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SPECIAL ARTICLE

Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021

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Available online 6 July 2021

The 17th St Gallen International Breast Cancer Consensus Conference in 2021 was held virtually, owing to the global COVID-19 pandemic. More than 3300 participants took part in this important bi-annual critical review of the 'state of the art' in the multidisciplinary care of early-stage breast cancer. Seventy-four expert panelists (see Appendix 1) from all continents discussed and commented on the previously elaborated consensus questions, as well as many key questions on early breast cancer diagnosis and treatment asked by the audience. The theme of this year's conference was 'Customizing local and systemic therapies.' A well-organized program of pre-recorded symposia, live panel discussions and real-time panel voting results drew a worldwide audience of thousands, reflecting the far-reaching impact of breast cancer on every continent. The interactive technology platform allowed, for the first time, audience members to ask direct questions to panelists, and to weigh in with their own vote on several key panel questions. A hallmark of this meeting was to focus on customized recommendations for treatment of early-stage breast cancer. There is increasing recognition that the care of a breast cancer patient depends on highly individualized clinical features, including the stage at presentation, the biological subset of breast cancer, the genetic factors that may underlie breast cancer risk, the genomic signatures that inform treatment recommendations, the extent of response before surgery in patients who receive neoadjuvant therapy, and patient preferences. This customized approach to treatment requires integration of clinical care between patients and radiology, pathology, genetics, and surgical, medical and radiation oncology providers. It also requires a dynamic response from clinicians as they encounter accumulating clinical information at the time of diagnosis and then serially with each step in the treatment plan and follow-up, reflecting patient experiences and treatment response.

Key words: adjuvant, genetic testing, neoadjuvant, radiation therapy, surgery, survivorship

INTRODUCTION

Despite the vast literature on managing early-stage breast cancer, not all clinical scenarios can be directly informed by data from randomized trials or other definitive treatment studies. Our approach to breast cancer is becoming progressively individualized, reflecting details of tumor size and nodal status, tumor subsets (and increasingly, subsets of subsets), genomic markers of risk, variations in patient age and health, the evolving and improving efficacy of systemic treatments, the shifting methods of radiation therapy, tailored surgical approaches to management of the axilla, prognostic factors, the widespread use of neoadjuvant treatment that provides information about dynamic response, and the subsequent use of post-neoadjuvant systemic treatment. The result is that, for a surprising number of clinical situations, there are insufficient definitive data from clinical trials to guide recommendations. Clinicians and patients must make inferences from canonical treatment studies, and customize them to individual situations, also informed by patient preferences and evolving clinical data.

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Since the last Consensus conference in 2019, breast cancer has surpassed lung cancer to become the most frequently diagnosed cancer in the world, underscoring the importance of global guidance for optimal treatment.[1] Fortunately, the past 2 years also have seen a continuous outpouring of data on management of breast cancer, reflecting growing understanding of the biology and treatment of early- and late-stage disease (Table 1). Owing to widespread screening mammography around much of the world, the increasing efficacy of targeted therapies such as endocrine and anti-human epidermal growth factor receptor 2 (anti-HER2) treatments, and greater access to effective health care, the mortality from breast cancer continues to decline in middle- and high-income countries.[1] However, there remain profound disparities among and within nations in terms of access to screening programs, high-quality treatment and supportive care for breast cancer. Many services remain unavailable, unaffordable, or beyond the capacity of the local health care system. The disruptions of the COVID-19 pandemic are likely to exacerbate these disparities in the short term, straining the health care resources of every country, affecting access to screening mammography,[2] and sometimes delaying necessary treatment.[3] As an international consensus panel, the St Gallen faculty are keenly aware of the differences in resources for detection and treatment of early breast cancer. There is universal commitment to reduce these disparities. At the same time, panelist recommendations are often affected by the availability of certain techniques, imaging modalities, molecular diagnostic approaches or treatment options, which vary from country to country, or even within nations.

The Panel sought to provide clinical guidance on common clinical situations in early breast cancer, including refined guidance on local-regional and systemic therapy that builds on its previous recommendations.[4] This year, there were strong interests in refining thresholds for treatment, the use of genomic signatures, evolving practices in radiation oncology, the utilization of ovarian suppression, and the surgical and systemic decision-making following neoadjuvant treatment. In addition, for the first time, the Panel addressed challenges in oligometastatic breast cancer management, and the treatment of ipsilateral recurrences or second cancers. The Panel also devoted more time this year to discussions of breast cancer survivorship, a recognition of the millions of women and men who have personal histories of breast cancer and who are coping with the psychological and physical side-effects of their cancer treatments. Guidance is intended to apply to the vast majority of patients with early breast cancer who are in reasonably good health, and who do not have medical, psychological, or social conditions that would preclude standard treatment. Votes reflect the opinions of the experts based on what they would advise in clinical practice. The Panel recognizes that treatment guidance may not be applicable to selected cases owing to patient preferences, treatment availability, or other individual circumstances.

GENETIC TESTING AND MANAGEMENT OF HEREDITARY BREAST CANCERS AND SYNDROMES

Hereditary, deleterious mutations account for 8%-10% of all breast cancers.[5-7] While *BRCA1/2* mutations account for about half of these cases, the remainder arise from less prevalent, and often less penetrant mutations found in up to two dozen different genes. As in the past, the Panel favored genetic counseling and germline genetic testing for patients whose age of breast cancer onset, family history of breast or other cancers, presence of male breast cancers and tumor subtype were more likely to identify a familial cause of breast cancer. Similarly, the Panel did not recommend universal genetic testing for all, though a growing percentage of panelists now favor genetic testing for all breast cancer patients diagnosed at age $<$65 years.

The Panel developed guidance for people harboring deleterious, hereditary mutations that predispose to breast cancer but who have not been diagnosed with breast cancer. Recent population-based studies have clarified the risk of breast cancer for many deleterious gene mutations, and clustered them into groups of high penetrance (carrying a threefold or more increased risk of breast cancer relative to the general population), intermediate penetrance (twofold to threefold risk), or low penetrance (onefold to twofold risk).[6,7] There are varied opinions as to the best way to treat or follow women with known genetic predisposition to breast cancer, and the panelists acknowledge that both age and the individual preferences of women, reflecting their perceptions of risk and general comfort with the various approaches, are the key drivers of these choices. The degree of penetrance of the gene, and the age of the woman with a genetic diagnosis, affected the recommendations for prophylactic mastectomy (Table 2). If a gene panel testing is chosen, the majority (67%) voted that the preferred panel should routinely include: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *PTEN*, *STK11*, *RAD51C* and *RAD51D*, and *TP53*. A minority (7%) voted that only *BRCA1* and *BRCA2* should be tested, and 17.2% of the panelists opted for the evaluation of *BRCA1/2* and *PALB2*. In general, the Panel favored consideration of risk-reducing mastectomy for women harboring highly penetrant genes (e.g. *BRCA1*, *BRCA2*, *TP53*, and *PALB2*), and surveillance with mammography and magnetic resonance imaging (MRI), for women with intermediate penetrance genes (e.g. *BARD1*, *CHEK2*, *CDH1*, *STK11*). For women with less penetrant gene mutations (such as *ATM*, *BRIP1*, *NF1*, *RAD51C*, *RAD51D*), the Panel strongly favored surveillance without prophylactic mastectomy.

Separately, the Panel discussed management of hereditary, *BRCA1*- or *BRCA2*-associated early-stage breast cancers. Before the conference, press statements became available, outlining the results of the OlympiA trial evaluating olaparib in the adjuvant setting. Following the St Gallen conference, the data from the OlympiA trial were published, showing a significant reduction in recurrence risk with adjuvant olaparib in HER2-negative, *BRCA1/2*-associated breast cancer.[8] Based on those newly available data, the Panelists were re-canvassed for treatment

Table 1. New studies in breast cancer since St Gallen 2019

Area	Discovery/innovation	Refs
Genetics and hereditary breast cancer	Large population-based studies define penetrance and risks of most common hereditary genes associated with breast cancer	6,7
	TBCRC048 trial shows that the PARP inhibitor, olaparib, has substantial effect in MBC for tumors with hereditary *PALB2* mutation or somatic *BRCA1/2* mutation	72
	The OlympiA trial demonstrates that adjuvant therapy with olaparib reduces recurrence in BRCA1/2-associated breast cancer	8
	Population studies suggest that age and family history criteria may miss many cases of hereditary breast cancer	73
Supportive care	Oyxbutynin shown effective for climacteric symptoms in breast cancer patients	74
	Quality-of-life studies demonstrate profound effects of ovarian suppression on bone health and sexual health in premenopausal women	75
COVID pandemic	Pandemic disrupts routine patient management, and prompts guideline revisions to prioritize treatment needs amid epidemic	76-78
	Rates of screening mammography plummet in wake of pandemic	79
Radiation therapy	Efficacy of hypofractionation for postmastectomy radiation	80
	Efficacy of hypofractionation for invasive breast cancer and DCIS after breast conserving surgery	56
	Use of ultra-hypofractionated radiation schedules after breast conserving surgery	21,22
	Efforts to standardize variations in radiotherapy practice and access	81-84
	Partial breast irradiation updates	25,85-89
	Long-term follow-up of the PRIME2 study confirms absence of survival benefit but reduction in local recurrence for postlumpectomy radiation in older women	23
DCIS	'Boost' after radiation therapy reduces in-breast recurrence; hypofractionation is as effective as 25 Fx treatments for DCIS after breast-conserving surgery	56,57
Surgery	E2108, a randomized trial of surgery in women with *de novo* stage IV breast cancer, showed that breast surgery does not improve overall survival, thereby contradicting the results of multiple observational studies, while prior randomized trials have provided conflicting data.	66
	BOMET MF 14-01: timing of primary breast surgery either at diagnosis or after systemic therapy provided a survival benefit similar to ST alone in *de novo* stage IV BOM BC patients. This is the follow-up study to their randomized trial.	90
	Several single-center series demonstrated low nodal failure rates in patients with biopsy proven clinically node-positive breast cancer undergoing sentinel lymph node surgery without axillary dissection, despite considerable false-negative rate after neoadjuvant chemotherapy	36,91-93
	SenTa, a prospective multicenter study, showed that targeted axillary dissection minimizes the false-negative rate of sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer, but detection rate of clipped lymph node was only 86.9%.	94
	The Oncoplastic Breast Consortium ranked optimal type and timing of reconstruction in the setting of postmastectomy radiotherapy as the most important of a list of 38 knowledge gaps in the field of oncoplastic breast surgery	95
	The Lucerne Toolbox: Consensus and Guideline that summarizes surgery after neochemo	96
Early-stage, ER-positive breast cancer: clinical	First reports of adjuvant CDK4/6 inhibitors show mixed results	50
	The MONARCH-E trial showed that adjuvant abemaciclib reduced recurrence in high-risk, ER+ breast cancer	48
	The PALLAS trial showed that adjuvant palbociclib did not reduce recurrence in high risk ER+ breast cancer	49
	The PENELOPE-b trial showed that adjuvant palbociclib did not reduce recurrence in high-risk ER+ breast cancer	44
	Data from ABCSG 16 suggest that extended duration adjuvant endocrine therapy beyond 7/8 years does not improve outcomes	97
	Data from NSABP B-42 suggest that 5 years of AI therapy after an initial 5 years of endocrine therapy can reduce breast cancer recurrence	46
	Ongoing follow-up of the SOFT and TEXT trials confirms the importance of tumor stage and grade as prognostic factors in premenopausal breast cancer	51,52
	Long-term follow-up from the TAILORx and MINDACT trials shows that there is no benefit to chemotherapy in postmenopausal women with tumors bearing low-risk genomic scores, but that chemotherapy can reduce the risk of recurrence in premenopausal women, likely due to chemotherapy-induced amenorrhea	53
	The RxPonder study shows that there is no benefit to chemotherapy in postmenopausal women with node-positive tumors bearing low-risk genomic scores, but that chemotherapy can reduce the risk of recurrence in premenopausal women, possibly due to chemotherapy-induced amenorrhea	98
Early-stage, ER-positive breast cancer: translational	Endopredict and response to neochemo and neoendocrine therapy—for gene expression and neochemo questions	99
	Independent validation of the PAM50-based Chemo-Endocrine Score in hormonal receptor-positive HER2-positive breast cancer treated with neoadjuvant therapy—also for use of gene expression before neochemo questions	30
	ADAPT trial—using oncotype and ki-67 for chemotherapy versus no chemotherapy	100
	HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis	101
	A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation	

