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Practice Guidelines

Guidelines for diagnosis and treatment of advanced breast cancer in China (2022 edition)☆

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ABSTRACT

Breast cancer is the most common cancer among women worldwide. It has been estimated that about 416 000 new cases and over 117 000 deaths of breast cancer occurred in China in 2020. Among the new cases of breast cancer diagnosed each year, 3–10% have distant metastasis at the time of initial diagnosis. In addition, approximately 30% of patients with early-stage breast cancer may eventually experience recurrence or metastases. The 5-year survival rate of patients with advanced breast cancer is only 20% with a median overall survival of 2–3 years. Although advanced breast cancer remains incurable at present, new therapeutic options and multidisciplinary treatment could be utilized to alleviate symptoms, improve quality of life, and prolong patients' survival. The choice of treatment regimens for patients with advanced breast cancer is very important, and the optimal treatment strategy beyond the first- and second-line therapy is often lacking. Herein, the China Advanced Breast Cancer Guideline Panel discussed and summarized recent clinical evidence, updated the guidelines for the diagnosis and treatment of advanced breast cancer based on the 2020 edition, and formulated the "Guidelines for diagnosis and treatment of advanced breast cancer in China (2022 edition)" for clinicians' reference.

Advanced breast cancer (ABC) includes locally advanced breast cancer and recurrent/metastatic breast cancer. Conventionally, locally advanced breast cancer comprise stages IIB (T3N0M0) and IIIA (T3N1M0) breast cancers that could be subject to radical resection, and stages IIIB and IIIC breast cancers with skin, chest wall, or regional lymph node involvement that are unable to receive curative surgical treatment. Of note, the locally advanced breast cancer mentioned in this guideline only refers to stage IIIB and IIIC breast cancer without distal metastasis and unable to receive curative surgical treatment upon initial diagnosis.

Multiple factors should be taken into consideration when treating ABC. It is often challenging for oncologists to choose appropriate treatment regimens for patients with ABC, especially after first- and second-line therapies, when no standardized recommendation could be offered. The median overall survival for ABC patients is 2–3 years, varying among patients with different molecular subtypes.[1,2] In recent years, the treatment landscape of ABC has evolved dramatically with the development of novel anti-cancer agents, such as CDK (cyclin-dependent kinase) 4/6 inhibitors and ADCs (antibody-drug conjugates). Based on the Guidelines for Clinical Diagnosis and Treatment of Advanced Breast Cancer in China (2020 edition), the China Advanced Breast Cancer Guideline Panel updated the 2022 edition of this guideline under the guidance of the Breast Cancer Expert Committee of National Cancer Quality Control Center of China, the Breast Cancer Expert Committee of China Anti-Cancer Association, as well as the Cancer Drug Clinical Research Committee of China Anti-Cancer Association. The definitions of levels of evidence and grades of recommendations referred in this guideline are listed in Table 1. Of note, this guideline only provides recommendations for the diagnosis and management of ABC patients within China. Considering the complexity of ABC treatment, local medical centers may need to take into account the local situation, drug accessibility, and characteristics of patients to provide multidisciplinary and individualized comprehensive treatment.

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Table 1
Definitions for levels of evidence and grades of recommendations.

	Definition
Levels of evidence	
IA	Evidence from at least one high-quality, large randomized controlled trial or meta-analysis, with significant clinical benefit.
IB	Evidence from at least one high-quality, large randomized controlled trial, with clinical benefit.
IIA	Evidence from randomized trials or meta-analysis with possible bias, with certain level of clinical benefit.
IIB	Evidence from randomized trials or meta-analysis with possible bias, with limited clinical benefit.
Grades of recommendations	
Priority	≥80% expert consensus, with definite indication, good accessibility, and covered by the National Medical Insurance System.
Recommended	50% ≤ expert consensus < 80%, with limited accessibility, or with definite clinical benefit, but the indication has not been approved in China.
Optional	Expert consensus <50%, low accessibility, with limited medical evidence, and not covered by the National Medical Insurance System.

1. Guideline principles

Breast cancer is the most common malignant tumor in women worldwide. In 2020, about 416 000 new cases, and more than 117 000 deaths of breast cancer were reported in Chinese female population.[3] Among new cases of breast cancer diagnosed each year, 3–10% of them have distant metastasis at the time of initial diagnosis.[4] Approximately 30% of patients with early-stage breast cancer can eventually develop metastatic disease. The 5-year survival rate of ABC was only 20%.[5] As a unique phase in the disease course, ABC has its own characteristics in terms of treatment options and response evaluation. In the meantime, patients with advanced breast cancer are often challenged with additional burdens from physical, psychological, and socioeconomical aspects.

The general principles of the diagnosis, treatment, and management of ABC applied in this guideline are listed below: (1) The involvement of a multidisciplinary team (including but not limited to medical oncology, radiology, surgery, pathology, gynecology, interventional therapy, nutrition, psycho-oncology, and palliative care) in the ABC treatment is important. Patients should be offered appropriate psychosocial care, supportive treatment and symptom-related intervention on a routine basis. The treatment should be individualized and comprehensive throughout the entire life cycle. (2) After the diagnosis of ABC is confirmed, treatment and care goals should be discussed by both health professionals and patients. The conversation should limit the use of terminologies and take place in private with respect to cultural differences. Information should be shared in written forms whenever possible. (3) Treatment plans should be selected based on individual conditions, considering both survival and quality of life. The willingness and affordability of the patients to certain treatment should be comprehensively taken into consideration. Family members should be encouraged to participate in the discussion. (4) Patients' subjective feelings reflect not only the severity of symptoms, but also the impact of the treatment on their quality of life. Therefore, the use of patient-reported outcomes (PROs) should be strongly encouraged. Besides, treatment-related adverse events and conditions, such as pain, fear for disease progression, memory loss, and sleep disorders can also greatly affect the quality of life. Consequently, additional attention should be paid to addressing patients' needs for homecare, employment, and social activities. (5) Some anti-cancer agents mentioned in this guideline have not been approved or available in the market in China yet. These agents should only be used after thorough discussion with patients. (6) Patients should be encouraged to participate in well-designed clinical trials. The general management principles of ABC are summarized in Table 2.

2. Principles for disease assessment of advanced breast cancer

For patients with recurrent disease, biopsy of the metastatic lesions should be performed at least once in the metastatic setting, if clinically feasible, to re-evaluate the expressions of biological markers (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]), especially upon the initial diagnosis of ABC.

Staging work-up for ABC patients should at least include history taking, physical examination, imaging and laboratory tests, including complete blood count, liver and renal function tests, as well as tumor biomarkers. If the use of trastuzumab or pertuzumab is considered, patients should also receive cardiac function evaluation (such as echocardiography).

Commonly used imaging examinations include chest contract CT, abdomen ultrasound (abdomen contrast CT or magnetic resonance imaging [MRI] if needed), bone scan, and positron emission tomography/computed tomography (PET-CT). Annual breast imaging can be considered for ABC patients with long-term stable disease or complete remission. For patients whose lesions cannot be accurately evaluated by commonly used imaging modalities (e.g., CT and MRI), PET-CT may be considered to distinguish recurrence and multiple primary lesions.[6] However, due to the lack of high-level evidence, PET-CT is not recommended as a routine examination method at present. Patients with central nervous system (CNS) symptoms or signs should receive brain imaging, including brain MRI or CT (contrast MRI is recommended as the first option). Brain screening is currently not recommended for patients without CNS symptoms. Patients with HER2-positive or triple-negative breast cancer (TNBC) have relatively higher chance of developing brain metastasis. Therefore more thorough medical history and physical examinations should be conducted, and brain imaging should be performed once brain metastasis is suspected.

Bone scan is a commonly used primary screening method for bone metastases, with high sensitivity but low specificity. It is difficult to use bone scan to distinguish osteoblastic and osteolytic lesions. Therefore, further CT (bone window) or X-ray should be performed for the diagnosis of bone metastases, and to determine the nature of the lesion (osteoblastic or osteolytic), as well as the severity of bone destruction. MRI has high resolution for soft tissue with good sensitivity to determine the relationship between lesion and spinal cord, and thus is the preferred screening test when vertebral metastasis is suspected.[7] PET-CT has high sensitivity and specificity in the diagnosis of bone metastasis, but is expensive and has a large radiation dose. At present, PET-CT is not recommended routinely for screening bone metastasis in clinical practice, but can be considered when the results may affect the clinical treatment strategy.[7] Bone biopsy is an invasive examination. When the clinical and imaging findings are inconsistent or the nature of lesions is difficult to be confirmed by conventional imaging examinations, bone biopsy of suspicious sites is recommended to determine whether there is bone metastasis. It is important to point out that the results of bone biopsy can be affected by decalcification, which may interfere with the receptor expression reading. Under such circumstances, the molecular subtyping of the sample should be cautiously determined based on comprehensive consideration of patients' past medical history.

As for the efficacy evaluation of osteolytic or mixed osteolytic and osteoblastic lesions, lesions are regarded as measurable if related soft tissues can be identified by CT or MRI.[8] Otherwise, simple bone lesions are regarded as non-measurable, as they would be difficult to be assessed

Table 2
General management principles of advanced breast cancer.

No.	Content
1	Multidisciplinary discussion in diagnosis and treatment of advanced breast cancer is crucial. The management should be comprehensive and throughout the life cycle.
2	Thorough discussion with patients should be made when making treatment decisions after balancing estimated survival as well as quality of life and considering affordability and sociopsychological needs.
3	Value the importance of patient-reported outcomes. Patients should be encouraged to document and report their symptoms.
4	For anti-cancer agents that are not in the market or have not been approved in China, full informed consent should be obtained before application.
5	Patients should be encouraged to participate in well-designed clinical trials.

Table 3
Principles for ABC evaluation.

No.	Content
1	Biopsy of metastatic lesions and molecular re-subtyping is encouraged.
2	Staging, response to therapy, and safety evaluation should be included in disease assessment.
3	Efficacy evaluation should be based on imaging examinations supplemented by dynamic monitoring of tumor markers.
4	Intervals between the disease evaluations should be determined based on patients' symptoms, types of treatment, and rates of disease progression.
5	For non-measurable lesions like bone metastasis, comprehensive evaluation with clinical symptoms, tumor markers, and imaging results are required.

Abbreviation: ABC, advanced breast cancer.

based on imaging scans. Currently in clinical practice, comprehensive efficacy evaluation is preferred based on clinical conditions and patients' CT or MRI imaging results, including changes of lesion density (CT), size, and volume. Cautions should be paid when evaluating bone metastasis.[9] Repair of lytic bone lesions on bone scan after treatment may show scintillation or increased activity and thus be misdiagnosed as disease progression. PET-CT is superior to CT and bone scan in terms of efficacy evaluation, but its further application is impeded by the lack of reproducibility and well-accepted diagnostic criteria. Currently, neither bone scan nor PET-CT are recommended to be used alone for treatment efficacy evaluation of bone metastasis.[10,11]

It is recommended to follow the Clinical Response Evaluation Criteria in Solid Tumors version 1.1 for response assessment. For non-measurable lesions, such as non-measurable bone metastasis, lymphangitis carcinomatosis, or pleural effusion, comprehensive evaluation should be performed based on symptoms, laboratory test results, tumor markers, and imaging results. Physicians should refrain from subjective judgement solely based on imaging results or tumor marker results, and patients' chief complaint should not be neglected.

Tumor biomarkers are auxiliary indicators for treatment efficacy evaluation. The changes of tumor biomarker levels could help to assess treatment efficacy, especially for unmeasurable lesions. Continuous elevation of tumor biomarkers during treatment may be an early sign of disease progression, and subsequent imaging examinations should be performed to determine whether disease progression exists. However, elevated tumor biomarkers cannot be used as the sole evidence to change treatment, and the level of biomarkers should be re-evaluated after 1–2 months.

