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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. 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. 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, and sometimes delaying necessary treatment. 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. 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. 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). 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. Based on those newly available data, the Panelists were re-canvassed for treatment.
Table 1. New studies in breast cancer since St Gallen 2019

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<th>Area</th>
<th>Discovery/innovation</th>
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| Genetics and hereditary breast cancer     | Large population-based studies define penetrance and risks of most common hereditary genes associated with breast cancer  
TBCRC048 trial shows that the PARP inhibitor, olaparib, has substantial effect in MBC for tumors with hereditary PALB2 mutation or somatic BRCA1/2 mutation  
The OlympiA trial demonstrates that adjuvant therapy with olaparib reduces recurrence in BRCA1/2-associated breast cancer  
Population studies suggest that age and family history criteria may miss many cases of hereditary breast cancer | 67, 72, 8, 73 |
| Supportive care                           | Oxybutynin shown effective for climacteric symptoms in breast cancer patients  
Quality-of-life studies demonstrate profound effects of ovarian suppression on bone health and sexual health in premenopausal women | 74, 75 |
| COVID pandemic                            | Pandemic disrupts routine patient management, and prompts guideline revisions to prioritize treatment needs amid epidemic  
Rates of screening mammography plummet in wake of pandemic | 76-78 |
| Radiation therapy                         | Efficacy of hypofractionation for postmastectomy radiation  
Efficacy of hypofractionation for invasive breast cancer and DCIS after breast conserving surgery  
Use of ultra-hypofractionated radiation schedules after breast conserving surgery  
Efforts to standardize variations in radiotherapy practice and access  
Partial breast irradiation updates | 80, 56, 21, 22, 81-84, 25, 85-90 |
| DCIS                                      | ‘Boost’ after radiation therapy reduces in-breast recurrence; hypofractionation is as effective as 25Fx 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.  
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.  
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  
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%.  
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  
The Lucerne Toolbox: Consensus and Guideline that summarizes surgery after neoadcoho | 66, 90, 38, 91-93, 94, 95, 96 |
| Early-stage, ER-positive breast cancer: clinical | First reports of adjuvant CDK4/6 inhibitors show mixed results  
The MONARCH-E trial showed that adjuvant abemaciclib reduced recurrence in high-risk, ER+ breast cancer  
The PALLAS trial showed that adjuvant palbociclib did not reduce recurrence in high risk ER+ breast cancer  
The PENELLOPE-b trial showed that adjuvant palbociclib did not reduce recurrence in high-risk ER+ breast cancer  
Data from ABCSG 16 suggest that extended duration adjuvant endocrine therapy beyond 7/8 years does not improve outcomes  
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  
Ongoing follow-up of the SOFT and TEXT trials confirm the importance of tumor stage and grade as prognostic factors in premenopausal breast cancer  
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  
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 | 48, 49, 44, 46, 51, 52, 53, 58, 99 |
| Early-stage, ER-positive breast cancer: translational | Endopredict and response to neochemo and neoendocrine therapy—for gene expression and neochemo questions  
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  
ADAPT trial—using onctoyte and ki-67 for chemotherapy versus no chemotherapy  
HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis  
A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation | 98, 99, 100, 101 |
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 1. Continued

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<thead>
<tr>
<th>Area</th>
<th>Discovery/innovation</th>
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<tbody>
<tr>
<td><strong>Advanced stage, ER-positive breast cancer:</strong></td>
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<tr>
<td><strong>clinical</strong></td>
<td>Long-term follow-up of trials of CDK4/6 inhibitors show survival benefit for the class of drugs</td>
<td>105,106</td>
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<td></td>
<td>The nextMONARCH trial shows that late use of tamoxifen adds to effects of abemaciclib in MBC</td>
<td>107</td>
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<tr>
<td></td>
<td>The PIK3CA kinase inhibitor, alpelisib, improves PFS in PIK3CA-mutated ER+ breast cancer</td>
<td>108</td>
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<td></td>
<td>Olaparib activity in women with ER+ HER2+ breast cancer</td>
<td>109</td>
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<tr>
<td><strong>Early-stage, HER2-positive breast cancer</strong></td>
<td>Long-term follow-up of the APHINITY trial shows OS benefit for pertuzumab in node-positive but not node-negative breast cancer</td>
<td>110</td>
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<td>The ATEMPT study shows equivalent long-term tumor control with trastuzumab emtansine compared with trastuzumab + paclitaxel for stage 1 breast cancer but without safety benefits</td>
<td>111</td>
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<td>Long-term follow-up of the ExteNet study suggests benefit for adjuvant neratinib in women with ER+ HER2+ breast cancer</td>
<td>112</td>
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<td>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</td>
<td>113</td>
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<tr>
<td><strong>Advanced-stage, HER2-positive breast cancer</strong></td>
<td>The HER2CLIMB trial demonstrates that adding tucatinib to capecitabine plus trastuzumab improves OS in advanced breast cancer</td>
<td>114</td>
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<td>The DESTINY trial shows high response rates for trastuzumab deruxtecan in advanced breast cancer</td>
<td>115</td>
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<td></td>
<td>The NALA study shows that neratinib + capecitabine improve PFS but not OS compared with lapatinib + capecitabine</td>
<td>116</td>
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<td><strong>Early-stage, triple-negative breast cancer</strong></td>
<td>The SYSUCC trial shows that metronomic, adjuvant capecitabine reduces recurrence risk</td>
<td>117</td>
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<td>The CBCG-10 trial showed that adding capecitabine to adjuvant chemotherapy reduces recurrence risk</td>
<td>118</td>
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<td></td>
<td>The Keynote-522 study showed that adding neoadjuvant pembrolizumab to AC/paclitaxel plus carboplatin chemotherapy improves rate of pCR and may reduce recurrence risk</td>
<td>119</td>
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<td>The IMPASSION031 study showed that adding neoadjuvant atezolizumab to nab-paclitaxel and anthracycline chemotherapy improves the rate of pCR</td>
<td>120</td>
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<td></td>
<td>The NeoTrip study showed that adding neoadjuvant atezolizumab to nab-paclitaxel and carboplatin chemotherapy did not improve the rate of pCR</td>
<td>121</td>
</tr>
<tr>
<td><strong>Advanced-stage, triple-negative breast cancer</strong></td>
<td>The KEYNOTE-199 trial showed that single-agent checkpoint inhibition did not improve OS compared with chemotherapy</td>
<td>122</td>
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<td>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</td>
<td>123</td>
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<td>The KEYNOTE-355 trial showed that adding pembrolizumab to chemotherapy improved outcomes in first-line therapy for tumors with CPS score &gt;10%</td>
<td>124</td>
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<td></td>
<td>The ASCENT trial showed that sacituzumab govitecan improved PFS and OS compared with standard chemotherapy in refractory TNBC</td>
<td>125</td>
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**Pathology**