Continued

Table 1. Continued

Area	Discovery/innovation	Refs
	Lobular breast cancer and Endopredict—largest phase III cohort of lobulars analyzed: lobular no different than invasive ductal	102
	Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial	103
	Correlative studies of the breast cancer index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine benefit: a Trans-aTTom Study. Sgroi et al.[104]	104
	An analysis of outcomes for neoadjuvant chemotherapy suggests that tumors with low ER expression <10% have outcomes similar to TNBC	9
Advanced stage, ER-positive breast cancer: clinical	Long-term follow-up of trials of CDK4/6 inhibitors show survival benefit for the class of drugs	105,106
	The nextMONARCH trial shows that late use of tamoxifen adds to effects of abemaciclib in MBC	107
	The PIK3CA kinase inhibitor, alpelisib, improves PFS in PIK3CA-mutated ER+ breast cancer	108
	Entinostat, an HDAC inhibitor, does not improve outcomes in advanced breast cancer	109
Early-stage, HER2-positive breast cancer	Long-term follow-up of the APHINITY trial shows OS benefit for pertuzumab in node-positive but not node-negative breast cancer	110
	The ATEMPT study shows equivalent long-term tumor control with trastuzumab emtansine compared with trastuzumab + paclitaxel for stage I breast cancer but without safety benefits	111
	Long-term follow-up of the ExteNet study suggests benefit for adjuvant neratinib in women with ER+ HER2+ breast cancer	112
	The KRISTINE study showed the TCHP was associated with improved disease-free survival compared with pertuzumab + trastuzumab emtansine owing to differences in local-regional recurrence	113
Advanced-stage, HER2-positive breast cancer	The HER2CLIMB trial demonstrates that adding tucatinib to capecitabine plus trastuzumab improves OS in advanced breast cancer	114
	The DESTINY trial shows high response rates for trastuzumab deruxtecan in advanced breast cancer	115
	The NALA study shows that neratinib + capecitabine improve PFS but not OS compared with lapatinib + capecitabine	116
Early-stage, triple-negative breast cancer	The SYSUCC trial shows that metronomic, adjuvant capecitabine reduces recurrence risk	117
	The CBCSG-10 trial showed that adding capecitabine to adjuvant chemotherapy reduces recurrence risk	118
	The Keynote-522 study showed that adding neoadjuvant pembrolizumab to AC/paclitaxel plus carboplatin chemotherapy improves rate of pCR and may reduce recurrence risk	119
	The IMPASSION031 study showed that adding neoadjuvant atezolizumab to nab-paclitaxel and anthracycline chemotherapy improves the rate of pCR	120
	The NeoTrip study showed that adding neoadjuvant atezolizumab to nab-paclitaxel and carboplatin chemotherapy did not improve the rate of pCR	121
Advanced-stage, triple-negative breast cancer	The KEYNOTE-199 trial showed that single-agent checkpoint inhibition did not improve OS compared with chemotherapy	122
	In contrast to the IMPASSION130 study of nab-paclitaxel ± atezolizumab, the IMPASSION131 trial did not show benefit for adding atezolizumab to paclitaxel in first-line therapy for PD-L1-positive breast cancer	123
	The KEYNOTE-355 trial showed that adding pembrolizumab to chemotherapy improved outcomes in first-line therapy for tumors with CPS score >10%	124
	The ASCENT trial showed that sacituzumab govitecan improved PFS and OS compared with standard chemotherapy in refractory TNBC	125
Pathology	An international consensus committee endorsed thresholds of Ki67 5% and 30% for rejecting or recommending adjuvant chemotherapy in ER+ early breast cancer	12

AC, doxorubicin/cyclophosphamide; AI, aromatase inhibitor; AR, androgen receptor; BOM BC, bone-only metastatic breast cancer; CDK4/6, cyclin dependent kinase 4 or 6; CPS, combined positive score; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PIK3CA, phosphatidylinositol 3-kinase alpha; PR, progesterone receptor; ST, systemic therapy; TCHP, docetaxel/carboplatin/trastuzumab/pertuzumab; TNBC, triple-negative breast cancer.

recommendations. Nearly all panelists (>93%) strongly endorsed adjuvant olaparib for women with stage II or III, HER2-negative cancers meeting the eligibility criteria of the OlympiA study. The majority of panelists (64%) favored olaparib therapy for all such patients, irrespective of estrogen receptor (ER) status or prior treatment with platinum-based chemotherapy. As a corollary, the Panel voted nearly unanimously (95%) to recommend genetic testing of patients meeting the OlympiA trial criteria to identify candidates for olaparib-based therapy.

PATHOLOGY AND SUBSETS

In clinical practice, early-stage breast cancers are divided into three subgroups based on expression of ER, progesterone receptor (PR), and HER2. Tumors are classified as ER- and/or PR-positive and HER2-negative (hereafter, ER-positive), HER2-positive, or by default, triple-negative breast cancer (TNBC). Approximately half of HER2-positive tumors are also ER-positive. These categorizations have definitive consequences for systemic treatment. Nearly all ER-positive tumors will be candidates for adjuvant endocrine therapy. The majority of TNBCs will warrant adjuvant chemotherapy, and the majority of HER2-positive cancers warrant anti-HER2 therapy in combination with chemotherapy. The historic 1% threshold for ER expression to justify endocrine therapy remains controversial. Studies suggest that tumors with 1%-9% ER expression on immunohistochemical staining, which account for <2% of all ER-

Table 2. Percentage of panelists recommending prophylactic mastectomy or surveillance for hereditary breast cancer syndromes as a function of age and gene mutation

Gene penetrance	Higher		Moderate		Lower	
Odds ratio for developing breast cancer	>3		2-3		1-2	
Gene examples	*BRCA1, BRCA2, PALB2, TP53*		*BARD1, CHEK2, CDH1, STK11*		*ATM, BRIP1, NF1, RAD51C, RAD51D, FANCC*	
Management recommendation	**Prophylactic mastectomy**	**Surveillance[a]**	**Prophylactic mastectomy**	**Surveillance[a]**	**Prophylactic mastectomy**	**Surveillance[a]**
Patient age ~40 years (%)	85	15	13	87	0	100
Patient age ~60 years (%)	46	54	4	96	0	100

[a] Includes mammogram and breast magnetic resonance imaging, with or without antiestrogen prevention.

positive cancers, have a less favorable prognosis than ER-positive cancers with ≥10% expression, often have a basal-like genomic signature[9] and respond to neoadjuvant chemotherapy akin to TNBC.[10] Yet other large retrospective studies suggest that outcomes for tumors with 1%-9% ER expression are intermediate between those truly ER-negative and ER-positive ≥10%.[11] The Panel was once more divided on the optimal ER threshold for initiation of endocrine therapy.

Determination of grade, proliferation (such as the Ki67 labeling index), and multigene assays such as the 70-gene signature test and 21-gene recurrence score help characterize the heterogeneity of ER-positive, early-stage breast cancers, and serve as prognostic markers for recurrence risk. ER-positive cancers are sometimes classified as 'luminal A-like' (lower grade, lower Ki67, strong ER/PR expression), or 'luminal B-like' (higher grade, higher Ki67, lower levels of ER/PR expression), subtype associations that tend to correlate with genomic markers of risk. There is persistent controversy over the precise thresholds for Ki67 that would justify chemotherapy treatment or not. The Panel generally supported recent working group recommendations that tumors with Ki67 ≤5% do not receive chemotherapy, whereas tumors with Ki67 ≥30% receive chemotherapy.[12] Most early-stage, ER-positive tumors, however, fall between these extremes.[13] When polled, the Panel could not define a consistent Ki67 threshold between 10% and 25% for recommending chemotherapy in ER-positive, node-negative breast cancer, and a large fraction of the Panel believe that such a threshold was simply not known (Figure 1).

Data continue to accumulate for utility of genomic signatures to identify the benefit of chemotherapy in early-stage, ER-positive, HER2-negative breast cancer. Adoption of these signatures in clinical practice has dramatically lowered the use of adjuvant chemotherapy in this subset of breast cancers, without adversely affecting clinical outcomes. The Panel's deliberations reflected the maturation of prospective studies built around these assays, including emerging data for use of the assays in both node-negative and limited (1-3 positive) node-positive cases. With mature data from prospective studies such as MINDACT, ADAPT, TAILORx, and RxPonder, in which patients were stratified for treatment based on well-established genomic signatures, panelists favored consideration of genomic signature testing in the vast majority of instances when chemotherapy is being considered for ER-positive, HER2-negative cancers, irrespective of grade or patient menopausal status (and in male breast cancer), and in both N0 or N1 clinical stage cases, but not in N2 or higher stage where chemotherapy is standard (see discussion below, and Figure 2). The Panel's enthusiasm for genomic assays is accompanied by the understanding that access to such testing is not available to most women around the world, a disparity in care that needs rectifying. As gene expression signatures are not universally accessible, by necessity the Ki67 score serves as a surrogate for defining proliferation and biological risk, particularly when combined with semi-quantitative measures of grade, ER, PR, and HER2 for many women.[14] Given the high-level evidence for clinical utility demonstrated by the genomic signatures in ER-positive breast cancer, and challenges in defining thresholds for treatment (above), Ki67 assessment will remain a necessary but less proven strategy for determining the role of adjuvant chemotherapy in ER-positive breast cancer for many women. The Panel believes it is critical that patients around the world have secure access to important, evolving molecular diagnostic assays for optimal management of breast cancer and determination of treatment value.[15]

Tumor infiltrating lymphocytes (TILs) and programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) expression may serve as prognostic markers in early- or late-stage TNBC, and PD-L1 testing is a predictive marker for the benefit of checkpoint inhibitors in advanced TNBC. However, the Panel again declined to endorse either of these approaches as routine pathological markers in early-stage TNBC. TILs appear to serve as a prognostic marker for response to neoadjuvant chemotherapy, but data are not considered adequate for choosing specific regimens or deciding whether to withhold chemotherapy treatment. PD-1/PD-L1 expression predicts benefit from addition of checkpoint inhibitors to chemotherapy in the treatment of metastatic TNBC. However, trials have not shown that PD-L1 expression predicts the improvement in pathological complete response (pCR) when checkpoint inhibitors are added to neoadjuvant chemotherapy, an approach which (as of this date) remains investigational for early-stage TNBC.

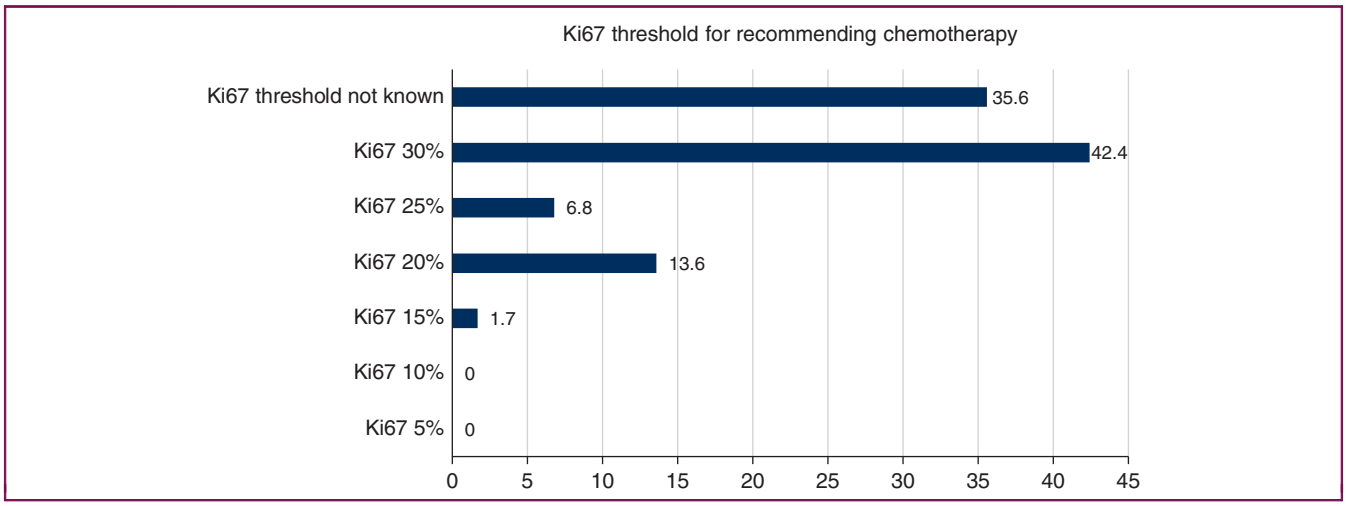

Figure 1. Defining threshold for Ki67 to recommend adjuvant chemotherapy in ER-positive, HER2-negative, node-negative breast cancer.
Numbers are percentage of panelists endorsing a Ki67 level.
HER2, human epidermal growth factor receptor 2.

