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SPECIAL ARTICLE

Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019

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Background: The 16th St. Gallen International Breast Cancer Conference 2019 in Vienna, Austria reviewed substantial new evidence on loco-regional and systemic therapies for early breast cancer.

Design: Treatments were assessed in light of their intensity, duration and side-effects, estimating the magnitude of clinical benefit according to stage and biology of the disease. The Panel acknowledged that for many patients, the impact of adjuvant therapy or the adherence to specific guidelines may have modest impact on the risk of breast cancer recurrence or overall survival. For that reason, the Panel explicitly encouraged clinicians and patients to routinely discuss the magnitude of benefit for interventions as part of the development of the treatment plan.

Results: The guidelines focus on common ductal and lobular breast cancer histologies arising in generally healthy women. Special breast cancer histologies may need different considerations, as do individual patients with other substantial health considerations. The panelists' opinions reflect different interpretation of available data and expert opinion where is lack of evidence and sociocultural factors in their environment such as availability of and access to medical service, economic resources and reimbursement issues. Panelists encourage patient participation in well-designed clinical studies whenever available.

Conclusions: With these caveats in mind, the St. Gallen Consensus Conference seeks to provide guidance to clinicians on appropriate treatments for early-stage breast cancer and guidance for weighing the realistic tradeoffs between treatment and toxicity so that patients and clinical teams can make well-informed decisions on the basis of an honest reckoning of the magnitude of clinical benefit.

Key words: St. Gallen Consensus, early breast cancer, radiation therapy, surgery, systemic adjuvant therapies

Introduction

The 16th St. Gallen International Breast Cancer Conference in 2019, held for the third time in Vienna, Austria, centered on individualized patient decision-making in early-stage breast cancer. A hallmark of the conference was the effort to base recommendations on the estimation of the magnitude of clinical benefit for specific treatments and interventions. This focus reflected several evolving factors in early-stage breast cancer, including a growing awareness of the importance of the long-term consequences of

treatment on patient's well-being and function, the essential role of the patient in selecting optimal treatment options, the real-world estimate of benefit in terms readily understood by clinicians as well as patients, and a burgeoning set of treatment opportunities that may offer equal clinical benefit with less toxicity, or provide for a measurable improvement in outcomes. Decades of clinical trials have consistently demonstrated that most treatment interventions carry similar relative reductions in recurrence across the spectrum of risk defined by anatomical stage. The absolute benefits, however, are governed by the baseline risk of tumor recurrence. Recent experiences in countries with widespread screening programs for detecting early-stage breast cancer suggest steadily improving outcomes for most women with early-stage breast cancer. Indeed, the 'baseline' prognosis for many women with small, early-detected cancers receiving standard multi-disciplinary therapy has become so favorable that new, active treatments contribute only marginally to further reductions in the risk of recurrence and rarely affect overall survival. In addition, the appreciation of the biological heterogeneity of tumors continues to refine treatment algorithms in early-stage breast cancer. Treatment guidelines are no longer driven exclusively by the anatomic stage of the tumor or the histological subset of breast cancer. Decisions about optimal surgical, radiation therapy and medical approaches are increasingly tailored based on the initial response to neoadjuvant systemic therapy (NST). These developments demand that routine care be provided by an experienced multidisciplinary team of radiologists, surgeons, radiation oncologists, pathologists, and medical oncologists, and also demand engagement with the patient in a process of shared decision-making built on a realistic estimate of the magnitude of benefit for each component of therapy. In response to this progress, the 2019 St. Gallen Consensus Conference Guidelines offer important and exciting innovations, new from 2017, that are transforming care (Table 1).

The past 2 years have seen remarkable progress in our understanding of the biology and treatment of both late- and early-stage breast cancer (Table 2). The St. Gallen Consensus Guideline focuses on early-stage breast cancer, where as a consequence of multiple developments—improving overall prognosis, better tools for risk stratification, and care by integrated teams of providers—treatment recommendations are increasingly individualized. Systemic therapy substantially lowers the risk of local-regional tumor recurrence, which enables less surgery of the breast and axilla in many cases. Cancers believed highly sensitive to effective systemic therapy, such as HER2-positive tumors treated with anti-HER2 regimens, might warrant different approaches or durations of local-regional treatment than cancers not as responsive to systemic interventions. Clinicians increasingly interpret response to preoperative therapy in order to tailor surgical options and the need for post-operative treatment. New targeted therapies are emerging for biologically defined cancer subtypes. Sophisticated pathology and genomic signatures assays substantially refine the anticipated prognosis for long-term outcomes and thus inform treatment recommendations. However, therapies that carry robust impact on outcomes in high-risk tumors may translate into negligible returns, if any, for low-risk cancers. For some patients, there is a clear move to escalate therapy, such as longer durations of anti-estrogen treatment, more utilization of ovarian function suppression (OFS), treatment of residual tumor after NST, and dual targeting with anti-HER2 drugs. In other settings, there is a movement to de-escalate treatment, including the shortening or omission of adjuvant chemotherapy, the avoidance of axillary surgery, and shortened courses of radiation treatment [58].

These advances pose challenges to consensus guidelines because it is more difficulty to confidently recommend treatments that apply to all patients, or even to all patients with a given stage or subset of breast cancer. They underscore the need for both clinicians and patients to explore the magnitude of benefit for a given treatment in the context of a particular cancer presentation. They invite opportunities for individual patients to articulate preferences regarding treatments that might afford narrow benefits, not affect overall survival, or carry substantial side-effects. Clinical trialists are also challenged to respond to these changes. There remains a vital need for improved treatment of patients at high risk of cancer recurrence, while for patients with low-risk tumors there are opportunities to explore which treatments might be judiciously, but safely, reduced or omitted. The former typically requires selection of high-risk tumors to create randomized trials of sufficient size to demonstrate activity; the latter often leads to single-arm studies that demonstrate adequate outcomes in cohorts which may be subject to biases of specific centers or clinical populations.

As a global consensus panel, the St. Gallen conference identified widespread variation in both patterns of care and access to treatment. Some of these disparities emerged when comparing less affluent societies against more affluent ones, and reflected profound differences in available resources for breast cancer screening, the availability of oncology services and specialty providers, and access to newer, more expensive diagnostics, treatments and supportive care. However, substantial differences in access to treatments exist among various developed countries, and many affluent countries have profound disparities between national health care systems and parallel, private systems, or based on socioeconomic and demographic factors. This heterogeneity in treatment styles and options was revealed through consensus discussions, and often affected the recommendations from panelists. Thus, while most recommendations reflect the broad majority of the Panel, few achieved fully uniform agreement, and many reflected the worldwide disparities in resources and access to integrated, multidisciplinary care and treatments.

