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SPECIAL ARTICLE

ESO–ESMO 4th International Consensus Guidelines for Breast Cancer in Young Women (BCY4)

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The 4th International Consensus Conference for Breast Cancer in Young Women (BCY4) took place in October 2018, in Lugano, Switzerland, 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 BCY3 with incorporation of new evidence to inform the guidelines. Areas of research priorities were also identified. This article summarizes the ESO–ESMO international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

INTRODUCTION

Despite the fact that breast cancer in young women (<40 years) is an uncommon disease in developed countries (4% of new estimated cases in the USA in 2017), 1 in 68 women will develop the disease by 40 years of age and 1 in 220 before the age of 30.[1,2] Since the mid-1990s, incidence rates have slowly increased (0.2% per year) among women under age 50,[1] with limited data confirming this trend in women <40 years.[3,4] Overall, breast cancer death rates decreased from the late-1980s in both younger and older women but the decline has slowed among women <50 years since 2007. In a recent analysis based on the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2008, patients aged <30 and 30–39 years had significantly inferior overall and breast cancer-specific survival than patients aged 40–49 and 50–59 years.[5] The less favourable outcome repeatedly reported in young women has several possible explanations.

Breast cancers arising in young women, as compared with their older counterparts, are characterized by higher proportion of grade 3, triple-negative and human epidermal growth factor receptor 2 (HER2) overexpression, lymphovascular invasion, lymphocytic infiltration and, on gene expression profiling, higher proportion of basal-like and HER2-enriched tumours.[6] Recent data seem to refute previous evidence of diagnostic delays in young women; in two large series, young age was not an independent predictor factor of delay in diagnosis.[7,8] Overall, young women still have less favourable outcomes than older women,[9–12] particularly for luminal-A like tumours and irrespective of stage at diagnosis.[13] Several mechanisms can potentially explain the worse outcome in young women with luminal-like breast cancer [e.g. less likelihood of chemotherapy-induced amenorrhea (CIA), lower prevalence of *PIK3CA* mutations and decreased adherence to adjuvant endocrine therapy (ET)].[10]

Most of our knowledge about breast cancer is based upon studies in older women and young women are underrepresented in contemporary research evaluating risk-stratification models and molecular tools.[14,15] Many young

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women may be at risk of being over-treated based solely on age considerations. Prospective trials dedicated to young patients are key to answering many of the outstanding questions to ensure appropriate treatment. Two such examples are the POSH cohort study, conducted at 127 hospitals in the UK,[16] and the Young Women's Breast Cancer Study (NCT01468246), coordinated by the Dana-Farber/Harvard Cancer Center in the USA. Preliminary data from these and other studies show a greater proportion of luminal B and estrogen receptor (ER) negative (ER−) tumours in young patients, increased risk of early relapse and a more unfavourable longer-term outcome for young women with ER+ tumours in particular compared with older women.[10,17–19] Treatment decisions in young women should not be driven by their age but rather by the biology of their breast cancer to ensure appropriate and tailored treatment and to avoid over-treatment that often occurs when decisions are driven by age alone.

A hereditary breast cancer predisposition is more common amongst young women and may influence decisions on both local and systemic disease management. Women with an identified germline mutation also need to tackle the additional challenges of future cancer risk, which may include risk-reducing surgeries,[20,21] cascade family risk assessment[22] and pre-implantation gestational testing.[23] All these decisions are often accompanied by extra psychosocial distress.[24]

The consequences of treatments, including premature menopause and impaired fertility, may have several medical and psychosocial implications[25,26]; thus, specialized multimodality care is paramount. Although young women with breast cancer are at increased risk of psychological distress at diagnosis and in long-term follow-up, growing resources are available to help them navigate the disease and survivorship.

Consistent with previous guidelines,[27–30] the panel defined 'young women' as women under the age of 40 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.

BCY4 took place in Lugano, Switzerland on 6–8 October 2018 with over 300 participants, including health professionals and patient advocates, who developed and presented their second manifesto. The BCY4 guidelines are developed by ESO (European School of Oncology) and ESMO (European Society of Medical Oncology) and are endorsed by EUSOMA (European Society of Breast Cancer Specialists). All recommendations are for standard care, outside of clinical trials. Importantly, diagnostic and treatment recommendations should be considered in the context of national regulatory approval, availability and reimbursement.

METHODOLOGY

Recommendations from BCY3 formed the basis for the current recommendations.[30] New and updated statements from BCY3 were circulated amongst the panellists before the BCY4 conference and were then presented, discussed, adapted and voted on during the final consensus session of BCY4. All panel members were instructed to vote on all questions; members with a potential conflict 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 particular question. Where there were areas of substantial controversy or disagreement, they were noted in the discussion of the recommendations. These recommendations were later circulated to panel members by e-mail for comments, updating based on recent reports, and corrections on content and wording.

Table 1 describes the new grading system used, as per ESMO guidelines methodology, adapted from Dykewicz et al.[31]; see http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. Statements without grading were considered justified standard clinical practice by the panel experts.

Table 2 lists the general guidelines for the management of young women with breast cancer.

Table 3 lists the assessment and treatment guidelines in early breast cancer.

Table 4 lists the general guidelines for treating young women with advanced breast cancer.

Table 5 lists the assessment and treatment guidelines for women carrying germline pathogenic gene variants.

Table 6 lists supportive and follow-up care guidelines.

Appendix 1 details the definition of menopause following CIA and supportive and follow-up care issues unchanged or slightly modified since BCY3.

Supplementary Table S1, *available at Annals of Oncology* online, lists all members of the BCY4 consensus panel and their disclosure of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

GENERAL CONSIDERATIONS WHEN CARING FOR YOUNG WOMEN WITH BREAST CANCER

Management of young women with breast cancer is multifaceted and requires specific and dedicated

Table 1. Levels of evidence and grades of recommendation

Levels of evidence (LoE)	
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 (GoR)	
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,…), 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.[31]

Table 2. General guidelines

Guidelines	LoE, GoR	Consensus
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, counselling on genetic predisposition, fertility, sexual health and socio-economic 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, counselling on genetic predisposition, fertility, sexual health and socio-economic 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 tumour (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumour stage, genetic status (if available) and patient's comorbidities and preferences.	Expert opinion	
Systematic research into age-specific host-tumour 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	100%
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, RT should *not* be reimbursed per fraction *nor* should physicians receive reimbursement for administering intravenous chemotherapy.	Expert opinion	100%
Male breast cancer		
Male breast cancer should be managed in accordance with international recommendations/ guidelines.	Expert opinion	100%
Clinical trials should allow for inclusion of male breast cancer *patients in both early and advanced settings.*	Expert opinion	100%

In green NEW BCY4 guidelines with consensus voting.

multidisciplinary care (medical and radiation oncologist, gynecologist, pathologist, radiologist, breast and plastic surgeon, nurse specialist, geneticist, physiotherapist, fertility, sexual therapy, and psychosocial experts). Their management is best provided in dedicated breast clinics or programs whose multidisciplinary structure and quality control assurance ensure qualified experience and care.[32,33] The panel therefore reinforced previous statements emphasizing the importance of multidisciplinary care while also recognizing that this is not always possible in settings with more limited resources. The panel further recommended that personalized psychosocial support, counselling on genetic predisposition, fertility, sexual health, and socio-economic consequences be incorporated into individual treatment planning. Life-long follow-up care is particularly relevant for young survivors, given the improved long-term survival with modern therapies. Specific guidelines for post-treatment survivorship care[34] are available to help not only oncologists but also primary care clinicians better manage potential long-term and late effects. Breast cancer patients in low- and middle-income countries are often younger than in high-income countries. Supportive care services are frequently limited in these countries; within the Breast Health Global Initiative (BHGI), nine key resources were identified and resource-stratified recommendations were developed for appropriate supportive care into survivorship.[35] Prospective cohort studies are collecting important data on young patients' concerns, in particular about fertility preservation,[25,36,37] selection of ovarian function preservation strategies,[37] psychosocial and quality of life issues after diagnosis.[38,39]

Despite significant improvements in both breast cancer therapies and outcomes, young age is also associated with increased risk of work-related challenges; data from different countries and social systems report financial

