Thus, the new anti-Trop-2 ADC brings additional treatment options to patients with advanced TNBC.

It is extremely difficult to cure a recurrent/metastatic breast cancer. A more realistic strategy is to prolong survival via less radical treatments. The optimal first-line treatments may include endocrine therapy and chemotherapy (or combined with molecularly-targeted therapy). Rational maintenance treatment may be considered in patients who have exhibited good therapeutic response. For patients who respond well to a given combination chemotherapy regimen but cannot tolerate the combined therapy due to severe adverse reactions, use of a single agent in the initial therapy for maintenance treatment may be considered to maximize disease control. An ideal maintenance chemotherapy protocol should be an effective single-agent therapy (e.g., oral chemotherapy drugs such as capecitabine and vinorelbine) that is relatively low-toxic and convenient for long-term use. HR-positive patients can also choose endocrine therapy for maintenance.

For patients with recurrent/metastatic breast cancer, if there is no response after three consecutive chemotherapy regimens or if the patient's ECOG performance status

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score is ≥3, chemotherapy is no longer recommended and gentle endocrine therapy and molecularly-targeted therapy can be considered. Alternately, only the best supportive care can be offered; or, the patients may be encouraged to participate in clinical trials. Here "no response" refers to that the patient has never obtained any benefit (or even remission) from a specific chemotherapy regimen. It does not include cases that remission has been obtained after chemotherapy but disease progression occurs after drug discontinuation.

Savage therapy for HR-positive advanced breast cancer

The previous treatment regimen and disease burden must be considered when selecting a first-line endocrine therapy for recurrent and metastatic breast cancer. Endocrine therapy should be continued as possible in patients who have benefited from the treatment until disease progresses; however, the tolerance to long-term drug use should also be assessed. In principle, a combination of endocrine therapy and chemotherapy is not recommended. For HR-positive/HER2-positive patients who are not suitable for salvage chemotherapy, endocrine combined with HER2-targeted therapy may be considered as the first-line treatment. In the first-line endocrine therapy for advanced breast cancer, the third-generation AIs achieved significantly longer PFS and higher ORR compared with TAM. For postmenopausal, HR-positive patients who have not received endocrine therapy or those who have failed adjuvant endocrine therapy with TAM, the third-generation AIs are recommended as the first-line endocrine therapy. In the PALOMA-2 study (42), compared with letrozole monotherapy, letrozole combined with a CDK4/6 inhibitor (palbociclib) significantly prolonged PFS; notably, about 43% of the subjects were endocrine therapy-naive, and about 47% had received adjuvant TAM treatment.

According to the PALOMA-3 study (43), in patients experiencing PD despite prior endocrine therapy (with AI or TAM), including patients with PD during adjuvant endocrine therapy or within 12 months after stopping treatment or those who experiencing PD during endocrine therapy for tumor relapse and metastasis, the combination of palbociclib with fulvestrant significantly prolonged PFS compared with fulvestrant alone, although the improvement in OS was not statistically significant; in the subgroup with sensitivity to previous endocrine therapy, however, the OS was significantly prolonged by 10 months. Approximately 70% of patients in the MONARCH2 study (44) experienced PD after AI therapy, and the findings confirmed that abemaciclib in combination with fulvestrant significantly prolonged PFS compared with fulvestrant alone. The MONARCHplus study (45), which included two groups of patients who failed TAM or AI treatment, showed that abemaciclib in combination with either non-steroidal AI or fulvestrant significantly improved PFS and ORR. Accordingly, NMPA has approved the use of abemaciclib in combination with AI as the first-line endocrine therapy in postmenopausal BC patients and also approved the combination of abemaciclib with fulvestrant for patients experiencing disease progression after previous endocrine therapy. The DAWNA-1 study (46) enrolled 361 patients (from 39 centers) with HR-positive/HER2-negative advanced breast cancer after failure of endocrine therapy. These subjects were randomized 2:1 to receive dalpiciclib plus fulvestrant or placebo plus fulvestrant. The investigator-assessed PFS was 8.5 months longer in the dalpiciclib plus fulvestrant group, along with a 58% reduction in the risk of disease progression or death. Therefore, dalpiciclib plus fulvestrant has been approved for use as a treatment option after AI failure. Clinical studies have demonstrated the value of CDK4/6 inhibitors combined with endocrine therapy in treating HR-positive advanced breast cancer; however, the mechanism of action, dosage, indications, and adverse effects are not completely consistent across different CDK 4/6 inhibitors. Thus, CDK 4/6 inhibitors and their combinations need to be selected rationally according to the included population of clinical studies and the specific conditions of patients.

