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REVIEW

Treating HR+/HER2− breast cancer in premenopausal Asian women: Asian Breast Cancer Cooperative Group 2019 Consensus and position on ovarian suppression

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Abstract

Purpose Breast cancer in young Asian women has distinctive clinicopathological characteristics; hence, we question the universal generalizability of treatment recommendations based on data from predominantly non-Asian postmenopausal women.

Methods The Asian Breast Cancer Cooperative Group (ABCCG) reviewed current ESO-ESMO and St. Gallen recommendations for treating hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) breast cancer in premenopausal women. Points disputed by ≥ 3/12 members were discussed, and statements on contentious issues formulated for anonymous voting; consensus required a ≥ 75% majority.

Results The ABCCG contends that: (1) Trials in premenopausal women are not only necessary, but also worthwhile if performed separately from others that also enroll postmenopausal participants. (2) Not all premenopausal women with HR+ early breast cancer need adjuvant ovarian function suppression (OFS). (3) Certain clinical factors might influence decision-making about prescribing OFS. (4) For early HR+/HER2− breast cancer in premenopausal patients with OFS, tamoxifen is preferred for intermediate-risk cases; for high risk, near-consensus supported aromatase inhibitor, despite no clear overall survival benefit versus tamoxifen. (5) Oncotype DX Breast Recurrence Score® has different treatment implications in patients aged ≤ 50 versus > 50 years. (6) High-risk patients (if premenopausal after chemotherapy) should receive adjuvant chemotherapy and OFS plus aromatase inhibitor. (7) For patients with advanced disease receiving OFS on a backbone of tamoxifen, gonadotrophin-releasing hormone agonists may be given 12-weekly. (8) For premenopausal women who decline OFS or oophorectomy, tamoxifen alone is still an option but is considered less effective; other monotherapies are also less effective than OFS plus such treatments.

Conclusion Premenopausal Asian women with breast cancer have unique disease characteristics and may benefit from treatment that differs somewhat from international guidelines. Given the great diversity of patients and clinical settings worldwide, the ABCCG advocates evidence-based yet flexible and individualized use of all potential options to improve breast cancer outcomes.

Keywords Asia · Premenopausal breast cancer · Treatment · Ovarian suppression · Combined endocrine therapy · CDK4/6 inhibitor

Abbreviations

ABCCG	Asian Breast Cancer Cooperative Group
ESO-ESMO	European School of Oncology and European Society for Medical Oncology
ABC4	ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer, fourth edition
HR+	Hormone receptor positive
HER2−	Human epidermal growth factor receptor 2 negative

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OFS	Ovarian function suppression
OFA	Ovarian function ablation
GnRHa	Gonadotrophin releasing hormone agonist

Introduction

Breast cancer in younger Asian women

The incidence of breast cancer in Asia has escalated over recent decades, especially among younger women [1–4]; growing by ~3% annually in China [5, 6], incidence rose from 20 to 44 per 100,000 during 1990–2014 [6]. With rates in some countries outstripping those of Europid populations [7, 8], many East Asian[1] women are diagnosed before age 50 [4, 9, 10].

The natural history of breast cancer in young women differs manifestly between Asians and non-Asians [10–13]; incidence peaks at age 40–50 in Taiwanese, Japanese, Chinese, and Koreans, but ~70 years in US women [11, 12]. Contrastingly, age-specific incidence curves of colorectal cancer are similar in US and East Asian women [12]; therefore, distinctly higher breast cancer incidence among younger Asian women cannot be ascribed entirely to westernization [12, 13]. Indeed, dissimilar age-specific incidence patterns of female breast and colorectal cancers in US Asians versus Whites resemble those differentiating East Asian from US women, implying that breast cancer in Asians has race-specific biological characteristics [12, 13]. Pertinently, East Asian women younger than 50 have higher prevalence of luminal A breast cancer and less basal-like subtype compared with Americans [13], and higher hormone receptor positivity (HR+) rates than in older women [14, 15]. HR overexpression implicates estrogen-related causality, which is supported by similar age-specific incidence patterns of endometrial cancer and breast cancer in East Asian women, that contrast alike to those in US women [15]. Rising breast cancer incidence in premenopausal Asian women hypothetically reflects interactions of environmental factors with genetic susceptibilities that conduce to oncogenic estrogen exposure [12, 15].