The Panel acknowledged that for many patients, the impact of adjuvant therapy or the adherence to specific guidelines may have modest impact on the risk of breast cancer recurrence or overall survival. For that reason, the Panel explicitly encouraged clinicians and patients to discuss the magnitude of benefit for interventions routinely as part of the development of the treatment plan. The guidelines focus on common ductal and lobular breast cancer histologies arising in generally healthy women. Special breast cancer histologies may need different considerations, as do individual patients with other substantial health considerations. The panelists' opinions reflect different interpretation of available data and expert opinion where is lack of evidence and sociocultural factors in their environment such as availability of and access to medical service, economic resources and reimbursement issues. Panelists encourage patient participation in well-designed clinical studies whenever available. With these caveats in mind, the St. Gallen Consensus Conference seeks to provide

Table 1. Changes in panel recommendations since 2017

Global perspectives	Worldwide, outcomes for early-stage breast cancer are improving owing to successful screening programs and improved multidisciplinary care. These advances are often associated with treatments which carry less morbidity than treatments in the past.
	Shared clinical decision making is essential when caring for individual breast cancer patients. In particular, patients should be informed about the expected magnitude of benefit of interventions in their individual case when deciding which therapies to pursue
	There are substantial variations around the world in availability of important treatments for breast cancer. Stakeholders should work to ensure that patients have access to essential treatments that improve survival for women with breast cancer
Surgical management	'No ink on tumor' is a sufficient surgical margin in most cases of primary invasive breast cancer, including patients with lobular breast cancer or extensive intraductal components, and after resection of residual palpable or imaging abnormalities following NST
	ALND can be omitted after SLNB with one to two positive lymph nodes after mastectomy if RNI was planned. ALND can be omitted after SLNB with one to two positive lymph nodes following breast conserving surgery for tumors larger than 5 cm if WBI is planned.
Neoadjuvant therapy	Neoadjuvant systemic therapy (NST) is the preferred initial approach in women with stage 2 or 3, HER2-overexpressing or triple-negative breast cancer
	NST increasingly enables selected women to avoid axillary dissection surgery, sparing women loss of function and lymphedema
	NST increasingly enables tailored approaches to therapy in TNBC and HER2-positive breast cancer that can improve long-term outcomes for women with breast cancer
ER+ adjuvant therapy and genomic signatures	More women with ER-positive breast cancer and limited involvement of axillary lymph nodes may avoid adjuvant chemotherapy
	More premenopausal women with intermediate/high risk ER-positive breast cancer should consider ovarian function suppression
	Genomic signatures may inform treatment recommendations for women with ER-positive breast cancers and limited nodal involvement
	Clinical-risk stratification provides prognostic information that, when added to the 21-gene recurrence score, could be used to identify women younger than age 50 women who may benefit from more effective therapy than tamoxifen alone
HER2+ and TNBC adjuvant therapy	Women with stage 2 or 3 HER2-positive breast cancer should consider adding pertuzumab in addition to trastuzumab
	Women with HER2-positive and residual tumor after NST should receive trastuzumab emtansine therapy in the adjuvant setting
	Women with triple-negative breast cancer and residual tumor after NST should consider capecitabine in the adjuvant setting
Adjuvant bisphosphonates	Bisphosphonates should be standard adjuvant therapy for postmenopausal patients with breast cancers

guidance to clinicians on appropriate treatments for early-stage breast cancer and guidance for weighing the realistic tradeoffs between treatment and toxicity, so that patients and clinical teams can make well-informed decisions on the basis of an honest reckoning of the magnitude of clinical benefit.

Pathology and subsets

Early-stage breast cancer is a heterogeneous disease and optimal treatment depends on pathological and molecular characterization of the tumor subset to classify tumors as estrogen receptor (ER) positive or negative, HER2-positive or negative, or by default, triple negative. The Panel discussed the role of endocrine therapy in tumors with low ER expression (<10%) that have a less favorable prognosis than tumors with higher levels of ER expression. Most contemporary clinical trials involving endocrine therapy limit enrollment to patients with tumors that are ≥10% ER-positive. In contrast, many trials for triple-negative disease exclude patients with tumors that have 1%–10% staining ER staining. There was general consensus that the benefits of endocrine therapy are lower or possibly absent when ER staining is 1%–10%. However, without clinical data, the Panel could not identify a clear threshold for withholding endocrine therapy and many panelists recommended adjuvant endocrine therapy for tumors with ≥1% ER expression [59].

In addition to these familiar biomarkers, the Panel recommended that tumor-infiltrating lymphocytes (TILs) be routinely characterized in triple-negative breast cancer (TNBC) because of their prognostic value. However, data are inadequate to recommend TILs as a test to guide neo/adjuvant treatment choices in TNBC, as treatments are largely governed by anatomic stage. Tumor PD-L1 or immune-cell PD-1 expression are recognized as markers that may predict benefit from immunotherapy treatment in advanced breast cancer. However, the Panel recommended against routine PD-L1 tumor or PD-1 immune cell testing in early-stage TNBC, as current treatment algorithms are not based on such testing.

Assessments of tumor grade, proliferation (e.g. Ki-67 labeling index), quantitative assessment of ER and progesterone receptor (PR), and multigene signatures capture some of the heterogeneity within ER-positive, HER2-negative breast cancers. The Panel believed strongly that genomic assays are valuable for determining whether or not to recommend adjuvant chemotherapy in

