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SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer

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The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer (MBC) was published in 2021. A special, hybrid guidelines meeting was convened by ESMO and the Korean Society of Medical Oncology (KSMO) in collaboration with nine other Asian national oncology societies in May 2022 in order to adapt the ESMO 2021 guidelines to take into account the differences associated with the treatment of MBC in Asia. These guidelines represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with MBC representing the oncological societies of China (CSCO), India (ISMPO), Indonesia (ISHMO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO). The voting was based on the best available scientific evidence and was independent of drug access or practice restrictions in the different Asian countries. The latter were discussed when appropriate. The aim of these guidelines is to provide guidance for the harmonisation of the management of patients with MBC across the different regions of Asia, drawing from data provided by global and Asian trials whilst at the same time integrating the differences in genetics, demographics and scientific evidence, together with restricted access to certain therapeutic strategies.

Key words: ESMO, guidelines, Pan-Asian, metastatic breast cancer, treatment

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INTRODUCTION

In 2020, female breast cancer accounted for 2 261 419 (11.7%) of an estimated 19.3 million new cases of cancer diagnosed worldwide, and was the most commonly diagnosed cancer.[1] It accounted for 684 996 (6.9%) new cancer deaths and was the fifth leading cause of cancer death worldwide.[1] Breast cancer accounts for one in four cancer

cases in women and one in six cancer deaths.[1] Men account for <1% of patients with breast cancer.[2]

Incidence rates for breast cancer are 88% higher in countries with a high/very high human development index compared with transitioning countries, and are rising in transitioning countries as well as in high income level Asian countries.[3] Among 21 regions assessed for global burden of disease for breast cancer, East Asia had the highest number of cases in 2019 and Southern Asia, Eastern Asia and Southeast Asia had the highest breast cancer-related disability-adjusted life year burden in 2019.[4] Between 1990 and 2019 Eastern Asia saw the largest increase in age-standardised incidence rates with an estimated annual percentage change of 2.81 [95% confidence interval (CI) 2.21-2.91].[4]

Risk factors for breast cancer include gender, age, genetic factors, family history and ethnicity. Modifiable risk factors, associated with lifestyle, include alcohol consumption, excess weight, physical inactivity and number of pregnancies. A review of the epidemiology of breast cancer in Asia[5] confirmed that an increased risk of breast cancer in Asian women was associated with older age, a family history of breast cancer, early menarche, late menopause, a high body mass index, being obese or overweight, exposure to tobacco smoke and a high dietary intake of fats or fatty foods. Conversely, the consumption of dietary fruits, vegetables and plant- and soy-based products was associated with a decreased breast cancer risk. Differences in the prevalence of and mortality from breast cancer have been reported for different Asian countries[6] and for different regions within individual countries such as India,[7] together with differences in age at diagnosis, and stage at presentation within and between Asian countries. It is unknown if this is due to adverse biology or a lack of systematic screening. Certainly, in the Republic of Korea and Japan, where there is routine screening, approximately 70% and 85% of patients, respectively, have stage I or II disease at diagnosis.[8,9]

It is reported that ∼2%-25% of breast cancer patients in Asia present with *de novo* metastatic disease compared with only 3%-10% of breast cancer patients in Europe and the US.[10] In addition, the profile of patients with breast cancer in certain countries in Asia is one of presentation with more severe disease, with a higher proportion of patients with locally advanced disease, and those with distant metastases more likely to have been detected due to symptoms and therefore more likely to have multiple involved sites at presentation.[11] The peak age for breast cancer diagnosis in Asia is younger ∼50 years of age compared with ∼70 years of age in Western populations.[12] Approximately 50% of breast cancer patients in Eastern Asia are premenopausal. There are also molecular differences between the breast tumours diagnosed in Asian versus Western patients.[13,14] For example, Asian breast cancer patients have a higher incidence of luminal B disease than their Western counterparts which is characterised by higher Ki-67 expression and more frequent *TP53* mutations. Luminal B tumours are also associated with a worse prognosis and are associated with resistance to endocrine therapies which has implications for patient management.[15]

For metastatic breast cancer (MBC), newer standard therapy options include targeted approaches such as cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitors, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors and anti-programmed death-ligand 1 (PD-L1) immunotherapy, depending on breast tumour subtype and molecular profile.

Guidelines and recommendations for the treatment and management of patients with breast/advanced breast cancer in Asia have been published for Japan,[16,17,18] India,[19] Korea,[20] China and other Asian countries, and are important for the standardisation of the diagnosis and treatment approaches with the aim of optimising the clinical outcomes for patients with MBC in Asia, particularly as Asian women are more likely to die from their disease than those in Western countries, with discrepancies in age at diagnosis and stage at presentation within and between different Asian countries. The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with MBC have recently been published (ESMO Clinical Practice Guidelines)[21] and a decision was taken by the ESMO, the Korean Society of Medical Oncology (KSMO) and nine Asian national oncology societies that these guidelines should be adapted for patients of Asian ethnicity. Consequently, representatives of ESMO, the Chinese Society of Clinical Oncology (CSCO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Japanese Society of Medical Oncology (JSMO), the Korean Society of Medical Oncology (KSMO), the Malaysian Oncological Society (MOS), the Philippine Society of Medical Oncology (PSMO), the Singapore Society of Oncology (SSO), the Taiwan Oncology Society (TOS) and the Thailand Society of Clinical Oncology (TSCO) convened for a hybrid virtual/face-to-face working meeting on 28 May 2022, hosted by KSMO in Seoul, to adapt the recent 2021 ESMO Clinical Practice Guidelines,[21] for use in the management of Asian patients with MBC. The main aim was to identify the differences in the management of patients with MBC between Europe (Western countries) and Asia and adapt the ESMO guidelines, accordingly, based on the best available scientific evidence generated by global and Asian trials. It is hoped that such evidence-based guideline recommendations will facilitate regulatory approval for the newer therapies in the Asian countries where approvals do not exist at present, and maybe influence reimbursement decisions. This manuscript summarises the Pan-Asian adapted guidelines developed at the meeting accompanied by the level of evidence (LoE), grade of recommendation (GoR) and percentage consensus reached for each recommendation.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines[21] was prepared in accordance with the principles of ESMO standard operating procedures (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology)

and was a KSMO—ESMO initiative endorsed by CSCO, ISMPO, ISHMO, JSMO, MOS, PSMO, SSO, TOS and TSCO.

An international panel of experts was selected from the KSMO ($n = 7$), the ESMO ($n = 6$) and two experts from each of the oncological societies of China (CSCO), India (ISMPO), Indonesia (ISHMO), Japan (JSMO), Malaysia (MOS), Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO). Only two of the seven experts from the KSMO (YHP and JHK) were allowed to vote on the recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). None of the additional KSMO members present and none of the ESMO experts were allowed to vote and were present in an advisory role only.

A modified Delphi process was used to review, accept or adapt each of the individual recommendations in the latest ESMO Clinical Practice Guidelines.[21] The 20 voting Asian experts were initially asked to vote YES or NO (one vote per society) on the 'acceptability' (agreement with the scientific content of the recommendation) and 'applicability' (availability, reimbursement and practical challenges) of each of the ESMO recommendations, in a pre-meeting survey followed by a hybrid virtual/face-to-face meeting (see Supplementary Methodology, available at https://doi.org/10.1016/j.esmoop.2023.101541). The 'Infectious Diseases Society of America-United States Public Health Service Grading System' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101541)[22] was used to define the LoE and strength (grade) of each recommendation.

RESULTS

In the initial pre-meeting survey, the 20 voting Asian experts reported on the 'acceptability' and 'applicability' of the 87 recommendations plus 5 sub-recommendations for the diagnosis, staging and treatment of patients with MBC, from the 2021 ESMO Clinical Practice Guidelines,[21] in eight categories, listed in the text below. This was subsequently updated to nine categories following new data[23] presented at the ASCO 2022 Annual Meeting (see 'recommendation 6a' below and Table 1).

During the pre-meeting survey there were 13 voting discrepancies in relation to scientific 'acceptability' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101541; 'recommendations 3b, 3c, 3h, 3k, 3o, 3p, 3q, 4a, 5b, 5c, 5d, 6b and 7d'), and 37 voting discrepancies in relation to the 'applicability' (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101541) across the 10 Asian societies.

1. Diagnosis, pathology and molecular biology—recommendations 1a-c

The diagnosis and management of patients with breast cancer is evolving towards a more personalised treatment approach due to improved tumour characterisation, facilitated by more sophisticated diagnostic testing, that includes molecular imaging and genomic expression profiling.

The algorithm for the diagnostic work-up of MBC proposed by ESMO[21] is presented in Figure 1. Patients presenting with either newly diagnosed or recurrent metastatic breast disease should have a biopsy to confirm histology and assess/re-assess tumour biology in terms of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status.

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO recommendations on diagnosis, pathology and molecular biology 'recommendations 1a-c' below and in Table 1.

1a. At first diagnosis of MBC, a biopsy should be carried out to confirm histology and assess/re-assess tumour biology including ER, PgR and HER2 status [I, B].

In relation to 'recommendation 1a' above, reporting of HER2 status should provide quantitative details on cellular percentages and patterns of staining and be classified and reported according to the standard American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP) 0, 1+, 2+, 3+ scores.[24,25] HER2-low disease is identified by an immunohistochemical (IHC) score of 2+ with a negative *in situ* hybridisation (ISH) result, or an IHC score of 1+. Breast cancer is scored 2+ if there is weak to moderate complete membrane staining in >10% of tumour cells or if the membrane staining is intense but in 10% of tumour cells. Score 1+ is defined by faint or barely perceptible incomplete membrane staining in >10% of tumour cells. Although HER2 negative, this latter type of tumour shows the expression of the protein. The continuous versus the discontinuous line depicts the different levels of evidence in current clinical practice. Where there is no IHC staining or membrane staining that is incomplete and is faint/barely perceptible in ≤10% of tumour cells the tumour is classed as HER2 0. Currently, more sensitive IHC assays are being explored in phase III trials in order to see whether HER2 'ultra-low' expression is also correlated with benefit from trastuzumab deruxtecan.

1b. Other therapeutically relevant biomarkers to be assessed as part of routine clinical practice include germline breast cancer gene 1/2 mutation (g*BRCA*m) status in HER2-negative MBC, PD-L1 status in triple-negative breast cancer (TNBC) and PIK3CA status in ER/PgR-positive, HER2-negative MBC [I, A; ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) score: I-A] (See Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101541).

1c. Genomic profiling and further diagnostic tests [e.g. on tumour tissue or circulating tumour DNA (ctDNA)] should only be carried out as part of routine clinical practice if the result will impact on treatment decisions, as guided by the ESCAT score, or if the patient can access appropriate clinical trials [V, B].

