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ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

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ABSTRACT

The 3rd International Consensus Conference for Breast Cancer in Young Women (BCY3) took place in November 2016, in Lugano, Switzerland organized by the European School of Oncology (ESO) and the European Society of Medical Oncologists (ESMO). Consensus recommendations for the management of breast cancer in young women were updated from BCY2 with incorporation of new evidence to inform the guidelines, and areas of research priorities were identified. This manuscript summarizes the ESO-ESMO international consensus recommendations, which are also endorsed by the European Society of Breast Specialists (EUSOMA).

1. Introduction

Breast cancer in young women (≤40 years) is an uncommon disease with a 0.40–0.45% cumulative risk by 40 years of age [1], representing less than 7% of all women diagnosed with breast cancer in developed countries [2]. Breast cancer in young women has greater morbidity than in older women and a greater case-fatality rate with increased risk of both local and systemic disease recurrence and death [3]. Young women are diagnosed with more advanced disease, have a greater proportion of triple negative and HER2/neu positive disease and have less favourable outcome than older women especially amongst endocrine-responsive tumours [4–9]. The consequences of treatments including premature menopause and impaired fertility have far reaching impact for these women both medically and psycho-socially, thus, specific multimodality care is paramount. Most of what we know about breast cancer is based upon studies in older women, and young women are under-represented in more contemporary research evaluating risk-stratification models and molecular tools [10,11]. Many young women may be at risk of being over-treated based solely on age considerations.

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A hereditary predisposition is more common amongst young women and may impact decisions on local and systemic disease management. Women with a hereditary predisposition syndrome also need to tackle the additional challenges of future cancer risk reduction which may include risk-reducing surgeries (including contra-lateral mastectomy and salpingo-oophorectomy) [12], cascade family risk assessment, pre-gestational testing, and these decisions are often accompanied by further psychosocial stress [13–15].

Although young women with breast cancer are at increased risk of psychological distress at diagnosis and in long-term follow-up [16,17] they have growing resources available to help them navigate the disease and survivorship [18]. Despite a number of ongoing prospective studies focused on young women, further research and intervention studies are needed in order to understand the unique biology of young women with breast cancer and improve outcomes in this population [5,19,20].

Consistent with previous guidelines [21,22], 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 metastatic disease before the age of 40. The application and use of consensus guidelines have previously been demonstrated to have a positive impact on breast cancer care [23,24].

BCY 3 took place in Lugano, Switzerland on November 10th-12th 2016 with over 300 participants including health professionals and patient advocates, who developed and presented their first manifesto. The BCY3 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).

2. Methodology

Recommendations from BCY2 formed the basis for the current recommendations [25]. New and updated statements from BCY2 circulated amongst the panellists prior to the BCY3 conference and were then presented, discussed, adapted and voted on during the final consensus session of BCY3. All panel members were instructed to vote on all questions; with members with a potential conflict of interest or who did not feel comfortable responding (e.g., due to lack of expertise on the topic) instructed to abstain for that particular question. Where there were areas of substantial controversy or disagreement, it is noted in the discussion of the recommendations. These recommendations were later circulated to panel members by email for comments, updating based on recent reports, and corrections on content and wording.

Table 1 describes the grading system used.[26] Statements without grading were considered justified standard clinical practice by the panel experts (see Tables 2–4).

Appendix 1 Definition of menopause following chemotherapy-induced amenorrhoea and Supportive & follow-up care issues unchanged or slightly modified since BCY2

Supplementary Table 1 lists all members of the BCY3 consensus panel and their disclosure of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

3. General considerations when caring for young women with breast cancer

Care of young women with breast cancer is complex and multifaceted and thus requires specific multi-disciplinary care (medical and radiation oncologist, breast and plastic surgeon, geneticist, fertility, sexual-therapy and psycho-social experts). It is well established that this care is best provided in dedicated breast clinics or services [27,28] especially for young patients [29]. The panel reinforced statements made in BCY1 & BCY2 emphasizing the importance of multi-disciplinary care while also recognizing that this is not always possible in settings with more limited resources. The panel further recommended that personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, and socio-economic impact be incorporated into individual treatment planning.

In addition to supporting development and use of navigation tools and training of navigators, the consensus highlighted the importance of developing scientifically validated, innovative and structured communication and supportive tools (e.g. online programs, web-based interventions) that should ideally be disseminated in different languages. This would help young patients to overcome barriers to accessing support, such as child and family care, work timetables and challenges of geographical distance from healthcare services. 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 reemphasized that many specific issues in the treatment of young women with breast cancer, in all settings of the disease, still lack evidence-based standards. Specifically, systematic research into age-specific tumor characteristics is needed. In particular, the prognostic and predictive impact of multi-gene expression profiles and mutational status to identify specific genomic aberrations that could open the door for tailored therapeutic interventions.

Extensive data suggest that tumours in younger women tend to be of more aggressive phenotypes. These studies suggested unique biology and aggressive phenotypes of tumors arising in younger patients [4–8,19,30–32], however, more recent studies indicate that the impact of age on prognosis is likely associated with subtype, with a worse prognosis amongst younger patients with luminal tumors [9]. This study was however based on a cohort of women for whom hormonal therapy options were limited to Tamoxifen, prior to publication of the SOFT and TEXT studies that support ovarian function suppression as a further treatment option [33,34].