LOCAL-REGIONAL THERAPY

Historically, surgery was the initial treatment of women with newly diagnosed breast cancer. That remains true for most women diagnosed with early-stage tumors, where deciding between a mastectomy and breast-conserving surgery depends on the size of the tumor, the extent of radiological changes in the breast, the anticipated cosmetic outcomes and the patient's candidacy for radiation treatment and personal preferences. Surgical resection to remove known malignancy and achieve 'no ink on tumor' margins is the standard, regardless of tumor histology or grade, or the patient's age. At the time of breast surgery, women additionally undergo axillary surgery to stage the axillary lymph nodes. Sentinel node biopsy (SNB) is the standard approach in patients presenting with a clinically negative axilla, whether undergoing mastectomy or breast-conserving surgery. Patients with negative sentinel nodes require no further axillary surgery. Women with T1-T2, clinically node-negative cancers with positive sentinel nodes who meet the criteria of the ACOSOG Z0011 trial[16] (breast-conserving surgery, with one or two positive sentinel lymph nodes) or the EORTC 10981-22023 AMAROS trial[17] [breast-conserving surgery or mastectomy, with positive sentinel node(s)], with planned breast radiation after breast-conserving surgery or axillary radiation after mastectomy, do not need additional axillary surgery in most cases. A complete axillary dissection remains standard for women with more than two positive sentinel lymph nodes, when

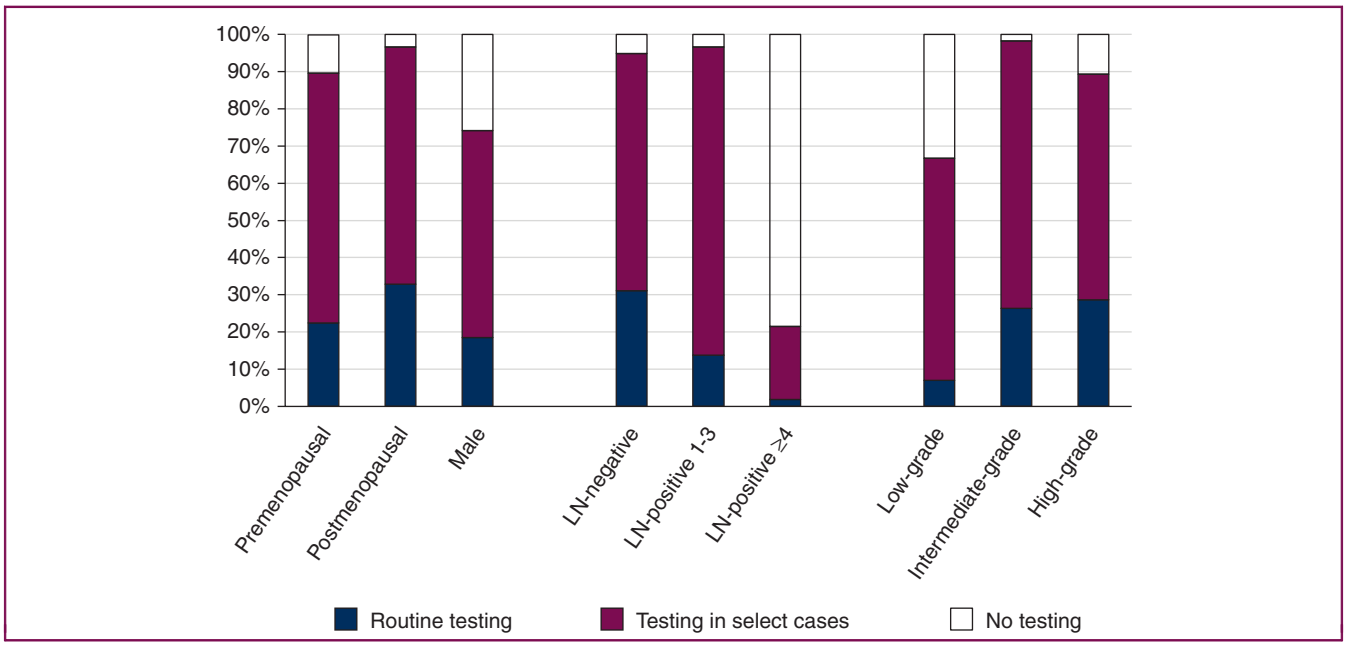

Figure 2. Panel recommendations for genomic signature testing in ER positive, HER2 negative early stage breast cancer.
Numbers denote percentage of panelists favoring routine testing, testing in select cases or no testing zones.

radiation therapy is to be omitted, or in the clinical situations when knowing the extent of axillary involvement would affect systemic or radiation recommendations.

Imaging and breast surgery

Most women presenting with screen-detected or other early breast cancers are potential candidates for breast-conserving surgery. Nonetheless, rates of mastectomy including contralateral mastectomy are increasing in many countries, reflecting patient preferences, fears of recurrence, improvements in reconstruction techniques, more widespread use of MRI imaging during the diagnostic evaluation, genetic testing[18] and lack of adequate physician-patient communication.[19] For women undergoing mastectomy who are likely to warrant postmastectomy radiation and wish breast reconstruction, the Panel favored autologous reconstruction approaches, either immediate or delayed with implant as the first step.

Among women undergoing breast-conserving surgery, the Panel did not identify a routine role for post-excision mammography provided that excision-specimen X-rays confirmed removal of known microcalcifications. The Panel supported baseline MRI imaging before neoadjuvant therapy for women who are potential candidates for breast conservation, though such MRI imaging is often highly sensitive while less specific, and is associated with a greater likelihood of (sometimes unnecessary) mastectomy.[20]

Some elderly patients may not require SNB, as finding metastatic disease to axillary nodes is not likely to change treatment recommendations. However, because the morbidity associated with SNB is relatively low, and because the finding of nodal involvement might alter treatment plans in a minority of patients, the majority of the Panel favored the procedure in women even those aged in their 80s who were undergoing surgery for breast cancer.

Radiation therapy. Radiation therapy is standard treatment following breast conserving surgery. Until recently, this meant treatment courses of 25 fractions of radiation therapy. Based on longer follow-up from multiple randomized trials, emerging studies, the 2021 Panel strongly recommended moderately hypofractionated radiation treatment courses, consisting of 15 or 16 treatments, as standard therapy, irrespective of tumor subtype or patient age. The Panel also strongly endorsed routine use of moderate hypofractionation in women receiving postmastectomy radiation and/or regional nodal irradiation (RNI), irrespective of patient age or tumor subtype, and endorsed these hypofractionated radiation therapy schedules among patients with reconstructions after mastectomy (Figure 3). There is growing interest in ultra-short course (five fractions) treatment approaches,[21,22] but the Panel did not endorse these as standard treatment as yet. The Panel urged caution in the use of partial breast irradiation, which has been studied largely in older patients with low-risk tumors, and recommended against partial breast approaches in lobular tumors or when lymphovascular invasion was present, in women <40 years of age, and in women with hereditary cancer syndromes. While genomic signatures have become highly influential in adjuvant

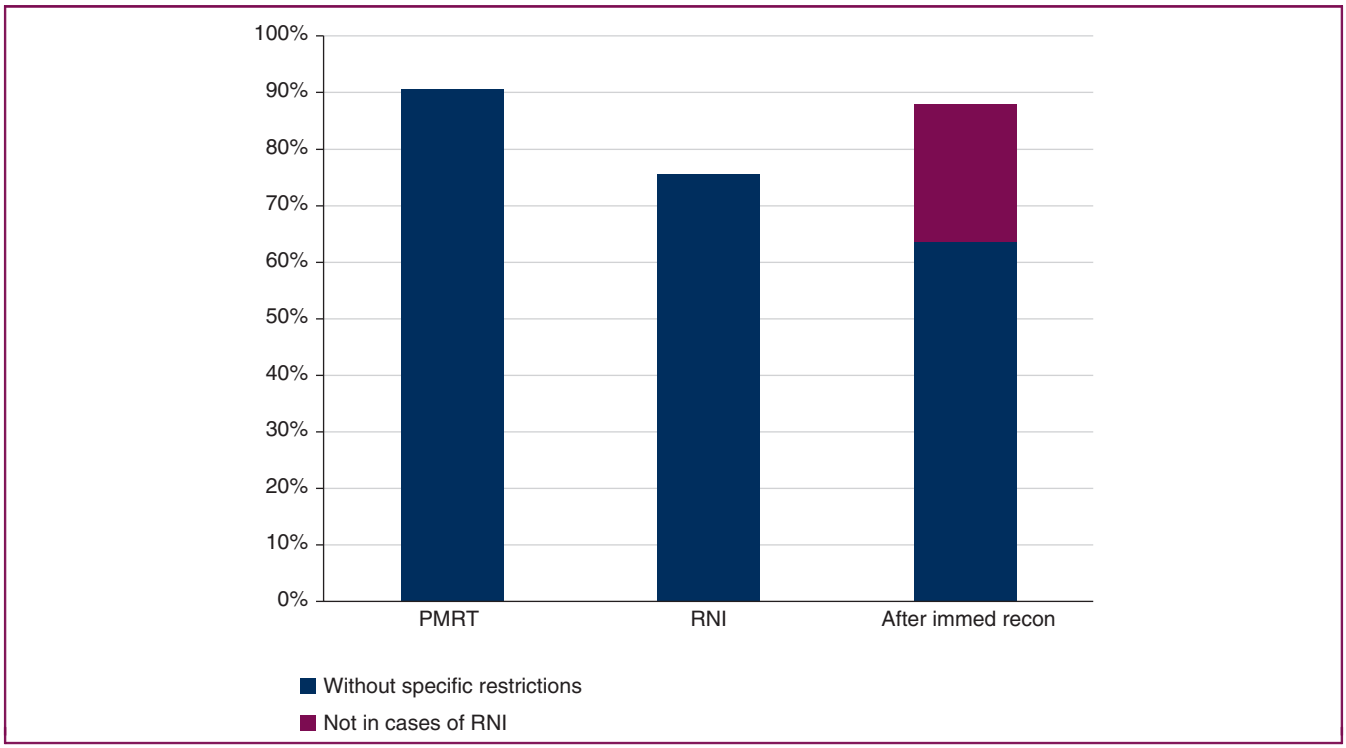

Figure 3. Moderately hypofractionated radiation therapy.
Percentage of panelists endorsing moderately hypofractionated schedules of radiation therapy.
After immed recon, after immediate reconstruction; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradiation.

treatment decisions for ER-positive, HER2-negative breast cancer, panelists recommended against using genomic signatures to determine whether to use radiation treatment after breast-conserving surgery, or to inform decisions on regional nodal or postmastectomy radiation.

The Panel considered the role of RNI in a variety of contexts. The Panel strongly voted against RNI for women with T2N0 tumors, regardless of tumor subtype, even when patients were receiving postsurgical breast or chest wall irradiation. Similarly, the Panel recommended against RNI in women with triple-negative or HER2-positive tumors, presenting with T2 stage tumors but a clinically negative axilla, who achieve a pCR to neoadjuvant treatment. However, the Panel strongly favored RNI for patients who initially presented with a clinically positive axillary node(s), even when such patients achieve a pCR with neoadjuvant therapy.

The Panel customized its approach to boost following breast-conserving surgery with radiation. Boost was favored in cases of high-grade cancers, extensive intraductal component [extensive intraductal component (EIC)-positive], or TNBC or HER2-positive subtypes, and in women $<$50 years of age.