2. Staging and risk assessment—recommendations 2a-m

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO recommendations

Table 1. Summary of Asian recommendations for the treatment of patients with MBC

Recommendations	Acceptability consensus
Recommendation 1: Diagnosis, pathology and molecular biology	
1a. At first diagnosis of MBC, a biopsy should be carried out to confirm histology and assess/re-assess tumour biology including ER, PgR and HER2 status [I, B].	100%
1b. Other therapeutically relevant biomarkers to be assessed as part of routine clinical practice include germline *BRCA1/2* mutation (g*BRCA*m) status in HER2-negative MBC, PD-L1 status in triple-negative breast cancer (TNBC) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) in ER/PgR-positive, HER2-negative MBC [I, A; ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) score: I-A].	100%
1c. Genomic profiling and further diagnostic tests [e.g. on tumour tissue or circulating tumour DNA (ctDNA)] should only be carried out as part of routine clinical practice if the result will impact on treatment decisions, as guided by the ESCAT scale, or if the patient can access appropriate clinical trials [V, B].	100%
Recommendation 2: Staging and risk assessment	
2a. The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen, and bone scintigraphy [II, A].	100%
2b. [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)—CT may be used instead of CT and bone scans [II, B].	100%
2c. There is no evidence that one staging or monitoring approach provides an OS benefit over another.	100%
2d. The imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability [III, B].	100%
2e. The interval between imaging and starting treatment should be $\leq$4 weeks.	100%
2f. Evaluation of response should generally occur every 2-4 months depending on disease dynamics, location, extent of metastasis and type of treatment [V, B].	100%
2g. Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm [IV, D]. Less frequent monitoring is acceptable, particularly for indolent disease.	100%
2h. If progression is suspected, additional tests should be carried out in a timely manner irrespective of planned intervals [V, B].	100%
2i. Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible flare during the first few months of treatment [III, C].	100%
2j. PET—CT might provide earlier guidance in monitoring bone-only/predominant metastases, but prospective trials are needed to study the impact on treatment decisions and OS [III, C].	100%
2k. Impending fracture risk should be evaluated by CT or X-rays. The spine instability neoplastic score provides reproducible risk assessment for vertebral metastases. In the case of suspected cord compression, MRI is the modality of choice [I, A].	100%
2l. Brain imaging should not be routinely carried out in all asymptomatic patients at initial MBC diagnosis or during disease monitoring. Patients with asymptomatic HER2-positive breast cancer or TNBC have higher rates of brain metastases at initial diagnosis of MBC, even as the first site of recurrence. This may warrant subtype-oriented brain imaging in asymptomatic patients with MBC if detection of CNS metastases will alter the choice of systemic therapy [V, C]. Randomised trials to determine the risks and benefits of brain screening are ongoing (NCT03881605).	100%
2m. Symptomatic patients should always undergo brain imaging, preferably with MRI [II, B].	100%
Recommendation 3: HR-positive, HER2-negative breast cancer	
First-line treatment	
3a. A CDK4/6 inhibitor combined with endocrine therapy (ET) is the standard first-line therapy for patients with ER-positive, HER2-negative MBC, since it is associated with substantial PFS and OS benefits and maintained or improved QoL [I, A; ESMO-MCBS v1.1 scores: 3-5].	100%
3b. ET alone in the first-line setting **may** be reserved for the small group of patients with comorbidities or a PS that precludes the use of CDK4/6 inhibitor combinations **[V, A].**	100%
3c. Pre- and perimenopausal women **should be offered** OFS **or ovarian ablation** in addition to all endocrine-based therapies **[I, A].**	100%
Second-line treatment	
3d. Selection of second-line therapy (chemotherapy versus further endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and consideration of the associated toxicity profile.	100%
3e. Alpelisib—fulvestrant is a treatment option for patients with PIK3CA-mutant tumours (in exons 7, 9 or 20), prior exposure to an AI (+/−CDK4/6 inhibitors) and appropriate haemoglobin A1c levels [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A].	100%
3f. Everolimus—exemestane is an option since it significantly prolongs PFS [I, B; ESMO-MCBS v1.1 score: 2]. Tamoxifen or fulvestrant can also be combined with everolimus [II, B]. If everolimus is used, stomatitis prophylaxis must be used.	100%
3g. PARP inhibitor monotherapy (olaparib or talazoparib) should be considered for patients with germline pathogenic *BRCA1/2* mutations [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] and as an option for those patients with somatic pathogenic or likely pathogenic *BRCA1/2* or germline *PALB2* mutations.	100%
3h. At least two lines of endocrine-based therapy are preferred before moving to chemotherapy **in the absence of endocrine refractory disease and/or imminent organ failure [V, A].**	100%
3i. In patients with imminent organ failure, chemotherapy is the preferred option.	100%
Beyond second-line treatment	
3j. For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting may represent an option [III, B].	100%
3k. Patients with tumours that are endocrine resistant should be considered for chemotherapy [V, B].	100%
3l. Sequential single-agent chemotherapy is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination chemotherapy is preferred [II, A].	100%
3m. Available drugs for single-agent chemotherapy include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents.	100%
3n. Rechallenge with anthracyclines or taxanes is feasible in patients with a DFI $\geq$12 months. If available, the use of liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge [II, B].	100%
3o. **Bevacizumab, if available, can be added to a taxane or capecitabine in the first- or second- line chemotherapy setting** [I, C; ESMO-MCBS v1.1 score: 2].	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
3p. **DPD genotyping or phenotyping may be considered before initiating fluoropyrimidine-based therapy. Based on genetic epidemiology studies, DPD genotyping or phenotyping may be considered upon unexpected or significant toxicities with fluoropyrimidine-based therapy [II, D].**	100%
3q. Chemotherapy should generally be **considered** until disease progression or intolerable toxicity (except for anthracyclines where the cumulative limit needs to be taken into account) [**I**, B].	100%
3r. The optimal sequence of therapy for patients with MBC has not been established. Available options should be discussed with the patient [I, A].	100%
Recommendation 4: HER2-positive breast cancer	
First-line treatment	
4a. Standard first-line treatment of HER2-positive MBC should be pertuzumab—trastuzumab—docetaxel regardless of HR status [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].	100%
4b. Docetaxel should be given for at least six cycles, if tolerated, followed by maintenance pertuzumab—trastuzumab until progression [I, A].	100%
4c. An alternative taxane (paclitaxel, nab-paclitaxel) may be substituted for docetaxel [II, A].	100%
4d. ET may be added to pertuzumab—trastuzumab maintenance after completion of chemotherapy for HER2-positive, HR-positive tumours. OFS should also be added for pre- and perimenopausal patients.	100%
4e. If chemotherapy is contraindicated in patients with HER2-positive, HR-negative MBC, HER2-targeted therapy without chemotherapy (e.g. trastuzumab or trastuzumab—pertuzumab) may be used; if taxane chemotherapy is contraindicated, a less toxic chemotherapy partner (e.g. capecitabine or vinorelbine) may be considered [III, C].	100%
4f. In selected cases of HER2-positive, HR-positive MBC where the patient is not suitable for first-line chemotherapy, ET (e.g. an AI) in combination with an HER2-targeted therapy, such as trastuzumab, trastuzumab—pertuzumab, trastuzumab—lapatinib or lapatinib, may be recommended [II, B].	100%
4g. The use of single-agent ET without HER2-targeted therapy in HER2-positive, HR-positive MBC is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies [III, C].	100%
4h. It is suggested that patients with metastatic recurrence within 12 months of receiving adjuvant trastuzumab—pertuzumab should follow the second-line therapy recommendations [II, B].	100%
Second-line treatment	
4i. Trastuzumab deruxtecan is the preferred second-line therapy after progression on a taxane and trastuzumab [I, A].	100%
4j. T-DM1 is a second-line treatment option after progression on a taxane and trastuzumab in cases where trastuzumab deruxtecan is not available [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].	100%
4k. Tucatinib—capecitabine—trastuzumab or trastuzumab deruxtecan may be used in the second-line setting in selected patients with brain metastases [II, A].	100%
Options for third-line treatment and beyond	
4l. Tucatinib—capecitabine—trastuzumab [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A], trastuzumab deruxtecan [III, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A] and T-DM1 [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] appear to be the most active treatment options in the third-line setting. The choice of treatment depends on prior second-line therapy, patient characteristics, toxicity profile and availability.	100%
4m. In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET) [I, C].	100%
4n. Neratinib [I, C; ESMO-MCBS v1.1 score: 1; ESCAT score: I-A; FDA approved, not EMA approved] and margetuximab [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA approved, not EMA approved] can be considered reasonable approaches for late-line scenarios. Although there are no comparative data, the most appropriate setting might be in patients who have exhausted all standard therapy options [V, C]. However, in HER2-positive MBC, there is no evidence for sequencing a TKI after a TKI.	100%
4o. Continued anti-HER2-based therapy is the current clinical standard for patients with HER2-positive tumours. If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, trastuzumab beyond progression should be considered [III, A].	100%
Recommendation 5: TNBC	
First-line treatment	
5a. If PD-L1 positive, the preferred option is chemotherapy in combination with an ICI.	100%
5a1. In the case of PD-L1 immune cell positivity (Ventana SP142), atezolizumab plus nab-paclitaxel should be the treatment of choice where the DFI is $\geq$12 months in countries where this indication is approved [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; EMA approved, not FDA approved].	100%
5a2. In the case of a CPS $\geq$10, pembrolizumab plus paclitaxel, nab-paclitaxel, or carboplatin—gemcitabine should be the treatment of choice where the DFI is $\geq$6 months [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA approved, not EMA approved].	100%
5b. If g*BRCA*m and PD-L1 negative, the preferred options are olaparib or talazoparib, **if available** [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] or platinum-based chemotherapy [II, A].	100%
5c. If PD-L1 negative and gBRCA-wild-type, the preferred option depends on previous treatment exposure, disease presentation, DFI and patient considerations.	100%
5c1. Taxane monotherapy is the most frequent option.	100%
5c2. Anthracyclines are an option in cases where there has been no prior exposure or if rechallenge is possible.	100%
5c3. In cases of imminent organ failure, combination therapy is preferred based on a taxane and/or anthracycline combination and including bevacizumab (first line only) if available.	100%
Progression after anthracyclines and taxanes	
5d. Sacituzumab govitecan (if available) **may be considered as** the preferred treatment option after taxanes [I, A; ESMO-MCBS v1.1 score: 4; FDA approved, not EMA approved].	100%
5e. After progression, all chemotherapy recommendations for HER2-negative disease also apply for TNBC, e.g. eribulin, capecitabine and vinorelbine.	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
5f. There are no data to support anti-androgen therapy, or inhibitors targeting PI3K, HER2 or AKT for advanced TNBC and therefore these cannot be recommended for routine use outside of a clinical trial setting.	100%
Recommendation 6: HER2-low MBC	
6a. Trastuzumab deruxtecan, if available, should be considered for patients with HR-positive or HR-negative HER2-low unresectable and/or metastatic breast cancer previously treated with one or two prior lines of chemotherapy [I, A; consensus = 100%] (Table 1 **and** Figures 2 **and** 5**).**	100%
Recommendation 7: Hereditary breast cancer (gBRCAm)	
7a. Patients with HER2-negative MBC and germline pathogenic or likely pathogenic variants in BRCA1 or BRCA2 should be offered treatment with a PARP inhibitor (olaparib or talazoparib), independent of HR status, as an alternative to chemotherapy [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].	100%
7b. **A PARP inhibitor can be offered to patients with *gBRCAm* MBC irrespective of prior treatment with anthracyclines—taxanes; patients with HR-positive tumours should not be** required to demonstrate complete endocrine resistance [II, B].	100%
7c. There is insufficient evidence to determine the optimal sequencing of PARP inhibitors with other active treatments such as chemotherapy—ICI combinations in mTNBC or ET and targeted therapy combinations in HR-positive disease [I, A].	100%
7d. Patients who may be considered for treatment with a PARP inhibitor should be offered genetic testing for pathogenic variants in *BRCA1* and *BRCA2* regardless of age, family history or breast cancer subtype [I, A].	100%
Recommendation 8: Site-specific management	
Primary stage IV disease	
8a. For patients with newly diagnosed stage IV breast cancer and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context [II, B].	100%
8b. Locoregional treatment of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is not routinely recommended [II, D].	100%
8c. In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated [II, A].	100%
8d. Surgery of the primary tumour may be considered for patients who may benefit from salvage surgery (e.g. those with bone-only metastases, a good response to initial systemic therapy, HR-positive tumours, HER2-negative tumours, age <55 years and those with OMD) [II, B]. **Surgery or RT of the primary tumour should be carefully considered for circumstances in which they provide added value for symptom palliation or prevention of complications [IV, C].**	100%
Oligometastatic disease	
8e. A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].	100%
8f. Patients with OMD should be discussed in a multidisciplinary context to individualise management [V, B].	100%
8g. Multimodality treatment approaches involving locoregional therapy [e.g. high conformal radiotherapy (RT), image-guided ablation, selective internal RT and/or surgery] combined with systemic treatments are recommended, tailored to the disease presentation in the individual patient [V, B].	100%
8h. Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting [II, C]; however, it is unknown if this leads to improved OS.	100%
Bone metastases and bone-modifying agents	100%
8i. A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].	100%
8j. An orthopaedic evaluation is advised in the case of significant lesions in the long bones or vertebrae as well as in patients with MSCC to discuss the possible role of surgery [IV, A].	100%
8k. RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A].	100%
8l. A single 8-Gy RT fraction is as effective as fractionated schemes in patients with uncomplicated bone metastases [I, A].	100%
8m. RT should be delivered after surgery for stabilisation or separation surgery for MSCC [III, B].	100%
8n. Bone-modifying agents (BMAs), e.g. bisphosphonates or denosumab, are recommended for patients with bone metastases, regardless of symptoms [I, A].	100%
8o. Zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments [I, B].	100%
8p. Denosumab should be administered every 4 weeks and is more effective than zoledronate in delaying first and subsequent SREs [I, B].	100%
8q. Before the initiation of BMAs, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed [III, A].	100%
8r. The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission [II, B].	100%
8s. The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting locoregional therapy [V, C].	100%
Brain metastases and leptomeningeal metastases	
8t. Brain metastases should be managed according to the recommendations outlined in the European Association of Neuro-Oncology-ESMO (EANO-ESMO) Clinical Practice Guideline (CPG) for the management of patients with brain metastases from solid tumours.	100%
8u. Leptomeningeal metastases should be treated according to the recommendations outlined in the EANO-ESMO CPG for the management of patients with leptomeningeal metastases from solid tumours.	100%
Recommendation 9: Long-term implications and survivorship	
9a. An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.	100%
9b. Patients should be informed about treatment choices and side-effect profiles of recommended systemic treatments.	100%
9c. All treatment should include formal patient education regarding side-effect management [I, A].	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
9d. Careful assessment of side-effects should occur at each visit. Electronic patient reported outcomes may be useful in this context.	100%
9e. QoL assessments should be incorporated into the evaluation of treatment efficacy.	100%
9f. Dose reduction and delay are effective strategies to manage toxicity in advanced disease [I, A].	100%