Table 2. Scientific and clinical research innovations since St. Gallen 2017

Topic	Finding	Ref.
Advanced stage, ER-positive breast cancer:clinical	The SOLAR-1 study demonstrates improved PFS with use of the PIK3Ca alpha-selective inhibitor, alpelisib, in combination with fulvestrant, for ER-positive advanced breast cancers harboring mutations in PIK3CA.	[1, 2]
	Maturing data from multiple trials of CDK 4/6 inhibitors—palbociclib, ribociclib, abemaciclib—show durable improvements in PFS when combined with endocrine therapy in first- or second-line treatment of ER-positive advanced breast cancer, and show emerging survival benefit	[3–6]
	A randomized trial, NCIC MA37, shows that palbociclib at 100 mg daily is as effective as the 125 mg dosing	
Advanced stage, ER-positive breast cancer:Laboratory	Resistance to antiestrogen therapies in advanced breast cancer is often related to acquisition of subclonal mutations in ESR1, which may change in dynamic ways of time	[7]
	ESR1 fusion transcripts contribute to estrogen-independent breast cancer cell growth and may contribute to resistance to endocrine therapy	[8]
	Cell-free (cf) or circulating tumor (ct) DNA can be identified in the plasma of patients with advanced breast cancer, and used to define tumor burden and mutations in ESR1 or PIK3CA associated with treatment resistance	[9]
Early stage, ER-positive breast cancer:clinical	Trials of extended adjuvant endocrine therapy beyond 5 years duration demonstrate that longer durations of AI treatment offer modest but measurable clinical benefit—especially in higher stage, ER-positive tumors—with ongoing side-effects	[10]
	The prospective, randomized TAILORx trial demonstrates that there is no clinical benefit for adding chemotherapy to endocrine therapy in the treatment of women with node-negative, T1/T2 tumors and 21-gene recurrence scores of 11–25	[11]
	Long-term follow-up of the SOFT trial of ovarian function suppression demonstrates that OFS reduces recurrence in younger women with ER+ breast cancer, particularly women with higher grade or higher stage cancers, with emerging survival benefit	[12]
	Data from the West German PlanB trial suggest low recurrence tumors treated with endocrine therapy alone have a favorable outcome, including those with limited nodal involvement	[13]
Advanced stage, HER2-positive breast cancer: clinical	The novel anti-HER2 antibody–drug conjugate, DS8201, shows high response rates in advanced, HER2+ breast cancer, and in HER2 1+ or 2+ 'low expressors'	[14]
	The NALA study, a randomized trial of neratinib plus capecitabine versus lapatinib plus capecitabine in advanced, HER2+ breast cancer, shows a PFS benefit for the neratinib-based regimen	[15]
	A randomized phase II study, KATE2, showed that adding the anti-PDL1 antibody, atezolizumab to trastuzumab emtansine improves PFS in women with advanced, HER2+ breast cancer expressing PD-L1	[16]
	A phase II study demonstrated that adding the anti-PD1 antibody, pembrolizumab, to trastuzumab yielded clinical response in trastuzumab-resistant, HER2-positive metastatic breast cancer	[17]
Early stage, HER2-positive breast cancer: clinical	The KATHERINE study showed that using trastuzumab emtansine instead of maintenance trastuzumab in women with residual invasive cancer following trastuzumab-based neoadjuvant chemotherapy improved DFS and OS	[18]
	The ShortHer and PERSEPHONE trials demonstrated that 6M of adjuvant trastuzumab was nearly but not quite as effective as 12 adjuvant duration	[19, 20]
	The randomized study, NSABP B-47, showed that adjuvant trastuzumab did not improve outcomes for women with HER2 1+ or 2+ but FISH negative breast cancers.	[21]
	The APHINITY trial demonstrated that adding adjuvant pertuzumab to trastuzumab reduced the risk of recurrence of HER2+ breast cancer, particularly node-positive or higher stage tumors	[22]
Late stage, TNBC: clinical	The Impassion130 trial showed that adding the anti-PD-L1 antibody, atezolizumab to nab-paclitaxel improves PFS, and may improve OS, in women with TNBC that are PD-L1 IC+ on biomarker testing	[23]
	The novel anti-trop2 antibody–drug conjugate, IMMU132, shows high response rates in advanced, refractory TNBC	[24]
	The novel anti-LIV1 antibody–drug conjugate, SGNLIV1, shows high response rates in advanced, refractory TNBC	
Early stage, TNBC: clinical	The CREATE-X study showed that women with residual triple-negative breast cancer using capecitabine in following neoadjuvant chemotherapy benefited significantly (or most) with improved DFS and OS	[25]
	A meta-analysis of trials of adjuvant chemotherapy intensity confirmed that regimens with dose-intense schedules, often requiring growth factor support, were more effective at preventing recurrence and improving OS	[26]
	Neoadjuvant trials demonstrate that adding an anti-PDL1 (durvalumab) or anti-PD1 (pembrolizumab) agent to standard chemotherapy improves the rate of pCR in TNBC	[27, 28]

Continued

Table 2. *Continued*

Topic	Finding	Ref.
	The CIBOMA/2004-01 GEIMCAM 2003-11 randomized phase III study did not show that adding adjuvant capecitabine after standard (neo)adjuvant anthracycline- and taxane-based chemotherapy reduced recurrence or improved survival	[29]
Adjuvant chemotherapy	Multiple randomized trials comparing docetaxel/cyclophosphamide versus anthracycline-based chemotherapy regimens suggest that the non-anthracycline 'TC' regimen may be an effective substitute, particularly in women with ER+, HER2 negative cancers and lower risk TNBC	[30–32]
	A randomized study shows that adding the COX-2 inhibitor, celecoxib, to adjuvant treatment does not reduce breast cancer recurrence	[33]
	A meta-analysis of adjuvant versus neoadjuvant chemotherapy showed no difference in distant recurrence or overall survival but neoadjuvant therapy was associated with a greater likelihood of local recurrence	[34]
Biomarkers	Tumor-infiltrating lymphocytes (TILs) were established as a favorable prognostic marker in TNBC patients received adjuvant/neoadjuvant chemotherapy	[35, 36]
Surgery	Long-term follow-up of the ACOSOG Z11 trial confirms that axillary dissection for one to two positive sentinel lymph nodes does not reduce local recurrence or improve OS	[37]
Hereditary breast cancer	Randomized trials with the PARP inhibitors olaparib and talazoparib demonstrate that this class of agents improves PFS and quality of life compared with standard chemotherapy in patients with advanced breast cancer and germline BRCA mutations	[38, 39]
	BRCA1 or BRCA2 reversion mutations detected in cfDNA may account for resistance to platinum chemotherapy or PARP inhibitor therapy in germline BRCA-associated breast cancer	[40]
	Algorithms for genetic testing that seek to identify patients with higher risk of harboring a deleterious mutation may nonetheless miss larger numbers of patients with such mutations	[41]
	Single agent treatment with the PARP inhibitor talazoparib as neoadjuvant treatment in women with germline BRCA mutations has substantial clinical activity	[42]
Radiation therapy	Trials comparing accelerated partial breast irradiation (APBI) versus whole breast irradiation in low-risk breast cancers showed comparably low rates of in-breast recurrence but with adverse cosmetic outcomes in the APBI treatment group in the RAPID trial	[43–46]
	A meta-analysis of trials that compared radiation versus not in low risk (recurrence score <18), stage 1, ER-positive breast cancer treated with lumpectomy found that omitting radiation therapy was associated with a higher risk of local recurrence but no effect on survival	[47]
DCIS	In women with DCIS, upstaging to invasive breast cancer at the time of surgical excision depends on clinical factors, particularly grade, and in low-risk populations has an incidence of 5%–20%	[48–50]
Supportive Care	Oxybutynin reduces hot flashes in breast cancer survivors	[51]
	Duloxetine reduces musculoskeletal/joint pain in women experiencing aromatase inhibitor-associated arthralgias	[52]
	Acupuncture reduces musculoskeletal/joint pain in women experiencing aromatase inhibitor-associated arthralgias	[53]
	A randomized intensive lifestyle intervention aimed at weight loss trial did not affect breast cancer recurrence risk	[54]
	Vaginal estrogen or testosterone therapy reduced symptoms of AI-associated vaginal dryness or loss of libido without causing increases in serum estradiol levels	[55]
	Prospective studies show that scalp cooling devices reduce alopecia in women receiving adjuvant chemotherapy, particularly with non-anthracycline regimens	[56, 57]