The panel reinforced statements in BCY1 & BCY2 that treatment of young women, both in the early and the advanced setting, should be driven by similar factor as for older women, i.e. by the biological characteristics of the tumour, including hormone receptors (HR), HER2/neu, proliferation and grade, tumour stage, patient's comorbidities and personal preferences, especially when benefits may be modest or options are equivalent in outcome (e.g., mastectomy versus breast conservation) [27,35]. The panel wished to emphasize that chemotherapy or treatment-induced amenorrhoea is not equivalent to menopause, and that the hormonal milieu of a young woman remains different from that of older women. Finally and importantly, young age alone is not a reason to prescribe more aggressive therapy.

3.1. Diagnosis & imaging for staging and follow-up

The panel re-confirmed that there is no evidence that the addition of MRI improves outcomes both in young and older women [36–38] and that ultrasound alone is not an acceptable or validated screening tool in young women. While the clinical availability and utilization of tomosynthesis has grown, no specific data are available about its use in young women, and as such, use and indications are the same as in other age groups. There is no clear role for routine screening by any imaging for early detection in healthy, average risk young women.

Table 1
Levels of evidence grading system [26].

Grade of Recommendation/Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

The panel emphasized that the timing of the menstrual cycle should be taken into account when planning and performing MRI (and mammography, if done) in order to optimize accuracy of imaging with optimal timing being in the first half of the menstrual cycle (day 7–10) [39].

For BRCA 1/2 mutation carriers and others at high risk based on family history or predisposing mutations in other genes (e.g. p53, PALB2, CHEK2, ATM), and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with MRI [40,41] and mammography with or without ultrasound is recommended in accordance with currently available guidelines (ESMO and NCCN) [42,43].

For BRCA 1/2 mutation and other cancer susceptibility genes carriers (e.g. RAD51C, p53, BRIP1) who have not undergone salpingo-oophorectomy, gynecologic surveillance every six months is recommended, beginning at age 30 or 5 years younger than the earliest diagnosis of a gynecological malignancy in the family, whichever comes earlier. Data supporting this approach as an effective screening method remain limited.

The panel supports following recently updated international guidelines (such as ESMO or NCCN) for screening and prevention in women with a hereditary cancer syndrome [42,44]. In countries where evidence-based national guidelines are available they may be used to guide local clinical practice.

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.

3.2. Genetic counseling and testing

The panel confirmed that genetic counseling should be offered for every young woman, irrespective of whether there's a family history of breast cancer or the tumor is of triple negative subtype. When possible and relevant to patient care (e.g. selection of breast surgery), counseling should be offered before the commencement of treatment. Practice should be in keeping with local guidelines and testing availability and reimbursement on a country-by-country basis.

Genetic testing has traditionally been conducted following formal genetic counseling, however as genetic testing becomes more widely available and in light of limited access to genetic counsellors/services in many settings, alternative strategies for informed decision making prior to genetic testing need to be further researched.

Genes to be tested for depend on personal and family history. Although BRCA1/2 are the most frequently mutated genes, other additional moderate-to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor. When a hereditary cancer syndrome is suspected and a mutation in BRCA1/2 has not been identified, multi-gene panel testing may be considered. Practice should be guided by high quality national/international guidelines. As commercially available multi-gene panels include different 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) [45].

The patient must be made aware that the presence of a predisposing mutation may impact clinical management, follow-up and decision making, as well as for other family members. Additionally, 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.

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 issues at breast cancer diagnosis, access to genetic counseling should be offered again during follow-up, to address issues of specific intensive surveillance and risk reduction of additional primary tumors, and risk assignment and stratification for relatives.

At the present time, the clinical utility and therapeutic implications of somatic BRCA1/2 mutations in breast tumors are yet to be established and need further research.

Table 2
BCY1 & BCY2 statements with only minor updates or no updates.