Studies of radiation therapy in older (age $\geq$70 years) women with ER-positive breast cancers who are taking adjuvant endocrine therapy have shown that radiation therapy does not improve survival but can lower in-breast recurrence.[23-25] For older women with a life expectancy of $>$10 years, the panelists took a nuanced, customized approach to radiation treatment, explicitly rejecting the notion that no such patients should receive radiotherapy. In general, the Panel favored radiation treatment of tumors $>$2.5 cm, cases of positive axillary node(s), or tumors with adverse biological features, and favored omitting radiation treatment in patients with shorter life expectancies, and those with stage I, ER-positive cancers, who are likely to be adherent with adjuvant endocrine therapy. It was, in part, to inform this decision that many panelists favor SNB even in older patients with ER-positive, HER2-negative cancers.

NEOADJUVANT THERAPY

For women with stage II or III tumors, preoperative or neoadjuvant systemic therapy offers clinical advantages, including tumor downstaging which may affect surgical options in the breast or axilla. Additionally, the use of preoperative treatment invites customization of therapy based on the extent of treatment response, which serves as a prognostic marker and can identify women with residual cancer who may require additional adjuvant systemic therapy. In 2019, the St Gallen panel endorsed preoperative systemic therapy as the preferred approach for women with stage II or III, HER2-positive or triple-negative cancers. Neoadjuvant therapy is also the standard for women with inflammatory breast cancer, who then undergo mastectomy if operable after induction treatment, and in other presentations of inoperable, locally advanced breast cancer.

Systemic treatments

Neoadjuvant therapy remains preferred for stage II or III, HER2-positive or TNBCs, and for many higher stage ER-positive breast cancers. Nearly a decade ago, regulatory authorities proposed using the surrogate, prognostic measurement of pCR as an endpoint for accelerated approval of regimens in the neoadjuvant setting.[26] Despite dozens of randomized trials with different regimens and agents, only one drug (pertuzumab) to date has garnered approval based on pCR. The audience and Panel were asked to reflect on that experience, and whether pCR was a suitable endpoint for defining standard regimens in early-stage breast cancer. The majority of both the Panel (60%) and the audience (83%) believed that pCR was not the appropriate endpoint for defining standard neo/adjuvant systemic regimens, favoring longer term endpoints such as disease-free or overall survival, typically required for full regulatory approval of new treatments. Of interest, the Panel strongly believed that 'all pCRs are the same.' That is, that the prognosis after achieving pCR in a given tumor subtype was similar whatever treatment was used to achieve that end. The implications of these two findings are that neoadjuvant trials intended to define standards of care should include long-term follow-up with robust data on recurrence and survival, and that risk stratification based on pCR following neoadjuvant therapy is a strategy for optimizing post-neoadjuvant treatment.

Preferred neoadjuvant regimens for HER2-positive tumors (trastuzumab and pertuzumab, paired with taxane chemotherapy and either anthracycline- or platinum-based chemotherapy), and for TNBC (dose-dense anthracycline- and taxane-based chemotherapy) were unchanged from 2019 (Table 3). For triple-negative tumors, the Panel did not recommend the addition of immune checkpoint inhibitors as neoadjuvant therapy, and panelists remain divided on the role of carboplatin in addition to anthracycline-, taxane-, and alkylator-based therapy; a majority (60%) voted against routine use of carboplatin.

There is growing interest in the use of neoadjuvant endocrine therapy in the treatment of ER-positive primary tumors. Small clinical experiences have suggested equal rates of clinical response for endocrine therapy as for chemotherapy, though neither approach routinely achieves a rate of pCR $>$10%.[27,28] For select individuals who might benefit from treatment response to optimize surgery in the preoperative setting, panelists favored neoadjuvant endocrine therapy in women with low-grade and/or low-genomic risk tumors, and endorsed genomic assays on core biopsies as a strategy for choosing which type of neoadjuvant therapy (chemotherapy or endocrine therapy) to pursue. Several studies suggest that a short-term decline in Ki67 during initial neoadjuvant endocrine therapy is a favorable prognostic finding, identifying a cohort of patients with endocrine-sensitive tumors, unlikely to benefit from neo/adjuvant chemotherapy.[29,30]

Post-neoadjuvant therapy is often customized by the extent of residual cancer following the preoperative

Table 3. Systemic therapy for HER2-positive or triple-negative breast cancers

Anatomic stage		Tumor subtype HER2+	TNBC
Stage I Typically as adjuvant therapy	T1a T1b T1c	TH—case by case TH TH	Chemotherapy—case by case TC chemotherapy AC/T chemotherapy
Stage II Neoadjuvant therapy preferred		AC/TH or TCH, with addition of P if neoadjuvant and/or node-positive	AC/T chemotherapy[b]
Stage III Neoadjuvant therapy preferred		AC/THP or TCHP[a]	AC/T chemotherapy[b]
Residual invasive cancer after neoadjuvant therapy		Trastuzumab emtansine	Capecitabine

A, anthracycline such as doxorubicin or epirubicin; C, cyclophosphamide; H, trastuzumab; HER2, human epidermal growth factor receptor 2; P, pertuzumab; T, taxane; TNBC, triple-negative breast cancer.

[a] Consider addition of adjuvant neratinib after trastuzumab if tumor is ER-positive and ≥4 positive lymph nodes, though the Panel noted there are no data for use in patients also receiving pertuzumab or trastuzumab emtansine.

[b] Some panelists favor inclusion of carboplatin in neoadjuvant therapy for TNBC.

treatment. Patients achieving a pCR after standard neoadjuvant chemotherapy should proceed to standard adjuvant therapy (for instance, maintenance anti-HER2 therapy, or endocrine therapy). The Panel endorsed adjuvant capecitabine for patients with residual TNBC,[31,32] and trastuzumab emtansine for patients with residual HER2-positive breast cancers, after standard neoadjuvant regimens, with a low threshold for treatment (including residual cancers <5 mm and node-negative). Most women with ER-positive cancer will have residual invasive cancer despite neoadjuvant chemotherapy or endocrine therapy. All women should receive adjuvant endocrine therapy regardless of response to neoadjuvant chemotherapy.[33] For women with higher burdens of residual cancer after neoadjuvant endocrine therapy (tumor >5 cm, residual positive lymph nodes), with adverse biological features (higher grade, higher genomic risk scores[34]), or with tumor progressing during neoadjuvant endocrine treatment, the Panel recommended adjuvant chemotherapy.

Axillary management after neoadjuvant therapy

Patients with clinically positive axillary lymph nodes after neoadjuvant therapy require axillary node dissection, whereas patients who present with a clinical N1 axilla, and who convert to a clinically negative axilla (cN0) after neoadjuvant treatment, are potential candidates for SNB. Those without residual nodal disease, when the initially sampled and clipped or at least three sentinel nodes are identified and resected, do not require axillary dissection.[35-37] However, retrospective data show that patients with residual cancer in sentinel nodes including micrometastases[38] have a substantial risk of additional nodal metastases in axillary nodes. Real-world data from the National Cancer Database suggested lower survival when substituting SNB and RNI for axillary dissection when residual nodal disease is present, unless patients were selected for limited residual nodal burden (only one positive node) and ER-positive tumors.[39] The Panel debated whether axillary radiation could replace axillary dissection in a patient who presented with a clinically negative axilla but was found to have residual cancer in sentinel nodes after neoadjuvant chemotherapy. The Panel recommended completion axillary dissection for patients with residual macrometastases; the majority of the Panel (73%) voted that axillary lymph node dissection (ALND) should be indicated following neoadjuvant chemotherapy when there is any residual macrometastatic cancer (>2 mm) in the SNB, or in 'just' one of three sentinel nodes (Figure 4). There was controversy in discussing individual situations of lower sentinel node tumor burdens (for instance, a micrometastasis in one of three sentinel nodes, or isolated tumor cells in one of three sentinel nodes). Many panelists felt axillary radiation could be an alternative to axillary dissection in such situations. Other panelists urged caution, noting persistent risks of residual axillary nodal involvement, and recommended awaiting the results of ongoing phase III trials[40,41] that compare axillary radiation with axillary dissection in this setting to determine whether axillary radiation can substitute for axillary surgery in the setting of chemotherapy resistant nodal disease, as has been shown in the chemotherapy-naive adjuvant setting after surgery.[17] Panelists did not believe that the availability of systemic treatment options such as capecitabine or trastuzumab emtansine for residual invasive cancer were sufficient to allow patients to avoid surgical management with axillary dissection.

SYSTEMIC THERAPY: ADJUVANT TREATMENT

Nearly all patients with invasive breast cancer are advised to receive adjuvant systemic therapy.[42] The threshold for initiation of treatment is very low, even among node-negative cancers (Figure 5). Panelists recommended adjuvant endocrine therapy for nearly all patients with ER-positive tumors that were even only microinvasive or ≥1 mm in size, for reducing distant recurrence, in-breast recurrence, and second breast cancers. The threshold for recommending adjuvant chemotherapy in TNBC, or chemotherapy plus anti-HER2 therapy in HER2-positive breast cancer, is ~5 mm. Indeed, nearly half of the panelists recommended chemotherapy and anti-HER2 therapy also for ER-negative, HER2-positive tumors <5 mm in size.

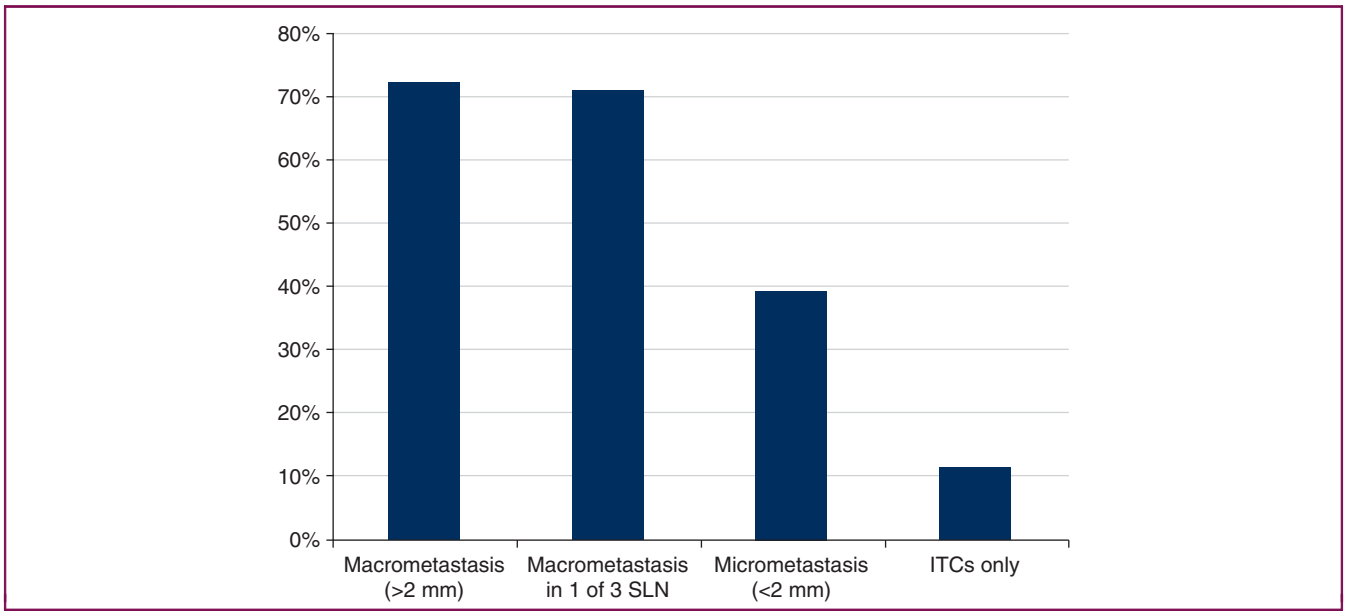

Figure 4. Is axillary dissection required for residual cancer in lymph nodes after standard neoadjuvant chemotherapy?[a]
Percentage of panelists favoring axillary dissection.
ITC, isolated tumor cells; SLN, sentinel lymph nodes.
[a] It was assumed that post-surgical radiation therapy would be given regardless.

HER2-positive or triple-negative tumors

Adjuvant regimen recommendations for triple-negative or HER2-positive therapy were largely unchanged from 2019 (Table 3). Neoadjuvant treatment is preferred for stage II or III tumors of these subtypes. For triple-negative cancers, dose-dense anthracycline and taxane-based regimens are preferred for stage II or III tumors. Panelists recommended against neoadjuvant or adjuvant use of immune checkpoint inhibitors in early-stage TNBC, pending maturation of disease-free and overall survival data. As mentioned above, panelists were again divided on the question of adding carboplatin in the neo/adjuvant treatment of TNBC; 60% recommend against adding to dose-dense anthracycline and taxane-based treatments.