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.	[I, A]	
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 (e.g. RT for childhood or young-adulthood malignancy).	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.	[II, C]	
No specific data about tomosynthesis are available in young women. Its use and indications are the same as in other age groups.	Expert opinion	
For *BRCA1/2* 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.	[II, A]	
For *BRCA1/2* 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	
Different diagnostic tools for staging and follow-up (e.g. whole body MRI) should be discussed with women harbouring germline *p53* pathogenic variants (Li-Fraumeni syndrome).	Expert opinion	89.5%
Other diagnostic tools (e.g. FDG-PET-CT) are under evaluation in Li-Fraumeni patients as well as in patients harbouring other germline pathogenic gene variants (e.g. *ATM* carriers).		
Risk-adapted early detection and surveillance tools should be researched in young women.	Expert opinion	
Genetic counselling and testing		
Every young woman with breast cancer should be offered genetic counselling 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 counselling should be offered again during follow-up, to address issues of surveillance and risk reduction of additional primary tumours 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.	Expert opinion	100%
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 on 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.).		
Genes to be tested for depend on personal and family history.	Expert opinion	
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 counsellor.		
Development of quality-controlled genetic counselling services is strongly encouraged.		
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.	Expert opinion	
As commercially available multi-gene panels include different panels of genes, the choice of the specific panel and quality-controlled laboratory is crucial.		
Risk communication and clinical recommendations need to be adapted to the increased complexity and uncertainty of multi-gene testing.		
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 counselling 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	94.7%
As commercially available multi-gene panels include different genes, the choice of the specific panel should be performed in quality-controlled laboratories.	Expert opinion	94.7%
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 tumours need to be further explored within a research setting before they can be used in routine clinical practice.	Expert opinion	94.7%
Early breast cancer loco-regional 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, A]	
Breast conserving surgery should be performed as the first option whenever suitable, as it provides the same overall survival than mastectomy.	[I, A]	
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 postoperative 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.	[I, C]	
There is no evidence of an increased false negative rate or a worse outcome in young patients undergoing SLNB, therefore the indications for SLNB are the same as in older patients.	[I, B]	

Continued

Table 3. Continued

Guidelines	LoE, GoR	Consensus
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.	[I, B]	
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 loco-regional 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.	[I, B]	
After BCS, 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.		
Indications of adjuvant RT are independent of *BRCA* status	Expert opinion	84%
Limited and discordant evidence is available for safety of RT in the presence of pathogenic gene variants in other predisposing genes (e.g. *p53*, *CHEK2*, *ATM*): in these patients the risk-benefit ratio needs to be individually discussed.		
Indications and schedules of hypofractionated radiotherapy are, in principle, the same as in other age groups.	[I, B]	
Indications and extension of nodal irradiation are the same as in other age groups.	[I, B]	
Indications for adjuvant RT are the same as for older patients.	[I, B]	
Data are stronger for benefits of postmastectomy RT for young women.	[I, B]	
PBI, or accelerated PBI, has not been sufficiently studied in young patients and should not be performed in this age group.	Expert opinion	84%
When postmastectomy RT is foreseen, the timing and technique of breast reconstruction should be discussed preoperatively	Expert opinion	100%
Adjuvant systemic treatment		
Endocrine therapy		
All young women should be counselled, 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 counselling/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.	[I, A]	
Tamoxifen alone for 5 years is indicated for low-risk patients.	[I, A]	
Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively postmenopausal.	[I, A]	
Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.	[I, A]	
The addition of a GnRH agonist (or ovarian ablation) to tamoxifen or an aromatase inhibitor is indicated in patients at higher risk of relapse.	[I, A]	
AIs without ovarian function suppression contraindicated in premenopausal women.	[I, A] [I, A]	
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.	[I, A]	
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.	Expert opinion	89.5%
3-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.		
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	84.2%
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.	[II, B]	94.7%
Chemotherapy		
A number of factors including patient and tumour characteristics and gene expression tests, where available, may be considered when deciding whether to administer adjuvant chemotherapy in young women with HR+ early breast cancer.	Expert opinion	

Continued

Table 3. Continued

Guidelines	LoE, GoR	Consensus
Commercially available gene expression signatures have not been widely studied in young women. Fewer data are available to establish their role in predicting the additional benefit of chemotherapy over endocrine therapy alone in HR+ breast cancer in this age group.		
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	100%
Tamoxifen alone was given in the vast majority of premenopausal women enrolled in the trials exploring these tests		
Available data suggest that a discussion of omitting adjuvant chemotherapy in very young women (≤35 years at diagnosis) with low-risk ER+ disease is appropriate in highly selected cases with favourable 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 tumour (including, but not limited to, ER/PR and HER-2 receptors, proliferation, and grade) and patient's comorbidities.	[I, A]	
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.	[I, A]	100%
The indication for dose-dense chemotherapy is independent of age.		
Standard duration of treatment (minimum of 4 and maximum of 8 cycles) should be prescribed.	[I, A]	
Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated.	[I, A]	
Young age by itself should not be an indication to prescribe a combination of cytotoxic agents.		
In patients with TNBC or *BRCA*-associated tumours the incorporation of platinum agents increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated.	[I, B]	
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.		
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	[I, A]	
There are no data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended.	[I, A]	100%
Anti-HER2 therapy		
One year treatment with adjuvant trastuzumab, together with chemotherapy, is indicated for women with HER-2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 0.5 cm), who have a left ventricular ejection fraction within normal limits and without significant cardiovascular risk factors, irrespective of age.	[I, A]	
In highly selected patients with small, node-negative, HER-2+ breast cancer, the administration of 12 weeks of weekly paclitaxel and trastuzumab without anthracyclines can	[II, B]	
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.	[I, A]	
In case of pathological residual disease after preoperative chemotherapy plus anti-HER2 therapy the patient should be offered to complete 1 year of adjuvant anti-HER2 therapy with TDM-1.	[I, A]	94.7%
In HER2+ patients at high risk of relapse 1 year of adjuvant pertuzumab + trastuzumab can be discussed, as in other age groups.	**[I, C]**	78.9%
In HER2+ patients at high risk of relapse (e.g. N+) and HR+, 1 year treatment with neratinib after trastuzumab can be discussed, as in other age groups. Neratinib has increased severe toxicity (e.g. diarrhea) and this needs to be clearly communicated to patients.	[I, A]	78.9%
There is no data about the efficacy of neratinib after 1 year of adjuvant trastuzumab AND pertuzumab or after adjuvant TDM1.		
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).	Expert opinion	
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.		
The management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.	Expert opinion	
Adjuvant bisphosphonate therapy may be considered in young women receiving ovarian suppression; however, data are limited in young women and impact on future progeny unknown.	[I, B]	

TNBC, triple-negative breast cancer.

problems due to reduction in working hours and long-term rate of unemployment in a significant proportion of patients.[40—43] Return to work should be one of the issues routinely addressed after completion of treatment and health professionals should refer patients to work reintegration programs, where available, early on in their care.

Nurse navigators and navigation tools may improve post-treatment surveillance and emotional health but their

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 4 ESO—ESMO, NCCN guidelines, Evidence-based national guidelines).	Expert opinion	
Therapeutic recommendations should not differ from those for older women with the same disease characteristics and extent.	[I, C]	
The BCY4 panel endorses the ESO—ESMO ABC4 guidelines for the management of ABC in premenopausal women.	[I, A]	
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, HER-2 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.	[I, C]	
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 enrolment of both pre- and postmenopausal women and men.	[I, A]	
Platinum agents have been demonstrated to be superior to taxanes in *BRCA*-associated advanced breast cancer.	[I, B]	
Single-agent PARP inhibitors (PARPi) have shown progression-free survival improvement in breast cancer patients harbouring a germline *BRCA* pathogenic gene variant. OS benefit has been seen for Olaparib in the first-line setting in a pre-planned subgroup analysis. 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	[I, A]	89.5%

effectiveness in improving breast cancer outcomes is still unclear.[44,45] The panel therefore reiterated the need to develop scientifically validated, innovative and structured communication and specific supportive tools (e.g. online programs, web-based interventions), ideally in different languages. Such tools would help young patients to overcome barriers to accessing support, such as child and family care, work timetables and challenges of geographical distance from health care services. The available evidence from randomized intervention studies addressing educational (e.g. information provision and self-management advice), physical (e.g. endurance and resistance training) and psychological (e.g. counselling and cognitive therapies) programs show home-based, multidimensional survivorship programs have a short-term beneficial effect of improving quality of life.[46]

Support groups for patients and their caregivers should be developed and promoted. Open discussion and shared decision-making in a culturally appropriate manner and supporting a proactive role by patients in their care is strongly encouraged.