AKT, protein kinase B; BMA, bone-modifying agent; *BRCA 1/2*, breast cancer 1 and 2 genes; CDK, cyclin-dependent kinase; CNS, central nervous system; CT, computed tomography; DFI, disease-free interval; DPD, dihydropyrimidine dehydrogenase; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; ET, endocrine therapy; FDA, Food and Drug Administration; g*BRCA*m, germline BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; MSCC, metastatic spinal cord compression; OMD, oligometastatic disease; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PFS, progression-free survival; PgR, progesterone receptor; PIK3CA, phosphatidylinositol-4, 5, bisphosphonate 3-kinase catalytic subunit alpha; QoL, quality of life; RT, radiotherapy; T-DM1, ado-trastuzumab emtansine; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer.

on staging and risk assessment 'recommendations 2a-m' below and in Table 1.

2a. The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen, and bone scintigraphy [II, A].

2b. [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)—CT may be used instead of CT and bone scans [II, B].[26,27]

2c. There is no evidence that one staging or monitoring approach provides an overall survival (OS) benefit over another.[27]

2d. The imaging modality chosen at baseline should be applied for disease monitoring to ensure comparability [III, B].

2e. The interval between imaging and starting treatment should be $\leq$4 weeks.

2f. Evaluation of response should generally occur every 2-4 months depending on disease dynamics, location, extent of metastasis and type of treatment [V, B].[26]

2g. Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm [IV, D]. Less frequent monitoring is acceptable, particularly for indolent disease.[28]

2h. If progression is suspected, additional tests should be carried out in a timely manner irrespective of planned intervals [V, B].[26]

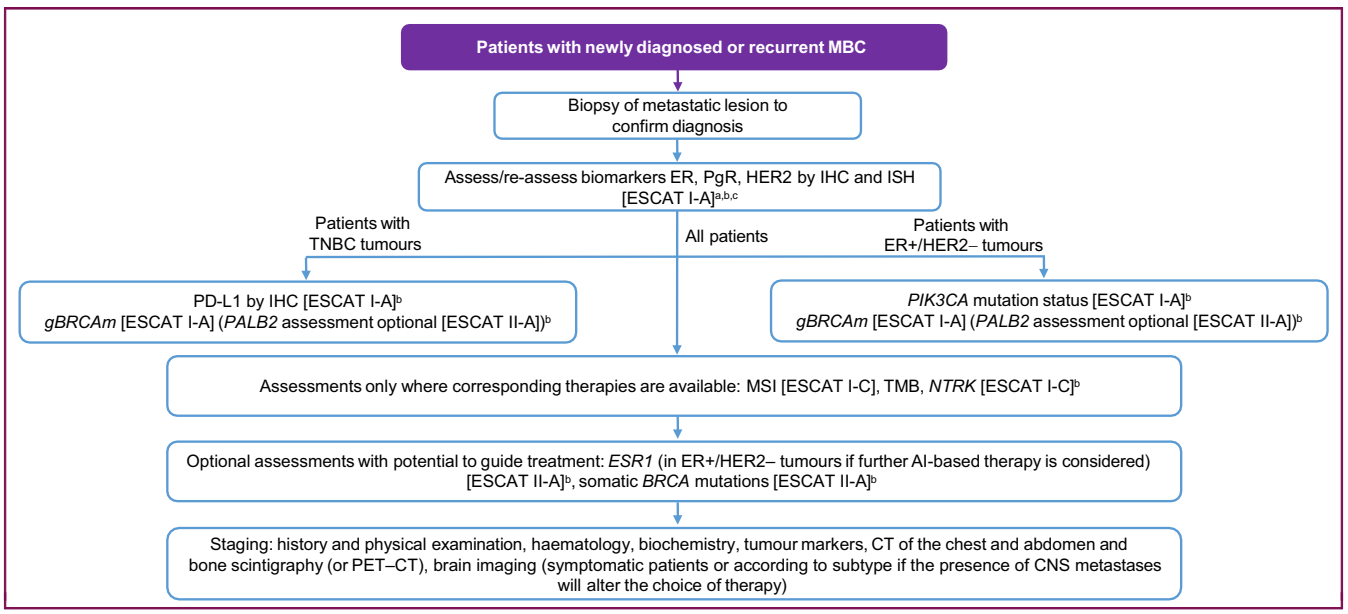

Figure 1. Diagnostic work-up and staging of MBC. Purple box: general categories or stratification; white boxes: other aspects of management.
AI, aromatase inhibitor; CNS, central nervous system; CT, computed tomography; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; gBRCAm, germline BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; MBC, metastatic breast cancer; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PgR, progesterone receptor; *PIK3CA,* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB, tumour mutation burden; TNBC, triple-negative breast cancer.
[a]If there are important differences in ER/PgR and HER2 status between the primary tumour and recurrence, patients should be managed according to receptor status of the recurrent disease biopsy.
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[133]
[c]Assess HER2-low status.

2i. Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible flare during the first few months of treatment [III, C].[27]

2j. PET—CT might provide earlier guidance in monitoring bone-only/predominant metastases, but prospective trials are needed to study the impact on treatment decisions and OS [III, C].[27,29]

2k. Impending fracture risk should be evaluated by CT or X-rays. The spine instability neoplastic score provides reproducible risk assessment for vertebral metastases.[30] In the case of suspected cord compression, magnetic resonance imaging (MRI) is the modality of choice [I, A].

2l. Brain imaging should not be routinely carried out in all asymptomatic patients at initial diagnosis of MBC or during disease monitoring. Patients with asymptomatic HER2-positive breast cancer or TNBC have higher rates of brain metastases at initial diagnosis of MBC, even as the first site of recurrence. This may warrant subtype-oriented brain imaging in asymptomatic patients with MBC if detection of central nervous system (CNS) metastases will alter the choice of systemic therapy [V, C]. Randomised trials to determine the risks and benefits of brain screening are ongoing (NCT03881605).[31]

2m. Symptomatic patients should always undergo brain imaging, preferably with MRI [II, B].

