



## Review

# Comparison of 4th ESO–ESMO international consensus guidelines for advance breast cancer and Chinese anti-cancer association committee of Breast Cancer Society guideline



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## ABSTRACT

The primary aim of the international advance breast cancer (ABC) guidelines are to guide treatment decisions in many different healthcare settings, but need adaptations due to different access to care. These guidelines are based on the most up-to-date evidence. However, Chinese experts have a different national condition and policies to face. The Chinese Anti-Cancer Association Committee of Breast Cancer Society guideline (CBCS guideline) is to guide treatments and to reflect unmet needs of Chinese breast cancer patients. Although, most of the recommendations in the two guidelines are the same, some of them are different.

In this article, with regard to country-specific peculiarities, a working group of Chinese breast cancer experts compare the similarities and differences between the ABC guideline and CBCS guideline and commented on the voting results of the ABC panelists. We also discuss why these differences exist, such as lack of access, different tumor biology and epidemiology, and even different culture. The money which patients have to pay out of pocket for their medical cost and the availability of drugs lie at the heart of the issues of guideline differences.

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## 1. Introduction

The 4th International Consensus Conference for Advance Breast

Cancer (ABC4) was held in Lisbon, Portugal on November 2–4, 2017. This version of guideline and the prior three versions build on the evidence based medicine and can be used to guide treatment decisions in many different healthcare settings, but need adaptations due to different access to care [1]. However, Chinese experts have a different national condition and policies to face. China is a country with poor resources and its universal medical insurance system has three main types of publicly financed insurance, including urban employee basic medical insurance, urban resident basic medical insurance and new cooperative medical scheme, covering 97.5% of the entire population in 2014. Under the system, patients still pay different percentages of the total medical cost out of pocket, and the rate of catastrophic payments for inpatients of urban employee's basic medical insurance is the lowest [2]. Overall, the quality of overall medical services is not satisfactory [3]. A recent study showed that 42.78% of cancer patients in China suffered from catastrophic health expenditure, and the situation needs a lot of reforms [4]. Fortunately, the seventeen anti-tumor targeted drugs have just been included into the Catalogue of Drugs for Basic National Medical Insurance in 2018.

The Chinese Anti-Cancer Association Committee of Breast Cancer Society guideline (CBCS guideline) was first published in 2007 and updated biannually in order to guide treatments and to reflect unmet needs of Chinese breast cancer patients [5–7]. The special needs mainly come from two parts, one is the interpretation of published trial data, for example, populations enrolled into the international clinical trials of the same design may be different from Caucasian counterparts and higher percentage of patients with prior chemotherapy are enrolled in endocrine clinical trials. The other is drug availability and patient affordability. Take human epidermal growth factor receptor 2 (HER2)-positive patients for example, neither pertuzumab, neratinib nor T-DM1 is regulatory approved in China. In order to adapt the ABC4 consensus for everyday practice in China, a group of 22 Chinese breast cancer experts representing different disciplines was set up to review the two guidelines and the voting results of ABC4 panelists, to identify the similarities and differences of ABC4 consensus and CBCS guidelines, and then to comment on the voting results of the ABC4 panelists. The interesting statements submitted by the group member had been discussed thoroughly together within the six senior oncologists. Only those unanimous statements are included in this article. The major similarities and differences of ABC4 and CBCS guidelines are summarized in [Table 1](#).

## 2. General statements

Although discrepancy between recurrent or metastatic lesions and the primary tumor exists, ABC4 panelists (87%) recommended considering the use of targeted therapy (endocrine therapy and/or anti-HER2 therapy) if there is any evidence of receptor positivity at any time (LoE/GoR: Expert opinion/B). The Chinese experts agree with this voting result. However, the rate of rebiopsy in the metastatic setting was relatively low in China. The possible reasons include low guideline acceptance in some hospitals, a short disease-free interval (e.g. less than 1 or 2 years), a concern of widespread dissemination and safety with rebiopsy. Chinese experts addressed that the informed consent should be obtained before rebiopsy due to the poor relationship between doctors and patients now in China. Additionally, decision making is more conservative with HER2 negative recurrent or metastatic lesion whose primary tumor is HER2 positive since anti-HER2 treatments are very expensive and patients have to pay a lot out of pocket even for medical insurance covered drugs.