In the ACE study (47), for postmenopausal HR-positive/HER2-negative advanced breast cancer patients who had previously failed tamoxifen and/or non-steroidal AI treatment, the combination of HDAC inhibitor chidamide with exemestane significantly prolonged PFS (7.4 *vs.* 3.8 months, versus exemestane); also, it was superior to exemestane in terms of ORR and clinical benefit rate. Chidamide has been approved in China for the indication of breast cancer. The expert group recommends that chidamide combined with AI can be used in advanced breast cancer patients who have failed on previous endocrine treatment (*Table 18*).

AIs can be used in patients who experience recurrence more than 12 months after end of adjuvant AI therapy. For patients with recurrence ≤12 months after end of adjuvant treatment or progression after first-line endocrine therapy with AI, use of another AI with different mechanism of action (e.g., switch a non-steroidal AI with a steroidal AI) may be helpful, which, however, has not been investigated

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Table 18 Recommendations of salvage endocrine treatment for HR positive breast cancer

Stratification	Level I recommendations	Level II recommendations	Level III recommendations
Without endocrine therapy	(I) AI + abemaciclib (1A)	(I) AI (1A)	TAM (2B)
	(II) AI+ palbociclib (1A)	(II) Fulvestrant (2A)	
		(III) Fulvestrant + CDK4/6 inhibitors (2A)	
TAM failure	(I) AI + abemaciclib (1A)	(I) AI (2A)	
	(II) AI + chidamide (1A)	(II) Fulvestrant (2A)	
	(III) AI + palbociclib (1B)	(III) Fulvestrant + CDK4/6 inhibitors (1B)	
Non-steroidal AI failure	(I) Fulvestrant + abemaciclib (1A)	(I) Steroid AI + CDK4/6 inhibitor (2A)	(I) Steroidal AI (2B)
	(II) Steroidal AI + chidamide (1A)	(II) Fulvestrant (2A)	(II) Fulvestrant + steroidal AI
	(III) Fulvestrant + dalpiciclib (2A)	(III) Steroid AI + everolimus (IB)	(III) TAM or toremifene (2B)
	(IV) Fulvestrant + palbociclib (1B)		(IV) Progesterone (2B)
Steroidal AI failure	(I) Fulvestrant + abemaciclib (1A)	(I) Fulvestrant (2A)	(I) Non-steroidal AI (2B)
	(II) Fulvestrant + dalpiciclib (2A)	(II) Non-steroid AI + CDK4/6 inhibitor (2A)	(II) TAM or toremifene (2B)
	(III) Fulvestrant + palbociclib (1B)		(III) Progesterone (2B)
CKD4/6 inhibitor failure	–	(I) Chidamide + ET (2A)	(I) Progesterone (2B)
		(II) Another CDK4/6 inhibitor + ET (2A)	(II) Toremifene (2B)
		(III) Participates in rigorously-designed clinical trial	

AI, artificial intelligence; TAM, tamoxifen; ET, endocrine therapy.

in large randomized controlled clinical studies. Drugs should be reasonably selected based on the patients' general conditions and the availability of drugs in China. If the disease progresses despite AI treatment, other drugs including progesterone (medroxyprogesterone or megestrol), toremifene, and TAM may also be used in the endocrine therapy for advanced breast cancer. Although there are no relevant evidences from large randomized controlled clinical studies, these drugs may be reasonably selected based on the patients' general conditions and the availability of drugs in China.