3. HR-positive, HER2-negative breast cancer—recommendations 3a-r

An algorithm for the treatment and management of patients with hormone receptor (HR)-positive, HER2-negative breast cancer is presented in Figure 2. Endocrine therapy (ET) is the principal treatment option for women with this type of MBC. However, because of epidemiological differences, Asian patients are younger when they are diagnosed with breast cancer than in Western countries, with 15% of female patients younger than 40 years of age and 55% younger than 50 years of age at the time of diagnosis.[12,32] Also, there is a higher incidence of luminal B breast cancer, higher incidence of *TP53* mutations and more active immune microenvironment in Asian patients with HR-positive, HER2-negative disease compared with their Western counterparts.[12,13] Luminal B tumours, as stated previously, are characterised by higher Ki-67 expression, have a worse prognosis and often show resistance to ET.[15]

Addition of CDK4/6 inhibitors abemaciclib, palbociclib and ribociclib to ET has been shown to improve progression-free survival (PFS) in patients (including Asian patients) with MBC in the first-line setting in the MONARCH 3,[33-35] PALOMA-2,[36,37] MONALEESA-2[38,39] and MONALEESA-7[40-42] trials, and confirmed in both a meta-analysis of the MONARCH 3, PALOMA-2, MONALEESA-2 and MONALEESA-7 trials[43] and a pooled analysis of the MONALEESA-2, -3 and -7 trials.[44] Improved PFS was also seen in the second- and subsequent-line settings when abemaciclib, palbociclib and ribociclib were added to ET in the MONARCH 2,[45] PALOMA-3[46,47] and MONALEESA-3[48] trials. This was despite the fact that the Asian patient cohorts contained more patients with luminal B and aggressive disease. Improved clinical outcomes have been reported for the CDK4/6 inhibitors in Asian patients compared with non-Asian patients,[36,41,43,44,49-52] with Asian patients showing an increased incidence of haematological toxicities, which could be managed using early dose adjustments, maintaining patient quality of life (QoL).

Treatment with abemaciclib or ribociclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement in patients who progressed after prior ET regardless of menopausal status.[53,54] Moreover, addition of the CDK4/6 inhibitor ribociclib to letrozole has been shown to improve OS in patients (including Asian patients) with MBC in the first-line setting in the MONALEESA-2[55] and MONALEESA-7 trials.[40,41] No OS benefit was observed for palbociclib with either fulvestrant or an aromatase inhibitor (AI) in the PALOMA-3[52] and PALOMA-2[36] trials, respectively. Furthermore, ET plus CDK4/6 inhibitors yield similar or better efficacy[56] when compared with chemotherapy, with or without targeted therapy, and are associated with less toxicity.[56,57] More recently, data from the randomised RIGHT choice study (NCT03839823) in pre- and perimenopausal women who had received no prior systemic ET or chemotherapy (conducted in 13 Asia Pacific and Middle Eastern countries) suggest that ribociclib plus ET may offer improved treatment efficacy compared with physician's choice combination chemeotherapy.[58] RIGHT choice study data further support treatment strategies with ovarian function suppression (OFS) and ET plus ribociclib as first-line treatments in patients with imminent organ failure.

First-line treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO recommendation on the use of CDK4/6 inhibitors in the first-line treatment of MBC ('recommendation 3a' below and in Table 1). However, there was some difference of opinion amongst the experts with regard to 'recommendations 3b and c' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101541), with the request that the wording be softened. Thus, 'should' in 'recommendation 3b' was replaced with '**may**' (see bold text), with 100% consensus. Similarly, 'must receive ovarian function suppression (OFS)' in the original 'recommendation 3c' was replaced with '**should be offered**' OFS or '**ovarian ablation**' (see bold text) with 100% consensus, due to the view of some of the Asian experts that tamoxifen is still a treatment option for pre- and perimenopausal women.[59] However, it should be noted that in the MONALEESA-7 trial in pre- and perimenopausal patients with ER-positive, HER2-negative MBC randomly assigned 1 : 1 to receive the CDK4/6 inhibitor ribociclib or placebo, both patient groups received OFS.[42] Thus, any patients in the metastatic setting should receive OFS.

3a. A CDK4/6 inhibitor combined with ET is the standard first-line therapy for patients with ER-positive, HER2-negative MBC, since it is associated with substantial

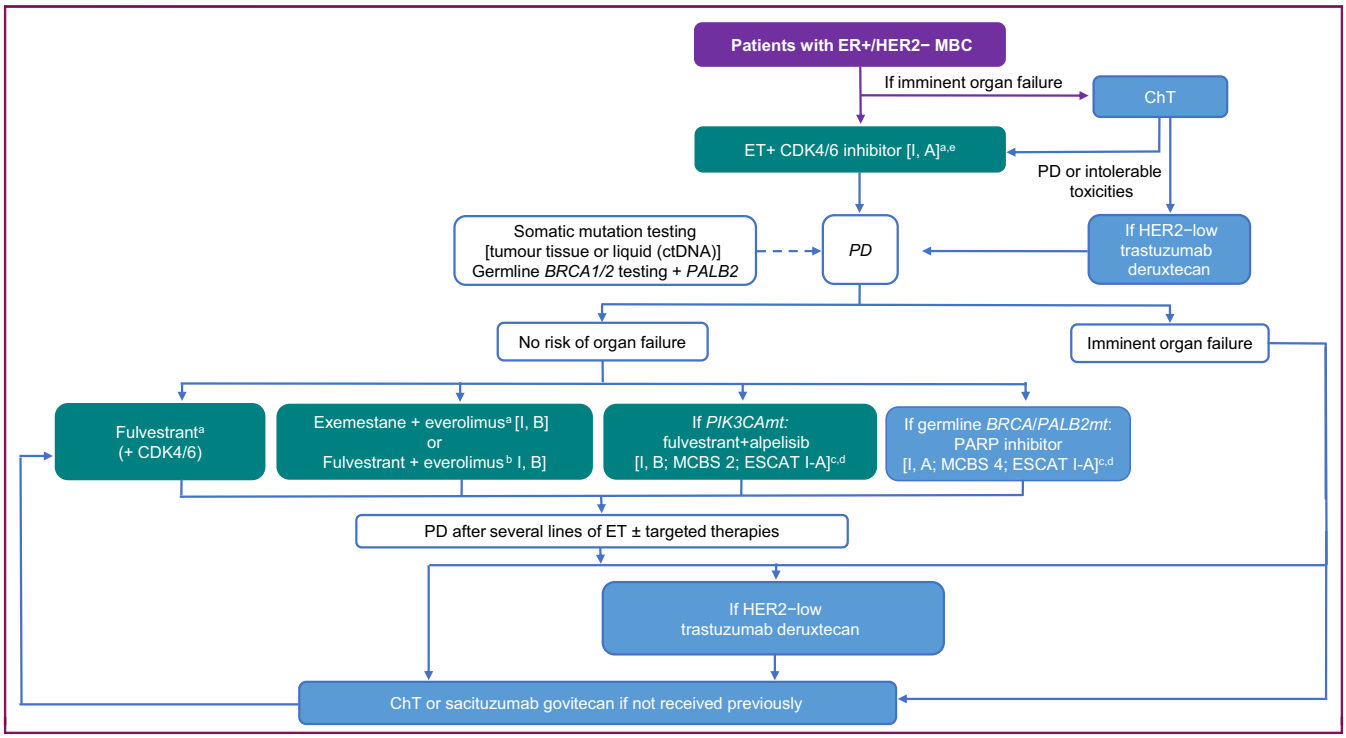

Figure 2. Treatment of ER-positive/HER2-negative MBC. Purple box: general categories or stratification; turquoise/green boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management; blue boxes: systemic anticancer therapy; dark blue boxes: trastuzumab deruxtecan in HER2-low. AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; ctDNA, circulating tumour DNA: EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
[a]OFS if the patient is premenopausal.
[b]Preferred if the patient is ESR1 mutation positive [ESCAT score: II-A].[d]
[c]ESMO-MCBS v1.1[134] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[d]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[133]
[e]If relapse <12 months after end of adjuvant AI: fulvestrant-CDK4/6 inhibitor;[a] if relapse >12 months after end of adjuvant AI: AI-CDK4/6 inhibitor.[a]

PFS and OS benefits and maintained or improved QoL [I, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 scores: 3-5].

3b. ET alone in the first-line setting **may** be reserved for the small group of patients with comorbidities or a performance status (PS) that precludes the use of CDK4/6 inhibitor combinations [**V, A; consensus = 100%**].

3c. Pre- and perimenopausal women **should be offered** OFS **or ovarian ablation** in addition to all endocrine-based therapies[59] [**I, A**; **consensus = 100%**].

Second-line treatment. In Asian patients who require first-line chemotherapy due to imminent organ failure, or who did not have access to a CDK4/6 inhibitor in the first-line setting, it is clinically acceptable to use ET plus a CDK4/6 inhibitor as a subsequent therapy in cases of progressive disease or intolerable toxicity.[45-47,50-52] Maintenance ET (single agent) following chemotherapy may be an option in clinically stable patients based on the judgement of the treating physician. The selection of chemotherapy versus further ET should be based on the extent and aggressiveness of the disease. After progression on ET plus CDK4/6 inhibitor therapy, determination of *PIK3CA* and ER1 (or *ESR1* if further AI therapy is being considered) as well as g*BRCA1/2m* status is recommended.[21]

Also, although there are little data on use of CDK4/6 inhibitors after progression on CDK4/6 inhibitors, rechallenge may be possible after a treatment-free interval of 12 months based on evidence regarding rechallenge with other therapies. In this setting the small, randomised, phase II MAINTAIN trial in patients whose cancer had previously progressed on any CDK4/6 inhibitor and any ET showed that continuing a CDK4/6 inhibitor (ribociclib) after progression on a CDK4/6 inhibitor (87% palbociclib) and changing the endocrine agent (fulvestrant/exemestane) is more effective than changing the endocrine agent alone.[60]

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 3d-g' below for the second-line treatment of patients with MBC.

3d. Selection of second-line therapy (chemotherapy versus further endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and consideration of the associated toxicity profile.[21]

3e. Alpelisib—fulvestrant is a treatment option for patients with *PIK3CA*-mutant tumours (in exons 7, 9 or 20), prior exposure to an aromatase inhibitor (AI) (+/−CDK4/6 inhibitors) and appropriate haemoglobin A1c levels[61-63] [I, B; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: 2; ESCAT score: I-A].

3f. Everolimus—exemestane is an option since it significantly prolongs PFS[64-67] [I, B; ESMO-MCBS v1.1 score: 2]. Tamoxifen or fulvestrant can also be combined with everolimus [II, B; off label]. If everolimus is used, stomatitis prophylaxis must be used.

3g. PARP inhibitor monotherapy (olaparib or talazoparib) should be considered for patients with germline pathogenic *BRCA1/2* mutations[68,69] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] and as an option for those patients with somatic pathogenic or likely pathogenic *BRCA1/2* or germline *PALB2* (partner and localiser of *BRCA2*) mutations.

However, some of the Asian experts did not accept that ESMO 'recommendation 3h' reflected the real-life situation with the observation that it would not be appropriate for patients who had progressed within 4-6 weeks of first-line ET to receive second-line ET before switching to chemotherapy. Thus, 'recommendation 3h' was revised (see bold text), with additional text added to more precisely describe the patient group this recommendation applied to.

3h. At least two lines of endocrine-based therapy are preferred before moving to chemotherapy **in the absence of refractory disease and/or imminent organ failure [V, A: consensus = 100%].**

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendation 3i' below:

3i. In patients with imminent organ failure, chemotherapy is the preferred option [III, B].

Trastuzumab deruxtecan can be considered second or later line in patients with HER2-low disease who have failed ET and more than one prior line of chemotherapy in the metastatic setting[23] (Figure 2). For emerging therapeutic strategies in patients with HER2-low MBC (IHC 1+ or IHC 2+/ISH−) according to ASCO/CAP 2018 guidelines,[24,25] see Section 6 below.