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. The panel reinforced previous statements[28—30] that treatment of young women, both in the early and the advanced setting, should be based on the same clinico-pathological factors as for older women. In particular, young age alone is not a reason to prescribe more aggressive therapies but the different hormonal milieu of a young woman deserves specific therapeutic considerations, e.g. when prescribing endocrine therapies.

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

Guidelines	LoE, GoR	Consensus
For survivors harbouring a *BRCA1/2* 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 tumour.	[II, B]	
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 RT.	[I, B]	
Radiation therapy should be carefully discussed on an individual basis for these patients.	[II, C]	
In the absence of evidence-based recommendations for risk-reducing surgery in patients harbouring pathogenic variants in low-moderate penetrance genes, decisions must be taken individually, mainly based on family history. For breast cancer survivors and asymptomatic carriers harbouring a *BRCA1/2* mutation, risk-reducing salpingo-oophorectomy (RRSO) should be discussed from the age of 35 provided that the woman has completed family planning. For *BRCA1* mutation carriers RRSO is recommended between age 35-40 and for *BRCA2* mutation carriers around age 40, 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	

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.	[II, B]	
All young women should be counselled regarding the risk of getting pregnant while on chemotherapy, endocrine or anti-HER-2 therapy, despite developing amenorrhea, and of the need for adequate non-hormonal contraception if they are sexually active and could become pregnant.	[I, B]	
Exogenous hormonal contraception is generally contraindicated in young cancer survivors, irrespective of disease subtype, and alternative strategies should be considered.	Expert opinion	Expert opinion
All young women should be referred for specialist counselling/consultation if interested in fertility preservation before commencement of any therapy.	Expert opinion	
The use of GnRH analogue 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 GnRH analogue use during chemotherapy *does not* replace established fertility preservation methods, which should still be offered to all young patients.	[I, B]	94.7%
All young women should be counselled 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 counselled, monitored and treated accordingly.	[I, A]	
Pregnancy after breast cancer should not be discouraged even in patients with HR positive disease, although all available data are retrospective.	[I, B]	
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. Outside of a clinical trial, patients with HR+ disease should complete at least 18–24 months of endocrine therapy before attempting pregnancy. Treatment should be resumed and completed according to initial planning after delivery and breastfeeding. All patients choosing to interrupt endocrine therapy in order to conceive should be encouraged to participate in prospective clinical trials gathering information about pregnancy after breast cancer.	Expert opinion	78.9%
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.	Expert opinion	
Young patients should be strongly encouraged to adopt the following healthy lifestyle changes: maintain BMI $\leq$ 25 perform regular aerobic exercise not to smoke to limit daily alcohol intake	Expert opinion	

Distinct patterns of somatic mutations have been demonstrated in young women compared to older women and may present opportunities for tailored therapeutics in the future.[47–51] Proliferation-related gene signatures and endocrine resistance features have been shown to be more frequent in young women[49–52]; for example, in a recent series, *GATA3* mutations were more frequent in women <45 years at diagnosis (125 out of almost 800 patients) and might be associated with endocrine resistance.[49] Targeting of stem cell features, which are highly expressed in young women, with Notch inhibitors and anti-RANKL monoclonal antibodies, may also be of promise in the future.[53] The panel reinforced the BCY3 recommendation that systematic research into age-specific tumour 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.

Panel members emphasized that, although not age-specific, 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 (RT) should not be reimbursed per fraction nor should physicians receive higher reimbursement for administering intravenous agents compared with oral chemotherapy or ET.

Screening and diagnostic imaging for staging and follow-up

The panel reinforced the recommendation that imaging and staging in young women should in principle follow standard algorithms as for older women.

There is no indication for routine screening by any imaging for early detection in healthy, average-risk young women.

Breast ultrasound remains the first diagnostic approach for clinical abnormalities in this age group and in pregnant/lactating women.[54] Data on superiority of tomosynthesis over digital mammography in young women and in those with dense breast are accumulating,[55–57] suggesting a potential benefit in the breast cancer work-up in these patient populations.

Preoperative MRI is associated with increased rates of ipsilateral mastectomy and contralateral prophylactic mastectomy in newly diagnosed breast cancer patients, irrespective of age[58]; its indication should strictly follow available recommendations.[59,60] Performance of MRI is generally superior to other clinical and imaging assessments after preoperative chemotherapy,[61] which is frequently prescribed in young women and may be considered in this setting.

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.[62,63] Patients should be informed that the optimal timing for planning and performing mammography and, if indicated, MRI is the first half of the menstrual cycle (day 7—14).[60]

The panel recommended that risk-adapted early detection and surveillance strategies be researched in young women. Once a cancer diagnosis has been established, recommended staging, including axillary assessment, does not differ from that for older breast cancer patients.

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,[64] should follow currently available guidelines.[21,65]

Screening and diagnostic imaging for other malignancies in women harbouring a mutation in a gene associated with hereditary breast and ovarian cancer syndrome. Different diagnostic tools for staging and follow-up [e.g. whole body MRI (WB-MRI)] should be discussed with women harbouring germline p53 (*TP*53) pathogenic variants [Li-Fraumeni syndrome (LFS)]. Cancer detection and surveillance for LFS should not utilize ionizing radiation due to the risk of secondary radio-induced malignancies.[66] Contrast-free WB-MRI has shown to be effective for cancer detection in asymptomatic carriers[67—69] and for staging and follow-up in breast cancer patients.[70] WB-MRI has been incorporated into several national and international guidelines for management of adult *TP*53 mutation carriers/patients in addition to gadolinium-enhanced breast and brain MRI.[65,71] In small series, F^{18}-FDG PET-CT has proven to be effective in cancer screening of LFS.[72,73] Despite radiation doses being two to three orders of magnitude smaller than those linked to secondary cancers, the availability of safer modalities (e.g. contrast-free WB-MRI) has so far prevented its incorporation in surveillance protocols.[71]

Ataxia-telangiectasia (AT) is an autosomal recessive neurodegenerative disorder caused by mutations in the ataxia-telangiectasia mutated (*ATM*) gene. Women harbouring *ATM* mutations have an increased risk of breast cancer.[74] Data on radiosensitivity in this population are controversial[75,76]; evidence-based guidelines for cancer screening are not available yet and additional evidence is needed before different imaging, such as F^{18}-FDG PET/CT or WB-MRI, can be confidently recommended.[75]

For *BRCA1/2* mutation and other cancer susceptibility genes carriers (e.g. *RAD51C, p53, BRIP1*) who have not undergone risk-reducing salpingo-oophorectomy (RRSO), the panel confirmed the indication of gynecologic surveillance every 6 months, beginning at age 30 or 5 years younger than the earliest diagnosis of a gynecological malignancy in the family, whichever comes earlier, according to available international guidelines.[21,65] No new data on monitoring of these women are available since BCY3; ongoing trials will perhaps help clarify a role for intensive screening in women wishing to delay RRSO.[77] In countries where evidence-based national guidelines are available they may be used to guide local clinical practice.

Genetic counselling and testing

The panel confirmed that genetic counselling should be offered for every young woman, irrespective of whether there is a family history of breast cancer or of the tumour subtype (e.g. triple negative). Routine practice should be in keeping with local guidelines and testing availability and reimbursement on a country-by-country basis.

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. Risk communication and clinical recommendations need to be adapted to the increased complexity and uncertainty of multi-gene testing. The patient must be made aware that the presence of a predisposing pathogenic gene variant may have an impact on her management, follow-up and decision-making in the setting of early breast cancer (as well as for family members). In women with advanced breast cancer, the presence of a germline mutation in *BRCA1/2* has an immediate and significant impact on treatment decisions and needs to be clearly communicated.

A fast-track process that 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, of poly (ADP-ribose) polymerase (PARP) inhibitors, etc.].

