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SPECIAL ARTICLE

Tailoring treatment to cancer risk and patient preference: the 2025 St Gallen International Breast Cancer Consensus Statement on individualizing therapy for patients with early breast cancer

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Background: Breast cancer is a global disease affecting millions of individuals. Ongoing advancements in multidisciplinary management of breast cancer patients warrant discussion and integration into standard treatment plans.

Design: The St Gallen Breast Cancer Consensus conference is an international, biennial meeting where experts make treatment recommendations for state-of-the-art care of early stage breast cancer.

Results: Important innovations in the 2025 St Gallen recommendations include updated guidance on genetic testing; endorsement of hypofractionated, and ultra-hypofractionated, radiation therapy schedules for larger numbers of patients; recommendation for platinum-based chemotherapy in triple-negative breast cancer, and use of biological risk markers to consider anthracyclines in other breast cancer subtypes; avoidance of sentinel lymph node surgery in many patients with low-risk, estrogen receptor (ER)-positive cancers; use of immunotherapy in triple-negative and certain ER low-positive tumors; guidance for re-irradiation and systemic therapy in the setting of local-regional recurrence; criteria to guide treatment of oligometastatic breast cancer; and important recommendations for improving survivorship by minimizing neuropathy symptoms and addressing sexual health concerns of breast cancer patients.

Conclusions: International, multidisciplinary guidance for early breast cancer is evolving and offers patients better outcomes, improved treatment choices, and greater concern for patient preferences and survivorship needs.

Key words: early breast cancer, adjuvant endocrine therapy, chemotherapy, immunotherapy, breast surgery, axillary surgery, radiation therapy, survivorship, local-regional recurrence, ductal carcinoma *in situ* (DCIS), oligometastatic breast cancer

INTRODUCTION

Breast cancer is diagnosed in >2.3 million people around the world each year, causing >670 000 deaths; over the next 25 years, global incidence rates are expected to increase by nearly 40%. Owing to effective screening and treatment programs for early stage disease, breast cancer mortality rates have declined in many high income countries,[1,2] yet the growing incidence of breast cancer poses substantial challenges for care worldwide. Treatment options are continuously refined, as clinical studies explore new approaches and methods that tailor treatments based on cancer stage and tumor biology. These developments underscore the need and importance of guidelines for multidisciplinary treatment of patients with early breast

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cancer, shaped by global perspectives in management, and contemporary clinical expertise.

The biennial St. Gallen International Breast Cancer Conference is designed to address these needs. The 19th conference was held in Vienna in March 2025, and assembled renowned experts in breast and reconstructive surgery, radiation oncology, medical oncology, gynecology, pathology, genetics, translational research, and radiology to articulate the standards of care for early breast cancer. The consensus panel (see Appendix 1), with representation from Europe, Asia, Africa, the Middle East, Australia, and the Americas (North, Central, and South), is tasked to define treatment through exploration of many clinical scenarios, with cases varying by tumor stage and biology, and by patient age, treatment options, and preferences. Using clinical vignettes that address both paradigmatic and challenging clinical situations, the panel develops tailored and individualized treatment approaches. The panel understands that many instances of breast cancer management require both the knowledge of the vast clinical literature, but also judgment to optimize care for a given patient. This is particularly important when there are gaps between clinical studies, or multiple potential treatment options. This consensus document represents the integrated guidance from the conference, including especially the panel votes and discussion. The complete list of panel questions and voting results can be found in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.09.007. The panel recommendations did not address rare, unusual histological types of breast cancer.

Hereditary breast cancer syndromes—genetic testing, risk-reducing surgery, and systemic treatment

As in previous meetings, the panel declined to endorse universal genetic testing for patients diagnosed with breast cancer, preferring a testing approach informed by likelihood of a hereditary cancer syndrome. Thus, the panel favors genetic testing for all patients diagnosed at age $\leq$50 years, and those with triple-negative breast cancer, male breast cancer, a strong family history, or known familial mutation. Women who have been diagnosed with early breast cancer and who harbor a pathogenic variant that predisposes to breast cancer face choices about optimal management of the contralateral breast. The panel recommends strong consideration of contralateral risk-reducing mastectomy for patients with pathogenic *BRCA1* or *BRCA2* variants, and consideration of such surgery for those with *PALB2* mutations. By contrast, the panel recommended intensified surveillance (regular examination, and annual mammogram and magnetic resonance imaging) for patients with lower penetrance pathogenic variants in *ATM*, *CHEK2*, *BARD1*, or *RAD51* genes.[3-5] Age was an important factor in considering treatment of the contralateral breast. Panelists recommended prophylactic risk-reducing surgery for younger women (e.g. age 45 years) with genetic predisposition to breast cancer, but were divided on the management choice of surgery or intensified surveillance for older women (e.g. age 65 years) owing to lower residual lifetime risks of second breast cancers. Patients with *BRCA1/2* or other less penetrant mutations undergoing risk-reducing unilateral or bilateral mastectomy can be offered nipple-sparing or skin-sparing mastectomies and reconstruction, as studies with intermediate duration of follow-up have shown low risks of local recurrence or second cancers among patients with pathogenic mutations.[6,7]

Patients with higher-risk, *BRCA*-associated early breast cancers warrant adjuvant therapy with the PARP inhibitor, olaparib, which improves overall survival.[8] Based on the activity of olaparib in the treatment of patients with *PALB2* pathogenic variant-associated breast tumors in the metastatic setting,[9] the panel recommends that patients with higher-risk *PALB2*-associated early breast cancers also receive adjuvant olaparib therapy.

Ductal carcinoma in situ

Ductal carcinoma *in situ* (DCIS) is a precancerous lesion frequently identified on screening mammography, and is treated to prevent development of invasive breast cancer. Surgery—either breast-conserving or mastectomy as necessitated by the extent of DCIS in the breast—is standard initial therapy. Patients undergoing mastectomy for DCIS do not require additional treatment. The panel considered what additional treatments would be indicated as treatment after breast-conserving surgery. For a 'typical' case of fully excised, grade 2 DCIS, the panel recommended adjuvant radiation therapy. In fact, 40% of panelists favored treatment regardless of the size of the area of DCIS, 49% for lesions 0.3 cm or larger, and 77% for lesions 1 cm or larger (Figure 1).

In addition, panelists favored adjuvant endocrine therapy. For a typical case of breast-conserving surgery with fully excised DCIS of 1-2 cm in size in a 40-year-old, 97% recommended radiation and 64% recommended adjuvant endocrine therapy; for a 55-year-old, 98% recommended radiation, and 59% recommended endocrine therapy. For a 70-year-old, there was a split vote with 64% favoring radiation with or without endocrine therapy, and 36% recommending post-operative surveillance, alone.

Recently, the COMET study described outcomes for patients with low-risk DCIS who were randomized to either active monitoring or treatment with surgery.[10] Surgery led to upstaging from DCIS to a diagnosis of invasive cancer in 9% of patients. In comparison with those randomized to guideline-concordant care, women randomized to active monitoring did not have a higher rate of invasive, ipsilateral cancer. However, the study had only 2 years of follow-up, and was affected by high rates of nonadherence to the randomly assigned treatment arms. Given those limitations, the panel continued to recommend definitive surgery in nearly all cases of DCIS as the standard management approach. The panel recommended against routine use of genomic tests to inform treatment decisions in DCIS.

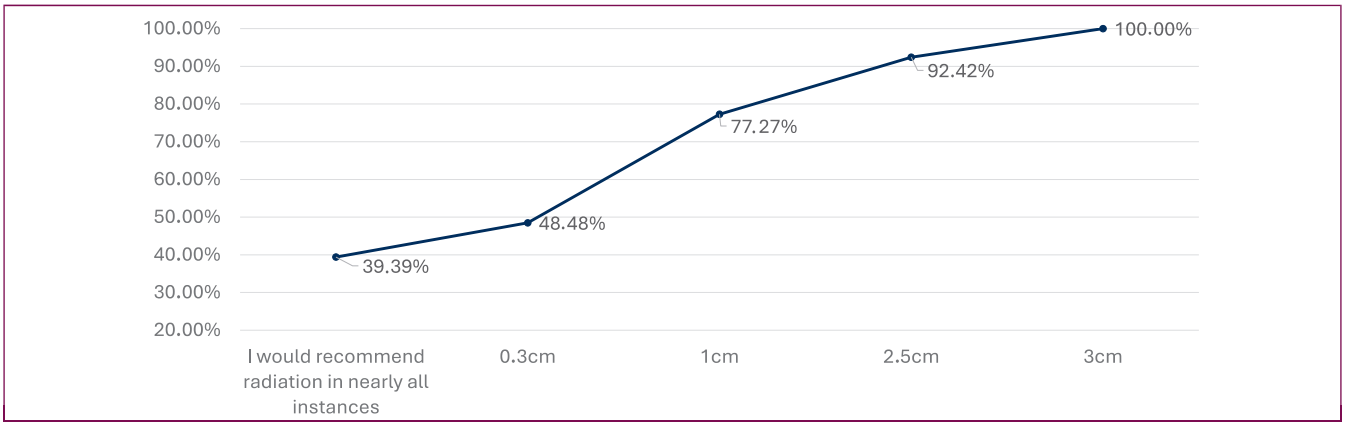

Figure 1. Radiation therapy recommendation after breast-conserving surgery for ductal carcinoma *in situ* (DCIS).
Percentage of panelists recommending radiation therapy after breast-conserving surgery for fully excised, grade 2, ER-positive DCIS as a function of DCIS lesion size.