Genomic data on young female breast cancer are limited, Asian data scarcer still. In The Cancer Genome Atlas dataset, age ≤45 years at diagnosis was associated with *GATA3* mutation and hyper-expression of genes involved in proliferation and endocrine resistance [16]. *TP53* mutations were more prevalent among 63 premenopausal Koreans/Singaporeans with relapsed breast cancer compared with non-Asians; 60/63 had alterations in cell cycle or p53 signaling [17]. Multi-omics likewise revealed distinctive molecular profiles in young Korean women [18].

Pharmacotherapeutic advances such as combined endocrine therapy and CDK4/6 inhibitors for HR+ breast cancer, continue to prolong survival in early and advanced disease [19, 20]. Certain regimens may particularly benefit Asians [21]; however, evidence remains preliminary and the optimal therapeutic strategies and patient profiles uncertain. Given distinctive clinicopathologic features of breast cancer in young Asian women, are current treatment guidelines universally generalizable? Guidelines should ideally be based on locally relevant epidemiologic data, practical to implement with available resources, and adaptable to diverse patients and circumstances [22, 23]. Regrettably, both premenopausal women and Asians have been underrepresented in global clinical trials [24–26]; consequently, international guidelines reflect evidence from predominantly postmenopausal Europid women. Recommendations on treating premenopausal women are limited and based largely on opinions of experts who treat relatively few young Asians. To address these issues, the Asian Breast Cancer Cooperative Group (ABCCG) reviewed ESO-ESMO [27] and St. Gallen [28] guidelines and formulated consensus recommendations on treating HR+/human epidermal growth factor receptor 2 negative (HR+/HER2−) breast cancer in premenopausal Asian women. Importantly, we do not mean to denigrate accepted international standards, but rather offer a complementary perspective intended to contribute to improving outcomes for young breast cancer patients everywhere.

Methods

Consensus process

The ABCCG is an independent association of Asian breast cancer experts, founded in October 2017 to foster collaborative data collection for epidemiology research and clinical/translational studies, and to disseminate its findings and ensuing advocacy internationally to improve the prognosis and outcomes of patients with breast cancer in Asia and beyond.

ABCCG members met in November 2018 to establish a consensus on issues pertaining to the management of premenopausal Asian women with HR+ breast cancer. The consensus process comprised two stages. An online premeeting survey in November 2018 elicited 12 ABCCG members' (listed authors) appraisal, with reasons, of recommendations for managing premenopausal breast cancer issued by the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017 (St.

[1] This consensus statement largely represents evidence from East Asian countries/regions, including China, Hong Kong, Japan, Singapore, Taiwan, and South Korea, for which robust epidemiologic data and expert knowledge of ABCCG members are available.

Gallen) [28], and the 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) [27]; the Appendix (Online resource 1) summarizes the survey results. Recommendations disputed by at least 3/12 members (25%) were discussed further at a subsequent consensus meeting, based on international clinical studies and, where evidence was equivocal, supplemented by ABCCG members' expert experiences and insights.

Eight contentious issues, especially concerning the use of ovarian function suppression/ablation (OFS/OFA) in premenopausal patients with HR+ early breast cancer, included: (1) trials of endocrine therapy in premenopausal patients; (2) the use of OFS for premenopausal patients with HR+ early-stage breast cancer; (3) the role of genetic and clinical tests in decision-making about using OFS for premenopausal patients with HR+ early breast cancer; (4) endocrine therapy with OFS for premenopausal patients with HR+ early breast cancer; (5) treatment implications of Oncotype DX Breast Recurrence Score for premenopausal patients with HR+ early breast cancer age ≤ 50 years; (6) OFS plus aromatase inhibition in patients with HR+ early breast cancer who remain premenopausal after adjuvant chemotherapy; (7) OFS using monthly versus 3-monthly gonadotrophin releasing hormone agonist (GnRHa) on the backbone of tamoxifen or aromatase inhibitor for premenopausal patients with HR+/HER2− metastatic breast cancer; and (8) options for premenopausal patients with HR+/HER2− metastatic breast cancer who decline OFS/OFA.

Consensus statements on each of these issues were debated and formulated, and anonymous keypad votes (yes, no, abstain) of 10 ABCCG members recorded; two absent members voted retrospectively but unaware of the meeting vote results. A majority of ≥ 75% of votes cast (assenting or dissenting) was required to endorse each final consensus position.