An international consensus committee endorsed thresholds of Ki67 5% and 30% for rejecting or warranting anti-HER2 therapy in combination with 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-

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AC, doxorubicin/cyclophosphamide; AI, aromatase inhibitor; AR, androgen receptor; BOM BC, bone-only metastatic breast cancer; CD4K/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.
positive cancers, have a less favorable prognosis than ER-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.

<table>
<thead>
<tr>
<th>Gene penetrance</th>
<th>Higher</th>
<th>Moderate</th>
<th>Lower</th>
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<tr>
<td>Odds ratio for developing breast cancer</td>
<td>≥3</td>
<td>2-3</td>
<td>1-2</td>
</tr>
<tr>
<td>Gene examples</td>
<td>BRCA1, BRCA2, PALB2, TP53</td>
<td>BARD1, CHEK2, CDH1, STK11</td>
<td>ATM, BRIP1, NF1, RAD51C, RAD51D, FANCC</td>
</tr>
<tr>
<td>Management recommendation</td>
<td>Prophylactic mastectomy</td>
<td>Surveillance*</td>
<td>Prophylactic mastectomy</td>
</tr>
<tr>
<td>Patient age ~40 years (%)</td>
<td>85</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>Patient age ~40 years (%)</td>
<td>46</td>
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* Includes mammogram and breast magnetic resonance imaging, with or without antiestrogen prevention.
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\textsuperscript{16} (breast-conserving surgery, with one or two positive sentinel lymph nodes) or the EORTC 10981-22023 AMAROS trial\textsuperscript{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

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**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.

**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 and lack of adequate physician-patient communication. 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.

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, 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 treatment decisions, they are not yet widely used in clinical practice.

**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 ≥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. 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. 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%. 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.

Post-neoadjuvant therapy is often customized by the extent of residual cancer following the preoperative...
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,\(^3\)\(^1\),\(^3\)\(^2\) 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.\(^3\)\(^3\) 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\(^3\)\(^4\)), 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.\(^3\)\(^5\)\(^6\)\(^7\) However, retrospective data show that patients with residual cancer in sentinel nodes including micrometastases\(^3\)\(^8\) 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.\(^3\)\(^9\) 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\(^\text{90,91}\) 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-naïve adjuvant setting after surgery.\(^\text{17}\) 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.\(^4\)\(^2\) 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.
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.
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. 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. 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), while also noting the importance of patient preferences here as OFS carries more substantial patient-reported side-effects. 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 with stage II or III, ER-positive breast cancers. Of these, the PALLAS and PENEOPE-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 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. Long-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. 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...
complicated, however, as subset analyses from each of these trials indicate that premenopausal women derive clinically important benefits from chemotherapy, though some pan-
elists 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 pre-
menopausal 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 amenor-
rhea 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.

Given these considerations, the Panel was surveyed on their approach to shared decision making with premeno-
pausal 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 premeno-
pausal women with node-negative cancers and recurrence score $\leq 25$, 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 $\leq 25$ or other lower risk genomic signatures, the Panel was divided.
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. 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; 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. 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. 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 TNBC and in other select cases.

**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, though it is still widely used. 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. Many supportive care
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. The Panel endorsed mindfulness-based stress reduction as a proven strategy to alleviate depressive symptoms in younger breast cancer survivors, 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. 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.

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**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.

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# APPENDIX 1

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