General recommendations	LoE
1. 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
2. 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
3. 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
4. In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, & socio-economic impact are highly recommended as part of the individual treatment planning.	Expert Opinion
5. Young age by itself should not be the reason to prescribe more aggressive therapy than in other age groups. Factors influencing choice of treatment should include but not be limited to the biological characteristics of the tumor (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumor stage, genetic status (if available) and patient's co-morbidities and preferences.	Expert Opinion
Screening, Diagnosis & imaging for Staging and Follow-up	
6. There is no clear role for routine screening by any imaging for early breast cancer detection in healthy, average risk young women.	IA
However, in the presence of a cancer predisposition syndrome (germline mutation in a known cancer predisposition gene), significant family history, or prior personal history of ionizing radiation to the chest, consideration may be given to screening breast MRI.	Expert Opinion
7. 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 particular in the setting of very dense breast tissue or consideration of a genetic predisposition or other individuals at high risk (i.e. radiotherapy for childhood malignancy).	IIC
Genetic Counseling and Testing	
8. Every young woman with breast cancer should be offered genetic counseling preferably before starting treatment. Practice should follow national/international guidelines on a country-by-country basis. For those women who are not ready to consider genetic issues at diagnosis, access to genetic counseling should be offered again during follow-up, to address issues of surveillance and risk reduction of additional primary tumors for the patient, and risk issues for relatives.	Expert Opinion
9. Genetic testing should be conducted only following genetic counseling with a genetic counselor (or other trained health professional) who explains the implications of the results. The patient must be made aware that the presence of a predisposing mutation may have an impact on her management, follow-up and decision making, as well as family members. Genes to be tested for are BRCA1 and BRCA2 (other additional high-penetrance genes can be tested if deemed necessary by the geneticist).	Expert Opinion
Early Breast Cancer Loco-regional Treatment	
10. Surgical treatment of young patients with EBC − while being tailored to the individual patient - should in general not differ from that of older patients.	IA
Breast conserving surgery should be performed as the first option whenever suitable, as it provides the same overall survival than mastectomy.	I A
11. 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
12. 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
13. In young women with the diagnosis of either invasive disease or pre-invasive lesions, who are not high-risk mutation carriers, there is no evidence for improved OS by performing risk-reducing bilateral mastectomy.	IB
14. 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
15. Indications for adjuvant RT are the same as for older patients.	IB
After breast-conserving surgery, breast radiation + boost are recommended. Young patients should be informed about the high local recurrence risk if RT is avoided after BCS and about the benefit of RT on reduction of local recurrence and improvement in OS. This must be balanced with information about the potential long-term toxicities.	
Partial breast irradiation (PBI) has not been sufficiently studied in young patients and should not be performed in this age group.	
16. Indications of adjuvant RT are independent of BRCA status	Expert Opinion
Adjuvant Systemic Treatment	
17. 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
18. Neoadjuvant ET should not be used in young women outside clinical trials.	Expert opinion
19. All patients with HR positive disease should receive adjuvant ET.	IA
Tamoxifen alone for 5 years is indicated for low risk patients.	IA
Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively post-menopausal.	IA
Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.	IA
The addition of a GnRH agonist (or ovarian ablation) to tamoxifen is indicated in patients at higher risk who remain premenopausal after chemotherapy.	IA
20. AIs alone are contra-indicated in pre-menopausal women.	IA
The combination of an aromatase inhibitor and a GnRH agonist (or ovarian ablation) should be considered in high risk patients if tolerated.	IA
21. 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. The optimal duration of GnRH agonist alone is currently unknown. The choice will depend on risk of relapse, toxicity and patient preferences.	IA
22. If a GnRH agonist is used in this age group, it should be given on a monthly basis (and not on a 3-monthly basis) to optimize ovarian suppression.	II B
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
23. Young patients (>35 years at diagnosis) with low risk HR positive disease have excellent outcomes with ET alone: the addition of adjuvant chemotherapy should not be standard but discussed on an individual basis.	IB
24. The indications for and the choice of adjuvant systemic treatment for invasive breast cancer should be driven, as for women in other age categories, by extent of disease and the biological characteristics of the tumor (including, but not limited to, ER/PR and HER-2 receptors, proliferation, and grade) and patient's comorbidities.	IA
25. For the time being, the type of systemic treatment of EBC is independent of BRCA or any other constitutional genetic status.	Expert Opinion

Table 2 (*continued*)

General recommendations	LoE
26. 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.	IA
27. Standard duration of treatment (minimum of 4 and maximum of 8 cycles) should be prescribed.	IA
Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated. Young age by itself should not be an indication to prescribe a combination of cytotoxic agents.	IA
28. 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 (tumor 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
29. 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.	
30. The management of inflammatory breast cancer in young women should be the same as in the older breast cancer population.	Expert Opinion
Advanced Breast Cancer	
31. 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 3 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.	IC
32. The BCY3 panel endorses the ESO-ESMO ABC 3 guidelines for the management of ABC in pre-menopausal women.	IA
33. 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
Germline BRCA 1/2 mutation carriers	
34. For survivors harboring a BRCA 1/2 or (other) strongly predisposing mutation, bilateral risk-reducing mastectomy may be considered, although there is no definite evidence that it leads to a survival benefit. Therapeutic decisions should reflect a balance between the risk of recurrence of the diagnosed breast cancer and the potential benefit of preventing an additional primary tumor.	IIB
35. 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 & ATM mutations, for which a very high risk of secondary cancers has been described after radiation therapy.	I B
Radiation therapy should be carefully discussed on an individual basis for these patients.	IIC
36. A platinum agent should be considered in the treatment of BRCA-associated advanced breast cancer.	IB
Supportive and follow-up care	
37. 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, gynaecologists and fertility experts, among others.	Expert Opinion
38. 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
39. All young women should be referred for specialist counselling/consultation if interested in fertility preservation prior to commencement of any therapy.	Expert Opinion
40. The use of GnRH analogue concomitant with adjuvant CT should be discussed on a case by case basis to preserve ovarian function and possibly fertility	I B
41. 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
42. Premature menopause and/or treatment related amenorrhea increase the risk of bone thinning and patients should be counselled, monitored and treated accordingly.	I A
43. Pregnancy after breast cancer should not be discouraged even in patients with HR positive disease. It should be noted that all currently available data available are retrospective/observational.	I B
44. 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
45. Young patients should be strongly encouraged to adopt the following healthy life style changes: • maintain BMI ≤25 • perform regular aerobic exercise • not to smoke • to limit daily alcohol intake	Expert Opinion

4. Early breast cancer

4.1. Loco-regional treatment

4.1.1. Surgery

Although young age is an independent risk factor for increased local recurrence [46,47], there is no evidence that mastectomy improves overall survival (OS) in young breast cancer patients, (unless clinically indicated) [48]. The panel remains concerned at the ongoing trend for routine bilateral mastectomies particularly in younger women. Whenever an obvious postoperative asymmetry is expected from BCS, oncoplastic repair techniques by a dedicated breast surgical team should be offered in order to maximize cosmetic and self-image results. 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 [49,50]. Immediate breast reconstruction with expanders, implants or flaps after mastectomy does not compromise survival outcome 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). Radiotherapy (RT) is not a stand-alone reason to postpone reconstruction.