Breast surgery

Since the development of breast-conserving surgery (BCS) for women with early breast cancer, a large body of both prospective and observational studies have not shown better survival or other oncological outcomes for mastectomy over BCS,[11,12] and BCS is associated with fewer surgical complications and better patient-reported outcomes.[13,14] However, many women who are candidates for BCS and do not have pathogenic hereditary mutations opt for mastectomy owing to improving reconstruction options, personal preferences, concerns for second breast cancers, or beliefs that the more extensive surgery would lessen the risk of recurrence and enhance survival.[15] Panelists strongly support patient choice in the decision of the type of primary breast surgery, and also believe that patients should be advised that BCS and radiation therapy is usually the best treatment option with comparable or superior cancer control results, less morbidity, fewer complications, and favorable patient-reported outcomes. Women with multiple (2 or 3) breast tumors in the ipsilateral breast may still be candidates for BCS and radiation, subject to surgical and aesthetic considerations.[16] Patients who typically require mastectomy include those with large tumors relative to the size of the breast (either at time of initial diagnosis if receiving initial surgery, or after neoadjuvant therapy), or those with extensive calcifications or DCIS in the breast, or with inflammatory breast cancer.

Axillary surgery

Clinical trials have demonstrated the safety of omitting axillary lymph node dissection among patients with a clinically negative axilla who have undergone sentinel lymph node (SLN) surgery, even if 1 or 2 sentinel nodes are positive.[17,18] An emerging literature supports the omission of SLN surgery in low-risk early breast cancers. Two randomized trials have explored the impact of SLN surgery omission among patients with grade 1 or 2, estrogen receptor (ER)-positive breast cancers who had a negative axillary ultrasound and underwent BCS and whole-breast irradiation, and also received adjuvant endocrine therapy.[19,20] Even though SLN surgery in the control arm identified metastatic cancer to lymph node(s) in ∼15% of patients, omission of SLN surgery was not associated with greater risk of local or distant cancer recurrence. The panel explored clinical subsets of patients treated with BCS in whom SLN surgery could be appropriately omitted following a negative axillary ultrasound. The panel recommended considering omission of SLN surgery among postmenopausal women with stage 1, ER-positive, HER2-negative tumors with grade 1 or 2 histology, but favored SLN surgery for premenopausal women, higher grade or larger tumors, and HER2-positive or triple-negative tumors.[21,22] The panel also recommended against omission of SLN surgery in women who had presented with clinical lymph node-positive disease but had achieved clinical resolution of axillary adenopathy through neoadjuvant therapy. Invasive lobular breast cancers often have a histologically different pattern of growth. Because ultrasonography is less sensitive for detecting axillary metastases from lobular tumors,[23] and the studies of omitting SLN surgery included few patients with lobular cancers, the panel voted (60% versus 40%) against omission of SLN surgery in patients with lobular cancers.

Most patients with clinically node-positive breast cancer at diagnosis, defined by palpable node(s) or pathological nodes identified on imaging or biopsy, need either neoadjuvant therapy to downstage the axilla, or upfront axillary lymph node dissection. Patients who achieve complete clinical response in the lymph nodes after neoadjuvant therapy can undergo SLN surgery with dual tracer or targeted axillary dissection. Those without nodal disease can omit axillary lymph node dissection as the risk of local-regional recurrence is very low.[24,25]

The surgical management of the axilla following neoadjuvant therapy in patients with residual disease in the SLN(s) remains more complicated. Residual disease in the axilla after neoadjuvant treatment is a marker of resistance to systemic therapy and an adverse prognostic factor. Most such patients will receive axillary radiation therapy, which is effective at preventing regional recurrence. Retrospective studies have suggested that patients with clinical response in the axilla but residual macrometastatic disease in

sentinel nodes after neoadjuvant chemotherapy may have acceptably low rates of regional cancer recurrence such that axillary dissection is not obligatory.[26-28] Tumor biology is an important consideration as is tumor burden; many patients with ER-positive, HER2-positive, or even triple-negative breast cancers will have the option of adjuvant systemic treatments that reduce recurrence risk.

The panel explored a variety of scenarios to define management of residual disease in the axilla after neoadjuvant chemotherapy (Table 1). Retrospective studies have shown that patients with residual isolated tumor cells (ITCs) but not micro- or macrometastases [pathological stage ypN0(i+)] in the lymph nodes after neoadjuvant therapy are at low-risk for local recurrence,[29] and the panel favored omission of axillary dissection for ITCs, only. In the instance of residual micrometastatic disease in the SLN(s), the panel recommendations differed by tumor subtype and by the extent of residual cancer. For patients with ER-positive, HER2-negative cancers with one of four SLNs affected by micrometastatic disease, the majority of the panel recommended against axillary dissection, favoring either nodal irradiation or observation. For other tumor phenotypes (HER2-positive, triple-negative) with micrometastases affecting one of four SLNs, and in all biologic subsets with two of four SLNs affected, panelists recommended nodal irradiation, axillary dissection, or both. The availability of effective post-neoadjuvant systemic therapy affected recommendations for axillary dissection in patients with residual macrometastases. For an ER-positive or HER2-positive tumor with a residual macrometastasis (3 mm) in one of four SLNs, the panel favored nodal irradiation without axillary dissection, while awaiting results from ongoing randomized trials. For triple-negative cancers with residual macrometastases, axillary dissection remains the standard of care. Patients with inflammatory breast cancer are advised to have axillary lymph node dissection regardless of clinical presentation or response to neoadjuvant therapy. Table 1 summarizes many of these recommendations.

Radiation therapy

Widespread screening programs for early detection of breast cancers, refinements in breast imaging that detect formerly occult lesions, prospective validation of prognostic markers for local recurrence, improvements in systemic adjuvant therapy, and randomized clinical trials of radiation therapy fractionation and volume schemes have transformed approaches to radiation therapy after surgery for early breast cancer while documenting progressively lower rates of local recurrence with optimal therapy. Collectively, these efforts have facilitated optimization of local treatments, including reduction in frequency and extent of axillary surgery for most women with a clinically negative axilla, as radiation therapy offers effective regional tumor control; the establishment of shortened courses of hypofractionated radiation treatment compared with the former traditional standard of 25 fractions; and the growing use of partial breast irradiation in well-defined, lower risk cases.

Table 2 summarizes current recommendations for the fractionation schedule and target volumes based on panel consensus from the 2023 and 2025 meetings. Risk stratification for local recurrence based on well-defined prognostic markers for local recurrence (age, T category, N category, grade, ER expression, lobular histology) is a vital component of treatment selection.[30,31] Moderate and ultra-hypofractionation are de-escalations in treatment time, and applicable across a spectrum of stages and tumor risks, and were preferred for all after BCS. The choice between moderate or ultra-hypofractionated and partial breast irradiation (PBI) schedules was affected by age (PBI is an option for patients aged >50 years), and body and breast habitus (PBI more favored for patients with higher body mass index and/or larger breasts). As discussed above, there is a growing opportunity to avoid SLN surgery in women with low-risk primary tumors. This cohort of low-risk tumors for whom omission of SLN surgery is an option as defined by age, and tumor stage, ER status, and grade, largely overlaps with the cohort of candidates for de-escalated radiation therapy (ultra-hypofractionated, or PBI) schedules, or even omission of radiation therapy altogether. In patients omitting SLN surgery, whole-breast irradiation offers therapeutic radiation therapy to sentinel nodes in 65% of cases, compared with coverage of 10% of cases with PBI.[32] The clinical impact of this incidental radiation dose to the SLNs is not precisely known. The panel was divided on the optimal approach for management of a postmenopausal woman aged in her 60s with a low-risk (ER-positive, grade 1-2), T1c cancer and negative axillary ultrasound, with 41% favoring whole-breast radiation without additional surgery, 29% PBI without additional surgery, and 29% favoring SLN surgery followed by PBI if

Table 1. Recommendations for axillary therapy for residual disease after neoadjuvant chemotherapy

Tumor subset	SLN tumor burden after neoadjuvant chemotherapy			
	ITCs	1 of 4 micrometastases	2 of 4 micrometastases	1 of 4 macrometastases
ER-positive, HER2-negative	No further therapy, or nodal RT	No further therapy, or nodal RT	Nodal RT or axillary dissection or both	Nodal RT (preferred) or axillary dissection
Triple-negative	No further therapy, or nodal RT	Nodal RT or axillary dissection or both	Nodal RT or axillary dissection or both	Axillary dissection and nodal RT
HER2-positive	No further therapy, or nodal RT	Nodal RT or axillary dissection or both	Nodal RT or axillary dissection or both	Nodal RT (preferred) or axillary dissection

ER, estrogen receptor; ITC, isolated tumor cell; RT, radiation therapy; SLN, sentinel lymph node.