Beyond second-line treatment. Treatment beyond the second-line setting needs to take into account the sensitivity/resistance to previous treatment(s), time to progression, *gBRCAm* status and overall tumour biology if available. The Pan-Asian panel of experts agreed with and accepted completely without change (**100% consensus**), the ESMO 'recommendations 3j-n' below for the treatment of patients with MBC beyond second line, after some discussion around 'recommendation 3k'.

3j. For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting may represent an option [III, B].

3k. Patients with tumours that are endocrine resistant should be considered for chemotherapy [V, B].

3l. Sequential single-agent chemotherapy is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination chemotherapy is preferred [II, A].

3m. Available drugs for single-agent chemotherapy include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents.

3n. Rechallenge with anthracyclines or taxanes is feasible in patients with a disease-free interval (DFI) ≥12 months. If available, the use of liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge [II, B].

Some of the Asian experts did not accept the ESMO 'recommendations 3o-q'. There was considerable discussion around whether the addition of bevacizumab conferred a survival advantage with several countries saying that the use of bevacizumab in combination with chemotherapy was not practised routinely. Thus, the original ESMO 'recommendation 3o' below:

3o. The combination of a taxane or capecitabine with bevacizumab, if available, is an option for the first line of chemotherapy [I, C; ESMO-MCBS v1.1 score: 2].

was revised to read as:

3o. **Bevacizumab, if available, can be added to a taxane or capecitabine in the first- or second-line chemotherapy setting**[70] [I, C; ESMO-MCBS v1.1 score: 2; **consensus = 100%**].

Due to the fact that dihydropyrimidine dehydrogenase (DPD) deficiency is rare in Asian countries compared with non-Asian countries, patients are not routinely tested for a lack of DPD activity, thus the original 'recommendation 3' below:

3p. If capecitabine is used, patients should undergo germline variant testing for the lack of the enzyme, DPD, before starting treatment.

was revised to read as follows:

3p. **DPD genotyping or phenotyping may be considered before initiating fluoropyrimidine-based therapy. Based on genetic epidemiology studies, DPD genotyping or phenotyping may be considered upon unexpected or significant toxicities with fluoropyrimidine-based therapy [II, D: consensus = 100%].**

A Japanese study reported no clear association between DPD and fluoropyrimidine-related toxicity (i.e. safety) in Asian patients.[71]

Also, some of the Asian experts disputed whether chemotherapy should be continued until disease progression as proposed in the original ESMO recommendation 3q and supported by two studies. The first of which is a systematic review and a meta-analysis of 11 randomised trials that showed longer first-line chemotherapy duration to be associated with a marginally longer OS and a substantially longer PFS.[72] The second study showed that in patients who achieved disease control within the first six cycles of paclitaxel gemcitabine (PG) therapy, maintenance PG chemotherapy conferred a better PFS and OS outcome when compared with observation.[73] However, the feeling amongst the experts was that the benefit was debatable and that maintaining chemotherapy until disease progression was not always practised. Thus, the wording of the original 'recommendation 3q' below was modified slightly, by replacing 'continued' with 'considered' as per the bold text below and the LoE revised.

3q. Chemotherapy should generally be **considered** until disease progression or intolerable toxicity (except for anthracyclines where the cumulative limit needs to be taken into account) [**I,** B; **consensus = 100%**].

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendation 3r' below:

3r. The optimal sequence of therapy for patients with MBC has not been established. Available options should be discussed with the patient [I, A].

Trastuzumab deruxtecan can be considered for second- or later-line chemotherapy in patients with HER2-low disease[23] (Figure 2). For emerging therapeutic strategies in patients with HER2-low MBC (IHC 1+ or IHC 2+/ISH−) according to ASCO/CAP 2018 guidelines,[24,25] see Section 6. Also, the TROPiCS-02 study in patients with heavily pre-treated HR-positive HER2-negative MBC has recently shown sacituzumab govitecan to significantly improve PFS over physician's choice chemotherapy with a 34% reduction in the risk of progression or death,[74] and to demonstrate a statistically significant improvement in OS (median 14.4 versus 11.2 months; hazard ratio 0.79, 95% CI 0.65-0.96; $P = 0.020$).[75] Thus, sacituzumab govitecan may represent a new treatment option for these patients after prior treatment that includes ET, CDK4/6 inhibitor therapy and at least two lines of chemotherapy, including taxane therapy, for advanced breast cancer, and may be offered to patients with HR-positive/HER2-negative disease. Unfortunately no Asian countries participated in the TROPiCS-02 study, therefore supporting data in Asian patients are limited. Elacestrant is an option for patients with ER-positive, HER2-negative, *ESR1*-mutated MBC progressing after at least one line of ET based on PFS data from the phase III EMERALD trial.[76]

4. HER2-positive breast cancer—recommendations 4a-o

An algorithm for the first- and second-line treatment and management of patients with HER2-positive breast cancer is presented in Figure 3.

First-line treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 4a-h' below for the first-line treatment of patients with HER2-positive MBC.

4a. Standard first-line treatment of HER2-positive MBC should be pertuzumab—trastuzumab—docetaxel regardless of HR status [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].[77,78]

4b. Docetaxel should be given for at least six cycles, if tolerated, followed by maintenance pertuzumab—trastuzumab until progression [I, A].

4c. An alternative taxane (paclitaxel, nab-paclitaxel) may be substituted for docetaxel [II, A].

4d. ET may be added to pertuzumab—trastuzumab maintenance after completion of chemotherapy for HER2-positive, HR-positive tumours.[79] OFS should also be added for pre- and perimenopausal patients.

4e. If chemotherapy is contraindicated in patients with HER2-positive, HR-negative MBC, HER2-targeted therapy without chemotherapy (e.g. trastuzumab or trastuzumab—pertuzumab[80]) may be used; if taxane chemotherapy is contraindicated, a less toxic chemotherapy partner (e.g. capecitabine or vinorelbine) may be considered [III, C, off label].

4f. In selected cases of HER2-positive, HR-positive MBC where the patient is not suitable for first-line chemotherapy, ET (e.g. an AI) in combination with an HER2-targeted therapy, such as trastuzumab,[81,82] trastuzumab—pertuzumab,[79] trastuzumab—lapatinib[83] or lapatinib,[84] may be recommended [II, B].

4g. The use of single-agent ET without HER2-targeted therapy in HER2-positive, HR-positive MBC is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies [III, C].

4h. It is suggested that patients with metastatic recurrence within 12 months of receiving adjuvant trastuzumab—pertuzumab should follow the second-line therapy recommendations [II, B].

Second-line treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 4i-k' below for the second-line treatment of patients with HER2-positive MBC.

4i. Trastuzumab deruxtecan is the preferred second-line therapy after progression on a taxane and trastuzumab[85] [I, A].

4j. Ado-trastuzumab emtansine (T-DM1) is a second-line treatment option after progression on a taxane and trastuzumab in cases where trastuzumab deruxtecan is not available [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].

4k. Tucatinib—capecitabine—trastuzumab[86] or trastuzumab deruxtecan may be used in the second-line setting in selected patients with brain metastases [II, A].

Options for third-line treatment and beyond. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations

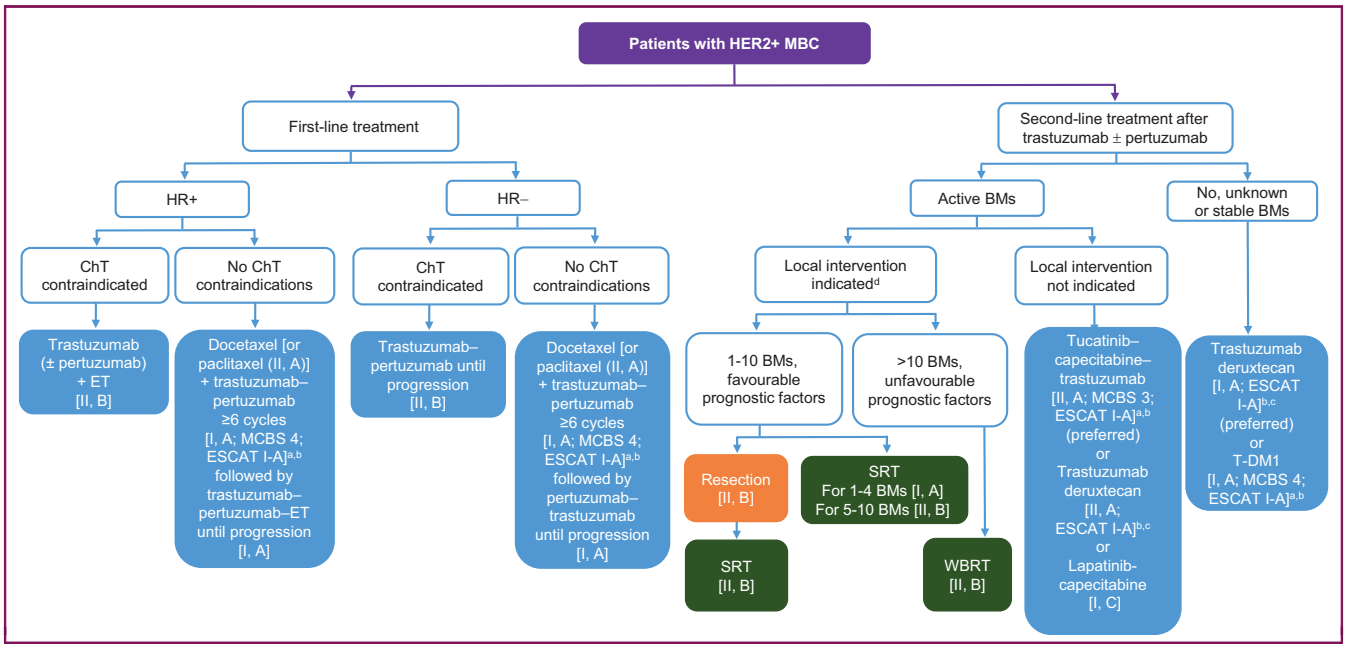

Figure 3. First- and second-line treatment of HER2-positive MBC. Purple box: general categories or stratification; orange box: surgery; green boxes: RT; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.

BMs, brain metastases; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PD, progressive disease; RT, radiotherapy; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy.

[a]ESMO-MCBS v1.1[134] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[133]

[c]Not FDA approved for use in second line.

[d]Keep on current systemic therapy unless PD outside CNS.

4l-o' below for the treatment of patients with HER2-positive MBC, third line and beyond. A treatment algorithm for third-line and beyond treatment of patients with HER2-positive MBC is presented in Figure 4.

4l. Tucatinib—capecitabine—trastuzumab[87] [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A], trastuzumab deruxtecan[85,88] [III, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A] and T-DM1[89] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A] appear to be the most active treatment options in the third-line setting. The choice of treatment depends on prior second-line therapy, patient characteristics, toxicity profile and availability.