Breast cancer bone metastasis

Bone emission computed tomography (ECT) and other examinations should be performed to identify any possible bone metastasis in breast cancer patients who suffer from symptoms such as bone pain or have any of the following conditions: (I) hypercalcemia, elevated alkaline phosphatase, and elevated lactate dehydrogenase; (II) abnormally elevated tumor markers (e.g., CEA and CA153); and/or (III) suspicious bone metastasis on other imaging modalities (1). However, abnormal tracer uptake on bone scan cannot ensure the diagnosis of bone metastases. ECT is recommended for the routine screening of breast cancer patients with suspicious bone metastasis symptoms including bone pain, pathologic fracture, increased alkaline phosphatase level, and hypercalcemia. It can also be used for routine examinations in patients with locally advanced breast cancer (above T3N1M0) and/or recurrent/metastatic breast cancer. If ECT reveals abnormal tracer uptake, CT using a bone window setting should be performed. If the original osteolytic lesion is transformed into bone calcification and the newly added lesions also show bone calcification, the treatment should be evaluated as effective. If the newly added lesions with increased tracer uptake exhibit the appearance of osteolytic lesions, it can be evaluated as "PD". Magnetic resonance imaging (MRI) is more sensitive but less specific than CT. MRI has definite advantages over CT in identifying neurovascular compression, vertebral body

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Table 19 Recommendations of bone modifying agents for breast cancer

Level I recommendations	Level II recommendations	Level III recommendations
Zoledronic acid (1A); denosumab (1A); ibandronic acid (2A)	Loading-dose ibandronic acid (2A); pamidronate disodium (1B)	Clodronate disodium (2B)

involvement, and spinal stability. It is an important tool for deciding the appropriateness of surgery and radiotherapy for bone metastases. However, abnormal MRI findings alone is not sufficient to make a diagnosis of bone metastasis, which should be based on other examinations/tests. Pathological examination of bone biopsy samples can help diagnose breast cancer bone metastases. For clinically suspicious bone metastases, especially in patients with a single bone lesion, bone biopsy should be performed to confirm the diagnosis. PET-CT is highly sensitive and specific in detecting the abnormal signals of breast cancer bone metastasis. However, the value of PET/CT in diagnosing bone metastasis still requires further investigations. Currently, it is not routinely recommended in clinical settings.

Clinically, skeletal-related events (SREs) include pathological fractures (vertebral fractures, non-vertebral fractures, and compression or deformation of the vertebral body), spinal cord compression, bone radiotherapy (for bone pain or for the prevention/treatment of pathological fractures or spinal cord compression), and bone surgery. SREs such as bone pain and bone injury are common complications of breast cancer bone metastasis and can seriously undermine quality of life. Among them, spinal cord compression is a cancer-related emergency requiring multidisciplinary consultations (including the inputs of orthopedic experts). Corticosteroids and dehydration treatment should be applied to promptly relieve the compression and reduce the limb dysfunction and even paraplegia caused by spinal cord compression (see Expert Consensus on Breast Cancer Bone Metastasis) (48) (*Table 19*).

The main goals of treatment for breast cancer bone metastases are to prevent and treat bone-related events, relieve pain, restore function, improve quality of life, control tumor progression, and prolong survival. The treatment of breast cancer bone metastasis should be based on systemic therapies including chemotherapy, endocrine therapy, molecularly targeted therapy, and immunotherapy. Factors affecting the choice of systemic treatment include: (I) the HR status and HER2 status; (II) age and menstrual status; and (III) whether the disease progresses slowly. Breast cancer bone metastasis generally is not directly life-threatening. Endocrine therapy is preferred in patients with HR-positive tumors that progress slowly and show no primary endocrine resistance. For patients with ER- and PR-negative tumors, short postoperative DFI, rapid disease progression, or HR-positive tumors and with primary endocrine resistance, single-agent chemotherapy is preferred in patients with a single bone metastasis or asymptomatic visceral metastasis, whereas combination chemotherapy should only be considered for patients with bone metastases requiring rapid symptom control or those with symptomatic visceral metastases. For patients with HER2-positive bone metastases, the treatment principle is the same as that for patients with metastases to other sites—combination with an HER2-targeted therapy is preferred.

The purposes of surgical treatment are to improve the patients' quality of life by resolving nerve compression, alleviating pain, and restoring limb functions. Patients with bone metastasis must be closely followed up. A proper decision-making on the surgery on the long bones with potentially pathological fractures is critically important to improve the patients' quality of life if an effective surgical treatment is performed before fracture and/or before spinal cord compression. Surgical procedures for breast cancer bone metastases include simple internal fixation, debridement plus internal fixation, lesion resection plus artificial joint replacement, decompression after spinal cord compression, and reconstruction for increasing spinal stability. Fixation can be selectively applied for pathological fracture or spinal cord compression, especially in breast cancer bone metastasis patients with an expected survival time of >3 months. Prophylactic fixation can be selectively applied in breast cancer bone metastasis patients meeting one or more of the following criteria: femoral metastasis sized >2.5 cm; metastasis to the neck of femur bone; bone cortical destruction >50%% and/or with an expected survival time of >3 months. After the bone metastases have been with multidisciplinary treatments, orthopedists should be timely consulted to determine the timing of surgery. Mirels classification is useful for assessing the risk of pathological fracture of long bones and determining the surgical indications.