Table 2. Recommendations for radiation therapy fractionation schedules and target volumes

Radiation zones(s)	Stage and Clinical Features	Fractionation			Target volume		
		Traditional (45-54 Gy in 23-28 Fx)	Moderate hypofractionation (40 Gy in 15/16 Fx)	Ultra-hypofractionation (26 Gy in 5 Fx)	WBI without boost	WBI + boost	PBI
Breast: low risk	T1N0, ER+ Gr 1-2 Age ≥50 years	Not preferred	Preferred	Preferred	Preferred	Not Preferred	Acceptable
Breast: int risk	T 2-3 cm N0 Gr 3 ER−	Not preferred	Preferred	Preferred	Preferred	Acceptable	Not preferred
Breast: higher risk	Lobular LVI+ N+ BRCA1/2 Age ≤40 years No adj Rx	Not preferred	Preferred	Preferred	Preferred	Preferred	Not preferred
Chest wall		Not preferred	Preferred	Acceptable	Preferred	Not Preferred	Not Preferred
Breast or chest wall with regional LN		Not preferred	Preferred	Not preferred	Optional; breast low risk	Optional; breast high risk	Not preferred
Implants or post reconstruction		Not preferred	Preferred	Not preferred	Preferred	Not preferred	Optional
Re-irradiation		Acceptable	Preferred	Not preferred	Not preferred	Not preferred	Preferred

adj, adjuvant; cm, centimeter; ER, estrogen receptor; Fx, fraction; Gr, tumor grade; Gy, gray; LN, lymph node; LVI, lymphovascular invasion; N, nodal status; PBI, partial breast irradiation; Rx, treatment; T, tumor size; WBI, whole breast irradiation.

node-negative. Stated another way, for patients meeting the criteria discussed above for avoiding SLN surgery, the panel largely preferred proceeding to radiation and did not recommend additional surgery in order to clarify whether whole-breast irradiation or PBI was preferred.

Multiple studies have explored the omission of radiation therapy after BCS in older women, typically enrolling patients aged ≥60 years with low-risk, ER-positive, stage 1 breast cancers. These trials have consistently shown that radiation therapy lowers the risk of in-breast recurrence among such patients, but does not alter overall survival.[33-36] Studies using genomic assays or surrogates [grade, quantitative ER, expression of progesterone receptor (PgR) and HER2, Ki67 level] for risk stratification have defined tumors with very low-risk of local recurrence in the absence of radiation therapy. These trials largely assume that patients are receiving adjuvant endocrine therapy. The panel considered the case of a healthy postmenopausal 69-year-old woman with low-risk, stage 1, ER-positive breast cancer with a life-expectancy of >10 years. More than 95% of the panel favored radiation therapy, with either moderate or ultra-hypofractionation and/or PBI approaches. In a separate vote, the panel strongly recommended both endocrine therapy and radiation treatment in such cases. These votes reflect multiple clinical considerations, including the efficacy of radiation at reducing in-breast recurrence, the convenience and tolerability of short courses of radiation therapy, the favorable life-expectancy for many older women, and the recognition that many patients may not accept multiple years of adjuvant endocrine treatment. Indeed, the recent EUROPA trial compared radiation versus endocrine therapy for similarly low-risk cancers in older patients, and reported better short-term quality of life for patients who received radiation but not endocrine therapy.[37]

There is persistent controversy over whether patients with ER-positive cancers with one positive node warrant postmastectomy radiation therapy with the panel split evenly between favoring radiation therapy or not. In most other instances of node-positive breast cancer or residual cancer in the breast or lymph nodes after neoadjuvant chemotherapy, the panel favored postmastectomy radiation treatment, and endorsed moderately hypofractionated regimens as the preferred schedule.[38] For women who present with stage 1 or 2 breast cancer and achieve a complete pathological response with chemotherapy (with or without targeted agents such as immune checkpoint inhibitors or anti-HER2 antibodies), the panel favored omission of postmastectomy radiation therapy.[39] For stage 3 presentations, including inflammatory breast cancer, postmastectomy radiation therapy remains the standard, even following excellent clinical response to treatment.

Systemic therapy: triple-negative breast cancer

Systemic therapy for triple-negative breast cancer (TNBC) has evolved since the demonstration that the addition of immunotherapy to neoadjuvant chemotherapy improves overall survival compared with chemotherapy alone.[40,41] Tumor-infiltrating lymphocytes (TILs) serve as a prognostic biomarker in early stage TNBC and are associated with higher pathological complete response (pCR) rates following neoadjuvant chemotherapy or chemoimmunotherapy.[42] The panel recommends neoadjuvant chemoimmunotherapy for patients with stage 2 or 3 TNBC. Neoadjuvant therapy is preferred as it allows incorporation of immune checkpoint inhibitors and enables treatment individualization based on the extent of residual disease at surgery. In patients with node-negative disease, neoadjuvant therapy is favored when

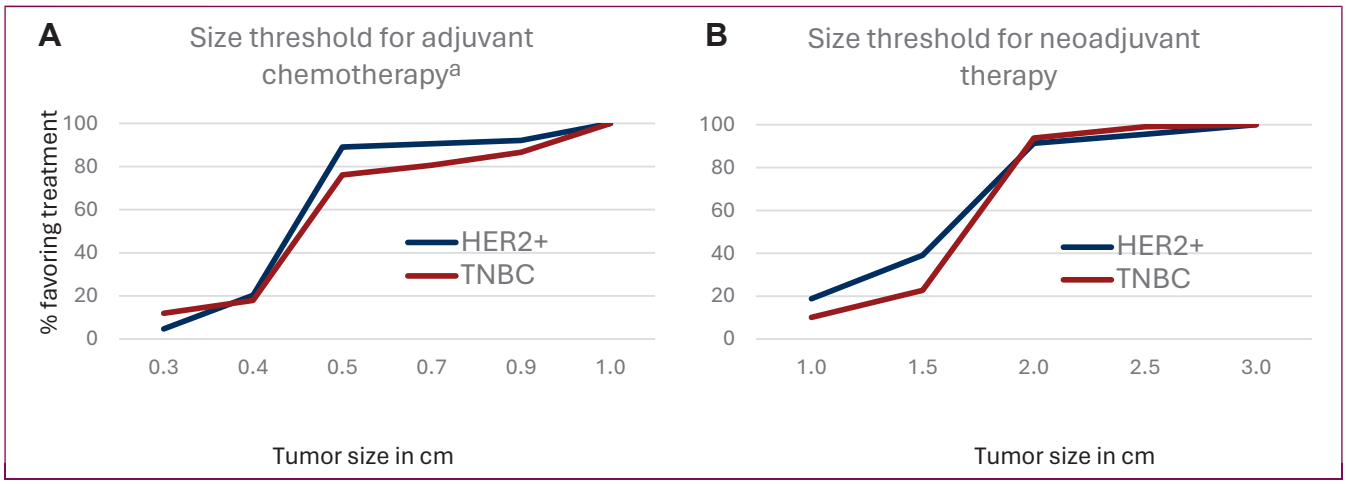

Figure 2. Size thresholds for adjuvant or neoadjuvant treatment of HER2-positive or triple-negative breast cancer.
Percentage of panelists recommending adjuvant therapy after breast-conserving surgery (A) or neoadjuvant therapy (B) for HER2-positive (blue line) or triple-negative invasive breast cancers (orange line), as a function of tumor size by examination or imaging.
[a]Chemotherapy in combination with anti-HER2 treatment of HER2-positive cancers. HER2+, HER2-positive; TNBC, triple-negative breast cancer.

the primary tumor measures approximately ≥2 cm by clinical assessment (Figure 2). Patients should be counseled regarding the increased toxicity associated with chemo-immunotherapy, particularly immune-related adverse events, including endocrinopathies, which may be permanent. Currently, there is no evidence supporting a benefit from immune checkpoint inhibitors when administered solely in the adjuvant setting for TNBC.[43] Accordingly, the panel does not recommend adjuvant checkpoint inhibitor therapy in the absence of prior neoadjuvant administration.