The response assessment for endocrine treatment and chemotherapy should be conducted every 2–3 months and every 2–3 cycles, respectively. The evaluation interval should be further determined based on comprehensive consideration of disease progression rate, tumor burden, as well as the treatment regimen. The interval might be shortened among patients with rapidly progressing disease or prolonged among patients with relatively stable disease. If disease progression is suspected or disease-related symptoms are presented, examinations should be performed as soon as possible. Patients' medical history and physical examination results should be carefully documented when conducting imaging tests. The principles for ABC evaluation are presented in Table 3.

3. Principles for ABC treatment

Most ABCs are incurable. The goal of treatment is to control tumor progression, alleviate symptoms, and prolong survival, while maintaining the quality of life. In recent years, the landscape of ABC treatment has been reshaped by a deeper understanding of tumor biology and the development of new anti-cancer agents. However, the general principle remains the same: the treatment for ABC should be based on molecular subtypes.

The specific treatment for each patient should be based on multiple factors, including the expressions of hormone receptor (HR) and HER2, previous treatment history (efficacy, adverse events, and tolerance), disease-free interval, tumor burden, age, general condition, menopausal status, comorbidities, etc. It is recommended that the genomic status of phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and germline breast cancer gene (*gBRCA*) mutations as well as expression of programmed cell death-ligand1 (PD-L1) be evaluated when associated targeted drugs are available. In addition, evaluation of microsatellite instability and tumor mutational burden should also be considered. The treatment decision should also be based on the severity of disease, patients' willingness for rapid control of disease and/or symptoms, and patients' social, economic, as well as psychological needs. Currently, no consensus has been made on which result should be used to guide treatment when the molecular subtype of the metastatic site is inconsistent with the primary site.[12,13] Under such circumstances, we recommend that the treatment decision be made mainly based on the molecular subtype of the metastatic site. For patients who have previously received endocrine therapy or anti-HER2 therapy, but presented with HR or HER2 negative disease in their metastatic lesions, treatment should be determined based on previous regimens, treatment sensitivity, and patients' overall performance status.

(1) Locally advanced breast cancer: Radical local treatment is recommended for locally advanced breast cancer, including mastectomy and repeated lumpectomy. Whether to conduct post-operative local radiation should be based on the recurrence site and previous radiation dosages. Systemic treatment should be actively given to patients who have achieved curative outcomes. Systemic treatment regimens could refer to adjuvant/neoadjuvant regimens while taking into consideration the treatment history. For patients who could not achieve curative outcomes, systemic treatment is recommended as the main treatment modality. Simultaneous local treatment can be given to patients with urgent need to alleviate symptoms or complications.[14]
(2) Newly diagnosed stage IV breast cancer: It remains controversial whether patients with stage IV breast cancer can benefit from resection of the primary lesion.[15] Current evidence suggests that no clear survival benefit has been seen in patients with advanced breast cancer who received resection of the primary tumor, ex-

Table 4
Principles for ABC treatment.

No.	Content
1	The treatment of advanced breast cancer should be principally based on molecular subtypes, with comprehensive consideration of disease progression rate, tumor biomarkers, previous therapies, drug accessibility, and patients' preferences.
2	The molecular subtype of the metastatic lesion is recommended as the main basis for treatment while taking into consideration the previous treatment history, treatment sensitivity, and patients' performance status to decide whether to give endocrine or anti-HER2 treatment.
3	Patients with locoregional recurrence should receive local treatments with curative intent if possible. Otherwise, systemic treatment should be mainly considered.
4	The resection of the primary lesion should be performed with caution for newly diagnosed stage IV patients, as the benefit is not definite.
5	The evidence of treatment for patients with oligometastatic disease is limited. Some patients may benefit from surgical resection.
6	With the development of novel anti-cancer agents, it is recommended to identify patients with HER2-low expression within the HER2-negative population.

Abbreviations: ABC: advanced breast cancer; HER2: human epidermal growth factor receptor 2.

cept for those with bone only metastases.[16] However, for selected patients with low metastatic burden and good response to systemic therapy, palliative surgery could be considered after discussing with patients, especially for the purpose of improving quality of life. Most existing evidence of the above recommendations come from retrospective studies, and the result is not yet conclusive from several prospective studies with limited sample sizes. More thoroughly designed prospective clinical trials are needed. Radiation therapy is a very important local treatment strategy and should be valued in ABC treatment.

(3) Oligometastatic breast cancer: Evidence of treatment for patients with oligometastatic disease is limited. Studies with limited sample sizes showed that, for patients with ≤ 3 metastatic lesions within 1 organ, systemic treatment combined with surgical resection of the metastatic lesions could improve patients' progression-free survival (PFS) and overall survival (OS) compared to systemic treatment alone. Patients with disease-free survival ≥ 2 years, single metastasis, or HR+ diseases are more likely to benefit from surgery.[17]

(4) HER2-low breast cancer: Recent clinical evidence including that of DESTINY-Breast04 revealed that patients with HER2-low expression could benefit from novel antibody-drug conjugates (ADCs). For patients whose HER2 expression was identified as negative in previous treatment, it is necessary to determine if they can be characterized as the HER2-low expression population to provide reference for future treatment options. Considering the heterogeneity of HER2-low breast cancer, we recommend multiple metastatic site biopsies to evaluate HER2 expression if allowed. At present, HER2-low expression is defined as 1+ by HER2 immunohistochemistry (IHC), or 2+ and negative by in situ hybridization (ISH). However, this definition may change correspondingly with the progression of clinical studies. A recent multi-center study showed that 54% of breast cancer patients in China could be characterized as HER2-low.[18]

(5) Elderly patients with breast cancer: Elderly patients should be given reasonable and effective anti-cancer treatment as much as possible according to individual conditions.

Principles for ABC treatment are listed in Table 4.

4. Treatment of unresectable locally advanced breast cancer

Approximately 20% of breast cancer cases are locally advanced breast cancer without distal metastasis upon initial diagnosis.[19]

Biopsy and histology examination should be performed before treatment initiation to determine the expression of ER, PR, HER2, Ki-67, PD-L1, etc. Testing for mutations like PIK3CA and BRCA is also recommended to assist treatment decision. Patients with locally advanced breast cancer have relatively high risk of developing distal metastasis and detailed staging evaluation including medical history, physical examination, laboratory testing, breast X-ray (ultrasound or MRI), chest and abdomen imaging, bone scan and PET-CT (optional) should be performed before treatment initiation.

Multidisciplinary treatment (systemic treatment, surgery, radiation therapy) is recommended if available and systemic treatment should be used as initial therapy.

Neoadjuvant strategies should be actively employed for newly diagnosed locally advanced patients who may have opportunity for curative surgery: (1) trastuzumab and pertuzumab combined with chemotherapy such as docetaxel, or docetaxel combined with carboplatin, or anthracycline combined with taxanes are recommended for patients with HER2-positive disease. If patients are eligible for radical surgical resection after initial systemic treatment, trastuzumab-based anti-HER2 adjuvant therapy should be continued post-operatively. For those who failed to achieve complete pathological remission, ado-trastuzumab emtansine (T-DM1) could be considered to be used as adjuvant therapy for 1 year. (2) anthracycline- and/or taxane-based regimen are preferentially recommended for patients with HR+ disease. (3) anthracycline- and taxane-based regimen are preferentially recommended for patients with triple-negative disease. Adding platinum agents, bevacizumab, or pembrolizumab to the treatment can also be considered.

For patients who are not eligible to receive curative treatment after neoadjuvant therapy, systemic treatment should be given as in the metastatic setting.

For patients who are eligible for surgery after systemic treatment, total mastectomy and axillary lymph node dissection remains the standard surgical procedure if breast-conserving surgery could not be performed.[20] Palliative mastectomy is not recommended in patients who are not eligible for surgery after systemic treatment or radiation therapy, unless the surgery could improve patients' overall quality of life.

For patients with inflammatory breast cancer that are ineligible for surgery, the treatment principle remains the same with non-inflammatory locally advanced breast cancer, where systemic treatment is preferred in the first line. Total mastectomy and axillary lymph node dissection is recommended for patients who responded well to systemic treatment, while breast-conserving surgery is not generally recommended in this population. Upon patients' request, immediate breast reconstruction surgery with autologous tissue flap may be considered after multidisciplinary team discussion and if sufficient technical skills are available. Local radiation therapy (chest wall and the lymphatic drainage area) should be performed even if patients achieved pathological complete remission.

The principles for unresectable locally advanced breast cancer treatment are presented in Table 5.

5. General principles of chemotherapy for ABC

Chemotherapy is an indispensable traditional treatment modality for ABC. Patients' willingness and the incurable nature of the disease should be fully taken into consideration when deciding the treatment regimen to balance survival and quality of life. Single or combined chemotherapy

Table 5
Principles of unresectable locally advanced breast cancer treatment.

No.	Content
1	Disease staging, molecular subtypes, and biomarkers should be assessed before treatment initiation.
2	Neoadjuvant therapy should be actively employed for patients with potential opportunities to receive curative treatment.
3	Palliative mastectomy is not routinely recommended for patients who are ineligible for surgery after receiving neoadjuvant therapy.
4	For inoperable inflammatory breast cancer, neoadjuvant treatment is recommended to seek potential radical surgery opportunities.

should be chosen appropriately during different stages of the disease course.

Patients with the following conditions are more likely to benefit from chemotherapy: ER- and PR- disease, HER2-positive disease, short disease-free survival after surgery (<2 years), rapid progression with symptoms, multiple visceral metastasis, and ER+ and/or PR+ disease that could not benefit from endocrine therapy.

Single-agent chemotherapy is the preferred regimen for ABC, especially in the following situations: relatively slow progression, low tumor burden, no major clinical symptoms, elderly patients, and patients with multiple comorbidities and limited tolerability. Combination chemotherapy is preferred for patients with better tolerability, rapidly progressing disease, obvious symptoms, large tumor burden, or visceral crisis requiring prompt symptom relief. The specific regimen should be based on what has been used in previous adjuvant settings, the disease-free interval, and patients' general conditions and affordability. Anthracycline and/or taxane-based regimens are recommended for chemotherapy-naïve (including adjuvant therapy) patients. Taxane-based regimens or taxane alone are recommended for taxane-naïve patients who failed in previous anthracycline treatment or who have reached accumulative dosage limitations. For patients who have received taxanes in the adjuvant treatment and with at least 1 year of interval between the last treatment and disease recurrence, taxanes could be rechallenged. Among other options, drugs that have not used in the adjuvant period or salvage therapy are preferred.

Meta-analysis showed that extending duration of first-line chemotherapy could prolong disease control time, and may prolong OS.[21] Therefore, first-line treatment could be continued until disease progression or intolerable toxicity. Single-agent chemotherapy may be considered as maintenance therapy. When a combined regimen proved to be effective, one agent from the combination with better safety profile and more convenient usage could be chosen as the maintenance therapy. For patients who cannot tolerate maintenance chemotherapy, their treatment can be discontinued. These patients should be followed-up regularly, and new treatment should be initiated once disease progression occurs. Metronomic chemotherapy is a reasonable treatment option for patients who do not require rapid tumor remission while valuing life quality. Agents that can be used as metronomic chemotherapy include oral cyclophosphamide, etoposide, capecitabine, vinorelbine, etc.

