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Annals of Oncology 28: 1700–1712, 2017
doi:10.1093/annonc/mdx308
Published online 21 June 2017

SPECIAL ARTICLE

De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

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The 15th St. Gallen International Breast Cancer Conference 2017 in Vienna, Austria reviewed substantial new evidence on loco-regional and systemic therapies for early breast cancer. Treatments were assessed in light of their intensity, duration and side-effects, seeking where appropriate to escalate or de-escalate therapies based on likely benefits as predicted by tumor stage and tumor biology. The Panel favored several interventions that may reduce surgical morbidity, including acceptance of 2 mm margins for DCIS, the resection of residual cancer (but not baseline extent of cancer) in women undergoing neoadjuvant therapy, acceptance of sentinel node biopsy following neoadjuvant treatment of many patients, and the preference for neoadjuvant therapy in *HER2* positive and triple-negative, stage II and III breast cancer. The Panel favored escalating radiation therapy with regional nodal irradiation in high-risk patients, while encouraging omission of boost in low-risk patients. The Panel endorsed gene expression signatures that permit avoidance of chemotherapy in many patients with ER positive breast cancer. For women with higher risk tumors, the Panel escalated recommendations for adjuvant endocrine treatment to include ovarian suppression in premenopausal women, and extended therapy for postmenopausal women. However, low-risk patients can avoid these treatments. Finally, the Panel recommended bisphosphonate use in postmenopausal women to prevent breast cancer recurrence. The Panel recognized that recommendations are not intended for all patients, but rather to address the clinical needs of the majority of common presentations. Individualization of adjuvant therapy means adjusting to the tumor characteristics, patient comorbidities and preferences, and managing constraints of treatment cost and access that may affect care in both the developed and developing world.

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

Introduction

The 15th St. Gallen International Breast Cancer Consensus Conference was held in March 2017 in Vienna, Austria. This meeting is a global, multidisciplinary conference with representatives from 160 nations and every continent. The highlight of the conference is the consensus panel, in which 52 panelists review and discuss specific areas of treatment with a focus on controversies in the management of early-stage breast cancer. The goal of this consensus process is to articulate important themes in management, and to provide guidance to clinicians around the world on how to think about and care for women with early-stage breast cancer. It is acknowledged that not all countries have equal access to therapeutic and diagnostic resources. In light of that, the Panel attempts to review less costly alternatives when they may be appropriately utilized (Table 1).

The theme for this year's conference was to focus on areas of 'escalation' or 'de-escalation'. That is—to identify areas where optimal care may be achieved with 'less' or 'more' treatment. The Panelists believe very strongly in the importance of evidence-based clinical care. At the same time, they recognize that data from randomized phase III studies are not always relevant to specific situations and may not be available to resolve important clinical decisions. The needs of a specific patient may be better defined through consideration of subset analyses or other individualized approaches to care. In these instances, the Panel voiced its expert judgment in order to assist in the care of individual women as best they could. The panel endorses treatment in well-designed clinical trials allowing access to best available care.

Ductal carcinoma *in situ*

Breast conserving surgery followed by radiation therapy remains the standard of care for ductal carcinoma *in situ* (DCIS) [1, 2] assuming adequate margins can be obtained. The majority of panel endorsed recent Surgical Society of Oncology (SSO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO) guidelines that recommended that a margin $\geq$2 mm is sufficient to avoid re-excision [3]. A substantial minority of the panel would accept narrower margins in individual cases, including 'no ink on DCIS'. The Panel acknowledged the recent trials showing that either aromatase inhibitors (AIs) or tamoxifen can be an effective adjuvant treatment options to lower the risk of recurrent DCIS [4, 5].

Primary surgery for early breast cancer

The Panel discussed whether women with multifocal (multiple areas of tumor in one quadrant) or multicentric (multiple areas of tumor affecting more than one quadrant) are candidates for breast conservation. The Panel strongly endorsed breast conservation for both multifocal and multicentric disease provided that surgical margins are negative, that radiotherapy is anticipated, and that the surgical resection would achieve adequate cosmesis. The Panel reiterated the 'no ink on tumor' rule for surgical margins of invasive breast cancer, and recommended this standard regardless of tumor biology or subtype [6].

A meta-analysis of single-center experiences suggests very low risk of local-regional recurrence following nipple-sparing mastectomy [7]. Based on these observations, the Panel endorsed nipple-sparing mastectomy as an appropriate surgical option. Additionally, the Panel specifically endorsed nipple-sparing mastectomy as an option for breast surgery in women with known hereditary *BRCA1/2* mutations provided that there was careful review of the retro-areolar tissue by pathology with no evidence for tumor in that region.

Based on the American College of Surgeons Oncology Group (ACOSOG) Z-11 trial, it has become standard to avoid axillary dissection in women with 1 or 2 positive sentinel lymph nodes who have had breast conservation and will be receiving whole breast radiation and adjuvant systemic therapy, regardless of tumor biology [8]. The Panel believed that either standard 'tangents' or 'high tangents' were appropriate radiation fields for such cases, and had no specific preference.

