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SPECIAL ARTICLE

ESO–ESMO fifth international consensus guidelines for breast cancer in young women (BCY5)

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We dedicate this manuscript in memory of a dear friend and colleague Bella Kaufman.

The fifth International Consensus Symposium for Breast Cancer in Young Women (BCY5) took place virtually in October 2020, organized by the European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO). Consensus recommendations for the management of breast cancer in young women were updated from BCY4 with incorporation of new evidence to inform the guidelines. Areas of research priorities as well as specificities in different geographic and minority populations were identified. This manuscript summarizes the ESO–ESMO international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

Key words: young women, breast cancer, fertility

INTRODUCTION

Only 4% of new breast cancer cases in the United States in 2019 occurred in women <40 years of age, with an estimated cumulative risk of 1 in 65 by the age of 40 years and 1 in 209 before 30 years of age.[1] In low- and middle-income countries (LMICs), breast cancer before menopause represents a much greater burden both in incidence (55% of total breast cancer cases compared to 25% in high-income countries) and death rates (8.5 and 3.3 deaths/100 000, respectively),[2-4] the highest mortality being reported in Africa (with the exception of southern Africa), Melanesia, the Caribbean and parts of south-central Asia (e.g. Afghanistan, Pakistan and Turkmenistan). Reports of increasing incidence of premenopausal breast cancer in some high-income industrialized countries (France, Italy, New Zealand, Norway)[2,5] may reflect changes in age demographics. In the United States, an increasing incidence of *de novo* metastatic disease has recently been reported in young black women.[6]

Compared with their older counterparts, breast cancers arising in young women are characterized by higher proportion of tumors with aggressive phenotypes[7] and less favorable outcomes irrespective of stage at diagnosis,[8,9] particularly in luminal-A like tumors.[10] Possible explanations for the poorer outcome in luminal-like tumors include different tumor or host biology, less chemotherapy-induced amenorrhea (CIA), suboptimal endocrine treatment and decreased adherence to adjuvant endocrine therapy (ET).

Young women are under-represented in contemporary research evaluating risk-stratification models and molecular tools resulting in young patients at risk of being

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over-treated based solely on age considerations. Prospective trials dedicated to young patients are key to answering many of the outstanding questions to ensure optimal management. Two such examples are the POSH cohort study, conducted at 127 hospitals in the UK,[11] and the Helping Ourselves, Helping Others: The Young Women's Breast Cancer Study (HOHO) conducted in the United States and Europe. These studies and others have demonstrated a greater proportion of luminal B and estrogen receptor-negative (ER−) tumors in young patients, increased risk of early relapse and a more unfavorable longer-term outcome for young women with ER+ tumors when compared to older women.[8,11]

Consistent with previous guidelines,[12-16] the panel defined 'young women' as women under the age of 40 years at breast cancer diagnosis and defined 'advanced breast cancer in young women' as diagnosis of inoperable locally advanced or metastatic disease before the age of 40 years.

Due to the coronavirus disease 2019 (COVID-19) pandemic, the fifth International Consensus Symposium for Breast Cancer in Young Women (BCY5) took place virtually on 10-11 October 2020 with over 1200 participants including health care professionals and patient advocates. The BCY5 guidelines are developed by the European School of Oncology (ESO) and European Society of Medical Oncology (ESMO) and are endorsed by the European Society of Breast Cancer Specialists (EUSOMA). All recommendations are for standard care, outside of clinical trials. All diagnostic and treatment recommendations should be considered in the context of national regulatory approval, availability and reimbursement.

METHODOLOGY

Recommendations from BCY4 formed the basis for the current recommendations; new and updated statements from BCY4 were circulated amongst the panelists before BCY5 and were then presented, discussed, adapted and voted on during the consensus session. All panel members were instructed to vote on all questions; members with potential conflicts of interest or who did not feel comfortable responding (e.g. due to lack of expertise on the topic) were instructed to abstain for that specific question. Substantial controversies or disagreements are noted in the discussion of the recommendations. These recommendations were later circulated to panel members by email for comments, updating based on recent reports and corrections as needed.

Previous recommendations not requiring update or only minor changes were not re-voted and remain part of the recommendations of BCY5.

Tables 1-6 describe the grading system used as per ESMO guidelines methodology (adapted from Dykewicz et al.[17]; see http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology), general guidelines for the management of young women with breast cancer including early and advanced disease, supportive care and follow-up and management of women with germline pathogenic variants (PVs). Statements without grading were considered justified standard clinical practice by the panel experts.

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System with their permission.

Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2022.07.007, presents the definition of menopause following CIA and detailed supportive and follow-up care issues, unchanged or slightly modified since BCY4.

BCY5 consensus panel members and their disclosure of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest are reported.

General considerations when caring for young women with breast cancer

Management of young women with breast cancer is multifaceted and requires specific and dedicated multidisciplinary care (including but not limited to medical and radiation oncologist, gynecologist, pathologist, radiologist, breast and plastic surgeon, nurse specialist, geneticist, physiotherapist, fertility, sexual therapy and psychosocial experts), best provided in dedicated breast centers, whose quality control assurance ensures qualified experience and care.[18] The panel recommended that personalized psychosocial support and counseling on genetic predisposition, fertility, sexual health and socioeconomic consequences be incorporated into individual treatment planning as well as lifelong follow-up care given the improved long-term survival with modern therapies and risks of late side-effects. Specific guidelines for post-treatment survivorship care[19] are available for health care providers.

Table 2. General guidelines

Guidelines	LoE/GoR	Consensus
Overall, the stage-specific outcome of young breast cancer patients has improved over the years due to diagnostic and treatment advances. Nonetheless, even in countries with universal health care, these improvements are significantly lower for women with low socioeconomic status (SES) compared to those with high SES. Every young breast cancer patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient-centered care, irrespective of her social status.	Expert opinion	100%
Many specific issues in the treatment of young women with breast cancer, both in the early and in the advanced settings, still lack definitive proven standards. Therefore, well-designed, independent, prospective randomized trials should be a global research priority.	Expert opinion	
The care of all young patients with breast cancer (either early stage, EBC, or advanced disease, ABC) should be discussed within a multidisciplinary team before any treatment decision making, and ideally provided in specialized breast clinics.	Expert opinion	
Navigators/navigation tools are of great assistance in optimizing patient care. Navigators should ideally be breast nurses but lay-health professionals with strong communication skills and sufficient experience may also address complex care issues and mixed cultural settings.	Expert opinion	
In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health and socioeconomic impact are highly recommended as part of the individual treatment planning.	Expert opinion	
In young women, innovative and structured communication and supportive tools (e.g. online programs, web-based interventions) should be developed and scientifically validated and disseminated in different languages. This would help young patients to overcome barriers to accessing support, such as child and family care, work timetables and distance issues.	Expert opinion	
In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health and socioeconomic impact are highly recommended as part of the individual treatment planning. Patient support groups should be developed and promoted. Open discussion and shared decision making should be promoted in a clear, culturally appropriate manner encouraging patients to be proactive in their cancer care.	Expert opinion	
Young age by itself should not be the reason to prescribe more aggressive therapy than in other age groups. Factors influencing choice of treatment should include but not be limited to the biological characteristics of the tumor [ER/PR, HER2, proliferation markers (e.g. Ki-67), histological grade], tumor stage, genetic status (if available) and patient's comorbidities and preferences.	Expert opinion	
Systematic research into age-specific host-tumor characteristics is needed. In particular, the identification of age-specific molecular, biological, radiomics-based and/or genomic aberrations with prognostic and predictive significance could open the door for tailored therapeutic interventions.	Expert opinion	
National reimbursement policies/algorithms rewarding treatment protocols per number of treatments, dosages, administration route/use of day hospital or planning complexity (in the case of radiation treatment planning) should be discouraged. For example—radiation therapy should not be reimbursed per fraction nor should physicians receive reimbursement for administering intravenous chemotherapy.	Expert opinion	
Risk factors		
Although data about whether obesity is a risk factor for breast cancer in premenopausal women are not conclusive, it can be said with certainty that obesity is a risk factor for a multitude of serious diseases. For the time being, young women should be encouraged to maintain BMI $\leq$25 kg/m^2.	Expert opinion	Y = 96% A = 4%
Pharmaco-prevention with tamoxifen has proven to be effective in reducing breast cancer occurrence in high-risk young women but is underutilized. Pharmaco-prevention indication, schedule and potential adverse events should be discussed with all young women at high risk of developing breast cancer.	IA	Y = 96% A = 4%
There is limited evidence to suggest specific lifestyle approaches (e.g. dietary habits, weight management and physical activity) for ovarian and breast cancer risk reduction among women with a germline *BRCA1/2* mutation compared to the general population. At this time, before obtaining solid data, recommendations about lifestyle behaviors should follow available guidelines for the general population.	Expert opinion	100%
Male breast cancer		
Male breast cancer should be managed in accordance with international recommendations/guidelines.		Expert opinion
Clinical trials should allow for inclusion of male breast cancer patients in both early and advanced settings.		Expert opinion
Transgender (TG) and nonbinary (NB) persons		
Knowledge about the risks of breast/gynecological cancers in TG and NB persons receiving gender-affirming hormone therapy is limited. Even less information exists regarding TG/NB individuals with known genetic predisposition. Cancer registries should include TG/NB identities, and further education and research should be implemented to fill the gap in information and counseling in this population.	Expert opinion	100%

In green, NEW/MODIFIED BCY5 guidelines with consensus voting.
ER, estrogen receptor; GoR, grades of recommendation; HER2, human epidermal growth factor receptor 2; LoE, levels of evidence; PR, progesterone receptor.