4m. In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combination[90-94] (e.g. with capecitabine, trastuzumab or ET) [I, C].

4n. Neratinib[95] [I, C; ESMO-MCBS v1.1 score: 1; ESCAT score: I-A; FDA approved, not EMA approved] and margetuximab[96] [I, B; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA approved, not EMA approved] can be considered as reasonable approaches for late-line scenarios. Although there are no comparative data, the most appropriate setting might be in patients who have exhausted all standard therapy options [V, C]. However, in HER2-positive MBC, there is no evidence for sequencing a tyrosine kinase inhibitor (TKI) after a TKI.[21]

4o. Continued anti-HER2-based therapy is the current clinical standard for patients with HER2-positive tumours. If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, trastuzumab beyond progression should be considered[21,97] [III, A].

5. TNBC—recommendations 5a-f

TNBC is defined by the absence of expression of ER and PgR, and low expression of HER2, and represents ∼10%-20% of all cancers in Asia.[98-101] An algorithm for the treatment of patients with metastatic TNBC (mTNBC) is presented in Figure 5.

First-line treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 5a1 and 5a2' below for the treatment of patients with PD-L1-positive, mTNBC, where the preferred treatment option is chemotherapy in combination with an immune checkpoint inhibitor (ICI) (see Table 1).

5a1. In the case of PD-L1 immune cell positivity (Ventana SP142), atezolizumab plus nab-paclitaxel should be the treatment of choice where the DFI is ≥12 months in countries where this indication is approved[102] [II, A;

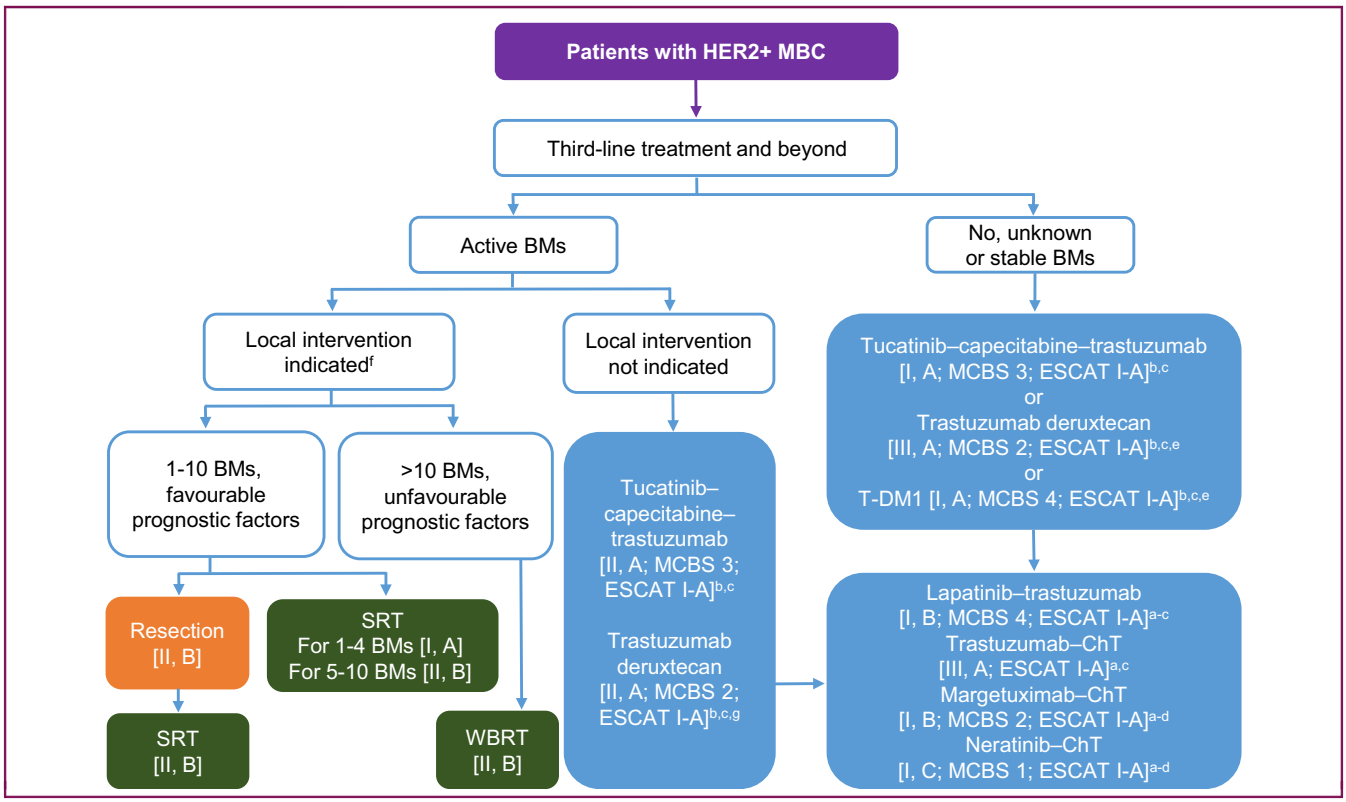

Figure 4. Third-line and beyond treatment of HER2-positive MBC. Purple box: general categories or stratification; orange box: surgery; green boxes: RT; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.
BMs, brain metastases; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PD, progressive disease; RT, radiotherapy; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy.
[a]There are no data for any of these combinations after tucatinib- and/or trastuzumab deruxtecan-based therapy.
[b]ESMO-MCBS v1.1[134] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluationforms-v1.1).
[c]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[133]
[d]FDA approved, not EMA approved.
[e]If not received as second-line therapy.
[f]Keep on current systemic therapy unless PD outside CNS.
[g]If not previously used, including all other drugs that are also a second-line treatment option.

ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; EMA approved, not FDA approved].

5a2. In the case of a combined positive score (CPS) ≥10, pembrolizumab plus paclitaxel or nab-paclitaxel should be the treatment of choice, or carboplatin—gemcitabine where the DFI is ≥6 months[103] [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A; FDA approved, not EMA approved].

However, since 'recommendation 5b' was not standard practice in several Asian countries due to a lack of availability, the original ESMO 'recommendation 5b' was modified as per the bold text below with 100% consensus.

5b. If g*BRCA*m and PD-L1 negative, the preferred treatment options are single-agent olaparib or talazoparib**, if available**[68,69,104,105] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A], or platinum-based chemotherapy[106-108] [II, A; **consensus = 100%**].

The Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 5c1 and 5c2' below, for the treatment of PD-L1-negative and *gBRCA*-wild-type TNBC, where the preferred option depends on prior treatment exposure, disease presentation, DFI and patient considerations.

5c1. Taxane monotherapy is the most frequent treatment option.[109]

5c2. Anthracyclines are an option in cases where there has been no prior exposure or if rechallenge is possible.

Other options include various combinations incorporating these two drugs together or not.[21] Nab-paclitaxel—carboplatin is also a valid option.[110]

Progression after anthracyclines and taxanes. Due to the fact that the antibody—drug conjugate sacituzumab govitecan is not widely approved or available in Asia (Table 2) the original 'recommendation 5d' was amended slightly as per the bold text below:

5d. Sacituzumab govitecan (if available) may **be considered as** the preferred treatment after taxanes[111,112] [I, **B**; ESMO-MCBS v1.1 score: 4; FDA and **EMA approved; consensus = 100%**].

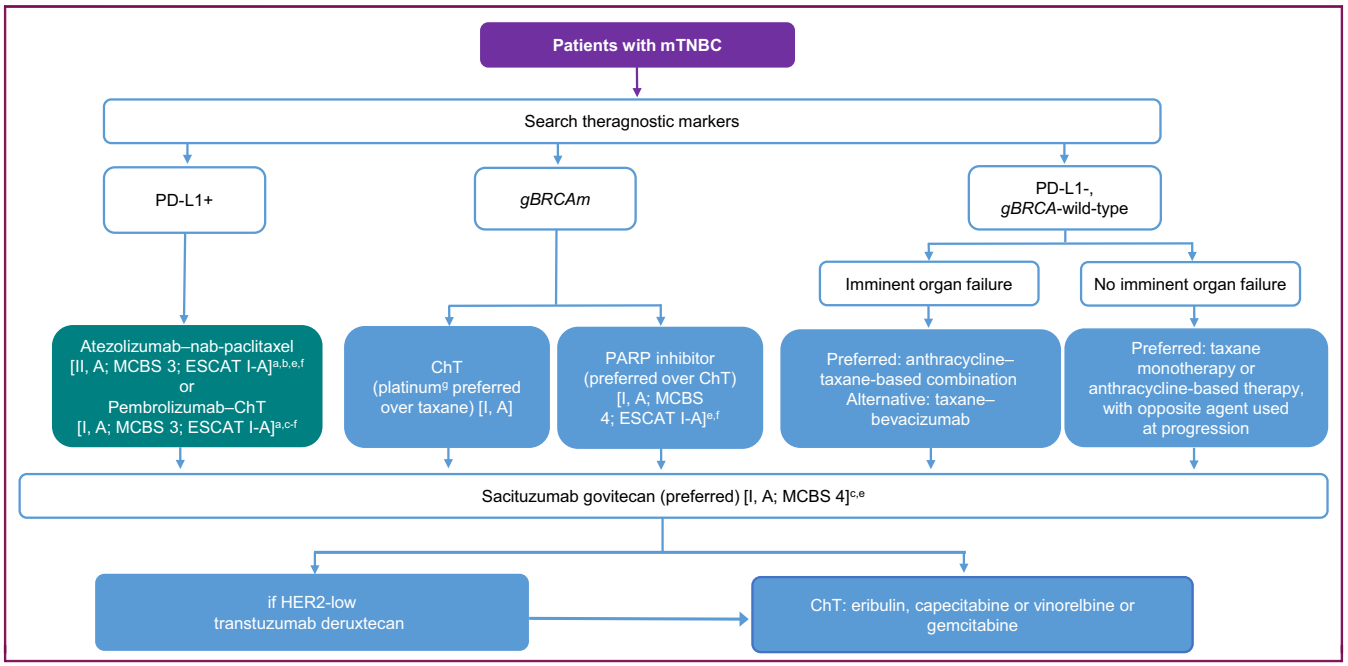

Figure 5. Treatment of mTNBC. Purple box: general categories or stratification; turquoise/green box: combination of treatments or other systemic treatments; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.
ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; gBRCAm, germline BRCA1/2 mutation; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1.
[a]May be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI.
[b]EMA approved, not FDA approved.
[c]FDA approved, not EMA approved.
[d]ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine/carboplatin.
[e]ESMO-MCBS v1.1[134] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[f]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[133]
[g]If not used previously.

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 5e and 5f' below, for the treatment of TNBC that has progressed on prior anthracycline and or taxane therapy.