The Panel discussed how this experience relates to women who have had mastectomy. The Panel recommended additional therapy to the axilla in women who had had mastectomy and sentinel

Table 1. Research recent findings and clinical implications

Field of treatment	Findings and implications
Genetics	Multi-gene panel testing for hereditary breast cancer becomes widespread, frequently identifying deleterious mutations in women with family history but negative *BRCA1/2* testing, and also introducing substantial numbers of variants of unknown significance [46].
Surgery of ductal carcinoma *in situ*	Meta-analysis and expert panel recommends ≥2 mm margins as optimal for women receiving breast conserving surgery and radiation therapy for DCIS [3].
Systemic therapy of ductal carcinoma *in situ* (DCIS)	Randomized trials comparing the aromatase inhibitor (AI), anastrozole, against tamoxifen as treatment of estrogen receptor (ER) positive DCIS showed that the AI was at least as effective as tamoxifen, with differences in side-effect profiles [4, 5].
Surgery of the axilla after neoadjuvant therapy	Prospective trials of sentinel node vs axillary node dissection for women with node-positive breast cancer following neoadjuvant chemotherapy showed that false-negative rates for sentinel lymph node (SLN) were in excess of 10%. However, the SLN mapping may be acceptable in selected cohorts [11–13].
Partial breast irradiation	In a randomized trial of low-risk patients with early breast cancer who received breast conserving surgery, accelerated partial breast irradiation was not inferior to standard whole breast irradiation [47].
Regional nodal irradiation	Randomized trials demonstrate reduced local-regional and distant metastatic recurrence, with emerging survival advantage, for regional nodal irradiation to supraclavicular, axillary and internal mammary lymph nodes when treating high-risk breast cancers following breast surgery. While reducing risk of recurrence, regional nodal irradiation was associated with greater risk of toxicity and may complicate reconstructive surgery [20, 21].
Neoadjuvant therapy: Chemotherapy	The inclusion of carboplatin with anthracycline- and taxane-based chemotherapy improved the rate of pathologic complete response (pCR) in triple negative breast cancer (TNBC) and translated into disease-free survival benefit though the role for such treatment when patients additionally receive standard alkylator therapy is less clear [48]. In an adaptive randomized trial, the addition of carboplatin and the PARP inhibitor, veliparib, improved the rate of pCR in TNBC [49]. There were inconsistent findings for the use of nab-paclitaxel instead of paclitaxel as neoadjuvant chemotherapy [50, 51].
Neoadjuvant therapy—*HER2* targeted therapy	Long-term follow-up of NeoSphere trial suggests disease-free survival advantage parallels increased rate of pCR with pertuzumab- and trastuzumab-based therapy [52]. The antibody–drug conjugate, ado-trastuzumab emtansine paired with pertuzumab was less effective at achieving pCR than the chemotherapy–trastuzumab–pertuzumab TCHP [53]. An adaptive randomized trial suggested that the dual tyrosine kinase inhibitor neratinib, might improve rates of pCR compared with trastuzumab-based regimens though this awaits confirmation [54].
Neoadjuvant therapy—endocrine therapy.	The addition of the cyclin-dependent kinase (*CDK*) 4/6 inhibitors to aromatase inhibitor treatment dramatically suppresses tumor cell proliferation [55–57]. Among women with low genomic scores, neoadjuvant endocrine therapy is associated with high rates of clinical response [58].
Post-neoadjuvant therapy—clinical trials	Ongoing trials are evaluating post-neoadjuvant therapy for patients who have residual cancer. Agents under investigation include *CDK* 4/6 inhibitors, poly ADP ribose polymerase (PARP) inhibitors, platinum agents, ado-trastuzumab emtansine, immunotherapy agents, and others. Adjuvant capecitabine may reduce recurrence in women with residual cancer after neoadjuvant chemotherapy [42].
Adjuvant therapy—Chemotherapy	The ABC trials suggest that inclusion of anthracylines in addition to taxanes and alkylator chemotherapy remains valuable for triple-negative and stage II/III ER positive cancers treated with adjuvant chemotherapy [59]. The addition of bevacizumab to chemotherapy did not improve long-term outcomes for triple-negative breast cancer [60]. Adjuvant capecitabine may reduce recurrence in TNBC when added to anthracycline- and taxane-based chemotherapy [61], and may reduce recurrence in women with residual cancer after neoadjuvant chemotherapy [42]. 'Dose-dense' chemotherapy scheduling is validated for reducing cancer recurrence while 5-fluorouracil was shown to not affect recurrence risk [62, 63].
Adjuvant therapy—*HER2* targeted therapy	Despite multiple trials demonstrating enhanced rates of pCR with the addition of lapatinib to trastuzumab-based neoadjuvant chemotherapy, long-term findings from the ALTTO study do not suggest reduced recurrence risk with adjuvant lapatinib [64]. The ExtaNet study suggests that extended anti-*HER2* treatment with the dual tyrosine kinase inhibitor, neratinib, reduces recurrence risk, particularly in ER positive, *HER2* positive tumors but is associated with significant rates of diarrhea [65]. Trastuzumab reduced risk even in small, sub-centimeter, node-negative breast cancers [66]. Paclitaxel and trastuzumab is an effective regimen for stage I breast cancers with low rates of recurrence [67]. Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity [90].
Adjuvant therapy—endocrine therapy	In premenopausal women with ER positive breast cancer, ovarian suppression reduces recurrence in high-risk tumors but is associated with more menopausal symptoms [32, 68]. In postmenopausal women, multiple trials have studied extended endocrine therapy with an aromatase inhibitor and have shown reduced rates of breast cancer events, including distant recurrence and contralateral breast cancers though the absolute benefit is modest [38, 41]. Randomized trials show equivalence between anastrozole and letrozole as adjuvant treatment [69].
Gene expression profiling for early-stage breast cancer: prospective studies	In the MINDACT trial, a 70-gene signature paired with clinical risk criteria identified patients with breast cancer who did not derive substantial benefit from adjuvant chemotherapy [23]. In the TAILORx and West German Plan B trials, a very low 21-gene recurrence score identified a cohort of patients with ER positive breast cancer and an excellent prognosis with endocrine therapy alone [24, 25].