Table 3. Assessment and treatment guidelines in early breast cancer

Guidelines	LoE/GoR	Consensus
Screening, diagnosis and imaging for staging and follow-up		
There is no clear role for routine screening by any imaging for early breast cancer detection in healthy, average-risk young women. Additional consideration may be given to ultrasound and breast MRI in young women particularly in the setting of very dense breast tissue or consideration of a genetic predisposition or other higher-risk individuals (i.e. radiation therapy for childhood or young adulthood malignancy).	IA Expert opinion	
Diagnosis, imaging and staging in young women should follow standard algorithms consistent with older women. Additional consideration may be given to ultrasound and breast MRI in young women with very dense breast tissue.	IIC	
Digital breast tomosynthesis (DBT) is more sensitive than digital mammography in dense breasts, is associated with marginal increase in radiation dose and should be the preferred diagnostic tool.	Expert opinion	Y = 80% N = 5% A = 15%
In patients with dense breasts, abbreviated magnetic resonance imaging (AB-MRI) may represent a valid alternative to conventional MRI with the advantages of short examination/interpretation times and low costs.	Expert opinion	Y = 45% N = 15% A = 40%
For *BRCA 1/2* mutation carriers and others at high risk based on family history or predisposing mutations in other genes (e.g. *p53, PALB2, CHEK2, ATM*), and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with MRI and mammography with or without ultrasound is recommended.	IIA	
For *BRCA 1/2* mutation and other cancer susceptibility genes carriers (e.g. *RAD51C, p53, BRIP1*) who have not undergone salpingo-oophorectomy, gynecologic surveillance every 6 months is recommended.	Expert opinion	
Annual whole body MRI and brain MRI should be offered to women harboring germline *p53* pathogenic variants (Li—Fraumeni syndrome) for staging and follow-up. Other diagnostic tools (e.g. FDG—PET—CT) are still under evaluation in Li—Fraumeni patients as well as in patients harboring other germline pathogenic gene variants (e.g. *ATM* carriers) and should not be part of routine staging and follow-up.	Expert opinion Expert opinion	Y = 75% A = 25% Y = 75% A = 25%
Risk-adapted early detection and surveillance tools should be researched in young women.	Expert opinion	
Genetic counseling and testing		
Recent literature suggests that health disparities remain amongst young women from minority or disadvantaged ethnic/racial backgrounds in utilizing and seeking genetic counseling services based on family history of malignancy, before a breast cancer diagnosis. Risk-reducing measures are also underutilized in minority BC patients harboring *BRCA1/2* pathogenic gene variants. Strategies to minimize racial/ethnic and social disparities in early access to genetic testing and risk management should be implemented to optimize preventive interventions	Expert opinion	Y = 96% A = 4%
Every young woman with breast cancer should be offered genetic counseling preferably before starting treatment. Practice should follow national/international guidelines on a country-by-country basis. For those women who are not ready to consider genetic issues at diagnosis, access to genetic counseling should be offered again during follow-up, to address issues of surveillance and risk reduction of additional primary tumors for the patient, and risk issues for relatives.	Expert opinion	
Genetic testing should be performed only after adequate information is provided by an appropriately trained health professional who explains the implications of the results, according to national/international regulations. The patient must be made aware that the presence of a predisposing mutation may have an impact on her management, follow-up and decision making, as well as family members. A fast-track process should be available when the identification of a pathogenic gene variant could change the therapeutic approach (e.g. indication for risk-reducing surgery, platinum derivatives, PARP inhibitors, etc.). Little is known about the clinical/psychosocial factors affecting the communication of genetic test results by young BC patients with parents and siblings, especially in non-Caucasian women. Further research and strategies to improve communication among families are needed and should be developed.	Expert opinion	100%
Genes to be tested for depend on personal and family history. Although *BRCA1/2* are the most frequently mutated genes, other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counselor or if they will impact therapeutic interventions. Development of quality-controlled genetic counseling services is strongly encouraged.	Expert opinion	100%
When a hereditary cancer syndrome is suspected and a mutation in *BRCA1/2* has not been identified, multi-gene panel testing may be considered. Practice should be guided by high quality national/international guidelines. As commercially available multi-gene panels include different panels of genes, the choice of the specific panel and quality-controlled laboratory is crucial.	Expert opinion	
Risk communication and clinical recommendations need to be adapted to the increased complexity and uncertainty of multi-gene testing. Health professionals should also be trained to address the related complex psychological scenarios.	Expert opinion	100%
The clinical utility (including risk assessment, screening and prevention recommendations) of moderate-risk genes identified on multi-gene panel testing is not yet established and this needs to be clearly communicated to patients in both the pre- and post-testing counseling consultations.	Expert opinion	
Multi-gene panel testing (when available) should be proposed when either a hereditary cancer syndrome is suspected and a pathogenic gene variant in *BRCA1/2* has not been identified and/or if the personal/family history can be explained by more than one gene. Practice should be guided by national/international guidelines.	Expert opinion	
As commercially available multi-gene panels include different genes, the choice of the specific panel should be performed in quality-controlled laboratories.	Expert opinion	
For the time being somatic *BRCA1/2* testing should not be used as an alternative or in addition to germline pathogenic gene variant identification. The therapeutic implications of somatic BRCA1/2 mutations in breast tumors need to be further explored within a research setting before they can be used in routine clinical practice.	Expert opinion	
Amongst individuals who do not have an identified low-/moderate-/high-risk germline mutation, polygenic risk score models, evaluating multiple factors for estimating breast cancer risk, are not yet ready for implementation in routine clinical practice.	Expert opinion	Y = 87% A = 13%

Continued

Table 3. Continued

Early breast cancer locoregional treatment		
Surgical treatment of young patients with EBC—while being tailored to the individual patient—should in general not differ from that of older patients.	I	
Breast-conserving surgery should be performed as the first option whenever suitable, as it provides the same overall survival than mastectomy.	IA	
Onco-plastic repair techniques should be discussed with all patients treated by BCS in order to maximize cosmetic results and optimize self-image whenever an obvious post-operative asymmetry can be estimated by a dedicated breast surgical team. Immediate breast reconstruction after mastectomy offers the same survival rates as mastectomy without reconstruction and should be offered to all patients except those with inflammatory breast cancer.	IC	
Immediate breast reconstruction after mastectomy is less frequent in patients with low socioeconomic status (SES) compared to those with high SES, even in countries with universal health care where the influence of reimbursement should be negligible. Immediate breast reconstruction is rarely available in patients from low- and middle-income countries. Every young BC patient should have access to immediate breast reconstruction and oncoplastic surgery if medically appropriate.	Expert opinion	100%
There is no evidence of an increased false-negative rate or a worse outcome in young patients undergoing SNLB, therefore the indications for SNLB are the same as in older patients.	IB	
In young women with the diagnosis of either invasive disease or pre-invasive lesions, who are not high-risk mutation carriers, there is no evidence for improved OS by performing risk-reducing bilateral mastectomy.	IB	
For all surgical decisions and particularly for risk-reducing mastectomy, patients must be given proper, thorough and unbiased information based on the available data, and adequate time to decide. Once an informed decision is made by the patient it should be respected. Additional psychosocial support should be offered given the potentially high anxiety and long-term sequela of patients making these difficult decisions.	Expert opinion	
Decisions about locoregional treatment after neoadjuvant chemotherapy should be made independent of age.	Expert opinion	
Mutation status should be part of the individual decision-making algorithm. Sufficient time to discuss the different options and adequate psychological support should be offered given the potential long-term sequela and implications.	Expert opinion	
Indications for adjuvant RT are the same as for older patients. After breast-conserving surgery, breast radiation + boost are recommended. Young patients should be informed about the high local recurrence risk if RT is avoided after BCS and about the benefit of RT on reduction of local recurrence and improvement in OS. This must be balanced with information about the potential long-term toxicities. Partial breast irradiation (PBI) or accelerated PBI has not been sufficiently studied in young patients and should not be performed in this age group.	IB	
Indications for post-operative RT are independent of *BRCA* status. Limited and inconclusive evidence is available in presence of pathogenic gene variants in other predisposing genes (e.g. CHEK2, ATM): in these patients the risk—benefit ratio needs to be individually discussed. For patients with a germline TP53 mutation, post-operative RT is relatively contraindicated and mastectomy is preferred. In these patients, post-mastectomy RT should be discussed only in cases of significant risk of locoregional recurrence. This underscores the importance of early genetic testing at the time of diagnosis to aid optimal treatment planning.	Expert opinion	Y = 87% A = 13%
Despite the fact that data on the efficacy and safety of hypofractionation are accumulating in premenopausal women, hypofractionation is not widely adopted as standard radiation therapy for young patients in many countries. Hypofractionated WBI schedules should replace standard fractionated WBI as gold standard for most patients irrespective of their age.	IB	Y = 74% A = 26%
Ultra-hypofractionated WBI or for the lymph node regions (such as in FAST-Forward) is not yet standard for young patients.	Expert opinion	Y = 61% N = 4% A = 35%
Indications and extension of nodal irradiation are the same as in other age groups.	IB	
Indications for adjuvant RT are the same as for older patients.	IB	
Data are stronger for benefits of post-mastectomy RT for young women.	IB	
Partial breast irradiation (PBI), or accelerated PBI, has not been sufficiently studied in young patients and should not be performed in this age group.	Expert opinion	
Post-mastectomy radiation therapy (PMRT) to implant-based breast reconstruction may be associated with a higher risk of capsular contracture. When PMRT is foreseen the timing and technique of the procedure should be discussed pre-operatively on an individual basis by all the specialists involved.	Expert opinion	Y = 85% N = 5% A = 10%
Adjuvant systemic treatment		
Endocrine therapy		
All young women should be counseled, before the onset of systemic therapy (either CT or ET), about the risks, associated symptoms and outcomes of treatment-related amenorrhea and premature menopause, referred for special fertility counseling/consultation and informed of available and approved ameliorative therapies.	Expert opinion	
Neoadjuvant ET should not be used in young women outside clinical trials.	Expert opinion	
All patients with HR-positive disease should receive adjuvant ET. Tamoxifen alone for 5 years is indicated for low-risk patients. Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively postmenopausal. Tamoxifen for 10 years should be considered in high-risk patients, if tolerated. The addition of a GnRH agonist (or ovarian ablation) to tamoxifen or an aromatase inhibitor is indicated in patients at higher risk of relapse.	IA IA IA IA IA	
AIs without ovarian function suppression are contraindicated in premenopausal women. The combination of an AI and a GnRH agonist (or oophorectomy) confers a significant absolute benefit in terms of freedom from distant recurrence and should be the preferred option in higher-risk patients.	IA	Y = 90% N = 5% A = 5%