Two thirds of the ABC4 panelists hold the opinions that primary endocrine resistance is defined as relapse while on the first 2 years

of adjuvant endocrine therapy (ET), or progression disease (PD) within the first 6 months of first-line ET for advanced breast cancer, while on ET. Secondary endocrine resistance is defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD  $\geq$  6 months after initiating ET for advanced breast cancer, while on ET (LoE/GoR: Expert opinion/n/a). Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid progression of disease which is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible (LoE/GoR: Expert opinion/n/a). The Chinese experts agree with this although there is no direct evidence, and the CBCS guideline just translated these definitions into Chinese. The clinical implication of these definitions is to guide the subsequent choice of ET only, ET combination with CDK4/6 or mTOR inhibitors, or chemotherapy.

Both ABC4 panelists and Chinese experts hold the similar attitude to overall survival (OS) benefit, but Chinese love it more due to religious and cultural differences. One Chinese saying is that a poor-quality living is much better than a good-quality death, so overall survival benefit is more appreciated than quality of life (QoL) in China. Chinese experts and patients quickly accepted the drugs showing OS benefit in the clinical trials, like trastuzumab and fulvestrant [8–10]. QoL issues are not fully addressed in both our real world practice and clinical trials, partially because the drug regulatory approval in China doesn't require these data. Now with more available psychological support and the educational efforts to overcome the misconceptions that still exist among both physicians and patients, QoL issue is receiving more and more attention and its importance has been emphasized in both clinical trial and clinical practice in China.

## 3. Locally advanced breast cancer

In ABC4 guidelines, locally advanced breast cancer (LABC) is defined as inoperable, non-metastatic locally advanced breast cancer. Considering the relatively higher risk of metastasis, a full-staging work-up is recommended for patients with LABC, including imaging of chest, abdomen and bone. PET-CT is also an acceptable option.

Systemic treatment should be considered as initial treatment for patients with inoperable LABC (LoE/GoR: III/A), though multidisciplinary treatment (systemic therapy, surgery and radiotherapy, RT) are required for most patients (LoE/GoR: I/A). As to systemic treatment, various treatments are available for patients with different molecular subtypes, thus a core biopsy is indispensable for treatment guidance. In hormone receptor positive (HR+) LABC, 85% of the experts agree on the consensus that chemotherapy (anthracycline- and taxane-based regimen) or endocrine therapy should be applied (LoE/GoR: I/A). Other tumor factors, such as grade and biomarker expression, and patient factors (menopausal status, performance status, comorbidities, preference) should be taken into consideration when deciding the sequence of these treatments (LoE/GoR: Expert opinion/A).

Nowadays, the possible benefit of preoperative RT has also been investigated, especially in patients with triple negative breast cancer [11]. For patients who are resectable after preoperative systemic therapy, local therapy including surgery and RT should be then applied. If the disease remains unresectable, RT should be considered to treat all sites of original tumor, with a boost to residual disease. Chinese experts hold similar opinions about LABC and emphasized that before starting any neoadjuvant treatment, a core biopsy of the breast and fine needle aspiration of all areas of