Continued

Table 1. *Continued*

Field of treatment	Findings and implications
Bone modifying therapy	A meta-analysis of adjuvant bisphosphonate therapy trials demonstrated reduced risk of recurrence in postmenopausal women [43]. Denosumab can reduce the risk of bone fracture and may reduce recurrence risk in postmenopausal women [44].
Survivorship	Prospective studies suggest that scalp cooling devices may reduce the incidence of alopecia in women with early-stage breast cancer receiving non-anthracycline-based chemotherapy [70, 45]. Interventions including exercise or duloxetine may reduce aromatase inhibitor-associated arthralgias [71].
Metastatic disease—immunotherapy	Anti-programmed death-1 (PD-1)/Programmed death-ligand 1 (PD-L1) antibodies have shown activity as single-agents or in combination with taxane-based chemotherapy in TNBC [72–74].
Metastatic disease—*CDK4/6* inhibitors	Randomized trials have shown that adding *CDK4/6* inhibitors to first- or second line endocrine therapy improves progression free survival [75–77].
Metastatic disease—*HER2* directed therapy	First-line therapy with ado-trastuzumab emtansine and pertuzumab was not superior to chemotherapy and trastuzumab or ado-trastuzumab emtansine, alone [78]. Adding pertuzumab to second-line chemotherapy in patients not previously treated with pertuzumab yielded small clinical benefit [79]. In the PERTAIN trial, adding pertuzumab to first-line trastuzumab and endocrine therapy improved progression free survival [80].
Molecular mechanisms of resistance to therapy	Activating mutations in the estrogen receptor *ESR1* gene arise in 30%–40% of recurrences on AI therapy and likely account for resistance to AI treatment in those cases [81].
BRCA-associated metastatic breast cancer	*BRCA*-mutated tumors show preferential benefit for carboplatin-based chemotherapy in palliation of metastatic disease [82]. The addition of veliparib to carboplatin and paclitaxel chemotherapy did not meaningfully improve outcomes in *BRCA*-associated advanced breast cancer [83]. Preliminary data from the Olympia D trial suggest that olaparib is a more effective treatment of *BRCA*-associated advanced breast cancer than non-platinum chemotherapy options.
Metastatic disease—phosphatidylinositol-4,5-bisphosphate 3-kinase (*PI3KC*)	*PI3K* mutations are common in advanced breast cancer. Randomized trials are evaluating the addition of *PI3K* inhibitors to endocrine therapy. These agents vary in their targeting of *PI3K* isoforms, and the trials differ in their inclusion and assessment of tumors by *PI3K* mutation status. To date, there are no clinically compelling outcomes from these studies [84–86]. There may be more activity with more alpha-selective agents in tumors with PI3K mutations.

node biopsy with macro-metastases affecting one or two lymph nodes. The Panel believed that either postsurgical radiation therapy or axillary dissection would be appropriate for such patients.

Breast surgery following neoadjuvant therapy

Neoadjuvant therapy serves two main goals. It provides effective systemic treatment (equivalent to adjuvant therapy) to prevent cancer recurrence, and allows de-escalating surgery for many women with larger tumors and/or axillary nodal involvement. The Panel addressed the question: 'Should the entire area of the original primary be resected after neoadjuvant therapy or should the resection include only the residual area of tumor?', and the panel deliberated about the appropriate surgical margins following neoadjuvant treatment [9]. The Panel recommended that the extent of residual tumor guide the extent of breast surgery, and that full resection of the initial tumor bed was not necessary. In general, the Panel favored the 'no ink on tumor' standard for surgical margins following neoadjuvant therapy. However, in cases of multifocal residual disease and/or cases of 'scattered' residual disease, many panelists expressed an expert opinion to favor more 'generous' margins. No single standard of care exists and the multidisciplinary team caring for the patient needs to exercise appropriate clinical judgment. Similarly, the Panel agreed that nipple-sparing mastectomy was an option for patients following neoadjuvant treatment provided the retro-areolar region lacked tumor involvement [10].

Axillary surgery following neoadjuvant therapy

The Panel deliberated on appropriate axillary surgery following neoadjuvant chemotherapy. In a woman who presented with a clinically negative axilla and who received neoadjuvant treatment, the Panel strongly believed sentinel node biopsy to be appropriate and favored the biopsy be carried out after neoadjuvant treatment.