Of note, a recent study has suggested that if genetic testing is performed only on breast cancer patients meeting National Comprehensive Cancer Network (NCCN) guidelines testing criteria, close to 50% of patients with a germline mutation associated with a hereditary ovarian and breast cancer syndrome would not be identified.[78] Although *BRCA1/2* are the most frequently mutated genes, testing for other additional moderate- to high-penetrance genes using a multi-gene panel may be considered if deemed indicated by the geneticist/genetic counsellor. As commercially available multi-gene panels include different genes, the choice of the specific panel and quality-controlled laboratory is crucial and should at least include high-penetrance genes (*BRCA1/2, p53, PTEN*) and moderate—high-penetrance genes (e.g. *CDH1, CHEK2, PALB2, RAD51C, BRIP1, ATM*).[79] Practice should be guided by national/international guidelines.

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 explained to patients in both the pre- and post-testing counselling consultations.

Multidisciplinary management of mutation carriers and high-risk individuals should be ideally provided in dedicated high-risk clinics, when available. Collaborative efforts to gather, pool and analyze data on the follow-up, screening and management of mutation carriers should be pursued. Clinical trials on risk reduction and optimal screening strategies for this group of women are strongly needed.

For women who are not ready to consider genetic testing at the time of diagnosis, access to genetic counselling should be offered on an ongoing basis, to address issues of tailoring surveillance and of risk reduction for additional primary tumours, and risk assignment and stratification for relatives. As well, women with previous limited testing should be considered for a more comprehensive contemporary panel to rule out an inherited mutation.

EARLY BREAST CANCER

Loco-regional treatment

Surgery. Although young age is an independent risk factor for increased local recurrence,[80,81] there is no evidence that mastectomy improves overall survival (OS) in young breast cancer patients (unless clinically indicated).[82] As stated previously, the panel remains concerned about the ongoing trend for routine bilateral mastectomies, particularly in younger women. Oncoplastic surgical techniques should be discussed with all patients scheduled for breast conserving surgery (BCS) where a potential postoperative asymmetry is anticipated and should always be performed by a dedicated breast surgical team in order to optimize cosmesis and patient body image. When mastectomy is indicated, skin- and nipple-sparing techniques with immediate breast reconstruction, when feasible, can provide adequate oncological control while also addressing cosmetic needs.[83,84] Immediate breast reconstruction (irrespective of technique) following mastectomy offers the same survival outcome rates as mastectomy without reconstruction, and should therefore be offered to all patients except those with inflammatory breast cancer (for whom delayed reconstruction, after the period of higher relapse risk, is recommended) or those with locally advanced disease at presentation with poor response to primary systemic therapy. RT is not a stand-alone reason to postpone reconstruction. When postmastectomy RT is foreseen, the panel-recommended timing and technique of breast reconstruction should be discussed preoperatively on an individual basis.

The panel confirmed that the indications for sentinel node biopsy (SLNB) and surgical management of patients with sentinel lymph node involvement should be the same as in older patients.

The optimal loco-regional treatment after preoperative chemotherapy remains controversial and decisions should be made independent of age.

Germline mutation status should be part of the individual decision-making algorithm when making choices about breast surgery. Sufficient time to discuss the different options and adequate psychological support need to be offered given the potential long-term physical and psychological impact of the different surgical interventions. In the absence of evidence-based recommendations for risk-reducing surgery in patients harbouring pathogenic variants in low—moderate penetrance genes, decisions must be taken individually, guided by family history and patient preference.

Radiation therapy. Indications for postoperative RT are the same as for older patients; however, data are stronger for benefits of postmastectomy radiation amongst young women. Indications and extent of nodal irradiation are the same as in other age groups. Following preoperative systemic therapy, irradiation fields should account for both initial, pre-treatment staging and post-treatment pathological staging. The panel reiterated past BCY recommendations on the need for modern techniques to minimize long-term side-effects and the routine indication for a boost to the site of the radical local excision in case of BCS.

Based on available literature, indications and schedules for hypofractionation are, in principle, the same as in other age groups.[85,86] Partial breast irradiation (PBI), or accelerated PBI, has not been sufficiently studied in young patients and the panel confirmed it should not be performed in this age group outside of clinical trials.

Indications for postoperative RT are independent of *BRCA* status. A recent study, evaluating prophylactic radiation to the unaffected contralateral breast amongst *BRCA* carriers treated for early breast cancer who declined contralateral mastectomy, included a limited number of young patients; the procedure should therefore not be performed outside the setting of a clinical trial.[87] There is limited and inconclusive evidence about the safety of radiation for those harbouring a pathogenic gene variant in other predisposing genes (e.g. *p53*, *ATM*); in these patients, the risk—benefit ratio needs to be individually discussed.

Adjuvant systemic treatment

Adjuvant systemic treatment decisions for invasive breast cancer should be based on extent of disease and the biological characteristics of the tumour [including, but not limited to, tumour size, nodal status, hormone receptor (HR) and HER2 overexpression or amplification, proliferation, and grade], patient's comorbidities and preferences (as for women in other age categories).

Gene expression signatures. 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 been demonstrated to be predictive of chemotherapy benefit.[14,15,88] It should be noted that women younger than 40 are grossly under-represented in both retrospective and prospective studies performed to date,

particularly in studies evaluating node-positive disease. Additionally, tamoxifen alone was the ET in the vast majority of premenopausal women enrolled in the trials exploring these tests.

In TAILORx, investigators evaluated the use of the 21-gene Oncotype Dx® recurrence score (RS) amongst women with HR+, HER2−, T1−2, node-negative disease, categorizing these individuals into low, intermediate or high risk of recurrence. While 30% of those with a low RS were premenopausal, only 4% of those were <40. For those with a low-risk RS, who were all assigned to ET alone, the 5-year distant recurrence-free survival was 99%.[14] For those with an intermediate risk RS, the 9-year distant recurrence-free survival was 94.5% for the ET-only group and 95% for those who received chemotherapy and ET.[88] Exploratory, unplanned subgroup analyses of women ≤50 suggested a benefit from chemotherapy amongst those with an intermediate RS within the range of 16−25[88] and further analyses suggested that clinical risk level combined with RS identified women ≤50 more likely to benefit from addition of chemotherapy to ET alone.[89] These analyses are not statistically robust and should be interpreted with caution. It is unclear if they have any clinical significance, if they indicate true benefit from chemotherapy or if they in fact suggest that these women need to have their ET optimized with ovarian function suppression (OFS) incorporated into their adjuvant care.

The MINDACT investigators evaluated the 70-gene signature, which classifies women into low or high risk for recurrence, irrespective of HR status. In this study, randomization was assigned based on both clinical risk and genomic risk. Those with low clinical and genomic risk did not receive chemotherapy, those with high clinical and genomic risk were assigned to chemotherapy and those with discordant risk profiles underwent randomization for type of method of risk assessment that would be used to determine use of chemotherapy.[15] Only 6.2% of the study population was <40,[90] thus it is difficult to draw clear conclusions whether the small absolute benefit (1.5%) reported with chemotherapy in distant disease-free survival amongst those with high clinical risk and low genomic risk would have been greater in the younger age groups because of limited numbers and statistical power.

In the WSG PlanB study, patients with up to three involved lymph nodes and RS ≤11 had an excellent 5-year distant disease-free survival without adjuvant chemotherapy.[91] Yet, no subgroup analysis for patients <40 years has been presented so far. Results from further studies (e.g. Rx-PONDER) and subgroup analyses or with longer follow-up (e.g. MINDACT) in endocrine-responsive, node-positive disease are awaited.

In conclusion, available data suggest that a discussion of omitting adjuvant chemotherapy in young and very young women (≤35 years at diagnosis) is appropriate in selected cases with favourable clinical and pathological features including low gene expression profiles where available. Commercially available, validated prognostic genomic assays in HR+ early breast cancer have not been developed to predict which ET is more appropriate according to genomic risk. Therefore, they should not be used at this time for selecting type or duration of ET.

Preoperative endocrine therapy. No new data are available about the role of preoperative ET in young women since BCY3, thus the BCY4 panel confirmed the previous general recommendation that preoperative ET should not be routinely recommended for young women outside of clinical trials.[92−94] In particular, it should be noted that clinical responses (not pathological) were reported both in the study by Torrisi et al.[92] and in the STAGE study[93] and no outcome follow-up data have been published. Some panellists believed the limited evidence available justifies considering this approach in selected patients, however.