If HR+ breast cancer patients responded well to previous chemotherapy, both chemotherapy and endocrine ± targeted therapy can be applied as maintenance therapy. Studies have shown that for patients whose disease did not progress for at least four cycles of chemotherapy, endocrine therapy had increased PFS and OS compared to chemotherapy as maintenance treatment, especially in endocrine-sensitive patients or patients without visceral metastasis.[22] A phase II study showed that for post-menopausal patients who remained disease control after 4–8 cycles of first-line chemotherapy, successive endocrine maintenance therapy was reasonable.[23] As both anthracycline and trastuzumab might show cardiac toxicity, the combination of these two drugs should be avoided. For advanced TNBC, chemotherapy remains to be the main treatment modality (please refer to the advanced TNBC section in this guideline). When patients develop progression on the first-line chemotherapy, single-agent or combination chemotherapy should be individually determined based on treatment tolerance, tumor burden, previous treatment efficacy, as well as potential cross-resistance. Drugs that are proved effective previously with prolonged disease control could be used again in later-line treatment. There is no standard treatment for patients who have failed multiple lines of chemotherapy and these patients are encouraged to participate in clinical trials or receive best supportive care.

Principles for chemotherapy in ABC patients are presented in Table 6.

6. Treatment for HR+ and HER2- ABC

6.1. Treatment principles

For HR+ HER2- ABC, combination therapy with endocrine therapy and CDK4/6 inhibitors is the preferred regimen for patients without visceral crisis. The evidence of using combination therapy with CDK4/6 inhibitors and endocrine therapy in patients with rapid tumor progression, diffuse visceral metastasis, severe symptoms, visceral crisis, or who require rapid tumor control, is limited. For such patients, more aggressive treatment is recommended, such as chemotherapy.[24]

Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory tests, and rapid progression condition of the disease. Visceral crisis not only refers to the presence of visceral metastases, but also implies that critical damage has occurred in visceral organs and urgent treatment is required. Visceral crisis includes: (1) pulmonary lymphangitis carcinomatosis that requires oxygen supplementation at rest; (2) difficulty of breath at rest that cannot be alleviated by pleural effusion drainage; (3) diffuse liver metastases with bilirubin >1.5 times of normal upper limit (without biliary obstruction); (4) diffuse bone marrow metastasis; (5) meningeal metastasis; (6) symptomatic cerebral parenchymal metastasis.[13,25–28]

The choice of endocrine therapy should be determined based on patients' sensitivity to previous endocrine treatment, classified as: (1) endocrine treatment-naïve patients: unknown sensitivity and resistance to endocrine treatment; (2) primary resistance to endocrine treatment: recurrence within 2 years after initiating adjuvant endocrine therapy, or disease progression occurred within 6 months of receiving the first-line endocrine therapy for ABC; (3) secondary resistance to endocrine treatment: all other clinical situations.[13]

For patients who are sensitive to previous endocrine treatment (progression-free time ≥ 6 months), additional lines of endocrine treatment could still be effective. Patients who still progressed after three continuous lines of endocrine therapy are unlikely to benefit from further endocrine treatment, and chemotherapy should be considered. During the endocrine treatment, response evaluation should be performed every 2–3 months. Upon disease progression, either continuous endocrine treatment or switch to chemotherapy could be considered based on patients' conditions. For patients who are not eligible for additional lines of endocrine therapy or whose disease progresses rapidly after endocrine therapy, chemotherapy may be considered. Once disease control is achieved, endocrine therapy can be used as maintenance therapy. This treatment strategy, though not examined in large randomized clinical trials, is commonly used in clinical practice, and has been recognized by most experts.

Currently, no evidence has shown that concurrent chemotherapy and endocrine therapy can provide additional benefit. Therefore, it is not recommended outside clinical trials. Due to the fact that the HR test-

Table 6
Principles of chemotherapy in ABC patients.

No.	Content
1	Patients with the following conditions are more likely to benefit from chemotherapy: ER- and PR- disease, HER2+ disease, short disease-free survival after surgery (<2 years), rapid progression with symptoms, multiple visceral metastasis, and ER+ and/or PR+ disease that could not benefit from endocrine therapy.
2	Conditions that favor single-agent chemotherapy: slow tumor progression, low tumor burden, mild symptoms, advanced age, multiple comorbidities, and poor tolerance.
3	Conditions that favor combination chemotherapy: rapid disease progression, severe symptoms, high tumor burden, visceral crisis, and good tolerance.
4	Chemotherapy regimens should be decided based on previous therapies, disease progression rates, and patients' performance status and affordability. Avoid using drugs that are cross-resistant to agents used in previous lines.
5	First-line treatment could be continued until disease progression or intolerable toxicity occurs.
6	After effective combination chemotherapy, single-agent chemotherapy as maintenance therapy or treatment discontinuation is both allowed according to patients' tolerability. In HR+ patients, chemotherapy can be continued or switched to endocrine ± targeted therapy for maintenance.
7	Metronomic chemotherapy could be considered for patients who value life quality and do not require rapid tumor remission.
8	Patients who failed multiple lines of treatment should be encouraged to participate in clinical trials.

Abbreviations: ABC, advanced breast cancer; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Table 7
Principles for the treatment of HR+ and HER2- ABC.

No.	Content
1	CDK4/6 inhibitors combined with endocrine therapy is the preferred regimen in patients without visceral crisis.
2	The occurrence of endocrine resistance should be determined based on previous endocrine treatment history.
3	For patients who are sensitive to previous endocrine treatment, additional lines of endocrine therapy could be considered after disease progression.
4	For patients who are not eligible for endocrine therapy, chemotherapy followed by endocrine therapy can be considered after achieving disease control.
5	Concurrent application of chemotherapy and endocrine therapy is not recommended (except in clinical trials).
6	Endocrine therapy might be considered in HR- ABC patients who show characteristics of HR+ disease.
7	Premenopausal HR+ patients are recommended to receive adequate ovarian suppression or ablation and then be treated in the same way as postmenopausal women. For patients who develop amenorrhea after chemotherapy, menopausal status should be determined with caution.
8	For patients with HER2-low disease, T-DXd could be considered after two or more lines of chemotherapy if the drug is available.

Abbreviations: CDK, cyclin-dependent kinase; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ABC: advanced breast cancer; T-DXd, Trastuzumab Deruxtecan.

ing can be false negative, the panel concluded that endocrine therapy may be attempted in ER and PR negative advanced breast cancer patients with features such as slow tumor progression, long relapse-free interval, bone only metastases, and soft tissue metastases. The American National Comprehensive Cancer Network Guideline also suggests to apply endocrine treatment to this special group of patients. ER+ and/or PR+ premenopausal patients are recommended to receive castration and be treated similarly to postmenopausal patients. For patients who experienced amenorrhea after chemotherapy, menopause status should be verified with caution, especially when aromatase inhibitor (AI) treatment is considered. It has been known that the menstrual cycle is more likely to resume in young patients than in older patients.

According to the results of DESTINY-Breast04 trial, trastuzumab deruxtecan (T-DXd) could be used in HR+ and HER2- ABC patients with HER2-low expression who developed resistance to previous endocrine treatment and 1–2 lines of chemotherapy if the drug is available. Patients need to be fully informed about the commercial approval status of the drug and the risk-benefit assessment prior to use.

Principles for the treatment of HR+ and HER2- ABC patients are presented in Table 7.

6.2. Treatment regimens

6.2.1. Treatment regimens for postmenopausal ABC patients with HR+ HER2- disease

(1) First-line treatment: CDK4/6 inhibitors combined with endocrine therapy are recommended as the first-line treatment.

The MONALEESA-2 trial has shown that the combination therapy of ribociclib and letrozole significantly prolonged PFS in postmenopausal patients compared to letrozole alone.[29,30] In the MONALEESA-3 trial, the combination therapy of ribociclib and fulvestrant significantly prolonged PFS in the first line setting compared to fulvestrant alone (33.6 vs. 19.2 months, HR = 0.55, 95% *CI*: 0.42–0.72).[31] Studies examining the quality of life in the MONALEESA-2 and MONALEESA-3 trials showed that ribociclib could maintain the quality of life in postmenopausal patients.[32–34] The PALOMA-2 study showed that the combination treatment of palbociclib and AI prolonged PFS compared to AI alone (27.6 vs. 14.5 months, HR = 0.563, $P < 0.0001$), with tolerable adverse effect. The quality of life in these patients was comparable to those who received single-agent endocrine treatment.[35] The results of the MONARCH-3 study showed that, the combination treatment of abemaciclib and AI significantly prolonged PFS compared to AI alone (28.18 vs. 14.76 months, HR = 0.54, $P = 0.000002$).[36] The PALOMA-4 and MONARCH Plus studies have further proved the efficacy of the combination therapy with CDK4/6 inhibitors and AI in Chinese patients.[37,38]

Currently, the OS benefit of this combination therapy in the first line setting has been proved in some studies. The MONALEESA-2 study indicated that the combination of ribociclib and letrozole significantly prolonged OS in post-menopausal patients compared to letrozole alone (63.9 vs. 51.4 months, HR = 0.76, $P = 0.004$).[39] The first-line subgroup analysis of the MONALEESA-3 study showed that the median OS in postmenopausal patients who received ribociclib and fulvestrant could reach as long as 67.6 months.[40] The secondary OS interim analysis of the MONARCH-3 study showed that compared to AI with placebo, AI combined with abemaciclib did not improve overall survival (67.1 vs. 54.5 months, HR = 0.754, $P = 0.0301$). Further follow-up is required to determine the OS value of abemaciclib.[41] The OS analysis of the PALOMA-2 study showed that the combination of letrozole and palbociclib failed to show significant improvement of OS compared to letrozole combined with placebo (53.9 and 51.2 months, respectively, HR = 0.956, 95% *CI:* 0.777–1.777). Sensitivity analysis excluding patients whose survival status were not accessible showed that the OS of patients who received combination therapy and AI alone was 51.6 and 44.6 months, respectively (HR = 0.869, 95% *CI:* 0.706–1.069).[42] The real-world P-Reality

X study has demonstrated that palbociclib combination therapy had a prolonged OS compared to the control group (57.8 and 43.5 months, respectively, HR = 0.72, $P < 0.0001$).[43] The DAWNA-2 study showed that combination therapy with letrozole or anastrozole and dalpiciclib significantly improved median PFS compared to that combined with placebo (30.6 and 18.2 months, respectively, HR = 0.51, $P < 0.0001$). Subgroup analysis demonstrated that regardless of the menopausal status, all patients could benefit from the combination therapy of dalpiciclib and AI in the first-line setting.[44]

No consensus has been reached on whether CDK4/6 inhibitors should be combined with AI or fulvestrant in the first-line setting. The PARSIFAL study compared the efficacy between palbociclib combined with fulvestrant and combined with letrozole in the first-line setting, but found no statistically significant differences between the two groups.[45] In the first-line treatment of advanced breast cancer, if patients cannot tolerate or use CDK4/6 inhibitors, single-agent AI or fulvestrant can be selected, and fulvestrant combined with anastrozole can also be considered.[46,47] Tamoxifen or toremifene may also be considered in economically disadvantaged regions or patients, depending on prior therapy and current disease status.

(2) Second and later-line treatment:

The MONALEESA-3 study showed that the combination treatment of ribociclib and fulvestrant could significantly prolong patients' PFS (20.5 and 12.8 months, respectively, HR = 0.60, $P < 0.001$) and OS (not attained vs. 40.0 months, HR=0.72, $P = 0.00455$). Explorative analysis demonstrated that the OS in patients who received ribociclib with or without fulvestrant was 53.7 and 41.5 months, respectively (HR = 0.726, 95% CI: 0.588–0.897).[31,48] It was verified in the PALOMA-3 study that, the PFS of patients treated with second-line palbociclib and fulvestrant was longer than that with fulvestrant alone (11.2 and 4.6 months, respectively, HR = 0.50, $P < 0.0001$). The same study also demonstrated clinically significant OS benefit (34.8 and 28.0 months, respectively, HR = 0.81, $P = 0.0221$).[49,50] Moreover, the MONARCH-2 study demonstrated significantly prolonged OS with abemaciclib and fulvestrant compared to fulvestrant alone (46.7 and 37.3 months, respectively, HR = 0.757, $P = 0.01$).[51]

The MONARCH plus and the DAWNA-1 studies further confirmed the efficacy of CDK4/6 inhibitors in the second-line treatment for Chinese patients. The MONARCH plus study showed that the PFS of abemaciclib combined with fulvestrant and fulvestrant alone was 11.5 and 5.6 months, respectively, HR = 0.376, $P < 0.0001$.[38] Prolonged median PFS was also shown in the DAWNA-1 study from the dalpiciclib + fulvestrant when compared to fulvestrant alone (15.7 and 7.2 months, respectively, HR = 0.42, $P < 0.0001$).[52]

There is no conclusion whether cross-line use of the same or different CDK4/6 inhibitors could benefit patients. The phase II MAINTAIN study showed that for patients who progressed after palbociclib or other CDK4/6 inhibitors during the advanced phase, continued use of ribociclib and endocrine treatment could improve patients' PFS (5.29 and 2.76 months, respectively, HR = 0.57, $P = 0.006$).[53] Further studies are needed to validate this conclusion and select patients that may benefit from cross-line treatment.