**Table 1**  
Major similarities and differences of ABC4 and CBCS guidelines.

Content	Similarity	Reasons or comments
General statements		
Percentage of pay out of pocket	No.	Medical insurance coverage is 97.5% in China, but patients have to pay different percentages of the medical cost, depending on insurance types [2].
Rebiopsy in the metastatic setting	Yes, but the rebiopsy rate is lower in China	1. Low guideline acceptance, a short disease-free interval and a concern of widespread dissemination and safety with rebiopsy. 2. The poor relationship between doctors and patients.
Definitions of primary and secondary endocrine resistance and visceral crisis	Yes.	Adaptation from ABC3.
Attitude to overall survival benefit	Yes, but with more passion.	Chinese attitude to living and death, but the situation is improving.
Evaluation of QoL in clinical trial	No.	No requirement by drug regulatory approval in China.
Locally Advanced Breast Cancer		
Staging workup	Yes.	NC
Chemotherapy for HR + LABC	Yes.	NC
Neoadjuvant radiation	Only in CBCS guideline.	Address the exploration to fully assess the role for TNBC patients [11].
Adjuvant chemotherapy after neoadjuvant chemotherapy	Only in CBCS guideline.	Address the completeness of all planned chemotherapy.
Adjuvant capecitabine for non-pCR patients	Only in CBCS guideline.	NC
Trastuzumab duration for neoadjuvant patients	Yes.	Chinese experts question the value of 1-y trastuzumab in patients who have received full-course neoadjuvant trastuzumab but with stable disease or even progressive disease.
SLNB for patients with initial diagnosis of cN0-cN1 who achieve clinical complete remission after neoadjuvant systemic therapy	Yes, but axillary dissection is still the standard treatment.	None of the tracers has been approved in China.
Local and Regional Recurrences		
Treatment principle	Yes.	Address the assessment of the feasibility of intensive local-regional therapy and to give detailed suggestions to different sites of regional recurrences in CBCS guideline.
Re-irradiation for local and regional recurrence	Yes, it could be considered in selected cases	Address to consider extent of the recurrence, time from the previous radiation, and ratio of toxicity to benefit.
Endocrine Therapy		
OFS approach	Yes, but more patients choose bilateral ovariectomy.	1. Coverage of hospitalization fees by medical insurance. 2. No standard evaluation and wide-accepted normal range of serum estradiol in China [24].
Premenopausal patients receiving OFS should be treated in the same way as post-menopausal.	Yes.	NC
Serial evaluation of serum estradiol to determine menopausal status.	Yes.	Remind Chinese doctors that the test results from Chinese hospitals may not be correct [24].
Endocrine therapy ± targeted drug for HR + disease	Yes, but more chemotherapy is prescribed.	1. Chemotherapy is relatively cheaper and covered by medical insurance. 2. Medical insurance policies in China. 3. Unavailability of CDK4/6 inhibitors. 4. No indication for breast cancer, e.g. everolimus in China. 5. Oral capecitabine is also an option.
Toxicity of palbociclib	Yes.	More hematological toxicity requiring dose interruptions and dose reductions but not the median treatment durations [27].
Targeted Therapy		
Dual blockade or mono-blockade for HER-2 positive inoperable LABC or metastatic breast cancer.	No, doublet chemotherapy (docetaxel and capecitabine) with trastuzumab is favored.	1. Dual blockade is too expensive for Chinese patients. 2. Unavailability of pertuzumab. 3. CHAT study showing a longer PFS of HTX vs HT (17.9 m vs 12.8 m) [29].
Later-line anti-HER2 treatment for HER2 positive breast cancer.	Yes.	NC
Value of T-DM1.	No.	It is not recommended simply because it is not commercially available in China.
Chemotherapy plus anti-HER2 treatment for HR + HER2+ disease	Yes.	Endocrine therapy plus anti-HER2 treatment is reserved for the highly selected patients.
Strong ER positivity as an indication of selection of endocrine and anti-HER2 therapy for HR + HER2+ disease.	Yes.	Substantial benefit of chemotherapy plus anti-HER2 treatment for this population.
Endocrine therapy plus anti-HER2 treatment as maintenance for HR + HER2+ disease.	Yes.	NC
Chemotherapy		
Combination chemotherapy or sequential monotherapy	Yes, but more doublet chemotherapy is used in China.	1. To improve efficacy or to mitigate drug-related specific toxicity, e.g. docetaxel-related febrile neutropenia [35]. 2. Professional promotion of Chinese doctors requires a lot of publications, so we design many combination chemotherapy trials. 3. Improvement of patient's compliance by a rapid tumor shrinkage with the combination chemotherapy in China.
Oral chemotherapy.	Yes, but we have more options.	We keep oral drugs, such etoposide [37].