The main purposes of radiotherapy in patients with breast cancer bone metastasis is to relieve bone pain and reduce

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the risk of pathological fractures. Its combinations with bone-modifying agents or molecularly-targeted antitumor agents can effectively improve the treatment effectiveness. Radiotherapy includes external-beam irradiation and radionuclide therapy. External-beam irradiation is a common effective method during the palliative therapy for bone metastases. The main indications of external-beam irradiation include: symptomatic bone metastases, for which the treatment is to alleviate pain and restore functions; and, selectively used for the prophylactic radiotherapy of metastasis to weight-bearing bones (e.g., spine and femur); and palliative radiotherapy after simple internal fixation, decompression, and reconstruction of spinal stability. The doses of external-beam irradiation include 40 Gy/20 fractions, 20 Gy/5 fractions, and 8 Gy/fraction. These doses have comparable efficacy in acute analgesia, and pain relief can be achieved for 23–35 weeks, although the dose of 8 Gy/session has a relatively high re-treatment rate. Clinically, appropriate radiotherapy fractionation should be selected according to the expected survival time and the tolerance dose of normal tissues related to the metastases. Single 8 Gy fraction is recommended for palliative radiotherapy in patients with limited life expectancy. Effective external-beam irradiation can achieve symptom relief in 50–80% of bone metastasis patients and achieve complete response in approximately 1/3 of patients; notably, such effect can last a long period of time. Stereotactic radiotherapy (SRT) has been increasingly used in bone metastases, with the advantage of providing a steep dose falloff around the target, which ensures the sparing of the normal tissue and/or the critical structures near the target. With the main indication being spinal metastatic lesions, SRT is more advantageous for patients with recurrent symptoms that require retreatment. Radionuclide therapy is useful in easing diffuse pain due to bone metastasis; however, in some patients, radionuclide therapy may result in high incidence of bone marrow suppression, which can only be restored slowly (about 12 weeks) and thus affect the implementation of chemotherapy. Therefore, the clinical use of radionuclide therapy should only be performed in carefully selected cases at the right time.

Breast cancer brain metastasis

Brain metastasis includes parenchymal and meningeal metastases. The clinical manifestations of brain parenchymal metastasis mainly include increased intracranial pressure and neurological dysfunction. The main symptoms and signs of increased intracranial pressure are headache, vomiting, and optic disc edema, which may be accompanied by increased blood pressure, visual disturbances, disturbances of consciousness, and incontinence. Due to the different locations of brain metastases, different symptoms and signs such as mental symptoms, epileptic seizures, aphasia, and visual field damage may occur.

The risk of brain metastasis is rising in patient with advanced breast cancer, mainly due to the following two reasons: (I) the availability of more effective systemic treatment of breast cancer has prolonged the survival of patients; and (II) the application of brain MRI has enabled the detection of more patients with asymptomatic brain metastases. The incidence of brain metastasis differs in patients with different types of breast cancer. Generally, the risk of brain metastasis is relatively high in patients with TNBC or HER2 positive breast cancer, suggesting the importance of monitoring the occurrence of brain metastasis in these patients. In addition, studies have shown that high histological grade High proliferative activity of the primary tumor, young age, high tumor burden, and *BRCA* gene mutations are also high-risk factors for brain metastasis. The most common site of brain metastases is the cerebrum. Less often, cancer spreads to the cerebellum and brain stem.

Meningeal metastasis is often associated with meningeal irritation, which is manifested as headache, vomiting, stiff neck, cognitive impairment, confusion, and epileptic seizures. It may be accompanied by cranial nerve damage and increased intracranial pressure. If the tumor also spreads along spinal membrane, spinal cord and spinal nerve root stimulation can occur, which is manifested as radicular pain and segmental sensory disturbance.