The abnormal gene expression caused by epigenetic changes is related to disease progression and resistance to endocrine therapy. It was demonstrated in the ACE study that, for post-menopausal HR+ HER2- ABC patients who failed previous tamoxifen and/or non-steroidal AI treatment, combined treatment of histone deacetylase inhibitors chidamide and exemestane prolonged the median PFS compared to placebo + exemestane (7.4 and 3.8 months, respectively, HR = 0.75, $P = 0.033$).[54] The combination treatment of chidamide and AI has been approved in China.

The resistance to endocrine therapy might be related to the activation of the PI3K/AKT/mTOR signaling pathway. The phase III randomized controlled clinical trial BOLERO-2 has confirmed that, for ABC patients who progressed upon non-steroidal AI treatment, mTOR inhibitor everolimus combined with exemestane markedly improved PFS when compared to exemestane alone (11.0 and 4.1 months, respectively, HR = 0.38, $P < 0.0001$). However, more adverse events occurred in the combination treatment group.[55,56] The phase II DESIREE study examined the dose escalation regimen of everolimus which showed that it retained the efficacy while reduced the incidence of stomatitis.[57] Everolimus could also be used in combination with letrozole, tamoxifen, or fulvestrant.[58–61] For HR+ ABC patients, a retrospective study has shown similar median PFS in sirolimus combined with endocrine therapy group and in everolimus combined with endocrine therapy group (4.9 and 5.5 months, respectively, HR = 1.56, $P = 0.142$), indicating potential replacement of everolimus with sirolimus in certain circumstances.[62]

Previous studies showed that patients with *PIK3CA* mutation were associated with worse prognosis and the efficacy of standard treatment was not comparable to those without mutation.[63] The SOLAR-1 study showed that for patients with PIK3CA mutation and previously treated with endocrine treatment (including CDK4/6 inhibitor treatment), PI3K inhibitor alpelisib combined with fulvestrant could significantly prolong patients' PFS compared to fulvestrant alone (11.0 and 5.7 months, respectively, HR = 0.65, $P < 0.001$).[64] The OS was also numerically prolonged in the combination group (39.3 and 31.4 months, respectively, HR = 0.86, $P = 0.15$).[65] The United States Food and Drug Administration (FDA) has approved the use of alpelisib in ABC, but this drug has not entered the Chinese market yet.

Pre-clinical studies demonstrated that resistance to CDK4/6 inhibitors was often accompanied by activation of the PI3K/AKT/mTOR signaling pathway. Inhibition of this activated pathway could effectively reverse the CDK4/6 resistance.[66,67] The phase I/II TRINITI-1 study explored the combined use of CDK4/6 inhibitors, mTOR inhibitors, and endocrine treatment after progression on CDK4/6 inhibitors, and showed that the median PFS was 5.7 months.[68]

The phase II BYLieve study is the first international multi-center clinical study that explored the use of combined targeted and endocrine treatment upon CDK4/6 inhibitor progression. The study showed that in HR+ HER2- ABC patients with *PIK3CA* mutation who progressed on previous CDK4/6 inhibitors and AI treatment, the 6-month progression-free survival rate of patients who received alpelisib and fulvestrant was 50.4%, and the median PFS was 7.3 months.[69,70]

PARP inhibitors are reasonable options for HR+ HER2- ABC patients with *gBRCA* mutation who are not eligible for endocrine treatment. For more information regarding the use of PARP inhibitors, please see section 8 of this guideline. For systemic therapy for post-menopausal HR+ HER2- ABC patients, please refer to Table 8.

6.2.2. Endocrine treatment options for pre-menopausal HR+ HER2- ABC patients

Castration therapy includes surgical castration (bilateral oophorectomy), medical castration (gonadotropin releasing hormone analogues), and radiation castration (pelvic radiation to ablate ovaries which is no longer routinely used due to high treatment failure rate). Gonadotropin releasing hormone (GnRH) analogues should be given to pre-menopausal patients continuously to inhibit ovarian function. For patients who need long-term ovarian inhibition, the best castration method should be selected based on patients' childbearing willingness, adherence to long-term injection, and costs.

For patients unwilling to undergo castration, tamoxifen or toremifene may be considered if resistance to selective estrogen receptor modulators (SERMs) are excluded.

Some studies specifically focused on pre-menopausal breast cancer patients. The MONALEESA-7 study was a large phase III clinical study that focused on pre-menopausal and peri-menopausal advanced breast cancer patients. The study showed that ribociclib combined with AI and ovarian function suppression (OFS) could significantly improve the PFS of pre-menopausal patients (23.8 and 13.0 months, respectively, HR = 0.553, $P < 0.0001$). The quality of life, with ESMO-MCBS score reaching 5, was also significantly improved in this group.[71] The up-

Table 8
Systemic therapy for post-menopausal HR+ HER2- ABC patients.

Treatment line	Priority	Recommended	Optional
First-line			
Primary endocrine resistance	Fulvestrant + CDK4/6 inhibitors (IA)	AI + CDK4/6 inhibitors (IA)	(1) AI + fulvestrant (IIA) (2) AI + everolimus (IIB) (3) Other endocrine therapy options (IIB)
Secondary endocrine resistance	AI + CDK4/6 inhibitors (IA)	(1) Fulvestrant + CDK4/6 inhibitors (IA) (2) AI + everolimus (IB)	(1) AI + fulvestrant (IIA) (2) Tamoxifen or toremifene (IIB)
Second- and later-line			
CDK4/6 inhibitor-naïve	(1) Fulvestrant + CDK4/6 inhibitors (IA) (2) AI + CDK4/6 inhibitors (IA) (3) AI + everolimus (IB)	(1) AI + chidamide (IB) (2) Endocrine therapy + alpelisib (for *PIK3CA* mutated tumors, IB) (3) PARP inhibitors (for patients with *gBRCA* mutation, IB)	(1) Fulvestrant (IIA) (2) AI (IIB) (3) Tamoxifen or toremifene (IIB) (4) Progesterone (IIB)
Post-CDK4/6 inhibitors	(1) Endocrine therapy + everolimus (IIA) (2) Endocrine therapy + alpelisib (for *PIK3CA* mutated tumors, IB)	(1) Endocrine therapy + chidamide (IIA) (2) Endocrine therapy + another CDK4/6 inhibitor (IIA)	PARP inhibitors (for patients with *gBRCA* mutation, IB)

Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; *gBRCA* mutation, germline breast cancer gene mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PARP, poly ADP-ribose polymerase.

dated results from the MONALEESA-7 study further validated that the combined treatment of ribociclib and endocrine therapy could improve OS (58.7 and 48.0 months, respectively, HR = 0.76) in pre-menopausal or peri-menopausal patients compared to endocrine therapy alone.[72]

For pre-menopausal ABC patients who failed SERMs treatment, the MIRACLE study demonstrated that patients who received everolimus combined with letrozole had prolonged median PFS compared to those who received letrozole alone (19.4 and 12.9 months, respectively, HR = 0.64, $P = 0.008$). In addition, 53 patients from the letrozole group crossed to the everolimus group and obtained an additional 5.5-month PFS (95% *CI:* 3.8–8.2 months) and the OS has not yet been reached.[61] For those patients, letrozole combined with everolimus is also a reasonable option.

6.2.3. Principles of using chemotherapy for HR+ HER2- ABC patients

The development of new endocrine agents has led to an increase of PFS and prolonged time to chemotherapy for ABC patients. Chemotherapy is still recommended for patients who may not benefit from endocrine treatment or who need rapid tumor burden reduction. For patients with primary endocrine resistance, chemotherapy may also be considered. Efficacy and adverse events should be balanced when selecting chemotherapy regimens. Single-agent chemotherapy should be prioritized. For detailed principles and regimens please refer to section 5.

Additionally, novel ADCs are emerging as alternative treatment options. According to the results of the DESTINY-Breast04 study, for HR+ HER2-low expression patients who previously received 1–2 lines of chemotherapy (progressed after at least one endocrine treatment and could no longer benefit from endocrine treatment), T-DXd treatment could significantly improve PFS (10.1 and 5.4 months, respectively, HR = 0.51, $P < 0.001$) and OS (23.9 and 17.5 months, respectively, HR = 0.64, $P = 0.003$) compared to chemotherapy of physicians' choice.[73] In August 2022, FDA approved T-DXd in treating ABC with low HER2 expression. However, this drug requires patients to receive at least one line of chemotherapy in the metastatic phase, or recurrence developed within six months after finishing adjuvant chemotherapy.[74]

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate. The phase I TROPiCS-02 clinical trial showed that for HR+ HER2- ABC patients who were previously heavily treated with endocrine therapy, CDK4/6 inhibitors, and 2–4 lines of chemotherapy, sacituzumab govitecan significantly prolonged PFS compared to single-agent chemotherapy of physicians' choice (5.5 and 4.0 months, respectively, HR = 0.66, $P = 0.0003$). The OS in the second interim analysis of two groups were 14.4 and 11.2 months, respectively (HR = 0.84, $P = 0.020$).[75]

7. Treatment for HER2-positive ABC

7.1. Treatment principles

Patients with recurrent and/or metastatic breast cancer is recommended to re-test for HER2 expression. For patients whose disease course does not meet the characteristics of HER2 status identified in primary lesions, the HER2 expression should be re-tested, especially in metastatic sites.[76] For HER2+ ABC patients, anti-HER2 treatment should be initiated as early as possible, unless contraindication existed. The application of anti-HER2 treatment should be cautiously decided in patients with unclarified HER2 status.

Patients with advanced breast cancer who have received trastuzumab in the (neo) adjuvant setting should still receive anti-HER2 therapy. For patients who developed recurrence within 12 months after completing trastuzumab, second-line anti-HER2 treatment is recommended. For patients who developed recurrence after 12 months of trastuzumab completion, combination therapy of trastuzumab and pertuzumab is recommended as the first line treatment. If pertuzumab is not available, trastuzumab combined with chemotherapy should be applied as an alternative option. Although anti-HER2 treatment is effective for HER2+ ABC patients, no large phase III trial has shown that chemotherapy can be spared in this population.

For patients with HR+ HER2+ ABC who can tolerate chemotherapy, anti-HER2 treatment in combination with chemotherapy is recommended. For patients who cannot tolerate chemotherapy or with slow progression, anti-HER2 treatment (dual targeted therapy is preferred) in combination with endocrine therapy should be considered. Compared to endocrine therapy alone, combined treatment could prolong patients' PFS.[77,78] The phase III randomized controlled trial SYSUCC-002, which was conducted by researchers in China, has demonstrated that, for HR+ HER2+ ABC patients, trastuzumab combined with endocrine treatment is non-inferior to trastuzumab combined with chemotherapy and with fewer adverse events.[79] If patients benefit from the first-line combination therapy of chemotherapy and anti-HER2 treatment, endocrine therapy combined with anti-HER2 treatment could be considered as maintenance therapy, despite a lack of evidence on this regimen from randomized clinical trials.