Besides establishing the ABCCG position on treating HR+/HER2− breast cancer in premenopausal Asian women, this report offers our perspective on evidence postdating current ABC 4 and St. Gallen guidelines; these include the final analyses of the SOFT & TEXT studies [29], and reports on others including MONALEESA [21, 30–32], PALOMA [33, 34], MONARCH [35, 36], SOLAR-1 [37], and other studies of PARP and PIK3 inhibitors [38–40].

Results and discussion

Clinical trials of endocrine therapy for early and advanced breast cancer

The ABCCG acknowledges that ABC 4 offered more guidance than did ABC 3 on managing premenopausal patients with metastatic breast cancer and agrees with ABC 4 that future breast cancer trials should enroll premenopausal women; however, there was no consensus supporting the ABC 4 recommendation that trials should enroll both pre- and postmenopausal women, and men (Table 1, Statement 1), with several members advocating separate trials for premenopausal women (and for men).

Table 1 Clinical trials of endocrine therapy for premenopausal patients with breast cancer

	Agree	Disagree	Abstain
Statement 1			
Future trials exploring new endocrine-based strategies should be designed to allow for enrolment of both pre- and postmenopausal women, and men.	8	4	0
Statement 2			
Resources should not be wasted running duplicate and separate trials for pre- and postmenopausal patients, but rather premenopausal patients should be eligible for trials if OFS or OFA is carried out.	3	9 (**75%**)	0

OFS ovarian function suppression, *OFA* ovarian function ablation

Bold font % result indicates consensus

The ABCCG disagrees with ABC 4 that separate or duplicate trials are unjustified (Table 1, Statement 2), because premenopausal breast cancer evidently differs from postmenopausal disease in certain regards. Besides somewhat different natural history of breast cancer in premenopausal versus postmenopausal women, disease characteristics also differ between Asians and Europid populations [12]. Furthermore, the ABC 4 guidance to treat HR+ advanced breast cancer the same way in premenopausal and postmenopausal women is based largely on expert opinion, rather than high-level evidence. Most ABC authors practice in Europe and North America, where only 20–30% of breast cancer patients are younger than 50 [41], whereas a higher proportion of Asian breast cancer patients are premenopausal [4, 9, 10, 12].

Distinctive clinicopathology in premenopausal Asian women may explain why Asian patients in MONALESSA-7 had even better outcomes compared with non-Asians [21]. Besides MONALEESA-7, only two other major trials of CDK4/6 inhibitor therapy for HR+/HER2− advanced breast cancer included premenopausal patients [30–36], among which premenopausal women accounted for only 21% of PALOMA-3 subjects [34], and 16% in MONARCH 2 [35]; MONALEESA 7 alone enrolled a homogenous cohort of premenopausal patients [32]. The ABCCG considers that trials which exclusively enroll premenopausal patients, such as MONALEESA-7, provide valuable evidence that combined endocrine and targeted therapy has comparable benefit in premenopausal patients with HR+ advanced breast

Table 2 Ovarian function suppression

	Agree	Disagree	Abstain
Statement 3			
Do you recommend that all premenopausal patients with ER+ early breast cancer should receive OFS as part of adjuvant therapy?	1	11 (**92%**)	0

ER+ estrogen receptor positive

Bold font % result indicates consensus

Table 3 Role of genetic and clinical tests results in deciding to use OFS

	Agree	Disagree	Abstain
Statement 4a[a]			
Do you think genomic test results could be one of the factors in your decision to use OFS?	5	5	1
Statement 4b			
Clinical factors according to subpopulation treatment effect pattern plot analysis based on SOFT & TEXT results could be a factor in helping to decide whether or not a patient receives OFS.	11 (**92%**)	1	0

OFS ovarian function suppression

Bold font % result indicates consensus

[a]One ABCCG member did not vote

cancer to that reported in similar studies of postmenopausal patients. As the only phase III clinical trial for 20 years focused on premenopausal patients with advanced disease, MONALEESA 7 provides solid evidence for using CDK4/6 inhibitors in such patients.

For these reasons, the ABCCG contends that specific treatment recommendations for young Asian women with breast cancer are warranted.

