ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer

K. H. Park[1]*, S. Loibl[2], J. Sohn[3], Y. H. Park[4], Z. Jiang[5], H. Tadjoedin[6], S. Nag[7], S. Saji[8], M. Md. Yusof[9], E. M. B. Villegas[10], E. H. Lim[11], Y.-S. Lu[12], S. Ithimakin[13], L.-M. Tseng[14], T. Dejthevaporn[15], T. W.-W. Chen[16], S. C. Lee[17], C. Galvez[18], S. Malwinder[9], T. Kogawa[19], J. Bajpai[20], B. Brahma[21], S. Wang[22], G. Curigliano[23,24], T. Yoshino[25], S.-B. Kim[26], G. Pentheroudakis[27], S.-A. Im[28], F. Andre[29], J. B. Ahn[3] & N. Harbeck[30]

[1]Division of Medical Oncology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea; [2]German Breast Group, Neu-Isenburg, Goethe University Centre for Haematology and Oncology, Bethanien, Frankfurt, Germany; [3]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul; [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [5]Department of Oncology, The Fifth Medical Center of PLA General Hospital, Bejing, China; [6]Department of Internal Medicine, Division of Hematology-Medical Oncology, Dharmais Hospital, National Cancer Center, Jakarta, Indonesia; [7]Department of Medical Oncology, Sahyadri Speciality Hospitals, Pune, Maharashtra, India; [8]Department of Medical Oncology, Fukushima Medical University, Fukushima, Japan; [9]Cancer Centre at PHKL, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [10]Cebu Cancer Institute, Perpertual Succour Hospital; Cebu Doctors' University Hospital, Cho-ing Hua Hospital, Cebu City, Philippines; [11]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [12]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [13]Division of Medical Oncology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [14]Department of Surgery, Taipei-Veterans General Hospital, and School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [15]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [16]Department of Oncology, National Taiwan University Hospital and Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan; [17]Department of Haematology-Oncology, National University Cancer Institute, Singapore (NCIS), Singapore, Singapore; [18]St. Luke's Medical Center Global City, Taguig City, Philippines; [19]Advanced Medical Development, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [20]Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India; [21]Department of Surgical Oncology, Dharmais Hospital, National Cancer Center, Jakarta, Indonesia; [22]Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China; [23]Istituto Europeo di Oncologia, IRCCS, Milan, Italy; [24]Department of Oncology and Haematology, University of Milano, Milan, Italy; [25]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [26]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [27]ESMO, Lugano, Switzerland; [28]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [29]Breast Cancer Unit, Department of Medical Oncology, Gustave Roussy, Villejuif, France; [30]Breast Center, Department of Obstetrics and Gynaecology and Comprehensive Cancer Center Munich, LMU University Hospital, Munich, Germany

Available online 12 April 2024

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer were updated and published online in 2023, and adapted, according to previously established standard methodology, to produce the Pan-Asian adapted (PAGA) ESMO consensus guidelines for the management of Asian patients with early breast cancer. The adapted guidelines presented in this manuscript represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with breast cancer representing the oncological societies of China (CSCO), Indonesia (ISHMO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO), co-ordinated by ESMO and KSMO. The voting was based on scientific evidence and was independent of the current treatment practices, drug access restrictions and reimbursement decisions in the different Asian regions represented by the 10 oncological societies. The latter are discussed separately in the manuscript. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with early breast cancer across the different regions of Asia, drawing on the evidence provided by both Western and Asian trials, whilst respecting the differences in screening practices, molecular profiling, as well as the age and stage at presentation. Attention is drawn to the disparity in the drug approvals and reimbursement strategies, between the different regions of Asia.

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

*Correspondence to: Prof. Kyong Hwa Park, Division of Medical Oncology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea. Tel: +82-2-920-6841; Fax: +82-2-2199-3918

E-mail: khpark@korea.ac.kr (K. H. Park).

INTRODUCTION

In 2020, there were an estimated 2.3 million new cases of female breast cancer worldwide,[1,2] accounting for 11.7% of all new cancer cases. Among women worldwide it accounted for 24.5% of cancer diagnoses, and, with nearly 700 000 deaths (15.5% among women and 6.9% of all cancer

deaths), was the single biggest cause of cancer death.[1,2] Male breast cancer is very rare, accounting for <1% of all cases of malignancies in men and <1% of all breast cancers worldwide.[3]

The incidence of breast cancer was lowest for the continent of Asia,[1,2] but with over a million new cases in 2020, it remained the most common cancer amongst Asian women, and accounted for 45.3% of all breast cancer cases worldwide.[4] In 2020, breast cancer was the second largest cause of cancer death behind lung cancer in Asian women and accounted for over half of all breast cancer-related deaths worldwide.[1,4,5] However, significant regional differences were observed with mainland China having the highest number of cases of breast cancer (416 371 cases and 117 174 deaths), accounting for 18.4% of global breast cancer cases in 2020 based on data from the GLOBOCAN cancer today database 2020, followed by Japan (92 024 cases and 17 081 deaths), South Korea (25 814 cases and 3009 deaths) and Singapore (3662 cases and 921 deaths),[4] with additional registry data available for Japan and Singapore.[6,7] The corresponding age-standardised incidence rates (ASIRs) per 100 000 of the population were 39.1, 76.3, 64.2 and 77.9 for mainland China, Japan, South Korea and Singapore, respectively, with the highest ASIRs corresponding to those regions with the highest human development indices in terms of life expectancy, education and national income.[4]

The mortality-to-incidence (M/I) ratio, defined as the number of deaths that occur compared to the number of breast cancers diagnosed each year, across Asia was 0.32, the second highest behind Africa, and higher than the world's average of 0.28.[8] Again, there were large regional variations in the M/I ratios between the different regions of Asia, with high-income countries such as Singapore, Japan and South Korea generally having higher incidences of breast cancer due to rapid westernisation in terms of nutritional and lifestyle changes and lower mortality rates due to access to improved treatment and screening programmes.[8-12] An important factor affecting mortality from breast cancer is stage at presentation,[13] which tends to be lower in women from high-income countries or regions and higher in women from low- and low-to-middle-income countries (LMIC) or regions.[8,14] For example, 63.4% of breast cancer diagnoses in the high-income regions of Asia were stage I and II compared with 33.6% and 43% in low- and LMICs, respectively.[8] Notably, the age of presentation for women with breast cancer in Asia peaks ∼10 years earlier than for women from western countries.[15-18] Also, estrogen receptor-positive (ER+) breast cancer is the most common subtype across Asia, ranging from 76% of breast cancer cases in Japan to 53% for women of Malay and Indian origin in Malaysia and Singapore.[14] The human epidermal growth factor receptor 2 (HER2)-positive status across Asia is more variable,[14,19] and is lowest in Japanese (15%) and Indian (17%) women, and highest in Hong Kong Chinese (43%) and Indonesian (45%) women.[14]

The most recent European Society for Medical Oncology Clinical Practice guidelines (ESMO) for the diagnosis, treatment and follow-up of patients with early breast cancer[20] were submitted for publication in 2023 and a decision was taken by ESMO and the Korean Society of Medical Oncology (KSMO) that these latest ESMO guidelines should be adapted for the management and treatment of patients of Asian ethnicity. This manuscript summarises the Pan-Asian adapted guidelines developed and agreed at a hybrid virtual/face-to-face working meeting that took place in Seoul on 23 September 2023 hosted by KSMO. Each recommendation is accompanied by the level of evidence (LoE), grade of recommendation (GoR) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.102974) and the percentage consensus reached.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines[20] was prepared in accordance with the principles of ESMO standard operating procedures (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a KSMO—ESMO initiative endorsed by the Chinese Society of Clinical Oncology (CSCO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), 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 Thai Society of Clinical Oncology (TSCO). An international panel of experts was selected from the KSMO ($n = 5$), the ESMO ($n = 3$) and two experts from each of the nine other oncological societies. Only two of the five expert members from the KSMO (JS and Y-HP) were allowed to vote on the recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). All 20 Asian experts provided comments on the pre-meeting survey and one consensus response per society (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974). Only one voting member per Asian society was present at the hybrid/face-to-face meeting. None of the additional members of KSMO and none of the ESMO experts or additional representatives of ESMO were allowed to vote and were present in an advisory role only (see Supplementary Material: Methodology, available at https://doi.org/10.1016/j.esmoop.2024.102974). All the Asian experts ($n = 20$) approved the revised recommendations.

RESULTS

A. Scientific adaptations of the ESMO recommendations

In the initial pre-meeting survey, the 20 voting Asian experts reported on the 'acceptability' of the 97 recommendations for the diagnosis, treatment and follow-up of patients with early breast cancer from the most recent ESMO Clinical Practice Guidelines[20] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974), in the eight categories outlined in the text below and in Table 1. A lack of agreement in the pre-meeting survey was established for 22 recommendations, 18 of which were discussed at the hybrid virtual/face-to-face working meeting in Seoul to adapt

the recently published ESMO Clinical Practice Guidelines. 'Recommendation 4h' was also discussed because several of the Asian experts left comments in their responses to the survey. For each of 'recommendations 1f, 4b, 4d and 5i' there were discrepancies relating to their applicability in certain regions of Asia and not their 'scientific applicability'. As a result, these were not discussed at the hybrid virtual/face-to-face meeting. No new recommendations were added, but the original ESMO recommendation 6d' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) was relocated to become 'recommendation 3v' in Table 1.

The guideline recommendations outlined in the text below and in Table 1 for the diagnosis, treatment and follow-up for Asian patients with early breast cancer have been agreed by the Pan-Asian panel of experts based exclusively on the available scientific evidence and their professional opinions. It is acknowledged that regional differences in availability of drugs, equipment and testing facilities, as well as reimbursement and access to treatment may affect the implementation of certain of these recommendations. Where possible, the recommendations have been amended to take into account these regional differences.

1. Screening, diagnosis, pathology and molecular biology—recommendations 1a-m

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 1b-f, 1g-k and m' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) without change (Table 1).[20]

In relation to 'recommendation 1a', based on data from the Korean Breast Cancer Society and the Korean Central Cancer Registry, the highest frequency of breast cancer in 2017 was observed in women 40-49 years of age, accounting for a third of all new cases.[21] As mentioned previously in the 'Introduction', this is nearly 10 years earlier than that observed in Europe and America,[17,18] suggesting that the ESMO recommended age for mammography screening of 50-69 years of age is too late for Asian populations. This is supported by the breast screening guidelines for several regions of Asia including Japan and Korea which recommend breast cancer screening for women over the age of 40 while Taiwan and mainland China recommend breast cancer screening for all women with an average risk of breast cancer aged 45-69.[22-25] Furthermore, a Korean population-based study reported a 31.98% net benefit in terms of breast cancer mortality reduction, from breast screening, in women aged 45-49 years.[26] Also, a net benefit of 22.42% was observed in women in the youngest, 40-44 years, age bracket.[26]

Taking into account the differences in the epidemiology of breast cancer observed across Asia and the benefit of breast cancer screening reported in the Korean study, the original ESMO 'recommendation 1a' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) was modified as per the bold text below and in Table 1 (**100% consensus**), to read as follows:

1a. Regular (every 2 years) mammography screening is recommended in women aged **45**-69 years [I, A]. Regular mammography may also be carried out in women aged 40-**44** and 70-74 years, **where there is emerging evidence of benefit** [I, B; **consensus = 100%**].

For 'recommendation 1l', there was a great deal of discussion around the benefit of screening for programmed death-ligand 1 (PD-L1). This was particularly the case for therapeutic regimens that included immune checkpoint inhibitors (ICIs) in patients with early-stage triple-negative breast cancer (TNBC). However, the results of the phase III KEYNOTE-522 study in treatment-naïve patients with stage II/III TNBC found that the addition of pembrolizumab to a neoadjuvant chemotherapy (ChT) regimen improved pathological complete responses (pCR) and event-free survival (EFS) rates (hazard ratio [HR] = 0.63; 95% confidence interval [CI] = 0.48-0.829), independent of PD-L1 status.[27] Furthermore, the phase III IMpassion031 study found the addition of atezolizumab to a neoadjuvant ChT regimen of nab-paclitaxel, doxorubicin and cyclophosphamide to improve pCR compared with ChT plus placebo, independent of PD-L1 status.[28]

Consequently, it was agreed that decisions regarding the inclusion of ICIs in treatment regimens were not likely to be affected by PD-L1 expression and as a result, the wording for 'recommendation 1l' remained unchanged with 100% consensus (Table 1).

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

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 2b-d' without change (Table 1).

For ESMO 'recommendation 2a' the reference text to be used for staging was discussed because in Korea the seventh, and not the eighth, edition of the TNM Classification of Malignant Tumours is the preferred edition.[29,30] There was also some discussion regarding how practical the whole staging paradigm of the eighth edition was to clinical practice. However, in the guidelines of the College of American Pathologists, TNM is a part of staging.[31] It was thus decided to leave the eighth edition in the recommendation but to shorten the recommendation, removing 'Union for International Cancer Control tumour—node—metastasis' from the original ESMO 'recommendation 2a' to read as the text below and in Table 1.

2a. Disease stage and final pathological assessment of surgical specimens should be made according to the World Health Organization classification of tumours and the eighth edition of the TNM staging system [V, A; **consensus = 100%**].