We support the use of trastuzumab biosimilars that have been approved in China for the treatment of HER2-positive breast cancer. Principles for HER2-positive ABC treatment are demonstrated in Table 9.

Table 9
Principles for the treatment of HER2-positive advanced breast cancer.

No.	Content
1	Re-evaluation of HER2 status in metastatic lesions is recommended for recurrent/metastatic patients.
2	Anti-HER2 therapy should be initiated as early as possible in HER2-positive patients unless contraindication existed.
3	The choice of anti-HER2 therapy in the advanced setting should take into account the type of anti-HER2 agents in the (neo) adjuvant setting and time to disease recurrence.
4	Combination of chemotherapy and anti-HER2 therapy is recommended.
5	Anti-HER2 therapy combined with endocrine therapy could be considered in HR+ HER2+ patients who are not eligible for chemotherapy or with slow disease progression.
6	We support the use of trastuzumab biosimilars in HER2-positive breast cancer treatment if their indications have been approved in China.

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

7.2. Treatment regimens

7.2.1. First-line treatment

For patients with HER2-positive ABC, first-line anti-HER2 treatment should be initiated as early as possible regardless of previous anti-HER2 treatment history. Treatment regimens should be individualized based on previous treatment history, tolerability and adverse events.

Trastuzumab and pertuzumab in combination with paclitaxel is recommended as the first-line anti-HER2 treatment. The CLEOPATRA study proved that adding pertuzumab to the combination of trastuzumab and paclitaxel could further prolong patients' PFS and OS. The median OS in trastuzumab and pertuzumab group was 57.1 months, which was 16.3 months longer than the trastuzumab alone group.[80] The Puffin study, which focused on Chinese patients, has shown that adding pertuzumab to trastuzumab and paclitaxel could further prolong patients' PFS.[81] Based on the above studies, the combination treatment of pertuzumab, trastuzumab, and docetaxel has been approved in China as the first-line treatment for HER2-positive ABC patients who are treatment-naïve to anti-HER2 therapy or chemotherapy.

For HER2-positive ABC patients who are trastuzumab-naïve, or develop recurrence or metastasis over one year after the completion of trastuzumab treatment, or are responsive to trastuzumab in the neoadjuvant setting, the combination therapy of pertuzumab, trastuzumab and paclitaxel is recommended.[80,81] When pertuzumab is not accessible, trastuzumab in combination with chemotherapy could be considered, especially for those who are trastuzumab-naïve. The efficacy and safety of trastuzumab combined with chemotherapy is superior to that of lapatinib combined with chemotherapy.[82] The tumor response rate of trastuzumab combined with paclitaxel could reach as high as 50–60% with significantly prolonged survival.[83] Besides paclitaxel, the combination treatment of trastuzumab with other chemotherapy agents are also proved to be effective and safe in clinical practice, such as vinorelbine,[84] capecitabine,[85] gemcitabine, etc.[86,87] Combination treatment with metronomic chemotherapy is also an alternative option.

A phase II study comparing the combination treatment of pyrotinib with capecitabine and the combination of lapatinib with capecitabine in HER2-positive ABC patients has shown that, in trastuzumab-naïve patients, the PFS in pyrotinib group was 12.5 months longer than that in the lapatinib group (18.1 and 5.6 months, respectively, HR = 0.37, $P = 0.0013$).[88] Based on this study, pyrotinib combined with capecitabine was approved in China for treating HER2-positive ABC patients who were previously treated with trastuzumab or trastuzumab-naïve. The PHILA study showed that for systemic treatment-naïve patients with HER2-positive recurrent or metastatic breast cancer, compared to placebo combined with trastuzumab and docetaxel, pyrotinib combined with trastuzumab and docetaxel could significantly improve the median PFS (24.3 and 10.4 months, respectively, HR = 0.41, $P < 0.0001$). This study further validates the efficacy of the combination therapy of pyrotinib, trastuzumab and docetaxel in the first-line anti-HER2 treatment.[89]

The combined anti-HER2 and chemotherapy treatment should last at least 6–8 cycles and the specific duration should be based on treatment efficacy and patients' tolerance. The best duration of anti-HER2 treatment is not validated. Anti-HER2 treatment could be continued if there is no disease progression or occurrence of intolerable adverse events. If HR+ HER2+ patients respond well to anti-HER2 therapy combined with chemotherapy, anti-HER2 therapy combined with endocrine therapy can be considered as maintenance therapy. Treatment discontinuation could be considered in patients with complete remission for years and the anti-HER2 treatment should be resumed once recurrence was identified.

7.2.2. Second- and later-line treatment

In patients who failed previous anti-HER2 treatment, continuous inhibition of the HER2 pathway is recommended, and anti-HER2 therapies should be continued in such patients.

The phase III PHOEBE study showed that for patients with trastuzumab-treated advanced disease, compared to lapatinib combined with capecitabine, pyrotinib combined with capecitabine significantly prolonged patients' median PFS (12.5 and 6.8 months, respectively, HR = 0.39, unilateral $P < 0.0001$).[90] Recently updated follow-up results showed that the median OS was also improved in pyrotinib group compared to the control group (not-attained vs. 26.9 months, HR = 0.69, unilateral $P = 0.02$).[91]

The NALA study compared neratinib combined with capecitabine and lapatinib combined with capecitabine in advanced patients who were previously treated with at least two lines of anti-HER2 therapies. The results showed that the neratinib group significantly improved the PFS, duration of response, and time to intervention for symptomatic central nervous system metastasis, but no significant benefit in OS was observed.[92] Based on this study, FDA approved the use of the combination therapy of neratinib and capecitabine in February 2022. However, this combination has not yet been approved in China. According to the HER2 CLIMB study, compared to placebo combined with trastuzumab and capecitabine, tucatinib combined with trastuzumab and capecitabine achieved significantly longer PFS (7.8 and 5.6 months, respectively, HR = 0.54, $P < 0.001$) and OS (21.9 and 17.4 months, respectively, HR = 0.66, $P = 0.005$).[93] In April 2020, FDA approved tucatinib for treating HER2+ ABC. However, this drug has not been approved in China yet.

Encouraging efficacy of T-DXd has been observed in HER2-positive ABC patients. The phase III DESTINY-Breast03 study has confirmed that for HER2-positive ABC patients who were previously treated with trastuzumab and paclitaxel, the PFS in the T-DXd group was significantly longer than that of the T-DM1 group (28.8 vs. 6.8 months, HR = 0.33, $P < 1 \times 10^{-6}$). The objective response rate (ORR) was also markedly improved in the T-DXd group (78.5% and 35.0% respectively, $P < 0.0001$).[94] The DESTINY-Breast01 study demonstrated that, T-DXd treatment alone could achieve an ORR of 62%, a median PFS of 19.4 months, and a median OS of 29.1 months in heavily treated patients.[95,96] T-DXd has been approved in China for treating HER2-positive ABC patients who have received one or more prior anti-HER2-based regimens.

The EMILIA study showed that for HER2-positive ABC patients who progressed on previous trastuzumab and paclitaxel treatment, T-DM1 significantly prolonged PFS (9.6 and 6.4 months, respectively,

Table 10
Systemic therapy for HER2-positive advanced breast cancer.

Treatment line	Priority	Recommended	Optional
First-line	(1) Trastuzumab + pertuzumab + taxanes (IA) (2) Trastuzumab + pyrotinib + taxanes (IB)	(1) Trastuzumab + chemotherapy (IB) (2) Trastuzumab + pertuzumab + other chemotherapy agents (IIA) (3) Pyrotinib + capecitabine (IIA)	Trastuzumab + pertuzumab + endocrine therapy for HR+ patients(IB)
Second-line	(1) Pyrotinib + capecitabine (IA) (2) T-DM1(IA)	(1) T-DXd (IA)	Trastuzumab + pertuzumab + chemotherapy
Third- and later-line	T-DXd (IA)	(1) Neratinib + capecitabine (IA) (2) Trastuzumab + chemotherapy (IB) (3) Margetuximab + chemotherapy (IIA) (4) Inetetamab + chemotherapy (IIA) (5) Trastuzumab + lapatinib (IIB) (6) Pyrotinib + chemotherapy (IIB) (7) Trastuzumab + pertuzumab + chemotherapy	Clinical trials

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

HR = 0.65, $P < 0.001$) and OS (30.9 and 25.1 months, respectively, HR = 0.68, $P = 0.0006$) compared to lapatinib combined with capecitabine.[97] Based on the EMILIA study and the bridging ELAINA study conducted in China, T-DM1 has been approved in China for HER2-positive ABC patients who were previously treated with trastuzumab and paclitaxel.

The SOPHIA study has demonstrated that for HER2-positive ABC patients who were previously treated with multiple lines of anti-HER2 treatment, novel HER2 monoclonal antibody margetuximab combined with chemotherapy significantly prolonged PFS compared to trastuzumab combined with chemotherapy (5.8 and 4.9 months, respectively, HR = 0.76, $P = 0.03$). However, the absolute gain in PFS was only 0.9 month.[98] The updated results of the SOPHIA study showed that the combined treatment of margetuximab and chemotherapy did not improve overall survival (21.6 and 21.9 months, respectively, HR = 0.95, $P = 0.62$).[99] In December 2020, FDA approved the use of margetuximab in treating HER2+ MBC patients who were previously treated with at least two lines of anti-HER2 treatment. Margetuximab has not been approved in China yet.

Inetetamab is a self-developed monoclonal anti-HER2 antibody in China. The HOPES study showed that for HER2 positive MBC patients who were previously treated with at least one line of chemotherapy, inetetamab combined with vinorelbine significantly prolonged PFS compared to vinorelbine alone (39.1 and 14.0 weeks, respectively, HR = 0.24, $P < 0.0001$).[100] Based on this result, inetetamab was approved in China for treating HER2 positive ABC.

Disitamab vedotin (RC48) is an antibody-drug conjugate self-developed in China. It is comprised of a novel humanized anti-HER2 IgG1 antibody, a cleavable linker, and a cytotoxic tubulin inhibitor, monomethyl auristatin E (MMAE). The efficacies of RC48 in HER2-positive and HER2-low expression patients are currently being evaluated in clinical trials.

Patients who failed multiple lines of anti-HER2 treatment should be encouraged to participate in clinical trials. The treatment regimens for HER2-positive ABC are summarized in Table 10.

8. Treatment for advanced TNBC

8.1. Treatment principles

As gBRCA1/2 mutation is the main gene mutation with therapeutic value and available treatment options in TNBC, it should be tested as early as possible, especially in young patients or patients with family history. However, the therapeutic significance of somatic BRCA1/2 mutation in breast cancer needs to be further validated and is not recommended for routine clinical practice.

For non-*gBRCA* mutated triple-negative advanced breast cancer, there is currently no evidence to support the use of specific treatment regimens, and the chemotherapy regimens can follow what is recommend for HER2-negative breast cancer. Platinum-based therapy is important for TNBC, especially for those with *gBRCA* mutation. PARP inhibitors are reasonable choices for patients with *gBRCA* mutation. However, this indication has not been approved in China. Therefore, full disclosure and discussion should be made with patients before using PARP inhibitors in TNBC. Alternatively, patients should be encouraged to participate in clinical trials.

Combination therapy of immune checkpoint inhibitors (ICIs) and chemotherapy can improve the survival of patients with PD-L1+ advanced TNBC. Currently no ICI has been approved in China for advanced TNBC; therefore, thorough discussion should be made with patients before initiating ICI treatment. PD-L1 expression should be evaluated with reliable methods. The combination of ICI and chemotherapy should refer to high-quality clinical trials. Patients are also encouraged to participate in well-designed clinical trials. Principles for the treatment of advanced TNBC are listed in Table 11.