Management of premenopausal patients with HR+ early-stage breast cancer

The ABCCG position on OFS differs from St. Gallen guidelines in several respects (Table 2, Statement 3). Panel members explained that patients in the ZEBRA study who received OFS had disease-free survival identical to those treated with combined cyclophosphamide, methotrexate, and fluorouracil [42]. Moreover, the benefit of adjuvant chemotherapy in premenopausal patients with early HR+ breast cancer was only evident amongst those with ovarian function suppression effects of chemotherapy [43]. Although ZIPP [44] and SOFT [29] reported significantly better disease-free and overall survival with tamoxifen plus OFS versus tamoxifen alone, the E-3193 [45] and ABCSG-12 [46] studies found no difference in outcomes between patients who received tamoxifen with versus without OFS. This discrepancy may reflect differences between the study populations and in OFS modalities and duration; for example, 71% of participants in ZIPP were premenopausal and 53% had HR+ early breast cancer, whereas the E-3193 study had a much smaller patient population and was underpowered to draw conclusions about how adding OFS to tamoxifen-affected survival.

ABCCG members also noted that, despite statistically significant differences in outcomes in the SOFT & TEXT study arms, the distant recurrence benefit of OFS in patients who did not receive chemotherapy was only 1%. Furthermore, OFS was associated with adverse events inimical to long-term adherence, such as increased vasomotor symptoms, poor libido, and disturbed sleep; adding OFS in the SOFT study doubled the osteoporosis rate compared to tamoxifen monotherapy (27.9% vs. 13.7%) [29]. It follows that adding OFS to standard adjuvant endocrine therapy may only have clinically meaningful outcomes in selected candidate patients.

The ABCCG recognizes that the value of genomic data in making decisions about the type and duration of endocrine therapy has not yet been assessed in prospective trials. While the members considered that integrating both clinical and genomic factors may have some value in risk assessment, it was emphasized that genomic classification has hitherto proven unsuccessful in selecting patients for specific endocrine therapies (Table 3, Statement 4a). The ABCCG further notes that subpopulation treatment effect pattern plot analysis by the SOFT & TEXT investigators showed that patients with low progestogen receptor expression and/or high Ki-67 expression derive greater absolute benefit from exemestane plus OFS versus tamoxifen with/without OFS [47] (Table 3, Statement 4b).

Table 4 Endocrine therapy for premenopausal patients having OFS

	Aromatase inhibitor	Tamoxifen	Abstain
Statement 5			
Which endocrine therapy is preferred as adjuvant therapy for early ER+ breast cancer in premenopausal patients with OFS?	2	7	3
Statement 5a[a]			
Which endocrine therapy is preferred as adjuvant therapy for early ER+/HER2− breast cancer in premenopausal patients with OFS at high risk?	8	2	1
Statement 5b			
Which endocrine therapy is preferred as adjuvant therapy for early ER+/HER2− breast cancer in premenopausal patients with OFS at intermediate risk?	1	11 (**92%**)	0

OFS ovarian function suppression, *ER+/HER2−* estrogen receptor positive/human epidermal growth factor receptor 2 negative

Bold font % results indicate consensus

[a]One ABCCG member did not vote

Table 5 Treatment implications of Oncotype DX Recurrence Scores® for patients ≤ 50 years old

	Agree	Disagree	Abstain
Statement 6			
RS score has different treatment implications in patients ≤ 50 versus > 50 years old.	11 (**92%**)	1	0
Statement 6a			
Discuss option of chemotherapy for patients with RS score ≥ 21–25.	12 (**100%**)	0	0
Statement 6b			
Discuss option of chemotherapy for patients with RS score ≥ 16–20.	8	0	4
Statement 6c			
Recommend avoiding chemotherapy for patients with RS score ≥ 11–15.	8	3	1
Statement 6d			
Consider chemotherapy for patients with RS score ≥ 11–15.	1	9 (**75%**)	2

RS Oncotype DX Breast Recurrence Score®

Bold font % results indicate consensus

Although the SOFT & TEXT studies reported better distant recurrence-free survival in the exemestane plus OFS arm compared with tamoxifen with/without OFS, the 8-year overall survival was similar between the exemestane and tamoxifen arms; however, tamoxifen plus OFS was superior to tamoxifen alone [29]. In addition, ABCSG-12 patients treated with aromatase inhibitor plus OFS had significantly worse overall survival compared to those treated with tamoxifen alone (HR = 1.63) [46].