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

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

Hereditary mutation status should be part of the individual

Table 3
BCY2 Modified statements.

General recommendations	LoE	% Consensus
46. In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, & socio-economic impact are highly recommended as part of the individual treatment planning.	Expert Opinion	100%
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.		
Genetic Counseling & Testing		
47. Genes to be tested for depend on personal and family history.	Expert Opinion	94%
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 counseling services is strongly encouraged.		
Screening, diagnosis & imaging for staging and follow-up		
48. For BRCA 1/2 mutation carriers and others at high risk based on family history or predisposing mutations in other genes (e.g. p53, PALB2, CHEK2, ATM), and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with MRI and mammography with or without ultrasound is recommended.	II A	Not voted
49. For BRCA 1/2 mutation and other cancer susceptibility genes carriers (e.g. RAD51C, p53, BRIP1) who have not undergone salpingo-oophorectomy, gynecologic surveillance every six months is recommended, beginning at age 30 or 5 years younger than the earliest diagnosis of a gynecological malignancy in the family, whichever comes earlier.	Expert Opinion	Not voted
Early breast cancer loco-regional treatment		
50. Indications and schedules of hypo-fractionated radiotherapy are, in principle, the same as in other age groups. Long-term toxicity data is needed.	I B	76.5% Agree 23.5% Abstain
51. Indications and extension of nodal irradiation are the same as in other age groups.	I B	82.4% Agree 17.6% Abstain
52. Indications for adjuvant RT are the same as for older patients.	I B	Not voted
Data are stronger for benefits of post-mastectomy RT for young women.	I B	
Adjuvant systemic treatment		
53. 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 favorable clinical and pathological features including low gene expression profiles where available.	Expert Opinion	88.2% Agree 11.8% Abstain
Patients with germline high-penetrance gene mutations		
54. For breast cancer survivors and asymptomatic carriers harboring a BRCA 1/2 mutation, risk-reducing salpingo-oophorectomy (RRSO) should be discussed from the age of 35 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.	Expert Opinion	82.4% Agree 11.6% Abstain
Indications and timing of risk-reducing salpingo-oophorectomy for other highly penetrant mutations should follow available international/national guidelines.		
Advanced breast cancer		
55. The BCY panel endorses the ABC3 statement that in triple-negative ABC patients (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant and/or metastatic setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option.	II B	100% Agree
Additional well designed and powered prospective randomized trials evaluating the role of platinum agents in the population of BRCA 1/2 mutation associated ABC are needed.	Expert Opinion	

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 surgical sequelae and implications.

4.1.2. Radiotherapy

Indications for adjuvant radiotherapy are the same as for older patients, however, data are stronger for benefits of post-mastectomy radiation amongst young women. Indications and extent of nodal irradiation are the same as in other age groups. Following neo-adjuvant therapy, irradiation fields should account for initial, pre-treatment staging and for post-treatment pathological staging. The panel reiterated BCY1 & BCY2 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.

Based on available literature, indications and schedules for hypo-fractionation, similar to those for older patients, may be considered in young women [51]. It should be emphasized that long term toxicity data are still needed. Given the high recurrence risk also outside the initial tumor area, partial breast irradiation is contra-indicated and should only be proposed within a clinical trial.

4.2. 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, tumor size, nodal status, HR and HER-2/neu over-expression, proliferation, and grade), patient's co-morbidities and preferences (as for women in other age categories).

4.2.1. Gene expression signatures

Available gene expression signatures are considered to add prognostic information to classic clinico-pathologic factors [6,8,52,53]. That being said, women <40 are grossly underrepresented in the retrospective studies performed to date, particularly in studies evaluating node positive disease. Available data from prospective, randomized trials are encouraging. TAILORx evaluated the use of the 21-gene recurrence score (RS) amongst women with HR+, HER2/neu negative, T1-2, node-negative disease [10]. The 21-gene RS categorizes these women into low, intermediate or high risk groups. While 30% of those with a low RS were premenopausal, only 4% of those were <40. To date the outcome for the low-risk score group, who were all assigned to endocrine therapy alone, was excellent with a distant recurrence free interval of 99% at 5 years. Results for the intermediate RS group who were

Table 4
New statements BCY3.