Based on the treatment pattern established in the Keynote 522 study, the panel recommends continuing adjuvant pembrolizumab after neoadjuvant therapy, regardless of the extent of treatment response. Patients with residual invasive tumor can receive concurrent capecitabine plus pembrolizumab, or if the tumor is BRCA1/2 associated, concurrent olaparib plus pembrolizumab.[44]

Table 3 lists preferred chemotherapy regimens by stage and tumor subtype. For TNBC, the panel recommended adjuvant chemotherapy for tumors as small as 0.5 cm, or larger (Figure 2). Multiple studies have demonstrated that adding carboplatin to anthracycline-, taxane-, and cyclophosphamide-based chemotherapy regimens can improve the rate of pCR and reduce the risk of recurrence in TNBC; however, no survival benefit has been shown.[45-47] For this reason, the panel favors including carboplatin with anthracycline, cyclophosphamide, and taxane-based chemotherapy and pembrolizumab in the Keynote 522 regimen. For patients with stage 2 or 3 TNBC who cannot or did not receive neoadjuvant chemotherapy with pembrolizumab, the four-drug chemotherapy regimen of anthracyclines, cyclophosphamide, taxane, and carboplatin is preferred for (neo)adjuvant treatment.

Systemic therapy: HER2-positive breast cancer

Anti-HER2 antibody therapy in combination with chemotherapy remains the mainstay of systemic treatment of early stage HER2-positive breast cancer. The tumor size threshold for systemic treatment with chemotherapy and trastuzumab is very low at ∼0.5 cm (see Figure 2); a substantial minority

Table 3. Chemotherapy regimens by tumor stage and subtype for patients warranting chemotherapy

T category	N category	TNBC	HER2-positive
T1ab (≤1 cm)	N0	TC	TH
T1c (1-2 cm)	N0	AC/T	TH +/− P
T2-T4	N0-N2	Preferred: neoadjuvant pembrolizumab + TCb/AC. Other option: if pembrolizumab not available, contraindicated, or not given, then adjuvant/neoadjuvant TCb/AC	Preferred: neoadjuvant TCbHP or THP. Other option AC/TH +/− P
Residual invasive tumor after neoadjuvant chemotherapy		Capecitabine (with ongoing pembrolizumab, if given), or olaparib (if BRCA pv associated) (with ongoing pembrolizumab, if given)	Trastuzumab emtansine
No residual tumor after neoadjuvant chemotherapy (i.e. pCR)		Pembrolizumab (if given in neoadjuvant treatment)	H + P (if given preoperatively)

AC, anthracycline (doxorubicin or epirubicin) and cyclophosphamide; AC/T, dose-dense anthracycline/cyclophosphamide followed by paclitaxel; H, trastuzumab; P, pertuzumab; pCR, pathological complete response; pv, pathogenic variant; TC, docetaxel and cyclophosphamide; TCb, docetaxel and carboplatin; TH, paclitaxel and trastuzumab; TNBC, triple-negative breast cancer.

(40%) of panelists even consider adjuvant therapy in cases of multiple foci of microinvasion. For patients with tumors ≥2 cm, or clinical nodal involvement, neoadjuvant therapy is preferred, and can lead to tailored treatment based on extent of residual cancer at surgery.

The non-anthracycline regimen of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCbHP) remains the preferred neoadjuvant regimen for patients with stage 2 or 3 HER2-positive breast cancer (see Table 3). However, a sequential regimen consisting of an anthracycline-based component followed by a taxane combined with anti-HER2 therapy is an appropriate alternative—particularly in settings where pertuzumab is unavailable or where tumor HER2 expression is heterogeneous.

Recent trials have demonstrated that an 18-week regimen of docetaxel, trastuzumab, and pertuzumab (THP), administered without carboplatin, achieves pCR rates comparable with those observed with TCbHP.[48,49] Although patients with HER2-positive cancers who achieve a pCR generally have an excellent prognosis, long-term data on recurrence outcomes for THP are currently lacking. The panel supports the use of either regimen, with a preference for TCbHP in patients with higher-risk disease, including stage 3 or inflammatory cancers.

A novel genomic assay is under development, incorporating the expression of 27 genes alongside clinical stage, to provide prognostic insight into pCR likelihood and recurrence risk in HER2-positive breast cancer.[50] Nevertheless, the panel does not currently recommend its use for routine clinical decision making. For tumors that are both HER2-positive and ER-positive, patients should receive HER2-targeted therapy as described above, in addition to adjuvant endocrine therapy.

Systemic therapy: ER-positive breast cancer

Globally, ER-positive, HER2-negative breast cancers are the most commonly diagnosed type of breast cancer. These represent the most biologically heterogeneous subset of breast cancers, with variations in histological appearance (lobular versus ductal), tumor grade and proliferation, and the degree of ER and PgR expression, and clinical outcomes affected by patient age and menopausal status. This heterogeneity has prompted development of genomic assays and predictive factors for risk stratification and treatment decision making on the role of adjuvant chemotherapy, in particular, which have profoundly changed therapeutic recommendations over the past decade. Recommendations for endocrine therapy (tamoxifen or aromatase inhibitors, with or without ovarian function suppression in younger women), are universal in patients with ER-positive tumors. Beyond that, systemic therapy treatment recommendations increasingly reflect matrixed consideration of tumor stage, tumor biology, patient age and menopausal status, genomic or multi-parameter risk assessment, and patient preferences when choosing among available endocrine therapies, chemotherapy regimens, and newer options of CDK4/6 inhibitors (CDK4/6i). Although pCR is less common in response to neoadjuvant chemotherapy in ER-positive tumors, especially luminal A/lower grade cancers, there is less prognostic significance to neoadjuvant response to chemotherapy in ER-positive tumors than among other phenotypes.[51,52]

In general, there is an escalation of treatment driven by increasing recurrence risk. Starting at a common point of diagnosis for lower risk tumors, a postmenopausal woman with a stage 1 ER-positive breast cancer with limited risk features would be appropriately treated with 5 years of endocrine therapy alone. For higher stage cancers or more aggressive tumor biology, chemotherapy and targeted therapies might be added, and the duration of endocrine treatment extended. For younger women, ovarian function suppression could be incorporated. These interventions represent risk-adapted recommendations tailored to the intrinsic risk of recurrence of the tumor as informed by stage and biology, and the potential benefits of the treatment in absolute terms.

ER-positive breast cancers have a relatively long natural history, with more recurrences after 5 years than in the first 5 years. Because of the generally favorable prognosis for such tumors, and the effectiveness of adjuvant therapy, second breast cancers and in-breast or regional recurrences constitute a substantial portion of 'events' in clinical trials. The panel voted explicitly that, in the absence of a survival benefit, the appropriate duration of follow-up on clinical trials of early ER-positive breast cancer was ideally a median of at least 5, and preferably 10, years before recommending a treatment. This longer horizon and perspective is important for the development of future clinical trials in this subset of breast cancers.

All systemic therapies involve trade-offs, as they are associated with significant toxicities and, in many cases, offer only modest clinical benefit. Importantly, there are no universally accepted thresholds for the magnitude of benefit required to justify the use of chemotherapy. In deliberations regarding adjuvant chemotherapy, the panel agreed that a minimum absolute reduction of 3%-5% in the risk of distant metastatic recurrence would be necessary to support a routine recommendation. This threshold is notably higher than the 1% benefit that has been cited as acceptable by patients in prior surveys of individuals who had received adjuvant chemotherapy.[53]

Similarly, in evaluating the use of adjuvant CDK4/6 inhibitors, the panel emphasized the importance of individualized risk assessment—preferably incorporating genomic testing—rather than relying solely on anatomic stage or histologic grade. There was strong support for the use of adjuvant CDK4/6 inhibitors in node-negative patients with high-risk genomic signatures, whereas enthusiasm was more limited in patients with minimal nodal involvement and low genomic risk, especially as most patients enrolled in adjuvant trials of CDK46i also received chemotherapy.