Besides being non-superior to tamoxifen in terms of overall survival, aromatase inhibitor therapy is also associated with detrimental cardiovascular effects and osteoporosis. Another issue is that monthly GnRHa injection for ≥ 3 years would likely be difficult to tolerate for women already on aromatase inhibitor therapy; exacerbated hot flushes may lead to lower adherence [48]. In South Korea, aromatase inhibitor is not licensed for adjuvant treatment of HR+ breast cancer in premenopausal women, so the only option approved in this setting is tamoxifen, with or without GnRHa. Consequently, and contrary to established guidelines that favor adjuvant aromatase inhibition plus OFS for premenopausal patients with early HR+ breast cancer, there was no ABCCG consensus to use aromatase inhibition (Table 4, Statement 5), even for patients considered to have high risk, although a near-consensus majority did favor this approach (Table 4, Statement 5a), and consensus to use tamoxifen for patients at intermediate risk (Table 4, Statement 5b).

Although premenopausal and postmenopausal participants in the TAILORx study had similar primary endpoint outcomes [49], exploratory analyses suggested that chemotherapy may be beneficial in patients aged 50 or younger who had an Oncotype DX Breast Recurrence Score of 11–25, in which case a cutoff for premenopausal patients may be useful. As only 13% of premenopausal patients in TAILORx received OFS, it remains unknown whether or

Table 6 Adjuvant chemotherapy and OFS plus aromatase inhibition

	Agree	Disagree	Abstain
Statement 7			
For high risk patients (high RS) who remain premenopausal after adjuvant chemotherapy, treatment with OFS plus aromatase inhibitor.	10 (**83%**)	0	2

OFS ovarian function suppression, *RS* Oncotype DX Breast Recurrence Score®

Bold font % result indicates consensus

Table 7 OFS on backbone of tamoxifen or aromatase inhibitor

	Agree	Disagree	Abstain
Statement 8a			
When tamoxifen is chosen for backbone endocrine therapy, if GnRHa is used in this age group it could be given on a monthly or 3-monthy basis.	11 (**92%**)	1	0
Statement 8b			
When aromatase inhibitor is chosen for backbone endocrine therapy, if GnRHa is used in this age group 3-monthly injection is acceptable.	4	7	1

OFS ovarian function suppression, *GnRHa* gonadotrophin-releasing hormone agonist

Bold font % result indicates consensus

not using adjuvant OFS may influence outcomes in such patients; however, as the result may hypothetically be similar, this warrants investigation.

The ABCCG endorses chemotherapy for postmenopausal patients with Breast Recurrence Score ≥ 26, which is defined as high risk, but not with lower scores. However, in consensus votes based on the TAILORx results, ABCCG members concurred that Oncotype DX Breast Recurrence Score results have different implications in women younger versus older than 50 (Table 5, Statement 6), and with the rationale to also discuss the possibility of chemotherapy with premenopausal patients with Breast Recurrence Score of ≥ 21–25 (Table 5, Statement 6a). There was also consensus against chemotherapy for patients with Breast Recurrence Score ≤ 15 (Table 5, Statement 6d), as is standard practice at the ABCCG members' institutions.

St. Gallen recommends tamoxifen alone for patients at low-risk, OFS plus tamoxifen or aromatase inhibitor for uncertain clinical risk and intermediate genomic risk (with chemotherapy to be considered), and OFS plus aromatase inhibitor with adjuvant chemotherapy in many cases for patients with intermediate/high clinical and genomic risk [28].

A consensus supported the St. Gallen recommendation for high-risk patients (Table 6, Statement 7); moreover, based on the results of TAILORx, the ABCCG regards chemotherapy as a valid option for patients with intermediate genomic risk who are younger than 50. Members cited practical issues in Asia, where aromatase inhibitors, including exemestane, are not approved for adjuvant treatment in Japan, and OFS therapy is not reimbursed in some countries; however, there was no consensus on treatment for patients at intermediate and high risk.

Determining the menopausal status of young women with breast cancer who have received various anti-cancer therapies can be problematic. The ABCCG advocates that menopausal status should be ascertained before administering chemotherapy; although 90% of premenopausal patients who receive adjuvant cytotoxic therapy may experience chemotherapy-induced amenorrhea, this is not always permanent and ~ 30% of patients recover premenopausal status [50]. NCCN Guidelines® recommend serial follicle stimulating hormone and/or estradiol assays to confirm the menopausal status of women who are premenopausal upon initiation of adjuvant chemotherapy if aromatase inhibitor is to be prescribed [51]. However, this recommendation would be challenging to follow in real-world clinical practice, as it requires a woman to be free from anti-cancer therapy (including adjuvant endocrine therapy) for a few months so that estradiol and follicle stimulating hormone can be measured accurately and repeatedly.