As in the past, panelists favored paclitaxel/trastuzumab for stage I, HER2-positive breast cancer. For stage II or III, HER2-positive cancers, panelists were split between anthracycline, taxane, and anti-HER2 regimens, and taxane-carboplatin and anti-HER2 regimens (Table 3). Pertuzumab was recommended for neoadjuvant treatment of clinical stage II or III, HER2-positive cancers, or in adjuvant therapy for node-positive cancers.

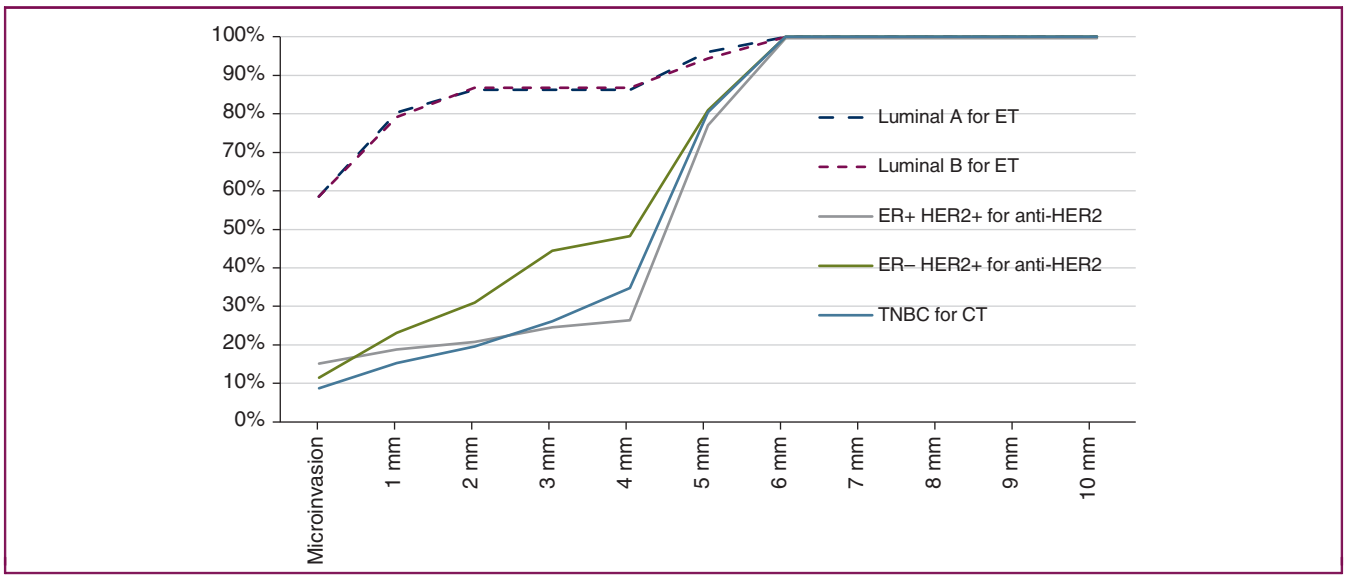

Figure 5. Size threshold for initiating systemic therapy by tumor type and treatment.
Percentage of panelists recommending therapy by tumor size.
CT, computed tomography; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Adjuvant endocrine therapy for ER-positive cancers

Recommendations for adjuvant endocrine therapy are outlined in Table 4. The Panel favors 5 years of tamoxifen- or aromatase inhibitor (AI)-based therapy for stage I, ER-positive cancers. For node-positive cancers, the Panel recommended extended therapy towards a duration of 10 years based on persistent risks of recurrence among such patients.[43] For premenopausal women who received an initial 5 years of ovarian function suppression (OFS) and tamoxifen for higher risk cancers, the Panel favored extended therapy with either ongoing tamoxifen or an AI (if the woman is postmenopausal, or with ongoing OFS), typically towards a goal of 10 years of therapy, though there may be negligible benefits of treatment beyond 7.5-8 years for average-risk tumors.[44] The Panel voted against the use of molecular diagnostics for deciding whether to extend adjuvant endocrine therapy.

As ongoing maturation of the SOFT and TEXT trials show persistent benefits for OFS in premenopausal women with ER-positive breast cancer, the Panel was more inclined this year to recommend OFS in younger women (Table 4),[45,46] while also noting the importance of patient preferences here as OFS carries more substantial patient-reported side-effects.[47] The Panel favored OFS in stage II or higher breast cancer, particularly among women <40 years of age, and those with higher grade, higher Ki67, or higher risk genomic signatures. Many panelists favored OFS in stage T1c, node-negative cancers with those same features. For premenopausal women who meet the criteria for adjuvant chemotherapy for ER-positive cancers, the Panel also recommended ovarian suppression.

In 2020, three large, randomized trials reported on short-term outcomes from adjuvant trials adding cyclin dependent kinase 4 or 6 inhibitors to standard adjuvant endocrine therapy in women[48-50] with stage II or III, ER-positive breast cancers. Of these, the PALLAS and PENELOPE-B studies using palbociclib did not show improvement in disease-free survival, while the MONARCH-E trial using abemaciclib did find improvement in the limited (<2 years) follow-up. To date, there are no known clinical or tumor-related factors to account for these differences. The Panel was divided on whether to endorse abemaciclib adjuvant therapy. A slim majority favored abemaciclib in cases of four or more positive axillary nodes, while a slim majority voted against abemaciclib in cases of stage II or III breast cancer. Longer term follow-up from these trials is awaited to settle this question.

Adjuvant chemotherapy for ER-positive breast cancer

Genomic signatures are increasingly driving customized, biologically-informed decisions on whether to offer chemotherapy in addition to endocrine therapy for women with ER-positive, HER2-negative early-stage breast cancers. Ongoing analyses of the TAILORx, RxPonder, MINDACT, and related studies of genomically-informed chemotherapy decision making deeply affected Panel recommendations for adjuvant chemotherapy in cases of ER-positive breast cancer.[51-53] Based on the convergent results from these studies, the Panel recommended against routine use of adjuvant chemotherapy in postmenopausal women with stage I or II (including one to three positive lymph nodes) breast cancers that had lower risk genomic signatures (defined as a recurrence score ≤25, or 'low risk' result on the 70-gene signature) (Table 4).

The recommendations for premenopausal women with lower-risk genomic signatures and tumor stage were more

Table 4. Systemic therapy for ER+ HER2− breast cancer

Anatomic stage	TN	Type and duration of endocrine therapy[a]	Ovarian suppression	Chemotherapy[d] Premenopausal	Postmenopausal
Stage I	T1ab N0	AI or Tam, 5 years	No OFS	No	No
	T1c N0	AI or Tam, 5 years	Consider OFS and AI/tam for higher risk, particularly those warranting chemotherapy, age <40 years, high-grade, or intermediate genomic scores (e.g. recurrence score 16-25)	Consider for favorable biology tumors especially if not pursuing OFS[c] Yes for less favorable biology tumors	No for favorable biology tumors[c] Yes for less favorable biology tumors
Stage II	N0 (node negative)	Consider extended therapy[b], especially after initial 5 years of tamoxifen	OFS and AI/tam for higher risk, particularly those warranting chemotherapy, age <40 years, high-grade, or intermediate genomic scores (e.g. recurrence score 16-25)	Consider for favorable biology tumors especially if not pursuing OFS[c] Yes for less favorable biology tumors	No for favorable biology tumors[c] Yes for less favorable biology tumors
	N1 (1-3+ LN)	Extended therapy[b]	OFS and AI/Tam	Consider for favorable biology tumors[c] Yes for less favorable biology tumors	No for favorable biology tumors[c] Yes for less favorable biology tumors
Stage III		Extended therapy[b]	OFS and AI/Tam	Yes	Yes

AI, aromatase inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; Tam, tamoxifen; TN, tumor size, nodal status.

[a] Historically, the St Gallen Panel has favored AI-based therapy in higher risk tumors defined by T and N stage, grade, and Ki67 score.

[b] Extended therapy implies 10 years of treatment, though some studies indicate that 10 years may not offer benefit beyond that seen with 7.5-8 years of endocrine therapy.

[c] *Favorable biology:* lower risk genomic signature [e.g. recurrence score ≤25 (node-positive) or 16-25 (node-negative), or 70-gene signature 'low']; strongly ER-positive with low to intermediate grade, and/or lower baseline Ki67, or decrease in Ki67 with preoperative exposure to endocrine therapy. *Less favorable biology:* higher risk genomic signature (e.g. recurrence score >25 or 70-gene signature 'high'); lower ER expression, intermediate to high grade, and/or higher baseline Ki67, or lack of decline in Ki67 with preoperative exposure to endocrine therapy.

[d] The Panel recommended anthracycline- and taxane-based adjuvant chemotherapy regimens for stage III, ER-positive cases; for stage I or II cases, the Panel was divided between taxane-based regimens (e.g. TC, 44%), anthracycline-only regimens (e.g. AC, 14%), and anthracycline- and taxane-based regimens (42%).

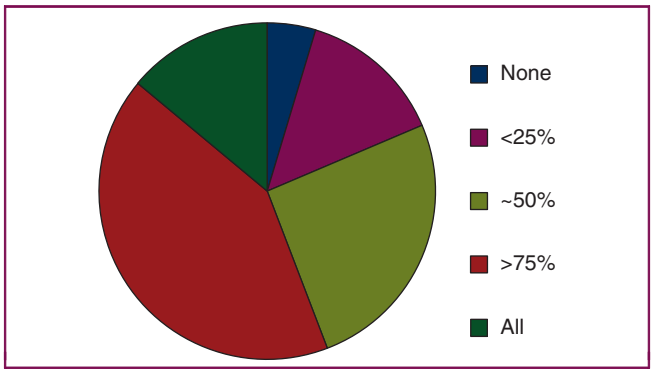

Figure 6. Estimated percentage of chemotherapy benefit due to ovarian suppression in premenopausal women with lower risk genomic signatures (recurrence score ≤25).

complicated, however, as subset analyses from each these trials indicate that premenopausal women derive clinically important benefits from chemotherapy, though some panelists believe ovarian suppression could be an appropriate substitute for chemotherapy. The dilemma in understanding each of these trials is the confounding effect of chemotherapy-induced ovarian function suppression, a common consequence of adjuvant chemotherapy in premenopausal women, and known to reduce recurrence.[54] A question is: how much of the chemotherapy-related reduction in recurrence among premenopausal women with ER-positive breast cancer is due to direct, 'cytotoxic' effects of chemotherapy, and how much is due to an indirect, ovarian suppression effect of chemotherapy? Several lines of evidence suggest that ovarian suppression effects may account for part of the benefit of chemotherapy in this cohort. The likelihood of chemotherapy-induced amenorrhea depends on patient age. An analysis according to age subgroups in TAILORx—namely age <40, 40-45 and 45-50 years—supports the argument that some chemotherapy benefits relate in part to ovarian suppression; benefits of chemotherapy were least noticeable in women least likely to experience chemotherapy-induced menopause (aged <40 years) and more pronounced among those more likely to experience treatment-related amenorrhea (aged >40 years).[52] And of course, OFS itself, achieved through gonadotropin-releasing hormone (GnRH) analogues or oophorectomy, shows substantial clinical benefit and enables AI-based therapy in younger women, interventions known to reduce risk as shown in the SOFT and TEXT trials 'STEPP' analyses.[55] Thus, it is possible, but not proven, that the use of endocrine treatment strategies beyond tamoxifen alone, such as OFS plus an AI, could account for the benefit seen with chemotherapy. Resolving this question definitively will require a large adjuvant trial fully dedicated to premenopausal women and investigating whether adjuvant chemotherapy adds any meaningful benefit to an 'optimal' endocrine treatment strategy in the presence of favorable gene expression signatures. The PERCHE trial, designed 15 years ago by the International Breast Cancer Study Group (IBCSG) under the leadership of A. Goldhirsch, attempted this but was closed due to limited accrual.