There are many ways to diagnose brain metastases, but with different roles. Contrast-enhanced MRI of the head is more sensitive for small lesions, edema, and meningeal metastases than contrast-enhanced CT and should be used as the preferred imaging method for the diagnosis of brain metastases. Contrast-enhanced CT can be performed in patients with contraindications for cranial MRI. PET/CT can reflect the difference in metabolic status between tumors and normal tissues, which is helpful for tumor diagnosis. However, it is not sensitive for small metastases in the brain. Thus, the clinical diagnosis of small metastases should also be based on the findings of contrast-enhanced MRI or contrast-enhanced CT of the head. Patients with central nerve metastasis-associated symptoms but without intracranial space-occupying lesions on MRI/CT should undergo lumbar puncture, which not only allows

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the measurement of cerebrospinal fluid pressure (CSFP) but also enables the routine, biochemical, and cytological examinations of the cerebrospinal fluid (CSF). However, CSF examination in patients with intracranial hypertension may increase the risk of brain herniation.

The treatment of brain metastases from breast cancer should follow a multidisciplinary treatment model, and the aim of treatment is to metastatic lesions, improve patient symptoms, improve quality of life, and maximize the survival time of patients. The treatments of breast cancer brain metastasis include surgery, radiotherapy, chemotherapy, and symptomatic/supportive treatment. The general treatment principle is: surgery and/or radiotherapy for brain metastases is preferred after comprehensive whole body assessment, and meanwhile a rational systemic treatment protocol can also be considered. Radiotherapy mainly includes whole-brain radiotherapy (WBRT) and SRT. For HER2-positive asymptomatic patients with limited number of brain metastases, systemic therapy can also be given first.

For patients with recurrence after local treatment of brain metastases, re-operation or SRT may be considered if there is no history of intracranial radiotherapy, the general condition is good, and the extracranial lesions are well controlled. WBRT (SRT with hippocampal protection) may also be considered, along with the use of memantine. If the size of the metastasis exceeds the indications of SRT and is not suitable for re-operation, WBRT can be considered. For patients experience relapse after WBRT, SRT can be considered. If relapse occurs after SRT, SRT or WBRT can be repeated. In short, the treatment strategy for recurrence after local treatment of brain metastases should consider the patient's physical condition, the control of extracranial lesions, the patient's quality of life, and the possible benefit from treatment.

Many studies have confirmed that less than 10% of patients presented with brain metastases within 5 mm of the hippocampus and no patient presented with a metastasis in the hippocampus itself. Among patients who had achieved the same degree of disease control in the RTOG 0933 study, WBRT with hippocampal avoidance reduced cognitive function decline by 30% compared with traditional WBRT. In the RTOG 0614 study, WBRT combined with memantine reduced cognitive function decline by 22%. In the NRG-CCG01 study, WBRT with hippocampal avoidance decreased cognitive function decline by 58% compared with conventional WBRT. Therefore, WBRT with hippocampal avoidance, combined with memantine if appropriate, is recommended for patients with good systemic condition, satisfactory control of extracranial lesions, and a distance of not less than 1cm between the lesion and the hippocampus, because such a protocol has high efficiency and low toxicity.

While there is no standard treatment for meningeal metastases, radiotherapy, intrathecal injection therapy, systemic therapy, and supportive therapy are all possible options based on the prognostic prediction and after multidisciplinary consultations. WBRT can be used for patients with extensive nodular lesions or symptomatic linear meningeal metastases, whereas focal radiotherapy is commonly indicated the treatment of localized, symptomatic meningeal metastases. Once cancer cells are detected in cerebrospinal fluid, intrathecal injection therapy can be considered, with attention to adverse effects.

Generally, the effectiveness of medications is far from satisfactory in treating breast cancer brain metastasis. Studies have shown that chemotherapy drugs including capecitabine, topotecan, and temozolomide may achieve certain responses in patients with brain metastases. In a phase II clinical study, lapatinib combined with capecitabine showed preliminary anti-tumour activity on intracranial and extracranial lesions. The median OS reached 17 months in patients treated with lapatinib combined with capecitabine followed by WBRT, and WBRT after drug treatment did not affect the overall efficacy. The HER2CLIMB study showed that tucatinib combined with trastuzumab and capecitabine significantly improved overall survival in patients with brain metastases compared to trastuzumab combined with capecitabine only. Other anti-HER2 small-molecule tyrosine kinase inhibitors (e.g., neratinib) have also shown certain activities against brain metastases. The PERMEATE study (49) investigated the efficacy and safety of pyrotinib in combination with capecitabine in the treatment of HER2-positive breast cancer brain metastases; it was found that the ORR of CNS was up to 74.6% in patients with brain metastases without local radiotherapy and was 42.1% in patients with brain metastases that progressed again after local radiotherapy, providing new evidence for the use of pyrotinib in patients with brain metastases.