Management of premenopausal patients with advanced breast cancer

ABC 4 recommends that endocrine therapy is preferred for HR+ breast cancer, even with visceral disease (unless there is visceral crisis or concern/proof of endocrine resistance), and that GnRHa, if used, should be taken monthly

Table 8 Options for premenopausal patients who decline OFS/OFA

	Agree	Disagree	Abstain
Statement 9a			
For premenopausal women who decline OFS, single-agent tamoxifen is less effective.	11 (**92%**)	1	0
Statement 9b			
For premenopausal women who decline OFS, single agent tamoxifen is the only available endocrine option.	6	6	0
Statement 9c			
For premenopausal women who decline OFS, single other endocrine agent is also less effective compared with OFS plus these treatments.	9 (**75%**)	1	2
Statement 9d[a]			
For premenopausal women who decline OFS, fulvestrant is another single-agent option that can be added, besides medroxyprogesterone acetate and megace.	5	5	

OFS ovarian function suppression, *OFA* ovarian function ablation

Bold font % results indicate consensus

[a]Two ABCCG members did not vote

to optimize OFS [27]. However, several ABCCG members disagreed that GnRHa, if used in this age group, should necessarily be monthly; the consensus supported GnRHa either monthly or 3-monthly if the backbone endocrine therapy is tamoxifen (Table 7, Statement 8a).

ABC 4 acknowledges the clinical challenge of determining the menopausal status of young patients who have already undergone some form of (adjuvant) anticancer therapy. Follicle stimulating hormone and estradiol measurements may be inaccurate in premenopausal patients taking adjuvant tamoxifen; tamoxifen use has been associated with increased levels of estradiol with follicle stimulating hormone diminution, partly due to cross-reactivity of tamoxifen and its metabolites in the estradiol assay [52, 53]. The ABCCG concurs with ABC 4 that the best way to confirm menopausal status and optimal timing and frequency of tests are not well established.

The ABCCG did not reach consensus on the preferred modality for OFS. A challenge facing Asian clinicians is that GnRHa is not reimbursable by healthcare systems in many countries; consequently, surgical oophorectomy or radioablation are common practices, with oophrectomy preferred for OFS. The ABCCG considered the frequency of GnRHa administration in this setting. GnRHa was used in three recent clinical trials of CDK 4/6 inhibitors that included premenopausal participants; in PALOMA-3 [34] and MONARCH 2 [35], GnRHa was administered at least 28 days before starting study treatment, while GnRHa was initiated concurrently with other study treatments in MONALEESA-7 [32]. Although data from Japan suggest that monthly or 3-monthly GnRHa regimens have similar efficacy and safety profiles [54, 55], these results should be interpreted cautiously, as both studies administered tamoxifen, not aromatase inhibitor, as the endocrine partner, and one only measured estradiol [55]. Nevertheless, ABCCG members contended that 3-monthly injections may enhance adherence to treatment, in terms of reducing both discomfort and out-of-pocket treatment costs.

The ABCCG recognizes that some premenopausal patients may decline OFS as a first-line therapy; therefore, although tamoxifen is considered less effective, it remains an option for such patients (Table 8, Statement 9a). In case of relapse on adjuvant tamoxifen, the ABCCG suggests that other single-agents such as medroxyprogesterone acetate, megace, high-dose fulvestrant [56], or toremifene [57] are feasible options, despite also being less effective (Table 8, Statement 9c). Pertinently, ABCCG members reported that weight gain associated with megace and medroxyprogesterone acetate, which lead western physicians to disfavor them, is a lesser issue in Asian patients.

ABCCG members also regard cytotoxic chemotherapy as an effective option for HR+ advanced breast cancer, especially for patients with endocrine-resistant disease; while cytotoxic chemotherapy is generally considered more toxic than endocrine therapy, agents such as capecitabine are well-tolerated by many patients and effective in maintaining clinical outcomes [58]. Furthermore, patient responses to different treatment modalities vary; some experience severe toxic effects of targeted therapy combined with endocrine therapy, whereas others have minimal adverse reactions to oral cytotoxic agents. Cytotoxic treatments have the additional advantage of generally costing less than targeted agents. The final results of the PEARL study of palbociclib plus exemestane or fulvestrant versus capecitabine are eagerly anticipated, as this is directly comparing the combined CDK4/6 inhibitor plus endocrine therapy versus cytotoxic chemotherapy [59].