Continued

Table 3. Continued		
Adjuvant systemic treatment		
Endocrine therapy		
Young women with stage I or II breast cancer who cannot take tamoxifen (due to contraindications or severe side-effects) may receive a GnRH agonist alone, oophorectomy or an aromatase inhibitor + GnRH agonist.	IA	
Recommendations for adjuvant GnRH agonist use are based on data from trials with monthly administration. Thus, current guidelines support monthly use to optimize ovarian function suppression, particularly in very young women (<35 years of age) and in those receiving an AI. 3-6 monthly use may be considered on a case-by-case basis with very close monitoring of ovarian function, when monthly use is not feasible or accepted by the patient.	Expert opinion	Y = 90% N = 5% A = 5%
Estradiol levels should be checked if there are concerns ovarian function is not suppressed, especially if a breakthrough bleeding occurs and/or the patient is on an AI; if done, the analysis should preferably be performed in the same laboratory, and when possible in a central reference laboratory. In cases of inadequate suppression alternative strategies should be discussed (oophorectomy or continuation of tamoxifen alone).	Expert opinion	
The method of ovarian suppression (surgical versus medical) requires balancing patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time and cost/availability.	Expert opinion	
Radiation to ovaries as a method of ovarian function suppression should be discouraged.	Expert opinion	Y = 40% N = 30% A = 30%
The addition of a GnRH agonist to tamoxifen can be considered in women at higher risk of relapse resuming ovarian function within 2 years after chemotherapy completion.	IIB	
Adjuvant CDK4/6 inhibitors		
Early data suggest that adjuvant abemaciclib combined with ET may be beneficial in patients with high-risk ER+ disease (3.5% absolute risk reduction in invasive disease-free survival), however follow-up time is short. 43% of patients were premenopausal with similar magnitude of benefit observed irrespective of menopausal status. High-risk features were defined in the clinical trial as ≥4 LN or 1-3 involved LN with other high-risk features (tumor size ≥ 5 cm, grade 3, Ki67 ≥20%). Abemaciclib could be considered for use in the described high-risk groups, when approved.	IB	Y = 61% N = 13% A = 26%
Chemotherapy		
Many factors, including patient and tumor characteristics and genomic signatures, should be considered when deciding whether to administer adjuvant chemotherapy in young women with HR+ early BC. Most young women enrolled in these studies were not treated with modern, risk-adapted ET. Available data in premenopausal women support the role for gene expression tests in predicting additional benefit of chemotherapy over ET alone but further data are needed in order to guide clinical practice and to determine whether the observed benefits are from the cytotoxic therapy or the chemotherapy-induced OFS.	IB	Y = 91% A = 9%
Commercially available prognostic genomic assays in HR+ early breast cancer have not been developed to predict which endocrine therapy is more appropriate according to genomic risk. Therefore, they should not be used at this time for selecting type or duration of endocrine therapy.	Expert opinion	
Available data suggest that a discussion of omitting adjuvant chemotherapy in very young women (≤35 years of age at diagnosis) with low-risk ER+ disease is appropriate in highly selected cases with favorable clinical and pathological features including low gene expression profiles where available.	Expert opinion	
The indications for and the choice of adjuvant systemic treatment for invasive breast cancer should be driven, as for women in other age categories, by extent of disease and the biological characteristics of the tumor (including, but not limited to, ER/PR and HER2 receptors, proliferation and grade) and patient's comorbidities.	IA	
For the time being, the type of systemic treatment of EBC is independent of *BRCA* or any other constitutional genetic status.	Expert opinion	
The optimal (neo)adjuvant CT regimen specifically for young women in terms of efficacy and long-term toxicity is currently unknown. As for all stage I-III breast cancer patients, the preferred regimens are standard anthracycline, alkylating and taxane-based regimens. The indication for dose-dense chemotherapy is independent of age.	IA	
Young age by itself should not be an indication to prescribe a more intense combination of cytotoxic agents. Standard duration of chemotherapy (minimum of 4 and maximum of 8 cycles) should be prescribed. Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated. The indication for dose-dense chemotherapy is independent of age.	IA	
In patients with TNBC or *BRCA*-associated tumors the incorporation of platinum agents increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated. Data on the impact of incremental increases in pCR on long-term outcome are not conclusive. The use of platinum derivatives has potential additional impact on fertility and increased toxicity that may compromise standard duration and dosing of systemic treatment, and this needs to be clearly communicated to patients.	IB	
For patients with TNBC not achieving a pCR after standard neoadjuvant regimens, the routine addition of adjuvant chemotherapy with 6-8 cycles of capecitabine may be considered	IA	
There are no data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended.	IA	
In patients with TNBC with indications for pre-operative chemotherapy, the addition of pembrolizumab (with the chemotherapy and for completion of 1 year following surgery) can be considered in selected young patients with high-risk disease, where approved, after careful consideration and discussion with the patient about the possibility of long-term side-effects.	IA	Y = 90% N = 10%

Continued

Table 3. Continued

Adjuvant PARP inhibitors		
Early data suggests that 1 year of adjuvant olaparib following the completion of (neo)adjuvant chemotherapy provides significant benefit in disease-free survival amongst women harboring a germline *BRCA1/2* mutation who have high-risk early breast cancer. High-risk features were defined in the clinical trial as stage 2-3, HER2 negative-TNBC: pT2Nx or pTxN1-3 or residual disease after NAST; HR+:pTxN2-3 or significant residual disease after NAST. It may also reduce the risk of further primary malignancies. Olaparib, once approved, should be offered to germline *BRCA1/2* mutation carriers that meet the inclusion criteria for the OLYMPIA trial and modifications which may be approved by the regulatory bodies.	IA	Y = 91% A = 9%
Anti-HER2 therapy		
One year treatment with adjuvant trastuzumab, together with chemotherapy, is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumor size >0.5 cm), who have a left ventricular ejection fraction within normal limits and without significant cardiovascular risk factors, irrespective of age.	IA	
In highly selected patients with small, node-negative, HER2+ breast cancer, the administration of 12 weeks of weekly paclitaxel and trastuzumab without anthracyclines can be considered The incorporation of neoadjuvant/adjuvant pertuzumab should be in keeping with current standards, as for older patients, in women with high-risk HER2+ breast cancer.	IIB IA	
In case of pathological residual disease (non-pCR) after pre-operative chemotherapy plus anti-HER2 therapy the patient should be offered to complete 1 year of adjuvant anti-HER2 therapy with TDM-1.	IA	Y = 85% N = 5% A = 10%
In HER2+ patients at high risk of relapse (e.g. N+) 1 year adjuvant pertuzumab + trastuzumab can be discussed, as in other age groups. Limited data are available on the efficacy of such treatment in women who received pertuzumab + trastuzumab as part of their pre-operative systemic therapy.	IC	Y = 90% N = 5% A = 5%
In HER2+/HR+ patients at high risk of relapse (e.g. significant nodal involvement), 1 year of treatment with neratinib after trastuzumab can be discussed, as in other age groups. There is no data about the efficacy of neratinib after 1 year of adjuvant trastuzumab AND pertuzumab or after adjuvant TDM1.	IC	Y = 80% A = 20%
General considerations in the adjuvant setting		
In view of the long potential life expectancy, particular attention should be paid to possible long-term toxicities of adjuvant treatments (e.g. secondary cancers, cardiovascular toxicity, irreversible ovarian failure, weight gain, cognitive function, bone health). Clinics dedicated to the assessment and management of early and late treatment side-effects and adherence to treatment and follow-up guidelines should be developed.	Expert opinion	
The management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.	Expert opinion	
Data are accumulating about disease-free survival improvement with adjuvant bisphosphonates among premenopausal women under OFS. Zoledronic acid q6 months may be discussed in young women receiving OFS. Optimal duration of treatment is uncertain, and risks and benefits should be considered on a case-by-case basis.	IA	Y = 57% N = 17% A = 26%

In green, NEW/MODIFIED BCY5 guidelines with consensus voting.
A, abstain; AIs, aromatase inhibitors; BC, breast cancer; BCS, breast-conserving surgery; CT, computed tomography; EBC, early breast cancer; ER, estrogen receptor; FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; GnRH, gonadotropin-releasing hormone; GoR, grades of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LoE, levels of evidence; MRI, magnetic resonance imaging; N, no; OFS, ovarian function suppression; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; PET, positron emission tomography; RT, radiation therapy; SNLB, sentinel lymph node biopsy; TDM-1, trastuzumab-emtansine; TNBC, triple-negative breast cancer; WBI, whole breast irradiation; Y, yes.

The National Comprehensive Cancer Network (NCCN) in Oncology and the Breast Health Global Initiative developed resource-stratified and harmonized guidelines/recommendations[20,21] and strategies to address the poor outcomes in LMICs for young women with breast cancer.[22] Prospective cohort studies are collecting data on young patients' concerns, in particular about fertility preservation,[23,24] selection of ovarian function preservation strategies[23] and psychosocial and quality-of-life (QoL) issues after diagnosis.[25]

Young women with a lower socioeconomic status (SES) have worse outcomes compared to those with a higher SES,[26] even in countries with universal health care[27,28] thought to be due to a higher frequency of comorbidities and limited access to health services. In some studies, differences persist after adjusting for all these factors. In particular, a large Norwegian report in premenopausal women (7501 patients aged 30-48 years at diagnosis) showed that 5-year relative survival improved steadily for patients with high SES (by 9% and 36%, for regional and distant disease, respectively), but remained unchanged for patients with low SES.[27] The BCY5 panel strongly and unanimously stated that every young breast cancer patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient-centered care, irrespective of her social status.