For ESMO 'recommendation 2e', several of the Pan-Asian panel of experts pointed out that, if available, positron emission tomography (PET)—computed tomography (CT) scanning is only used if conventional methods, such as CT or

Table 1. Summary of Asian consensus recommendations for the treatment of patients with early breast cancer

Recommendations	Acceptability consensus
1. Screening, diagnosis, pathology and molecular biology	
1a. Regular (every 2 years) mammography is recommended in women aged **45**-69 years [I, A]. Regular mammography may also be carried out in women aged 40-**44** and 70-74 years, **where there is emerging evidence of benefit** [I, B]	100%
1b. Screening in women with a strong family history or known germline BRCA1/2 mutations (gBRCA1/2m) and other high-risk pathogenic variants (PVs) should follow the ESMO CPG for risk reduction and screening of cancer in hereditary breast—ovarian cancer syndromes [III, A]	100%
1c. Diagnosis is based on clinical examination and imaging including bilateral mammography and ultrasound (US) of both breasts and regional lymph nodes (LNs) or two-dimensional digital mammography in the symptomatic setting [I, A]	100%
1d. Digital breast tomosynthesis (with or without synthetic mammography) and contrast-enhanced mammography can be considered as alternatives, where available and appropriate [II, B]	100%
1e. Magnetic resonance imaging (MRI) of the breasts is recommended in case of uncertainties following standard imaging and in special clinical situations (e.g. familial breast cancer associated with gBRCA1/2m and other high-risk PVs, lobular cancers, suspicion of multifocality and/or multicentricity, presence of breast implants) [I, A]	100%
1f. Assessment of distant metastases (bone, liver and lung) is recommended only in patients with stage IIb and higher disease (especially with extended LN involvement), patients with a high risk of recurrence and/or in symptomatic patients [III, A]	100%
1g. Pretreatment pathological assessment including a complete histomorphological, immunohistochemical and molecular assessment, if applicable, is recommended at the time of diagnosis, and should include primary tumour histology and axillary node histology/cytology (if node involvement is suspected clinically) [I, A]	100%
1h. Assessment should include histological type, grade and immunohistochemistry (IHC) evaluation of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) biomarkers and a proliferation marker such as Ki-67. FISH testing should be carried out in cases of an equivocal HER2 IHC score (HER 2+) [I, A; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score for HER2 FISH: I-A]	100%
1i. Tumours should be grouped into biological subtypes, defined by routine histology and IHC results as luminal A-like, luminal B-like, HER2-positive and triple-negative [I, A]	100%
1j. In cases of hormone receptor (HR)-positive/HER2-negative EBC with uncertainty about indications for adjuvant chemotherapy (ChT) (after consideration of all clinical and pathological factors), gene expression assays and endocrine response assessment in the preoperative setting can be used [II, B]	100%
1k. Tumour-infiltrating lymphocytes (TILs) may add prognostic and predictive information, particularly in triple-negative breast cancer (TNBC), but there are no distinct TIL thresholds for treatment decisions [I, B]	100%
1l. Programmed death-ligand 1 (PD-L1) expression levels should not be used to guide treatment decisions in EBC [I, E]	100%
1m. Germline testing and genetic counselling for PVs in BRCA1/2 should be offered to patients who met the respective national criteria and to those who are candidates for adjuvant olaparib therapy according to the OlympiA trial [I, A; ESCAT score: I-A]	100%
2. Staging and risk assessment	
2a. Disease stage and final pathological assessment of surgical specimens should be made according to the World Health Organization classification of tumours and the eighth edition of the TNM staging system [V, A]	100%
2b. Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, A]	100%
2c. A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with: - clinically positive axillary nodes; - large tumours (e.g. 5 cm); - aggressive biology; and - clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, A]	100%
2d. The complete medical and family history must be evaluated, including menopausal status (if in doubt, serum estradiol and follicle-stimulating hormone levels should be measured) [V, A]	100%
2e. [18F]2-fluoro-2-deoxy-D-glucose (FDG)—positron emission tomography (PET)—CT scanning may be **an option for** high-risk patients and when conventional **CT/bone scan** methods are inconclusive [II, B]	100%
3. General management principles	
3a. Where available, treatment should be carried out in specialised breast units/centres by a specialised MDT that can refer patients to other specialties [III, A]	100%
3b. Participation in clinical trials is recommended [V, A]	100%
3c. Treatment strategy should be based on the tumour burden (size and location of the primary tumour, number of lesions and extent of LN involvement) and biology (pathology, including biomarkers and gene expression), as well as the age, menopausal status, general health status and patient preferences [I, A]	100%
3d. Age should be considered in relation to other factors and should not be the primary determinant for treatment decisions [IV, A]	100%
3e. Fertility and fertility preservation should be discussed with younger premenopausal patients (irrespective of stage of disease) before the initiation of any systemic treatment [V, A]	100%
Patient communication and shared decision making	
3f. Information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable manner [V, A]	100%
3g. The use of reliable, patient-centred websites or similar sources of information is recommended [V, A]	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
3h. Patients should be actively involved in all management decisions and should have equitable access to the full range of reproductive care options including pregnancy counselling, contraception and fertility preservation [V, A]	100%
Locoregional treatment	
3i. BCS with post-operative RT is the **recommended** local treatment option for the majority of patients with EBC **(when compatible with patient preference and available resources)** [I, A]	100%
3j. If mastectomy is indicated/preferred, breast reconstruction should be offered, except for primary inflammatory and other high-risk disease where delays in systemic/radiation treatment would compromise care [V, A]	100%
3k. SLNB is the standard axillary surgery in all cN0 patients [I, A]	100%
3l. In the absence of prior PST patients with micrometastatic spread and those with limited SLN involvement (1-2 affected SLNs) in cN0, following BCS with subsequent WBRT, including the lower part of the axilla and adjuvant systemic treatment, do not need further axillary surgery [II, A]	100%
3m. ALND following positive SLNB with <3 involved SLNs is generally recommended only in case of **suspected** high axillary disease burden, or with impact on further adjuvant systemic treatment decisions [II, A]	100%
3n. Surgical planning following PST should consider the post-PST situation [II, A]	
3o. WBRT is recommended after BCS [I, A]	100%
3p. APBI is an alternative treatment to WBRT in patients with invasive and *in situ* breast cancer at low-risk of local recurrence[82-84] [I, A]	100%
3q. PMRT is recommended for high-risk EBC, including involved resection margins, ≥ 4 involved ALNs, T3-T4 tumours and in the presence of combinations of other risk factors [I, A]	100%
3r. PMRT should be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs [I, A]	100%
3s. Nodal RT is recommended for patients with involved LNs (the extent of nodal volumes depends on risk factors including the number of involved LNs, N-stage and response to PST) [I, B]	100%
3t. If indicated, PMRT can be administered after immediate breast reconstruction [III, A]	100%
3u. Hypofractionated schedules are recommended: moderate (i.e. 15-16 fractions of ≤ 3 Gy per fraction daily for all indications of post-operative RT) and ultra-hypofractionated [i.e. 26 Gy in five daily fractions for whole-breast or chest wall (without reconstruction) irradiation] [I, A]	100%
3v[a]. The use of dose-dense schedules of ChT, with granulocyte colony-stimulating factor (G-CSF) support, should be considered given their documented benefit over non-dose-dense schedules [I, **B**]	100%
4. Management of ER-positive/HER2-negative EBC	
4a. All luminal-like cancers should be treated with ET [I, A]	100%
4b. Most luminal A-like tumours do not require ChT, except those with high disease burden [I, A]	100%
4c. In cases of uncertainty about indications for adjuvant ChT (after consideration of all clinical and pathological factors), gene expression assays and**/or** endocrine response assessments **may** be used to guide decisions on adjuvant ChT [I, **B**]	100%
4d. Luminal B-like HR-positive, HER2-negative tumours should be treated with ChT followed by ET. Consider ChT in high clinical risk (e.g. multinode-positive, premenopausal node-positive, locally advanced) and 0-3 involved LNs with high-risk features (e.g. high-risk gene expression assay result) [I, A]	100%
4e. Premenopausal patients should receive either tamoxifen alone (luminal A-like, stage I) [I, A], or in case of a high risk of recurrence, ovarian suppression with either OFS—tamoxifen [I, A] or OFS—AI [I, A]	100%
4f.Postmenopausal patients should receive an AI or tamoxifen followed by AIs [I, A]	100%
4f.1. Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A]	100%
4g. Bisphosphonates are recommended in women without ovarian function (postmenopausal or undergoing OFS), especially if at high risk of relapse [I, B] or treatment-related bone loss [I, A]	100%
4h. Abemaciclib for 2 years in addition to ET after completion of locoregional therapy should be considered in patients with stage III or high-risk stage II EBC [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A]	100%
4i. Extended ET beyond 5 years should be considered in high-risk EBC [I, A]; 7-8 years' treatment duration seems sufficient for most patients at high risk [I, A]	100%
4j. Following completion of (neo)adjuvant and locoregional therapy, 1 year of adjuvant olaparib is recommended for patients with *gBRCA1/2m* and HER2-negative, HR-positive EBC with multiple positive LNs after primary surgery or residual high-risk EBC after neoadjuvant ChT [I, A; ESMO-MCBS v1.1 score: A; ESCAT score: I-A]	100%
4k. ET should be given concomitantly with adjuvant olaparib in *gBRCA1/2m* carriers [I, A; ESMO-MCBS v1.1 score: A; ESCAT score I-A]	100%
4l. Olaparib and abemaciclib should not be combined due to overlapping toxicities but may be considered sequentially with olaparib first [V, A]	100%
5. *Management of HER2-positive EBC*	
5a. HER2-directed therapy (with initial concurrent ChT) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment [I, A]. Administration can be combined—if indicated—with RT and ET [I, A]. In selected low-risk situations, 6 months of anti-HER2 therapy may be non-inferior. Regular cardiac assessments are recommended (before, during and following therapy) with the option of additional assessments before the start of any ChT treatment [II, B]	100%
5b. For patients with clinical stage II-III HER2-positive breast cancer (e.g. T >2 cm or node-positive), neoadjuvant systemic ChT with anti-HER2 therapy comprising trastuzumab—pertuzumab is the preferred option [I, A]	100%
5c. For the ChT backbone, anthracycline—taxane or taxane—carboplatin regimens are evidence-based independent of neoadjuvant or adjuvant use [I, A]	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
5d. Dual blockade with HP (versus trastuzumab alone) combined with ChT achieves higher pCR rates and is recommended for neoadjuvant therapy [I, A; ESMO-MCBS v1.1 score: C]	100%
5e. Patients with residual invasive disease (non-pCR after neoadjuvant ChT and anti-HER2 therapy) should receive adjuvant treatment with T-DM1 for up to 14 cycles [I, A; ESMO-MCBS v1.1 score: A]	100%
5f. For patients with stage I (T1a-b N0) HER2-positive EBC, primary surgery may be carried out [III, B], followed by adjuvant administration of 12 weeks of paclitaxel plus 1 year of trastuzumab if clinical stage is confirmed by pathology [III, B; ESMO-MCBS v1.1 score: A]	100%
5g. For patients with pathological stage II or III cancer treated with initial surgery, adjuvant ChT combined with 12 months of anti-HER2 therapy should be given [I, A; trastuzumab ESMO-MCBS v1.1 score: A; HP ESMO-MCBS v1.1 score: A]	100%
5h. In patients with node-positive disease, the addition of pertuzumab to trastuzumab should be strongly considered in the adjuvant setting irrespective of HR status [I, A; ESMO-MCBS v1.1 score: A; ESCAT score: 1A]	100%
5i. Patients with high-risk HR-positive tumours may be considered for extended treatment with neratinib (concurrent with ET) for 1 year after completion of 1 year of trastuzumab or trastuzumab-based therapy [I, B; ESMO-MCBS v1.1 score: no evaluable benefit]	100%
6. *Management of TNBC*	
6a. HER2-negative tumours with 1%-9% ER and/or PgR expression (ER-/PgR-low) are a heterogeneous group, some of which behave biologically similarly to TNBCs; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR-positive breast cancer [II, B]	100%
6b. TNBC tumours should be treated with ChT with or without an ICI (pembrolizumab) [I, A; ESMO-MCBS v1.1 score for pembrolizumab: A], except for some node-negative special histological subtypes such as secretory or adenoid cystic carcinomas or very low clinical risk (pT1a pN0) tumours [II, B]	100%
6c. ChT should be administered for 12-24 weeks (4-8 cycles) regardless of whether an ICI is added [I, A]	100%
6d. For cT1c-4 N0, or any N-positive TNBC, neoadjuvant treatment is preferred [I, A]	100%
6e. cT2-4 N0 or any N-positive (stage II-III) TNBC should be treated with neoadjuvant ChT plus pembrolizumab unless there are risk factors for excessive ICI-associated immune toxicity [I, A; ESMO-MCBS v1.1 score: A]	100%
6f. Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase [I, A] and for nine 3-week cycles during the adjuvant phase, regardless of pCR status [I, A; ESMO-MCBS v1.1 score: A]	100%
6g. Patients receiving pembrolizumab should be monitored very closely for the risk of immune-related adverse events throughout treatment and following the ESMO CPG for the management of toxicities from immunotherapy [V, A]	100%
6h. An ICI should not be given solely as adjuvant therapy without prior neoadjuvant ICI treatment [V, D]	100%
6i. In patients with gBRCA1/2m and high-risk TNBC (non-pCR or pathological stage II-III), 1 year of adjuvant olaparib is recommended [I, A; ESMO-MCBS v1.1 score: A; ESCAT: I-A]	100%
6i.1. **In patients with germline BRCA mutations with residual disease after ICI-containing neoadjuvant therapy, the concurrent adjuvant use** of ICIs and olaparib can be considered on an individual basis [V, C]	100%
6j. Patients with residual disease who did not receive ICIs should be offered adjuvant capecitabine for 6-8 cycles [I, A]	100%
6j.1. The combination of olaparib and capecitabine should not be used in patients with *gBRCA1/2m* [I, E]	100%
6j.2. **In patients with residual disease after ICI-containing neoadjuvant therapy, the concurrent adjuvant use** of ICI and capecitabine can be considered on an individual basis [V, C]	100%
7. *Management of special situations*	
7a. Treatment of elderly patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used [II, B]	100%
7b. A geriatric assessment should be carried out before making treatment decisions [II, A]	100%
7c. Tamoxifen is the standard adjuvant ET for male patients with breast cancer [IV, A]	100%
7d. As with premenopausal women with breast cancer, a gonadotropin-releasing hormone agonist (GnRHa) may be added in higher-risk male patients with breast cancer, and a combination of an AI and GnRHa should be considered in cases where tamoxifen is contraindicated [IV, B]	100%
7e. An AI must be administered with a gonadotropin-releasing hormone agonist when used as adjuvant ET in male patients with breast cancer [IV, A]	100%
7f. In male patients with breast cancer, ChT, ET, anti-HER2, ICI, CDK4/6 inhibitor and PARP inhibitor therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients [IV, A]	100%
7g. DCIS should be preferentially treated with BCS and WBRT or, in cases of extensive or multicentric DCIS, mastectomy [I, A]	100%
7h. Both tamoxifen and AIs may be used after local BCT for DCIS to prevent local recurrence and to decrease the risk of developing a second primary breast cancer [I, B]	100%
7i. Following mastectomy for DCIS, tamoxifen or AIs might be considered to decrease the risk of contralateral breast cancer in patients with a high risk of new breast tumours [II, B]	100%
8. *Follow-up, long-term implications and survivorship*	
General follow-up considerations	
8a. Regular follow-up visits are recommended every 3 months in the first 3 years post-treatment (every 6 months for low-risk EBC), every 6 months from years 4-5 and annually thereafter. The interval of visits can be adapted to the risk of relapse and patient needs [V, A]	100%
8b. Annual bilateral (after BCT) or contralateral mammography (after mastectomy), plus US and breast MRI when needed, is recommended [II, A]	100%
8c. Breast cancer survivors should participate in national screening programmes for other cancers [V, B]	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
8d. In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other **non-breast imaging for detection of relapse** are not recommended [I, D] **but may be considered on an individual basis [V, C]**	100%
8e. Symptom-directed investigations should be considered as indicated [V, B]	100%
8f. Regular bone density evaluation is recommended for patients on AIs or undergoing OFS [I, A]	100%
8g. In asymptomatic patients with normal cardiac function who have received potentially cardiotoxic treatment, cardiac follow-up should be carried out as clinically indicated [III, B]	100%
8h. For patients on tamoxifen, an annual gynaecological examination **may be considered** [V, **C**]; however, routine transvaginal US is not recommended [V, D]	100%
Reproductive and sexual considerations	
8i. Premature menopause, infertility and potential sexual dysfunction should be discussed and addressed with each patient when appropriate, before the start of adjuvant therapy for EBC [V, A]	100%
8j. Premenopausal patients considering pregnancy should be informed that available evidence suggests that pregnancy seems to be safe after breast cancer treatment [III, A]	100%
8k. For women desirous of pregnancy, temporary interruption of adjuvant ET after 18-30 months of ET, allowing a wash-out period of 3 months, and attempting to get pregnant in a period of up to 2 years, followed by resumption of ET, does not appear to impact short-term breast cancer outcome in lower-risk HR+, HER2− EBC [III, A]	100%
Psychosocial considerations	
8l. Patients should be encouraged to adopt a healthy lifestyle, exercise regularly, avoid being overweight and minimise alcohol intake [II, A].	100%
8m. Long-term survivorship considerations, including psychological needs and issues related to work, family and sexuality, should be addressed [V, A]	100%

AI, aromatase inhibitor; ALN, axillary lymph node; ALND, axillary lymph node dissection; APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; BCT, breast-conserving therapy; CDK4/6, cyclin-dependent kinase 4/6; ChT, chemotherapy; CPG, clinical practice guidelines; CT, computed tomography; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Molecular Oncology; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; ET, endocrine therapy; FDG, [18F]2-fluoro-2-deoxy-D-glucose; FISH, fluorescence *in situ* hybridisation; g*BRCA1/2*m, germline *BRCA1/2* mutations; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HP, trastuzumab/pertuzumab; HR, hormone receptor; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; LNs, lymph nodes; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N, node; OFS, ovarian function suppression; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PgR, progesterone receptor; PMRT, post-mastectomy radiotherapy; PST, primary systemic therapy; PVs, pathogenic variants; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; T-DM1, ado-trastuzumab; TILs, tumour-infiltrating lymphocytes; TNBC, triple-negative breast cancer; TNM, tumour—node—metastasis; US, ultrasound; WBRT, whole-breast radiotherapy.