5e. After progression, all chemotherapy recommendations for HER2-negative disease also apply for TNBC, e.g. eribulin, capecitabine and vinorelbine.[21]

5f. There are no data to support anti-androgen therapy, or inhibitors targeting PI3K, HER2 or AKT (protein kinase B) for advanced TNBC and therefore these cannot be recommended for routine use outside of a clinical trial setting.[21]

Trastuzumab deruxtecan can be considered second and third line in patients with HER2-low disease[23] (Figure 5). For emerging therapeutic strategies in patients with HER2-low MBC (IHC 1+ or IHC 2+/ISH−) according to ASCO/CAP 2018 guidelines,[24,25] see Section 6 below.

6. HER2-low MBC—recommendation 6a

Following encouraging efficacy data for trastuzumab deruxtecan from a phase I trial in HER2-low MBC,[113] the results from the pivotal phase III DESTINY-Breast04 trial in patients with confirmed HER2-low MBC randomised 2 : 1 to receive trastuzumab deruxtecan ($n = 373$ patients) versus physicians' choice treatment (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) ($n = 184$ patients), presented at the ASCO 2022 Annual meeting,[23] reported median PFSs of 9.9 (95% CI 9.0-11.3) months and 5.5 (95% CI 4.2-6.8) months for patients receiving trastuzumab deruxtecan and physicians' choice treatment, respectively ($P < 0.0001$) and corresponding median OSs of 23.4 (95% CI 2.0-24.8) months and 16.8 (95% CI 14.5-20.0) months ($P = 0.0010$). Median follow-up was 18.4 months and median treatment duration 8.2 months.

Importantly, these results show a statistically significant and clinically meaningful improvement in both PFS and OS in patients with HER2-low unresectable and/or metastatic breast cancer regardless of HR status.[23] This is important because ∼55% of patients classified as having HER2-negative MBC actually have tumours expressing low levels of HER2.

Thus, the Asian experts retrospectively approved, with **100% consensus**, the following new recommendation.

6a. **Trastuzumab deruxtecan, if available, should be considered for patients with HR-positive or HR-negative, HER2-low unresectable and/or metastatic**

Table 2. Summary of applicability (availability) of drugs, equipment and testing for metastatic breast cancer according to Asian country as of March 2023

Drugs/equipment	Availability										Comments (if 'N' please explain why)
	CSCO	ISHMO	ISMPO	JSMO	KSMO	MOS	PSMO	SSO	TOS	TSCO	
	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	
[^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)—CT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Palbociclib	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Abemaciclib	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Ribociclib	N	Y	Y	N	Y	Y	Y	Y	Y	Y	CSCO: not approved. JSMO: failed to establish the same recommended dose in Japanese patients.
Alpelisib	N	Y	Y	N	Y	Y	Y	Y	Y	Y	KSMO: approved, but not reimbursed. CSCO: not approved. JSMO: under investigation.
Everolimus	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Fulvestrant	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Trastuzumab	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Pertuzumab	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Trastuzumab deruxtecan	N	N	N	Y	Y	N	N	Y	Y	N	KSMO: approved, but not reimbursed. SSO: not routinely available; stocked in some hospital pharmacies. CSCO: not approved. ISHMO: registered, awaiting approval from Indonesian FDA ISMPO: not marketed, but individual patients can import. Cost constraints. PSMO may avail of company's early access programme.
Tucatinib	N	N	N	N	N	Y	N	Y	N	N	SSO: not stocked in hospital pharmacies, but available upon request. MOS: by special import permit. CSCO: not approved. ISHMO: registered, awaiting approval from Indonesian FDA. JSMO: under investigation. ISMPO: not marketed, but individual patients can import. Cost constraints.
Neratinib	Y	N	N	N	N	Y	Y	Y	Y	N	SSO: not stocked in hospital pharmacies, but available upon request. PSMO: neratinib approved and marketed by STA. KSMO: approved but not reimbursed in adjuvant setting, and not approved for MBC. ISHMO: registered, awaiting approval from Indonesian FDA. ISMPO: not marketed, but individual patients can import. Cost constraints. JSMO: no study in Japan.
Margetuximab	N	N	N	N	N	N	N	N	N	N	PSMO: no local presence of manufacturer. CSCO: not approved. ISHMO: registered, awaiting approval from Indonesian FDA JSMO: no study in Japan. ISMPO: not marketed, but individual patients can import; cost constraints.
TDM1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Atezolizumab	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	KSMO: approved, but not reimbursed.
Pembrolizumab	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	KSMO: approved, but not reimbursed.
Olaparib	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	KSMO: approved, but not reimbursed.
Talazoparib	N	N	N	N	Y	Y	N	Y	Y	N	PSMO: no local presence of manufacturer. KSMO: approved, but not reimbursed. MOS: patient access program. CSCO: not approved. ISMPO: not marketed, but individual patients can import; cost constraints. JSMO: under investigation. ISHMO: registered, awaiting approval from Indonesian FDA.
Sacituzumab govitecan	Y	N	N	N	N	Y	N	Y	N	N	SSO: not stocked in hospital pharmacies, but available upon request. PSMO: no local presence of manufacturer. MOS: special import permit from Singapore. CSCO: approved by NMPA 10 June 2022. ISMPO: not marketed, but individual patients can import; cost constraints. JSMO: under investigation. ISHMO: registered, awaiting approval from Indonesian FDA.
***BRCA* mutation assays**	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Zoledronate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Denosumab	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Lapatinib	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	

Continued

Table 2. Continued

Drugs/equipment	Availability										Comments (if 'N' please explain why)
	CSCO	ISHMO	ISMPO	JSMO	KSMO	MOS	PSMO	SSO	TOS	TSCO	
	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	Y/N?	
Drugs currently only approved in Asia											
Pyrotinib	Y[135-137]	N	N	N	N	N	N	N	N	N	Conditionally approved in 2018 and fully approved in July 2020.
Dalpiciclib	Y[131]	N	N	N	N	N	N	N	N	N	Approved by NMPA in combination with fulvestrant for relapsed or progressed HR+ HER2− breast cancer. Under investigation for 1st- (NCT03966898), ≥2nd-line (NCT03927456) and adjuvant treatment (NCT04842617) of HR+ HER2− breast cancer.
Trilaciclib under investigation	N	N	N	N	N	N	N	N	N	N	Under investigation only.

BC, breast cancer; CSCO, Chinese Society of Clinical Oncology; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HER2−, HER2 negative; HR+, hormone receptor positive; ISMPO, Indian Society of Medical and Paediatric Oncology; JSMO, Japanese Society of Medical Oncology; KSMO, Korean Society for Medical Oncology; MOS, Malaysian Oncological Society; N, no; NMPA, National Medicinal Products Administration; STA, Specialised Therapeutics Asia; SSO, Singapore Society of Oncology; TOS, Taiwan Oncology Society; Y, yes.

breast cancer previously treated with one or two prior lines of chemotherapy [I, A; consensus = 100%] (Table 1 and Figures 2 and 5).

Trastuzumab deruxtecan is already approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial,[114] and second line based on the results of the DESTINY03 trial.[85]

7. Hereditary breast cancer (gBRCAm)—recommendations 7a-d

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendation 7a' below for the treatment of patients with g*BRCA*m MBC.

7a. Patients with HER2-negative MBC and germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* should be offered treatment with a PARP inhibitor (olaparib or talazoparib), independent of HR status, as an alternative to chemotherapy[68,69] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].

However, the Asian experts did not agree with the original ESMO 'recommendation 7b' below, supported by a *post hoc* subset analysis of a randomised study which suggested that there was improved OS in patients receiving the PARP inhibitor olaparib, who had not received prior chemotherapy for metastatic disease.[115]

7b. Prior treatment with anthracyclines—taxanes should not be required before offering patients with MBC and a g*BRCA*m treatment with a PARP inhibitor; nor should HR-positive patients be required to demonstrate complete endocrine resistance [I, D].

In several Asian countries standard practice is for olaparib only to be offered after resistance to anthracyclines and taxanes, and in Japan olaparib is only approved for use after anthracycline—taxane therapy.

Thus, the wording and level and GoR for 'recommendation 7b' were revised as indicated by the bold text below:

7b. **A PARP inhibitor can be offered to patients with g*BRCA*m MBC irrespective of prior treatment with anthracyclines—taxanes; patients with HR-positive tumours should not be** required to demonstrate complete endocrine resistance [**II, B; consensus = 100%**].

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 7c and d' below for the treatment of patients with g*BRCA*m MBC.

7c. There is insufficient evidence to determine the optimal sequencing of PARP inhibitors with other active treatments such as chemotherapy—ICI combinations in mTNBC or ET and targeted therapy combinations in HR-positive disease [I, A].

7d. Patients who may be considered for treatment with a PARP inhibitor should be offered genetic testing for pathogenic variants in *BRCA1* and *BRCA2* regardless of age, family history or breast cancer subtype [I, A].

8. Site-specific management—recommendations 8a-u

Primary stage IV disease. The incidence of newly diagnosed breast cancer patients presenting with stage IV disease with an intact primary tumour can be high, up to 25% in some settings (typically in those regions where screening is not routinely available). The role of locoregional breast surgery in these patients is unclear,[116-118] and the role of systemic therapy is not optimal.[116,119]

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 8a-c' below for the treatment of patients with primary stage IV disease.

8a. For patients with newly diagnosed stage IV breast cancer and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context [II, B].

8b. Locoregional treatment of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is not routinely recommended [II, D].

8c. In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated [II, A].

However, there was considerable debate around the original ESMO 'recommendation 8d' below, which the Asian experts did not consider to be supported by the evidence from three trials, namely the Tata Memorial Cancer Center Trial, the phase III ABCSG-28 POSYTIVE trial and the phase III MF07-01 trial.[116-118] However, unplanned subgroup analyses at longer follow-up for the MF07-01 trial showed that the risk of death was statistically lower in patients receiving locoregional therapy followed by systemic therapy than in those receiving systemic therapy alone for those patients with ER/PgR-positive (hazard ratio 0.64, 95% CI 0.46-0.91; $P = 0.01$), HER2-negative (hazard ratio 0.64, 95% CI 0.45-0.91; $P = 0.01$) disease, those younger than 55 years (hazard ratio 0.57, 95% CI 0.38-0.86; $P = 0.007$) and patients with solitary bone-only metastases (hazard ratio 0.47, 95% CI 0.23-0.98; $P = 0.04$).[118]

8d. Surgery of the primary tumour may be considered for patients with bone-only metastasis, HR-positive tumours, HER2-negative tumours, patients aged <55 years, patients with oligometastatic disease (OMD) and those with a good response to initial systemic therapy.

'Recommendation 8d' was therefore revised with the addition of the bold text below:

8d. Surgery of the primary tumour may be considered for patients who may benefit from salvage surgery (e.g. those with bone-only metastases, a good response to initial systemic therapy, HR-positive tumours, HER2-negative tumours, age <55 years and those with OMD) [II, B]. **Surgery or radiotherapy (RT) of the primary tumour should be carefully considered for circumstances in which they provide added value for symptom palliation or prevention of complications [IV, C consensus = 100%].**

Oligometastatic disease. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 8e-h' below for the treatment of patients with OMD. A treatment algorithm for the management of patients with OMD is presented in Figure 6.