Table 1 (continued)

Content	Similarity	Reasons or comments
Carboplatin-containing regimens for mTNBC	Yes, but more favor of cisplatin-containing regimens.	1. Publication of cisplatin/gemcitabine trial in high-impact factor journals which was listed as level Ib evidence in German AGO guideline [38–40]. 2. Hospitalization fee covered by medical insurance 3. Higher anti-tumor activity with cisplatin [41]. 4. Carboplatin related thrombocytopenia is tough to manage.
PARPi (olaparib or talazaparib) for patients with BRCA-associated advanced TNBC	No	1. No approval in China. 2. No head-to-head trial comparing platinum with PARP inhibitors. 3. No overall survival benefit.
Advanced Male Breast Cancer Treatment of male breast cancer	Yes	Clinical needs, although there are no solid evidences available.
AI combined with OFS	Yes.	NC

Notes: NC, no comments; QoL, quality of life; HR+, hormone receptor positive; LABC, locally advanced breast cancer; TNBC, triple-negative breast cancer; pCR, pathological complete remission; SLNB, sentinel lymph node biopsy; OFS, ovarian function suppression.

clinical-suspicious lymph node metastasis are required for treatment decision. Subsequent strategy should be tailored upon tumor's response to systemic therapy. Local treatment should be considered to reduce local recurrence risk. In the CBCS guideline, more detailed suggestions on RT are given for LABC patients. RT should be planned based on the clinical stage of patients prior to systemic treatment, including chest wall (or breast), supra/sub-clavicular node, and internal mammary lymph nodes irradiation (if involved or of high suspicion) [12,13]. There was a controversial discussion over the necessity and recommendations of adjuvant systematic therapy after local therapy. Based on the opinions of Chinese experts, the bottom-line is to continue planned chemotherapy if not completed preoperatively which is still common in China, followed by endocrine therapy in patients with HR-positive disease. As for HER2 negative breast cancer who has residual invasive disease on pathological testing, the addition of adjuvant capecitabine therapy is also recommended by CBCS guideline [14].

In patients with inflammatory or non-inflammatory HER2-positive LABC, who achieve complete remission after appropriate neoadjuvant systemic therapy and locoregional treatment, the duration of adjuvant anti-HER2 therapy should be 1 year for curative intent (LoE/GoR: I/A). 85% of the ABC4 panelists agreed on this new statement. Based on the evidence of NOAH trial [15], Chinese experts recommend continuing trastuzumab for up to 1 year for HER2 positive LABC patients who have received trastuzumab in neoadjuvant setting. The duration of adjuvant anti-HER2 treatment for those who have obtained pathologic complete remission with previous neoadjuvant treatment was not touched in CBCS guidelines 2017, but more than half of Chinese experts question the value of continuing the same anti-HER2 treatments up to one year in patients whose best response is stable or even progressive disease and who have received radical local treatments.

Sentinel lymph node biopsy (SLNB) can be an option for patients with axillary low burden of disease (cN0–cN1) upon initial diagnosis who achieve clinical complete remission (ycN0) after neoadjuvant systemic therapy, if all the recommendations for sentinel node are followed (i.e. dual tracer, clipping/markings positive nodes, minimum of three sentinel nodes). 62% of the panelists voted for this statement, thus was added in ABC4 guidelines (LoE/GoR: III/B). In fact, none of the tracers has been approved in China. However, the Chinese experts agree with this new statement but emphasize that axillary dissection is still the standard treatment in LABC patients with primarily pathological-confirmed axillary metastasis by fine-needle aspiration or core biopsy, even when they have been SLN negative after systematic treatment.

#### 4. Local and regional recurrences

In ABC4 guidelines, there is not a separate part of description for local and regional recurrences as compared with CBCS guidelines 2017. Chest wall and regional recurrences are listed as one of the specific sites of metastases [7]. When chest wall or regional recurrence occurs, there are many treatment options. First line systemic therapy or intensive local-regional therapy can be an option, but choice depends on biology. Chinese experts recommend that the feasibility of intensive local-regional therapy should be evaluated first. Therapy strategies include surgical excision and/or RT with or without chemotherapy [16–18]. It may be aggressive but help patients to get a chance for curing the disease. First-line systemic therapy, such as endocrine therapy, may be ineffective and progressive disease make the subsequent local-regional therapy more difficult. For patients who have already been irradiated before, 95% of the ABC4 panelists agree that re-irradiation could still be considered in selected cases (LoE/GoR: Expert opinion/C).