T1/T2 N0 ER-positive breast cancers, and recognized the value of such tests in patients with ER-positive tumors and limited nodal involvement (see below). Such tests are not universally accessible, largely owing to costs above routine pathology testing. Expert pathology review including determination of grade, ER/PR levels, and proliferation likely serves as a surrogate for broad classification of ER-positive tumors into more favorable 'luminal A-like' or less favorable 'luminal B-like' cancers. However, such assessments lack the robust validation of some genomic tests for critical decision-making including whether to recommend adjuvant chemotherapy.

Local-regional therapy: overview

In contemporary practice, an increasing percentage of women with stage 2 or 3 breast cancer are receiving primary systemic therapy (NST). This inversion of the historical patterns of practice—surgery first followed by systemic therapy—has implications for defining the optimal extent of surgical and radiation treatments, which are now informed both by the initial stage at diagnosis and by the response to NST. The Panel recommended that most radiation therapy dose and volume prescriptions be based upon previously defined guidelines for primary breast

Table 3. Management of axilla following neoadjuvant systemic therapy

Baseline nodal status	Post-NST nodal status	Axillary surgery	Nodal pathology findings	Additional axillary surgery	Regional nodal irradiation
cN0	cN0	SLNB	pN0	None	No
			pN1	AxLND (preferred) or AxRT	Yes if adverse factors[a]
cN1	cN0	SLNB+	pN0	Consider AxRT	Yes if adverse factors[a]
			pN1	AxLND (preferred) or AxRT	Yes
cN1	cN1	AxLND	pN0	None	Yes if adverse factors[a]
			pN1	None	Yes

Patients with pN2 or pN3 warrant AxLND and regional nodal irradiation.

[a]Adverse risk factors: age < 40; grade 3; TNBC; T3–4; poor in-breast response to NST.

SLNB, sentinel lymph node biopsy; SLNB+, targeted axillary approaches in combination with SLNB or >2 resected sentinel lymph nodes; AxLND, axillary lymph node dissection; AxRT, axillary radiation therapy.

surgery cases, though in some specific instances (below) radiation therapy recommendations may be tailored by NST response and subsequent surgical findings.

Local-regional therapy: surgery

Surgical margins

The Panel discussed the optimal surgical margins following breast conserving surgery in women who will be receiving post-surgical radiation therapy, and reiterated its endorsement of the 'no ink on tumor' standard [60]. This recommendation was endorsed regardless of tumor histology (lobular versus ductal carcinoma) or the presence of an extensive intraductal component, and irrespective of tumor histological grade. For women undergoing NST, the Panel recommended that the optimal resection remains removal of all known residual as opposed to original tumor lesions with a margin goal of 'no ink on tumor' regardless of the presence of unifocal or multi-focal disease. Wider margins—as had been recommended in previous consensus reports—are no longer recommended as long as the residual tumor bed and areas of persistent abnormal imaging have been excised with careful pathological review of the specimen. However, the Panel did not support these more limited surgical approaches for women with inflammatory breast cancer. The Panel endorsed similar 'no ink on tumor' margins for women undergoing skin-sparing and/or nipple-sparing mastectomy, particularly when radiation therapy is planned. Panelists urged caution for skin-sparing surgery when imaging suggested close proximity of the tumor to the skin, and the Panel was divided on preservation of the nipple-areolar complex in cases with centrally located tumors.

In the instance of focally positive margins at breast conserving surgery, the majority of the Panel favored re-excision, especially when the extent of margin involvement was anything beyond truly minimal. In certain cases when the area of focally involved margin is smaller (e.g. 1 mm wide), the panel was split as to whether re-excision would be essential and outweigh the risk and burden of re-excision. Recent studies including population-based registries [61, 62] suggest that limited, focal positive margins in the setting of breast conserving therapy and radiation therapy with a boost to the primary tumor bed may be associated with acceptably low risks of local recurrence, even if still numerically higher (2.9% versus 1.1% at 5 years following re-excision) than when there is 'no ink on tumor'. This may inform clinical practice especially when re-excision would have deleterious cosmetic impact or necessitate a mastectomy. Anecdotally, most panelists acknowledged accepting instances of microscopic involvement of margins (<1 mm wide) provided that patients were undergoing radiation therapy.

Managing positive sentinel lymph nodes

Sentinel node biopsy is the standard approach for patients presenting with a clinically negative axilla and undergoing breast conserving surgery. Based on the results of the ACOSOG Z11 trial, a study of women with cT1-2, cN0 cancers and tumor involvement of one or two sentinel lymph nodes [37], completion of axillary dissection is not indicated when patients will be receiving post-lumpectomy radiation therapy and appropriate systemic adjuvant therapy. The Panel addressed questions of surgical management of the axilla in certain instances not meeting the 'Z11' criteria. For women presenting with tumors larger than 5 cm and with one to two positive lymph nodes, the Panel endorsed omitting axillary dissection following sentinel node biopsy, provided that regional nodal irradiation (RNI) including the axilla was planned as a component of local-regional treatment. The Panel advised that women undergoing mastectomy who have positive sentinel lymph nodes warrant additional therapy to the axilla, either completion axillary dissection or regional radiation therapy [63]. The Panel believed that axillary dissection after mastectomy could be omitted in patients with one to two positive sentinel lymph nodes provided that RNI is planned (see Table 3). In cases when no radiation was planned, or when chest wall-only radiation was planned, the Panel recommended completion axillary dissection after mastectomy in women with positive sentinel lymph nodes. Elderly patients presenting with clinical stage 1 disease and tumors with favorable biology may not need sentinel node biopsy if it is unlikely to change treatment [64].

Table 4. Systemic therapy for HER2-positive or triple-negative breast cancers

Stage		Tumor Subtype	
		HER2+	TNBC
Stage 1	T1a	TH – case by case	Chemotherapy – case by case
Typically as adjuvant therapy	T1b	TH	TC chemo
	T1c	TH	AC/T chemo
Stages 2 and 3		AC TH (± P)	AC/T chemotherapy ± platinum[a]
Neoadjuvant therapy is preferred		or TCH (± P)	
		Consider neratinib in N2, ER+ tumors not receiving P	
Residual invasive cancer after NST		Trastuzumab emtansine	capecitabine

N2 = 4+ positive lymph nodes.