There was more controversy regarding sentinel node surgery for women who presented with a clinically positive axilla, and had a clinical response with down staging to a clinically negative axilla. The Panel believed sentinel node biopsy, as opposed to axillary dissection, to be adequate if at least three or more negative sentinel nodes were detected and examined [11–14]. Because of concerns for false-negative results with limited sampling, sentinel node surgery was generally considered not adequate if only one or two negative sentinel nodes were identified. The Panel recommended that patients with a clinically positive axilla or with macrometastases identified in sentinel nodes after neoadjuvant therapy undergo completion axillary dissection [15]. The Panel was split on whether residual micro-metastatic lymph node involvement warranted completion dissection after neoadjuvant therapy.

Radiation therapy after breast surgery

Because of high levels of evidence for safety and long-term efficacy, the Panel believed that hypo-fractionated treatment was an appropriate standard for the majority of patients, particularly those over age 50 years, and that this represented an opportunity for

treatment de-escalation [16]. The Panel also recognized partial breast irradiation as an option for women meeting the low-risk criteria put forward by the ASTRO/European Society for Radiotherapy and Oncology (ESTRO) guideline though acknowledged that there was less evidence for this approach [17]. For women with intermediate or higher clinical risk, the Panel preferred whole breast irradiation. In another instance of de-escalation, the Panel believed that 'boost' could be omitted in patients aged ≥60, with low grade tumor features and/or favorable tumor biology who will be taking adjuvant endocrine therapy [18, 19].

Two recent randomized trials have shown improved oncological outcomes in terms of disease free survival for regional nodal irradiation (RNI) for women with higher risk breast cancers [20, 21]. The Panel recommended RNI in patients with pN1 (one to three positive nodes) cancers and adverse clinical features including young age (≤40 years), adverse biology such as low or negative estrogen receptor (ER) expression, high grade features, and extensive lympho-vascular invasion (LVI), and all patients with four or more positive lymph nodes. For women pN1 with lower risk features the potential benefits of RNI should be weighed against risks for toxicity, including pneumonitis and lymphedema. The Panel recommended post-mastectomy radiation therapy (PMRT) in all patients with four or more positive lymph nodes and/or pT3 tumors. For pN1 with lower risk features the use of PMRT should be weighed against risks for toxicity, including increased of complications following breast reconstruction.

Table 2 summarizes treatment recommendations for locoregional therapies.

The Panel acknowledged the limited data for tailored radiation therapy based on neoadjuvant treatment response, and recommended that both baseline and post-treatment cancer stage be considered in planning whether and how to administer radiation therapy. Finally, in the sentinel node-era, it is likely that radiation treatment decisions will need to be made with less complete staging information. Ongoing clinical trials including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51 and Alliance A11202 studies will inform this decision.

Characterization of tumor biology, subtypes, and genomic signatures

The St. Gallen Consensus has for years led in the development of treatment tailored toward clinical and biological subsets of breast cancer. In broad clinical terms, there are four subtypes of breast cancer that call for distinct treatment approaches: triple-negative tumors, for which chemotherapy is both effective and the only available therapy; *HER2* positive tumors regardless of ER status, for which anti-*HER2* therapy and chemotherapy are indicated; and two types of ER positive breast cancer, both of which are treated with endocrine therapy. For many of these patients with hormone receptor positive disease, chemotherapy can be omitted. ER and progesterone receptor (PR) status is determined by immunohistochemistry (IHC); human epidermal growth factor receptor (*HER2*) status is determined by IHC and/or *in situ* hybridization assays. In addition, tumors are characterized by grade and proliferative fraction (most commonly assessed by Ki-67 immunostaining), factors that may affect the recommendation for chemotherapy in ER positive tumors (Table 3). The Panel raised an issue of caution about reproducibility of IHC for Ki67 and its use to make clinical decisions, due to the variability of this assay. If used, panelists suggested to calibrate a common scoring method in order to achieve high inter-laboratory reproducibility in Ki67 scoring on centrally stained tissue microarray slides [88, 89]. Although these data are potentially encouraging, suggesting that it may be possible to standardize scoring of Ki67 among pathology laboratories, clinically important discrepancies persist. The Panel recommended against routine reporting of tumor infiltrating lymphocytes for early breast cancer.

As a clinical 'short-hand', tumors are often classified as 'luminal-A like' or 'luminal-B like' based on routine pathology. Luminal A-like tumors are typically low grade, strongly ER/PR positive, *HER2* negative and have low proliferative fraction. Luminal-B-like tumors are ER positive but may have variable degrees of ER/PR expression, are higher grade, and have higher proliferative fraction. The Panel acknowledged that these classifications based on routine histopathology were clinically valuable, and could be used to inform adjuvant treatment decisions. Specifically, the panel agreed that either grading or Ki-67 could be used to distinguish between the Luminal—A- and B-like (Table 3).

However, the panel agreed that, when available, gene expression signatures were preferable to standard pathology, when adequate reproducibility is not granted. There was considerable discussion concerning the indication for gene expression signatures [22]. The panel agreed that there was no role in clinical low risk cases [such as pT1a/b, grade 1 (G1), ER high, N0] and similar settings where chemotherapy would not be indicated under any circumstances. The Panel agreed that a number of gene expression signatures served as prognostic markers in the setting of adjuvant endocrine therapy in node-negative breast cancers, including the 21 gene recurrence score, the 70 gene signature, the PAM50 ROR score®, the EpClin score®, and the Breast Cancer Index®. The Panel endorsed all of these assays for guiding the decision on adjuvant chemotherapy in node-negative tumors as they all identify node-negative cases at low risk, with an excellent prognosis that would not warrant chemotherapy [23–27].