The International Breast Cancer Study Group (IBCSG) randomized phase II trial (IBCSG 41-13 TREND), evaluating the efficacy of the gonadotropin-releasing-hormone (GnRH) antagonist degarelix versus the GnRH agonist (GnRHa) triptorelin as preoperative treatment in 51 premenopausal patients receiving letrozole, showed partial responses in 45% of patients, which is comparable to the available evidence in postmenopausal women.[95] OFS was achieved more quickly and maintained more effectively with degarelix than with triptorelin. This observation might deserve additional studies to test if this intervention could also translate into better disease control.

Adjuvant endocrine therapy. The updated results of the SOFT and TEXT studies, after a median follow-up of 8 and 9 years, respectively,[96] confirmed that tamoxifen alone remains the standard of care in women at low risk of relapse, as defined by clinical and immuno-histochemical 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, OFS with tamoxifen or exemestane is associated with a significant improvement in outcomes compared with tamoxifen alone. The identification of women most likely to benefit from treatment escalation is still challenging.[97] In SOFT/TEXT, traditional prognostic features (i.e. patient age, tumour size, grade, lymph node status, ER, progesterone receptor, and Ki67 expression) were combined into a single continuous value called 'composite risk.' In HR+/HER2− patients, the absolute improvement in the 8-year freedom from distant recurrence ranged from <1% to >15% from lowest to highest composite risks, respectively.[98] An OS benefit was also evident in SOFT patients who received adjuvant chemotherapy followed by OFS plus oral ET (4.3% and 2.2% absolute improvement with tamoxifen and exemestane, respectively) but not in TEXT patients (93.4% versus 93.3%). At longer follow-up, young women with HR+ breast cancer have excellent outcomes, often with ET alone.[99] Although the relative efficacy of escalating ET is independent of age, women <35 years have the largest magnitude of absolute improvement in outcomes with OFS.[96,100] OFS timing in

women receiving adjuvant chemotherapy has been a long-standing matter of debate. A nearly identical breast cancer-free interval was observed in women with HR+/HER2− disease in SOFT who received GnRHa sequential to chemotherapy and in women in TEXT who received chemotherapy concurrent to GnRHa, overall and in the subgroup of women <40 years at diagnosis, who are less likely to develop CIA.[101] GnRHa concomitant with chemotherapy has the added benefit of ovarian function protection[102−106]; the safety of concurrent administration has also been shown in this setting.[102]

If GnRHa is to be given in combination with tamoxifen or an aromatase inhibitor (AI), the panel reiterated to give treatment for 5 years based on the SOFT and the TEXT data. In contrast to tamoxifen, an AI should not be given without OFS in premenopausal patients.

After 5 years of adjuvant ET, the risk of recurrence continues for over 20 years. In a recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis (62 923 patients disease-free after 5 years of ET, 15% of whom were <44 years at diagnosis), the risk of distant recurrence was strongly correlated with stage.[107] No new data about extended ET for premenopausal women have been published since BCY3. Therefore, BCY4 reinforces the previous recommendation that extending tamoxifen beyond 5 years should be considered in high-risk patients, if tolerated, based on the ATLAS (premenopausal women represented 10% of the overall population) and aTTom trials.[108,109] The role of extended OFS and tamoxifen or an AI beyond 5 years is unknown given there are no data from studies testing this strategy.

The randomized phase III ASTRRA study showed that adding 2 years of OFS to tamoxifen significantly improved the 5-year DFS (3.6% absolute improvement), compared to tamoxifen alone, in women with late (within 2 years) resumption of ovarian function after chemotherapy.[110] This new treatment possibility is more relevant for older premenopausal women who may experience late ovarian function recovery after CIA. A small phase II randomized trial, published after BCY4, randomized premenopausal women with HR+, node-positive, or tumour size ≥4 cm breast cancer who had received tamoxifen for 2−3 years to continue tamoxifen or switch to anastrozole plus goserelin for a total treatment duration of 5 years.[111] After a median follow-up of 34 months, the preliminary efficacy data show that switching to an AI plus GnRHa was associated with more adverse events (especially bone-related events) with no improvement in disease outcomes (15.2% of patients had DFS events in the switching group versus 13.8% patients in the tamoxifen group).

AIs alone are contraindicated in premenopausal women. BCY4 also reiterated that caution must be taken when considering an AI in premenopausal women who became postmenopausal during the course of treatment due to the potential for recovery of ovarian function.[112] The criteria for defining menopausal status following CIA are defined in the BCY2 paper[29] and reported in Appendix 1.

BCY4 confirmed that hormone levels should be checked if there are concerns that ovarian function is not suppressed, especially if breakthrough bleeding occurs and/or the patient is on an AI. Estradiol assays are not standardized and, especially in presence of very low levels of estradiol, can detect cross-reacting estrogen metabolites; a gas chromatography/mass spectroscopy method should therefore be preferred to monitor therapy in women with breast cancer.[113] 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.[114]

Based on limited available data and concerns about suboptimal OFS with tri-monthly formulations, monthly formulations of GnRHa are preferred,[115] especially in women <35 years of age and in those receiving an AI. A 3-monthly administration 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.

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. Very limited evidence is available on patients' preferences about either approach. In a recent small Australian survey, half of women indicated a preference to non-pharmacological OFS but only a minority recollected this option having being discussed at diagnosis.[116] Inconvenience with monthly GnRHa injections was the main driver toward a preference for non-pharmacological methods; women should also be informed about the possible failure of pharmacological ovarian suppression,[114] the potential occurrence of pregnancy[117] and the need to use non-hormonal contraceptive methods. On the other hand, permanent menopause and potential surgical complications should be discussed in case of non-pharmacological methods, which can be the option of choice in women carrying *BRCA* mutations. Cost considerations (US$5072 for 2 years of goserelin versus US$3966 with oophorectomy)[118] may also play a role, especially in countries with limited resources where GnRHa availability and out-of-pocket costs are problematic.

Younger age is associated with lower adherence and persistence to adjuvant ET.[119,120] Amongst breast cancer patients, non-adherence and early discontinuation of ET have been associated with reduced OS.[121] In the SOFT/TEXT studies, early discontinuation of all assigned ET was approximately 20%,[96] consistent with available evidence.[122]

Determinants of treatment persistence include side-effects, perception of recurrence risk and estimated impact of therapy, social support, the patient-doctor relationship, and the continuity of follow-up care.[123] All efforts must be made to address and identify any of these barriers to treatment adherence and to motivate patients by carefully explaining the expected degree of benefit of the different treatment options.

GnRH agonists and ovarian function preservation. Since BCY3, accumulating evidence supports the efficacy and safety of temporary OFS with GnRHa during chemotherapy to preserve ovarian function, with no significant impact on

disease outcomes.[102,103] BCY4 therefore states the use of GnRHa concomitant with (neo-) adjuvant chemotherapy should be offered to all patients who wish to preserve ovarian function, after discussion of the associated additional toxicity. Efficacy for protection of fertility is still insufficient, especially on different age groups and with different chemotherapy regimens; therefore, BCY4 panellists clearly state GnRHa use during chemotherapy does not replace established fertility preservation methods, which should still be offered to all young patients.

Neo/adjuvant chemotherapy. The additional benefit, if any, of adjuvant chemotherapy in young patients with low-risk HR+ early breast cancer under optimal ET is still undetermined and age should not be the sole reason to prescribe adjuvant chemotherapy in women <40 years at diagnosis.

The role of gene expression signatures in identifying patients with HR+ breast cancer who may not need chemotherapy has been discussed above. Notably, in the SOFT and TEXT studies, for patients who did not receive chemotherapy (8% and 21% node positive in each trial, respectively) the 8- and 9-year rate of freedom from breast cancer exceeded 90%, respectively, with similar favourable outcomes in the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 trial, in which 95% of women did not receive chemotherapy.[96,124]

In the last EBCTCG meta-analysis involving taxane- or anthracycline-based regimens, proportional risk reductions were not significantly affected by age.[125] No studies have specifically investigated different chemotherapy regimens or scheduling in young women. Sequential regimens have at least equal or superior efficacy over combination regimens and are better tolerated.[126] The indication for dose-dense chemotherapy is independent of age.[127] Both a sequential regimen of anthracycline-based chemotherapy followed by adequately dosed Cyclophosphamide/Methotrexate/Fluorouracil (CMF) (oral or day 1 and 8 every 21 days intravenously) or weekly paclitaxel and a combination of a taxane and cyclophosphamide may be valid alternatives.[128,129] In a recently published joint analysis of North American studies that included 31%–38% of patients under 50, there appeared to be a benefit for incorporation of an anthracycline with a taxane in women with high-risk disease or unfavourable features.[130] Similar to older women, standard duration of treatment should include between 4 to 8 cycles of treatment.