Panel members re-emphasized that national reimbursement policies/algorithms rewarding treatment protocols per number of treatments, dosages, administration route/use of day hospital or planning complexity (in the case of radiation treatment) should be discouraged. For example, radiation therapy (RT) should not be reimbursed per fraction, nor should physicians receive higher reimbursement for administering intravenous agents compared to oral chemotherapy or ET. To this end, the panel endorses the 12th European Breast Cancer Conference Manifesto.[29]

A significant proportion of young patients experience work- and insurance-related challenges in the first 2 years after diagnosis,[30-33] but little is known about the impact of late effects of cancer treatment (e.g. fatigue and arm morbidity) on

Table 4. Assessment and treatment general guidelines in advanced breast cancer

Guidelines	LoE/GoR	Consensus
In ABC, age alone is not a reason to prescribe more aggressive therapy and International Consensus Guidelines for management of advanced breast cancer must be applied (ABC guidelines, NCCN guidelines, evidence-based national guidelines). Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.	Expert opinion IC	
The BCY5 panel endorses the ESO–ESMO ABC5 guidelines for the management of ABC in premenopausal women.	IA	100%
Clinical and pathologic characteristics predicting for CNS recurrence often overlap with factors that indicate increased risk for general metastatic dissemination (i.e. young age, ER- and PR-negativity, HER2 overexpression, high proliferation and genomic instability). Although young age has been associated with an increased risk of CNS metastases, surveillance and therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.	IC	
Preliminary data suggest BC patients harboring *BRCA* mutations present a higher incidence of CNS involvement and a worse outcome compared to non-carriers, irrespective of BC subtype. No data on the efficacy of PARPi on CNS involvement are available as none of the phase III PARP trials included patients with active CNS metastases. In subgroup analyses, talazoparib benefit persisted in patients who had stable/treated brain metastases on study entry. Inclusion of patients with active CNS metastases should be encouraged in all studies investigating new therapies (unless medically contraindicated)	Expert opinion	Y = 87% N = 4% A = 9%
Many trials in HR+ ABC have not included premenopausal women. Despite this, we recommend that young women with ER+ ABC have adequate ovarian suppression or ablation and then be treated in the same way as postmenopausal women with endocrine agents ± targeted therapies. Future trials exploring new endocrine/endocrine-biological strategies should be designed to allow for enrollment of both pre- and postmenopausal women and men.	IA	
Platinum agents have been demonstrated to be superior to taxanes in BRCA-associated advanced breast cancer.	IB	
The BCY5 panel endorses all the ABC5 ESMO–ESO statements on PARPi for patients with a germline *BRCA* mutation. Platinum and PARP inhibitors have not been compared in the advance setting and preferential use of either or optimal sequencing of these treatments is unknown	IA	Y = 83% N = 0 A = 17%
Phase II data suggest a benefit for PARPi in patients with ABC harboring somatic *BRCA1/2* mutations or a germline *PALB2* mutation. Somatic *BRCA1/2* mutations and germline *PALB2* mutations are not common; however, tailoring of treatment based on these alterations may be considered with caution on a case-by-case basis. This data underscores the importance of molecular tumor boards and of pooling of data in international registries.	IIB Expert opinion	Y = 87% N = 0 A = 13%
Very little is known about psychosocial challenges and dying concerns in young parents with ABC. Most of the data refer to Caucasian, upper-, middle-class women within nuclear families. In general, patients express concerns for their children and their co-parent, and personal concerns which impact their QoL contribute to the emotional and psychological distress, and increase family dysfunction. Further research in this setting is needed on patients from diverse backgrounds, non-nuclear families, on the co-parent, parents and caregivers.	Expert opinion	100%

In green, NEW/MODIFIED BCY5 guidelines with consensus voting.

A, abstain; BC, breast cancer; BCY5, fifth International Consensus Symposium for Breast Cancer in Young Women; CNS, central nervous system; ESMO, European Society of Medical Oncology; ESO, European School of Oncology; GoR, grades of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LoE, levels of evidence; N, no; NCCN, National Comprehensive Cancer Network; PARPi, poly (ADP-ribose) polymerase inhibitors; QoL, quality of life; Y, yes.

long-term work ability.[34] Given the length of working years ahead for these women, the BCY5 panel firmly stated that awareness and referral to appropriate resources should be available and further research in this setting is needed.

Panel members re-emphasized that many specific issues in the treatment of young women with breast cancer, in all settings of the disease, still lack evidence-based standards and that systematic research into age-specific tumor characteristics is needed which could open the door for more tailored therapeutic interventions.

Risk factors

Lifestyle-associated risk factors should be discussed with young women as part of public health initiatives.[35] Data are inconclusive on whether or not obesity is a risk factor for breast cancer in premenopausal women and increasing body mass index (BMI) seems inversely correlated with breast cancer risk in young women.[36] Increases in the waist-to-hip ratio, which measures central adiposity, are associated with increased risk of premenopausal breast cancer. As obesity is associated with increased risk of many serious health issues, the BCY5 panel stated that health care professionals should inform young women about breast health and other modifiable breast cancer risk factors in general (e.g. maintaining a BMI $\leq$25 kg/m^2, as well as limiting alcohol consumption, smoking and physical inactivity).[35]

Diagnostic imaging for screening, staging and follow-up

1. **Screening**: There is no indication for routine screening by any imaging technique in healthy, average-risk young women. Surveillance in high-risk women, based on family history or pathogenic gene variants in predisposing genes, and for those at increased risk because of a personal history of therapeutic radiation in childhood or young adulthood,[37] should follow available guidelines.
2. **Staging and follow-up**: The panel reinforced the recommendation that imaging and staging in young women including axillary assessment should in principle follow standard algorithms as for older women.

Breast ultrasound remains the first diagnostic approach for clinical abnormalities in this age group and in pregnant/

Table 5. Additional considerations in women with hereditary-associated breast cancer

Guidelines	LoE/GoR	Consensus
For survivors harboring a *BRCA 1/2* or (other) strongly predisposing mutation, bilateral risk-reducing mastectomy may be considered, although there is no definite evidence that it leads to a survival benefit. Therapeutic decisions should reflect a balance between the risk of recurrence of the diagnosed breast cancer and the potential benefit of preventing an additional primary tumor.	IIB	
For the time being, the radiotherapy treatment of EBC is independent of *BRCA* or any other constitutional genetic status, with the exception of germline *TP53* and *ATM* mutations, for which a very high risk of secondary cancers has been described after radiation therapy. Radiation therapy should be carefully discussed on an individual basis for these patients.	IB IIC	
In the absence of evidence-based recommendations for risk-reducing surgery in patients harboring pathogenic variants in low—moderate-penetrance genes, decisions must be taken individually, mainly based on family history. For breast cancer survivors and asymptomatic carriers harboring a *BRCA 1/2* mutation, risk-reducing salpingo-oophorectomy (RRSO) should be discussed from the age of 35 years provided that the woman has completed family planning. For *BRCA1* mutation carriers RRSO is recommended between age 35 and 40 years and for BRCA2 mutation carriers around age 40 years, always respecting patient's preferences and considering the family history. Indications and timing of risk-reducing salpingo-oophorectomy for other highly penetrant mutations should follow available international/national guidelines.	Expert opinion	
Salpingectomy with delayed oophorectomy remains investigational and should preferably be carried out only within a clinical trial.	Expert opinion	Y = 85% N = 10% A = 5%
Currently, the evidence on the reduction of BC risk and mortality by oophorectomy is conflicting and likely limited to *BRCA1* carriers.	Expert opinion	Y = 53% N = 17% A = 30%

In green, NEW/MODIFIED BCY5 guidelines with consensus voting.
A, abstain; BC, breast cancer; EBC, early breast cancer; GoR, grades of recommendation; LoE, levels of evidence; N, no; y, yes.

lactating women.[38] Given the data on diagnostic superiority of digital breast tomosynthesis (DBT) over digital mammography in young women and in those with dense breasts,[39] with only marginal increase in radiation dose, a majority of the BCY5 panel stated that DBT is the preferred diagnostic tool.

Pre-operative magnetic resonance imaging (MRI) is associated with increased rates of ipsilateral mastectomy and contralateral prophylactic mastectomy in newly diagnosed breast cancer patients, irrespective of age[40]: its indications should strictly follow available recommendations.[41] MRI is generally superior to other clinical and imaging assessments after pre-operative chemotherapy.[42] The optimal timing for carrying out mammography and MRI is the first half of the menstrual cycle (days 7-14).[43] Recent data show that abbreviated MRI (AB-MRI), i.e. the acquisition of only two sequences, before and immediately after the administration of gadolinium, has equivalent performances to standard MRI protocols in diagnostic clinical settings.[44] Although validation with prospective multicenter trials is pending, almost half of the BCY5 panelists agreed that AB-MRI may represent a valid alternative to conventional MRI for persons with dense breasts with the advantages of short examination/interpretation times and low costs.

The panel re-confirmed that in average-risk patients, imaging surveillance after primary breast cancer treatment should follow the same guidelines as in older women.

Genetic counseling and testing

The panel confirmed that genetic counseling should be offered to every young woman, irrespective of tumor subtype [e.g. triple-negative (TN) disease] or family history of breast cancer as studies have reported that if testing is carried out based on traditional testing guidelines (largely guided by personal and family history of malignancy), close to 50% of persons with a germline mutation would not be identified.[45] A fast-track process, which enables testing before commencement of therapy, should be available when the identification of a pathogenic gene variant could change the therapeutic approach [e.g. indication for risk-reducing surgery, platinum derivatives, poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi)]. Although *BRCA1/2* genes are the most frequently mutated genes, testing for other additional moderate- to high-penetrance genes using a multi-gene panel may be considered, if they will impact therapeutic interventions. In a recent study, genes most commonly associated with breast cancer in woman aged $\leq$45 years were *BRCA, BRCA2, ATM, CHEK2* and *PALB2*[46] due to prevalence and impact. The clinical utility (including risk assessment, screening and prevention recommendations) of moderate-risk genes identified on multi-gene panel testing and polygenic risk score models are not yet established or ready for clinical practice.

Multidisciplinary management of mutation carriers and high-risk individuals should ideally be provided in dedicated high-risk clinics, when available. Clinical trials focusing on risk reduction and optimal screening strategies for this group of women are strongly needed. Unaffected carriers should be encouraged to participate in clinical trials evaluating risk-reducing strategies such as the BRCA-P study evaluating denosumab in women harboring a PV in *BRCA1* who have not undergone risk-reducing mastectomy (NCT04711109). With the recent shift to 'oncologist-led mainstream' testing where the surgeon or oncologist refers for testing, and counseling and interpretation are provided following test results,[47,48] education and training of the involved health care professionals is needed to provide optimal risk communication and clinical recommendations.