[a]Some panelist prefer including platinum-based chemotherapy in women with BRCA1/2 associated breast cancers though data for this are inconsistent.

H, trastuzumab; P, pertuzumab; A, anthracycline chemotherapy; Cb, carboplatin chemotherapy; C, cyclophosphamide chemotherapy; T, taxane chemotherapy.

Sentinel lymph node biopsy after NST

NST is a common treatment of women with clinically involved axillary nodes (see Table 3). Patients with clinically positive nodes after NST are advised to have a completion axillary dissection. The Panel considered a patient who presented with a clinically positive (cN1) axillary node and received NST that downstaged the axilla to clinically negative. In such instances, the Panel allowed for sentinel node biopsy instead of axillary dissection, provided that three or more sentinel nodes were identified and all were negative. Because of a higher rate of false-negative findings with more limited sentinel node assessments [65–67], the Panel was split on whether one or two negative sentinel nodes represented adequate axillary surgery. Targeted axillary approaches including clipping of positive nodes at diagnosis may allow avoidance of axillary dissection if the targeted axillary surgery after NST removes the marked node and one or two additional sentinel nodes, and all are negative [63, 68].

Women with residual nodal disease after NST on sentinel node biopsy generally warrant completion axillary dissection. Even in the setting of micrometastatic residual cancer at sentinel node biopsy after NST, the Panel strongly favored completion axillary dissection unless RNI was planned. Patients who present with cN2 axillary disease should undergo completion axillary dissection regardless of response to NST, and receive RNI. Table 3 gives an overview of local treatment (both surgery and irradiation) of axillary levels I–III and interpectoral nodes tailored to NST response.

Local-regional therapy: radiation

Following breast conserving surgery, whole breast irradiation remains the standard treatment recommendation for optimal outcomes. The Panel recommended hypofractionated radiation treatment schedules as preferred for most patients after breast conservation [69]. Given the limited clinical data, panelists were split as to whether hypofractionated treatment was appropriate for women receiving postmastectomy chest wall irradiation and/or RNI.

Two recently presented trials [43, 44] added to the existing evidence that equally low risks of local recurrence are obtained in selected women with low-risk breast cancer undergoing accelerated partial breast irradiation (APBI) compared with whole breast irradiation. Less favorable cosmetic outcomes were seen after APBI in the RAPID trial, so the Panel did not broadly endorse APBI techniques. APBI may be appropriate for carefully selected patients at low risk of local recurrence as defined by international guidelines.

RNI improves survival in node-positive breast cancer [70]. The Panel uniformly endorsed RNI in cases of involvement of four or more axillary lymph nodes. In cases of one to three positive lymph nodes, Panelists favored RNI, regardless of mastectomy or breast conserving surgery, in cases with adverse prognostic factors such as triple-negative, HER2, and luminal B cancers, and in women with residual disease after NST.

The Panel recommended postmastectomy radiation therapy to the chest wall and regional lymph nodes in cases of four or more positive nodes, or one to three positive nodes with triple-negative histology. The Panel was divided on whether women should receive postmastectomy radiation in cancers that are HER2-positive and/or ER-positive with one to three involved lymph nodes, and in cases of larger (>5 cm) node-negative tumors. Postmastectomy radiation was not recommended for T2N0 cancers. Postmastectomy radiation therapy recommendations are the same for women undergoing immediate reconstruction. The Panel acknowledged that radiation therapy after reconstruction may have a negative effect on the cosmetic appearance of the reconstructed breast and recognized that patient preference is important in this decision, but articulated concerns about foregoing important oncological treatments.

Many patients with stage 2 or 3 breast cancers will receive NST (see Table 4). The Panel urged caution when attempting to make postmastectomy radiation therapy recommendations tailored by response to NST. That said, the Panel recommended PMRT in women with one to three residual involved lymph nodes after NST. Even in the case of a cT3cN0 TNBC with a complete pathological response to NST, a majority of the Panel favored postmastectomy radiation treatment.

Table 5. Systemic therapy for ER+ HER2− breast cancer

Stage		Ovarian Suppression	Type and duration of endocrine therapy	Chemotherapy
Stage 1	T1ab	No OFS	AI or tam (5 years)	No
	T1c	No OFS	AI or tam (5 years)	Individualized decision based on: T size, N status, histological subtype, LVI, grade, proliferation, quantitative hormone receptor expression, genomic signatures, and patient preferences
Stage 2	Node-negative	OFS and AI/tam for higher risk historically warranting chemo (e.g large T, age < 35, high grade, adverse gene signature	• AI preferred as initial therapy. • Extended therapy favored (especially after initial 5 years of tamoxifen)	
	Node-positive	OFS and AI/tam	• AI based. • Extended therapy.	
Stage 3		OFS and AI/tam	• AI based. • Extended therapy.	Yes

[a]Some consider OFS along same criteria as stage 2, node-negative.
AI, aromatase inhibitor; Tam, tamoxifen; LVI, lymphovascular invasion; OFS, ovarian function suppression.

Older women might avoid radiation therapy after breast conserving surgery for stage 1 breast cancer as randomized trials have shown that post-surgical radiation therapy does not improve overall survival [71, 72]. The Panel tended to favor radiation after breast conserving surgery in women age 70 years who were otherwise in good health with substantial life-expectancy, as radiation therapy meaningfully lowers the risk of in-breast recurrence. However, the Panel recommended against radiation in the 'oldest' of the elderly, age 80 years or greater.