Nodal status is a strong prognostic factor regardless of gene expression signature. The Panel agreed that gene expression signatures offered information that can refine the prognosis for node-positive breast cancers. However, the Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node-positive cases. The 21-gene recurrence score and the 70-gene signature have now been evaluated in prospective studies including small numbers of node-positive cancers. In the prospective trial (MINDACT), only patients with node-negative, or one to three positive nodes were included. Patients with low-risk tumor scores and a limited degree of nodal involvement appear to have a good prognosis with or without chemotherapy [28, 29].

The Panel reviewed similar data showing that some gene expression signatures appear to be prognostic for late recurrence of ER positive breast cancers after 5 years of adjuvant endocrine therapy [30, 31]. However, the Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting.

Table 2. Treatment recommendations for loco-regional therapy

Local therapy	Theme	De-escalation	Escalation
Primary surgery: invasive breast cancer	Margins	Re-excision and mastectomies can be avoided with margins no larger than no tumor on ink	Re-excision for larger margins discouraged including cases with aggressive biology
	Multifocal and multicentric disease	Breast conservation if margins clear and RT anticipated	Mastectomy in other cases
Surgery for DCIS	Margins	2 mm margins sufficient to avoid second surgery	Re-excision for larger margins discouraged
Surgery after neoadjuvant chemotherapy in case of downstaging in breast and axilla	Surgery of the breast	Resection of residual disease and not original tumor area	Resection of the original tumor area in cases of refractory disease
	Margins	No tumor on ink in concentric shrinkage/unifocal residual disease	Consider re-excision (2 mm margins) in multifocal residual disease/'scattered' remission
	Sentinel lymph node biopsy in cN (−) at diagnosis	Appropriate in most cases	Axillary dissection if sentinel lymph node metastasis detected
	Sentinel lymph node biopsy in cN (+) at diagnosis	Appropriate only if three or more lymph nodes detected as sentinels	Axillary dissection in most cases outside of clinical trials
Radiotherapy			
	Hypofractionation	Strong recommendation for ages ≥50 and node negative	Consider standard radiotherapy regimens for all others
	Partial breast irradiation	Consider for ASTRO/ESTRO low risk group, especially when receiving adjuvant endocrine therapy	Consider whole breast irradiation for all others
	Boost	Omit boost in patients ≥60 years, low grade, or favorable biological profile	Consider boost in other patients
	Post-mastectomy radiation therapy (PMRT)	Consider omitting radiotherapy in women with pT1–pT2, pN1 (1–3), and favorable biological profile	PMRT in patients with pT3 or four or more positive lymph nodes
	Regional nodal irradiation (RNI)	Consider omitting RNI in N1 (1–3 positive lymph nodes) in the absence of adverse clinical factors	RNI in N1 cancers and adverse clinical features (≤40 years, low or negative estrogen receptor (ER), G3, extensive lympho-vascular invasion) or > 3 positive nodes

Table 3. Definition of subtypes

Clinical grouping	Notes[a]
Triple negative	Negative ER, PR and *HER2*
Hormone receptor-negative and *HER2*-positive	ASCO/CAP guidelines
Hormone receptor-positive and *HER2*-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-negative – a spectrum of ER+/HER2-negative	ER and/or PgR positive ≥1%
High receptor, low proliferation, low grade (luminal A-like)	Multi-parameter molecular marker 'good' if available.[b] High ER/PR and clearly low Ki-67 or grade.
Intermediate	Multi-parameter molecular marker 'intermediate' if available. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high grade (luminal B-like)	Multi-parameter molecular marker 'bad' if available. Lower ER/PR with clearly high Ki-67, histological grade 3.

[a]Basal like breast cancer and *HER2*-enriched subtype can be defined by genomic assay only.
[b]No role for gene testing in clinical pathologic low risk cases (pT1a, pT1b, G1, ER high, pN0).

The Panel discussed the routine indications for multigene testing in ER positive breast cancer. The principal role is to recommend for or against adjuvant chemotherapy. In patients who are not candidates for adjuvant chemotherapy owing to comorbid health conditions or tumor stage/risk, or in patients who 'obviously' need adjuvant chemotherapy, typically including stage III breast cancer, there is no routine need for genomic tests. In general, the zone 'in between' is where genomic assays may be most valuable. These would often be patients with tumors between 1 and 3 cm, with zero to two or three positive lymph nodes, and intermediate proliferative fraction. Multigene assay should not be the only factor considered in making a decision to proceed or to avoid chemotherapy. This broad description is intended to give guidance to clinicians and was not intended to deny access of patients with other clinical presentation where the refined prognosis available by genomic assay might reasonably inform the adjuvant chemotherapy decision.