For women who are not ready to consider genetic testing at the time of diagnosis, access to genetic counseling should

Table 6. Supportive and follow-up care guidelines

Guidelines	LoE/GoR	Consensus
Young women with breast cancer face specific physical, psychosocial and sexual issues that should be addressed by a multidisciplinary group of providers including breast medical, surgical and radiation oncologists, breast care nurses, social workers, psycho-oncologists, gynecologists and fertility experts, among others.	Expert opinion	
Young women with breast cancer are at higher risk for psychosocial distress. Patients' distress and psychosocial needs should be regularly assessed. Psychosocial care should be available and integrated in routine cancer treatments and follow-up. Partners and family members should be involved early on and couple-based psychosocial interventions should be promptly proposed if needed.	IIB	
The specific psychosocial distress pertaining to body image, sexuality and sexual dysfunction resulting from premature menopause, treatment-related amenorrhea, weight gain, hair loss and breast surgery should be routinely addressed by the health care team in order to ensure provision of appropriate information and support. This needs to be carried out in a culturally appropriate manner.	Expert opinion	100%
All young women should be counseled regarding the risk of getting pregnant while on chemotherapy, endocrine or anti-HER2 therapy, despite developing amenorrhea, and of the need for adequate non-hormonal contraception if they are sexually active and could become pregnant. Exogenous hormonal contraception is generally contraindicated in young cancer survivors, irrespective of disease subtype, and alternative strategies should be considered.	IB Expert opinion	
All young women (irrespective of stage of disease) should be informed about approved fertility preservation options and referred for specialist counseling/consultation if interested in fertility preservation before commencement of any therapy. Women should be informed that currently available methods of fertility preservation generally allow for timely start of chemotherapy schedules. The BCY5 panel endorses the ABC guidelines statement that the impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).	Expert opinion	Y = 96% A = 4%
Physicians' knowledge and familiarity with the available international guidelines on fertility preservation, pregnancy after BC and management of BC during pregnancy should be increased in order to facilitate and improve evidence-based individualized management of young patients with BC.	Expert opinion	Y = 96% A = 4%
The use of GnRH analog concomitant with (neo)adjuvant CT should be offered to reduce the risk of premature ovarian failure, possibly preserve ovarian function and reduce damage to fertility. Concomitant GnRHa use during chemotherapy does not replace established fertility preservation methods, which should still be offered to all young patients. The effectiveness of GnRHa does not seem to depend on the time of administration in relation to commencement of chemotherapy.	IB	Y = 70% N = 20% A = 10%
Biomarkers such as AMH levels may predict ovarian function after chemotherapy though data are limited.	Expert opinion	Y = 85% A = 15%
All young women should be counseled about the risks and associated symptoms and outcomes and management of treatment-related amenorrhea and premature menopause before the onset of systemic therapy (either CT or ET) and informed of available ameliorative therapies.	Expert opinion	
Premature menopause and/or treatment-related amenorrhea increase the risk of bone thinning and patients should be counseled, monitored and treated accordingly.	IA	
Pregnancy after breast cancer should not be discouraged even in patients with HR-positive disease or those harboring a germline BRCA mutations. While pregnancy itself does not appear to increase the risk of recurrence the discussion about pregnancy should take into account the patient's prognosis based on initial stage and biology. Pending results of prospective clinical trials, patients with HR+ disease who are unwilling to wait till the end of adjuvant ET should complete at least 18-24 months of ET before attempting pregnancy. Treatment should be resumed and completed according to initial planning after delivery and breast-feeding.	IIA Expert opinion	Y = 95% A = 5% Y = 95% A = 5%
There are limited data on breast-feeding after BC. Lactation can be carried out from the unaffected breast and data suggest that lactation from the previously affected breast may sometimes be feasible, depending on the type of surgery and radiation. Women should be counseled at the time of receipt of radiation therapy that they most likely will not be able to breast-feed from the irradiated breast. Young BC survivors who pursue a pregnancy and are interested in breast-feeding should have access to lactation counseling by trained health professionals.	Expert opinion	Y = 96% A = 4%
Breast cancer during pregnancy		
Treatment of patients with breast cancer during pregnancy should be decided on an individual basis according to international guidelines within an expert multidisciplinary team, expanded to include obstetricians and perinatologists, and according to patients' preferences. Whenever possible, women with a diagnosis of pregnancy during breast cancer should be managed by a multidisciplinary teams with expertise in this field.	Expert opinion	Y = 91% N = 4% A = 5%
Pregnancy termination has not been shown to improve patient prognosis and should not be promoted for such reason.	IVA	100%
In principle, standard chemotherapy can be offered to most patients, based on the gestational age, tumor stage and biology.	IIB	100%
Exposure to ET, bone-modifying agents and anti-HER2 therapies should be avoided during pregnancy. If treatment cannot be delayed until delivery (e.g. in case of ABC), treatment choices should be carefully discussed with the patient to ensure maternal benefit and reduce fetal risk.	IIB	Y = 91% A = 9%
Patients diagnosed in the few years after pregnancy have worse prognosis. Further research is warranted to better understand their biology and define treatment strategies accordingly.	Expert opinion	Y = 85% A = 15%

Continued

Table 6. Continued

Other issues		
Young patients should be strongly encouraged to adopt the following healthy lifestyle changes: maintain BMI ≤25 perform regular aerobic exercise not to smoke to limit daily alcohol intake	Expert opinion	
Young BC survivors experience significant job- and insurance-related issues, and potential financial toxicity following diagnosis.	Expert opinion	Y = 96% A = 4%
Awareness and referral to appropriate resources should be available for all young patients.		Y = 96%
Further research in this setting is needed in order to plan targeted interventions and avoid unnecessary difficulties.	Expert opinion	A = 4%
Many young BC patients use integrative medicine (complementary and alternative therapies). Health professionals should proactively promote open communication about integrative medicine with their young BC patients.	Expert opinion	Y = 91% N = 9%
To ensure patient safety and quality of treatments, when possible, supervised and established integrative medicine services should be provided within the oncology service at the treating institution.	Expert opinion	Y = 78% A = 17% N = 5%

In green, NEW/MODIFIED BCY5 guidelines with consensus voting.
A, abstain; ABC, advanced breast cancer; AMH, anti-Müllerian hormone; BC, breast cancer; BCY5, fifth International Consensus Symposium for Breast Cancer in Young Women; BMI, body mass index; CT, computed tomography; ET, endocrine therapy; GnRHa, gonadotropin-releasing hormone agonist; GoR, grades of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LoE, levels of evidence; N, no; Y, yes.

be offered on an ongoing basis, and women with previous limited testing should be considered for a more comprehensive contemporary panel in survivorship. Strategies to minimize recently documented racial/ethnic and social disparities in early access to genetic testing and risk management should be implemented to optimize risk-reducing interventions.[49] Research is needed to assess the psychosocial factors affecting the communication of genetic test results by young breast cancer patients with parents and siblings, especially in non-Caucasian women.

Screening for other malignancies and risk-reducing surgery recommendations for women harboring a pathogenic gene variant

In patients harboring a pathogenic germline variant in *TP*53 (Li—Fraumeni syndrome, LFS), the use of ionizing radiation should be discouraged to avoid increasing the risk of secondary radio-induced malignancies.[50] Annual brain and whole body MRI (WB-MRI) is recommended as contrast-free WB-MRI has shown to be effective for cancer detection in asymptomatic carriers and during follow-up in breast cancer patients.[51,52] [^{18}F] 2-fluoro-2-deoxy-D-glucose—positron emission tomography—computed tomography (FDG—PET—CT) scan has also been proven to be effective in cancer screening of patients with LFS, but the availability of safer modalities (e.g. contrast-free WB-MRI) has limited its incorporation in surveillance protocols.[53]

For those with a *BRCA1/2* mutation and other breast cancer-associated susceptibility genes, timing of risk-reducing salpingo-oophorectomy (RRSO) and gynecologic surveillance should follow international guidelines. Ongoing trials will possibly help clarify the role for salpingectomy with delayed oophorectomy in women wishing to delay RRSO and early onset of menopause (ClinicalTrials.gov Identifier: NCT02321228, NCT01907789, NCT01608074). For now salpingectomy with delayed oophorectomy remains investigational.

Transgender and nonbinary persons

Knowledge about the risks of breast/gynecological cancers in transgender (TG) and nonbinary (NB) persons receiving gender-affirming hormone therapy is limited.[54] Even less information exists regarding TG/NB individuals with known genetic predisposition. Cancer registries should include TG/NB identities, and further education and research is needed to fill the gap in information and counseling in this population.

EARLY BREAST CANCER

Locoregional treatment

Surgery. Although young age remains an independent risk factor for increased locoregional recurrence, irrespective of the type of surgery carried out, especially in patients with human epidermal growth factor receptor 2-positive (HER2+) and TN disease, a decreasing trend in locoregional recurrence is reported across continents. The panel remains concerned about the expanding international trend for bilateral mastectomies, particularly in younger women[55] despite no improvement in long-term survival.[56] Communication strategies to optimize decision making for surgical treatment of breast cancer should be implemented to encourage appropriate breast-conserving surgery (BCS). Decision aid tools focused on the needs of young, average-risk breast cancer patients are being developed and evaluated and should become a research priority.[57]

Oncoplastic surgical techniques should be discussed with all patients scheduled for BCS if post-operative asymmetry is anticipated and should always be carried out by a dedicated breast surgical team. When mastectomy is indicated, skin- and nipple-sparing techniques with immediate breast reconstruction (IBR) can provide oncological control while also addressing cosmetic needs.[58] IBR (irrespective of technique) following mastectomy offers the same survival outcome rates as mastectomy without reconstruction[59] and should be offered to all patients except those with inflammatory breast cancer for whom delayed reconstruction is recommended (given the need for extensive radiation and the recommendation to wait until the highest relapse risk passes) and those with locally advanced disease at presentation with poor response to primary systemic therapy. The increasing use of pre-operative therapy for stage 2-3

disease particularly in the more aggressive subtypes has reduced past concerns that wound healing complications from IBR will delay any necessary systemic therapy. Higher SES is associated with higher IBR rates among both young and older women, including in countries with universal health care.[60,61] IBR is rarely available for patients from LMICs.[62] The BCY5 panel unanimously stated that every young breast cancer patient should have access to IBR and oncoplastic surgery if medically appropriate.