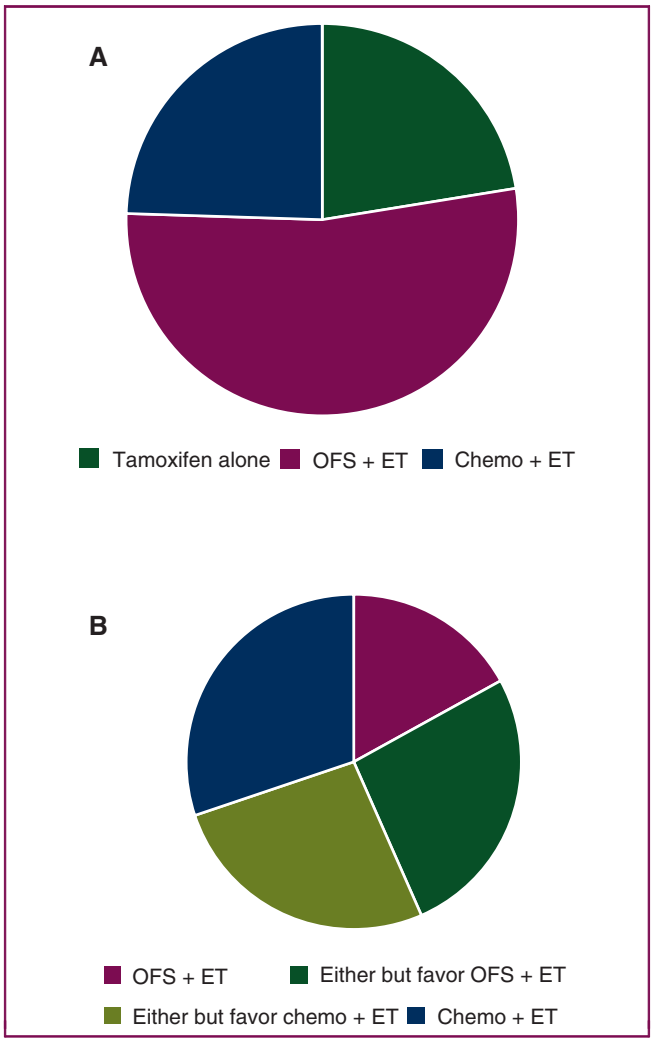

Figure 7. Panelist recommendations for optimal therapy for premenopausal, ER-positive cancers by stage and recurrence score (RS).
(A) Node-negative, RS 16-25. (B) Node-positive (one to three positive nodes), RS ≤25.
Chemo, chemotherapy; ET, endocrine therapy; OFS, ovarian function suppression.

Given these considerations, the Panel was surveyed on their approach to shared decision making with premenopausal women with ER-positive, HER2-negative cancers and lower-risk genomic signatures, and whether such patients should consider ovarian suppression with tamoxifen or an AI in lieu of chemotherapy. Three-quarters of the Panel believe that at least half of the 'benefit' of chemotherapy in this situation is due to ovarian suppression, with a majority of the Panel even believing that 75%-100% of the effect was due to ovarian suppression (Figure 6). These impressions affected panel recommendations (Table 4). For premenopausal women with node-negative cancers and recurrence scores 16-25, or other lower risk genomic signatures, three-quarters of the Panel voted for endocrine therapy, including half who favored ovarian suppression, while only one-quarter favored chemotherapy and endocrine therapy (Figure 7). For premenopausal women with one to three positive axillary nodes and recurrence score ≤25 or other lower risk genomic signatures, the Panel was divided

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between ovarian suppression and endocrine therapy versus chemotherapy and endocrine therapy (Figure 7).

There are no data as yet for using genomic signatures to define the role of adjuvant chemotherapy in ER-positive, stage III breast cancers. The historical standard is adjuvant chemotherapy, though the growing evidence in stages I and II breast cancer suggest that there may be a minimal role for chemotherapy in many such tumors. Nonetheless, the Panel consistently favored adjuvant chemotherapy in stage III cancers including lobular breast cancers (Table 4). Concern was raised by half of the panelists regarding the use of genomic signatures in patients with high-risk tumors such as pT3N1 or patients with more than three positive nodes, as in these settings, the use of adjuvant chemotherapy would be recommended regardless of the genomic signature results. Only in the instance of very low risk biology—recurrence score <11, or grade 1 with Ki67 $<10\%$, did a substantial fraction of the Panel believe that chemotherapy might be omitted in stage III, ER-positive breast cancer.

DUCTAL CARCINOMA *IN SITU*

Ductal carcinoma *in situ* (DCIS) is a precursor lesion to invasive breast cancer, usually identified through mammographic screening. Surgical excision is the mainstay of therapy; most women are candidates for breast-conserving surgery, whereas some may require mastectomy based on the extent of DCIS in the breast. Radiation therapy after breast-conserving surgery reduces the recurrence risk of DCIS or invasive breast cancer in the ipsilateral breast; moderately hypofractionated treatment schedules are as effective as standard fractionation treatment schedules in management of DCIS.[56,57] The addition of boost lowers recurrence rates in non-low-risk DCIS cases. The Panel recommended boost in cases with larger areas of DCIS or other factors associated with increased risk of recurrence including margins <2 mm and the presence of comedonecrosis, but not in low-risk cases. As with management of invasive breast cancer in older women, the Panel supported omission of radiation therapy in women >70 years of age with DCIS bearing low risk features. Adjuvant endocrine therapy can further reduce the risk of recurrence in DCIS treated with breast conservation and radiation therapy, as well as prevent contralateral disease. Either tamoxifen or an AI are options;[58] panelists tended to favor tamoxifen based on the side-effect profile.

IPSILATERAL BREAST CANCER RECURRENCE

Even with contemporary management of breast-conserving surgery and radiation therapy, isolated, in-breast recurrences account for 5%-15% of all recurrent cancer events in women with early-stage breast cancer.[59,60] In addition, some patients develop true, second cancers in the ipsilateral breast. Traditionally, the recommended treatment was mastectomy in light of the previous breast radiation. Limited single-center experiences have suggested that repeat breast-conserving surgery could be an effective option for women with isolated, in-breast recurrences.[61] In the 2021 consensus voting, repeat attempts at breast conservation were particularly favored by the Panel in the setting of low-risk (small, luminal A-type) breast cancers, presumably when additional radiation therapy might not be required. The Panel acknowledged that breast conservation with re-irradiation could be an option instead of mastectomy for some women with ipsilateral recurrence or second breast cancer arising >5 years after initial breast conservation and radiation. However, the Panel was split 50/50 on offering second attempts at breast conservation when re-irradiation was not a clinical option. In any case, mastectomy need no longer be considered absolutely 'obligatory' for ipsilateral breast recurrence. Following ipsilateral breast recurrence, it is usually standard to offer further adjuvant therapy informed by prior treatment and tumor biology, including consideration of: endocrine therapy for ER-positive tumors; anti-HER2 therapy for HER2-positive tumors; and chemotherapy for TNBCs[62] and in other select cases.[63-65]

OLIGOMETASTATIC BREAST CANCER

Some breast cancer patients are diagnosed with *de novo*, stage IV breast cancer at the time of presentation. Randomized trials have compared optimal systemic therapy with or without breast surgery among such patients; breast surgery in the setting of stage IV breast cancer does not improve overall survival,[66] though it is still widely used.[67] Occasionally, women with newly diagnosed breast cancer are found to have oligometastatic cancer on staging evaluation, usually defined as having one, or possibly two sites of metastatic cancer outside the breast and regional lymph nodes. One example would be a patient with an isolated metastasis to the sternum or other solitary bone lesion; another would be an isolated pulmonary nodule or lymph node. Such possible metastatic sites warrant tissue biopsy to clarify the diagnosis, as other benign or malignant conditions can have similar radiological appearances. The Panel considered specific instances of a patient presenting after surgery for stage II breast cancer, then found to have an isolated metastasis in the sternum, or other isolated bone metastasis or lung nodule, that could be treated with definitive radiation therapy (bone) or excision (lung). In each instance, the Panel favored treating the patient with multi-modality, curative intent, including definitive additional treatment to the site of metastatic disease. For patients in whom more sites of metastatic cancer were identified, such as three or more bone lesions, the Panel favored following standard treatments for advanced breast cancer, with palliation of the metastatic sites through local therapy as indicated by symptoms.

SURVIVORSHIP

Breast cancer treatments bring a myriad of side-effects, including changes to the body, hair loss, chemotherapy-related toxicities, and health and well-being consequences from estrogen deprivation.[33] Many supportive care

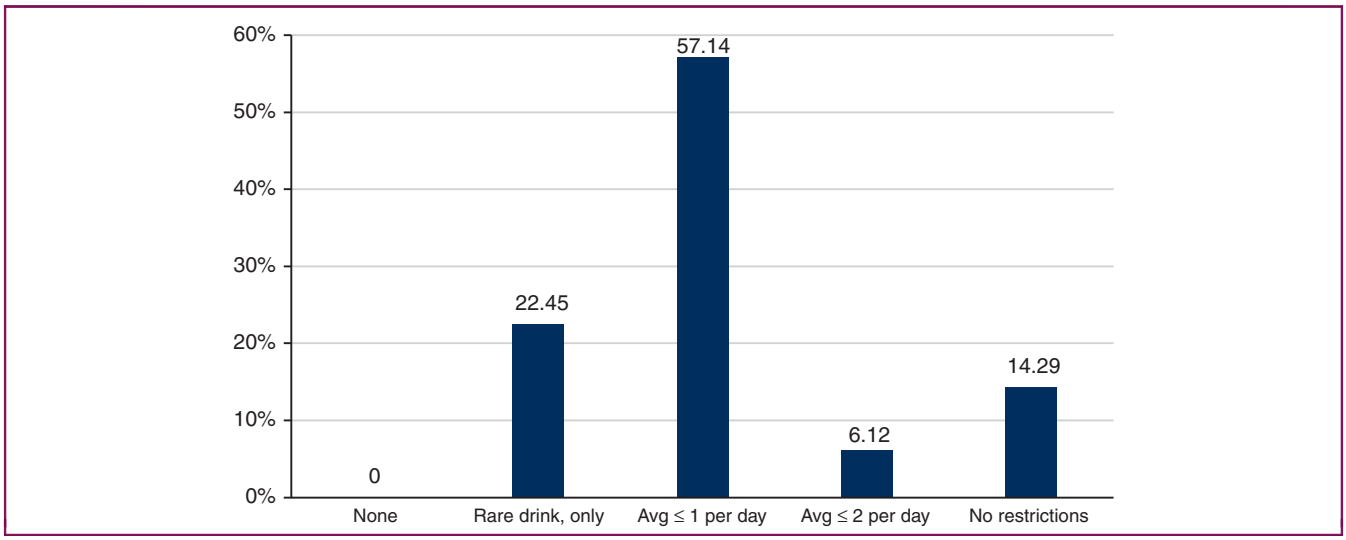

Figure 8. Panelists advice on alcohol consumption: how many drinks can a breast cancer survivor consume without increasing the risk of cancer recurrence?
Percentage of panelists voting in favor.
Avg, average.

interventions have been developed to mitigate some of these side-effects. The Panel this year addressed emerging data on several interventions that can improve quality of life in breast cancer survivors. It strongly endorsed the routine use of scalp cooling 'cold-caps' to reduce alopecia, particularly for non-anthracycline-based chemotherapy regimens.[68] The Panel endorsed mindfulness-based stress reduction as a proven strategy to alleviate depressive symptoms in younger breast cancer survivors,[69] and endorsed aerobic exercise as a standard way to address a variety of adverse effects including fatigue and sleep disturbance. Symptoms of vaginal atrophy are common in women on adjuvant endocrine therapy. While these symptoms may be relieved with topical vaginal estrogens, there are concerns that such products could cause transient clinically relevant increases in systemic estrogen levels.[70,71] Nonetheless, panelists indicated that they would commonly prescribe intravaginal estrogens to relieve symptoms of vaginal atrophy in women on AIs and symptoms unresponsive to non-hormonal interventions, with the acknowledgement that we are not fully certain of their safety. Because of epidemiological studies linking alcohol consumption to breast cancer risk, breast cancer survivors often ask about the safety of drinking alcohol following a breast cancer diagnosis. Panelists overwhelming believed that some alcohol consumption after breast cancer diagnosis was unlikely to affect recurrence; the majority suggested limiting consumption to an average of one drink per day or less (Figure 8); none suggested that abstinence was necessary.