General recommendations	LoE	% Consensus
56. 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.	Expert Opinion	100%
This would help young patients to overcome barriers to accessing support, such as child and family care, work timetables and distance issues.		
57. Systematic research into age-specific tumor characteristics is needed. In particular, the prognostic and predictive impact of multi-gene expression profiles and mutational status to identify specific genomic aberrations that could open the door for tailored therapeutic interventions.	Expert Opinion	94%
Genetic Counseling & Testing		
58. 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	94%
As commercially available multi-gene panels include different panels of genes, the choice of the specific panel and quality-controlled laboratory is crucial.		
59. 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	88%
60. The therapeutic implications of somatic BRCA1/2 mutations in breast tumors need to be further explored within a research setting before they can be used in routine clinical practice.	Expert Opinion	88%
61. The multidisciplinary management of mutation carriers and high-risk individuals should be ideally provided in dedicated high-risk clinics.	Expert Opinion	94%
Screening, diagnosis & imaging for staging and follow-up		
62. No specific data about tomosynthesis are available in young women. Its use and indications are the same as in other age groups.	Expert Opinion	82%
63. Risk-adapted early detection and surveillance tools should be researched in young women.	Expert Opinion	88%
Neo-/Adjuvant systemic treatment		
64. 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.	IB	56% Agree 6% Abstain 38% Did not vote
65. A number of factors including patient and tumor 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. Further research on this subject is needed.	Expert Opinion	88%
Commercially available gene expression tests have not been widely studied in young women. Less 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.		
66. 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 be discussed, as in other age groups.	Expert Opinion	65%
67. The incorporation of neo-adjuvant/adjuvant pertuzumab should be in keeping with current standards, as for older patients, in women with HER2+ breast cancer.	IB	56% Agree 6% Abstain 38% Did not vote
68. In patients with TNBC or BRCA-associated tumors the incorporation of platinum agents increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated. Data on the impact of incremental increases in pCR on long term outcome are not conclusive.	IIA	77%
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.		
69. For patients with TNBC not achieving a pCR after standard neoadjuvant regimens, the routine addition of adjuvant chemotherapy (such as capecitabine or metronomic CM) is not recommended; however, it may be considered in highly selected patients, as in other age groups.	IIB	65%
70. There are no data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended.	Expert opinion	65%
Loco-regional treatment after neo-adjuvant therapy		
71. The optimal loco-regional treatment after neoadjuvant chemotherapy is still controversial. Decisions should be made independent of age.	Expert Opinion	82%
72. 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	88%
Advanced breast cancer		
73. Many trials in HR+ ABC have not included pre-menopausal women.	IA	94%
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 post-menopausal women with endocrine agents and targeted therapies such as an aromatase inhibitor or fulvestrant plus a CDK 4/6 inhibitor or exemestane with everolimus.		
Future trials exploring new endocrine/endocrine-biological strategies should be designed to allow for enrollment of both pre- and post-menopausal women.		
74. Olaparib monotherapy may be considered in women with ABC harboring a germline BRCA mutation in early lines of therapy.	IB	56% Agree 6% Abstain 38% Did not vote
Supportive and follow-up care		
75. Young women with breast cancer are at higher risk for psychosocial distress. Patients' distress and psychosocial needs should be regularly assessed.	IIB	100%
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.		

randomized to hormonal therapy alone or chemotherapy followed by endocrine therapy have not yet been published. The MINDACT study 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 [11]. Only 6.2% of the study population was <40 [54], 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. Results from further studies, in endocrine-responsive, node positive disease (X-PONDER, PLAN B) are awaited.

In conclusion, available data suggest that a discussion of omitting adjuvant chemotherapy in very young women (≤35 years at diagnosis) is appropriate in highly selected cases with favorable clinical and pathological features including low gene expression profiles where available. Importantly, age per itself should not be the sole reason to prescribe adjuvant chemotherapy in women <40 years at diagnosis.

Further research on this subject is needed.

4.2.2. Neo-adjuvant endocrine therapy (ET)

No new data are available about the role of neo-adjuvant ET in young women since BCY2 was published [55], thus BCY3, reinforced the BCY1 & BCY2 recommendation that neo-adjuvant ET should not be routinely recommended for young women outside of clinical trials.

The International Breast Cancer Study Group (IBCSG) randomized phase II Trial (IBCSG 41-13 TREND) evaluating the efficacy of the GnRH antagonist degarelix versus triptorelin as neo-adjuvant treatment in 50 pre-menopausal patients receiving letrozole is no longer recruiting, and results are awaited.

4.2.3. Adjuvant endocrine therapy

The benefits of adjuvant endocrine therapy for women with HR+ breast cancer are well established for all age groups [56,57] and the publication of the TEXT and SOFT studies, that assessed ovarian function suppression (OFS) with Tamoxifen or Exemestane compared to Tamoxifen alone, introduced choices beyond Tamoxifen for young women with breast cancer [34,58]. Tamoxifen alone remains the standard of care in women at low-risk of relapse, defined by clinical, immune-histochemical and genomic parameters, when available. Aromatase inhibitors (AIs) alone are contra-indicated in pre-menopausal women. Until the publication of the SOFT and the TEXT trials, the only other study that had evaluated a combination of OFS and an AI in this population was the ABCSG-12 [59]. ABCSG-12 trial showed no benefit for OFS with an AI compared to OFS and tamoxifen. However it is important to point out that the study populations were different – including the fact that a greater proportion of women were >40 in the Austrian trial, the treatment schedule was shorter and the study had less statistical power than the SOFT and TEXT studies. One of the encouraging observations in the SOFT and TEXT studies is that young women with HR+ breast cancer have excellent outcomes, often with endocrine therapy alone. Those that appeared to derive the greatest benefit from the addition of OFS (by GnRH agonist (GnRHa) or oophorectomy) to Tamoxifen or Exemestane in SOFT were the women <35 and those who had received chemotherapy and remained pre-menopausal as per study protocol [60]. This is in keeping with past observations that very young women (<35 years) appear to derive the greatest benefit from combined endocrine therapy after adjuvant chemotherapy [61,62]. In the TEXT and SOFT combined analysis, OFS plus the AI exemestane significantly reduced the risk of recurrence, as compared with tamoxifen plus OFS [34,58]. It remains unknown whether it is beneficial to commence the GnRHa concomitant to or following the adjuvant chemotherapy, although commencing the GnRHa just prior to beginning chemotherapy has the added potential benefit of ovarian function protection [63–65].

If GnRHa is to be given in combination with tamoxifen or AI, the panel recommends to give treatment for 5 years based on the SOFT and the TEXT data, if tolerated.