Adjuvant endocrine therapy: premenopausal women

Tamoxifen is the historical standard adjuvant endocrine therapy for premenopausal women. The Panel reviewed data from recent trials of adjuvant ovarian function suppression (OFS) that demonstrated that OFS can lower the risk of breast cancer recurrence in higher risk cancers [32]. The Panel identified age $\leq$35 and/or involvement of 4 or more lymph nodes as factors arguing for inclusion of OFS. In general, based on published reports, women with sufficient tumor risk so as to warrant chemotherapy may wish to consider OFS. The Panel believed OFS could be paired with either tamoxifen or an AI (Table 4) [33, 34]. Chemotherapy may cause transient or permanent menopause in younger women. The Panel urged caution when interpreting laboratory assays of pituitary—ovarian function such as estradiol, follicle-stimulating hormone, or luteinizing hormone levels in women treated with chemotherapy, and encouraged use of gonadotropin-releasing hormone (GnRH) agonist therapy to achieve OFS when there was any clinical ambiguity regarding menstrual function, particularly if an AI is administered (Table 4).

Adjuvant endocrine therapy: postmenopausal women

A vast literature supports the use of tamoxifen or AIs in the adjuvant treatment of postmenopausal women. Large randomized trials have shown that initial treatment with AIs may reduce recurrence risk and improve survival compared with tamoxifen alone. The Panel noted that tamoxifen alone is still appropriate for some patients. Slightly more than half of the panelists believed that an AI should be used at some point during the course of adjuvant therapy. Factors that favored the use of an AI include node positivity, high Ki67, high grade, lobular histology, and *HER2* positivity. In women at high risk of recurrence, the panel favored the use of an AI as initial therapy. The Panel acknowledge that the importance of patient preference and tolerability of therapy, particularly given the modest differences between tamoxifen and AIs even in somewhat high-risk patients (Table 4) [36, 37].

Over the past decade, multiple trials have examined the role of extended adjuvant endocrine therapy beyond 5 years of treatment. Options include extended tamoxifen to 10 years, extended AI therapy to 10 years, or 5 years of tamoxifen and then switching to an AI. The benefits of extended therapy include reductions in risk of loco-regional and distant recurrence and in contralateral breast cancer. The Panel deliberated on which women should receive longer durations of therapy. In general, the Panel recommended longer durations in women with moderate to high risk of recurrence, typically defined as stage II or III breast cancer. In women with stage I cancers, the Panel favored only 5 years of treatment (Table 4). Based on data from recently presented studies, the Panel was more inclined to recommend extended therapy in women who had received tamoxifen as initial therapy, and in women where secondary prevention was an important treatment goal [38–41]. The Panel underscored the importance of patient preference and tolerability in this treatment decision, as extended therapy is associated with ongoing menopausal symptoms and risks to bone health, and yields only modest benefits in terms of preventing breast cancer recurrence, especially in patients who have completed 5 years of AI therapy (Table 4).

The Panel recommended that premenopausal women who are at high risk for recurrence and have concluded 5 years of tamoxifen should extend endocrine therapy for up to 10 years (Table 4) [35].

Which patients should receive adjuvant chemotherapy?

Triple-negative breast cancer

The Panel recommended adjuvant chemotherapy for triple-negative breast cancer (TNBC) stage T1b pN0 and higher; the majority recommended against routine adjuvant chemotherapy for pT1a pN0 TNBC (Table 4). The Panel preferred anthracycline- and taxane-based chemotherapy for most patients, but particularly for those with stage II and III disease. The Panel clearly recommended against routine use of platinum-based chemotherapy in unselected TNBC cases. In *BRCA1/2* associated cancers, the Panel was evenly split on whether to recommend adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy in addition to a taxane and anthracycline. Acceptable regimens included dose-dense and non-dose-dense anthracycline-, taxane-, and alkylator chemotherapy schedules (Table 5).

HER2 positive breast cancer

The Panel recommended adjuvant chemotherapy and anti-*HER2* therapy for *HER2* positive, stage pT1b pN0 and higher breast cancers; it recommended against routine adjuvant chemotherapy and anti-*HER2* therapy for pT1a pN0 *HER2* positive breast cancers. The Panel believed that the paclitaxel–trastuzumab regimen was sufficient for most stage 1, *HER2* positive cancer but recommended anti-*HER2* therapy be paired with additional chemotherapy agents for stage II or III cancer (Table 5).

Table 4. (Neo)-Adjuvant systemic treatment recommendations for ER positive/*HER2* negative early breast cancer

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
	ER positive & HER2-negative		
High receptor, low tumour burden (pT1a, pT1b), no nodal involvement (pN0), low proliferation, low grade or low "genomic risk"	Endocrine therapy alone according to menopausal status		
Premenopausal	Tamoxifen 5 years	No role for extended adjuvant tamoxifen beyond 5 years No OFS	
Postmenopausal	Tamoxifen or AI for 5 years	The majority of the panel recommended against extended adjuvant endocrine therapy beyond 5 years	
High/Intermediate degree of ER and PgR expression, intermediate tumour burden pT1c, pT2, pN0 or pN1 (1-3), intermediate or high proliferation or grade, and/or intermediate "genomic risk"	Endocrine therapy according to menopausal status plus adjuvant chemotherapy		
Premenopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	OFS plus tamoxifen or OFS plus exemestane		Consider addition of chemotherapy in selected cases Extended adjuvant endocrine therapy with tamoxifen in some cases
Premenopausal intermediate/high "clinical risk" (node positive) "intermediate/high genomic risk"	OFS plus exemestane plus adjuvant chemotherapy in many cases		Chemotherapy Extended adjuvant endocrine therapy with tamoxifen
Post-menopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	AI up front Chemotherapy in many cases		Bisphosphonates
Postmenopausal "intermediate/high genomic risk" and intermediate/high "clinical risk" (node positive)	Chemotherapy AI as first endocrine therapy for at least 3-5 years		Extended adjuvant AI according to risk and tolerability Bisphosphonates Denosumab has been shown to reduce bone-health related events in breast cancer patients
Intermediate to low ER and PR expression Higher tumor burden (typically T3 and/or N2-3) More proliferative / higher Ki67 "Intermediate to high genomic risk markers"	Adjuvant chemotherapy plus endocrine therapy according to menopausal status		
Premenopausal high risk	Adjuvant chemotherapy and OFS + AI (if premenopausal after chemo)		Extended adjuvant AI according to risk and tolerability
Postmenopausal high risk	Adjuvant chemotherapy and AI		Extended adjuvant AI according to risk and tolerability Bisphosphonates Denosumab has been shown to reduce bone-health related events in breast cancer patients