[a]In the original survey sent to the Pan-Asian panel of experts, 'recommendation 3v' was originally labelled as 'recommendation 6d'. 'Recommendations 6e-6k.2' in the survey have been relabelled accordingly.

bone scan-based methods have proven inconclusive. Thus, the wording for 'recommendation 2e' was modified as per the bold text below and in Table 1 to read as follows:

2e. [18F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)—CT scanning may be **an option for** high-risk patients and when conventional **CT/bone scan** methods are inconclusive [II, B; **consensus = 100%**].

A proposed algorithm for the diagnostic work-up and staging of early breast cancer is presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102974.

3. General management principles—recommendations 3a-v

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 3a-c, e-h, j-k and n-u' without change (Table 1).

While there was consensus amongst the Pan-Asian panel of experts regarding ESMO 'recommendation 3d' that age should not be the primary determinant of treatment decisions, there was some discussion that for very young patients age could be an important factor in addition to biology. Long-term follow-up data from the SOFT and TEXT trials, in premenopausal women with estrogen/progesterone receptor-positive (ER/PgR+) early breast cancer, showed 5 years of exemestane and ovarian function suppression (OFS) to significantly improve the 12-year overall survival (OS) in women under 35 years of age (4.0%).[32] Despite these data, it was generally agreed that cancer stage and biology should always be the primary determinants of treatment decisions, although age is an important factor for patients with hormone receptor-positive/HER2-negative (HR+/HER2−) breast cancer. Therefore 'recommendation 3d' remained unchanged (100% consensus).

There was a great deal of discussion around ESMO 'recommendation 3i' regarding the benefits of breast-conserving surgery (BCS) plus radiotherapy (breast-conserving therapy [BCT]) over radical mastectomy due to a discrepancy in the data from Italian and Dutch studies.[33,34] However, findings reported by the Korean Breast Cancer Registry, which evaluated 45 770 patients with early breast cancer, found that the 10-year OS for those receiving BCT was better than for those receiving radical mastectomy (HR = 1.541; 95% CI = 1.392-1.707; $P < 0.001$).[35] The breast cancer-specific survival rate was also better for the BCT cohort (HR = 1.541; 95% CI = 1.183-1.668; $P < 0.001$).[35] There was further discussion regarding women carrying a germline *BRCA* pathogenic variant (*BRCA*-

positive) where mastectomy is frequently the preferred option in many regions of Asia. In a Chinese study investigating BCT in women with *BRCA*-positive breast cancer, the 5-year cumulative recurrence-free survival (RFS) was comparable for patients receiving BCT (HR = 0.95; 95% CI = 0.89-1.00) and those receiving mastectomy (HR = 0.93; 95% CI = 0.85-1.00), after adjustment for clinicopathological characteristics and systemic treatment.[36] Within the *BRCA*-positive cohort there was no significant difference in disease-free survival (DFS) (HR = 1.17; 95% CI = 0.57-2.39; $P = 0.68$) or survival (HR = 1.44; 95% CI = 0.22-9.44; $P = 0.70$) for patients receiving BCT compared with those receiving mastectomy.[36] These results are in line with a meta-analysis comparing BCT with mastectomy in *BRCA*-positive women which concluded that survival outcomes are comparable between the two treatment options.[37]

It was therefore agreed that the clinical need is not there for mastectomy with reconstruction, but it may still be the preferred treatment for regions such as the Philippines and Indonesia where radiotherapy (RT) is not widely available in all hospitals and patients may not be willing or able to afford to travel to distant RT facilities. Also, in many regions of Asia, tumours are typically T2 and T3 at diagnosis which it was felt may impact on the relevance of findings from clinical trials where tumours are typically smaller. ESMO 'recommendation 3i' was agreed however, but the wording was modified as per the bold text below and in Table 1 to read as follows:

3i. BCS with post-operative RT is the **recommended** local treatment option for the majority of patients with early breast cancer **(when compatible with patient preference and available resources)** [I, A; **consensus = 100%**].

While there was consensus for ESMO 'recommendations 3l and 3m' it was highlighted that across Asia, there is a wide variation in stage of presentation. Less-developed regions are more likely to have patients presenting with later-stage breast cancer than more-developed regions.[16,38] For example, more than half of patients present with stage III or IV breast cancer in India compared with 76% presenting with stage I or II disease in South Korea.[16] For those regions where advanced disease is more common, the relevance of ESMO 'recommendations 3l and 3m' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) was questioned.

Regarding 'recommendation 3l', the long-term follow-up of the phase III IBCSG 23-01 randomised trial in patients with sentinel lymph node (SLN) micrometastases found the DFS at 10 years was 76.8% (95% CI = 72.5-81.0) for patients who did not have axillary lymph node dissection (ALND) versus 74.9% (95% CI = 70.5-79.3) for patients who underwent ALND (HR = 0.85; 95% CI = 0.65-1.11; log-rank $P = 0.24$; $P = 0.0024$ for non-inferiority).[39] It was thus agreed that the need for further axillary surgery was not required in this group of patients and the panel of Pan-Asian experts agreed with 'recommendation 3l', with a minor modification, removing the word 'eventually', to read as below and in Table 1 with 100% consensus:

3l. In the absence of prior primary systemic treatment (PST) patients with micrometastatic spread and those with limited SLN involvement (1-2 affected SLNs) in cN0 following BCS with subsequent whole-breast RT (WBRT) including the lower part of the axilla, and adjuvant systemic treatment, do not need further axillary surgery [II, A; **consensus = 100%**].

The Pan-Asian panel of experts agreed that routine ALND was not required for patients with breast cancer who, following SLN biopsy (SLNB), were found to have metastases to 1 or 2 SLNs. Thus ESMO 'recommendation 3m' was agreed with the minor modifications shown in bold below and in Table 1:

3m. ALND following positive SLNB with <3 involved SLNs is generally recommended only in **the** case of **suspected** high axillary disease burden, or with impact on further adjuvant systemic treatment decisions [II, A; **consensus = 100%**].

There was a robust discussion around ESMO 'recommendation 3v' (originally recommendation 6d in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) and the administration of granulocyte colony-stimulating factor (G-CSF) with dose-dense schedules of ChT to reduce post-ChT febrile neutropenia. In a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), dose-dense ChT was found to provide a benefit over standard schedule ChT for disease recurrence (10-year gain = 3.4%; 95% CI = 2.2% to 4.5%; log-rank 2 $P < 0.0001$), breast cancer mortality (10-year gain 2.4%; 95% CI = 1.3% to 3.4%; log-rank 2 $P < 0.0001$) and all-cause mortality (10-year gain = 2.7%; 95% CI = 1.6% to 3.8%; log-rank 2 $P < 0.0001$).[40] Similar results were found with subgroup analyses based on ER and PgR status, HER2 status, grade, Ki-67-status and histological type.[40] Furthermore, it was found that primary prophylaxis with G-CSF mandated in all 2-weekly dose-dense adjuvant ChT schedules led to lower levels of grade 3-4 neutropenia and neutropenic sepsis than in control arms.[40] The benefits of prophylactic use of G-CSFs were also reported in a retrospective Japanese study investigating the use of G-CSF or pegfilgrastim (the pegylated form of G-CSF analogue, filgrastim) with perioperative ChT in patients with early breast cancer over a 10-year period from January 2010 to October 2020.[41] It was noted that febrile neutropenia-related hospitalisations decreased in the last half of the study time despite the use of escalated regimens and that prophylactic pegfilgrastim likely contributed to this reduction [odds ratio (OR) of 0.879; 95% CI = 0.778-0.993; $P = 0.0384$].[41] Furthermore, a meta-analysis of the primary use of prophylactic G-CSF in trials using a docetaxel plus cyclophosphamide regimen found the risk of febrile neutropenia was reduced by 92.3% with prophylactic G-CSF (pooled OR = 0.077; 95% CI = 0.013-0.460; $P = 0.005$).[42] However, despite these results, there is still some question over the benefits of G-CSF in ICI-containing ChT regimens and not all regions of Asia use dose-dense schedules for all subtypes of early breast cancer, for example node-

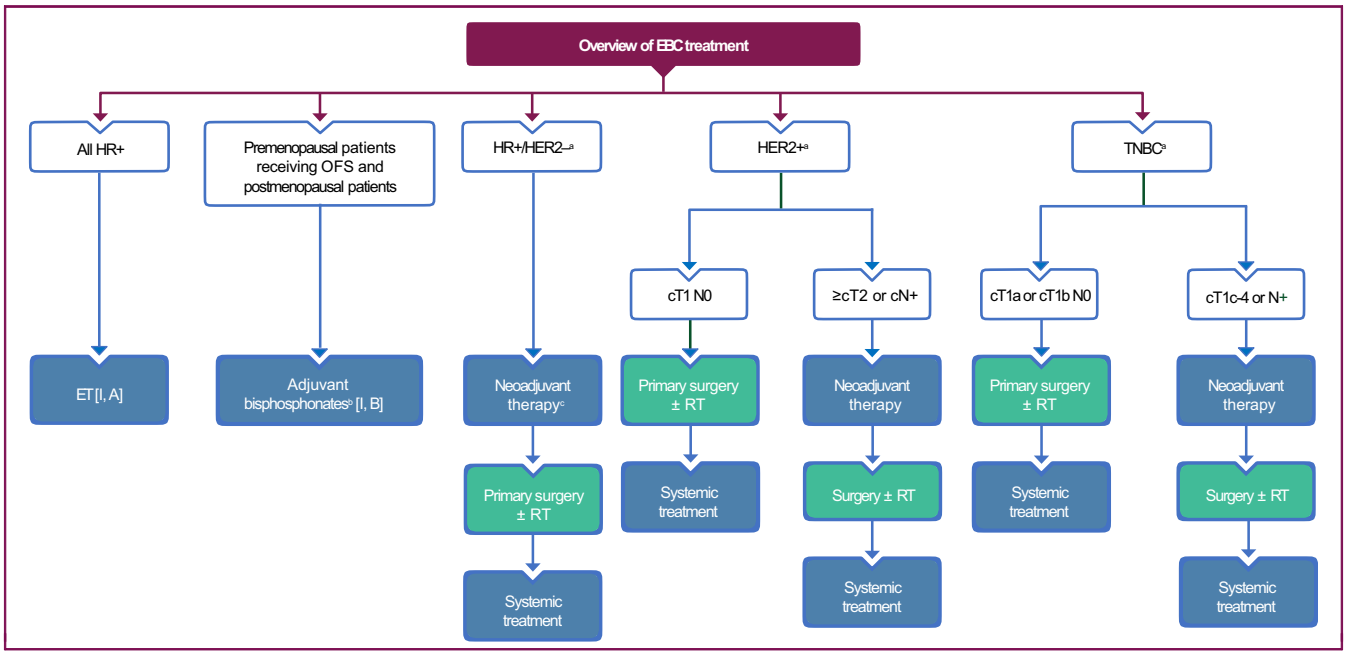

Figure 1. EBC treatment overview. Burgundy box: general categories or stratification; blue boxes: systemic anticancer therapy; turquoise boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management.
ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer.
[a]See Figure 2 for management of ALN involvement and Figures 3-5 for systemic therapy according to breast cancer subtype. Recommendations for special situations (elderly patients, male breast cancer and DCIS) are described in the CPG text and in Table 1.
[b]Bisphosphonates are approved for bone metastases and osteoporosis and not for prevention of relapse.
[c]If ChT is indicated, it may be given in the neoadjuvant setting.

negative disease. Thus, as a result of these discrepancies and the uncertainty over the benefits of G-CSF use with all ChT regimens, the GoR for 'recommendation 3v' was downgraded from 'A' to 'B' with 100% consensus, as is shown in bold below and in Table 1:

3v. The use of dose-dense schedules of ChT, with granulocyte colony-stimulating factor (G-CSF) support, should be considered given their documented benefit over non-dose-dense schedules [I, **B: consensus = 100%**].

Figure 1 presents a proposed algorithm for the treatment of early breast cancer and Figure 2 presents a proposed algorithm for the management of axillary lymph node involvement.

4. Management of ER-positive/HER2-negative early breast cancer—recommendations 4a-l

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 4a,b d-f.1 and i-l', without change (Table 1).

For ESMO 'recommendation 4c', the routine use of gene expression assays for guiding decisions on adjuvant ChT was questioned because, while the data of the West German Study Group Plan B trial demonstrated the potential for such assays in patient stratification,[43] they are not routinely used or widely accessible throughout Asia. Similar concerns were made regarding the accessibility and routine use of endocrine response assessment. Therefore, while the Pan-Asian panel of experts agreed about the science of both gene expression assays and endocrine response assessment, they downgraded the GoR from 'A' to 'B' and modified the wording, changing the word 'can' to 'may' as shown in bold below and in Table 1, as follows:

4c. In cases of uncertainty about indications for adjuvant ChT (after consideration of all clinical and pathological factors), gene expression assays and/**or** endocrine response assessment**s may** be used to guide decisions on adjuvant ChT [I, **B**; **consensus = 100%**].