Systemic therapy: endocrine treatment

ER-positive tumors in postmenopausal women

Adjuvant endocrine therapy is well established as the standard for women with ER-positive breast cancer. In postmenopausal women, the options include either tamoxifen or an aromatase inhibitor (AI). AI therapy can be administered either as initial endocrine therapy or after 2–5 years of tamoxifen. Based on long-term follow-up of studies comparing tamoxifen and AI therapy showing small (2%–3%) reductions in 10-year recurrence risk with AI treatment, the Panel preferred that most patients consider AI therapy at some point during their course of adjuvant treatment [73]. Because of overall risk, a more meaningful clinical benefit with AI-based therapy may be realized in: stage II/III cancers; tumors with higher grade or with high Ki-67 labeling index; lobular breast cancers, which show sensitivity to AI therapy [74]; and cancers that are both ER-positive and HER2-positive (Table 5). The Panel was open to initial therapy with tamoxifen followed in sequence by an AI, especially in lower risk cancers, though most would opt for initial treatment with an AI. Five years of treatment has been the historical duration of adjuvant endocrine treatment therapy but many recurrences happen after 5 years [75]. Multiple trials have now suggested that extended therapy for up to a total of 10 years of treatment can reduce recurrence risk by several percentage points in high risk patients [10]. Women with higher risk cancers—those with involved lymph nodes at diagnosis and higher risk genomic signature scores—are at greater risk for late recurrence and thus derive more absolute numerical benefit from extended therapy [76, 77]. Thus, for higher risk stage 3 cancers and node-positive stage 2 cancers, the Panel strongly endorsed extended adjuvant endocrine therapy (see Figure 1 and Table 5). For stage 1 cancers, the Panel generally favored capping treatment at 5 years. For stage 2, node-negative cancers, the Panel tended to recommend extended adjuvant endocrine therapy, especially in women who received tamoxifen as their initial treatment. The Panel preferred a duration of therapy of 10 years for women receiving extended adjuvant treatment. On a case-by-case basis, panelists acknowledged treating very high risk individuals (e.g. more than 10 positive lymph nodes) for longer durations, and conversely, that the marginal benefits of treatment beyond 7–8 years are likely to be very modest [78]. Patients who have been on endocrine therapy for 5 years are likely to have well informed impressions on the tolerability of adjuvant endocrine therapy, and these considerations are important in deciding on the duration of treatment.

ER-positive tumors in premenopausal women

Long-term data show that OFS paired with either tamoxifen or an AI can reduce recurrence compared with tamoxifen alone in premenopausal women with early-stage breast cancer [12]. The Panel recommended OFS based on clinical risk factors including patient age, and tumor stage and pathological features (Table 5). In general, panelists favored OFS in young women (e.g. ≤35 years), node-positive cases (especially two or more lymph nodes), and tumors with high grade and/or adverse results of genomic signatures, though molecular tests were not routinely used in canonical trials of OFS. In essence, the Panel felt that cases which would historically warrant chemotherapy should additionally receive OFS. For instance, in a case discussion of a 33 year old woman with a T1, node-positive, ER, and PR positive grade 3 tumor advised to receive chemotherapy, the Panel uniformly endorsed OFS and either tamoxifen or an AI in addition to chemotherapy treatment. The Panel recommended 5 years of OFS when administered. Premenopausal women with low risk, node-negative cancers may be treated with adjuvant tamoxifen alone.

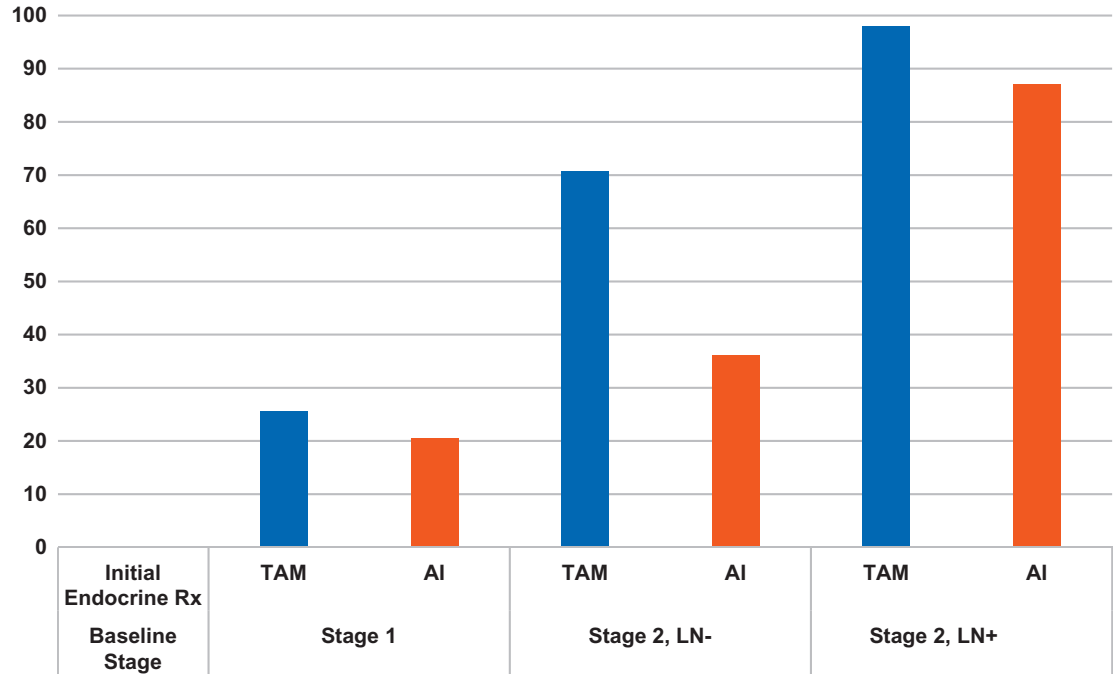

Figure 1. Percent of panelists recommending extended endocrine therapy based on stage and initial treatment (TAM and AI refer to type of initial therapy during the first 5 years).

Systemic therapy: chemotherapy

Chemotherapy for ER-positive, HER2-negative tumors

Standard treatment of women with ER-positive, HER2-negative breast cancer includes adjuvant endocrine therapy. Some women with ER-positive tumors will gain additional benefit from chemotherapy, whereas many such patients can safely avoid chemotherapy. Stage remains an important determinant of recurrence risk and hence the need for chemotherapy (Table 5); in general, women with stage 3, ER-positive breast cancer warrant adjuvant chemotherapy. The Panel specifically recommended chemotherapy in women with four or more affected lymph nodes, including those with lobular carcinoma and/or grade 1 or luminal A breast cancers. In contrast, women with ER-positive, node-negative tumors <1 cm rarely warrant chemotherapy.

Between those extremes of stage, the recommendation for adjuvant chemotherapy is based upon consideration of: patient age, anatomic stage, tumor size, the presence of absence of lymphovascular invasion, the extent of nodal involvement, and tumor pathology including grade, proliferation assays such as Ki67 labeling index, and increasingly, the results of gene expression signature (genomic) assays, particularly among cases when Ki67 testing is not available or where results are ambiguous or unreliable. The Panel strongly endorsed the value of genomic assays for determining whether to recommend chemotherapy in T1/T2 N0 tumors, T3 N0 tumors, and TxN1 (one to three positive LN).

The Panel reviewed recent data from prospective clinical trials that incorporated genomic assays into clinical decision-making for ER+ tumors [11, 13, 79, 80]. In women with low-risk genomic signature tumors, there is no significant benefit to adding chemotherapy to endocrine therapy in node-negative cancers, nor—in all likelihood—cancers with limited nodal involvement (for instance, one or two affected lymph nodes) when they are naturally or iatrogenically postmenopausal. The Panel consistently voted to avoid chemotherapy in such cases. The Panelists took note of TailorX results: women with node-negative cancers and recurrence scores ≤ 25 do not need chemotherapy. They discussed, based on subgroup analysis, whether patients of age <50 years with node-negative cancer and RS 21–25 should receive appropriate chemoendocrine therapy, OFS + Tam/AI, tamoxifen, or chemotherapy plus endocrine therapy including OFS, without reaching a consensus.