No new data about extended endocrine therapy for premenopausal women has been published since BCY2. Therefore BCY3 reinforces the BCY1 & BCY2 recommendation that extending tamoxifen beyond 5 years should be considered in higher-risk patients, based on the ATLAS (premenopausal women represented 10% of the overall population) and aTTom trials. Individual patient decisions must take into account the risk for late relapse, the estimated absolute benefit of extended endocrine therapy, and quality-of-life issues for the individual patient [66,67]. BCY3 reiterated that caution must be taken when considering switching to an AI after Tamoxifen in women who were pre-menopausal at diagnosis and appeared to become post-menopausal during the course of treatment due to the potential for recovery of ovarian function [68].

The role of extended endocrine therapy in pre-menopausal women, beyond five years of OFS and Tamoxifen or an AI, is unknown given there are no data available from testing this strategy directly.

The criteria for defining menopausal status following chemotherapy-induced amenorrhoea, as defined previously in the BCY2 paper, are in Appendix 1.

BCY3 reinforced 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, while taking into account that estradiol assays are not standardized, and their accuracy and interpretation can be problematic in presence of very low levels of estradiol [69]. This is based on reports, including the SOFT-EST sub-study, that OFS does not achieve optimal estrogen suppression in up to a 17% of patients after 12 months of treatment [70].

Based on limited available data and concerns about suboptimal ovarian function suppression with tri-monthly formulations, monthly formulations of GnRH analogues are preferred [71].

Younger age is associated with lower adherence and persistence to adjuvant ET [72,73]. Amongst breast cancer patients, non-adherence and early discontinuation of endocrine therapy have been associated with reduced overall survival [74]. In the SOFT and TEXT studies treatment discontinuation occurred in approximately 17% of all patients, and non-adherence with OFS reached 21.9% at 4 years [33,34]. Depression has been repeatedly found to be a predictor of adherence in women with breast cancer [75] and given that approximately 50% of women in the SOFT/TEXT studies reported depression, this is a substantial concern. Another important issue that has been demonstrated to be associated with non-initiation or delays in initiation of endocrine therapy is desire for future fertility [73]. Therefore all efforts must be made by the treating health professionals to promote adherence by addressing fertility concerns, ensuring screening for and treatment of depression and by addressing treatment-induced toxicity.

Healthcare providers should closely follow young patients on endocrine therapy in order to promptly manage side effects or discuss treatment adjustments according to individual tolerance, and consider a change of therapy when necessary.

4.2.4. GnRH agonists & ovarian function preservation

GnRH agonists appear to preserve ovarian function in women receiving chemotherapy [63–65], reducing the risk of early menopause and increasing the chances for future fertility, and should be discussed as an option with all patients interested in potentially preserving fertility and/or ovarian function who are candidates for chemotherapy, irrespective of tumor subtype.

4.2.5. Adjuvant bisphosphonates

While the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis confirmed the lack of benefit of adjuvant bisphosphonates among premenopausal women [76], for premenopausal women receiving OFS (who were considered as postmenopausal in the EBCTCG meta-analysis), recent guidelines [77] have recommended use of bisphosphonate therapy for prevention of disease recurrence. The panel suggests that this may be considered for young women receiving ovarian suppression, emphasizing that there is limited data [59] and that there are concerns about how this strategy may affect growth and development of future progeny in women who are interested in future fertility.

4.2.6. Neo/adjuvant chemotherapy

The additional benefit, if any, of adjuvant chemotherapy in young patients with low risk HR+ early breast cancer under optimal endocrine therapy is still undetermined. All prospective randomized trials have failed in recruiting enough patients to definitively answer whether adjuvant chemotherapy is of benefit in young women with low risk HR+ breast cancer [78,79]. However, the data from the TAILORx and MINDACT studies, as discussed above, appear encouraging that chemotherapy may be omitted in some cases with low genomic risk. In the SOFT and TEXT studies, patients who did not receive chemotherapy (8% and 21% node-positive in each trial, respectively) the 5 year BCFI was 96% and 97%, respectively with similar favorable outcomes in the ABCSG trial, in which 95% of women did not receive chemotherapy [58,59,80].

The panel restated that there is no evidence to recommend a specific chemotherapy regimen for young women requiring neo/adjuvant chemotherapy. In the last EBCTCG meta-analyses involving taxane- or anthracycline-based regimens, proportional risk reductions were little affected by age [81]. Sequential regimens have at least equal or superior efficacy over combination regimens and are better tolerated although this has not been evaluated specifically in young women [82]. A sequential regimen of anthracycline based chemotherapy followed by adequately dosed CMF (oral or Day1 and 8 every 21 days intravenously) or a combination of a taxane and cyclophosphamide may be valid alternatives [83,84]. 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 unfavorable features [85]. Similar to older women, standard duration of treatment should include between 4 and 8 cycles of treatment.

The incorporation of platinum agents in TNBC or BRCA-associated tumors in the neo-adjuvant setting to improve pathological complete response rates (pCR) may be considered, however, remains controversial. While the Geparsixto study demonstrated a benefit in DFS with incorporation of a platinum agent amongst TNBC [86], it is important to note that the chemotherapy regimen used did not include an alkylating agent (such as the standard, cyclophosphamide), making these results difficult to interpret and apply in standard clinical practice. Additionally, the CALGB 40603 did not demonstrate an improvement in DFS after platinum incorporation to a standard AC-T regimen despite improvements in pCR [87].