There was a great deal of discussion around ESMO 'recommendation 4g' and the use of bisphosphonates in the early breast cancer setting. In the phase III AZURE trial the use of the bisphosphonate zoledronic acid did not improve either the 7-year OS (adjusted HR = 0.93; 95% CI = 0.81-1.08; $P = 0.37$) or the invasive disease-free survival (iDFS) (HR = 0.93; 95% CI 0.82-1.05; $P = 0.22$) rate compared to the control group for premenopausal and perimenopausal women, independent of ER status, tumour stage and lymph node involvement.[44] Preclinical evidence suggests that the lack of efficacy of bisphosphonates in these women may be, at least in part, due to the levels of estrogens,[45] and the Pan-Asian panel of experts therefore agreed that there was no benefit in treating premenopausal women with bisphosphonates which could be detrimental for younger patients with reduced bone density. In the EBCTCG meta-analysis of randomised trials investigating adjuvant bisphosphonate treatment in early breast cancer, it was found that for postmenopausal women, there was a significant reduction in disease recurrence (first-event rate ratio [RR] = 0.86; 95% CI = 0.78-0.94; 2p = 0.002), distant recurrence (RR = 0.82;

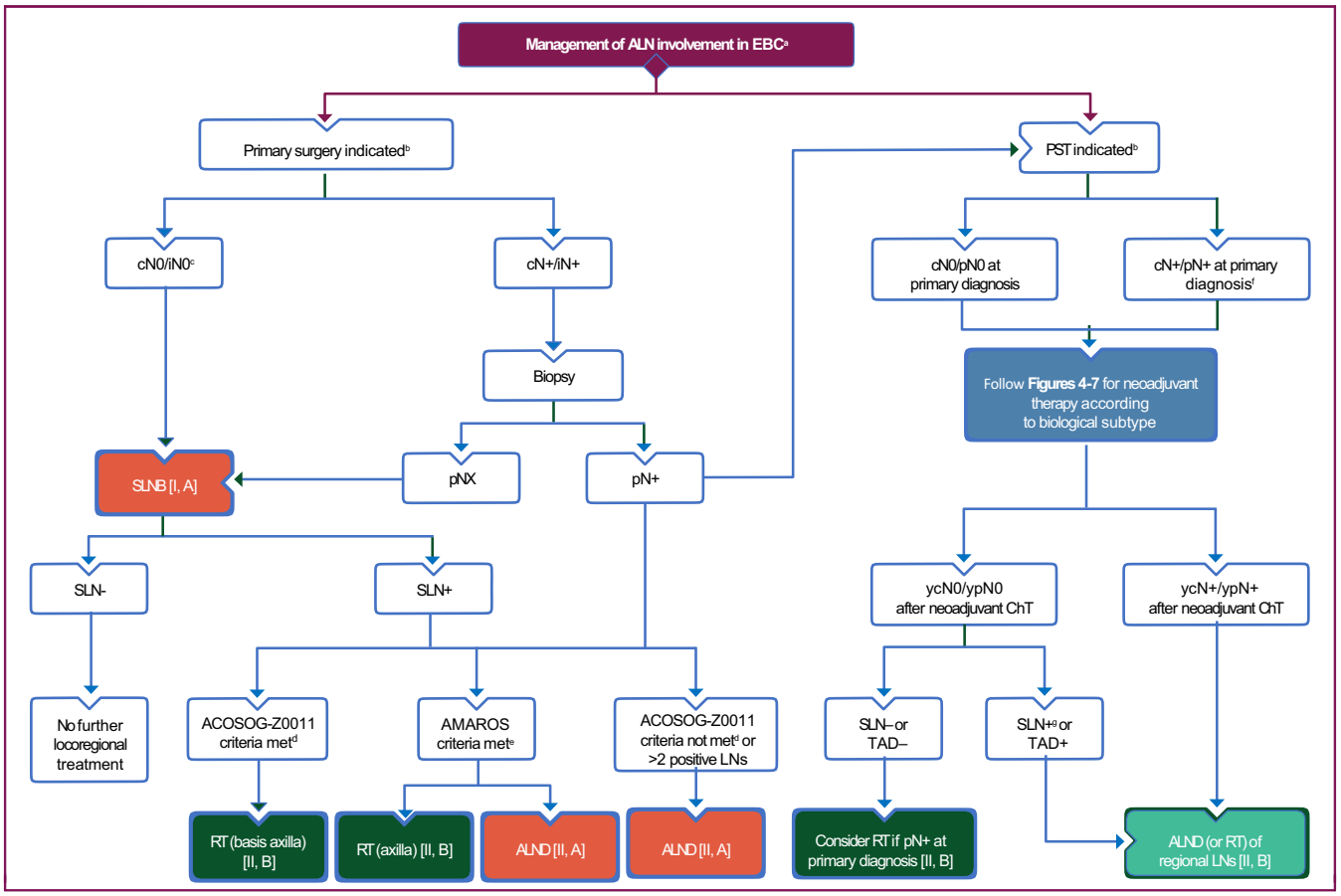

Figure 2. Management of ALN involvement in EBC. Burgundy box: general categories or stratification; orange boxes: surgery; blue box: systemic anticancer therapy; dark green boxes: radiotherapy; turquoise box: combination of treatments or other systemic treatments; white boxes: other aspects of management.
ALN, axillary lymph node; ALND, axillary lymph node dissection; c, clinical; ChT, chemotherapy; CT, computed tomography; EBC, early breast cancer: i, imaging; ITC, isolated tumour cell; LN, lymph node; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N, node; p, pathological; PET, positron emission tomography; PST, primary systemic therapy; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; US, ultrasound. .
[a]Discuss in MDT whether number of LNs is important for systemic therapy allocation.
[b]See Figure 1 for an overview of primary surgery and neoadjuvant therapy indications.
[c]Imaging (axillary US is preferred but MRI and PET—CT may be used in specific cases where more detailed imaging is required).
[d]Refers to ACOSOG-Z0011 trial eligibility criteria.[75]
[e]Refers to AMAROS trial eligibility criteria.[76] OTOASOR trial criteria can also be considered.[77]
[f]Inflammatory breast cancer and patients with N2 or N3 stage disease should receive ALND unless otherwise defined in a clinical trial.
[g]If ITCs are detected, consider axillary and locoregional RT as an alternative to ALND if an impact on adjuvant systemic treatments is not anticipated.

95% CI = 0.74-0.92; 2p = 0.0003), bone recurrence (RR = 0.72; 95% CI = 0.60-0.86; 2p = 0·0002), and breast cancer mortality (RR= 0·82; 95% CI = 0.73-0.93; 2p = 0·002).[46] However, there is no specific evidence of the effect that adjuvant bisphosphonate treatment has on disease recurrence in postmenopausal Asian women with early breast cancer and, while there was consensus that the use of bisphosphonates should be used for treating postmenopausal women with treatment-related bone loss, it was suggested that bisphosphonates are not routinely used to stop disease recurrence in Asia. As a result, the GoR for the use of bisphosphonates in patients at high risk of relapse was downgraded from 'A' to 'B' in 'recommendation 4g' as per the bold text below and in Table 1:

4g. Bisphosphonates are recommended in women without ovarian function (postmenopausal or undergoing OFS), especially if at high risk of relapse [I, **B; consensus = 100%**] or treatment-related bone loss [I, A; **consensus = 100%].**

For ESMO 'recommendation 4h' there was some discussion about whether the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor ribociclib should also be incorporated into the recommendation based on the exciting interim data from the phase III NATALEE trial in patients with HR+/HER2− early breast cancer which evaluated adjuvant ribociclib with endocrine therapy versus endocrine therapy alone which showed the 3-year iDFS to be significantly longer in the combination group (90.4%) compared with endocrine therapy alone (87.1%; $P = 0.0014$).[47] However, because ribociclib has, at present, not been given approval for use in early breast cancer by either the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), the wording for 'recommendation 4h' remained unchanged (**100% consensus**). Recently reported results from a pre-planned OS interim analysis of high-risk early breast cancer patients randomised to receive endocrine therapy for at least 5 years plus or minus the CDK4/6 inhibitor abemaciclib for 2 years showed the benefit of abemaciclib in terms of

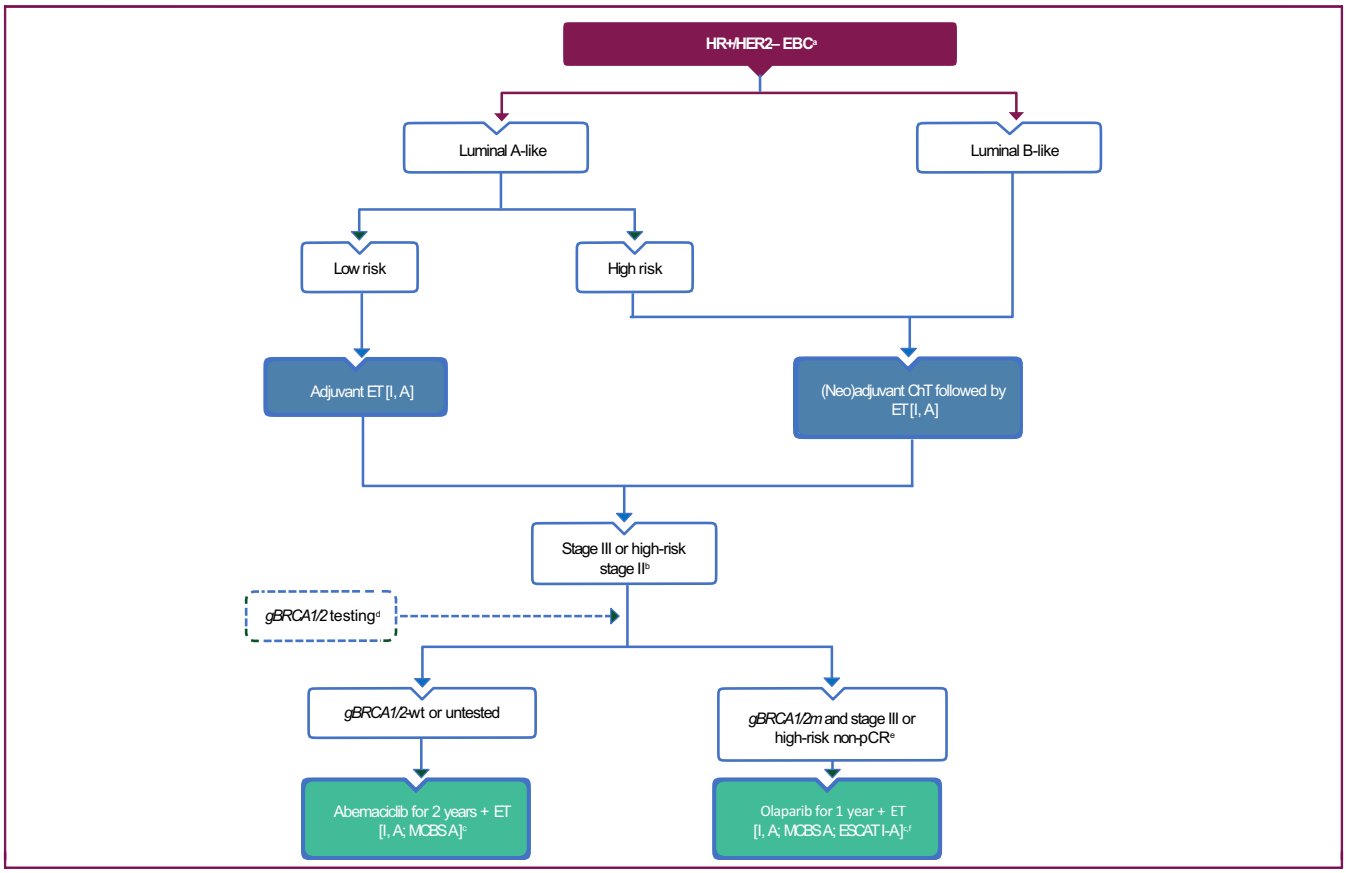

Figure 3. Management of HR-positive, HER2-negative EBC. Burgundy box: general categories or stratification; blue boxes: systemic anticancer therapy; turquoise boxes: combination of treatments or other systemic treatments; white boxes: other aspects of management; dashed line: optional recommendation.
ChT, chemotherapy; CPS+EG, pretreatment clinical stage and post-treatment pathological stage, estrogen receptor and tumour grade; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Medical Oncology; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2;* germline *BRCA1/2;* HER2, human epidermal growth factor receptor 2; HR, hormone receptor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; pCR, pathological complete response; wt, wild type.
[a]See Figure 1 for the role of surgery in HR-positive, HER2-negative EBC.
[b]Stage N1 with primary tumour >5 cm, and/or grade 3 and/or Ki-67 ≥20%.
[c]ESMO-MCBS v1.1[78] 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/esmo-mcbs-evaluation-forms).
[d]If *gBRCA1/2* testing is appropriate and feasible.
[e]Patients with HR-positive tumours and non-pCR after neoadjuvant ChT require a CPS+EG score ≥3 to receive olaparib.
[f]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[79]

iDFS and distant RFS with HRs of 0.68 (95% CI = 0.60-0.77) and 0.675 (95% CI = 0.59-0.77), respectively.[48] These data suggest that the addition of abemaciclib to endocrine therapy reduces the risk of a patient developing invasive disease and distant disease recurrence beyond the pivotal 5-year mark in the adjuvant setting. Follow-up of OS is ongoing.

A proposed algorithm for treatment of HR+/HER2− early breast cancer is presented in Figure 3.

5. Management of HER2-positive early breast cancer—recommendations 5a-i

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 5a-g and i', without change (Table 1).[20]

For ESMO 'recommendation 5h' the benefit of the addition of pertuzumab to trastuzumab for the adjuvant treatment of patients with HER2-positive breast cancer was discussed based on the findings of the phase III APHINITY trial, where the OS benefit at both the 6-year (HR = 0.85; 95% CI = 0.67-1.07; $P = 0.17$) and 8-year (HR = 0.83; 95% CI = 0.68-1.02; $P = 0.078$) follow-up failed to reach statistical significance.[49,50] There was, however, a consistent improvement in iDFS where 88.4% of patients in the pertuzumab group versus 85.8% of patients in the placebo group were event-free at the 8-year follow-up, which corresponded to an absolute benefit of 2.6% (95% CI for the difference = 0.7-4.6).[49] Subgroup analysis of iDFS data based on node status revealed that patients receiving pertuzumab with node-positive HER2-positive breast cancer had a 4.53% difference in EFS at the 6-year follow-up (95%