The question of whether or not to incorporate platinum agents in the preoperative setting for triple-negative or *BRCA*-associated tumours remains unresolved. The CALGB 40603 phase II study evaluated the addition of carboplatin (with or without bevacizumab) to standard doxorubicin/cyclophosphamide-paclitaxel; despite the improvement in pathological complete response (pCR) from the addition of carboplatin, this did not translate into an improvement in outcome.[131] The GeparSixto phase II study randomized patients with stage II–III triple-negative disease to receive preoperative chemotherapy with paclitaxel and non-pegylated liposomal doxorubicin with or without carboplatin or bevacizumab or both. In this study, 23% of the patients were <40 years and 17.2% harboured a *BRCA1/2* mutation. The addition of carboplatin increased the pCR and improved the DFS in non-*BRCA* patients but not amongst those harbouring a *BRCA* mutation.[132,133] It is worth noting that in this study the chemotherapy protocol did not include an alkylating agent. In a recent review and meta-analysis of randomized trials investigating platinum-based versus platinum-free preoperative chemotherapy in triple-negative breast cancer (TNBC), pCR rates among non-*BRCA* carriers were increased by the addition of carboplatin but not amongst the 96 *BRCA*-mutated patients included in two trials.[134] Notably, there was no improvement in event-free survival or OS from the addition of platinum but there was a significant increase in hematological toxicity. In the phase III BrighTNess study, the addition of veliparib and carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide was evaluated in the preoperative setting for women with TNBC. There was no additional benefit from adding veliparib in addition to that achieved by adding carboplatin in obtaining pCR, nor in the non-*BRCA* or *BRCA*-mutant patients[135] and outcome data is yet immature. Thus, while use of a platinum agent in this setting can certainly be considered, the limitations of the data need to be communicated clearly to the patients, including the additional toxicity that may compromise standard duration and dosing of systemic treatment, and the potential for additional gonado-toxicity. There is still no data on the use of platinum agents in the adjuvant setting.

For patients with triple-negative disease not achieving a pCR after standard preoperative regimens, addition of 6–8 cycles of capecitabine may be considered, as in other age groups.[136]

Adjuvant anti-HER-2 therapy. The benefit of adjuvant trastuzumab appears independent of age in all published studies[9] and prescription considerations for anti-HER2 therapies should be the same as for other age groups.

Several studies have evaluated shorter duration regimens of trastuzumab. Only one study demonstrated non-inferiority of 6 months compared with 1 year of trastuzumab.[137] A recent meta-analysis evaluating shorter durations of trastuzumab compared with 1 year of treatment concluded that 1 year of treatment was superior and should be considered standard of care.[138] For women with HER2+, node-positive or high-risk node-negative breast cancer (tumour size ≥0.5 cm), with a normal left ventricular ejection fraction and without significant cardiovascular risk factors, 1 year of anti-HER2 treatment remains standard of care. Nonetheless, the panel agreed that shorter trastuzumab duration can be discussed in highly selected low-risk patients on an individual basis.

In selected patients with small, node-negative, HER2+ breast cancer, administration of 12 weeks of weekly paclitaxel and trastuzumab (followed by completion of 1 year of trastuzumab) without anthracyclines can be discussed. At 7-year follow-up, very few distant recurrences occurred with this regimen in the APT study and the OS was 95%.[139]

The panel confirmed the addition of pertuzumab to trastuzumab in the preoperative setting may be offered, when available, as in other age groups.[140] Based on data from the APHINITY study (13.6% of patients were <40 in each treatment arm) the addition of pertuzumab to trastuzumab may be offered in the adjuvant setting for patients at high risk of relapse but the panel acknowledged no information is available on the efficacy of such a treatment in women who received double HER2-blockade as preoperative therapy.[141]

In case of residual pathological disease after preoperative chemotherapy and anti-HER2 therapy, completion of 1 year of adjuvant anti-HER2 therapy with trastuzumab-emtansine (TDM-1) has become standard of care. In the interim analysis of the KATHERINE study (20% of patients were <40 in each treatment arm), the 3-year invasive disease-free survival was improved by 11.3% in patients receiving TDM-1 compared with standard trastuzumab, irrespective of the extent of residual disease, HR status and type of preoperative HER2-targeted therapy (18% of patients received trastuzumab + pertuzumab in both arms).[142]

Neratinib demonstrated an outcome benefit in patients with high-risk HER2+ disease when given for a year after completion of 1 year of trastuzumab—in particular, a significant benefit was seen in the HR+ subgroup. Neratinib can cause significant toxicity, particularly diarrhea, which needs to be managed prophylactically.[143] There is no data about the efficacy of neratinib after 1 year of adjuvant trastuzumab + pertuzumab or after post-neoadjuvant TDM-1. The panel agreed neratinib can be discussed, if available, as in other age groups, in patients at high risk of relapse (e.g. node+, HR+); the increased toxicity needs to be clearly communicated to patients.

Adjuvant bisphosphonates. As no new data on the benefit of adjuvant bisphosphonates among premenopausal women emerged after BCY3, the panel confirms they may be considered for young women receiving OFS. A recent case-control study evaluating the effect of recent bisphosphonate exposure on pregnant women demonstrated no major teratogenic effects; however, increased rates of neonatal complications and spontaneous abortions were reported.[144] Given the long half-life of currently used bisphosphonates, caution is needed in women interested in future fertility.

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 BCY4 panel endorses the ESO—ESMO ABC4 guidelines for the management of advanced breast cancer (ABC) and reiterated that young age alone should not be a reason to prescribe more aggressive therapy.[145] In particular, BCY4 endorses the ABC4 statements that (i) young women with ER+ ABC should have adequate OFS/ovarian function ablation and then 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 for enrolment of both pre- and postmenopausal women, and men.

BCY4 panel members recognize that this field has evolved in recent years. Notably, the MONALEESA-7 trial, which evaluated ET and ribociclib in ABC, was designed exclusively for women who were pre/perimenopausal at diagnosis. The study was the first study of cyclin-dependent kinase (CDK) inhibitors with ET in ABC to demonstrate both a significant progression-free survival (PFS) and OS advantage favouring the ribociclib arm.[146,147] The Young-PEARL phase II study, in tamoxifen-pretreated premenopausal women with ER+/HER2− ABC, showed palbociclib plus exemestane and OFS prolonged PFS versus capecitabine (20.1 versus 14.4 months, respectively; HR: 0.659; $P = 0.0469$).[148]

As for older women with the same disease characteristics, young age by itself is not an indication to prescribe combination chemotherapy over sequential use of monotherapy.

Young women with ABC have unique medical and psychosocial concerns that need to be considered and addressed.[149] Although 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.

Loco-regional relapse. Young age is a risk factor for local relapse; therefore, careful attention to margin status is warranted in young women.[150] Following loco-regional relapse, BCY4 confirmed chemotherapy should be considered in women with ER− tumours, as demonstrated in the CALOR study.[151,152] 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.** The BCY4 panel confirmed BCY2/3 recommendations for prevention, surveillance, treatment and risk-reducing strategies. There are conflicting retrospective data whether therapeutic mastectomy plus contralateral risk-reducing mastectomy has an impact on survival in a woman with early breast cancer in the context of a hereditary cancer syndrome. Two studies suggested a survival benefit amongst those that at diagnosis were under the age of 50 and had early stage disease with favourable features,[153,154] while other studies have failed to demonstrate a benefit.[155] It should be communicated to patients that breast imaging is a screening/surveillance tool for detecting early disease whereas surgery is a risk-reducing procedure for actively reducing the risk of the

development of disease.[154,156,157] Breast MRI surveillance is the preferred surveillance modality for high-risk women,[158] when available.