8.2. Treatment regimens

Currently, chemotherapy remains the main treatment strategy for advanced TNBC. Phase II and phase III studies conducted by researchers in China demonstrated that the combination of cisplatin with docetaxel or gemcitabine was superior to that of non-platinum-based combination therapy.[101,102]

8.2.1. First-line treatment

For PD-L1 negative patients with *gBRCA* mutation, platinum-based chemotherapy doublets or platinum monotherapy are preferred. For patients with *gBRCA* mutation, the TNT study showed that carboplatin was more effective than docetaxel.[103] In a phase II study conducted by Chinese researchers, docetaxel combined with cisplatin significantly prolonged PFS and OS compared with docetaxel combined with capecitabine. The efficacy of platinum-based therapy was further confirmed in the CBCSG006 study, the GAP study, and real-world studies.[101,102,104,105]

The PARP inhibitor olaparib is a first-line option for patients with advanced TNBC and gBRCA mutation. For patients previously treated with anthracycline and/or paclitaxel, the phase III OlympiAD study has proved that olaparib significantly prolonged patients' PFS and improved their quality of life with acceptable toxicity compared to treatment of physician's choice.[106] OS benefit was not observed in the whole cohort (median survival in the treatment group and the control group was 19.3 and 17.1 months, respectively, HR = 0.90, $P = 0.513$). But for chemotherapy-naïve patients, the median OS in the olaparib group was significantly improved compared to those in the chemotherapy group (22.6 and 14.7 months, respectively, HR = 0.51, $P = 0.02$).[107] FDA has approved the use of olaparib in ABC patients with *gBRCA* mutation. However, this indication has not been approved in China yet.

Table 11
Principles for the treatment of advanced triple negative breast cancer.

No.	Content
1	*gBRCA1/2* mutation should be tested as early as possible, especially in young patients with family history.
2	There are no data supporting specific chemotherapy regimen for patients without *gBRCA* mutation.
3	Platinum is a more favorable chemotherapy option for patients with *gBRCA* mutation.
4	PARP inhibitors are reasonable treatment options for patients with *gBRCA* mutation.
5	Checkpoint inhibitors in combination with chemotherapy are reasonable treatment options for patients with positive PD-L1 expression.

Abbreviations: gBRCA mutation, germline breast cancer gene mutation; PD-L1, programmed death ligand 1; PARP, poly ADP-ribose polymerase.

The combination therapy of ICIs and chemotherapy has shown encouraging efficacy in TNBC patients with PD-L1 expression. The IMpassion 130 study showed that for advanced TNBC patients with positive PD-L1 expression, atezolizumab combined with nab-paclitaxel could significantly prolong the PFS (7.5 and 5.0 months, respectively, HR = 0.62, $P < 0.001$) and OS (25.4 and 17.9 months, respectively, HR = 0.67) compared to placebo combined with nab-paclitaxel.[108,109] However, inconsistent result has been reported in the IMpassion 131 study, which showed that the PFS between the atezolizumab combined with paclitaxel group and the placebo combined with paclitaxel group was not significantly different. The efficacy of combination therapy of ICIs and chemotherapy might vary based on what type of chemotherapy was used. FDA granted accelerated approval of atezolizumab in TNBC in March 2019, but revoked the grant in August 2021. The KEYNOTE-355 study has demonstrated that for PD-L1-positive patients (combined positive score, CPS ≥ 10), combination of pembrolizumab and chemotherapy resulted in prolonged PFS (9.7 and 5.6 months, respectively, HR = 0.65, $P = 0.0012$) and OS (23.0 and 16.1 months, respectively, HR = 0.73, $P = 0.0093$) compared to chemotherapy alone. Subgroup analysis showed that PFS and OS benefit was consistent in patients with CPS of 10–19 and CPS ≥ 20.[110–112] Based on the results of the KEYNOTE-355 study, FDA granted accelerated approval of pembrolizumab in such a population in November 2020. The phase II FUTURE-C-PLUS study, which was conducted in China, explored the efficacy and safety of adding famitinib to camrelizumab and nab-paclitaxel in the first-line treatment for TNBC patients with immunomodulatory subtype and showed considerable anti-tumor activity with acceptable toxicity.[113] ICIs have not yet been approved in treating advanced TNBC in China.

8.2.2. Second- and later-line treatment

For TNBC patients with *gBRCA* mutation, platinum-based chemotherapy doublet or platinum monotherapy could be considered, if patients did not receive platinum in the first-line setting, PARP inhibitors can also be considered. Besides olaparib, the phase III EMBRACA study has shown that compared to chemotherapy of physicians' choice (capecitabine, eribulin, gemcitabine or vinorelbine), the next-generation PARP inhibitor, talazoparib significantly improved PFS (8.6 and 5.6 months, respectively, HR = 0.54, $P < 0.001$), 24-week ORR (62.6% and 27.2% respectively, $P<0.001$) and clinical benefit rate (68.6% and 36.1%, respectively, $P < 0.001$), but not OS (19.3 and 19.5 months, respectively, HR = 0.848, $P = 0.17$) in patients with gBRCA1/2 mutation. Talazoparib had tolerable toxicity, with better PRO results compared to the chemotherapy group.[114,115] Talazoparib has been approved by FDA, but it has not entered the Chinese market yet. Additionally, when combined with platinum-based chemotherapy, PARP inhibitors might further benefit HER2 negative ABC patients with *gBRCA* mutation. The BROCADE3 study showed that adding PARP inhibitor veliparib to the combined treatment of carboplatin and paclitaxel could significantly prolong patients' PFS (14.5 and 12.6 months, respectively, HR = 0.71, $P = 0.0016$).[116]

The answers to questions, including comparison between PARP inhibitors and platinum-based chemotherapy, the optimal treatment strategy of PARP inhibitors and platinum (combination or sequential), and the efficacy of PARP inhibitors in tumors that have progressed after platinum-based therapy, need to be further explored. It is recommended that platinum-based chemotherapy be used as the initial treatment in patients with visceral crisis or rapid progression disease until further clinical evidence is generated.

A phase II study evaluating the use of pembrolizumab and niraparib in patients with advanced or metastatic TNBC indicated the potential benefit of combining PARP inhibitors with ICIs, especially for those with *gBRCA* mutation.[117]

The KEYNOTE-119 study explored the use of single-agent ICI pembrolizumab in second and later lines of treatment and has shown that the efficacy of single-agent pembrolizumab was not superior to that of chemotherapy.[118] Many studies are currently ongoing to examine the use of immunotherapy in advanced TNBC.

For advanced TNBC patients without *gBRCA* mutation, chemotherapy agents that had not been used previously are recommended for second-line treatment. Sacituzumab govitecan is also an alternative option. A phase II single-arm clinical trial showed that TNBC patients receiving sacituzumab govitecan at second and later lines achieved a median ORR of 33.3% and a median remission time of 7.7 months.[119] Based on this study, FDA granted accelerated approval of sacituzumab govitecan in April 2020. In the confirmative phase III ASCENT study, sacituzumab govitecan significantly improved PFS (5.6 and 1.7 months, respectively, HR = 0.41, $P < 0.001$) and OS (12.1 and 6.7 months, respectively, HR = 0.48, $P < 0.001$) compared to single-agent chemotherapy of physician's choice in paclitaxel-treated advanced TNBC patients without CNS metastasis.[120] In June 2022, sacituzumab govitecan was approved in China as second- and later-line treatment for advanced TNBC.

The DESTINY-Breast04 study enrolled 557 patients with low HER2 expression who have received first- or second-line chemotherapy, among which there were 58 TNBC patients. In the TNBC subgroup, T-DXd has also shown prolonged PFS (8.5 and 2.9 months, respectively, HR = 0.46, 95% CI: 0.24–0.89) and OS (18.2 and 8.3 months, respectively, HR = 0.48, 95% CI: 0.24–0.95) compared to chemotherapy of physician's choice.[73]

Other treatment options include adding bevacizumab or AKT inhibitors to chemotherapy. Adding bevacizumab to chemotherapy could improve the PFS but not OS of ABC patients.[121] Considering the adverse events, bevacizumab is not recommended for routine use in advanced TNBC patients. However, its use in combination with chemotherapy may provide benefits to patients with multi-drug resistance and could be chosen when treatment options are limited. A phase II study evaluated the efficacy of AKT inhibitors combined with chemotherapy, and demonstrated that this combination prolonged PFS in TNBC patients, especially in those with *PIK3CA/AKT/PTEN* pathway activation.[122] Large phase III studies are currently ongoing to further validate the value of AKT inhibitors.[123]

Enzalutamide has been shown to be effective in androgen receptor (AR)-positive TNBC patients who progressed upon standard treatment. Relevant phase III study is currently ongoing.[124] Biomarker studies aiming to optimize and standardize AR testing should be further conducted. The treatment regimens for TNBC are summarized in Table 12.

9. Management of different metastatic sites

9.1. Bone metastases

Bone is one of the most common metastatic sites for breast cancer.[125,126] For diagnosis and evaluation of bone metastasis, please refer

Table 12
Systemic therapy for triple negative advanced breast cancer.

Treatment line	Priority	Recommended	Optional
First-line			
PD-L1+	–	Immune checkpoint inhibitors+chemotherapy (IA)	–
PD-L1-, no *gBRCA* mutation	Combined or single-agent chemotherapy (IA)	–	–
PD-L1-, with *gBRCA* mutation	Combined or single-agent platinum-based chemotherapy (IA)	PARP inhibitors (IB)	–
Second- and later-line			
No *gBRCA* mutation	Combined or single-agent chemotherapy (IA)	Sacituzumab govitecan (IB)	–
gBRCA mutation	Combined or single-agent platinum-based chemotherapy (IA)	PARP inhibitors (IB)	–
Low HER2 expression	–	T-DXd (IB)	–

Abbreviations: *gBRCA*, germline breast cancer gene; HER2, human epidermal growth factor receptor 2; PARP, poly ADP-ribose polymerase; PD-L1, programmed death ligand 1; T-DXd, trastuzumab deruxtecan.

to the principles in the ABC evaluation section. Once a patient experiences bone pain, pathological fracture, elevated alkaline phosphatase (ALP), spinal or nerve compression, hypercalcemia, etc., further examination should be performed to verify the extent and severity of bone metastasis. MRI is preferred for patients with vertebral involvement to determine the existence of spinal cord compression, and CT bone windows are preferred if ribs and pelvis involvement is speculated. The most common subtype of breast cancer in patients with bone metastasis is the HR+ HER2- subtype, accounting for 64.4% of all cases.[125] For HR+ HER2- patients with bone metastasis only, combination therapy of CDK4/6 inhibitor palbociclib with AI could reach a PFS of 36.2 months.[35]

The goals of comprehensive treatment for bone metastasis in breast cancer is to control tumor progression, prevent and treat skeletal-related events (SREs), alleviate pain, restore function, improve quality of life, and prolong survival.[127] Systemic therapy should be the backbone treatment. Bone modulators such as bisphosphonates and denosumab can help to prevent and reduce SREs, and therefore should be used as the underlying treatment for breast cancer patient with bone metastases, even after systemic progression occurs, until developing of intolerable adverse events.[128] The recommended dosing interval of bone modulator is every 4 weeks. The optimal duration of this treatment is currently unknown. There were evidence which showed that the efficacy of zoledronic acid every three months was non-inferior to the regular monthly dosing in terms of preventing the occurrence of SREs.[129] For isolated bone metastases, the optimal timing of initiation and duration of using bone modulators have not been determined. For patients with risk of developing bone metastasis-related events, bone modifying agents should be given as early as possible. For patients with relatively low risk, such as patients with isolated sternum, rib, or osteogenic metastasis, treatment with bone modifying agents might be delayed.