Chinese experts agree with these statements and added more detailed description of radiation including assessing the location of recurrent site and its relative position to previous radiation field. And in patients suffering with lymphedema after previous radiation, MRI with contrast or PET/CT scan are recommended for the differential diagnosis between relapse and fibrosis [19]. Our panel holds a rather conservative attitude towards the value of re-irradiation and emphasize that the time interval between prior and planned radiation, risk for late normal tissue toxicities from the sum of two courses and possible benefit in terms of local control should all be taken into consideration before re-irradiation.

Treatment details referring different site of regional recurrence are also defined in CBCS guidelines [20]. In patients with axillary recurrence, axillary dissection and prophylactic RT to chest wall and infra-supra clavicular nodes (in patients without previous radiation) should be considered. In case of supraclavicular recurrence, RT to chest wall and infra-supra clavicular nodes are recommended by the Chinese experts. In patients with internal mammary nodes recurrence, RT to chest wall, infra-supra clavicular nodes and internal mammary nodes should be considered [21].

In addition to local therapy, systemic chemotherapy should also be considered. The CALOR trial offers important data for the use of chemotherapy after surgical resection of locoregional recurrence, especially when ER was negative, but it does not exclude its use for patients with ER-positive isolated locoregional recurrences [22]. Besides, for patients that are not suitable for local treatment, systemic treatment should be given according to principles of

metastatic breast cancer (LoE/GoR: Expert opinion/B).

## 5. Endocrine therapy

The median age at diagnosis of breast cancer in China is 45–55 years compared with 64 years in the Caucasian, with 62.9% of women diagnosed while still premenopausal [23]. For this part of patients, ABC4 panelists (95%) recommend that premenopausal women with ER-positive advanced breast cancer should have adequate ovarian function suppression/ovarian function ablation (OFS/OFA) and then be treated in the same way as post-menopausal women. Adequate OFS can be obtained through bilateral ovariectomy, continuous use of luteinising hormone-releasing hormone agonists (LHRHa) or OFA through pelvic radiation therapy. The latter one is not always effective and therefore is the least preferred option. Bilateral ovariectomy and LHRHa are the most used methods in China. However, the choices should balance among patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time and cost. The hospitalization fees for bilateral ovariectomy can be covered by our medical insurance systems, so a relatively higher percentage of patients in China chose operations. 85% of the panelists (LoE/GoR: expert opinion/B) advocate that efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered in young women. Chinese experts agree with this recommendation and follow it in daily clinical practice, however, it should be kept in mind for Chinese doctors that there is no standardized assay for blood hormones and no wide-accepted normal range of these hormones of postmenopausal women in China [24]. In addition of serial evaluation of serum estradiol, we stress careful observation of biological changes indicating possible recovery of ovary function, such as menstruation and/or periodic occurrence of menopausal symptoms.

For estrogen receptor (ER+) positive and HER2-negative (HER2-) advanced breast cancer, a majority of the ABC4 panelists (93%) agreed that patients should preferably receive endocrine therapy (ET), even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance (LoE/GoR: I/A). The Chinese group of experts agreed with it, but added that attainment of clinic benefit of any-line endocrine therapy, besides the first-line treatment, indicates necessity of subsequent endocrine treatment except occurrence of visceral crisis. However, when compared with countries with enough resources, chemotherapy is more commonly prescribed in China. The primary cause is that medical insurance policies set limits of the percentage of drug costs over the total medical care expenses, so doctors choose prescribing chemotherapy. Now with the propaganda of the ABC4 and CBCS guidelines in China, the situation is improving.

With the development of drug industries, there are many choices of endocrine agents for ER-positive/HER2-negative advanced breast cancer rightnow. So far, CDK4/6 inhibitors, such as palbociclib, abemaciclib and ribociclib, demonstrated an impressive ORR and PFS advantage in combination with the aromatase inhibitor or fulvestrant in randomized phase 3 studies [25,26]. However, the optimal therapeutic sequence of the currently available endocrine treatment options is unknown. ABC4 panelists (90%) suggested that the addition of a CDK4/6 inhibitor to an AI or fulvestrant is one of the preferred treatment options for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women (LoE/GoR: I/A). The Chinese group of experts agree with these votes, but emphasize that Asian patients show similar efficacy but higher hematological toxicity, e.g. neutropenia, leading to more dose interruptions and reductions but not the median treatment durations [27]. However,