Symptomatic and supportive treatment is one of the main treatments for breast cancer brain metastases as it can improve the quality of life of patients and help the implementation of radiotherapy and drug treatment. For patients with intracranial hypertension, mannitol, glucocorticoids (e.g., dexamethasone), diuretics, and other drugs should be routinely used to alleviate the symptoms

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Table 20 Treatment of breast cancer brain metastases

Stratification	Level I recommendations	Level II recommendations
For patients presenting with a limited number of brain metastases	(I) Well-controlled extracranial disease, KPS ≥60 points	(I) SRT may be considered for lesions sized ≤3.5 cm (1B)
	(i) Surgical resection (1A); postoperative SRT to the resection cavity	(II) SRT may be considered for inoperable lesions (1B)
	(ii) Direct SRT for patients who do not need surgery or with biopsy-confirmed metastases	(III) Anti-HER2 therapy can be considered firstly in HER2-positive patients with controllable local symptoms (2A)
	(II) Poorly-controlled extracranial disease, with low KPS score	(IV) WBRT (with hippocampal avoidance)
	(i) Whole-brain radiotherapy (WBRT) (2A)	
	(ii) Supportive care (2A)	
For patients with diffuse brain metastases	WBRT (with hippocampal avoidance) (1A)	Anti-HER2 therapy can be considered firstly in HER2-positive patients with controllable local symptoms (2A)
Meningeal metastasis	Radiotherapy (2A)	Intrathecal injection (2B)

SRT, stereotactic radiotherapy; WBRT, Whole-brain radiotherapy.

of cerebral edema. For patients with intractable brain edema after radiotherapy, bevacizumab may be given to attenuate brain edema. It is usually administered at 7.5 mg/kg once every 2 weeks for a median of 4 cycles. Patients with epilepsy should be treated with antiepileptic drugs (*Table 20*).

Management of breast cancer patients during pandemic of coronavirus disease 2019 (COVID-19)

In 2020, the COVID-19 pandemic posed huge challenge to the standardized diagnosis and treatment of breast cancer. In the context of COVID-19, medical professionals have to adjust the diagnosis and treatment plans based on research evidence and expert experience. With the normalization of COVID-19 prevention and control worldwide, the expert group made the following recommendations for breast cancer treatment based on the original strategies and real-world data (50).

Patient manage during the preoperative neoadjuvant treatment

During the preoperative neoadjuvant therapy for HER2-positive patients, combination with albumin paclitaxel may be considered on top of trastuzumab plus patuximab. For TNBC, chemotherapy (e.g., albumin paclitaxel) may be applied alone or in combination with weekly carboplatin, during which the treatment response should be closely observed, and the medications should be timely adjusted according to the blood cell amounts

Patient manage during the postoperative adjuvant treatment

The indications for adjuvant chemotherapy should be strictly followed, and unnecessary chemotherapy should be avoided. For patients who need chemotherapy, carefully weigh the pros and cons and try to choose a chemotherapy regimen with low risk of granulocytopenia. Strictly calculate the chemotherapy dose and never exceed the maximum recommended dose. Prophylactic WBC-raising measures should be strictly implemented during chemotherapy, for which long-acting granulocyte colony-stimulating factor is recommended.

In terms of adjuvant endocrine therapy for HR-positive patients, oral AIs are preferred for postmenopausal women, oral tamoxifen is the treatment of choice for low-risk premenopausal patients, and a once-every-3-month long-acting agent may be used in high-risk patients who need ovarian function suppression.

Management of recurrent/metastatic breast cancer

For HR-positive patients experiencing recurrence/metastasis, endocrine therapy is preferred as it helps reduce

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the risk of infection. Endocrine therapy combined with targeted drugs can improve the efficacy, and therefore such combinations can be considered if conditions allow. For safety considerations, however, the use of such combinations must be strictly indicated. Use drugs with low pulmonary toxicity whenever possible.