The use of platinum agents can further adversely impact fertility and increased toxicity 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 (such as capecitabine or metronomic CM) is not recommended. However, 8 cycles of capecitabine may be considered in selected high risk young patients, as in other age groups, based on the recently published CREATE-X data, given the large overall survival advantage demonstrated [88]. Careful consideration should be given to whom these study results are applicable noting that in this study approximately 27% of patients did not receive adjuvant radiotherapy, despite the presence of residual disease following neo-adjuvant chemotherapy.

A pooled analysis of individual patient data from eight prospectively randomized controlled trials of the German Breast Group, demonstrated that young women ($n = 1453$) are more likely to achieve a pCR after neoadjuvant chemotherapy than older women, with a pCR rate of 20.9 vs. 17.7 vs. 13.7%; $p < 0.001$, for <40, 40–49 and $\geq$ 50 years old, respectively - especially in HR+/HER2- and triple negative disease [89]. However, despite these increased pCR rates, age was an important prognostic factor in this study only among women with HR+/HER2-disease.

There are not yet data on the use of platinum derivatives in the adjuvant setting and therefore these cannot be recommended.

4.2.7. Adjuvant anti-HER-2 therapy

The benefit of adjuvant trastuzumab appears independent of age in all published studies and should be prescribed as for older women [8].

In highly selected patients with small, node-negative, HER-2+ and ER+ breast cancer, the administration of 12 weeks of weekly paclitaxel and trastuzumab without anthracyclines can be discussed, as in other age groups [90].

The incorporation of neo-adjuvant pertuzumab should be in keeping with current standards, as for older patients [91]. It is not yet clear how the recently published results of the APHINITY trial (13.6% of patients <40 in each treatment arm) will impact clinical practice.

4.2.8. Side effects of adjuvant therapy

In view of the longer 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).

4.2.9. Inflammatory breast cancer

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

5. Advanced breast cancer (ABC)

The BCY3 panel endorses the ESO-ESMO ABC 3 guidelines for the management of ABC [92] and reiterated that young age alone should not be a reason to prescribe more aggressive therapy.

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 have unique medical and psychosocial concerns that need to be considered and addressed.

While pregnancy in the setting of ABC is not considered safe or desirable from a medical perspective, nevertheless concerns for fertility and family planning need to be cautiously discussed and

explored even in the setting of advanced disease.

While in the past many trials in endocrine responsive ABC have not included pre-menopausal women, BCY3 panel recognized and encouraged the fact that this field has in fact evolved in recent years to more commonly allow for inclusion of pre-menopausal women who are receiving OFS with a GnRH analogue.

5.1. Loco-regional relapse

Young age is a risk factor for local relapse. Therefore careful attention to margin status is warranted in young women. Following loco-regional relapse, chemotherapy should be considered, particularly in women with HR-negative tumors, as demonstrated in the CALOR study [93]. For ER+ disease, endocrine therapy should be given and for HER-2+ disease trastuzumab is recommended albeit based on only expert opinion level of evidence.

6. BRCA mutation carriers

The BCY3 panel confirmed BCY2 recommendations for prevention, surveillance, treatment and risk reducing strategies. In particular (i) there is still no definitive evidence that 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 and, (ii) 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 [94–96]. Breast MRI surveillance is the preferred surveillance modality for high-risk women [41], when available.

For breast cancer survivors and asymptomatic carriers harboring a BRCA 1/2 mutation, risk-reducing salpingo-oophorectomy (RRSO) should be discussed from the age of 35 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.

There remains no definitive conclusion on the best chemotherapy regimen for BRCA-associated breast cancer patients in the adjuvant/neo-adjuvant setting and the panel recommended that standard prognostic features should be used to decide treatment in the early disease setting [97].

The role of platinum agents in the neo-adjuvant setting in BRCA carriers was described above.

Following the results of the TNT study, the use of a platinum agent should be considered in the advanced breast cancer setting of BRCA-associated ABC [98].

Promising results are emerging for the use of Poly (ADP-ribose) polymerase (PARP) inhibitors amongst women with BRCA-mutated ABC. Specifically, the results of the Phase II BROCADE study were presented at the San Antonio Breast Cancer Symposium (2016) – the study randomized patients to taxol and carboplatin with or without Veliparib and demonstrated improved overall response rate favoring the Veliparib arm. The recently published phase III OlympiAD study comparing Olaparib monotherapy to standard chemotherapy amongst patients with ABC harboring a germline BRCA mutation in early lines of therapy (up to two previous lines of chemotherapy) demonstrated a superior response rate, progression free survival and toxicity profile for Olaparib [99]. Of note, in this study patients had received a prior anthracycline and taxane, those that were HR+ had progressed on at least one line of endocrine therapy, and patients had not relapsed within 12 months of neo/adjuvant platinum therapy or progressed during platinum therapy in the advanced setting.

7. Supportive and follow-up care

Follow-up care in young women should follow the same guidelines as in older women [100] and supportive treatment/prevention of specific symptoms and side effects should follow current recommendations. It should be emphasized that breast nurses and other supportive care staff can play a critical role in providing survivorship care and support for young patients and their families.

Clinics dedicated to the assessment and management of early and late treatment side effects, adherence to treatment and follow-up guidelines should be developed.

7.1. 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 undergo a menopausal transition with treatment [101,102]. 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. Social issues that need to be addressed include return to work, family planning, financial loss.