when the CBCS guideline was formulated, CDK4/6-related clinical trials are still under progress in China and the CDK4/6 inhibitors are not commercially available at that time. Therefore, they have not been recommended in CBCS guidelines. Fortunately, palbociclib was approved by the Chinese Food and Drug Administration on July 31, 2018. Its first-line combination with aromatase inhibitors is approved to be used in postmenopausal female patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. Despite its approval, the high medical expense will limit its use in China. Moreover, everolimus is not approved for treatment of breast cancer in China and has been demonstrated no overall survival benefit compared with single agent capecitabine [28]. For this reason, single-agent oral capecitabine is also an option for this patient population.

## 6. Targeted therapy

For HER2-positive disease, dual anti-HER2 blockade combined with single agent taxane is recommended in patients who has been previously exposed to trastuzumab and those who not. Chinese experts hold the similar opinions. However, due to economic issue and availability of pertuzumab, Chinese experts recommend trastuzumab plus combination chemotherapy, especially with docetaxel/capecitabine for first-line use of inoperable LABC and metastatic breast cancer [29]. It is a reasonable option, particularly for those who need a rapid tumor shrinkage. Patients progressing on an anti-HER2 therapy combined with cytotoxic agents should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway (LoE/GoR: I/A). After first-line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER2-based therapies in the second line (versus lapatinib + capecitabine) and 'third-line and beyond' (versus treatment of physician's choice) [30,31]. T-DM1 should be preferred in patients who have progressed through at least one line of trastuzumab-based therapy, because it provides an OS benefit (LoE/GoR: I/A). The evidence is sufficient and Chinese experts agree with this recommendation. But the second line and above rescue treatment of T-DM1 in HER2+ breast cancer is not strongly recommended in CBCS guidelines. That is because T-DM1 has not been approved in China rightnow. Chinese government and experts are now making great efforts to help accessing treatments with a high clinical benefit. The relevant clinical trials have finished and T-DM1 is expected to be approved in 2019.

As for ER+/HER2+ advanced breast cancer, ABC4 panelists (80%) agree with highly-selected ER+/HER2+ advanced breast cancer patients treated with endocrine therapy + anti-HER2-targeted therapy as first-line therapy (LoE/GoR: I/B). Compared with ET + anti-HER2 monoblocade, ET + dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) provides a benefit in PFS in the first-line setting [32]. Therefore, ET + dual anti-HER2 blockade can be an option under the premise of considering high costs and lack of OS benefit so far (LoE/GoR: I/B). In CBCS guidelines, endocrine therapy + dual anti-HER2 blockade is not recommended. Although some clinical trials like ALTERNATIVE and PERTAIN have provided some outcomes [32,33], the Chinese experts do not recommend dual anti-HER2 blockade therapy since its high cost-benefit ratio and unavailability of pertuzumab in China at that time. We believe that strong expression of ER/PR is not a necessary condition for selecting endocrine + anti-HER2 therapy, this patient population can be well managed with chemotherapy + anti-HER2 therapy as first-line treatment [34]. However, this strategy can be taken in patients with contraindications to chemotherapy, a strong preference against chemotherapy, a long disease-free interval or low disease burden, even if ER/PR

expression is at relatively low level [7].

Based on the facts of more patients and doctors choosing chemotherapy + anti-HER2 therapy as the first-line therapy, endocrine + anti-HER2 monoblocade as a maintenance treatment is very common in China, and we also have a consensus on maintenance therapy. In this point, ABC4 panelists give the same recommendation. They also mentioned that duration of maintenance therapy should be prolonged until disease progression, unacceptable toxicity or patient request and needs to be evaluated in clinical trials, and there are no data to decide on choice of single-agent anti-HER2 or dual blockade (LoE/GoR: n/a/B) for the maintenance.