Endocrine therapy. Endocrine therapy is a uniform recommendation for patients with ER-positive breast cancers. For T1abN0 cancers (≤1 cm in size), endocrine

therapy alone is almost always sufficient therapy given the favorable long-term outcomes.[54] The duration of endocrine therapy depends on tumor stage and biology.[55] For low-risk cancers, 5 years is standard. With progressive increases in risk, longer durations are recommended. For instance, a T1cN0, grade 2 tumor would normally warrant 5 years of therapy. However, if the genomic risk score was 'high,' or if there was involvement of at least one SLN, then a majority of panelists favored 7-8 years of treatment, and for multiple (≥3) positive lymph nodes, panelists recommended 10 years of endocrine therapy.[56]

Ovarian function suppression (OFS) is an important endocrine treatment for premenopausal women with early stage breast cancer. Long-term outcomes show that in higher-risk tumors, OFS reduces recurrence both by itself and by enabling use of aromatase inhibitor treatment instead of tamoxifen, particularly in women with higher-risk breast cancers (age ≤35 years, grade 3 tumors, node-positive, persistent premenopausal state after chemotherapy) improves overall survival.[57]

Chemotherapy. The development of genomic signatures that predict chemotherapy benefit in ER-positive breast cancer has greatly simplified treatment decision making, especially among postmenopausal women. Among postmenopausal women with N0 and N1 category presentations, tumors with low- to intermediate-risk genomic assay scores do not benefit from the addition of adjuvant chemotherapy to endocrine therapy.[58-60] In many centers, surrogates for genomic signatures such as quantitative ER levels, PgR expression, grade and Ki67 are used to make similar treatment decisions. Tumors >1 cm or affecting lymph nodes, and that are associated with high genomic risk or equivalent biomarker findings, typically warrant adjuvant chemotherapy.

The first centers on situations where there is discordance between anatomic stage and biological risk, as among women with higher stage (i.e. stage 3) ER-positive tumors, as there are no randomized data to date on whether such cancers might benefit from chemotherapy in the setting of lower risk genomic signatures or with favorable biomarkers (such as luminal A-like phenotypic features). This lack of data posed a dilemma for panelists. For instance, for a 60-year-old postmenopausal woman with tumor affecting three positive axillary lymph nodes and low-risk genomic score (21-gene recurrence score of 13), only 30% favored chemotherapy. For the same case but with four positive lymph nodes (hence, N2 and stage 3), 65% favored chemotherapy, and if the genomic score was intermediate-risk (21-gene recurrence score of 20), 89% favored chemotherapy. Similarly, for a stage 3, low-grade, strongly ER-positive, T3 lobular cancer affecting a single lymph node, there was limited enthusiasm for neo/adjuvant chemotherapy given the likelihood of low genomic risk and lower rates of pCR in this tumor histology, though the panel acknowledged the lack of data for such presentations.[61,62] These votes highlight the limits of stage, risk assessment, and treatment data at present.

A second area of controversy centers on the role of chemotherapy in premenopausal women. A consistent finding across pivotal trials evaluating chemotherapy guided by genomic signature scores is that chemotherapy reduces the risk of distant recurrence specifically in premenopausal patients. However, because these trials did not uniformly incorporate OFS as part of the adjuvant treatment protocol—and since chemotherapy often induces ovarian suppression in younger women—it remains uncertain to what extent the observed benefit is attributable to the direct cytotoxic effects of chemotherapy versus its endocrine impact via chemotherapy-induced menopause. The panel endorsed a highly individualized approach in this setting (see Figure 3A). Endocrine therapy alone was recommended for premenopausal women with node-negative tumors bearing low 21-gene recurrence scores of 12 or less. For patients with low-intermediate or intermediate scores, OFS was more frequently recommended, with chemotherapy added as recurrence risk increased based on tumor stage and genomic or pathobiological profile. Among premenopausal women with nodal involvement (Figure 3B), panelists were more inclined to recommend the combination of OFS and chemotherapy. In younger women, particularly those <35 years, and in some cases

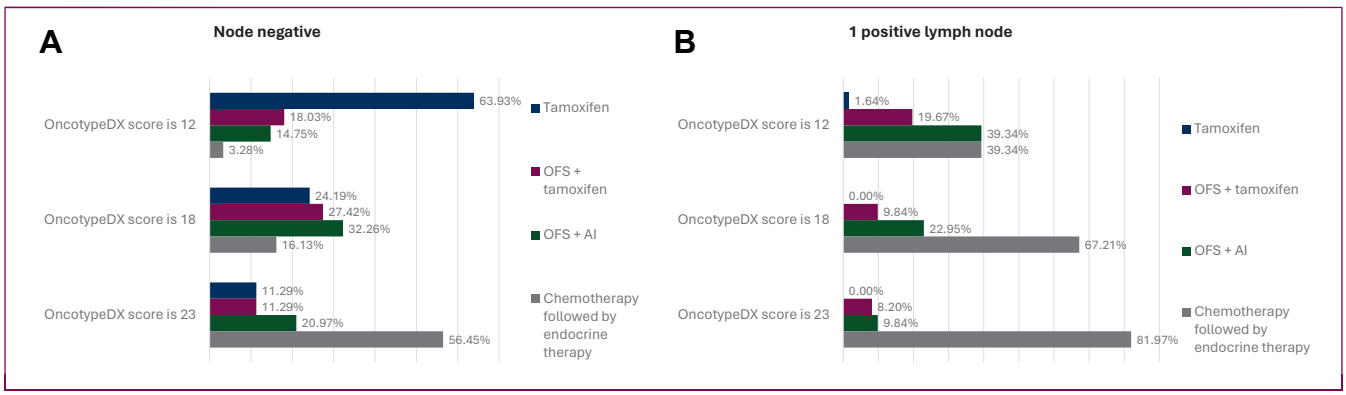

Figure 3. Recommendations for estrogen receptor-positive breast cancer in premenopausal women by recurrence score and stage.
Panelists were asked for adjuvant treatment recommendations for a premenopausal, 42-year-old woman with a 1.4 cm, grade 2 breast cancer, as a function of nodal status (A) node-negative; (B) one positive node, and as a function of the OncotypeDX 21-gene recurrence score. Treatment options were tamoxifen (dark blue), ovarian function suppression + tamoxifen (OFS +Tam, light blue), OFS + AI (pink) and chemotherapy + endocrine therapy (ET, black).
AI, aromatase inhibitor.

<40 years of age, OFS and chemotherapy were strong recommendations. Emerging evidence suggests that extending OFS beyond 5 years may provide additional reduction in recurrence risk.[63]

Anthracycline- and taxane-based regimens have been the mainstay for ER-positive tumors warranting chemotherapy.[64] Given the rare but serious cardiac and leukemia risks of anthracyclines, and prospective studies suggesting that not all patients with ER-positive tumors might need anthracyclines,[65] panelists explored which cohorts of patients warranted anthracycline-based chemotherapy. Among the cohort of patients needing chemotherapy, panelists favored non-anthracycline regimens for node-negative and high genomic or biological risk (e.g. 21-gene recurrence score 26-30; MammaPrint High 1) features, and favored anthracycline- and taxane-based regimens for node-positive and/or extremely high genomic or biological risk (e.g. 21-gene recurrence score >30; MammaPrint High 2) features. When genomic risk scores are not available, considerations of grade and Ki67 score can likely inform similar treatment stratification.

CDK4/6 inhibitors. Recent adjuvant trials have demonstrated that the addition of CDK4/6i can lower the risk of breast cancer recurrence.[66,67] These trials selected for tumors by stage and risk profile (grade, Ki67 score) and thus captured a cohort at 'greater' risk for recurrence than seen, for instance, in the trials of endocrine therapy ± chemotherapy, and nearly all the patients in these studies had received chemotherapy treatment. As discussed earlier, the panel favored using a more risk-adapted approach for considering which patients should receive adjuvant CDK4/6i treatment, informed by genomic signature and stage. In general, panelists recommended CDK4/6i in cases that would ordinarily receive adjuvant chemotherapy, including higher stage cancers, tumors with lower hormone-receptor expression or high grade or genomic risk signatures, and younger, premenopausal woman who also receive OFS. There was controversy for intermediate-risk cases (such as tumors T2N0 or with a single positive lymph node) with favorable biomarker features where the panel was divided between endorsing CDK4/6i or not. Similarly, there was controversy as to whether CDK4/6i could substitute for chemotherapy. As it is plausible that the risk reduction achieved with adjuvant CDK4/6i therapy would, as a consequence, diminish the likely absolute benefits of chemotherapy, many panelists had a higher threshold to recommend chemotherapy when adjuvant CDK4/6i could be an option. Additional data will be needed to resolve these issues more explicitly.