Table 5. Adjuvant systemic treatment recommendations for triple negative and *HER2* positive early breast cancer

Subtypes according to clinical-pathologic and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
Ductal triple negative pT1a node negative		No routine adjuvant chemotherapy for stage pT1a pN0.	
Higher T and N stage	Neoadjuvant therapy for stage II or III is suggested as initial treatment approach. Chemotherapy should include anthracycline and taxanes	Dose-dense adjuvant chemotherapy preferred by only a minority of the consensus panel	No consensus on post-neoadjuvant treatment in case of residual disease. In *BRCA1/2* associated cancers, the Panel was evenly split on whether to recommend (neo)adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.
ER negative & *HER2*-positive			
pT1a node negative	No systemic therapy	No systemic therapy	
pT1 b,c node negative	Chemotherapy plus trastuzumab	Consider paclitaxel plus 1 year trastuzumab without anthracyclines	Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity [90][a]
Higher T or N stage	Neoadjuvant therapy for stage II or III is the preferred initial treatment approach. Anthracycline followed by taxane with concurrent trastuzumab continued to 12 months	Patients may be treated with TCH regimen	Dual anti-*HER2* therapy with pertuzumab and trastuzumab with chemotherapy as the preferred option in the neoadjuvant setting Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity [90][a]
ER positive and *HER2*-positive	As above plus endocrine therapy appropriate to menopausal status		Extended adjuvant therapy with neratinib after 1 year of trastuzumab may reduce recurrence in ER positive subgroup[a]

[a]The Panel did not answer the question on dual blockade in the adjuvant setting since data on APHINITY trial were not available. The Panel did not answer the question on extended adjuvant therapy with neratinib.

The Panel recommended a duration of 1 year of adjuvant trastuzumab alone, based on current evidence (Table 5). At the time of the Consensus Conference data of APHINITY trial were not available. In women who received neoadjuvant anti-*HER2* therapy with dual blockade pertuzumab and trastuzumab, the Panel recommended completion of one year of trastuzumab alone but did not recommend adjuvant pertuzumab based on current evidence.

The majority of the Panel endorsed adjuvant use of adequately evaluated biosimilar trastuzumab, according to the criteria of extrapolation defined between regulatory agencies.

There is evidence from a single randomized trial that extended adjuvant therapy with neratinib after 1 year of trastuzumab may reduce recurrence in *HER2* positive breast cancer, particularly in ER positive, *HER2* positive cancers. The Panel did not specifically address the role of this agent pending further study (Table 5).

ER positive, HER2 negative breast cancer

Treatment decisions for chemotherapy in ER positive breast cancers can be guided by either IHC/pathology or by gene expression signatures. The Panel identified traditional pathology factors as relative indications for adjuvant chemotherapy including node-positive stage, extensive LVI, high Ki-67, and low hormone-receptor expression. The role of young age, per se, as an indication for chemotherapy was less strongly endorsed given the growing appreciation for tumor biology as the determinant of outcome and the potential role for ovarian suppression.

The Panel recommended against adjuvant chemotherapy in women with stage 1 or 2, luminal-A-like cancers (strongly ER and PR positive, *HER2* negative, with lower grade and proliferation markers), especially when genomic assays predicted the lack of benefit for chemotherapy treatment. The Panel recommended against adjuvant chemotherapy in women with luminal-B-like tumors with low genomic risk scores on the 21- or 70-gene signatures, when presenting with limited nodal involvement [23–25]. Some of the panelists urged caution about withholding adjuvant chemotherapy in node positive patients until more gene expression data in women treated with and without chemotherapy are available that will allow to safely de-escalate treatment in the ER+/*HER2* negative, N1-3 subset. In cases of intermediate genomic scores or greater, the Panel recommended chemotherapy in

luminal-B-like and/or node-positive cancers. The Panel preferred standard anthracycline- and taxane-based chemotherapy for most patients with ER positive breast cancer warranting chemotherapy.

Neoadjuvant therapy and post-neoadjuvant therapy

The Panel strongly endorsed the use of neoadjuvant therapy for stage II or III, *HER2* positive or triple-negative breast cancer as the preferred initial treatment approach, particularly when there is any suggestion that treatment response might enable de-escalation of surgery or radiotherapy. For *HER2* positive cancers, the Panel endorsed dual anti-*HER2* neoadjuvant therapy with pertuzumab and trastuzumab with chemotherapy as a commonly administered option. For triple-negative cancers, the Panel recommended similar approaches to those that would be used in adjuvant therapy (Table 5).