For patients with persistent or localized pain due to bone metastases, imaging assessment is required to determine if a pathological fracture is imminent or has occurred. For patients that may develop or have developed long-bone fracture, orthopedic evaluation is needed. Surgical fixation could be conducted prior to localized radiation therapy. Radiation therapy could be an option for patients with no risk of developing fracture. If patients develop any symptoms or signs of spinal compression, MRI should be performed to fully assess the severity of this oncology emergency. Surgical decompression should be considered first under such circumstances. Radiotherapy may be an option if there is no feasible decompression and fixation treatment.[130] The total dosage and fractionated dosage of radiotherapy should be determined based on the site of metastasis, neighboring organs, pain level and previous treatment. For patients with vertebral and para-vertebral metastasis, stereotactic radiosurgery (SRS) could be applied with caution to obtain a higher level of biological effective dose if technically allowed.

It has been estimated that up to 3% of patients who received bisphosphonate or denosumab developed osteonecrosis of the jaw (ONJ).[131] The risk factors of developing ONJ include poor baseline dental condition, and dental procedures conducted during treatment. Therefore, before receiving bisphosphonate and denosumab, patients are encouraged to receive dental examination and avoid dental procedures or invasive oral procedures during treatment.[132] The levels of serum calcium, creatinine, phosphate, and magnesium should be monitored to avoid occurrence of hypophosphatemia and hypocalcemia.

In terms of treatment response evaluation of bone metastases, it should be re-emphasized that bone scan cannot be used to determine the response. Similarly, CT should be used with caution, especially for patients with osteoblastic repair who respond to treatment. Please refer to the principles for ABC evaluation section for details. Principles for bone metastasis management are presented in Table 13.

9.2. Brain metastases

About 15% of ABC patients would develop brain metastasis (BM),[133] especially for those with HER2+ and triple-negative diseases. For HER2+ and TNBC patients with high-risk of developing brain metastases, brain MRI could be considered during routine follow-up. Brain metastasis usually develops early in the disease course in TNBC and associates with poor prognosis due to a lack of effective treatment strategies. For HER2+ breast cancer, brain metastasis could occur anytime during the advanced disease stage.[134]

The diagnosis of brain metastasis should be based on brain contrast MRI. If differential diagnosis with other brain tumors is needed, biopsy or surgical resection could be performed. After brain metastasis is confirmed, local treatment strategy (radiation or surgery) should be applied based on patients' general conditions, estimated survival, control of extra-cranial disease, the number and site of intracranial metastases and potential surgical risks. In addition to local treatment, systemic antitumor treatment should also be given according to the molecular subtype of the primary or metastatic lesion. For patients with poor prognosis, such as those with <70 of Karnofsky Score, uncontrolled extracranial diseases, or a lack of effective systemic treatment regimen, the best supportive of care could be applied, combined with or without radiotherapy.[135]

Compared to radiotherapy alone, surgical resection combined with radiotherapy could further increase local control rate, prolong symptom control duration, and median survival. Of note, surgical treatment-related survival benefit is mainly seen in patients without extra-cranial metastases or with stable extra-cranial disease. Compared to surgery alone, surgical resection + radiotherapy could improve local control rate and reduce the occurrence of distal brain metastasis by 66.0%.[136]

9.2.1. Surgery and radiation

(1) Principles of local treatment for single brain metastasis: Treatment strategies include surgery + post-operative radiotherapy, SRS, whole-brain radiotherapy (WBRT) plus memantine with hippocampal-avoidance (HA-WBRT + memantine), or hypofractionated stereotactic radiotherapy (HSRT). Lesions larger than 3–4 cm with mass effect could be evaluated by experienced neurosurgeons and the option of surgical resection should be discussed with patients. Lesions with no mass effect could be treated with SRS or surgery based on comprehensive evaluation of sur-

Table 13
Principles for the management of bone metastases.

No.	Content
1	HR+ HER2- breast cancer is the most common subtype of breast cancer that tends to develop bone metastases.
2	The goal of comprehensive treatment for bone metastases in breast cancer is to control tumor progression, prevent and treat SREs, relieve pain, restore function, and improve quality of life.
3	Systemic treatment should be the backbone treatment for bone metastases, and bone-modifying agents are recommended to be applied as early as possible for patients with risk of developing SREs.
4	The risk of developing pathological fractures should be routinely evaluated and appropriate surgery or radiation therapy should be given if necessary.
5	Spinal cord compression is an oncologic emergency that needs to be evaluated promptly with MRI. Surgical decompression should be prioritized.
6	The dose of radiotherapy for bone metastasis needs to be determined based on the site of metastasis, adjacent organs, pain level, and whether additional treatment is required.
7	Both bisphosphonate and denosumab can cause osteonecrosis of the jaw. Patients should monitor their dental condition, maintain optimal oral hygiene, and avoid invasive dental procedures during treatment. Serum calcium, creatinine, phosphate, and magnesium levels should be monitored during treatment.
8	Bone scan cannot be used for treatment response evaluation. CT bone window is recommended instead.

Abbreviations: CT, computed tomography; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MRI, magnetic resonance imaging; SRE, skeletal-related event.

gical risks, benefits, and patients' preferences. For unresectable lesions larger than 3–4 cm that are ineligible for SRS based on multi-disciplinary discussion, HSRT or HA-WBRT + memantine could be considered.

(2) Principles of local treatment for patients with limited number (2–4) of BMs: treatment strategies include surgery for large symptomatic lesions with post-operative radiation therapy and SRS for smaller lesions, or SRS ± (HA-WBRT + memantine), HSRT, or (HA-WBRT + memantine) ± SRS to treat unresectable lesions larger than 3–4 cm. The application of SRS should be discussed with eligible patients. For symptomatic patients with unresectable lesions and not eligible for SRS or HSRT, HA-WBRT + memantine is recommended, and SRS could be considered later. If brain lesion are over 3–4 cm with mass effect, surgical resection possibility for the major lesion should be discussed. SRS or HSRT could be given to the tumor bed and other lesions after resection, with or without HA-WBRT + memantine.
Supplementation of WBRT after SRT could significantly reduce the intracranial recurrence rate, but may lose the cognition protection of SRT alone.[137] Therefore, treatment decisions should be made based on the condition of intracranial lesions, estimated survival, and the preferences of the patients and families.

(3) Principles of local treatment for multiple brain metastases (≥5 sites): SRS or HA-WBRT+ memantine is recommended.

(4) Principles of local treatment for leptomeningeal metastases: WBRT + memantine is recommended.

9.2.2. *Systemic therapy*

Continuation of systemic therapy according to the molecular subtype of the primary tumor is recommended, especially after WBRT. These patients are more likely to benefit from systemic treatment, perhaps due to the damage of blood-brain barrier (BBB). Drugs that can better penetrate BBB are preferred especially for patients with leptomeningeal metastasis. The risk for brain metastasis in HER2-positive breast cancer patients would accumulate with disease course. Ultimately, around 50% of patients would develop brain metastasis if the disease course is long enough.[138] In recent years, some breakthroughs have been achieved in treating HER2+ breast cancer with brain metastasis.

(1) Monoclonal antibodies: WBRT and brain metastasis may affect the integrity of BBB, thus increase the penetration of trastuzumab and strengthen the efficacy of anti-HER2 treatment. A retrospective study showed that the 1-year survival rate could be improved by continuous anti-HER2 treatment after completion of brain radiotherapy for HER2-positive patients with brain metastasis.[139] If brain metastases occur during treatment of HER2-positive metastatic breast cancer, patients can still derive survival benefit from continued trastuzumab treatment. Studies have shown that no statistical difference was identified between trastuzumab and lapatinib in preventing brain metastasis, while trastuzumab was reported to be associated with survival benefit.[140]

(2) Tyrosine-kinase inhibitors (TKIs): The HER2 CLIMB study demonstrated that for HER2-positive ABC patients with brain metastasis, adding tucatinib to capecitabine plus trastuzumab significantly prolonged the intracranial PFS (9.9 and 4.2 months, respectively, HR = 0.32, $P < 0.00001$) and OS (21.6 and 12.5 months, respectively, HR = 0.60). The benefit was consistent in patients with either stable or active brain metastasis in subgroup analysis.[141,142] FDA has approved the use of tucatinib in HER2 ABC patients, including those with brain metastasis. However, tucatinib has not been approved in China. In patients with asymptomatic brain metastasis of smaller size, lapatinib combined with capecitabine could be cautiously applied as initial treatment, with radiation therapy as back-up salvage treatment.[143] The phase II single-arm PERMEATE study showed that the intra-cranial ORR of radiation-naïve patients with brain metastasis and of patients who progressed after radiation therapy was 74.6% and 42.1%, respectively, after receiving pyrotinib and capecitabine. Further phase III clinical trials are needed to validate this combination therapy in HER2+ breast cancer patients with brain metastasis.[144]

(3) ADCs: The KAMILLA study showed that the ORR in patients with brain metastasis who received T-DM1 was 21.4%, with a median PFS of 5.5 months. 49.3% of the patients enrolled in this study were intra-cranial radiation-naïve. Therefore, T-DM1 could be considered as a treatment option for HER2+ patients with brain metastasis.[145] The DESTINY-Breast03 study showed that among patients with brain metastasis, the median PFS in T-DXd and T-DM1 groups were 15.0 and 3.0 months, respectively, and the ORR for intracranial lesions were 63.9% and 33.4%, respectively.[146] The subgroup analysis in the DAISY study showed that the ORR was 62.5% in patients with non-active brain metastasis and treated with T-DXd. The efficacy of T-DXd has also been shown in low HER2 expression cohort.[147] More studies are required to validate the efficacy of ADCs in treating brain metastasis.

Patients with brain metastases should receive brain contrast MRI according to disease development. For triple-negative and HER2+ breast cancer patients, the frequency of brain MRI should be increased. Principles for the management of brain metastases in ABC patients are listed in Table 14.

9.3. *Metastases to other sites*

Management principles for ABC metastases to other sites are summarized in Table 15.

Table 14
Principles for the management of brain metastases.

No.	Content
1	Contrast MRI of the head is recommended for diagnosing brain metastases, and biopsy could be performed if necessary.
2	Brain metastases should be treated with combined local and systemic therapy.
3	Local therapy for brain metastases should take into consideration patients' symptoms, tumor resectability, and the number and size of metastatic lesions.
4	It is recommended to continue systemic therapy according to the molecular subtype of the primary tumor, taking into consideration the ability of the agents to penetrate the blood-brain barrier.
5	Contrast MRI of the head should be dynamically monitored during treatment.

Abbreviations: MRI, magnetic resonance imaging.

Table 15
Principles for the management of other metastatic sites.

No.	Content
1	No evidence exists to determine the optimal local therapy that might improve survival for patients with liver metastases.
2	For patients with malignant pleural effusion, thoracentesis should be performed for the purpose of diagnosis, symptom relief, and medication infusion within the chest.
3	For patients with locoregional recurrence, the possibility of curative local therapy should be evaluated, and systemic therapy should be used.

(1) Liver metastases: There has been no prospective randomized controlled trial that focuses on patients with liver metastases. Studies have demonstrated that for HR+ HER2- ABC patients with liver metastases, CDK4/6 inhibitors combined with endocrine treatment could result in significant survival benefit. A pooled analysis of the MONALEESA studies showed that both first-line and second-line combination therapy with ribociclib and endocrine therapy were associated with significantly prolonged PFS and OS in patients with visceral metastasis, including those with liver metastases and multiple metastatic sites (≥3).[148] The PALOMA-2 and PALOMA-3 studies demonstrated that, palbociclib combined with endocrine treatment could significantly improve PFS in patients with liver metastases.[149] The MONARCH2 and MONARCH3 joint analysis also showed that patients with liver metastases could benefit from treatment of abemaciclib combined with AI or fulvestrant.[150] Currently, there is no evidence regarding the optimal local treatment strategies that may improve survival (surgery, SRS, intra-hepatic chemotherapy, etc.).