Table 4 outlines the St Gallen recommendations for adjuvant therapy for ER-positive cancers. In general, there is 'less' treatment of lower risk cancers (defined by stage and biological features), and therapeutic escalation based on increasing risk. Precise thresholds for treatment as defined in eligibility for trials (e.g. node-positive versus -negative, or >2 cm versus ≤2 cm, or grade 3 but not grade 2) are guides but not definitive benchmarks for therapy because risk extends across a multidimensional spectrum that reflects age, stage, grade, Ki67, and biological risk.

ER low-positive tumors. A small percentage of ER-positive tumors express very low levels of ER, scored as between 1% and 9%; these tumors are a heterogeneous group with some having luminal, ER-positive type molecular features, and others basaloid or 'triple-negative' signatures.[68] Although such tumors derive less benefit from endocrine therapy, the panel recommends that adjuvant endocrine therapy remains the norm. Recent studies demonstrated that adding immunotherapy to neoadjuvant AC/T chemotherapy in higher stage, grade 3, ER-positive cancers improved rates of pathological complete response.[69,70] In considering a case of a patient with clinical stage 2 breast cancer, high grade, that had ER low-positive at 5%, the panel recommended neoadjuvant AC/T with an immune checkpoint inhibitor. There are no data for concurrent use of adjuvant CDK46i with immunotherapy.

Local-regional recurrence

Local-regional recurrences (LRRs) of breast cancer without concurrent development of metastatic disease constitute a substantial fraction of breast tumor recurrences over time. The traditional treatment principles include surgical excision of overt tumor, irradiation of previously un-irradiated

Table 4. St Gallen overview of adjuvant therapy for estrogen receptor (ER)-positive breast cancers

Anatomic stage	T	N	Biological risk	Endocrine therapy			Chemotherapy		CDK4/6i
				Pre-meno	Post-meno	Duration (years)	Pre-meno	Post-meno	
I	T1ab	N0	N/A	Tam	ET	5	N	N	N
	T1c	N0	Low	Tam	ET	5	N	N	N
			Low-int	OFS + ET	AI	5	N	N	N
			Int	OFS + AI	AI	5	Y	N	N
			High	OFS + AI	AI	7-8	Y	Y	N
II			Low			7-8	+/−	N	Risk-adapted
			Low-int				Y	N	
			Int				Y	N	
			High	OFS + AI	AI		Y	Y	
III			N/A	OFS +AI	AI	10	Y	Y	Y

ET, endocrine therapy]either tamoxifen (tam) or aromatase inhibitor (AI)]; Int, intermediate; meno, menopause; N, no; N/A, not applicable; OFS, ovarian function suppression; Y, yes.

areas, and delivery of appropriate (neo)adjuvant therapy using agents or regimens not previously or recently administered, all with curative intent. There remain few prospective studies to guide optimal systemic treatment of LRR.[71]

The historical approach to LRR after BCS and radiation therapy was mastectomy. There are growing data for the safety and utility of re-irradiation including PBI after repeat BCS for LRR.[72,73] In a substantial shift in management guidance, the panel favored newer approaches that facilitate ongoing breast conservation (if enabled by the extent of tumor recurrence) and permit re-irradiation of the breast. The timing of the LRR had a substantial effect on enthusiasm for efforts at breast conservation and re-irradiation. As shown in Figure 4, the panel was comfortable with re-irradiation for tumors arising 5 years or more after irradiation, a function of both tolerability of radiation therapy and of likely effectiveness of radiation given the prior treatment.

In addition to the option of additional BCS, the panel favored repeated efforts at SLN surgery as part of surgical and staging management for LRRs.

The growing repertoire of agents effective in the initial treatment of early stage breast cancer has implications for treatment of LRRs. For instance, the panel recommended incorporation of immune checkpoint inhibitor treatment with induction chemotherapy in local recurrence of a TNBC for a patient who had previously received adjuvant chemotherapy but not immunotherapy, and recommended the use of adjuvant CDK4/6i and endocrine therapy in patients previously treated with endocrine agents alone, based on the efficacy of these agents in other contexts in early and advanced-stage breast cancer, and despite the present lack of studies for these treatments specifically in the context of LRR. Similarly, agents such as taxanes and alkylators can be recommended or safely reintroduced as (neo)adjuvant treatment, and emerging therapies for treatment of advanced ER-positive or HER2-positive tumors can be recommended as treatments for LRRs.

Oligometastatic breast cancer

Presentations of metastatic breast cancer with a limited or finite number of metastatic sites (so called, oligometastatic breast cancer) are not uncommon situations at the time of initial diagnosis of early breast cancer. The optimal management of these patients is controversial. Randomized studies have not shown that early local therapy with breast surgery improves outcomes for patients with known metastatases.[74,75] Similarly, metastasis-directed therapy to oligometastatic sites has not been shown to improve outcomes in women with stage IV breast cancer.[76] However, retrospective studies exploring outcomes for patients with oligometastatic disease at time of initial diagnosis, and who are naïve to systemic therapy, have suggested that judicious clinical management including definitive local-regional therapy, (neo)adjuvant type systemic treatments, and treatment of metastatic sites can achieve long-term tumor control with substantial periods of progression-free survival. The dilemma has been to define which clinical situations and tumor types are most amenable to definitive local-regional and systemic therapy in the setting of metastatic disease to achieve favorable long-term outcomes.

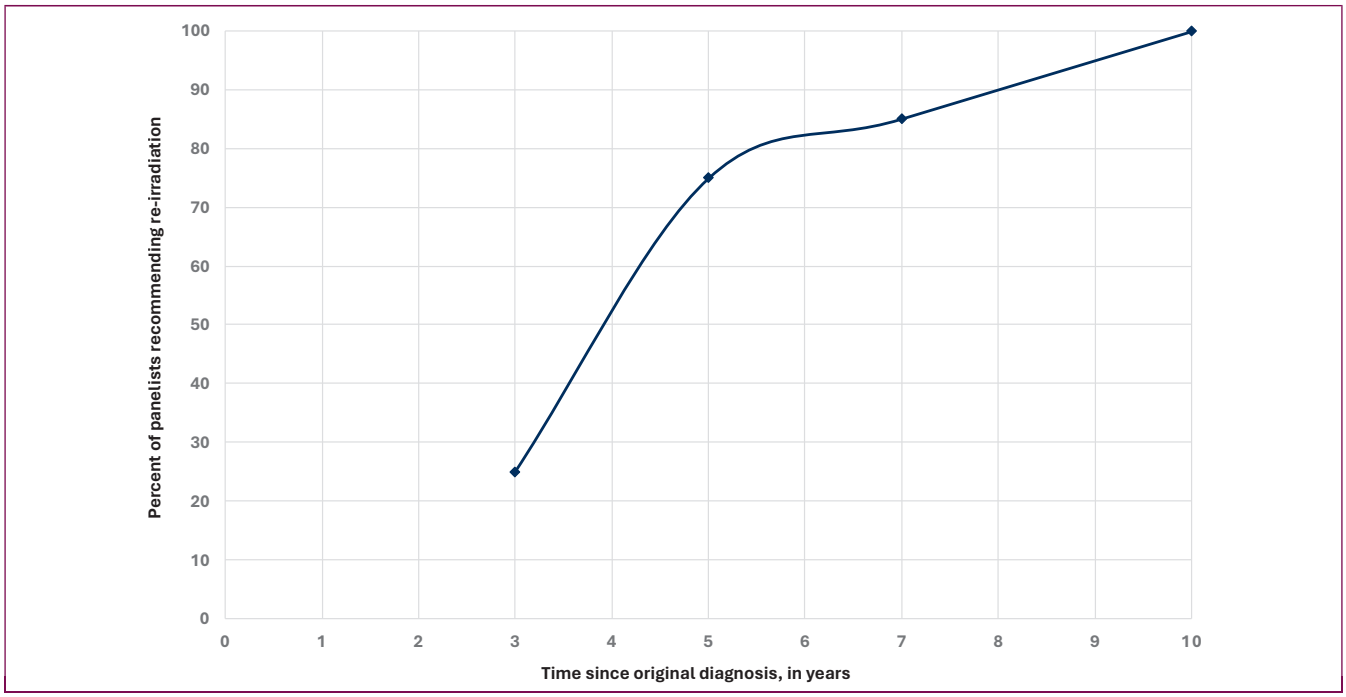

Figure 4. Panelist recommendations for re-irradiation for local-regional recurrence as a function of time since initial diagnosis.
Percentage of panelists endorsing partial breast irradiation for local-regional recurrence in the breast, of a formerly T2N0, ER-positive, HER2-negative breast cancer, as a function of time since original treatment with breast-conserving surgery and whole-breast radiation.