The Panel recommended also against chemotherapy in lobular breast cancers and low-grade, luminal A breast cancers that are node-negative and/or affecting one to three axillary nodes.

The Panel discussed the management of premenopausal women with node-negative cancers where retrospective subset analyses have questioned whether there is a benefit for chemotherapy in a group of patients with tumors falling in the intermediate range of the OncotypeDX Recurrence Score [11], which could be due to direct effects of cytotoxic chemotherapy or to chemotherapy-induced amenorrhea. There was no consensus whether to recommend chemotherapy in addition to endocrine therapy in such cases, with panelists split between favoring chemotherapy and endocrine therapy or preferring OFS plus either tamoxifen or an AI.

Genomic signature testing is not always accessible. In situations where multigene signature assays are not available, clinicians integrate traditional pathology (T size, grade, ER/PR, proliferation) to assign ER-positive, node-negative tumors to low- or high-risk, and largely on that basis, recommend adjuvant chemotherapy or not. Prospective studies have shown that such

approaches can identify low-risk groups with a favorable prognosis in the absence of chemotherapy [12, 81]. Given robust validation from prospective, randomized trials, panelists preferred using genomic signatures for basing the critical yes/no chemotherapy decision. However, the St. Gallen Consensus Panel has acknowledged in the past [58] that such pathology approaches are reasonable when tumor stage and pathological features suggest low risk, and when genomic testing is not readily accessible.

The Panel discussed the preferred chemotherapy regimen for women receiving adjuvant chemotherapy for ER-positive breast cancers [30, 31]. For node-negative, ER-positive cancers, the Panel recommended alkylator- and taxane-based regimens without inclusion of an anthracycline. Traditionally, the Panel has favored anthracycline-based regimens for higher risk tumors.

Chemotherapy for triple-negative breast cancers

Chemotherapy is the mainstay of neo/adjuvant treatment of TNBC. Based on a recent meta-analysis [26], the Panel endorsed 'dose-dense' treatment as the preferred approach for anthracycline- and taxane-based neo/adjuvant chemotherapy regimens. Standard 'dose-dense' regimens typically include accelerated schedules of anthracycline- and alkylator-based therapy, followed sequentially by accelerated or weekly taxane treatments. The Panel strongly endorsed the use of NST as the preferred approach to stage 2 or 3 TNBC (Table 4). This preference is based on the opportunity to surgically downstage many patients, to deliver effective systemic therapy, to gain insights into the prognosis for a given patient, and to tailor both local and systemic therapy based on the extent of residual disease. The Panel recommended anthracycline-, alkylator-, and taxane-based chemotherapy as the preferred regimen for many women with stage T1cN0 disease and virtually all of those with higher stage TNBC. A majority of panelists indicated a preference for taxane- and alkylator-based chemotherapy, without anthracyclines, in stage T1ab ($\leq$1 cm) N0 TNBC. Panelists decide on a case-by-case basis whether to give adjuvant chemotherapy in T1a ($\leq$0.5 cm) N0 tumors.

Several trials have studied whether incorporating platinum-based chemotherapy improves outcomes in TNBC [82–84]. Studies of NST have consistently shown that adding platinum-based chemotherapy improves the rates of complete pathological response in TNBC, though the effect on long-term disease recurrence remains less certain, especially if a different alkylator (i.e. cyclophosphamide) has already been included in the treatment regimen. The Panel voted against the routine inclusion of platinum-based chemotherapy in women already slated to receive alkylator-, taxane-, and anthracycline-based regimens. The Panel favored inclusion of platinum-based chemotherapy among women with known, deleterious germline BRCA1/2 mutations, though data on this scenario are limited and this opinion was far from unanimous.

Patients with TNBC who have residual invasive cancer following NST have a higher risk of recurrence. Data from a single randomized trial suggest that such patients benefit from the addition of adjuvant capecitabine therapy [25] though capecitabine has not been shown in traditional adjuvant trials to improve on outcomes seen with standard chemotherapy regimens alone [29]. The Panel recommended that patients with residual invasive cancer, especially those with nodal involvement and/or more than 1 cm of residual tumor in the breast, are offered adjuvant capecitabine after completing taxane-, anthracycline-, and alkylator-based chemotherapy.

Systemic therapy for HER2-positive breast cancers

Anti-HER2 therapy paired with chemotherapy is an essential component of neo/adjuvant treatment of HER2-positive breast cancer. The Panel strongly endorsed the use of NST as the preferred approach to stage 2 or 3 HER2-positive tumors (Table 4), for similar reasons as in TNBC: to improve surgical options, to deliver effective systemic treatment, to obtain prognostic information, and to tailor therapy based on the extent of residual disease. The majority of the Panel endorsed anthracycline-, alkylator-, and taxane-based chemotherapy in combination with trastuzumab- and pertuzumab-based treatment as the preferred approach for stage 2 or 3, HER2-positive tumors, in either the adjuvant or neoadjuvant setting, though many panelists frequently prescribe non-anthracycline regimens such as docetaxel/carboplatin/trastuzumab/pertuzumab [22, 85, 86]. For stage 1, HER2-positive tumors, panelists confirmed paclitaxel plus trastuzumab, without pertuzumab-based therapy, as adjuvant therapy. However, some panelists favored inclusion of pertuzumab when offering neoadjuvant therapy in HER2-positive, ER negative, and clinical stage 1 cancers.

Several trials have addressed the option using $<$12 months of adjuvant trastuzumab-based therapy in early stage, HER2-positive breast cancer [19, 20, 87, 88]. These studies have shown a narrow reduction in recurrence risk with 12 months of therapy compared with shorter (3 or 6 month) durations. Thus, the Panel recommended 1 year of trastuzumab-based treatment as the preferred duration while acknowledging that the benefits of 12 months over 6 months is likely to be very modest based on results from those trials.

Extended anti-HER2 therapy with neratinib in the adjuvant setting after one year of trastuzumab may further reduce the likelihood of tumor recurrence [89]. The Panel recommended neratinib in cases of node-positive, ER-positive, HER2-positive breast cancers, especially those with four or more affected lymph nodes treated with trastuzumab-based therapy. The Panel did not endorse routine use of neratinib in patients previously treated with pertuzumab-based therapy owing to a lack of data among such a population.