## 7. Chemotherapy

ABC4 guideline recommend sequential monotherapy as the preferred choice over combination chemotherapy for advanced breast cancer. Anthracycline or taxane and other options, such as capecitabine, vinorelbine, are available and effective. Chinese experts agree with this ABC4 recommendation, but added that the doublet chemotherapy which has been tested to be effective with manageable toxicity is also an acceptable option [35]. In fact, combination chemotherapy is more commonly prescribed in China than in Western countries, and the combination therapy mostly comprises newly emergent drugs, such as epirubicin + cyclophosphamide rather than adriamycin + cyclophosphamide, new formulations of paclitaxel (such as nab-paclitaxel or liposomal paclitaxel) rather than Cremophor EL paclitaxel. There are three main reasons. First, doctors want to improve the efficacy or mitigate drug-related specific toxicity of the approved drugs (e.g. docetaxel-related febrile neutropenia in the clinical trial of docetaxel with or without capecitabine) [36]. Second, professional promotion of Chinese doctors requires a lot of published articles, so we design many combination chemotherapy trials since the combination provides more space to optimize the treatment. Up to now, Chinese doctors have had a lot of publications on investigator-initiated clinical trials, although these are mostly small size phase II trials. It is the trial experiences that impact on our routine clinical practice. Third, a rapid tumor shrinkage or symptom relief with the combination will improve patient's compliance in China. With the advent of ABC 1 to 4 consensus and other guidelines, we are happy to see the big increase of sequential monotherapy and adherence to guidelines in the management of advanced breast cancer patients in China. Another significant difference between the two guidelines on chemotherapy is that Chinese experts still keep some the old oral chemotherapy agents, such as etoposide [37].

For the management of triple-negative breast cancer, chemotherapy is still the mainstay. As ABC4 guideline refers, for non-BRCA-associated advanced TNBC, there are no data supporting different or specific chemotherapy recommendations. However, for advanced TNBC previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin is an important treatment option. Chinese experts agree with this recommendation, but are more in favor of cisplatin-containing regimens. Carboplatin-containing regimen for the metastatic disease is kept for patients who cannot tolerate cisplatin or old compromised patients. There are mainly four reasons. First, cisplatin-containing doublet with gemcitabine is published in high-impact factor journals and the patient population is exclusively Chinese patients [38–40], so it is recommended in the CBCS guideline and listed as level Ib evidence in German AGO guideline. Second, since the hospitalization fee is covered by medical insurance here in China, longer hospital stay by administration of cisplatin is not a financial issue, although it actually reduces the social support for patients such as to be at home, closer to family

and friends. Third, it is reported that cisplatin has a higher anti-tumor activity than carboplatin [41]. Last, carboplatin-induced severe thrombocytopenia is usually a tough case. Therefore, cisplatin-containing regimen is more preferred in China.

Besides chemotherapy, a PARPi (olaparib or talazaparib) is a reasonable treatment option for patients with BRCA-associated advanced TNBC in the ABC4 guideline. Chinese experts agree with this recommendation, but olaparib was approved for treatment of patients with ovarian cancer, not for breast cancer in China. Chinese experts stressed that more data are needed, since there has been no head-to-head trial comparing of platinum with PARP inhibitors and no overall survival benefit has been demonstrated in any trial.

## 8. Advanced male breast cancer

Male breast cancer is a rare malignance that accounts for approximately less than 1% of all breast cancer. Because of the low incidence, there are few prospective randomized clinical trials and intensive scientific research which can provide information for treatment of male breast cancer. All ABC4 panelists and Chinese group of experts preferred endocrine therapy for ER-positive male advanced breast cancer unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response. For male patients with advanced breast cancer, panelists suggested AI should be used with a LHRHa or orchidectomy. In order to improve the outcome of this special disease, clinical trials requiring more international co-operation are waited.

## 9. Conclusions

The ABC4 guideline has been released in 2018 and guides the oncologists in daily clinical practice worldwide. Chinese experts agree with majority of the recommendations, however, we have a different national condition and policies to face. The money which patients have to pay out of pocket for their medical cost and the availability of drugs lie at the heart of the issues of guideline differences. The CBCS guideline was formulated to standardize the clinical activities in China and maintain our own country-specific peculiarities. Overall, medical strategy for advanced breast cancer in China is now gradually approaching to the international standards.

## Conflicts of interest

The authors report no conflicts of interest in this work.

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