For patients with HER2-positive recurrent/metastatic breast cancer, taxanes combined with trastuzumab is the preferred first-line treatment and may be continued if a clinical response is achieved. When second- or later-line therapies are required for patients with HER2-positive advanced breast cancer, use orally-administered targeted drugs whenever possible, which can be administered alone or in combination with oral chemotherapy drugs.

For patients with advanced TNBC, single-agent chemotherapy can be used, which is more convenient for safety management and regimen adjustment. Oral chemotherapy drugs such as capecitabine and vinorelbine can also be considered. In patients who cannot continue to receive infusion chemotherapy, switching to oral chemotherapy may be feasible.

Patient management in special periods

Whole-process case management is particularly important in the context of COVID-19 pandemic or during other major public health emergencies. The general principle is to minimize the impact of COVID-19 on tumor treatment, protect tumor patients from virus infection, and maximize the continuity of anti-tumor therapy.

COVID-19 vaccination in patients with breast cancer

Strong evidence shows COVID-19 vaccination is one of the most effective means in preventing SARS-CoV-2 infection, alleviate the symptoms of COVID-19, and lower the case-fatality rate. It is a key measure to establish herd immunity. However, while breast cancer patients are also part of the "herb", controversies remain no direct evidence on whether breast cancer patients can receive COVID-19 vaccination and on the timing of vaccination. Surveys in China and abroad have shown that the vast majority of breast cancer patients are willing to be vaccinated against COVID-19. By referring to academic articles on COVID-19 and the safety data of other vaccines, the CSCO BC expert group reached a consensus on COVID-19 vaccination after consultations and voting (51). The main recommendations are as follows.

Necessity for COVID-19 vaccination among breast cancer patients

The vast majority of breast cancer patients do not have immunity against SARS-CoV-2; even worse, they may be susceptible to COVID-19 due to the compromised immune status. After careful consideration of the safety and effectiveness of COVID-19 vaccination, most of the experts believe that when condition allows, breast cancer patients should timely receive COVID-19 vaccine.

COVID-19 vaccination in patients with breast cancer

Unvaccinated patients with pathologically confirmed breast cancer should undergo surgery first, followed by selective vaccination according to the recovery status; if only the first dose of COVID-19 vaccine has been administered, it is recommended that the patient receive the surgery 1 week after the first dose or 1 week before the second dose. The interval between surgery and vaccination should be more than 1 week. In addition, nearly half of the experts believe that the decision to vaccinate is not associated with the surgical procedure; rather, more attention should be paid on the physical recovery after surgery.

Timing of COVID-19 vaccination in patients with early-stage breast cancer

COVID-19 vaccination should be suspended in patients who are receiving neoadjuvant chemotherapy or neoadjuvant chemotherapy plus targeted therapies; for patients receiving neoadjuvant endocrine therapy, COVID-19 vaccination may be initiated after careful assessment.

It is recommended to suspend COVID-19 vaccination in breast cancer patients undergoing adjuvant chemotherapy, and the vaccination may be initiated one month after completion of adjuvant chemotherapy. For breast cancer patients who have already received their first dose of COVID-19 vaccine, the vaccination can be completed as planned; however, concurrent chemotherapy should be avoided.

COVID-19 vaccination after assessment is recommended for patients receiving postoperative adjuvant targeted therapy alone or combined with adjuvant endocrine therapy. COVID-19 vaccination is recommended for patients receiving adjuvant endocrine therapy. COVID-19 vaccination is not recommended for breast cancer patients receiving postoperative adjuvant radiotherapy.

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Timing of COVID-19 vaccination among patients with advanced breast cancer

The physical status and immune function of patients with recurrent/metastatic breast cancer are quite different from those in the early-stage patients, and the decision to vaccinate or not should be based on criteria different from those for early-stage breast cancer patients.

COVID-19 vaccination may be considered during oral capecitabine treatment after careful assessment.

COVID-19 vaccination is not recommended for patients who are orally administered with pyrotinib, CDK4/6 inhibitors, or chidamide.

COVID-19 vaccination is also not recommended for patients using PD-1/PD-L1 inhibitors.