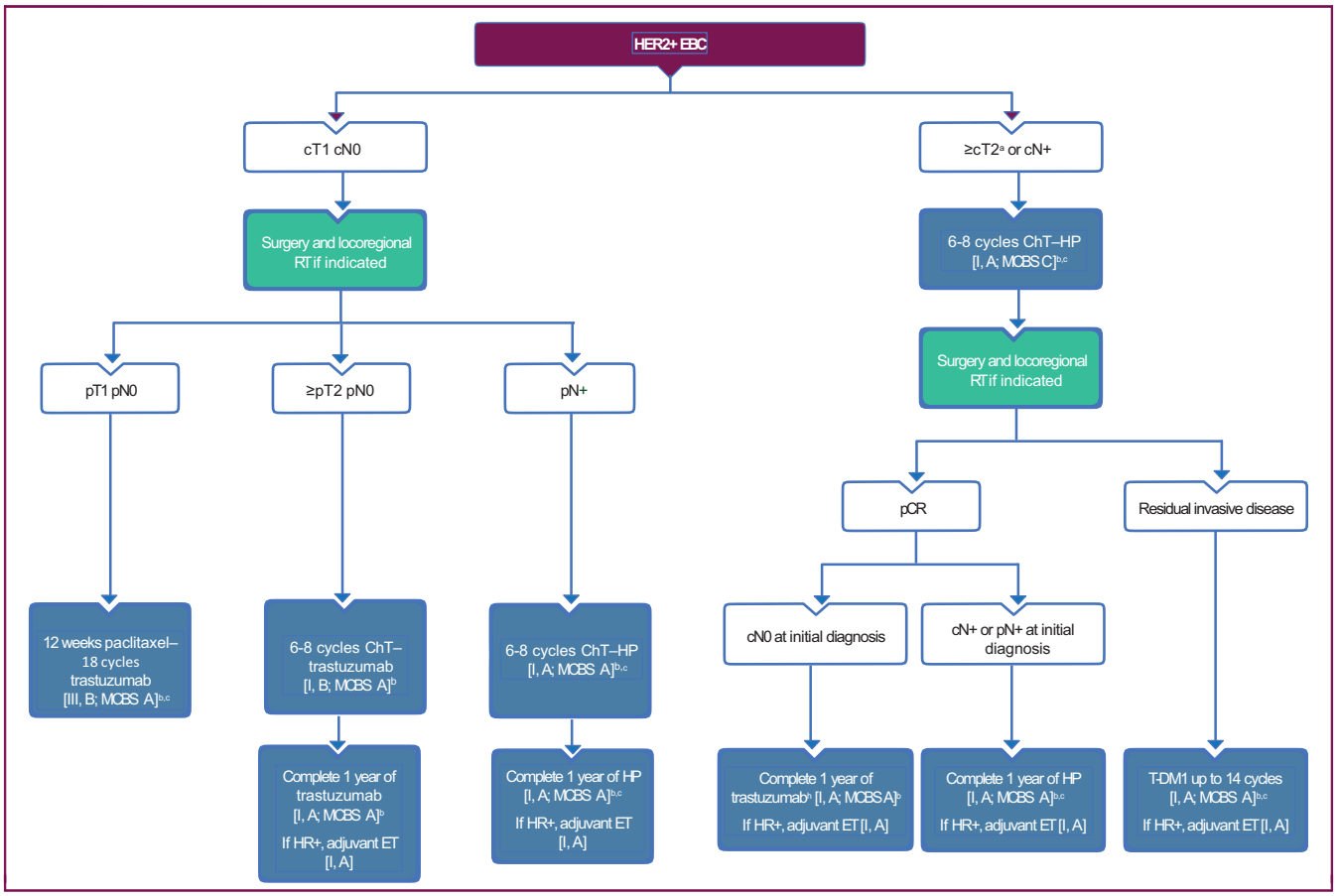

Figure 4. Management of HER2-positive EBC. Burgundy box: general categories or stratification; blue box: systemic anticancer therapy; turquoise box: combination of treatments or other systemic treatments; white boxes: other aspects of management.
c, clinical; ChT, chemotherapy; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Molecular Oncology; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HP, trastuzumab—pertuzumab: HR, hormone receptor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; T-DM1, trastuzumab emtansine.
[a]Tumours <2 cm can be considered for neoadjuvant therapy.
[b]ESMO-MCBS v1.1[78] 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/esmo-mcbs-evaluation-forms).
[c]ESCAT score I-A if HER2 gene amplification by FISH/chromogenic *in situ* hybdidisation. ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[79]

CI = 1.92-7.14) compared to those receiving placebo, and there was no clear benefit seen in the node-negative patients (0.07% difference in iDFS event-free survival; 95% CI = −2.02-2.17). Analysis by HR status revealed that there was a benefit for addition of pertuzumab in both the HR+ (2.47% difference in iDFS event-free rate; 95% CI for the difference = −0.66-5.60) and HR− (3.0% difference in iDFS event-free rate; 95% CI for the difference = 0.76-5.23) subgroups. Further stratification of the iDFS data revealed that while patients in the node-positive subgroup benefited from pertuzumab irrespective of whether they were HR+ (4.81% iDFS EFS; 95% CI = 1.59% to 8.03%) or HR− (4.10% iDFS EFS; 95% CI = −0.34% to 8.55%), there was no clear benefit for the node-negative subgroups (for the node-negative HR+ subgroup, iDFS EFS = 0.14%; 95% CI −2.47% to 2.74%; and for the node-negative HR− subgroup, iDFS EFS = −0.05%; 95% CI = −3.85% to 3.47%).

Thus, based on these results, the Pan-Asian panel of experts agreed with ESMO 'recommendation 5h' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) without modification with 100% consensus (Table 1).

Figure 4 presents an algorithm for the treatment of HER2-positive early breast cancer.

6. Management of TNBC—recommendations 6a-j.2

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 6a-e and g-i, j and j.1' without change (Table 1).[20]

Experts from three of the Asian medical societies disagreed with ESMO 'recommendation 6f' because it was felt that the benefit of adjuvant pembrolizumab for early TNBC is unclear, particularly with respect to pCR status. However, in the randomised phase III KEYNOTE-522 trial investigating the addition of pembrolizumab to neoadjuvant ChT in patients with early TNBC, the 5-year EFS was 81.3% (95% CI = 78.4% to 83.9%) in the pembrolizumab group compared

with 72.3% (95% CI = 67.5% to 76.5%) in the placebo group.[51] The distant disease progression- or distant RFS rates at 5 years were 84.4% for patients receiving pembrolizumab and 76.8% for patients receiving placebo (HR = 0.64; 95% CI = 0.49-0.84).[51] Recently presented data from a prespecified, non-randomised, exploratory analysis reported 5-year EFS rates for the pembrolizumab and placebo groups of 92.2% versus 88.2% for patients with a pCR, and 62.6% versus 52.3% for patients without a pCR.[51]

Thus, it was agreed that the original ESMO 'recommendation 6f' (Table 1) which read:

6f. Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase [I, A] and for nine 3-week cycles during the adjuvant phase, regardless of pCR status or administration of RT [I, A; ESMO-MCBS v1.1 score: A]

Should be modified to remove 'or administration of RT', which it was felt was unnecessary, although RT can be given with this combination as shown below and in Table 1:

6f. Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase [I, A] and for nine 3-week cycles during the adjuvant phase, regardless of pCR status [I, A; ESMO-MCBS v1.1 score: A; **consensus = 100%**].

The observation that poly (ADP-ribose) polymerase (PARP) inhibitors upregulate PD-L1 in breast cancer cells and synergise with ICIs in a syngeneic breast cancer tumour model provides a strong rationale for the combination of olaparib with ICIs in early TNBC.[52] However, for ESMO 'recommendation 6i.1' concern was raised by members of the Pan-Asian panel of experts regarding the safety of the combination of the PARP inhibitor, olaparib, with ICIs. At present, there are no data for olaparib plus ICIs in early TNBC but it is anticipated that the randomised phase II KEYLYNK-009 study comparing the efficacy of adjuvant olaparib plus pembrolizumab with ChT plus pembrolizumab following induction with first-line ChT in patients with locally recurrent inoperable TNBC will provide important data.[53] Data regarding the safety of olaparib plus ICIs can be found in the phase Ib/II KEYNOTE-365 study of pembrolizumab plus olaparib in patients with metastatic castration-resistant prostate cancer where it was reported that the treatment-related adverse events (TRAEs) for the combination were consistent with either agent alone.[54] Thus, the panel of experts agreed with ESMO 'recommendation 6i.1' but felt the recommendation needed more clarity regarding the recommended use of olaparib plus ICIs and ESMO 'recommendation 6i.1', which read:

6i.1 The combination of ICIs and olaparib may be considered on an individual basis [V, C]

and was amended to read as below and in Table 1, with the changes shown in bold (100% consensus):

6i.1. **In patients with germline *BRCA* mutations with residual disease after ICI-containing neoadjuvant therapy, the concurrent adjuvant use** of ICIs and olaparib may be considered on an individual basis [V, C**; consensus = 100%**].

As with 'recommendation 6i.1', there were some concerns about ESMO 'recommendation 6j.2' regarding safety. There were also doubts regarding the efficacy of the combination of pembrolizumab with capecitabine. The addition of adjuvant capecitabine after neoadjuvant ChT treatment was assessed in the Japanese/Korean CREATE-X study where, compared with the ChT-alone group, the addition of capecitabine was found to improve both DFS (69.8% versus 56.1%; HR for recurrence, second cancer or death = 0.58; 95% CI = 0.39-0.87) and the OS rate (78.8% versus 70.3%; HR for death = 0.52; 95% CI =0.30-0.90) for patients with TNBC.[55] The efficacy reported in the CREATE-X study was consistent with findings from a meta-analysis which found addition of capecitabine to ChT improved DFS (HR = 0.818; 95% CI = 0.713-0.938; $P = 0.004$) and OS (HR = 0.778; 95% CI = 0.657-0.921; $P = 0.004$) in the TNBC subgroup.[56] In addition, in a phase III trial conducted by the South China Breast Cancer Group, 1-year low-dose capecitabine maintenance therapy was found to significantly improve the 5-year DFS compared to the observation group (82.8% versus 73.0%; HR for risk of recurrence or death = 0.64; 95% CI = 0.42-0.95; $P = 0.03$), and there was also a numerical improvement in the 5-year OS but it was not significant (85.5% versus 81.3%; HR = 0.75; 95% CI = 0.47-1.19; $P = 0.22$).[57] Most toxicities from the combination of pembrolizumab and capecitabine in a phase II study in pretreated triple-negative and HR+, HER2-endocrine-refractory metastatic breast cancer were found to be low-grade and consistent with capecitabine monotherapy, including elevated liver tests, skin rash, fatigue, hand—foot syndrome and cytopenias.[58] In this biomarker-unselected cohort, there was no improvement for the combination of pembrolizumab plus capecitabine [12-month progression-free survival (PFS) = 20.7%; 95% CI = 8.4% to 36.7%; 12-month OS = 63%; 95% CI = 43.2% to 77.6%) over historical data,[58] but in a small phase Ib study consisting of 14 patients that investigated the early treatment of metastatic TNBC, the combination of pembrolizumab plus capecitabine showed superior response rates [overall response rate (ORR) = 43%] compared with pembrolizumab plus paclitaxel (ORR = 25%).[59]

Thus, while at present there are no data for the efficacy of ICIs plus capecitabine in the adjuvant setting for early TNBC, the panel agreed that the ESMO 'recommendation 6j.2' should be modified to provide clarity, over when the combination could be considered, to read as per the bold text below and in Table 1 (100% consensus):

6j.2. **In patients with residual disease after ICI-containing neoadjuvant therapy, the concurrent adjuvant use** of ICI and capecitabine can be considered on an individual basis [V, C**; consensus = 100%**]

A proposed algorithm for the management of triple-negative early breast cancer is presented in Figure 5.

7. Management of special situations—recommendations 7a-i

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 7a-h' without change (Table 1).

For ESMO 'recommendation 7i', the survival benefit and safety of tamoxifen and aromatase inhibitors (AIs) following

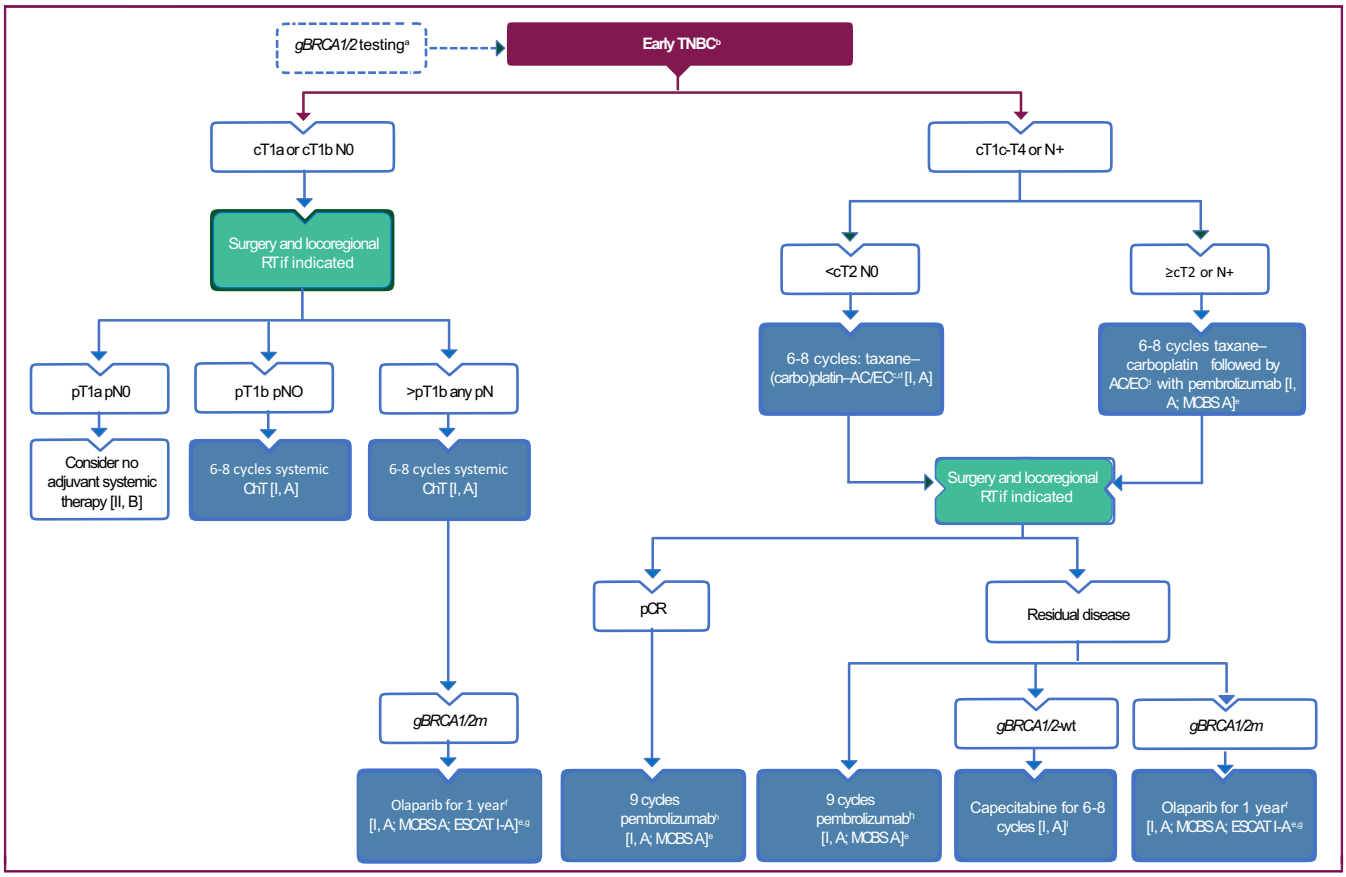

Figure 5. Management of early TNBC. Burgundy box: general categories or stratification; blue box: systemic anticancer therapy; turquoise box: combination of treatments or other systemic treatments; white boxes: other aspects of management; dashed line: optional recommendation.

AC, doxorubicin—cyclophosphamide; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; EC, epirubicin—cyclophosphamide; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Molecular Oncology; ER; estrogen receptor; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2,* germline *BRCA1/2*; *gBRCA1/2m,* germline *BRCA1/2*; mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; PgR, progesterone receptor; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer; wt, wild type.

[a]See the ESMO CPG for risk reduction and screening of cancer in hereditary breast—ovarian cancer syndromes.[80]

[b]HER2— tumours with 1%-9% ER and/or PgR expression (ER-low/PgR-low) are a heterogeneous group, some of which behave biologically similarly to TNBC; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET, compared with classical HR+ breast cancer [II, B].

[c]These evidence-based regimens without ICIs are sequential: anthracycline-based therapy followed by a taxane or taxane—carboplatin or vice versa.

[d]According to OlympiA inclusion criteria.[81]

[e]ESMO-MCBS v1.1[78] 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/esmo-mcbs-evaluation-forms).

[f]Indicated as adjuvant therapy for patients with *gBRCA1/2m* tumours and non-pCR or _pT2 or _pN1 if treated with initial surgery.

[g]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[79] ESCAT applicable if *HER2* gene amplification by FISH.

[h]Only if pembrolizumab was given preoperatively.