Emerging evidence and future directions

The ABCCG consensus meeting concluded with updates on recent therapeutic advances, including mTOR inhibitors [60, 61] and other potential new agents for treating of HR+ breast cancer, specifically PARP inhibitors [39, 62] and PI3K inhibitors [37, 40, 63, 64]. The ABCCG concluded that at present, there are too few data to make specific recommendations about the role of PARP or PIK3 inhibitors; however, as these may later become options for HR+ advanced breast cancer, the ABCCG will follow developments and issue updated consensus statements accordingly.

Summary

Breast cancer in young Asian women has distinctive clinicopathological characteristics; therefore, treatment that differs in some respects to that recommended for postmenopausal women, particularly regarding ovarian suppression, might conduce to optimizing patients' quality of life and outcomes. However, there are remaining unmet needs to better understand and treat breast cancer in premenopausal women, especially in Asia; more comprehensive genomic data are urgently needed. Among major therapeutic advances in the management of HR+/HER2− breast cancer, CDK4/6 inhibitors are becoming established as important weapons in the arsenal for treating advanced disease. Although most clinical trials have involved only postmenopausal patients, PALOMA-3, MONARCH-2, and MONALESSA-7 also enrolled premenopausal and perimenopausal women, and the reported clinical outcomes affirm that, with the use of OFS, effective treatment for postmenopausal HR+/HER2− advanced breast cancer could similarly be applied to premenopausal patients. Notwithstanding recent advances, the potential benefits of alternative chemotherapeutic approaches that are also known to be expedient and effective should not be overlooked. Given the great diversity of patients and clinical settings worldwide, the ABCCG advocates evidence-based yet flexible and individualized use of all potential options to improve outcomes for young women with breast cancer everywhere.

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Compliance with ethical standards

Conflict of interest The authors have all participated as faculty members of Novartis Breast Cancer Advisory Boards, and received personal fees, reimbursement of travel expenses, and/or hospitality for their service in this capacity. However, the ABCCG is a professional association that was constituted and operates independently of Novartis and which sets its own research agenda. The article discusses specific Novartis products within the context of the current breast cancer therapeutic landscape, which the authors strove to review impartially. All views expressed are the authors' own, and do not necessarily represent those of Novartis. The authors declare competing interests. WY reports consultancy/advisory roles and receipt of personal fees for Novartis, Pfizer, AstraZeneca, Eli Lilly, Roche, and Amgen. TU reports receiving personal fees and non-financial support from Novartis KK, and personal fees from Chugai, Eisai, AstraZeneca KK, and Taiho. CHL reports a consultancy/advisory role for Novartis. QL reports a consultancy/advisory role and personal fees for Novartis, and receipt of personal fees from Pfizer, Roche, AstraZeneca, and Eisai. KHL reports consultancy/advisory roles with Novartis, AstraZeneca, Roche, Ono, Eisai, Bayer, and Samsung Bioepis. RL reports a consultancy/advisory role with Novartis. YN reports research funding and a consultancy/advisory role for Roche Diagnostics, and consultancy/advisory roles for Novartis, Pfizer, Taiho, Nippon Kayaku, Eli Lilly, AstraZeneca, Merck Serono, Bayer, Meiji Seika, Chugai, and Eisai. YHP reports research funding and consultancy/advisory roles for Novartis, Pfizer, Eisai, and research funds from AstraZeneca, and Roche. SAI reports research funding from AstraZeneca, research funds and a consultancy/advisory role for Pfizer, and consultancy/advisory roles with Novartis, Hanmi, Roche, Pfizer, Amgen, and Eisai. HL reports research funding and a consultancy/advisory role for Roche Diagnostics, and consultancy/advisory roles with Novartis, Pfizer, Eli Lilly, and AstraZeneca. YSY reports personal fees and a consultancy/advisory role for Novartis, receiving personal fees and non-financial support from Pfizer, AstraZeneca, Lilly, and non-financial support from Eisai, and Roche. YSL reports receiving research funds and personal fees from Novartis, Pfizer, Roche, and Merck Sharp & Dohme, and personal fees from Boehringer Ingelheim.

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