Table 5. St Gallen criteria for pursuing definitive local-regional treatment in oligometastatic breast cancer

Criteria	Examples
Limited oligometastatic disease	Typically 1-2 sites
Metastatic lesions amenable to definitive local therapy	Bone lesion that can be radiated; contralateral axillary lymph node that can be surgically excised; liver lesion amenable to stereotactic radiotherapy or focal ablation
Effective systemic treatment options as (neo)adjuvant therapy exist and are accessible	Estrogen receptor-positive tumors: endocrine therapy with targeted therapy and/or chemotherapy; HER2-positive tumors: chemotherapy and anti-HER2 antibody therapy or ADCs; TNBC: chemotherapy and immunotherapy or ADCs
Demonstration of tumor response to systemic induction therapy	Significant treatment response in both breast, regional lymph node, and metastatic treatment sites

ADC, antibody-drug conjugate; TNBC, triple-negative breast cancer.

The panel reviewed several clinical scenarios involving presentations of stage IV breast cancer with oligometastatic disease. In general, the panel supported the use of definitive local-regional therapy and (neo)adjuvant systemic therapy with the aim of achieving long-term tumor control in selected cases associated with the following clinical features: limited oligometastatic disease, typically involving no more than one or two metastatic sites; availability of highly effective systemic treatments; demonstration of substantial response to initial systemic therapy; and metastasis-directed therapy could be feasibly delivered via surgery, radiation therapy, or both.

When these criteria were met (see Table 5), the panel recommended proceeding with definitive breast and axillary surgery, along with appropriate radiation therapy, in alignment with multi-modality treatment with curative intent.

Survivorship and surveillance

Improvements in supportive care have dramatically reduced the side effects of adjuvant therapy, particularly chemotherapy. Multi-agent antiemetic therapy to prevent nausea and vomiting, growth factor support to prevent neutropenia and neutropenic complications and to facilitate dose-dense chemotherapy; and cold caps to minimize chemotherapy-related alopecia are all standard parts of treatment plans for early stage breast cancer patients. Recently, the POLAR trial demonstrated that use of cooling gloves or compression gloves during taxane-based chemotherapy for early breast cancer reduced peripheral neuropathy in the hands.[77] The panel recommended routinely offering cooling or compression gloves to such patients.

Following definitive treatment of early breast cancer, patients are followed for management of treatment-related side effects, second cancers, local-regional recurrence, or symptoms that could herald metastatic recurrence. There are extensive emerging data on the role of circulating tumor DNA (ctDNA) testing and monitoring in patients with early breast cancer. However, the panel believes that currently, there is no role for tumor-specific genomic testing or ctDNA monitoring for targetable mutations (for instance, *ESR1* mutations) in routine management of early breast cancer, and that the prognostic value of such testing with currently available technology is not of sufficient impact as to justify such testing at present.

The historical standard for surveillance after early breast cancer consists of regular examinations and elicitation of symptoms, and annual mammography. The Mammo-50 trial examined the frequency of screening mammography among breast cancer survivors in the UK National Health Service system. Patients who were >50 years of age, with ER-positive breast cancers, and free of known recurrence at 3 years after surgery were randomized to annual or biennial screening mammograms and were found to have no difference in rate of cancer recurrence or other oncological outcomes.[78] However, the panel voted to recommend annual mammography as standard surveillance at this time. The panel recommends that patients receive a minimum of 5 years follow-up of care under the guidance of a cancer-focused health care team. The panel strongly encouraged clinicians to discuss and manage the multifactorial sexual health concerns that are prevalent in breast cancer survivors following breast surgery, endocrine therapies, and other treatments.[79] Panelists acknowledged the unknown impact of immunotherapy on future fertility and childbearing as an important area for discussion with patients.

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REFERENCES

1. Kim J, Harper A, McCormack V, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. *Nat Med*. 2025;31:1154-1162.
2. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45.

3. Breast Cancer Association Consortium, 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.
4. 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.
5. Yadav S, Boddicker NJ, Na J, et al. Contralateral breast cancer risk among carriers of Germline pathogenic variants in *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2*. *J Clin Oncol*. 2023;41(9):1703-1713.
6. Moshe N, Haisraely O, Globus O, et al. Breast cancer outcomes after skin- and nipple-sparing mastectomy in BRCA pathogenic mutation carriers versus non-BRCA carriers. *Radiother Oncol*. 2025;205:110710.
7. Webster AJ, Shanno JN, Santa Cruz HS, et al. Oncologic safety of nipple-sparing mastectomy for breast cancer in BRCA gene mutation carriers: outcomes at 70 months median follow-up. *Ann Surg Oncol*. 2023;30(6):3215-3222.
8. Geyer CE Jr, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33(12):1250-1268.
9. 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(36):4274-4282.
10. Hwang ES, Hyslop T, Lynch T, et al. Active monitoring with or without endocrine therapy for low-risk ductal carcinoma *in situ*: the COMET randomized clinical trial. *JAMA*. 2025;333(11):972-980.
11. 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(16):1233-1241.
12. Rajan KK, Fairhurst K, Birkbeck B, et al. Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy for early-stage breast cancer: meta-analysis. *BJS Open*. 2024;8(3):zrae040.
13. de Boniface J, Szulkin R, Johansson ALV. Medical and surgical post-operative complications after breast conservation versus mastectomy in older women with breast cancer: Swedish population-based register study of 34 139 women. *Br J Surg*. 2023;110(3):344-352.
14. Gulis K, Ellbrant J, Bendahl PO, et al. Health-related quality of life by type of breast surgery in women with primary breast cancer: prospective longitudinal cohort study. *BJS Open*. 2024;8(3):zrae042.
15. Mamtani A, Morrow M. Why are there so many mastectomies in the United States? *Annu Rev Med*. 2017;68:229-241.
16. Boughey JC, Rosenkranz KM, Ballman KV, et al. Local recurrence after breast-conserving therapy in patients with multiple ipsilateral breast cancer: results from ACOSOG Z11102 (Alliance). *J Clin Oncol*. 2023;41(17):3184-3193.
17. 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. *JAMA*. 2017;318(10):918-926.
18. Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol*. 2023;41(12):2159-2165.
19. Gentilini OD, Botteri E, Sangalli C, et al., SOUND Trial Group. Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: the SOUND randomized clinical trial. *JAMA Oncol*. 2023;9(11):1557-1564.
20. Reimer T, Stachs A, Veselinovic K, et al. Axillary surgery in breast cancer - primary results of the INSEMA trial. *N Engl J Med*. 2025;392(11):1051-1064.
21. Morrow M. Sentinel-lymph-node biopsy in early-stage breast cancer - is it obsolete? *N Engl J Med*. 2025;392(11):1134-1136.
22. Park KU, Somerfield MR, Anne N, et al. Sentinel lymph node biopsy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2025;43(14):1720-1741.
23. Morrow E, Lannigan A, Doughty J, et al. Population-based study of the sensitivity of axillary ultrasound imaging in the preoperative staging of node-positive invasive lobular carcinoma of the breast. *Br J Surg*. 2018;105(8):987-995.
24. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455-1461.
25. Montagna G, Mrdutt MM, Sun SX, et al. Omission of axillary dissection following nodal downstaging with neoadjuvant chemotherapy. *JAMA Oncol*. 2024;10(6):793-798.
26. Boughey JC, Yu H, Switalla K, et al. Oncologic outcomes with de-escalation of axillary surgery after neoadjuvant chemotherapy for breast cancer: results from > 1500 patients on the I-SPY2 clinical trial. *Ann Surg Oncol*. 2025;32(5):3278-3291.
27. Muslumanoglu M, Cabioglu N, Igci A, et al. Combined analysis of the MF18-02/MF18-03 NEOSENTITURK studies: ypN-positive disease does not necessitate axillary lymph node dissection in patients with breast cancer with a good response to neoadjuvant chemotherapy as long as radiotherapy is provided. *Cancer*. 2025;131(1):e35610.
28. van Hemert AKE, van Loevezijn AA, Baas MPD, et al. Omitting axillary lymph node dissection in breast cancer patients with extensive nodal disease and excellent response to primary systemic therapy using the MARI protocol. *Breast*. 2025;80:104411.
29. Montagna G, Laws A, Ferrucci M, et al. Nodal burden and oncologic outcomes in patients with residual isolated tumor cells after neoadjuvant chemotherapy (ypN0i+): the OPBC-05/ICARO study. *J Clin Oncol*. 2025;43(7):810-820.
30. Shaitelman SF, Anderson BM, Arthur DW, et al. Partial breast irradiation for patients with early-stage invasive breast cancer or ductal carcinoma in situ: an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2024;14(2):112-132. Erratum in: *Pract Radiat Oncol*. 2024;14(6):613.
31. Kaidar-Person O, Strnad V, Ratosa I, et al. In regard to Shaitelman et al. *Pract Radiat Oncol*. 2024;14(6):608-612.
32. Behzadi ST, Moser R, Düsberg M, et al. Partial breast irradiation after sentinel lymph node biopsy omission: is it a valid alternative to whole breast Irradiation? Analysis of the dose to the sentinel lymph node region during whole breast irradiation vs. partial breast irradiation. *Breast*. 2025;82:104523.
33. Jagsi R, Griffith KA, Harris EE, et al. Omission of radiotherapy after breast-conserving surgery for women with breast cancer with low clinical and genomic risk: 5-year outcomes of IDEA. *J Clin Oncol*. 2024;42(4):390-398.
34. Kunkler IH, Williams LJ, Jack WJL, et al. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med*. 2023;388(7):585-594.
35. Kunkler IH, Williams LJ, Jack WJ, et al., PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266-273. Erratum in: *Lancet Oncol*. 2015;16(3):e105.
36. 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(19):2382-2387.
37. Meattini I, De Santis MC, Visani L, et al. Single-modality endocrine therapy versus radiotherapy after breast-conserving surgery in women aged 70 years and older with luminal A-like early breast cancer (EUROPA): a preplanned interim analysis of a phase 3, non-inferiority, randomised trial. *Lancet Oncol*. 2025;26(1):37-50.
38. Wong JS, Uno H, Tramontano AC, et al. Hypofractionated vs conventionally fractionated postmastectomy radiation after implant-based reconstruction: a randomized clinical trial. *JAMA Oncol*. 2024;10(10):1370-1378.
39. Mamounas EP, Bandos H, White JR, et al. Omitting regional nodal irradiation after response to neoadjuvant chemotherapy. *N Engl J Med*. 2025;392(21):2113-2124.
40. Schmid P, Cortes J, Dent R, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. *N Engl J Med*. 2024;391(21):1981-1991.
41. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent

of pathological complete response. *Ann Oncol*. 2022;33(11):1149-1158.
42. El Bairi K, Haynes HR, Blackley E, et al. The tale of TILs in breast cancer: a report from The International Immuno-Oncology Biomarker Working Group. *NPJ Breast Cancer*. 2021;7(1):150.
43. Ignatiadis M, Bailey A, McArthur H, et al. Adjuvant atezolizumab for early triple-negative breast cancer: the ALEXANDRA/IMpassion030 randomized clinical trial. *JAMA*. 2025;333(13):1150-1160.
44. Boucher JL, Konieczny KL, Mukallari B, et al. Safety and tolerability of adjuvant combination treatments following KEYNOTE-522 for early-stage or locally advanced breast cancer with residual disease. *J Oncol Pharm Pract*. 2025. https://doi.org/10.1177/10781552251333650
45. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. *Ann Oncol*. 2018;29(12):2341-2347.
46. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol*. 2022;33(4):384-394.
47. Shepherd JH, Ballman K, Polley MC, et al. CALGB 40603 (Alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer. *J Clin Oncol*. 2022;40(12):1323-1334.
48. Chen XC, Jiao DC, Qiao JH, et al. De-escalated neoadjuvant weekly nab-paclitaxel with trastuzumab and pertuzumab versus docetaxel, carboplatin, trastuzumab, and pertuzumab in patients with HER2-positive early breast cancer (HELEN-006): a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2025;26(1):27-36.
49. Gao HF, Li W, Wu Z, et al. De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): a multicentre, open-label, randomised, phase 3 trial. *J Clin Oncol*. 2025;43(suppl 17):abstract LBA500.
50. Tolaney SM, Tung N, Wolff AC, et al. HER2DX genomic test in early-stage HER2-positive breast cancer. *ESMO Open*. 2024;9(12):103987.
51. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172. Erratum in: *Lancet*. 2019;393(10175):986.
52. Symmans WF, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. *J Clin Oncol*. 2017;35(10):1049-1060.
53. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now? *Ann Oncol*. 2005;16(11):1786-1794.
54. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol*. 2002;20(20):4141-4149.
55. Curigliano G, Burstein HJ, Gnant M, et al. Understanding breast cancer complexity to improve patient outcomes: the St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. *Ann Oncol*. 2023;34(11):970-986. Erratum in: *Ann Oncol*. 2025;36(3):351.
56. Gnant M, Fitzal F, Rinnerthaler G, et al. Duration of adjuvant aromatase-inhibitor therapy in postmenopausal breast cancer. *N Engl J Med*. 2021;385(5):395-405.
57. Francis PA, Fleming GF, Pagani O, et al. 15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the SOFT and TEXT trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T)+OFS. *J Clin Oncol*. 2025;43(suppl 16). abstract 505.
58. 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(2):111-121.
59. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729.
60. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347.
61. Weiser R, Polychronopoulou E, Hatch SS, et al. Adjuvant chemotherapy in patients with invasive lobular carcinoma and use of the 21-gene recurrence score: a National Cancer Database analysis. *Cancer*. 2022;128(9):1738-1747.
62. Huppert LA, Wolf D, Yau C, et al. Pathologic complete response (pCR) rates for patients with HR+/HER2− high-risk, early-stage breast cancer (EBC) by clinical and molecular features in the phase II I-SPY2 clinical trial. *Ann Oncol*. 2025;36(2):172-184.
63. Valenza C, Zheng Y, Milano M, et al. Extended endocrine therapy after 5 years of adjuvant LHRH-agonist in premenopausal patients with node-positive hormone receptor (HR)-positive early breast cancer. *J Clin Oncol*. 2025;(suppl 16). abstract 537.
64. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. *Lancet*. 2023;401(10384):1277-1292.
65. Geyer CE Jr, Blum JL, Yothers G, et al. Long-term follow-up of the anthracyclines in early breast cancer trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 [NRG Oncology]). *J Clin Oncol*. 2024;42(12):1344-1349.
66. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90.
67. Hortobagyi GN, Lacko A, Sohn J, et al. A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. *Ann Oncol*. 2025;36(2):149-157.
68. 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(7):729-734.
69. Cardoso F, O'Shaughnessy J, Liu Z, et al. Pembrolizumab and chemotherapy in high-risk, early-stage, $ER^{+}/HER2^{-}$ breast cancer: a randomized phase 3 trial. *Nat Med*. 2025;31(2):442-448.
70. Loi S, Salgado R, Curigliano G, et al. Neoadjuvant nivolumab and chemotherapy in early estrogen receptor-positive breast cancer: a randomized phase 3 trial. *Nat Med*. 2025;31(2):433-441.
71. 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(11):1073-1079.
72. Arthur DW, Winter KA, Kuerer HM, et al. Effectiveness of breast-conserving surgery and 3-dimensional conformal partial breast reirradiation for recurrence of breast cancer in the ipsilateral breast: the NRG oncology/RTOG 1014 phase 2 clinical trial. *JAMA Oncol*. 2020;6(1):75-82.
73. Diskin B, Sevilimedu V, Morrow M, et al. Management of ipsilateral breast tumor recurrence following breast conservation surgery for ductal carcinoma in situ: a data-poor zone. *Ann Surg Oncol*. 2024;31(13):8843-8847.
74. Khan SA, Zhao F, Goldstein LJ, et al. Early local therapy for the primary site in de novo stage IV breast cancer: results of a randomized clinical trial (EA2108). *J Clin Oncol*. 2022;40(9):978-987. Erratum in: *J Clin Oncol*. 2022;40(12):1392.
75. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol*. 2015;16(13):1380-1388.

76. Reddy JP, Sherry AD, Fellman B, et al. Adding metastasis-directed therapy to standard-of-care systemic therapy for oligometastatic breast cancer (EXTEND): a multicenter, randomized phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2025;121(4):885-893.
77. Michel LL, Schwarz D, Romar P, et al. Efficacy of hand cooling and compression in preventing taxane-induced neuropathy: the POLAR randomized clinical trial. *JAMA Oncol*. 2025;11(4):408-415.
78. Dunn JA, Donnelly P, Elbeltagi N, et al. Annual versus less frequent mammographic surveillance in people with breast cancer aged 50 years and older in the UK (Mammo-50): a multicentre, randomised, phase 3, non-inferiority trial. *Lancet*. 2025;405 (10476):396-407.
79. Falk SJ, Bober S. Cancer and female sexual function. *Obstet Gynecol Clin North Am*. 2024;51(2):365-380.