[i]Only for ICI-naïve patients.

mastectomy for ductal carcinoma *in situ* (DCIS) in high-risk patients was discussed. The benefit of AIs for breast cancer prevention was demonstrated in the international phase III IBIS-II trial comparing anastrozole with placebo in postmenopausal women at increased risk of developing breast cancer where, at 10-years, a 49% reduction in breast cancer was observed (HR = 0.51; 95% CI = 0.39-0.66; $P < 0.0001$).[60] In this study, there were no significant differences in the major AEs, except for a 28% reduction in the incidence of cancer outside the breast with anastrozole.[60] In the 9-year follow-up of the phase III NSABP B-35 study of patients with DCIS undergoing lumpectomy plus radiotherapy, there was no significant DFS benefit for anastrozole compared with tamoxifen (HR = 0.89; 95% CI = 0.75-1.07; $P = 0.21$), but patients in the anastrozole group had a superior breast cancer-free interval compared with the tamoxifen group (84.7% versus 83.1%; HR = 0.73; 95% CI = 0.56-0.96; $P = 0.023$), particularly in patients who had invasive disease (HR = 0.62; 95% CI = 0.42-0.90; $P = 0.0123$).[61] Patients in the anastrozole group also had a reduced incidence of contralateral breast cancer (HR = 0.64; 95% CI = 0.43-0.96; $P = 0.0322$) and again, this benefit over tamoxifen was more pronounced in those patients with invasive disease (HR = 0.52; 95% CI = 0.31-0.88; $P = 0.0148$). The only notable differences between the two groups in terms of AEs was thrombosis or embolism which

is a known side-effect of tamoxifen (2.7% versus 0.8% for the anastrozole group).[61]

Thus, based on these results, the Pan-Asian panel of experts agreed with ESMO 'recommendation 7i' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974) without modification with 100% consensus (Table 1).

8. Follow-up, long-term implications and survivorship—recommendations 8a-m

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 8a-c, e, g and i-m' without change (Table 1).

It was felt that there was a discrepancy between the real-world practice for testing asymptomatic patients in Asia and ESMO 'recommendation 8d'. Results from both Canadian retrospective chart reviews revealed the low diagnostic value of routine staging investigations, such as CT scans and bone scans, in asymptomatic early breast cancer patients.[62] These were also the findings of two prospective trials comparing patients that received frequent laboratory tests, bone scan and chest roentgenography.[63,64] Such findings, as well as studies demonstrating the use of unnecessary tests and screening, have led to many professional bodies publishing lists of tests and procedures that are unlikely to be of benefit to the patient.[65-68]

While it was agreed that over testing can lead to overtreatment, there is a potential benefit for such tests in high-risk patients. Thus, ESMO 'recommendation 8d' which reads:

8d. In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other imaging are not recommended [I, D]

was modified as per the bold text below and Table 1, with a revision in the GoR, to read as follows:

8d. In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other **non-breast imaging for detection of relapse** are not recommended [I, D] **but may be considered on an individual basis [V, C; consensus = 100%].**

Tamoxifen is associated with an increased risk of endometrial cancer in postmenopausal women[69] and the American College of Obstetricians and Gynecologists recommend that postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia and cancer.[70] However, it was felt that postmenopausal and higher-risk women would be treated with AIs and that endometrial hyperplasia can be misleading without vaginal bleeding. It was also agreed, based on the study by Love and colleagues,[71] that there was no evidence for the use of transvaginal ultrasound (US) for gynaecological examination in women taking tamoxifen.

Thus, ESMO 'recommendation 8h' was modified, and the GoR was downgraded from:

8h. For patients on tamoxifen, an annual gynaecological examination is recommended [V, B]; however, routine transvaginal US is not recommended [V, D]

to read as per the bold text below, and in Table 1 (100% consensus):

8h. For patients on tamoxifen, an annual gynaecological examination **may be considered** [V, **C; consensus = 100%**]; however, routine transvaginal US is not recommended [V, D].

Figure 6 presents a proposed algorithm for the adjuvant endocrine therapy in HR+ early breast cancer.

B. Applicability of the recommendations

Following the hybrid virtual/face-to-face meeting in Seoul, the Pan-Asian panel of experts agreed and accepted completely (100% consensus) the revised ESMO recommendations for the diagnosis, treatment and follow-up of early breast cancer in patients of Asian ethnicity (Table 1). However, the applicability of each of the guideline recommendations is impacted by the individual drug and testing approvals and reimbursement policies for each region. The drug and treatment availability for the regions represented by the 10 participating Asian oncological societies represented is summarised in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.102974, and individually for each region in Supplementary Tables S4-S13, available at https://doi.org/10.1016/j.esmoop.2024.102974.

Throughout Asia, most health care provision relies on both public and private insurance. In poorer regions public funding is more limited than in richer regions and patients are more likely to pay 'out of pocket' for both biomarker-related diagnostic tests and drugs. Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.102974, provides an overview of the availability of biomarker-related tests and drugs for the diagnosis and treatment of early breast cancer revealing that the majority are approved in most regions of Asia. In terms of biomarker-related diagnostic tests, immunohistochemistry (IHC), with the frequent exception of PD-L1, are, to some extent, covered by public health care provision in all regions of Asia, whereas genetic testing and next-generation sequencing (NGS)-based assays do not tend to be reimbursed. However, in regions where there is a disparity with the provision of oncology services, for example, in India, standardised laboratories for the provision of diagnostic tests are only located in the first and second tier cities. With the exceptions of neratinib (which is not approved for the treatment of early breast cancer in Indonesia, Japan, the Philippines and Thailand) and ribociclib (which is not approved for the treatment of early breast cancer in Japan and Korea), drugs for the treatment of early breast cancer have been approved across all regions of Asia although there may be differences in the indications they are approved for (i.e. trastuzumab is approved solely for metastatic disease in Indonesia, whereas in Taiwan approval is for LN+2 disease). Although many drugs for the treatment of early breast cancer are approved across Asia, a major limitation to their provision by the public sectors of the different regions is affordability.

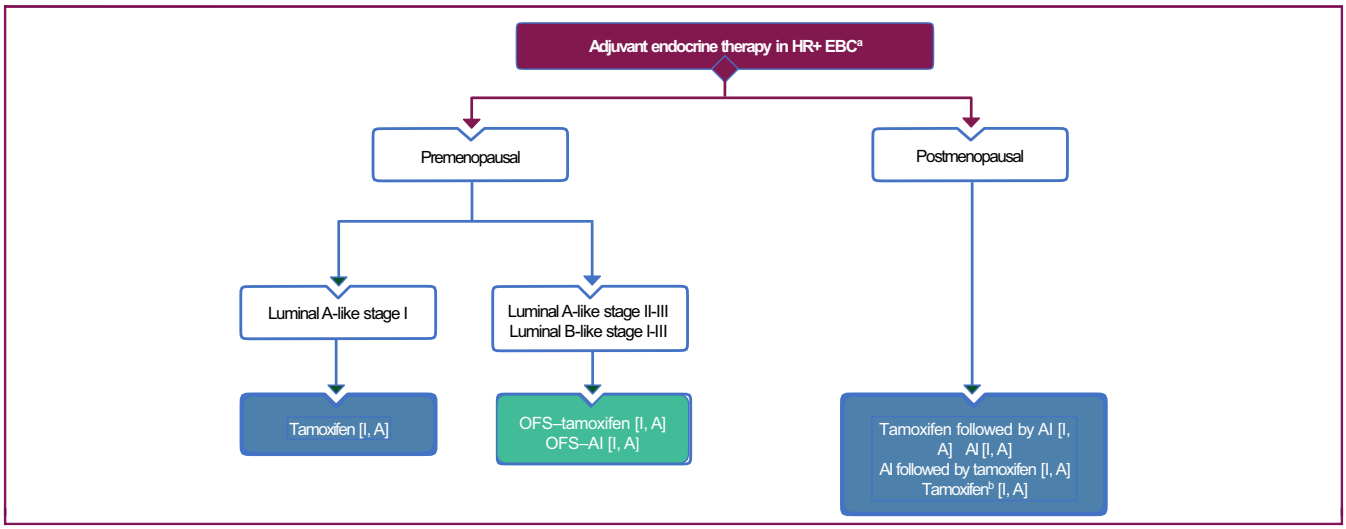

Figure 6. Management of adjuvant endocrine therapy in HR-positive EBC. Burgundy box: general categories or stratification; blue boxes: systemic anticancer therapy; turquoise box: combination of treatments or other systemic treatments; white boxes: other aspects of management.
AI, aromatase inhibitor; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OFS, ovarian function suppression.
[a]See Figure 1 for the role of surgery in HR-positive, HER2-negative EBC.
[b]Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A].

CSCO

In mainland China (China), the health care system is covered by social insurance for 80% of the population while 10% of the population have private insurance. Biomarker-related diagnostic tests, including IHC assessment of ER, progesterone receptor (PgR), Ki67 and HER2, as well as HER2 *in situ* hybridisation are covered by insurance, meaning that the 10% of patients without insurance will be out of pocket for these tests (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.102974). There is, however, no reimbursement for PD-L1 IHC, germline or somatic mutation analysis or gene expression risk signature assays. Those without insurance are the only patients likely to be out of pocket for trastuzumab, trastuzumab emtansine (T-DM1) and neratinib but there is no reimbursement in China for drugs such as abemaciclib, ribociclib, olaparib, pertuzumab and pembrolizumab (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.102974). In China, the pan-HER receptor tyrosine kinase inhibitor pyrotinib is approved for the neoadjuvant treatment of early breast cancer. It is estimated that it takes around 1 year for drugs to be approved in China after they have received FDA or EMA approval, and it can take a further 3 months for new drugs to become available. The biggest limiting factors around accessing new treatments is whether they are covered by insurance, and it is availability of new biomarker-related diagnostic tests in hospitals which is the greatest limitation on access for patients.

ISHMO

The health care system is weak in Indonesia with limited financial prowess and resources. The structure is further aggravated by the lack of awareness of patients and health care providers. National insurance covers the cost of IHC for ER, PgR, HER2 and Ki-67 but does not cover PD-L1 IHC, HER2 *in situ* hybridisation or gene expression assays (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.102974). Sequencing for germline or somatic *BRCA1/2* mutations is also not covered and, in Indonesia, NGS is only applied for *BRCA1/2* mutations. While most drugs used for the treatment of early breast cancer are available in Indonesia, their prices make them unaffordable for national insurance and, depending on the drugs, private insurance and employers/social insurance may not cover the cost (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.102974). For example, trastuzumab is only covered by national insurance for metastatic breast cancer but for the estimated 20% of the population with private insurance, the cost of trastuzumab is covered for early breast cancer. Bureaucracy of The Indonesian Food and Drug Authority (BPOM) is one of the biggest factors limiting access to new treatments and new biomarker-related diagnostic tests. The average time for approval following EMA/FDA approval is roughly 2 years and it can take, on average, a further 2 years for new drugs to become available for use in Indonesia following national approval.

ISMPO

In India both private and public health care systems exist and it is estimated that 60% of health expenditure in India is private, including through private insurance, which is taken out by $<$20% of the population, and out-of-pocket expenses. The public health system has various government schemes which cover up to 40% of total health expenditure. With 30% to 40% of the population covered by employers/social insurance schemes, 40% to 50% of patients will be out of pocket for biomarker assays and drugs. In terms of

biomarker tests, IHC for ER, PgR, Ki67, PD-L1 and HER2 expression, as well as HER2 *in situ* hybridisation, are fully reimbursed, whereas gene expression assays and genetic testing including somatic and germline testing for *BRCA1/2* mutations are not (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.102974). One of the main challenges for provision of those assays that are reimbursed is that standardised labs are only located in first- and second-tier cities in India. Most drugs for treating early breast cancer have been given approval in India with full reimbursement available for those who are covered by insurance. In India, it can take between 1 and 5 years for approval of drugs to be given approval following EMA or FDA approval. The length of time to approval is affected by the complexity of the drug and the presence of the pharmaceutical company in India. Once approval has been given, it can take several months to a year for new drugs to become available due to factors such as manufacturing, distribution and reimbursement. Furthermore, access to new treatments and biomarker-related diagnostic tests are affected by cost, health inequities and infrastructure as well as insurance, geographical location and cultural factors. A lack of knowledge and awareness by health care practitioners in smaller towns in India greatly affects the prescription of diagnostic tests.

JSMO

The Japanese health care system relies on a combination of public and private providers and emphasises preventive care, leading to one of the highest life expectancies and low infant mortality rates in the world. All citizens are required to have health insurance, either through their employers or the government and ∼40% of patients have private insurance to cover cancer treatment in addition to universal health care insurance. As a result of this system, very few patients pay entirely out of pocket but typically will pay a portion (0% to 30%) of costs. Most diagnostic tests for breast cancer are available in Japan although the only gene expression risk signature assay that currently has approval and is reimbursed is the Oncotype Dx assay which patients are expected to pay for upfront before receiving a reimbursement of 70% or more of the cost (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.102974). NGS assays for somatic mutations and IHC for PD-L1 are only indicated for patients with metastatic disease. At present, ribociclib and neratinib are not approved in Japan for the treatment of early breast cancer but the oral fluoropyrimidine S-1, which comprises a combination of tegafur, gimeracil and oteracil potassium, has approval for the adjuvant treatment of high- and intermediate-risk HR+ HER2− early breast cancer[72] (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.102974). Regulatory approval of diagnostic tests by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan can be a rigorous and time-consuming process where manufacturers must demonstrate the safety and efficacy of these diagnostic tests. Access to new treatments and the specific timeline for a new drug's availability in Japan can vary widely depending on the drug's complexity, market demand and various regulatory and commercial considerations. In general, new drugs may be reimbursed <6 months after permission by the PMDA.

KSMO

In Korea, cover of health care costs is provided to all Korean citizens, including foreigners who have lived in Korea for >6 months, by the National Health Insurance (NHI) system. However, in addition to the NHI coverage, patients with private insurance can pay a part of their health care costs including those for non-reimbursed, expensive new drugs, based on their insurance policy. Typically, only 10% of patients in Korea pay in full (out of pocket) for their treatment, with 15% covered by private insurance and the remaining 75% of patients covered by employers' or social insurance. Cancer patients are categorised as having 'serious disease' with 95% of costs covered for most biomarker-related diagnostic tests, including IHC for ER, PgR and Ki67 as well as *HER2 in situ* hybridisation and *BRCA1/2* mutation analysis by Sanger sequencing. For NGS-based sequencing, there is partial reimbursement with patients with stage I-II disease paying 90% and patients with stage III disease paying 80% of costs and there is no reimbursement for gene expression risk signature assays (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.102974). Both trastuzumab and T-DM1 are covered by NHI, meaning most patients will not be 'out of pocket', whereas for abemaciclib, olaparaib, neratinib and pembrolizumab which are approved for the treatment of early breast cancer, there is no reimbursement. This is also the case for pertuzumab in the adjuvant setting although 70% of the cost will be reimbursed for neoadjuvant pertuzumab (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.102974). With the emergence of many expensive drugs the limited resources of the NHI budget is becoming a major issue and the biggest limiting factor to accessing new treatments is reimbursement with the requirement for more self-payment. This is because Korea has been categorised as a developed region resulting in the costs of drugs being set at a much higher level than they were previously. In relation to diagnostic tests, the companion diagnostics associated with newer drugs require specific machines which are not available in the pathology labs of all hospitals. There is also a need for greater standardisation of certain diagnostic tests across the different treatment centres and laboratories throughout Korea.