(2) Malignant pleural effusion: Patients with malignant pleural effusion needs systemic treatment plus local procedure. For patients with unknown diagnosis, thoracentesis could be performed to determine diagnosis, even though false-negative results can be commonly observed in clinical settings. Drainage could be performed for symptomatic pleural effusion. After thorough drainage, chemotherapy agents or biological modulators could be injected.

(3) Chest-wall and regional (lymph nodes) recurrence: (1) Due to concurrent risks of developing distal metastases, patients should receive comprehensive evaluation, including chest, abdomen, and bone imaging. (2) When R0 resection is feasible and the risk of complications is low, surgical resection should be considered. (3) Local radiotherapy could be considered in radiation-naïve patients. (4) For patients who received previous radiotherapy, repeated radiation might be given to the entire or partial chest wall region. (5) Apart from local treatment (surgery, radiotherapy), systemic treatment should be given (chemotherapy, targeted therapy, endocrine therapy, etc.) if distal metastases exist. (6) Local or regional treatment followed by chemotherapy could improve long-term survival for HR- patients. (7) Local or regional treatment followed by endocrine therapy could improve long-term survival for HR+ patients. (8) Systemic treatment should be determined based on tumors' biological characteristics, previous treatment history, disease-free interval, and patients' performance status, comorbidities. (9) For patients who are not eligible for receiving radical local treatment, palliative systemic therapy should be given following the principles of ABC treatment, and palliative local treatment could also be considered.

10. Treatment for male ABC patients

Male breast cancer is a rare disease that accounts for approximately 1% of all breast cancers.[151] Currently, no randomized clinical trial has been conducted to specifically focus on male ABC patients. In recent years, increasing clinical trials have started to enroll male patients. Existing evidence on male ABC mainly comes from retrospective analysis or real-world studies.

(1) Endocrine treatment: Around 90% of all male breast cancers are HR-positive.[151,152] Endocrine therapy strategies for advanced male breast cancer are mostly derived from the treatment of female breast cancer. Tamoxifen is the standard recommendation for male ABC. For male ABC patients receiving AI treatment, luteinizing hormone–releasing hormone (LHRH) receptor agonists or orchiectomy should be given concurrently because AI treatment could trigger elevated level of androgen or follicle-stimulating hormone (FSH) by negative feedback, and testicles are important sites for estrogen production in males. AI monotherapy (without LHRH analogue) could only result in 50–70% reduction of estrogen level in male patients, compared to 95% in female patients. The AR positivity rate in male breast cancer patients could reach about 95%. Orchiectomy is an effective treatment with postoperative tumor remission rate of 32–67%.[153]

(2) Cdhemotherapy: As most male breast cancer patients express at least one of the hormone receptors, chemotherapy is usually used in patients who are resistant to endocrine treatment, ER-, or with high tumor burden. The treatment regimen could follow similar principles in female patients. Single-agent sequential chemotherapy is preferred over combination chemotherapy. A multi-center case report study that enrolled 23 male ABC patients showed that 48.0% of patients treated with eribulin received tumor response with good tolerance.[154]

(3) Targeted therapy: FDA has approved the use of palbociclib combined with AI or fulvestrant in treating male ABC based on real-world data and the PALOMA-2 and PALOMA-3 studies with good safety profiles.[155] Therefore, the combination therapy with palbociclib and AI as well as LHRH agonists or orchiectomy is an important treatment option for male HR+ HER2- ABC patients. HER2-positive breast cancer is rare in the male population. The use of anti-HER2 treatment in this population has only been reported in case reports.[156–158] These case reports demonstrated that trastuzumab could alleviate symptoms and prolong survival for some male HER2-positive ABC patients. The efficacy of other targeted therapies is not clear and needs further validation in male breast cancer patients. Considering the significant benefit of targeted therapy that has been observed in female breast cancer, and the absence of any

Table 16
Principles for the management of advanced male breast cancer.

No.	Content
1	Management of advanced breast cancer in males is similar to that in females. For those who are receiving AI, a GnRH analog or orchiectomy should be applied concurrently.
2	Chemotherapy is usually used in patients who are resistant to endocrine therapy or with high tumor burden. Single agent chemotherapy is preferred over combination chemotherapy.
3	The use of targeted therapy in male ABC patients, including anti-HER2 treatment and CDK4/6 inhibitors, is recommended to follow the principles in female advanced breast cancer.

Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; GnRH, Gonadotropin- Releasing Hormone; HER2, human epidermal growth factor receptor 2; CDK: cyclin-dependent kinase.

Table 17
Principles for the supportive care of advanced breast cancer.

No.	Content
1	Individualized supportive care should be given to patients upon confirmed diagnosis of advanced breast cancer.
2	Patient-reported outcome measures should be encouraged for collecting patients' subjective experience during the disease course.
3	Possible comorbidities and symptoms associated with advanced breast cancer should be closely monitored and managed.
4	The impact of menopausal symptoms and sexual health issues on quality of life should not be ignored.
5	Hormone replacement therapy is not recommended for relieving menopausal symptoms, but its use should be ultimately decided by the patient.

biological theory that there might be gender differences in responses to targeted therapy, male ABC patients with HER2 or PD-L1 expression or *PIK3CA* and *gBRCA* mutation are recommended to be treated similarly as female pat ients.[159,160] Principles for the management of advanced male breast cancer are summarized in Table 16.

11. Supportive treatment

The limited life expectancy of patients with ABC underlies the importance of maintaining life quality. Individualized care and supportive treatment should be given to patients since the day of diagnosis of ABC, taking into account their physical and psychological conditions. Effective management of the adverse events is also required to improve the quality of life. We recommend using the patient-reported outcome measures as a part of routine clinical practice to record the overall performances and subjective experiences of the patients. To choose the appropriate patient-reported outcome measures, please refer to the comprehensive management guideline for breast cancer follow-up and healthcare (2022 edition).[161]

For common symptoms that related to the treatment of advanced breast cancer, such as fatigue, dyspnea, peripheral neuropathy, hand-foot syndrome, oral mucositis, and musculoskeletal symptoms caused by AI, close monitoring is recommended to achieve comprehensive management. Cancer-related fatigue is often experienced by ABC patients, which limits their physical, psychological, and social functions. The cause for cancer-related fatigue is complicated. We recommend that cancer related fatigue be measured by patient-reported outcome. Non-medication interventions such as physical exercise are recommended, and proper medical treatment can also be given if necessary. When ABC patients develop shortness of breath, reasons such as pleural effusion, pulmonary embolism, cardiac dysfunction, anemia, and treatment-related adverse events should be considered and managed accordingly. Chemotherapy-induced peripheral neuropathy is very common and has limited evidence on prophylaxis and treatment. Wearing cold gloves and socks might help reduce the risk and severity of peripheral neuropathy. Hand-foot syndrome is a common adverse event of capecitabine and liposomal doxorubicin. Hyperkeratinization and fungal infection of the hand and foot should be treated in time. Patients are recommended to wear comfortable shoes to avoid friction and heating, and to use topical urea cream or ointment for hand and foot care. Oral mucositis is a common adverse event of everolimus. Patients should be advised to improve oral hygiene and use steroid-containing mouthwash and toothpaste for prevention and treatment. The dose of everolimus can be adjusted if necessary.

Menopausal symptoms and sexual health are two major issues affecting the quality of life of patients, but they may not be properly managed due to the neglect or shame exhibited by either side of the doctor and the patient. It is necessary to build trust with patients and encourage them to express relevant problems, so corresponding supportive treatment can be arranged.

Many treatment strategies for ABC could result in estrogen deficiency, which could lead to menopausal symptoms, including flush, night sweat, sleep disorders, fatigue, arthralgia, cognitive dysfunction, depression, and vaginal dryness. Considering the fact that most breast cancer is hormone-derived, hormone replacement therapy (HRT) is generally not recommended for managing menopausal symptoms. However, when these symptoms significantly affect patients' quality of life, the decision of whether to utilize HRT should be determined by the patient after thorough communication.[162,163] For mild to moderate menopausal symptoms, psychological consultation, physical exercise, and cognitive behavioral therapy are considered as effective non-medicine interventions.[164–168] For patients with flushes, venlafaxine, oxybutynin, gabapentin, and clonidine might be considered.[169–172] For patients with sleep disorders, melatonin is a treatment option.[173,174] Drug-drug interactions should be taken into consideration when treating menopausal symptoms. Traditional Chinese medicine or acupuncture could also be considered.[175]

Retrospective studies have demonstrated that, compared to healthy controls or patients with ovarian cancer, patients with breast cancer are associated with more severe sexual health problems, such as decrease or loss of libido, decreased satisfaction during intercourse, or dyspareunia.[176] Dyspareunia usually occurs secondary to vaginal dryness, and non-hormonal lubricant is recommended to relieve vaginal dryness and pain.[177–179] Low-dose estrogen-containing topical agents could also be applied if the patient is non-responsive to non-hormonal lubricant.[180–184] For premenopausal patients with breast cancer, contraceptive measures without hormone are recommended. Principles for supportive treatment of ABC are summarized in Table 17.

12. Summary

The treatment of ABC is complicated due to diverse disease characteristics, patients' conditions, and limited available treatment options. For first- and second-line treatment, there are generally more clinical data and standardized regimens. However, recommendations for later lines are relatively limited due to the lack of high-level evidence. The adjuvant therapy of breast cancer has undergone substantial changes over the last decades, resulting in a corresponding change in the setting

of prior therapies and mechanisms of resistance in advanced breast cancer, making previous findings observed from the ABC trials potentially unsuitable for current treatment. Therefore, well-designed clinical trials are urgently needed in the advanced setting to explore the optimal treatment strategy (including dosing, regimen, and biomarkers). In the meantime, multi-disciplinary team collaboration should be promoted to provide more precise and individualized comprehensive treatment, and ultimately prolong patients' overall survival and improve their quality of life.

For detailed use of chemotherapy regimens, please refer to the Guidelines for Rational Drug Use in Breast Cancer.[185] Commonly used chemotherapy regimens are listed below:

Single-agent chemotherapy

(1) Recommended agents: doxorubicin, epirubicin, paclitaxel, capecitabine, gemcitabine, vinorelbine (intravenous or oral), eribulin, and liposomal doxorubicin.
(2) Other agents: docetaxel, nab-paclitaxel, carboplatin, cisplatin, oral cyclophosphamide, and oral etoposide.

Combination chemotherapy

(1) Commonly used combination regimens: epirubicin + docetaxel (ET), epirubicin + cyclophosphamide (EC), docetaxel + capecitabine (TX), gemcitabine + paclitaxel/docetaxel (GT), gemcitabine + carboplatin/cisplatin (GC), and utidelone + capecitabine.
(2) Other combination regimens: cyclophosphamide + doxorubicin + fluorouracil (CAF), fluorouracil + epirubicin + cyclophosphamide (FEC), doxorubicin + cyclophosphamide (AC), paclitaxel + bevacizumab, cyclophosphamide + methotrexate+fluorouracil (CMF).

Recent advances in chemotherapy for advanced breast cancer include the non-taxane tubulin inhibitor eribulin and the epothilone analogue utidelone. The phase III 304 study which focused on Chinese population showed statistically significant improvement of PFS in the eribulin group compared to that in the vinorelbine group (HR = 0.80, $P = 0.036$).[186] Eribulin has been approved in China for the treatment of locally advanced or metastatic breast cancer patients who have previously received at least two chemotherapy regimens (including anthracycline and taxane). A phase III study conducted in the Chinese population found that, for ABC patients who failed anthracycline and taxane treatment, utidelone combined with capecitabine could significantly prolong PFS (8.44 vs. 4.27 months, HR = 0.46, $P < 0.0001$) and OS compared to capecitabine alone (19.8 vs. 16.0 months, HR = 0.75, $P = 0.0142$).[187] Utidelone has been approved in China to be used in combination with capecitabine for recurrent or metastatic breast cancer who have previously received at least one chemotherapy regimen. The previous regimens should include an anthracycline or taxane.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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