Timing of COVID-19 vaccination for patients participating in clinical trials

For patients participating in a clinical trial, it is recommended that decision on COVID-19 vaccination should be made on the basis of the specific protocols of clinical trials and the stages of the research. If a patient has already received the first dose of COVID-19 vaccine before entering the subject screening period, he or she can complete the vaccination as planned and then the suitability or eligibility for the study will be re-considered. If the patient has already entered the subject screening period, it is recommended to suspend COVID-19 vaccination. COVID-19 vaccination should be avoided as much as possible during the initial phase of a clinical trial, so as to avoid any impact on the interpretation of study results. Patients achieving stable disease after treatment and entering the maintenance phase of the study or the follow-up period may receive the COVID-19 vaccine.

Artificial intelligence (AI)-assisted decision-making on diagnosis and treatment

AI represents a new direction in the era of precision medicine. Big data, deep learning, advances in computing technology, and new healthcare model have offered opportunities for the development of AI in medicine. AI has been applied in medical imaging, pathology, and decision support systems.

Intelligent imaging helps tumor diagnosis and response evaluation

Intelligent imaging technologies have played certain roles in lesion diagnosis, response evaluation, and even molecular type prediction. When applied to distinguish benign and malignant lesions based on plain and enhanced images, the intelligent imaging was only inferior to senior radiologists with 20 years of experience. It was also found that the three-dimensional (3D) imaging information integrating clinical information and dynamically enhanced imaging information can be used as a biomarker to identify molecular subtypes of breast cancer, especially when applied for the prediction of TNBC. Al-assisted diagnosis can help doctors diagnose diseases more quickly and accurately, thus improving the efficiency and accuracy of diagnoses.

AI-based pathology accelerates the qualitative and quantitative identification of tumors

AI-based pathology has been applied in a variety of tumors (e.g., breast cancer), mainly for cytological screening, differentiation of malignant from benign lesions, morphological quantitative analysis, and histological classification. It was found that the HER2 scoring results for breast cancer specimens were highly agreed between an AI-based pathology system and human pathologists. In terms of molecular pathology, AI-based analysis of the massive genetic information has become an indispensable element for the development of precision medicine. AI-based pathology reduces the workload of pathologists; more importantly, it makes up for the shortcomings of the subjective analysis performed by human pathologists, improves the qualitative and quantitative identification of tumors, increases the accuracy of pathological diagnoses, and offers patients with personalized treatment opinions and improved cancer prognosis prediction. Thus, it promotes the development of precision pathology.

Intelligent decision-making enriches the clinical decision-making models

R&D of intelligent decision-making systems is to integrate the learning and analysis capabilities of AI tools and the experience of human experts, thus optimizing decision-making process. The CSCO BC collaboration team compared the decision-making performance between an AI system and professional doctors in 2,000 cases (52) and found that the IBM-system Watson for Oncology (WFO) had good feasibility and effectiveness in decision-making for breast cancer treatment. It helped clinicians save time and effort, and its auxiliary applications can further

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improve the standardization of decision-making by human doctors.

Meanwhile, intelligent decision-making systems with independent intellectual property rights have also emerged in China. The phase III clinical study of breast cancer intelligent decision-making based on CSCO BC big data and CSCO BC guidelines suggested that the intelligent decision-making system based on CSCO guidelines on breast cancer diagnosis and treatment had good performance in decision-making for different types of breast cancer at different stages. In 2019, the CSCO AI system (53) was officially released, and its nationwide application has dramatically promoted the development of intelligent decision-making systems in China. As an important medium for disseminating CSCO BC guidelines and promoting standardized diagnosis and treatment, CSCO AI has integrated five key functions including intelligent decision-making, evidence support, toxicity alert, cost estimation, and patient follow-up. In 2021, based on the original functions, CSCO AI adds new functions including patient toxicity management, clinical study enrollment reminders, and bone metastasis diagnosis and treatment reminders, thus promoting the clinical application of the intelligent system.

We will also regularly collect clinical information and user feedback to further optimize the CSCO AI system, establish and improve a medical ecosystem comprised of intelligent decision-making, toxicity alert, disease management, and resource sharing, integrate case management systems, and provide assistance to the full-course management of Chinese breast cancer patients.

AI represents a future. Intelligent systems can not only help clinicians save time and energy but also will further improve the precise diagnosis and treatment of tumors. Therefore, the expert group encourages the implementation of AI-related clinical research and the R&D of AI systems with independent intellectual property rights in China.

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Footnote

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