NST is the preferred approach for stage 2 or 3, HER2-positive tumors and achieves robust rates of pathological complete response (Table 4). In women with residual invasive HER2-positive breast cancer following NST, the introduction of adjuvant trastuzumab emtansine therapy substantially reduced the risk of recurrence, an absolute benefit of 8%–12% risk reduction [18]. Based on these data, the Panel strongly recommended trastuzumab emtansine for women with residual invasive cancer following NST with trastuzumab- or with trastuzumab- and pertuzumab-based regimens (Table 4). The Panel advised that patients who achieve a pathological complete response with anti-HER2-based therapy do not require the addition of trastuzumab emtansine. They should receive adjuvant trastuzumab or trastuzumab plus pertuzumab as originally offered in their initial NST regimen.

Table 6. Clinical and research priorities

- Ongoing efforts to define for individual patients the likely benefits of specific therapies based on tumor stage and biological features, and on the efficacy of treatment, to allow patients to make decisions informed by quantifiable estimates of benefit as well as considerations of side-effects and personal preferences including no treatment options.
- Development of tailored treatment approaches (surgical, medical, and radiotherapeutic) based on response of individual patients to treatment in the preoperative/neoadjuvant setting so as to both spare patients unnecessary therapy and treat patients when there is ongoing therapeutic need.
- Development of clinical trials that reflect the current, low-risk, favorable outcomes for many women with early-detected breast cancers who are still in need of new insights on optimizing therapy.
- Exploration of immunotherapy approaches in early-stage breast cancer driven by robust end points reflecting the natural history of breast cancer, notably overall survival.
- Worldwide efforts to assure that women with curable, early-stage breast cancer have access to technologies and treatments that are life-altering including genetic testing, essential biomarker analyses, and critical therapeutics.
- Evaluation of strategies to minimize symptoms of therapy for early-stage breast cancer, including lymphedema, chemotherapy-related side-effects, endocrine therapy-related side-effects, neuro-cognitive issues, and overall quality of life.

Adjuvant bisphosphonates

Randomized trials supported by a meta-analysis have suggested that adjuvant bone modifying therapy can reduce the risk of tumor recurrence in postmenopausal women [90]. In addition, bisphosphonate therapy can help reduce osteopenia or osteoporosis, common problems in women with breast cancer treated with ovarian suppression or with estrogen deprivation strategies. The Panel recommended routine use of adjuvant zoledronic acid or clodronate in postmenopausal women. In addition, the Panel favored the use of zoledronic acid in premenopausal women with ER-positive breast cancer receiving GnRH agonist therapy with either an AI or tamoxifen [81]. In these settings, bisphosphonate therapy contributes to a 4% to 8% reduction in cancer recurrence at 5 years without improving overall survival. The Panel did not recommend substituting the RANK ligand inhibitor, denosumab, for bisphosphonates [91].

Ductal carcinoma *in situ*

Ductal carcinoma *in situ* (DCIS) is a precancerous lesion frequently identified through screening mammography. The historical standard treatments for DCIS have included surgery—either lumpectomy and radiation therapy in women undergoing breast conserving surgery, or mastectomy, in order to prevent the subsequent development of invasive breast cancer or recurrent DCIS. Risk stratification based on the extent of DCIS and its histological features can identify a relatively low-risk population of women with a recurrence risk of ~10% after breast conserving surgery through a decade of follow-up. Randomized trials have shown that even such low-risk patients might still benefit from post-lumpectomy radiation therapy [92], reducing the risk of in-breast recurrence or invasive cancer. Given the modest absolute benefits of radiation therapy in such cases, and lack of a survival impact for treatment of DCIS, the Panel believed that women with favorable prognostic features (low- or intermediate-grade, absence of comedonecrosis, age >50 years) and generous surgical margins—typically in excess of 0.5 cm—may forego radiation treatment and endocrine therapy if they were willing to accept a slightly greater risk of in-breast recurrence.

Future directions

The Panel identified important clinical and research priorities in early stage breast cancer (Table 6). These included ongoing efforts to individualize or tailor treatments for specific women with particular types of breast cancer, exploration of immunotherapy approaches in early breast cancer, and continued efforts to reduce the symptoms associated with treatment. Notably, the Panel also recognized the critical importance of assuring access to essential, life-saving treatments for breast cancer including appropriate multi-modality treatment and access to valuable tests and therapeutics so that women around the globe can receive optimal treatment for curable breast cancer.

Genetic testing

Hereditary breast cancer accounts for 5%–10% of all breast cancers. The Panel recommended genetic counseling and germline genetic testing using multigene panels for women with: strong family history of breast cancer, breast cancer onset younger than age 35, and women less than age 60 with TNBC. The Panel did not endorse universal genetic testing for all women with breast cancer though some panelists believe this is likely to become a practice in the near future.

Survivorship

Some women wish to become pregnant after a breast cancer diagnosis. Randomized trials have demonstrated that the use of GnRH agonist therapy during neo/adjuvant chemotherapy improves preservation of ovarian function and promotes the likelihood of subsequent pregnancy [93, 94]. The Panel strongly endorsed the use of OFS during chemotherapy as a strategy for fertility preservation in women with either ER-positive or ER negative cancer who seek to optimize long-term fertility.

For women contemplating pregnancy after a breast cancer diagnosis, the Panel recommended restaging scans before attempted conception. The optimal timing of pregnancy after a breast cancer diagnosis is not known, nor is the impact of interrupting adjuvant endocrine therapy, which is obligatory in women considering pregnancy. The Panel recommended a minimum of 18 months following diagnosis before anticipated pregnancy, though acknowledged that this is an arbitrary suggestion. It is important that women anticipate resuming antiestrogen therapy following attempted or successful pregnancy.

The Panel advised good general health habit for breast cancer survivors including encouraging appropriate body mass index and exercise goals for maintenance of general well-being. There are no data at present that diet or lifestyle changes affect cancer recurrence risk among breast cancer survivors.

The panelists agreed that patients should be informed about magnitude of benefit of interventions with small to marginal benefit and be offered no treatment as a reasonable alternative.

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Appendix: St Gallen International Consensus Conference on Primary Therapy of Early Breast Cancer 2019

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16.	Francis	Prudence	Peter McCallum Cancer Centre	8006	Melbourne	Australia
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18.	Garber	Judy	Dana-Farber Cancer Institute	2215	Boston, MA	USA
19.	Gardishar	William J.	Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University	60611	Chicago, Illinois	USA
20.	Gelmon	Karen	BC Cancer, Medical Oncology,	V5Z4	Vancouver, BC	Canada
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22.	Gulluoglu	Bahadir	Marmara University School Of Medicine	34899	Istanbul	Turkey
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31.	Osborne	C. Kent	Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine	77030	Houston, Texas	USA
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