For breast cancer survivors and asymptomatic carriers harbouring a *BRCA1/2* mutation, RRSO should be discussed from the age of 35. Optimally, family planning should be completed before RRSO. For *BRCA1* mutation carriers, RRSO is recommended between age 35 and 40 and for *BRCA2* mutation carriers between ages 40 and 45, always respecting patient's preferences and considering the family history. Indications and timing of RRSO for other highly penetrant mutations may be postponed to age 45—50, following available international/national guidelines. Salpingectomy (removal of the fallopian tubes) alone is *not* the standard of care; clinical trials are ongoing (ClinicalTrials.gov Identifier: NCT02321228, NCT01907789, NCT01608074).

There remains no definitive conclusion on the best chemotherapy regimen for *BRCA*-associated breast cancer patients in the neo/adjuvant setting and the panel recommended that standard prognostic features should be used to decide treatment in early disease.[159]

The role of platinum agents in the preoperative setting in *BRCA* carriers was discussed above.

The superiority of a platinum agent, compared with taxanes, was confirmed in the ABC setting for *BRCA*-associated triple-negative disease, based on the results of the TNT trial.[160]

The use PARP inhibitors amongst women with *BRCA*-mutated ABC has been established following the publication of two phase III studies confirming superiority over chemotherapy of physician choice (that notably did not include a platinum agent).

As expected by the prerequisite of a *BRCA1* or *BRCA2* mutation, median age in these studies was around 45 years. The OlympiAD study demonstrated superiority of olaparib including a superior response rate and PFS with a more favourable toxicity profile.[161] In a predefined subgroup analysis, an OS benefit of 7.9 months (22.6 versus 14.7) favouring olaparib was noted amongst patients who had not received prior chemotherapy in the metastatic setting. In this study, patients had received a prior anthracycline and taxane, those that were HR+ had progressed on at least one line of ET, and patients had not relapsed within 12 months of neo/adjuvant platinum therapy or progressed during platinum therapy in the advanced setting. The EMBRACA study had a similar design and demonstrated the superiority of talazoparib.[162] The inclusion criteria slightly differed from that of the OlympiAD study—in the EMBRACA study patients had to have received a prior anthracycline and/or taxane, those that were HR+ could have received a previous line of ET but this was not mandatory, and patients must not have relapsed within 6 months of neo/adjuvant platinum therapy or progressed during platinum therapy in the advanced setting.

Of note, somatic *BRCA1/2* pathogenic gene variants in breast tumours can be found in a very small proportion of patients not harbouring germline mutations[163] and are classified tier IIIA by the ESMO Scale of Clinical Actionability of molecular Targets (ESCAT).[164] At present, the clinical utility and therapeutic implications of somatic *BRCA1/2* mutations in breast tumours is not established and is the subject of ongoing research. For the time being, somatic *BRCA1/2* testing should not be used as an alternative to germline testing.

Male breast cancer. Male breast cancer accounts for about 1% of all breast cancers.[165] Although in the USA the incidence increased slightly until 2000 and then plateaued, followed by a slight decrease from 2000 to 2005,[166] the available European data show, overall, a stable incidence from 1970 to 2000 with a slight increase from the second half of the 1990s onward.[167] The International Male Breast Cancer Program, run under the BIG and NABCG umbrellas and, coordinated by the European Organization for Research and Treatment of Cancer (EORTC) and TBCRC, allowed characterizing 1483 male patients (1.6% <40 years) diagnosed between 1990 and 2010 in 93 centres/9 countries worldwide.[168] The analysis confirmed male breast cancer is usually ER-, progesterone receptor (PA) and androgen receptor-positive and HER2-negative. Of note, 56% patients had T1 tumours but only 4% had BCS and ER was highly positive in >90% of cases but only 77% received adjuvant ET. In the time period analyzed, overall mortality decreased significantly over time (44.8% in 1990—1995 versus 26.9% in 2006—2010), whereas a less pronounced improvement was registered in breast cancer specific mortality (15.1% in 1990—1995 versus 7.6% in 2006—2010).

A recent analysis of the SEER population identified 151 male patients diagnosed with breast cancer <40 years between 1988 and 2012. Younger patients had less grade 1—2 (42.38% versus 55.18%) and HR+ (67.5% versus 76.68% for ER status and 54.30% versus 67.29% for PR status) tumours compared with the 6930 male patients with breast cancer diagnosed at ≥40 years.[169] In this observational study, young patients had a significantly better OS but a comparable breast cancer specific survival compared with older male patients.

For the first time, BCY4 included a statement on male breast cancer, recommending routine management in accordance with international recommendations/guidelines[167] and strongly supporting inclusion of male breast cancer patients in clinical trials in both the early and advanced settings.

Supportive and follow-up care

Follow-up care in young women should follow the same guidelines as in older women[34,170,171] and supportive treatment/prevention of specific symptoms and side-effects should follow current recommendations. It should be emphasized that breast care nurses[45] and other supportive care staff can play a critical role in providing survivorship care and support for young patients and their families.

Standardized patient-reported outcome measurements (PROMs) may allow easy and efficient collection of most common side-effects along the full cycle of breast cancer

treatment, enabling their monitoring in routine clinical practice and the development of targeted interventions.[172,173]

Electronic devices and online applications are convenient and efficient tools for gathering information from patients and allow real-time integration of patient-reported outcome (PRO) data in the electronic medical record and earlier interventions by the health care team.[173]

Dedicated survivorship clinics that address assessment and management of early and late treatment toxicities and treatment adherence are valuable in this population.

Psychosocial issues. Young women have been documented to be at greater risk of psychosocial morbidity after a diagnosis of breast cancer, particularly those who receive chemotherapy and/or undergo a menopausal transition with treatment.[174,175] 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 and/or familial psychosocial interventions should be promptly proposed during the different phases of the disease. Social issues that need to be addressed include return to work, family planning and financial loss.

Considerations and recommendations by the BCY4 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 remain mostly unchanged since BCY3 and appear in Appendix 1.

Patient advocacy statements. BCY4 included a patient advocacy workshop and the advocacy group presented a manifesto that was developed and presented in the panel consensus session of the conference. They identified the following key areas of concern for young women with breast cancer that need prioritization by the medical community:

1. Quality of life during treatment, with the importance of recognition of the individual's needs and preferences
2. Post-treatment survivorship care addressing psychosocial, economic and health-related issues (including ongoing and late side effects of treatment)
3. Fertility and pregnancy after breast cancer
4. Importance of clinical trials for young women with breast cancer
5. Provision of support for patients and their immediate support networks

Conclusions

Since BCY3, progress has been made. In particular, 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 POSITIVE study has almost finished recruitment to prospectively address the issue of pregnancy after breast cancer and ET interruption amongst women with HR+ early breast cancer. However, there is still an ongoing need for further research and clinical trials that specifically address several clinical and prognostic aspects and concerns of young women with breast cancer.

The multidisciplinary approach remains the backbone of care to ensure a holistic, comprehensive management strategy addressing the often complex oncological, surgical, fertility, genetic, psychosocial and lifestyle factors to ensure optimal outcomes for young women with breast cancer.

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APPENDIX 1

Defining menopausal status following chemotherapy

Chemotherapy may cause transient or permanent damage to the oocyte pool and ovarian reserve, depending on the chemotherapy regimen and cumulative dose, the pre-existing ovarian reserve, and the age of the woman.[176] Menopause occurs when the remaining follicle count reaches 1000 or below. While natural onset menopause is defined as 12 months after the last menstrual period, CIA is often mistaken for true menopause, even though menses may resume even after more than a year from the end of chemotherapy. As such, in the absence of a clear-cut definition, menopausal status following chemotherapy can be empirically diagnosed in case of amenorrhea for at least $\geq$2 years, a persistent postmenopausal hormonal profile and a vaginal ultrasound indicating the ovaries are no longer functioning.