The panel confirmed that the indications for sentinel lymph node biopsy and surgical management of patients with sentinel lymph node involvement should be the same as in older patients and that, despite the fact that optimal locoregional treatment after pre-operative chemotherapy remains controversial, decisions should be made irrespective of age.

Germline mutation status should be part of the individual decision-making algorithm when young women are making breast surgery choices. In the absence of evidence-based recommendations for risk-reducing surgery in patients with PVs in low—moderate-penetrance genes, decisions must be tailored to the individual, guided by family history and patient preference.

Radiation therapy. Indications for post-operative RT are the same as for older patients[63]; however, data are more robust for benefits of post-mastectomy radiation therapy (PMRT) amongst young women. PMRT after implant-based breast reconstruction is associated with higher risk of reconstructive failure (>15%) and capsular contracture (>30%). Rates of capsular contracture are lower with PMRT with tissue expanders, but reconstructive failure is more common.[64] These complications may translate into poor aesthetic outcomes, decreased satisfaction and lower QoL. Given the lack of definitive evidence for optimal reconstructive algorithms and techniques (implant-based or autologous tissue reconstructions), shared decision making with the patient and optimal integration of plastic surgery and radiation oncology are crucial.[65] When PMRT is foreseen, the panel recommended that timing and technique of the reconstructive procedure should be discussed pre-operatively on an individual basis by all the specialists involved. PMRT is not a stand-alone reason to postpone reconstruction.

Indications and extent of nodal irradiation are the same as in other age groups.[63] Modern techniques to minimize long-term side-effects are necessitated. The use of respiratory control is the most common approach to reduce the dose to heart and lungs, offering a more favorable irradiation geometry by inflating the lungs and increasing the distance between the heart and the chest wall.[66] A boost to the site of the radical local excision in case of BCS remains standard pending the results of modern randomized trials (e.g. the Young Boost Phase III trial—NCT00212121).

The BCY5 panel affirmed that moderately hypofractionated whole breast irradiation (WBI) schedules should replace standard fractionated WBI as gold standard for most patients. Ultra-hypofractionated schedules were either not tested in premenopausal women, such as in the FAST trial (once-weekly five fractions),[67] or not mature yet for long-term adverse effects as in the FAST-Forward Trial (five fractions in 1 week with 15% of premenopausal patients enrolled).[68] The BCY5 panel therefore recommended against ultra-hypofractionated WBI or for irradiation of the lymph node regions (such as in FAST-Forward) for young patients.

As partial breast irradiation (PBI), or accelerated PBI, has not been sufficiently studied in young patients,[63] the panel recommended against its use outside of clinical trials.

Indications of post-operative RT are independent of BRCA status. Prophylactic radiation to the unaffected contralateral breast in BRCA carriers who decline contralateral mastectomy should not be carried out outside of clinical trials.[69] Although a recent study demonstrated fewer ipsilateral breast recurrences amongst BRCA1/2 carriers who had undergone PMRT compared to those without PMRT,[70] further data are needed. There is limited evidence about the safety of radiation for those harboring a moderate-penetrance pathogenic gene variant (e.g. CHEK2, ATM)[71] and the risk—benefit ratio needs to be individually discussed, but there is no clear contraindication to RT. PMRT may be discussed in cases of significant risk of locoregional recurrence in patients with a germline *TP53* mutation, for whom radiotherapy is otherwise contraindicated to the high risk of secondary malignancies. These recommendations underscore the importance of early genetic testing at the time of diagnosis to aid optimal treatment planning.

Adjuvant systemic treatment

Adjuvant systemic treatment decisions for invasive breast cancer should be based on the extent of disease and biological characteristics of the tumor (including, but not limited to, tumor size, nodal status, hormone receptor and HER2 overexpression/amplification, Ki67, proliferation and grade), patient's comorbidities and preferences similar to as in older women.

Gene expression signatures

Although gene expression signatures, such as Oncotype Dx, MammaPrint, Prosigna, Endopredict and Breast Cancer Index, provide additional information on an individual's recurrence risk and some signatures have demonstrated clinical utility for adjuvant chemotherapy decision making,[72-74] women younger than 40 are grossly underrepresented in both retrospective and prospective studies. Additionally, most of the premenopausal patients in these studies did not receive contemporary risk-adapted ET.

In TAILORx, patients with a low-risk recurrence score (RS), defined as RS 0-10 (30% of whom were premenopausal but only 4% aged <40 years), had a 5-year distant recurrence-free survival of 99%[72] with ET alone. For those with an intermediate-risk RS (RS 11-25), the 9-year distant recurrence-free survival was 94.5% for the ET-only group and 95% for those who received chemotherapy and ET.[73] Exploratory, unplanned subgroup analyses of women aged ≤50 years suggested a benefit from chemotherapy amongst those with an intermediate RS within the range of 16-25[73] and further analyses suggested that clinical risk level

combined with RS identified women aged ≤50 years to be more likely to benefit from the addition of chemotherapy to ET alone.[75] Only 13% of premenopausal women received ovarian function suppression (OFS).

The RxPONDER trial randomized patients with low—intermediate-risk RS (0-25) with 1-3 lymph nodes to either ET alone or chemotherapy plus ET: 33% of participants were premenopausal, 2.9% were <40 years of age and 21.5% were aged 40-49 years. While no benefit was demonstrated in the postmenopausal population with the addition of chemotherapy, in the premenopausal women an absolute benefit of 5.2% favoring chemotherapy was demonstrated both for low and intermediate RS, with an invasive disease-free survival (iDFS) of 94.2% versus 89% [hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.38-0.76].[76] In the ET-only arm, 16% received OFS compared to only 3% in the chemotherapy arm.

In the WGS ADAPT ER+/HER2− study, all patients with 0-3 involved lymph nodes and a low RS of 0-11 received ET alone [mostly tamoxifen in pre- and aromatase inhibitor (AI) in postmenopausal patients]. Those with intermediate RS (12-25) were given 3 weeks of ET before surgery. Patients with a Ki67 ≤10% in the surgical specimen were considered endocrine responders and received ET alone (of whom 23.3% were aged ≤50 years), while those with a Ki67 >10% were classified as endocrine non-responsive and received chemotherapy in addition to ET (of whom 64.7% were aged ≤50 years). Amongst endocrine responders with an RS of 12-25 and limited nodal burden (up to two nodes), despite no data in women <40 years of age, there was no difference in outcome between the low and intermediate RS groups, with a 5-year distant DFS (DDFS) of 96.8% and 97.4%, respectively, in patients aged ≤50 years. Outcome was also similar to that of patients aged >50 years with 0-3 nodes and RS 0-25 who received ET alone.[77] Derived from the ADAPT data, the ENREP algorithm (https://enrep.info) can help to estimate endocrine responsiveness based on clinical and immunohistochemical factors.

The MINDACT trial assessed all patients for recurrence risk by both clinical—pathological factors (clinical risk) and MammaPrint (genomic risk) and assigned those with clinical low/genomic low to ET alone. Patients with high clinical/high genomic risk were assigned to CT followed by ET. Patients with discordant risk profiles underwent randomization to determine use of chemotherapy.[74] Only 6.2% of the study population was aged <40 years.[74] An exploratory analysis demonstrated a 5% benefit in distant metastases-free survival favoring the addition of chemotherapy in women ≤50 years of age who were clinically high risk, genomic low risk[78] but it is unclear if these results indicate true benefit from chemotherapy or a chemoendocrine effect given among the ≤50-year-old patients who did not receive chemotherapy, 55% received tamoxifen alone for 5 years, and only 20% received OFS.[79]

Favorable outcomes were seen in the SOFT and TEXT studies and the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 trial, among premenopausal patients with low-risk disease who did not receive chemotherapy.[80,81] In SOFT—TEXT—amongst women aged <35 years with HER2− disease only 57 women (out of 442) did not receive chemotherapy—94% were node negative, 84% had T1 and 23% grade 1 tumors. In this group, 14% had an early invasive breast cancer event (including three distant recurrences and one death) at 6-year and 5.6-year follow-up in TEXT and SOFT, respectively.[82] Thus, omitting adjuvant chemotherapy in young and very young women (≤35 years old at diagnosis) may be appropriate in selected cases with favorable clinical, genomic and pathological features.

Pharmaco-prevention

Five years of tamoxifen 20 mg daily reduces breast cancer risk by 35%-40% and is recommended as pharmaco-prevention for women with an elevated breast cancer risk.[83] Despite the risk—benefit ratio being in favor of tamoxifen in all women <50 years of age, irrespective of the degree of risk, the uptake of tamoxifen for breast cancer prevention is low (10%-12%).[84] Higher-risk premenopausal women appear more likely to accept tamoxifen,[84] with the main reasons for non-initiation being concerns about side-effects, tamoxifen being perceived as a 'cancer drug', minimal benefit and fertility concerns.[84,85] Low-dose tamoxifen (5 mg/day for 3 years) may be an alternative to full-dose tamoxifen in women with breast intraepithelial neoplasia given its efficacy and limited toxicity.[86,87] The BCY5 panel recommends discussing pharmaco-prevention with young women at high risk of developing breast cancer.

Pre-operative endocrine therapy

There are no new data regarding pre-operative ET in young women since BCY4. The BCY5 panel agreed with the published American Society of Clinical Oncology (ASCO) guidelines[88] that pre-operative ET should not be routinely recommended for young women outside of clinical trials. Nevertheless, a short pre-operative ET (2-4 weeks) with subsequent Ki67 determination in the surgical specimen for assessing endocrine responsiveness may help adjuvant treatment decision making as demonstrated by the ADAPT trial also for young women.[89] Trials evaluating the efficacy of cyclin-dependent kinase (CDK) 4/6 inhibitors plus ET in the pre-operative setting are ongoing.