MOS

In Malaysia there is a dual health care system consisting of a limited but fully funded health care system provided by the Ministry of Health (MOH) Hospitals and University Hospitals which is available for everyone, and a private health care system which provides services to patients who are insured

or willing to pay, with no reimbursement from the government. While certain innovator drugs are listed in the MOH formulary for the respective indications, their prescriptions are subject to very strict MOH criteria and the annual budget allocations. For example, trastuzumab is only indicated for stage II-III early breast cancer and prescribed for up to a maximum of nine cycles, while ribociclib use in metastatic HR+ HER2− cancer is restricted to the first-line setting only and available for a limited number of patients per year. There is, however, a shortage of oncology specialists and an imbalance in the distribution of oncology facilities across Malaysia.[73] Approximately 65% of the population of Malaysia, including members of the civil service and those without health care insurance, receive treatment subsidised by the MOH but patients treated at government facilities have the option to access private centres for diagnostic tests that are not covered by the MOH health care system. The same is also true for drugs that are not covered by the MOH where patients can purchase them for treatment at an MOH hospital. Diagnostic tests that are available free of charge through the MOH include IHC for ER, PgR and HER2, as well as HER2 FISH (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.102974), although turnover time may be long. Germline testing for *BRCA1/2*, NGS-based assays and IHC for PD-L1 are not available through the MOH, meaning that patients either need insurance to cover the costs or they will be out of pocket (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.102974). It takes ∼1 year for a drug that has received FDA approval to be approved by the MOH drug bureau although when drugs are approved by either the FDA or EMA, they can be obtained immediately via a special import licence allowed by the MOH.

PSMO

The health care system in the Philippines is primarily a mix of public and private health care providers. It consists of government-run hospitals, local health units and an extensive network of private health care facilities which collectively strive to provide health care services to the Filipinos. Social insurance (PhilHealth) costs 110 USD per person and 95% of the population use it. However, it is barely enough to cover anticancer medicines. In the Philippines, ∼20% of patients with early breast cancer will receive reimbursement for biomarker-related diagnostic tests, including IHC for ER, PgR and HER2 expression, which are available through government hospitals only and not reimbursed for private patients. IHC for PD-L1 expression is available through patient programmes and is not reimbursed, nor is HER2 *in situ* hybridisation which is only available to 60% of patients. Sanger sequencing for *BRCA1/2* mutations is available at a 50% reduced cost through an existing patient programme, while NGS for somatic mutations is only accessible to half of patients with no reimbursement (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2024.102974). Most drugs are available through patient access programmes although there is no reimbursement, with the exception of trastuzumab for which half of the cost is reimbursed through patient access programmes. Thanks to the 2018 Philippine National Cancer Control Act,[74] any drugs that are given approval in other countries will be streamlined for approval in the Philippines and it takes, on average, between 4 and 12 months for new drugs to become available. Cost and affordability are the biggest factors for accessing new drugs and biomarker-related tests. There is also limited access to new biomarker-related diagnostic tests and tools which are only available in specialised centres.

SSO

The health care system is Singapore is funded by both public and private insurance. The public system is funded through individual enforced savings (MediSave) and national health insurance which consists of three tiers: basic [MediShield Life (MSHL)], Integrated Shield Plan (ISP; which is a tie-up with private insurance) and the Enhanced Integrated Shield Plan (EISP; a tie-up with private insurance + riders). It is estimated that over half of Singapore citizens are covered by ISP. All IHC assays and selected FISH panels for early breast cancer diagnostics are entirely covered by the health care system, whereas genetic and gene expression profiling, including germline and somatic mutation screening, are not reimbursed (Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2024.102974). In 2022 the Cancer Drug List (CDL) was created which is updated monthly and lists the drugs deemed cost-effective according to accepted health technology assessment methods. Drugs on the CDL are covered by MSHL and ISP, whereas drugs not on the CDL can be covered by the EISP. It is estimated that 90% of cancer drugs in common usage are on the CDL with all drug costs for early breast cancer covered by the health care system in Singapore. Time to approval for new drugs to treat early breast cancer is typically <6 months from the time of EMA or FDA approval and they become available within about a month following approval. The biggest limiting factors for the health care system in Singapore is regarding the provision of genetic and transcriptional assays and, at present, there is assessment about whether they should be covered by national health insurance.

TOS

In Taiwan nearly 100% of the population are covered by National Health Insurance (NHI). The monthly payments out of pocket for NHI are relatively low although the financial coverage for reimbursement by NHI in Taiwan is basically 'all-or-none' (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2024.102974). The financial burden is huge and expected to increase further in the era of immuno-oncology and precision medicine. Therefore, despite approval by the Taiwan FDA which is largely a scientific evaluation based on the design and results of the individual pivotal trials, reimbursement is based on cost-

effectiveness, the availability of other medications for the same indication and future budget burden. Sequencing and NGS-based assays are not reimbursed but, with the exception for PD-L1, IHC-based diagnostic tests for early breast cancer are (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2024.102974). Targeted therapies for treating early breast cancer are currently not reimbursed in Taiwan except for trastuzumab and biosimilars. With no co-payment system, the biggest limiting factor with regard to accessing the newer treatment therapies and diagnostic tests in Taiwan is the necessity for patient out-of-pocket payment.

TSCO

Thailand has three national health insurance schemes [Civil Servant Medical Benefit Scheme (CSMBS), Social Security Scheme (SSS) and Universal Coverage Scheme (UCS)], with beneficiaries from different sectors. All three Thai schemes allow the use of drugs in the national list of essential medicines, with expanded benefits for individuals covered by one of the CSMBS. Basic drug accessibility is afforded by the two other Thai schemes. In terms of biomarker-related diagnostic tests for early breast cancer, IHC for ER, PgR, Ki-67 and HER2 but not PD-L1 are covered (Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2024.102974). Those patients covered by the SSS (∼20% of the population) are not reimbursed for germline *BRCA1/2* mutation analysis and there is no reimbursement at all for NGS or gene expression assays. It is estimated that <1% of the population will be out of pocket for drug costs. It takes ∼2 years for a new drug to be approved in Thailand once it has been approved by the EMA or FDA and between 6 and 8 months for new indications of previously approved drugs. Once approval has been given for drugs in Thailand, it can take 3-6 months for them to become available due to supply management and hospital listings, but this will be for use without reimbursement. It can take years for a drug that has been approved to be added to the list of indications that are reimbursed. This is especially the case for high-cost drugs. The biggest limiting factors for accessing new treatments and diagnostic tests are financial, including reimbursement issues. Another limiting factor for diagnostic tests in Thailand is the turn-around time.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the hybrid virtual/face-to-face meeting in Seoul showed >85% concordance with the ESMO recommendations for the diagnosis, treatment and follow-up of patients with early breast cancer[20] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102974). Following the 'face-to-face' discussions, revisions were made to the wording of 'recommendations 1a, 2e, 3i, 3l, 3m, 4c, 6f, 6i.1, 6j.2, 8d and 8h', and for 'recommendations 3v, 4c, 4g, 8d and 8h' the GoR was downgraded at least for part of the recommendation '(Table 1), resulting in a 100% consensus being achieved in terms of *acceptability* for all the recommendations listed in Table 1. After the consensus meeting, revisions to the wording of 'recommendations 1e, 1g, 1i, 1m, 5b, 5c, 6c and 7d' were made to make them consistent with the revisions requested by the reviewers of the original ESMO guidelines.[20] These recommendations therefore constitute the consensus clinical practice guidelines for the diagnosis, treatment and follow-up of patients with early breast cancer in Asia. The variations in the availability for the patients of diagnostic testing, drugs and therefore treatment possibilities, between the different regions, reflect the differences in the organisation of their health care systems and their reimbursement strategies, and will have a significant impact on the implementation of the scientific recommendations in certain of the regions of Asia. Thus, it is anticipated these guidelines may be used to guide policy initiatives to improve the access of all patients with early breast cancer, across the different regions of Asia, to state-of-the-art cancer care, including the enrolment into clinical trials, whilst recognising the constraints imposed by the heterogeneous socioeconomic situations of the different countries and regions of Asia.

ACKNOWLEDGEMENTS

The authors would like to thank the leaders of ESMO and KSMO for their support in facilitating this hybrid virtual/face-to-face meeting. They would also like to thank Klizia Marinoni and Fiona Perdomo from the Scientific and Medical Division of ESMO for the project management and scientific coordination, Herdee Gloriane Luna of ESMO Leaders Generation Programme for her participation, Zarina Othman and Aries Low from the ESMO Singapore Office for the logistical support and Minhee Kim of KSMO for the logistic organisation of the hybrid virtual/face-to-face meeting of experts. Anne Kinsella and Nick Davies of Cancer Communications and Consultancy Ltd, Cheshire, UK are acknowledged for their contribution to the preparation of the manuscript.

FUNDING

All costs relating to this consensus conference were covered by ESMO central dedicated funds (no grant numbers are applicable). There was no external funding of the event or the manuscript production.

DISCLOSURE

KHP declares speaker's engagement from Novartis and Roche; steering committee/advisory board role from AstraZeneca, Celltrion, Daiichi Sankyo, Eli Lilly and Pfizer; stocks/shares from IMBDx, OncoMASTER and SolBio, institutional research grant from AstraZeneca; licencing fees from Aston Sciences; non-remunerated research support from Boryung, Celcuity, Celltrion, Eli Lilly and IMBDx. SL declares employment from GBG Forschungs GmbH, speaker's engagement from AstraZeneca, DSI, Gilead, Medscape, Novartis, Pfizer, Roche, Seagen and Stemline-Menarini; steering committee/advisory board role from AbbVie, Amgen, AstraZeneca, BMS, Celgene, Daiichi Sankyo,

DSI, EirGenix, Gilead, GSK, Lilly, Merck, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Roche, Sanofi and Seagen; institutional funding/research grant from AbbVie, AstraZeneca, Celgene, Greenwich Life Sciences, Immunomedics/Gilead, Molecular Health, Novartis, Pfizer and Roche; PI role from Roche; institutional licencing fees from VM Scope GmbH; non-renumerated activity as member of ESMO, German Cancer Society (DKG), ASCO, German Gynaecological Oncology Society (AGO); non-renumerated advisory role from AGO; non-renumerated PI role from PI Aphinity; institutional patents for EP19808852.8, EP14153692.0, EP21152186.9 and EP15702464.7 (non-financial interest). JS declares institutional research grant from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GSK, Lilly, MSD, Novartis, Roche, Sanofi and Seagen; stocks/shares from Daiichi Sankyo. YHP declares writing/speaker's engagement from AstraZeneca, Daiichi Sankyo, MSD, Novartis, Pfizer and Roche; advisory board role from AstraZeneca. Daiichi Sankyo, MSD, Novartis Pfizer and Roche; institutional research grant from AstraZeneca, MSD, Pfizer and Roche; non-remunerated PI role from AstraZeneca, Daiichi Sankyo, Lilly, MSD, Novartis, Pfizer and Roche. SN declares speaker's engagement from Dr Reddys, Pfizer and Roche; local PI role from AstraZeneca and Roche; non-renumerated advisory role from IMA; non-renumerated NGO role from WCI; non-renumerated activity as member of ASCO and ISMPO. SS declares speaker's engagement from AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Exact Sciences, Kyowa Kirin, MSD, Novartis, Ono, Pfizer, Taiho and Takeda; institutional research grant from Chugai, Daiichi Sankyo and Taiho; funding as local PI from AstraZeneca, Chugai, Daiichi Sankyo, MSD and Sanofi; non-renumerated member of board of directors for Breast International Group, Japan Breast Cancer Research Group, Japanese Breast Cancer Society, Japanese Society of Medical Oncology. MMY declares speaker's engagement from Amgen, Docquity, GSK, Mundi Pharma and Zuellig Pharma; advisory board role from AstraZeneca, Eisai, Eli Lily, Johnson and Johnson, MSD, Novartis, Pfizer, Roche and Specialised Therapeutics; local PI role from ARCUS 10, Astellas, AstraZeneca, MSD, Novartis and Mundi Pharms; owner interest in Integrated Oncology Centre (Kuala Lumpur); non-renumerated NGO advisory role from Breast Cancer Women Association and KANWORK; non-renumerated advisory role from Malaysia Medical Council (special education subcommittee) and Malaysian government (Health Technology Assessment of cost-effectiveness of neo-adjuvant anti-HER2 therapy for the treatment of early breast cancer). EHL declares speaker's engagement from Roche; advisory board role from DKSH, Eisai, Novartis and Pfizer. YSL declares advisory board role from Novartis, Eli Lilly, MSD, Roche, Pfizer, AstraZeneca, Eisai, Daiichi Sankyo and Gilead; local PI role from Novartis, Roche, Pfizer, MSD, Eli Lily, Eisai, AstraZeneca, Gilead and Jellox; non-renumerated leadership role from Novartis. SI declares speaker's engagement from Novartis and Zuellig Pharma. TD declares speaker's engagement from AstraZeneca, Dr. Reddy, Novartis and Zeullig Pharma; advisory board role from AstraZeneca, Daiichi- Sankyo and MSD; funding as local PI from Pfizer and Roche. TWWC declares speaker's engagement from AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Novartis, Pfizer, Roche and TTY; advisory board role from AstraZeneca, Blueprint, Daiichi Sankyo, Eisai, Novartis and TTY; institutional research grant from AstraZeneca and Eisai. SCL declares steering committee/advisory board role from AstraZeneca, Eli Lilly, MSD, Novartis, Pfizer and Roche; institutional research grant from ACT Genomics, ASLAN Pharmaceuticals, Eisai, Karyopharm, MSD, Pfizer and Taiho; local PI role from AstraZeneca, BMS, Daiichi Sankyo, Novartis and Roche. CG declares employment by ICONplc. SM declares speaker's engagement from AstraZeneca and Dr Reddy; advisory role from AstraZeneca and Jensen Oncology; funding as local PI from Jensen; Institutional funding from Novartis; non-renumerated member role from Malaysian Oncological Society. TK declares speaker's engagement from Daiichi Sankyo; institutional research grant from Daiichi Sankyo and Eli Lilly. JB declares local PI role from Eli Lilly, MSD, Novartis, Paxman Coolers Ltd, Roche, Samsung Bioepis and Sun Pharma; institutional research grant from Intas Pharmaceuticals; non-renumerated leadership role from ESMO, Immuno-Oncology Society of India (IOSI), Indian cooperative Oncology Network, Indian Society of Medical and Paediatric Oncology, SITC and Teenage Young Adult Cancer Foundation; non-renumerated advisory role from Novartis. BB declares non-renumerated leadership role for Indonesian Journal of Cancer; editorial board member for Microsurgery Journal; non-renumerated activity as member of Indonesian Society of Surgical Oncology (ISSO) and Indonesian Surgeons Association. SW declares speaker's engagement from AstraZeneca, NOVATS, Pfizer and Roche; institutional research grant from Pfizer; local PI role from AstraZeneca, Pfizer and Roche. GC declares speaker's/writer's engagement from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer and Roche; advisory role from AstraZeneca, BMS, Celcuity, Daiichi Sankyo, Ellipsis, Exact Sciences, Lilly, Merck, Pfizer, Roche and Veracyte; funding as coordinating PI from Relay Therapeutics; institutional funding from Astellas, AstraZeneca, Blueprint Medicine, BMS, Daiichi Sankyo, Kymab, Merck, Novartis, Philogen, Relay Therapeutics, Roche and Sanofi; non-renumerated advisory role for Italian National Health Council Europa Donna patient advocacy association, EUSOMA and Fondazione Beretta Cancer Research Foundation; non-renumerated activity as chair of ESMO Clinical Practice Guidelines, advisory role from Europa Donna and Fondazione Beretta; member of board of directors for Lega Italiana Lotta ai Tumori; officer, Italian National Health Council as advisor for Ministry of Health. TY declares speaker's engagement from Bayer Yakuhin, Chugai Pharmaceutical, Merck Biopharma, MSD, Ono Pharmaceutical and Takeda Pharmaceutical; consultancy role from Sumitomo Corp; institutional research grant from Amgen, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, FALCO Biosystems, Genomedia Inc., Molecular Health GmbH, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer Japan, Roche Diagnostics, Sanofi, Sysmex Corp and Taiho