Supportive and follow-up care issues unchanged or slightly modified since BCY3

Fertility, contraception and premature menopause. Fertility and family planning are major concerns for young women with breast cancer. In the ongoing prospective cohort study Helping Ourselves, Helping Others (HOHO): The Young Women's Breast Cancer study, conducted in the USA and Europe in nearly 1000 young breast cancer patients, almost 2/3 of women discussed fertility issues before starting therapy, >50% were concerned about becoming infertile after treatment, and 15% decided not to follow prescribed therapies because of fertility concerns.[25,26] Many young women will still be fertile after treatment and some will be interested in having a future biologic child. Discussion of these issues at diagnosis, elicitation of patient interest in future fertility and appraising patients of the risks of amenorrhea and potential infertility as well as premature menopause have been recommended by other guideline panels as an important component of quality oncology care and are reinforced here. Appropriate early referrals for fertility preservation strategies, based on existing practice guidelines[177,178] and techniques[179] as well as psychosocial support surrounding this extremely complex issue should also be made. The majority of the panel recognizes that this is one of the most difficult and emotionally challenging issues facing young survivors. Pregnancy during active treatment of breast cancer should be discouraged due to risk of teratogenesis, so effective contraception is recommended and proactive counselling should be provided for each patient. Exogenous hormonal contraception is generally contraindicated in breast cancer survivors and alternative strategies (i.e. barrier methods such as condoms, cervical diaphragm and copper IUDs, or male contraception) should be considered.[180] The safety of levonorgestrel-releasing intrauterine device (IUD) (Mirena®), which delivers high local but low systemic doses of progestogen is controversial; a large epidemiological study has suggested that its use may increase the risk of developing breast cancer[181] whereas a meta-analysis of three randomized clinical trials assessing its efficacy on preventing tamoxifen-induced endometrial lesions in 359 breast cancer patients did not show an increased incidence in breast cancer recurrence and cancer-induced death.[182] In the absence of definitive data, the panel recommends patients should be advised to use alternative non-hormonal contraception.

Premature menopausal symptoms may include vasomotor symptoms, sleep disturbance, fatigue and weight gain as well as sexual dysfunction—all of which can be very distressing for young women.[39] For hot flashes, megestrol acetate and medroxyprogesterone acetate have been proven effective[183–185]; however, long-term safety data is limited. Numerous studies exist that evaluated the use of non-hormonal medications and acupuncture in the management of hot flashes but this is beyond the scope of these guidelines.

Sexual functioning. Sexual dysfunction is a major issue having significant impact on quality of life both amongst women with CIA[38] and amongst women receiving OFS and oral ET.[186] This issue encompasses vaginal dryness, dyspareunia, decreased libido, body-image concerns, anxiety and depression, fatigue and side-effects from medications (including antidepressants). The panel reiterated that appropriate counselling should be available, sexual health should be included in the survivorship care plan and further research is needed to improve management. First-choice treatment includes non-hormonal therapies, e.g. vaginal moisturizers, lubricants and gels.[187] In patients where aforementioned measures do not help, consideration of limited and selective use of hormonal agents with a conversation about the lack of data on risk may be considered. There is a growing body of evidence to suggest that low-dose vaginal hormones [e.g. 10-μg estradiol-releasing intravaginal tablet or 4-μg estrogen vaginal insert and intravaginal dehydroepiandrosterone (prasterone)] may be safe during concurrent use with an AI[188,189]; however, safety data is limited and follow-up short, with one of the key challenges being lack of uniformity and clear cut-off definitions of serum estrogen/estradiol levels and variability in serum estrogen levels over time during AI use as illustrated in the SOFT-EST sub-study.[114,190] Vaginal CO_2 laser therapy has been shown to improve symptoms in 10 observational studies but no data from randomized trials are available yet.[191] The US Food and Drug Administration recently issued a warning against CO_2 laser therapy in the absence of long-term data on safety, efficacy and health economic costs.

Pregnancy after breast cancer. All retrospective available data report no detrimental effect of a subsequent pregnancy on breast cancer outcome,[192–195] also in women with HR+ disease.[196] Therefore, the BCY4 panel confirmed pregnancy after breast cancer should not be discouraged, even though definitive data from prospective clinical trials are needed.[193] In a recent survey about fertility concerns, maternity desire and interest in a study of ET interruption to

allow pregnancy (212 young patients with HR+ early breast cancer), 37% of respondents were interested in such a study with higher interest (57%) reported in younger patients (≤30 years).[197] The prospective global cooperative POSITIVE study (IBCSG 48-14/BIG 8-13, NCT02308085) is actively recruiting with the aim of assessing the safety and feasibility of interrupting ET for pregnancy after breast cancer.

Outside of a clinical trial, the BCY4 panel recommended that patients with HR+ disease should discuss with their physician the uncertainties about the timing of pregnancy after diagnosis, complete at least 18–24 months of ET before attempting pregnancy and take into account the individual prognosis based on initial stage and biology. Treatment should be resumed and completed according to initial planning after delivery and breastfeeding.

Bone health. Bone health should be checked regularly (similar to older women) in young women with breast cancer, especially in those receiving OFS plus oral ET. Of note, in contrast with its effects on bones in postmenopausal women, tamoxifen can cause bone loss in premenopausal patients, likely because it is a weaker agonist in the bones than the premenopausal endogenous estrogens it is blocking.[198,199] As a consequence, in all young patients special emphasis on dietary education [i.e. adequate intake of calcium through diet and supplements (1000 mg/day) and vitamin D (800–1000 UI/day)] and regular weight-bearing exercise is needed.[200] Treatment-related bone loss should be managed accordingly, independent of age. Recent joint Cancer Care Ontario and American Society of Clinical Oncology (ASCO) guidelines on use of adjuvant bisphosphonates support the use of 6-monthly zoledronate or daily clodronate for postmenopausal women eligible for systemic therapy, with the definition of postmenopausal women including women under OFS.[201]

Cognitive impairment. Neurocognitive symptoms ('onco or chemo brain') are frequently described among young breast cancer survivors. The recently published results of the UMBRELLA study confirm that chemotherapy is associated with impaired subjective self-reported cognitive functioning in breast cancer patients up to 2 years after diagnosis and the impact is most pronounced in younger patients.[202] Chemotherapy-induced cognitive impairment is likely multifactorial[203] but neither the predictors nor the possible interventions are well understood. Previous investigations in a small sample of patients showed MRI changes in cerebral white matter 3–5 months after chemotherapy, which correlated with performance decreases in verbal memory and attention.[204] In the same group of patients, white matter alterations and reduced cognitive performance recovered 3–4 years after treatment. Almost all patients in the chemotherapy group became menopausal in this time interval, which was not the case amongst those who did not receive chemotherapy or in the control group.[205] Hormonal changes linked with ET and CIA can influence cognition and MRI findings; larger samples are therefore needed to assess the differential effects of treatment and menopausal status on cognitive function. Few specific investigations have been conducted in premenopausal women. In the ZIPP trial (6 cycles of CMF ± 2 years of goserelin, goserelin plus tamoxifen, or tamoxifen), no effect of treatment on patients' self-evaluation of memory and concentration was shown.[206] Cognitive function has been prospectively investigated in patients participating in the CO-SOFT substudy. Despite the small sample size (86 participants), no evidence was provided that adding OFS to adjuvant oral ET substantially affects global cognitive function.[207] A recent meta-analysis comparing cognitive effects in patients receiving ET versus controls and tamoxifen versus AIs showed verbal learning/memory was the only domain where ET patients performed worse than both non-cancer and breast cancer controls, suggesting specific adverse effects on this domain. Tamoxifen and AI patients did not differ from one another overall but subgroup analyses indicated that tamoxifen patients performed better than non-steroidal AI patients in all domains except processing speed and psychomotor efficiency, but showed few performance differences relative to steroidal AI patients.[208] Given the wider use of AIs in young women, additional studies assessing differences between steroidal and non-steroidal AIs are warranted. Patient-reported symptoms (forgetfulness, difficulty with concentration, fatigue, distractibility and difficulty with word finding) rarely correlate with neuroimaging studies and neuropsychiatric evaluation.

Lifestyle changes. The panel reiterated that young patients should be strongly encouraged to adopt healthy lifestyle changes that include maintaining healthy BMI (≤25), performing regular aerobic exercise (equivalent of at least 150 min/week of at least moderate intensity),[209] not smoking and limiting alcohol intake.

Breast cancer during pregnancy. Management of patients with breast cancer during pregnancy is outside the scope of these guidelines and should follow established recommendations.[210] In general, pregnant women, from the second trimester, can and should be treated as closely as possible to the general guidelines keeping in mind that hormonal agents and anti-HER2 therapies should be avoided during gestation. Recent evidence from a prospective/retrospective registry show similar OS for patients diagnosed during pregnancy compared with non-pregnant patients, supporting the indication to start treatment while continuing pregnancy.[211]