8e. A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].

8f. Patients with OMD should be discussed in a multidisciplinary context to individualise management [V, B].

8g. Multimodality treatment approaches involving locoregional therapy (e.g. high conformal RT, image-guided ablation, selective internal RT and/or surgery) combined with systemic treatments are recommended, tailored to the disease presentation in the individual patient [V, B].

8h. Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting [II, C]; it is unknown if this leads to improved OS.

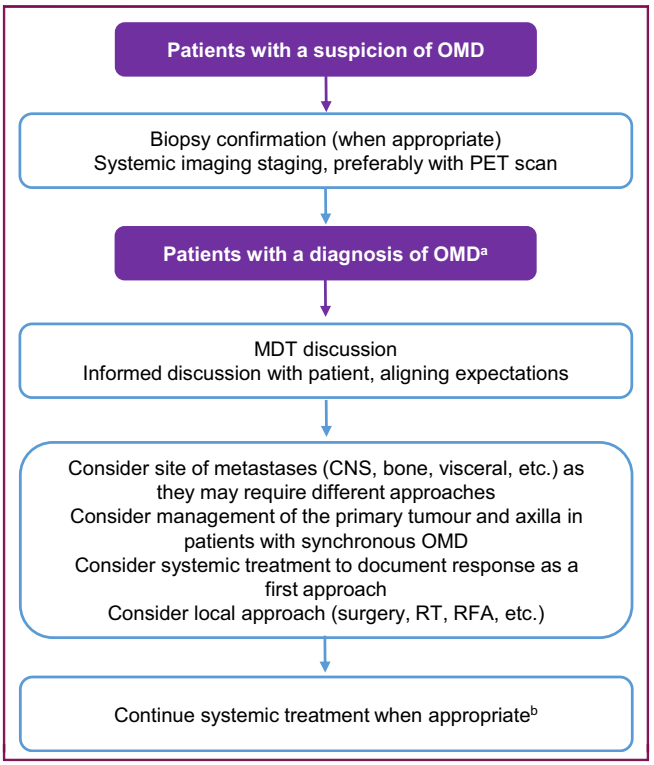

Figure 6. Treatment of OMD. Purple boxes: general categories or stratification; white boxes: other aspects of management.
CNS, central nervous system; MDT, multidisciplinary team; OMD, oligometastatic disease; PET, positron emission tomography; RFA, radiofrequency ablation; RT, radiotherapy.
[a]Consider elements in current definitions, i.e. limited or low-volume metastatic disease; up to five lesions in total, not necessarily in the same organ; all potentially amenable to receive local treatment.
[b]The duration of systemic treatment remains a topic of debate.

Bone metastases and bone-modifying agents. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 8i-s' below for the treatment of patients with bone metastases.

8i. A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].

8j. An orthopaedic evaluation is advised in the case of significant lesions in the long bones or vertebrae as well as in patients with metastatic spinal cord compression (MSCC) to discuss the possible role of surgery [IV, A].

8k. RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A].

8l. A single 8-Gy RT fraction is as effective as fractionated schemes in patients with uncomplicated bone metastases [I, A].

8m. RT should be delivered after surgery for stabilisation or separation surgery for MSCC [III, B].

8n. Bone-modifying agents (BMAs), e.g. bisphosphonates or denosumab, are recommended for patients with bone metastases, regardless of symptoms [I, A].

8o. Zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments [I, B].
8p. Denosumab should be administered every 4 weeks and is more effective than zoledronate in delaying first and subsequent SREs [I, B].
8q. Before the initiation of BMAs, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed [III, A].
8r. The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission [II, B].
8s. The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting locoregional therapy [V, C].

Brain metastases and leptomeningeal metastases. Again, the Pan-Asian panel of experts also agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 8t and u' below for the treatment of patients with brain and leptomeningeal metastases.

8t. Brain metastases should be managed according to the recommendations outlined in the European Association of Neuro-Oncology-ESMO (EANO-ESMO) Clinical Practice Guideline (CPG) for the management of patients with brain metastases from solid tumours.[120]
8u. Leptomeningeal metastases should be treated according to the recommendations outlined in the EANO-ESMO CPG for the management of patients with leptomeningeal metastases from solid tumours.

9. Long-term implications and survivorship—recommendations 9a-f

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendations 9a-f' below for the treatment of patients with MBC.

9a. An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.
9b. Patients should be informed about treatment choices and side-effect profiles of recommended systemic treatments.
9c. All treatment should include formal patient education regarding side-effect management [I, A].
9d. Careful assessment of side-effects should occur at each visit. Electronic patient reported outcomes may be useful in this context.
9e. QoL assessments should be incorporated into the evaluation of treatment efficacy.
9f. Dose reduction and delay are effective strategies to manage toxicity in advanced disease [I, A].

Availability of diagnostic tests, drugs and equipment

Following the hybrid virtual/face-to-face working meeting, hosted by KSMO, the Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the adapted ESMO guidelines listed in Table 1.

The drug and treatment availability for each of the 10 Asian countries is summarised in Table 2, and the ESMO-MCBSs for the different systemic therapy options and new therapy combinations for the treatment of MBC are presented in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101541, and https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=&mcbs_score_cards_form%5Btumour-type%5D=Breast+Cancer. Resource limitations are the most important barrier to offering optimal diagnosis and treatment to patients with MBC across the different Asian countries. Eight significant discrepancies in the availability of systemic therapies involving more than one country were identified in Table 2.

The first of these discrepancies is seen for the CDK4/6 inhibitor ribociclib (Table 2) for China and Japan and impacts on the ability of the physicians in these two countries to implement 'recommendation 3a' (Table 1). Ribociclib is the only CDK4/6 inhibitor tested as first-line treatment for premenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with a gonadotropin-releasing hormone (GnRH) analogue plus an AI[40,42,121] and the results from the pivotal MONALEESA-7 trial of first-line therapy with ribociclib plus letrozole with a GnRH analogue in premenopausal patients showed a significant OS benefit compared with placebo plus letrozole with a GnRH analogue. Ribociclib has also been evaluated plus ET for postmenopausal patients,[38,39,54,55] with HR-positive, HER2-negative advanced or metastatic breast cancer. Recent results from the pivotal MONALEESA-2 trial of first-line therapy with ribociclib plus letrozole in postmenopausal patients showed a significant OS benefit compared with placebo plus letrozole.[55] Median OS was >12 months longer in patients receiving ribociclib than in those receiving placebo.[55] The second discrepancy is for the PIK3CA inhibitor alpelisib (Table 2). Alpelisib, when given in combination with fulvestrant, has been shown to provide PFS and OS benefits in patients with postmenopausal *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced breast cancer or MBC previously treated with ET.[61-63,122] Again the lack of approvals and lack of reimbursement in the cited countries impact on the implementation of 'recommendation 3e' (Table 1) in these countries.

The next four discrepancies are related to the lack of availability of trastuzumab deruxtecan, tucatinib, neratinib and margetuximab in the majority of the 10 countries (Table 2) and impact on the available treatment choices in the second- and subsequent-line settings for patients with HER2-positive breast cancer as detailed in 'recommendations 4j, k, l and n' (Table 1). Trastuzumab deruxtecan, in particular, is emerging as the preferred therapy in this setting,[85] and for patients with HER2-low disease.[23] Tucatinib is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for the treatment of patients with advanced unresectable or metastatic HER2-positive

breast cancer, including those with brain metastases, who have received prior anti-HER2-based regimens in the metastatic setting.[87,123] The kinase inhibitor neratinib in combination with capecitabine has shown modest PFS and OS gains over lapatinib—capecitabine but significantly improved PFS and time to intervention for CNS disease compared with lapatinib—capecitabine.[95] In a phase III trial, the HER2 antibody margetuximab plus chemotherapy showed acceptable safety and a statistically significant improvement in PFS compared with trastuzumab plus chemotherapy in patients with HER2-positive advanced breast cancer after progression on two or more prior anti-HER2 therapies.[96] However, neratinib and margetuximab ('recommendation 4n' above) are currently only approved by the FDA for the treatment of MBC. Again, the lack of availability of any of these drugs in certain Asian countries (Table 2) restricts the treatment options available and is at odds with the recommendations agreed by the Asian experts in Table 1.

The PARP inhibitor talazoparib used for the treatment of patients with advanced breast cancer and germline *BRCA* mutations[68,124] ('recommendations 3g, 5b and 6a' in Table 1) is currently only available in 4 out of the 10 Asian countries and is not reimbursed in 1 of the 4 countries (Table 2). Finally, the anti-trophoblast cell-surface antigen 2 (Trop-2) antibody—drug conjugate sacituzumab govitecan, recommended for the treatment of TNBC following progression after anthracycline and taxane therapy ('recommendation 5d' in Table 1), is currently only available in 3 of the 10 Asian countries (Table 2).[111,112,125] Sacituzumab govitecan benefits patients with previously treated mTNBC compared with standard-of-care chemotherapy, regardless of germline *BRCA1/2* mutation status,[125] and has recently become available in China. However, there are drugs that are only approved for use in Asia and more specifically China. These include the pan-HER2 inhibitor pyrotinib which has been approved in China in combination with capecitabine for HER2-positive MBC patients previously treated with anthracycline or taxane therapy as second-line standard-of-care treatment,[126-129] and has recently been shown in combination with trastuzumab and docetaxel to prolong PFS in patients with HER2-postive MBC compared with placebo.[130] The CDK4/6 kinase dalpiciclib[131,132] has been approved in China for advanced HR-positive, HER2-negative breast cancer, and trilaciclib is under investigation.

Also, there are tumour-agnostic drug approvals. For example, the drugs larotrectinib and entrectinib are approved for patients with solid tumours expressing a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101541) and provide a treatment option for patients who have exhausted all other therapy options.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the hybrid virtual/face-to-face working meeting showed >80% concordance (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101541) with the ESMO recommendations for the treatment of patients with MBC. Following the virtual 'face-to-face' discussions, revisions were made to the wording of 'recommendations 3c, 3h, 3o, 3p, 5b, 5d, 7b and 8d' and the addition of a new recommendation 'recommendation 6a' (Table 1) and resulted in a **100% consensus** being achieved in terms of 'acceptability' for all the recommendations listed in Table 1.

Thus, the recommendations listed in Table 1 can be considered to constitute the consensus clinical practice guidelines for the treatment of patients with MBC in Asia. As mentioned previously, the acceptance of each recommendation by each of the Asian experts was based on the available scientific evidence and was independent of the approval and reimbursement status of certain procedures and drugs in their individual countries. A summary of the availability of the recommended treatment modalities and recommended drugs, as of March 2023, is presented for each participating Asian country in Table 2 and will obviously impact on some of the disease and patient management strategies that can be adopted by certain Asian countries.

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