SUMMARY

The 2021 St Gallen Consensus Conference highlighted important strategies to customize treatment of patients with early-stage breast cancer. Significant changes from past guidance include: evolving practices in management of the axilla after neoadjuvant therapy; broader utilization of hypofractionated approaches to radiation therapy; omission of chemotherapy in postmenopausal women with one to three positive axillary nodes and low-risk genomic signatures; adjuvant-type therapy for women with oligometastatic breast cancer; and advances in supportive care and survivorship that hopefully will allow women with a history of early-stage breast cancer to have fewer side-effects from treatment. The Panel will reconvene in 2023 for the next consensus conference.

FUNDING

None declared.

DISCLOSURE

For the complete conflict of interest statement please refer to Supplementary Appendix S1 available at https://doi.org/10.1016/j.annonc.2021.06.023.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of Incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Song H, Bergman A, Chen AT, et al. Disruptions in preventive care: mammograms during the COVID-19 pandemic. *Health Serv Res*. 2021;56:95-101.
3. Freer PE. The Impact of the COVID-19 pandemic on breast imaging. *Radiol Clin North Am*. 2021;59:1-11.
4. Burstein HJ, Curigliano G, Loibl S, et al. 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. *Ann Oncol*. 2019;30:1541-1557.
5. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer*. 2017;123:1721-1730.
6. Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med*. 2021;384:440-451.

7. Dorling L, Carvalho S, Allen J, et al. Breast cancer risk genes — association analysis in more than 113,000 Women. *N Engl J Med*. 2021;384:428-439.
8. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384:2394-2405.
9. Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30:729-734.
10. Villegas SL, Nekljudova V, Pfarr N, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors — an analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer*. 2021;148:159-170.
11. Viale G, Regan MM, Maiorano E, et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. *J Clin Oncol*. 2007;25:3846-3852.
12. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the international Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst*. 2020;113:808-819.
13. Denkert C, Budczies J, Regan MM, et al. Clinical and analytical validation of Ki-67 in 9069 patients from IBCSG VIII + IX, BIG1-98 and GeparTrio trial: systematic modulation of interobserver variance in a comprehensive in silico ring trial. *Breast Cancer Res Treat*. 2019;176:557-568.
14. Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in breast cancer: recommendations from the international Ki67 in breast cancer working Group. *J Natl Cancer Inst*. 2011;103:1656-1664.
15. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol*. 2015;26:1547-1573.
16. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *J Am Med Assoc*. 2017;318:918-926.
17. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303-1310.
18. Mamtani A, Morrow M. Why are there so many mastectomies in the United States? *Annu Rev Med*. 2017;68:229-241.
19. Jagsi R, Hawley ST, Griffith KA, et al. Contralateral prophylactic mastectomy decisions in a population-based sample of patients with early-stage breast cancer. *JAMA Surg*. 2017;152:274-282.
20. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. *Breast Cancer Res Treat*. 2017;165:273-283.
21. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613-1626.
22. Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of fast: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol*. 2020;38:3261-3272.
23. Kunkler IH, Williams LJ, Jack W, et al. Abstract GS2-03: prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women =/> 65 years with early invasive breast cancer: 10 year results, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS2-03-GS2-03.
24. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31:2382-2387.
25. Fastner G, Sedlmayer F, Widder J, et al. Endocrine therapy with or without whole breast irradiation in low-risk breast cancer patients after breast-conserving surgery: 10-year results of the Austrian Breast and Colorectal Cancer Study Group 8A trial. *Eur J Cancer*. 2020;127:12-20.
26. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med*. 2012;366:2438-2441.
27. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer*. 2007;110:244-254.
28. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in premenopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. *Breast Cancer Res*. 2020;22:54.
29. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1443-1454.
30. Harbeck N, Gluz O, Kuemmel S, et al. Abstract GS4-04: endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 response after preoperative endocrine therapy: Primary outcome results from the WSG-ADAPT HR+/HER2- trial, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS4-04-GS4-04.
31. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376:2147-2159.
32. Lluch A, Barrios CH, Torrecillas L, et al. Phase III trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). *J Clin Oncol*. 2020;38:203-213.
33. Burstein HJ. Systemic therapy for estrogen receptor-positive, HER2-negative breast cancer. *N Engl J Med*. 2020;383:2557-2570.
34. Harbeck N, Gnant M. Breast cancer. *Lancet*. 2017;389:1134-1150.
35. Boughey JC. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. *J Am Med Assoc*. 2013;310:1455-1461.
36. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, et al. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. *Eur J Surg Oncol*. 2021;47:804-812.
37. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0—T4, N1—N2) who receive neoadjuvant chemotherapy. *Ann Surg*. 2016;263:802-807.
38. Moo T-A, Edelweiss M, Hajiyeva S, et al. Is low-volume disease in the sentinel node after neoadjuvant chemotherapy an indication for axillary dissection? *Ann Surg Oncol*. 2018;25:1488-1494.
39. Almahariq MF, Levitin R, Quinn TJ, et al. Omission of axillary lymph node dissection is associated with inferior survival in breast cancer patients with residual N1 nodal disease following neoadjuvant chemotherapy. *Ann Surg Oncol*. 2021;28:930-940.
40. Henke G, Knauer M, Ribi K, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. *Trials*. 2018;19:667.
41. Alliance for Clinical Trials in Oncology. Comparison of axillary lymph node dissection with axillary radiation for patients with node-positive breast cancer treated with chemotherapy. Available at https://clinicaltrials.gov/ct2/show/NCT01901094?term=Alliance+A011202&draw=2&rank=1. Accessed May 18, 2021.
42. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Prim*. 2019;5:66.

43. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377:1836-1846.
44. Gnant M, Steger G, Greil R, et al. Abstract GS3-01: a prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy − results from 3,484 postmenopausal women in the ABCSG-16 trial, in General Session Abstracts. *Am Assoc Cancer Res*. 2018;78. GS3-01-GS3-01.
45. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379:122-137.
46. Pagani O, Francis PA, Fleming GF, et al. Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TEXT and SOFT. *J Clin Oncol*. 2020;38:1293-1303.
47. Bernhard J, Luo W, Ribi K, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. *Lancet Oncol*. 2015;16:848-858.
48. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2021;22:212-222.
49. Loibl S, Marmé F, Martin M, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer—The Penelope-B trial. *J Clin Oncol*. 2021;39:1518-1530.
50. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38:3987-3998.
51. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22:476-488.
52. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. *N Engl J Med*. 2019;380:2395-2405.
53. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. Abstract GS3-00: first results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS3-00-GS3-00.
54. Swain SM, Jeong J-H, Geyer CE, et al. Longer therapy, Iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med*. 2010;362:2053-2065.
55. Regan MM, Francis PA, Pagani O, et al. Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: TEXT and SOFT Trials. *J Clin Oncol*. 2016;34:2221-2231.
56. Offersen BV, Alsner J, Nielsen HM, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma In Situ in a randomized Phase III Trial: The DBCG HYPO Trial. *J Clin Oncol*. 2020;38:3615-3625.
57. Chua BH, Link E, Kunkler I, et al. Abstract GS2-04: a randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast (BIG 3-07/TROG 07.01), in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS2-04-GS2-04.
58. Sestak I, Cuzick J, Bonanni B, et al. Abstract GS2-02: 12 year results of anastrozole versus tamoxifen for the prevention of breast cancer in postmenopausal women with locally excised ductal carcinoma in-situ, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS2-02-GS2-02.
59. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233-1241.
60. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-Gene expression assay in breast cancer. *N Engl J Med*. 2018;379:111-121.
61. Gentilini O, Botteri E, Veronesi P, et al. Repeating conservative surgery after Ipsilateral breast tumor reappearance: criteria for selecting the best candidates. *Ann Surg Oncol*. 2012;19:3771-3776.
62. Wapnir IL, Price KN, Anderson SJ, et al. Efficacy of chemotherapy for ER-negative and ER-positive isolated locoregional recurrence of breast cancer: final analysis of the CALOR Trial. *J Clin Oncol*. 2018;36:1073-1079.
63. Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol*. 2014;15:156-163.
64. Fitzal F, Bjelic-Radisic V, Knauer M, et al. Impact of breast surgery in primary metastasized breast cancer. *Ann Surg*. 2019;269:1163-1169.
65. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: Protocol MF07-01. *Ann Surg Oncol*. 2018;25:3141-3149.
66. Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108). *J Clin Oncol*. 2020;38. LBA2-LBA2.
67. Lane WO, Thomas SM, Blitzblau RC, et al. Surgical resection of the primary tumor in women with de novo stage IV breast cancer. *Ann Surg*. 2019;269:537-544.
68. Rugo HS, Klein P, Melin SA, et al. Association between use of a scalp cooling device and alopecia after chemotherapy for breast cancer. *J Am Med Assoc*. 2017;317:606-614.
69. Ganz P, Bower JE, Partridge AH, et al. Abstract GS2-10: targeting depressive symptoms in younger breast cancer survivors: a randomized controlled trial of mindfulness meditation and survivorship education, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS2-10-GS2-10.
70. Sánchez-Rovira P, Hirschberg AL, Gil-Gil M, et al. A phase II prospective, randomized, double-blind, placebo-controlled and multicenter clinical trial to assess the safety of 0.005% estriol vaginal gel in hormone receptor-positive postmenopausal women with early stage breast cancer in treatment with aromatase inhibitor in the adjuvant setting. *Oncologist*. 2020;25:e1846-e1854.
71. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer. *JAMA Oncol*. 2017;3:313-319.
72. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol*. 2020;38:4274-4282.
73. Kurian AW, Bernhisel R, Larson K, et al. Prevalence of pathogenic variants in cancer susceptibility genes among women with postmenopausal breast cancer. *J Am Med Assoc*. 2020;323:995-997.
74. Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr*. 2020;4:pkz088.
75. Ribi K, Luo W, Walley BA, et al. Treatment-induced symptoms, depression and age as predictors of sexual problems in premenopausal women with early breast cancer receiving adjuvant endocrine therapy. *Breast Cancer Res Treat*. 2020;181:347-359.
76. de Azambuja E, Trapani D, Loibl S, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: breast cancer. *ESMO Open*. 2020;5:e000793.
77. Coles CE, Aristei C, Bliss J, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clin Oncol*. 2020;32:279-281.
78. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat*. 2020;181:487-497.