Adjuvant endocrine therapy

Based on the updated results of the SOFT and TEXT studies[80] and in line with existing guidelines,[16,90,91] BCY5 confirmed that tamoxifen alone remains the standard of care in premenopausal women at low risk of relapse, as defined by clinical and immunohistochemical parameters, who did not receive adjuvant chemotherapy. More than 97% of these women are free of distant recurrence and alive at 8 years, with no additional benefit by escalating ET to OFS plus tamoxifen or exemestane.

In women at higher risk of relapse, adding OFS to ET is associated with a significant improvement in outcomes

including distant recurrence compared to tamoxifen alone.[80] In high-risk patients, the combination of OFS and an AI should be the preferred option and OFS and tamoxifen for those with toxicity to the AI. An overall survival (OS) benefit was evident in the SOFT study amongst patients who received adjuvant chemotherapy followed by OFS plus oral ET; however, this was not yet demonstrated in the TEXT study. Given that the risk of disease recurrence continues for >20 years,[92] long-term follow-up will be key to ascertain if the positive effects on DFS will translate into improvements in OS and also to define potential longer-term safety issues (e.g. second primaries), particularly relevant in young patients.

An online tool (https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/) has been developed for clinicians to use in daily practice to estimate individual risk-based benefit of escalating ET for women with HER2− disease. This is a composite measure of the distant recurrence risk according to traditional prognostic features (i.e. patient age, tumor size, grade, lymph node status, ER, progesterone receptor and Ki67 expression) derived from the SOFT—TEXT population.[93] Although the relative efficacy of escalating ET is independent of age, women aged <35 years have the largest magnitude of absolute improvement in outcomes with OFS.[80,82] OFS timing (concurrent versus sequential) in women receiving adjuvant chemotherapy does not impact breast cancer outcomes. Notably, in women <40 years old who are less likely to develop CIA,[94,95] gonadotropin-releasing hormone agonist (GnRHa) concomitant with chemotherapy has the added benefit of ovarian function protection.[96]

GnRHa in combination with tamoxifen or an AI should be prescribed for 5 years based on the SOFT/TEXT data. A shorter duration was associated with excellent mid- and long-term outcomes in women with lower or intermediate risk who did not necessarily receive chemotherapy (ABCSG-12 in which only 5% received chemotherapy and the ASTTRA trials).[81,97] Adding OFS to tamoxifen significantly improves the 5-year DFS, compared to tamoxifen alone, including in women with late (within 2 years) resumption of ovarian function after chemotherapy,[97] suggesting that ovarian function should be monitored long term. Switching from 2-3 years of tamoxifen to Ais plus goserelin for a total treatment duration of 5 years versus continuing tamoxifen alone was associated with more adverse events but no improvement in disease outcomes in a small phase II trial with short follow-up.[98]

Extending tamoxifen beyond 5 years should be considered in high-risk patients[99,100] as the risk of recurrence continues for >20 years.[92] The impact of extended OFS and tamoxifen or an AI beyond 5 years is unknown.

OFS always needs to be given in young women with otherwise intact ovarian function who receive an AI. AIs alone are contraindicated in premenopausal women: caution must be taken when considering an AI in premenopausal women who became amenorrheic during the course of treatment due to the potential for recovery of ovarian function.[101,102] The criteria for defining menopausal status following CIA are defined in the BCY2 paper[14] and reported in Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2022.07.007.

BCY5 confirmed that hormone levels should be checked under GnRH therapy if there are concerns that ovarian function is not suppressed, especially if breakthrough bleeding occurs and/or the patient is on an AI. A gas chromatography/mass spectroscopy method, if available, is preferred to monitor therapy.[103,104] The updated results of the SOFT-EST sub-study, at over 4 years of treatment, were consistent with the first-year results showing that OFS does not achieve optimal estrogen suppression in up to 17% of patients.[105]

Based on the limited available data[106-108] and concerns about suboptimal OFS with depot formulations, monthly formulations of GnRHa are preferred,[90] especially in women <35 years of age and in those receiving an AI. However, when monthly use is not feasible or accepted by the patient, 3-6 monthly administration may be considered on a case-by-case basis with close monitoring of ovarian function.[107]

The method of ovarian suppression (surgical versus medical) requires balancing patient's wish for potentially preserving fertility and compliance with frequent injections over a long period of time and cost/availability. The BCY5 panel was divided when discussing radiation to ovaries as a method of OFS: a narrow majority voted that it should be discouraged if alternatives exist. New RT techniques better delineate the position of the ovaries, thus improving effectiveness and minimizing the adverse events.[109]

Younger age is associated with lower adherence and persistence to adjuvant ET,[82,110] which has been associated with reduced OS.[111] Determinants of treatment persistence[112] may vary according to race and ethnicity[113,114]: potentially modifiable factors should be identified with targeted interventions.[115,116]

Three recently reported neo/adjuvant trials investigating the impact of adding the CDK4/6 inhibitors abemaciclib[117] and palbociclib[118,119] to ET have provided mixed results. Almost 50% of enrolled patients were premenopausal in each trial. In the PALLAS adjuvant trial, 3-year iDFS did not differ between the two arms (88.2% with palbociclib and 88.5% with ET). Similarly, in PENELOPE-B, at a median follow-up of 42.8 months, palbociclib did not improve the 3-year iDFS in women with residual invasive disease after preoperative chemotherapy (81.2% with palbociclib, 77.7% with placebo). However, the monarchE study which added abemaciclib to standard ET demonstrated an absolute 3.5% improvement in the 2-year iDFS (92.2% versus 88.7%), and 5.4% at 3 years.[117,120] There are several possible reasons for different findings including the patient populations, rates of discontinuation and the specific CDK4/6 inhibitor. Longer follow-up and the results of ongoing trials (NATALEE trial—NCT03701334; ADAPTcycle trial—NCT4055493; ADAPTlate trial—NCT4565054) may provide more data but the BCY5 panel stated that abemaciclib could be considered in high-risk patients similar to those enrolled in the monarchE study (≥4 involved nodes, or 1-3 involved nodes with other

high-risk features, i.e. tumor size ≥5 cm, grade 3, Ki67 ≥20%).

GnRH agonists and ovarian function preservation

In line with the most recent guidelines focused on fertility after cancer,[121,122] BCY5 confirmed that the use of GnRHa concomitant with (neo)-adjuvant chemotherapy should be offered to all patients to reduce the risk of premature ovarian insufficiency and possibly preserve ovarian function. It is important to note that there are no clinical data whether use of a GnRHa for the purpose of ovarian function suppression is necessary or recommended during use of post-neoadjuvant capecitabine, olaparib and immunotherapy (noteworthy, in the CREATE-X study evaluating post-neoadjuvant capecitabine, over half of the patients were premenopausal; however, no data are available about GnRHa use). The recently reported results from the OPTION trial[123] suggest that patients experience a short-term decrease in QoL from the addition of goserelin to chemotherapy to preserve ovarian function, a price that women may decide to pay if adequately informed.

Because fertility outcome data after temporary OFS during chemotherapy are still insufficient,[96] the BCY5 panel confirmed that GnRHa use during chemotherapy does not replace established fertility preservation methods, which should be offered to all young patients interested in subsequent pregnancies. The efficacy of GnRHa in preserving the ovarian reserve seems unrelated to the timing of administration before chemotherapy,[124,125] but scheduling after oocyte cryopreservation should be coordinated between the fertility and oncology teams to avoid a potential ovarian hyperstimulation syndrome.[126] Anti-Müllerian hormone may predict ovarian function recovery after GnRHa during chemotherapy.[124,127-129]

Neo/adjuvant chemotherapy

Proportional risk reductions with taxane- and/or anthracycline-based adjuvant regimens are not significantly affected by age[130]: since no studies have specifically investigated different chemotherapy regimens/scheduling in young women previous statements remain valid. At the time of BCY5, the majority of the panel did not support routine use of non-anthracycline-based regimens. While anthracyclines have long been the backbone of neo/adjuvant chemotherapy, they carry long-term risks of cardiac failure and leukemia/myelodysplastic syndromes. In light of these risks, numerous studies have evaluated non-anthracycline-based regimens and there is now a growing body of evidence supporting non-anthracycline-based regimens for endocrine-responsive tumors with a low tumor burden that require chemotherapy and in HER2 overexpressing tumors.[131,132] The recent shift in practice and the emergent data will be formally discussed and voted upon in a consensus statement at BCY6.

The question of whether to incorporate platinum agents in the pre-operative setting for TN- or *BRCA*-associated tumors remains unresolved.[16,133] A recent study comparing Acx4 to 4 cycles of cisplatin in the neoadjuvant setting for *BRCA*-associated triple-negative breast cancer (TNBC) demonstrated that Doxorubicin and cyclophosphamide was superior to the 4 cisplatin cycles for achieving pathological complete response (pCR).[134] The BRIGHTNESS neoadjuvant study reported that pCR and event-free survival (EFS) were inferior for paclitaxel monotherapy compared to either carboplatin/paclitaxel or carboplatin/paclitaxel/veliparib, all followed by 4 cycles of cyclophosphamide and doxorubicin in TNBC.[135] While platinum agents may be considered in selected patients, risk of additional gonado-toxicity should be considered. There are still no data on the use of platinum agents in the adjuvant setting. For patients with TN disease without a pCR after standard pre-operative regimens, addition of 6-8 cycles of capecitabine may be considered, as in other age groups.[136] Recent data demonstrated that substituting a platinum for capecitabine in this setting did not improve outcomes.[137]

The phase III KEYNOTE 522 study evaluated the incorporation of immunotherapy in the pre-operative setting. Pembrolizumab with chemotherapy was compared to placebo with chemotherapy followed by a year of pembrolizumab or placebo, respectively. In the most recent update, a benefit is seen for pCR (64.8% versus 51.2%, $P = 0.00055$) and for EFS [91.3% versus 85.3%, HR 0.63 (95% CI 0.43-0.93)] favoring the pembrolizumab arm.[138] An important consideration is immune-related endocrinopathies, some of which are irreversible, and the impact on female fertility and ovarian function recovery is for the time being unknown. The IMPASSION-031 randomized patients to pre-operative chemotherapy with or without atezolizumab followed by a year of atezolizumab or placebo. pCR was superior for the atezolizumab arm, 58% versus 41% ($P = 0.0044$),[139] but outcome data are awaited. GeparNuevo, a phase II study with 174 patients, evaluated incorporation of durvalumab in the pre-operative setting alone, and demonstrated superior pCR, iDFS, DDFS and OS favoring the durvalumab-containing arm.[140] The incorporation of pembrolizumab in this setting may be considered in young women.