Pharmaceutical. SBK declares speaker's engagement from Legochem Bioscience; advisory board role from AstraZeneca, Beigene, DaeHwa Pharma, Daiichi Sankyo, ISU Abx, Lily, Novartis, OBI Pharma and Samsung Bioepics; institutional research grant from DongKook Pharm Co, Novartis and Sanofi-Genzyme; ownership interests in Genopeaks. GP declares employment by ESMO; non-renumerated membership of ASCO, Hellenic Cooperative Oncology Group (HeCOG) and Hellenic Society of Medical Oncology. SAI declares advisory board from AstraZeneca, Bertis, Daiichi Sankyo, Eisai, GSK, Hanmi, Idience, Lilly, MSD, Novartis, Pfizer and Roche; local/coordinating PI role from AstraZeneca, Daiichi Sankyo, Eisai, Hanmi, Lilly, MSD, Novartis, Pfizer and Roche; institutional grant funding from AstraZeneca, Boryung Pharm, Dae Woong, Wisai, Pfizer and Roche. FA declares advisory board role from AstraZeneca, Gilead, Guardant Health, Lilly France, Medimmune, N-power Medicine and Relay Therapeutics; institutional research grant from AstraZeneca, Daiichi, Lilly, Novartis, Pfizer and Roche; founder of Pegacsy. JBA declares non-renumerated PI role from Boryung and MSD. NH declares speaker's engagement from Art Tempi, AstraZeneca, Daiichi Sankyo, Gilead, Lilly, Medscape, MSD, Novartis, Onkowissen, Pierre Fabre, Roche, Sanofi, Seagen, Viatris and Zuelligpharma; advisory board role from Gilead, Pfizer, Sandoz-Hexal, Sanofi and Seagen; institutional funding from AstraZeneca, BMS, Daiichi Sankyo, Lilly, MSD, Novartis, Palleos, Pierre Fabre, Seagen, TRIO and WSG; independent data monitoring committee role for Roche; ownership and other interests from West German Study Group and WSG (husband); non-renumerated activity as member for AGO breast guideline committee and ESO/ESCO breast cancer education programs; founding editor of Breast Care Journal. All other authors have declared no conflicts of interest.

REFERENCES

1. Ferlay J, Ervik M, Lam F, et al., editors. *Global Cancer Observatory: Cancer Today.* International Agency for Research on Cancer; 2020. Available at https://gco.iarc.fr/. Accessed March 21, 2024.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality Worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Ottini L, Palli D, Rizzo S, et al. Male breast cancer. *Crit Rev Oncol/Hematol*. 2010;73(2):141-155.
4. Lei S, Zheng R, Zhang S, et al. Global patterns of breast cancer incidence and mortality: a population-based cancer registry data analysis from 2000 to 2020. *Cancer Commun (Lond)*. 2021;41(11):1183-1194.
5. Ng CJ, Teo CH, Abdullah N, et al. Relationships between cancer pattern, country income and geographical region in Asia. *BMC Cancer*. 2015;15:613.
6. National Registry of Disease Singapore. 2023. Available at https://nrdo.gov.sg/. Accessed March 21, 2024.
7. Cancer statistics Japan. 2020. Available at https://ganjoho.jp/reg_stat/statistics/stat/cancer/14_breast.html. Accessed March 21, 2024.
8. Lim YX, Lim ZL, Ho PJ, et al. Breast Cancer in Asia: incidence, mortality, early detection, mammography programs, and risk-based screening initiatives. *Cancers (Basel)*. 2022;14(17):4218.
9. Zhang S, Wang H, Liu B, et al. Socioeconomic status index is an independent determinant of breast cancer screening practices: evidence from Eastern China. *PLoS One*. 2022;17(12):e0279107.
10. Momenimovahed Z, Tiznobaik A, Taheri S, et al. A review of barriers and facilitators to mammography in Asian women. *Ecancermedicalscience*. 2020;14:1146.
11. Choi E, Lee YY, Suh M, et al. Socioeconomic inequalities in cervical and breast cancer screening among women in Korea, 2005-2015. *Yonsei Med J*. 2018;59(9):1026-1033.
12. Zeng H, Ran X, An L, et al. Disparities in stage at diagnosis for five common cancers in China: a multicentre, hospital-based, observational study. *Lancet Public Health*. 2021;6(12):e877-e887.
13. Cancer Research UK. Survival. 2023. Available at https://www.cancerresearchuk.org/about-cancer/breast-cancer/survival. Accessed March 21, 2024.
14. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. *Asian Pac J Cancer Prev*. 2015;16(7):2857-2870.
15. Green M, Raina V. Epidemiology, screening and diagnosis of breast cancer in the Asia-Pacific region: current perspectives and important considerations. *Asia Pac J Clin Oncol*. 2008;4:S5-S13.
16. Leong SP, Shen ZZ, Liu TJ, et al. Is breast cancer the same disease in Asian and Western countries? *World J Surg*. 2010;34(10):2308-2324.
17. Howlader N, Cronin KA, Kurian AW, et al. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):619-626.
18. Williams LJ, Fletcher E, Douglas A, et al. Retrospective cohort study of breast cancer incidence, health service use and outcomes in Europe: a study of feasibility. *Eur J Public Health*. 2018;28(2):327-332.
19. Yu AYL, Thomas SM, DiLalla GD, et al. Disease characteristics and mortality among Asian women with breast cancer. *Cancer*. 2022;128(5):1024-1037.
20. Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35:159-182.
21. Kang SY, Kim YS, Kim Z, et al. Breast cancer statistics in Korea in 2017: data from a breast cancer registry. *J Breast Cancer*. 2020;23(2):115-128.
22. Hamashima C, , Japanese Research Group for the Development of Breast Cancer Screening GHamashima CC, et al. The Japanese guidelines for breast cancer screening. *Jpn J Clin Oncol*. 2016;46(5):482-492.
23. Kim Y, Jun JK, Choi KS, et al. Overview of the National Cancer screening programme and the cancer screening status in Korea. *Asian Pac J Cancer Prev*. 2011;12(3):725-730.
24. Wu TY, Chen SL. Breast cancer screening practices and related health beliefs among Taiwanese Nurses. *Asia Pac J Oncol Nurs*. 2017;4(2):104-111.
25. Breast cancer screening guideline for Chinese women. *Cancer Biol Med*. 2019;16(4):822-824.
26. Choi E, Jun JK, Suh M, et al. Effectiveness of the Korean National Cancer Screening Program in reducing breast cancer mortality. *NPJ Breast Cancer*. 2021;7(1):83.
27. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556-567.
28. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396(10257):1090-1100.
29. Brierley J, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. 8th ed. Chichester, West Sussex, UK; Hoboken, NJ: John Wiley & Sons, Inc.; 2017.
30. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer. *TNM Classification of Malignant Tumours*. 7th ed. Chichester, West Sussex, UK; Hoboken, NJ: Wiley-Blackwell; 2010.
31. American Joint Committee on Cancer. AJCC Breast Cancer Staging System Manual. 8th ed. 2018. Available at http://www.breastsurgeonsweb.com/wp-content/uploads/downloads/2020/2010/AJCC-Breast-Cancer-Staging-System.pdf. Accessed March 21, 2024.
32. Pagani O, Walley BA, Fleming GF, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-

up of the combined TEXT and SOFT trials. *J Clin Oncol*. 2023;41(7):1376-1382.
33. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-1232.
34. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol*. 2016;17(8):1158-1170.
35. Kim H, Lee SA-O, Nam SJ, et al. Survival of breast-conserving surgery plus radiotherapy versus total mastectomy in early breast cancer. *Ann Surg Oncol*. 2021;28:5039-5047.
36. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within BRCA1/2 mutation carriers and noncarriers with breast cancer in the Chinese population. *Gland Surg*. 2020;9(3):775-787.
37. Davey MG, Davey CM, Ryan EJ, et al. Combined breast conservation therapy versus mastectomy for BRCA mutation carriers - a systematic review and meta-analysis. *Breast*. 2021;56:26-34.
38. Fan L, Goss PE, Strasser-Weippl K. Current status and future projections of breast cancer in Asia. *Breast Care (Basel)*. 2015;10(6):372-378.
39. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. *Lancet Oncol*. 2013;14(4):297-305.
40. Early Breast Cancer Trialists' Collaborative Group. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet*. 2019;393(10179):1440-1452.
41. Shibata N, Yoshinami T, Tamaki K, et al. Real-world data analysis of perioperative chemotherapy patterns, G-CSF use, and FN status in patients with early breast cancer. *Breast Cancer Res Treat*. 2023;201(2):265-273.
42. Do T, Medhekar R, Bhat R, et al. The risk of febrile neutropenia and need for G-CSF primary prophylaxis with the docetaxel and cyclophosphamide regimen in early-stage breast cancer patients: a meta-analysis. *Breast Cancer Res Treat*. 2015;153(3):591-597.
43. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017;165(3):573-583.
44. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol*. 2014;15(9):997-1006.
45. Canuas-Landero VG, George CN, Lefley DV, et al. Oestradiol contributes to differential antitumour effects of adjuvant zoledronic acid observed between pre- and post-menopausal women. *Front Endocrinol (Lausanne)*. 2021;12:749428.
46. Group EBCTC. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet*. 2015;386(10001):1353-1361.
47. Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: primary results from the phase III NATALEE trial. *J Clin Oncol*. 2023;41(suppl 17):LBA500.
48. Harbeck N, Rastogi P, O'Shaughnessy J, et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: results from a preplanned monarhE overall survival interim analysis, including 5-year efficacy outcomes. *Ann Oncol*. 2023;34:S154-S1335.
49. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;33(9):986-987.
50. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39(13):1448-1457.
51. Schmid P, Cortes J, Dent RA, et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab plus placebo for early-stage TNBC: updated EFS results from the phase III KEYNOTE-522 study. *Ann Oncol*. 2023;34:S1254-S1335.
52. Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. *Clin Cancer Res*. 2017;23(14):3711-3720.
53. Rugo HS, Llombart-Cussac A, Andre F, et al. KEYLYNK-009: a phase II/III, open-label, randomized study of pembrolizumab (pembro) plus olaparib vs pembro plus chemotherapy after induction with first-line pembro plus chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC). *J Clin Oncol*. 2020;38(suppl 15):TPS596.
54. Yu EY, Piulats JM, Gravis G, et al. Pembrolizumab plus olaparib in patients with metastatic castration-resistant prostate cancer: long-term results from the phase 1b/2 KEYNOTE-365 cohort a study. *Eur Urol*. 2023;83(1):15-26.
55. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159.
56. van Mackelenbergh MT, Seither F, Mobus V, et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - a meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. *Eur J Cancer*. 2022;166:185-201.
57. Wang X, Wang SS, Huang H, et al. Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: the SYSUCC-001 randomized clinical trial. *J Am Med Assoc*. 2021;325(1):50-58.
58. Shah AN, Flaum L, Helenowski I, et al. Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2-negative endocrine-refractory metastatic breast cancer. *J Immunother Cancer*. 2020;8(1):e000173.
59. Page DB, Chun B, Pucilowska J, et al. Pembrolizumab (pembro) with paclitaxel (taxol) or capecitabine (cape) as early treatment of metastatic triple-negative breast cancer (mTNBC). *J Clin Oncol*. 2019;37(suppl 15):1015.
60. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet*. 2020;395(10218):117-122.
61. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet*. 2016;387(10021):849-856.
62. Kamel D, Youssef V, Hopman WM, et al. Staging investigations in asymptomatic early breast cancer patients at the cancer centre of Southeastern Ontario. *Curr Oncol*. 2021;28(3):2190-2198.
63. Ghezzi P, Magnanini S, Rinaldini M, et al. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. *J Am Med Assoc*. 1994;271(20):1587-1592.
64. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. *J Am Med Assoc*. 1994;271(20):1593-1597.
65. Gradishar WJ, Anderson BO, Balassanian R, et al. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(3):324-354.
66. Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: the American Society for Radiation Oncology's top 5 list. *Pract Radiat Oncol*. 2014;4(6):349-355.
67. Landercasper J, Bailey L, Berry TS, et al. Measures of appropriateness and value for breast surgeons and their patients: the American Society of Breast Surgeons Choosing Wisely (®) Initiative. *Ann Surg Oncol*. 2016;23(10):3112-3118.
68. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol*. 2012;30(14):1715-1724.
69. Cheng WF, Lin HH, Torng PL, Huang SC. Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated

premenopausal and postmenopausal breast cancer patients. *Gynecol Oncol*. 1997;66(2):233-237.
70. American College of Obstetricians and Gynecologists (ACoG). Published by ACOG. Tamoxifen and uterine cancer. 2014. Available at https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2014/2006/tamoxifen-and-uterine-cancer.pdf. Accessed March 21, 2024.
71. Love CDB, Muir BB, Scrimgeour JB, et al. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *J Clin Oncol*. 1999;17(7):2050-2054.
72. Toi M, Imoto S, Ishida T, et al. Adjuvant S-1 plus endocrine therapy for oestrogen receptor-positive, HER2-negative, primary breast cancer: a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(1):74-84.
73. Barrios C, de Lima Lopes G, Yusof MM, et al. Barriers in access to oncology drugs - a global crisis. *Nat Rev Clin Oncol*. 2023;20(1):7-15.
74. Philippines Cot. REPUBLIC ACT No. 11215. 2023. Published by the Republic of Philippines. 2018. Available at https://lawphil.net/statutes/repacts/ra2019/ra_11215_12019.html. Accessed March 21, 2024.
75. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *J Am Med Assoc*. 2017;318(10):918-926.
76. ClinicalTrials.gov. Comparison of complete axillary lymph node dissection with axillary radiation therapy in treating women with invasive breast cancer (AMAROS). *U.S. National Library of Medicine*; 2023. Available at https://clinicaltrials.gov/ct2/show/NCT00014612.
77. Savolt A, Peley G, Polgar C, et al. Eight-year follow up result of the OTOASOR trial: the optimal treatment of the axilla - surgery or radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol*. 2017;43(4):672-679.
78. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
79. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.
80. Sessa C, Balmana J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol*. 2023;34(1):33-47.
81. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384(25):2394-2405.
82. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet*. 2017;390(10099):1048-1060.
83. Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. *Lancet Oncol*. 2022;23(1):e21-e31.
84. Strnad V, Yashar C. Breast brachytherapy. *Brachytherapy*. 2021;20(5):976-983.