79. Nyante SJ, Benefield TS, Kuzmiak CM, et al. Population-level impact of coronavirus disease 2019 on breast cancer screening and diagnostic procedures. *Cancer*. 2021;127:2111-2121.
80. Wang S-L, Fang H, Song Y-W, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:352-360.
81. Poortmans PM, Weltens C, Fortpied C, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I—III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1602-1610.
82. Marta GN, Ramiah D, Kaidar-Person O, et al. The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: an international consortium report. *Clin Oncol*. 2021;33:322-330.
83. Kaidar-Person O, Vrou Offersen B, Hol S, et al. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. *Radiother Oncol*. 2019;137:159-166.
84. Cardoso F, MacNeill F, Penault-Llorca F, et al. Why is appropriate healthcare inaccessible for many European breast cancer patients? — the EBCC 12 manifesto. *Breast*. 2021;55:128-135.
85. Bhattacharya IS, Haviland JS, Kirby AM, et al. Patient-reported outcomes over 5 years after whole- or partial-breast radiotherapy: longitudinal analysis of the IMPORT LOW (CRUK/06/003) phase III randomized controlled trial. *J Clin Oncol*. 2019;37:305-317.
86. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. *J Clin Oncol*. 2020;38:4175-4183.
87. Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet*. 2019;394:2165-2172.
88. Kaidar-Person O, Meattini I, Zippel D, et al. Apples and oranges: comparing partial breast irradiation techniques. *Rep Pract Oncol Radiother*. 2020;25:780-782.
89. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet*. 2019;394:2155-2164.
90. Soran A, Dogan L, Isik A, et al. The effect of primary surgery in patients with de novo stage IV breast cancer with bone metastasis only (protocol BOMET MF 14-01): a multi-center, prospective registry study. *Ann Surg Oncol*. 2021;28(9):5048-5057.
91. Piltin MA, Hoskin TL, Day CN, et al. Oncologic outcomes of sentinel lymph node surgery after neoadjuvant chemotherapy for node-positive breast cancer. *Ann Surg Oncol*. 2020;27:4795-4801.
92. Wong SM, Basik M, Florianova L, et al. Oncologic safety of sentinel lymph node biopsy alone after neoadjuvant chemotherapy for breast cancer. *Ann Surg Oncol*. 2021;28:2621-2629.
93. Martelli G, Barretta F, Miceli R, et al. Sentinel node biopsy alone or with axillary dissection in breast cancer patients after primary chemotherapy. *Ann Surg*. 2020. In press, https://journals.lww.com/10.1097/SLA.0000000000004562
94. Kuemmel S, Heil J, Rueland A, et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (TAD) in node-positive breast cancer patients. *Ann Surg*. 2020. In press, https://journals.lww.com/10.1097/SLA.0000000000004572
95. Weber WP, Morrow M, de Boniface J, et al. Knowledge gaps in oncoplastic breast surgery. *Lancet Oncol*. 2020;21:e375-e385.
96. Dubsky P, Pinker K, Cardoso F, et al. Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. *Lancet Oncol*. 2021;22:e18-e28.
97. Mamounas EP, Bandos H, Lembersky BC, et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:88-99.
98. Dubsky PC, Singer CF, Egle D, et al. The EndoPredict score predicts response to neoadjuvant chemotherapy and neoendocrine therapy in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients from the ABCSG-34 trial. *Eur J Cancer*. 2020;134:99-106.
99. Pascual T, Fernandez-Martinez A, Tanioka M, et al. Independent validation of the PAM50-based chemo-endocrine score (CES) in hormone receptor-positive HER2-positive breast cancer treated with neoadjuvant anti-HER2-based therapy. *Clin Cancer Res*. 2021;27:3116-3125.
100. Schettini F, Pascual T, Conte B, et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis. *Cancer Treat Rev*. 2020;84:101965.
101. Prat A, Guarneri V, Paré L, et al. A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation. *Lancet Oncol*. 2020;21:1455-1464.
102. Sestak I, Filipits M, Buus R, et al. Prognostic value of EndoPredict in women with hormone receptor-positive, HER2-negative invasive lobular breast cancer. *Clin Cancer Res*. 2020;26:4682-4687.
103. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the adjuvant tamoxifen—to offer more? (aTTom) trial. *Ann Oncol*. 2019;30:1776-1783.
104. Sgroi DC, Treuner K, Zhang Y, et al. Abstract GS4-09: correlative studies of the breast cancer index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine benefit: a trans-aTTom study, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;81. GS4-09-GS4-09.
105. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381:307-316.
106. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382:514-524.
107. Hamilton E, Cortes J, Ozyilkan O, et al. nextMONARCH: abemaciclib monotherapy or combined with tamoxifen for metastatic breast cancer. *Clin Breast Cancer*. 2020;21(3):181-190.
108. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380:1929-1940.
109. Connolly RM, Zhao F, Miller KD, et al. Abstract GS4-02: E2112: randomized phase 3 trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. A trial of the ECOG-ACRIN cancer research group, in General Session Abstracts. *Am Assoc Cancer Res*. 2021;80. GS4-02-GS4-02.
110. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39:1448-1457.
111. Tolaney SM, Trippa L, Barry W, et al. Abstract GS1-05: TBCRC 033: a randomized phase II study of adjuvant trastuzumab emtansine (T-DM1) vs paclitaxel (T) in combination with trastuzumab (H) for stage I HER2-positive breast cancer (BC) (ATEMPT), in General Session Abstracts. *Am Assoc Cancer Res*. 2020;80. GS1-05-GS1-05.
112. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET Trial. *Clin Breast Cancer*. 2021;21:80-91.e7.
113. Hurvitz SA, Martin M, Jung KH, et al. Neoadjuvant trastuzumab emtansine and pertuzumab in human epidermal growth factor receptor 2-positive breast cancer: three-year outcomes from the phase III KRISTINE study. *J Clin Oncol*. 2019;37:2206-2216.
114. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382:597-609.

115. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382:610-621.
116. Saura C, Oliveira M, Feng Y-HH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with $\geq$ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38:3138-3149.
117. Wang X, Wang S-S, Huang H, et al. Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment. *J Am Med Assoc*. 2021;325:50.
118. Li J, Yu K, Pang D, et al. Abstract GS1-08: adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (cbcsg010): an open-label, randomised, multicentre, phase 3 trial, in General Session Abstracts. *Am Assoc Cancer Res*. 2020;80. GS1-08-GS1-08.
119. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382:810-821.
120. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396:1090-1100.
121. Gianni L, Huang C-S, Egle D, et al. Abstract GS3-04: pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 michelangelo randomized study, in General Session Abstracts. *Am Assoc Cancer Res*. 2020;80. GS3-04-GS3-04.
122. Winer EP, Lipatov O, Im S-A, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:499-511.
123. Miles DW, Gligorov J, André F, et al. LBA15 Primary results from IMpassion131, a double-blind placebo-controlled randomised phase III trial of first-line paclitaxel (PAC) $\pm$ atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). *Ann Oncol*. 2020;31:S1147-S1148.
124. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396:1817-1828.
125. Bardia A, Tolaney SM, Loirat D, et al. LBA17 ASCENT: a randomized phase III study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). *Ann Oncol*. 2020;31:S1149-S1150.

APPENDIX 1

St Gallen Consensus conference panelists					
Last name	**First name**	**Affiliation**	**Specialty**	**City**	**Country**
Aebi	Stephan	Tumorzentrum LUKS, Luzerner Kantonsspital	Medical Oncology	Lucerne	Switzerland
André	Fabrice	Institut Gustave Roussy	Medical Oncology	Villejuif	France
Barrios	Carlos	1. Oncoclinicas Group, Brazil. 2. LACOG. Latin American Cooperative Oncology Group	Medical Oncology	Porto Alegre	Brazil
Bergh	Jonas	Karolinska Institutet and University Hospital, Dept of Oncology, Radiumhemmet, CCK	Medical Oncology	Stockholm	Sweden
Bonnefoi	Herve	University of Bordeaux 2	Medical Oncology	Bordeaux	France
Bretel Morales	Denisse	GECOPERU	Surgery	Lima	Peru
Brucker	Sara	Universitäts-Frauenklinik Tübingen	Gynecology	Tuebingen	Germany
Burstein	Harold	Dana-Farber Cancer Institute	Medical Oncology	Boston	USA
Cameron	David	The University of Edinburgh	Medical Oncology	Edinburgh	UK
Cardoso	Fatima	Champalimaud Cancer Centre	Medical Oncology	Lisbon	Portugal
Carey	Lisa	UNC — Lineberger Comprehensive Cancer Center	Medical Oncology	Chapel Hill	USA
Chua	Boon	UNSW Sydney/Prince of Wales Clinical School	Radiation Oncology	Randwick NSW	Australia
Ciruelos	Eva	Medical Oncology Department, Breast Cancer Unit	Medical Oncology	Madrid	Spain
Colleoni	Marco	European Institute of Oncology	Medical Oncology	Milano	Italy
Curigliano	Giuseppe	European Institute of Oncology	Medical Oncology	Milano	Italy
Delaloge	Suzette	Gustave Roussy, Department of Cancer Medicine	Medical Oncology	Villejuif	France
Denkert	Carsten	Institut für Pathologie, Charité—Universitätsmedizin Berlin	Pathology	Berlin	Germany
Dubsky	Peter	Brustzentrum Hirslanden Klinik St. Anna, Lucerne	Medical Oncology	Lucerne	Switzerland
Ejlertsen	Bent	DBCG Secretariat and Department of Oncology, Rigshospitalet	Medical Oncology	Copenhagen	Denmark
Fitzal	Florian	Medical University Vienna, Department of Surgery	Surgery	Vienna	Austria
Francis	Prudence	Department of Medical Oncology, Peter McCallum Cancer Centre	Medical Oncology	Melbourne	Australia
Galimberti	Viviana	European Institute of Oncology	Surgery	Milan	Italy
Gamal El Din Mohamed Mahmoud	Hebatallah	National Cancer Institute, Cairo University, Surgical Oncology Department	Surgery	Cairo	Egypt
Garber	Judy	Dana-Farber Cancer Institute	Genetics	Boston, MA	USA
Gnant	Michael	Medical University Vienna	Surgery	Vienna	Austria
Gradishar	William	Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University	Medical Oncology	Chicago, Illinois	USA
Gulluoglu	Bahadir	Marmara University School Of Medicine, Department of General Surgery, Breast & Endocrine Surgery Unit	Surgery	Istanbul	Turkey
Harbeck	Nadia	Breast Center, LMU University Hospital	Gynecology	Munich	Germany
Huang	Chiun-Sheng	Department of Surgery and Breast Center, National Taiwan University Hospital	Surgery	Taipei	Taiwan
Huober	Jens	Kantonsspital St. Gallen, Breast Center	Surgery	St. Gallen	Switzerland
Ilbawi	Andre	World Health Organization/ Department of Noncommunicable Diseases	Public Health		WHO Cancer Control Programme
Jiang	Zefei	Fifth Medical Center of Chinese PLA General Hospital	Medical Oncology	Beijing	PRC
Johnston	Steven	The Royal Marsden Hospital	Medical Oncology	London	UK

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Last name	**First name**	**Affiliation**	**Specialty**	**City**	**Country**
Lee	Eun Sook	National Cancer Center Korea	Surgery	Goyang-si Gyeonggi-do	Republic of Korea
Loibl	Sibylle	GBG Forschungs GmbH (German Breast Group)	Gynecology	Neu-Isenburg	Germany
Morrow	Monica	Memorial Sloan-Kettering Cancer Center	Surgery	New York	USA
Partridge	Ann	Dana-Farber Cancer Institute	Medical Oncology	Boston, MA	USA
Piccart	Martine	Institut Jules Bordet	Medical Oncology	Brussels	Belgium
Poortmans	Philip	Iridium Kankernetwerk & University of Antwerp/Faculty of Medicine and Health Sciences	Radiation Oncology	Wilrijk-Antwerp	Belgium
Prat	Aleix	Hospital Clinic of Barcelona	Medical Oncology	Barcelona	Spain
Regan	Meredith	Dana-Farber Cancer Institute, Dept of Biostatistics and Computational Biology	Statistics	Boston MA	USA
Rubio	Isabella	Clinica Universidad de Navarra	Surgery	Madrid	Spain
Rugo	Hope	UCSF Helen Diller Family Comprehensive Cancer Center	Medical Oncology	San Francisco CA	USA
Rutgers	Emiel	Netherlands Cancer Institute, Department of Surgery	Surgery	Amsterdam	The Netherlands
Sedlmayer	Felix	Paracelsus Medical University Clinics, Department of Radiotherapy and Radio-Oncology	Radiation Oncology	Salzburg	Austria
Semiglazov	Vladimir	N. N. Petrov National Cancer Centre	Medical Oncology	St. Petersburg	Russian Federation
Senn	Hans-Joerg	Foundation St. Gallen Oncology Conferences (SONK)	Medical Oncology	St. Gallen	Switzerland
Shao	Zhiming	Fudan University Cancer Hospital/Breast Surgery	Surgery	Shanghai	PR China
Spanic	Tanja	Europa Donna	Representative of ED	Ljubljana	Slovenia
Tesarova	Petra	Charles University Hospital and 1st Medical Faculty, Department of Oncology	Medical Oncology	Prague	Czech Republic
Thürlimann	Beat	Kantonsspital St. Gallen	Medical Oncology	St. Gallen	Switzerland
Tjulandin	Sergei	N. N. Blokhin Cancer Research Center	Medical Oncology	Moscow	Russian Federation
Toi	Masakazu	Breast Center Unit, Kyoto University Hospital	Surgery	Kyoto city	Japan
Trudeau	Maureen	Sunnybrook Health Sciences Centre	Medical Oncology	Toronto	Canada
Turner	Nicholas	The Royal Marsden Hospital, Breast Unit	Medical Oncology	London	UK
Vaz Luis	Inez	Gustave Roussy	Medical Oncology	Villejuif Cedex	France
Viale	Giuseppe	University of Milan/Institute of Oncology	Pathology	Milano	Italy
Watanabe	Toru	Hamamatsu Oncology Center	Medical Oncology	Nakaku, Hamamatsu	Japan
Weber	Walter P.	Klinik für Allgemeinchirurgie, Universitätsspital Basel	Surgery	Basel	Switzerland
Winer	Eric P.	Dana-Farber Cancer Institute	Medical Oncology	Boston, MA	USA
Xu	Binghe	National Cancer Center/Cancer Hospital	Medical Oncology	Beijing	China