Adjuvant anti-HER2 therapy

The benefit of adjuvant trastuzumab appears independent of age[141] and anti-HER2 therapies should be the same as for other age groups. No additional data from randomized studies were published after BCY4; therefore, all recommendations remain unchanged.

Adjuvant bisphosphonates

As new data on DFS improvement with adjuvant bisphosphonates among premenopausal women emerged after BCY4,[142] the panel stated that zoledronic acid q6 months may be discussed in young women receiving OFS but given the limited data on long-term outcomes,[143] risks and benefits should be balanced on a case-by-case basis. Optimal treatment duration and dosing interval are

uncertain and alternative schedules are under investigation.[144] As a result of the long half-life of bisphosphonates, caution is needed in women interested in future conception, given the increased rates of neonatal complications and spontaneous abortions in a recent case-control study on pregnant women.[145] There are no data for benefit from adjuvant denosumab in young women.

Side-effects of adjuvant therapy

In view of the long life expectancy of young women, the panel reinforced the need to monitor potential long-term toxicities (i.e. cardiovascular, bone morbidity, cognitive impairment, secondary malignancies).

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer should be managed the same as for the older breast cancer population.

Advanced breast cancer

The BCY5 panel endorses the ESO—ESMO ABC5 guidelines for the management of advanced breast cancer (ABC)[146] and reiterated that young age alone should not be a reason to prescribe more aggressive therapy including combination chemotherapy over sequential use of monotherapy. BCY5 panelists endorse the ABC5 statements that (i) young women with ER+ ABC should have adequate OFS/ovarian function ablation and be treated as postmenopausal women, with endocrine agents, with or without targeted therapies and (ii) that future trials exploring new endocrine-based strategies should allow enrolment of pre- and postmenopausal women, and men, recognizing nonetheless that this field has evolved in recent years.

Young women with ABC have unique medical and psychosocial concerns that need to be considered and addressed.[147] While pregnancy in the setting of ABC is not considered safe or desirable from a medical perspective, concerns for fertility and family planning need to be cautiously discussed and explored even in the setting of advanced disease. In patients with long-term responses and prolonged progression-free survival (e.g. in HER2+ disease), the safety of interrupting anti-HER2 therapies for patients who may be interested in a pregnancy is unknown.

Locoregional relapse

Young age is a risk factor for local relapse. Therefore, careful attention to margin status is warranted in young women.[148] Following locoregional relapse, BCY5 confirmed that chemotherapy should be considered in women with ER− tumors, as demonstrated in the CALOR study.[149] For ER+ disease, ET should be given and for HER2+ disease, trastuzumab-based therapy is recommended albeit based only on expert opinion level of evidence.

Unique populations

***BRCA* mutation carriers.** There remains no definitive conclusion on the optimal chemotherapy regimen for *BRCA*-associated breast cancer in the neo/adjuvant setting and the panel recommended that standard prognostic features should be used to decide treatment in early disease.

The role of PARPi in the early breast cancer setting has been established by the OlympiA study which randomized patients with *BRCA1/2*-associated breast cancer to a year of adjuvant olaparib or placebo. The study included patients with high-risk features defined as stages 2 and 3, TNBC with residual disease after pre-operative chemotherapy or node positive or pT2 irrespective of nodal status or ER+ disease with four or more involved lymph nodes or significant residual disease after pre-operative chemotherapy. The median age in this study was 42 (range 36-50) years, most patients being premenopausal. At a median follow-up of 2.5 years, the 3-year iDFS was improved by 8.8% in the olaparib group.[150] Noteworthy is the observation of fewer new primary malignancies in the olaparib treatment arm, which may be particularly important for younger patients. The BCY5 panel stated that olaparib should be offered to germline *BRCA1/2* mutation carriers who meet the OLYMPIA inclusion criteria or the regulatory approval criteria.

The BCY5 panel endorses all the ABC5 statements on systemic treatment for patients with a germline *BRCA* mutation, germline *PALB2* mutation and somatic *BRCA1/2* mutations, recognizing the importance of molecular tumor boards and of data pooling in international registries.

Preliminary data suggest that breast cancer patients harboring *BRCA* mutations present a higher incidence of central nervous system (CNS) involvement. Although subgroup analyses in both OlympiAD and EMBRACA showed a benefit in persons with stable/treated brain metastases, none of the phase III PARPi trials included patients with active CNS metastases.[151] BCY5 panelists encourage the inclusion of patients with active CNS metastases in studies investigating new therapies.

MALE BREAST CANCER

Male breast cancer accounts for ~1% of all breast cancers; the lifetime risk is ~1 : 1 000, and represents a small minority in males <40 years.[152,153] Breast cancer in young men is rare; however, it would likely amplify the psychological distress already experienced by men with a breast cancer diagnosis. Treatment should follow international guidelines,[154] men should be included in clinical trials, particularly in trials exploring ET as the expected differential efficacy in males versus females is greatest in this setting, germline testing carried out to aid in treatment and prevention measures and distinctive histopathologic and genomic features investigated.[155,156]

Supportive and follow-up care

Many breast cancer patients use integrative medicine (complementary and alternative therapies—CAM)[157] but very few data are available in young women. In a recent

German study, 62.5% of 827 young breast cancer patients had used CAM. Its use was significantly higher in women with higher educational level and employment status, and in those feeling they had not received sufficient information.[158] The BCY5 panel stated that health professionals should proactively promote open communication about integrative medicine with their young breast cancer patients. As effectiveness and safety of many therapies remain under-explored, the BCY5 panel also approved that, if possible, supervised and established integrative medicine services should be provided within the oncology service.

BCY5 confirmed that follow-up care and supportive treatment/prevention of specific symptoms and side-effects in young women should follow the same guidelines as in older women. New shared-care models involving cancer specialists, general practitioners and breast nurses are being evaluated to improve cost-effectiveness.

The panel also reiterated that standardized patient-reported outcome measurements may enable timely collection of treatment side-effects, enabling the development of targeted interventions.

Dedicated survivorship clinics that assess and manage early and late treatment toxicities and treatment adherence are valuable in this population.

Psychosocial issues. Young breast cancer patients are at greater risk of psychosocial morbidity, not only during the active treatment period but also long term[159] and when facing ABC.[160] Psychosocial care should be available and integrated in routine cancer treatments and follow-up. The BCY5 panel recommended that the specific psychosocial distress pertaining to body image, sexuality and sexual dysfunction resulting from premature menopause, treatment-related amenorrhea, weight gain, hair loss and breast surgery should be routinely addressed by the health care team in a culturally appropriate manner to ensure provision of appropriate information and support.

Partners and family members should be involved early on and couple-based and/or familial psychosocial interventions should be promptly proposed during the different phases of the disease. Offspring having a mother diagnosed with breast cancer may experience high levels of psychological distress.[161] Partners of young breast cancer survivors (3-8 years post-treatment) report poorer overall, physical, social, psychological and spiritual QoL compared to partners of healthy women.[162-164] Social issues that need to be addressed include return to work, family planning and financial loss. The scarce data about end-of-life concerns of young patients with ABC derive from Caucasian, upper-/middle-class women within nuclear families and include worries about children and co-parents which affect their QoL and family functioning.[165] The BCY5 panelists recognized that further research in this setting is needed on patients from diverse backgrounds, non-nuclear families, on the co-parent, parents and caregivers.

Despite not being the topic of BCY5, we recognize the impact of COVID-19 pandemic on patients' psychological health[166] due to disruption of oncology service organization and perceived increased loneliness.

Considerations and recommendations by the BCY5 panel for fertility preservation, contraception and premature menopause, sexual functioning, pregnancy after breast cancer, bone health, cognitive impairment, lifestyle changes and breast cancer during pregnancy are updated in Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2022.07.007.

Patient advocacy statements

BCY5 included the second patient advocacy workshop, and for the third time, included a patient advocacy-dedicated session for young women with breast cancer and the consensus session included two young breast cancer survivors as panelists. Since BCY3, a closed Facebook group for young breast cancer survivors has been active and now has over 53 active global members. The importance of the worldwide breast cancer community to work together was apparent throughout the meeting.

At BCY5, a presentation was made announcing Project 528, the first-ever global needs assessment of young adults diagnosed with breast cancer. This will be a global survey that is created in true partnership with Young Survival Coalition and Europa Donna Slovenia to learn the global needs of young adults. Project 528 has four clear goals: (i) identify the unmet needs of young adults diagnosed with breast cancer and their caregivers; (ii) understand the geographic difference in patient experiences; (iii) discover existing services available to young adults diagnosed with breast cancer globally; and (iv) understand the QoL burden of young adults diagnosed with breast cancer.

Everyone interested in participating in this important survey are encouraged to sign up and learn more at https://project528.youngsurvival.org.

CONCLUSIONS

Since BCY4, progress has been made. More clinical trials in the metastatic setting are incorporating young women with breast cancer by allowing for OFS as an acceptable surrogate for physiological menopause. The impact of germline mutations in BRCA1/2 has now substantial therapeutic implications in both early breast cancer and ABC. One of the many challenges in the treatment of premenopausal ER+ early breast cancer is how to incorporate and interpret gene expression signatures into treatment algorithms to determine which patients need chemotherapy in addition to optimal ET. Urgent research is needed to address adherence to available treatments, health disparities and needs of minorities, and a global effort is required to help bridge the gaps in LMICs. A multidisciplinary approach remains the backbone of care to ensure optimal outcomes for young women with breast cancer given their many concerns and care needs.

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