Considerations and recommendations by the BCY3 panel for fertility, 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 BCY2 and appear in Appendix 1.

7.2. Patient advocacy statements

For the first time, BCY3 included a patient advocacy session for young women with breast cancer. At the conclusion of the workshop the advocacy group presented a manifesto that was developed and presented in the panel consensus session of the conference. They identified the following five 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

8. Conclusions

Since BCY2, progress has been made - in particular, more clinical trials in the metastatic setting are accommodating the incorporation of young women with breast cancer by allowing for OFS as an acceptable surrogate for physiological menopause and the POSITIVE study commenced recruitment to prospectively address the issue of pregnancy after breast cancer and endocrine therapy 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.

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 [103]. Menopause occurs when the remaining follicle count reaches 1000 or below. While natural onset menopause is defined as twelve months after the last menstrual period, chemotherapy induced amenorrhoea 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 amenorrhoea for $\geq$2 years, a post-menopausal hormonal profile and a vaginal ultrasound indicating the ovaries are no longer functioning.

Supportive & follow-up care issues unchanged or slightly modified since BCY2

Fertility, Contraception and Premature Menopause: Fertility and family planning are major concerns for young women with breast cancer [16,104]. 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 [105] and are reinforced here. Appropriate early referrals for fertility preservation strategies, based on existing practice guidelines as well as psychosocial support surrounding this extremely complex issue should also be made. There was recognition by the majority of the panel that this is one of the most difficult and emotionally challenging issues facing young survivors, which is complicated by limitations of the data, particularly with regards to predicting fertility as well as safety of interventions. Pregnancy is prohibited due to risk of teratogenesis during active treatment of breast cancer so effective contraception is recommended and proactive counseling should be done on this issue 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 [106]. The safety of levonorgestrel-releasing intrauterine device (IUD) (Mirena®), which delivers high local but low systemic doses of progestogen is controversial: studies in breast cancer survivors are small and have not included recurrence or new cancers as an endpoint [107]. In the absence of prospective data 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 [108]. For hot flashes studies of megestrol acetate and medroxyprogesterone acetate have been performed and appeared efficacious [109–111], 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 chemotherapy-induced amenorrhea [112] and amongst women receiving OFS and oral endocrine therapy [33,34]. This issue encompasses vaginal dryness, dyspareunia, decreased libido, body image concerns, anxiety and depression, fatigue and side-effects from medications (including anti-depressants). Appropriate counseling should be available and vaginal moisturizers and lubricants should be prescribed [113]. Sexual health should be included in the survivorship care plan and further research is needed to improve management [114]. 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 vaginal estrogens may be safe during concurrent use with an AI [115,116], 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 [70].

Pregnancy after breast cancer: all retrospective available data report no detrimental effect of a subsequent pregnancy on breast cancer outcome [117–122]. In particular, in a recent multicenter, retrospective cohort study in which 333 patients who became pregnant any time after BC were matched (1:3) to patients with BC with similar HR status, nodal status, adjuvant therapy, age, and year of diagnosis, no difference in DFS was observed between pregnant and non-pregnant patients in the HR+ population at a median follow-up of 5 years following conception [119]. Therefore, pregnancy after breast cancer should not be discouraged, even though definitive data from prospective clinical trials are needed [120]. A prospective global cooperative study, the POSITIVE study is actively recruiting with the aim of assessing the safety and feasibility of interrupting endocrine therapy for pregnancy after breast cancer – enrolment in the study should be strongly encouraged among women who desire early pregnancy after diagnosis, as this will likely be the only prospective study on pregnancy after breast cancer.

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 endocrine therapy. Of note, in contrast with its effects on bones in post-menopausal women, tamoxifen can cause bone loss in premenopausal patients, likely because it is a weaker agonist in the bones that the premenopausal endogenous estrogens it is blocking [123,124]. 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 [125]. Treatment-related bone loss should be managed accordingly, independent of age. Recent joint Cancer Care Ontario & ASCO guidelines on use of adjuvant bisphosphonates support the use of 6 monthly zoledronate or daily clodronate for post-menopausal women eligible for systemic therapy, with the definition of post-menopausal including women under OFS.

Cognitive impairment: Neurocognitive symptoms ("onco or chemo brain") are frequently described among young breast cancer survivors [126,127]. Patient-reported symptoms (forgetfulness, difficulty with concentration, fatigue, distractibility and difficulty with word finding) rarely correlate with neuro-imaging studies and neuro-psychiatric evaluation. Neither the biological basis for this syndrome, nor the predictors, nor any interventions, are well understood although recent investigations suggest a relationship with structural changes occurring in cerebral white matter and several investigations are underway [128,129]. While much of the prior work has focused on the effects of chemotherapy, endocrine

therapy may also adversely affect cognition [130–133], although few specific investigations have been conducted and none in young 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 [134]. Cognitive function has been prospectively investigated in patients participating in the CO-SOFT sub-study - despite the small sample size (86 participants), no evidence was provided that adding OFS to adjuvant oral endocrine therapy substantially affects global cognitive function [135].

Lifestyle changes: The panel endorsed 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) [136], not smoking and limiting alcohol intake.

Breast cancer during pregnancy: management of patients with breast cancer during pregnancy is outside of scope of these guidelines and should follow established recommendations [137]. In general pregnant women can and should be treated as closely as possible to the general guidelines for breast cancer in young women. Patients should be enrolled in prospective registration studies [138].

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2017.07.017.

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