Patients with residual cancer after neoadjuvant chemotherapy are at greater risk for recurrence than those who achieve complete pathologic response. At this juncture, there are no published data that additional therapy—beyond 'standard' treatment—reduces recurrence risk in women with residual disease [42]. The Panel was ambivalent about the role of additional therapy in the post-neoadjuvant setting, and there was no consensus on whether additional therapy should routinely be added, or which treatment might be preferred. A recent trial used capecitabine in this setting with very encouraging results, but the panelists noted the absence of confirmatory data and the historical lack of substancial benefit for adjuvant capecitabine. Ongoing clinical trials are evaluating the role of therapeutic escalation with various treatments including additional chemotherapies, targeted agents, anti-*HER2* therapies, PARP inhibitors, and immune checkpoint inhibitors in this setting.

Adjuvant use of bone modifying therapy

Based on a meta-analysis of multiple trials, the Panel strongly endorsed the use of bisphosphonates as adjuvant treatment of postmenopausal women with breast cancer [43, 87]. Preferred regimens include zoledronic acid every 6 months for 5 years, or daily oral clodronate for 3 years. The Panel recommended against such treatments for premenopausal women who are continuing to have regular menstrual cycles. However, a majority of the Panel favored this option for premenopausal women receiving OFS. Denosumab has been shown to reduce bone-health related events in breast cancer patients and may reduce recurrence but only a minority of panelists favored the option of substituting denosumab for bisphosphonates [43, 44].

Survivorship and quality of life

The Panel endorsed scalp cooling devices to reduce the likelihood of alopecia related to neo/adjuvant chemotherapy with non-anthracycline regimens [45].

The Panel endorsed lifestyle, diet, and weight management strategies appropriate to the general population, acknowledging that there are as yet no data that specific diet, lifestyle, or weight interventions affect the risk of breast cancer recurrence.

Considerations in special populations

Elderly patients

The Panel resolutely endorsed the statement that there is no absolute age limit for adjuvant chemotherapy but rather the recommendation should depend on the health status of the patient, the risk of cancer recurrence, the likely benefit of therapy, and patient preferences. The Panel acknowledged that many older patients (greater than age 65 years) with ER positive, *HER2* negative, low clinical and/or genomic risk and taking adjuvant endocrine therapy could omit radiation therapy after breast conserving surgery, particularly those with multiple comorbid health conditions.

Pregnancy after breast cancer

There are few data to guide the optimal timing of pregnancy after breast cancer, and this is an important area of ongoing research. Given the known benefits of adjuvant endocrine therapy, panelists generally favored an approach that involved 18–24 months of treatment with endocrine before pregnancy, and reiterated the importance of resuming endocrine treatment after pregnancy.

Male breast cancer

The vast majority of male breast cancers are ER positive. The Panel recommended that men with ER positive tumors should receive adjuvant tamoxifen. For men with true contraindications to tamoxifen, the Panel believed GnRH agonist therapy and an AI could be an alternative.

Testing for hereditary breast cancer

The Panel endorsed genetic testing of *BRCA*-1 and *BRCA*-2 for patients with strong family history of breast cancer regardless of age; for women diagnosed at age $\leq$40 years regardless of tumor subtype, or for women with triple-negative breast cancer age $\leq$60 years. Germline multigene panel testing may be offered to patients who meet criteria for hereditary cancer syndromes, including breast and ovarian or Lynch syndrome; and is particularly appropriate in cases of early-onset breast cancer or in women with strong family history of breast cancer when *BRCA1/2* testing has been uninformative.

Discussion

Conclusions

The conference endorsed recent trial evidence supporting areas of 'escalation' or 'de-escalation' of local and systemic therapies. A large number of treatment recommendations are shown although a significant variation in the level of agreement was noted. In fact, among more than 200 questions, only a few statements

(radiation in 4 or more positive nodes, distinction between luminal A- and luminal B-like in order to identify important clinical categories) resulted in 100% concordance. The large variation in the degrees of support is reflected in the votes recorded in supplementary Appendix S1, available at *Annals of Oncology* online. The Panel recognized that recommendations are not intended for all patients, but rather for the majority of them in common clinical situations. Fine-tuning of adjuvant therapies for the patient of today implies that the available treatments need to be adjusted to the patient's tumor characteristics, co-morbidities, economic constraints and acceptance of therapies.

Acknowledgements

We gratefully thank all participants of the 15th St. Gallen International Breast Cancer Conference for their many useful suggestions. In addition to Panel members, we also thank Carmen Criscitiello, European Institute of Oncology, Milano and Michael Knauer, Kantonsspital, St. Gallen, for their substantial assistance in the collection of voting results. In recognition of their outstanding contribution as longstanding co-authors of several former St. Gallen consensus manuscripts, we especially want to thank Aron Goldhirsch, Alan Coates and Richard Gelber for their legacy and for their fundamental support of the conference-development and its consensus manuscript during the last 30 years.

Funding

None declared.

Disclosure

Conflict of interest statements from all presenters and Panel members were available on-line during the conference and are listed in supplementary Appendix S1, available at *Annals of Oncology* online.

References

1. Burstein HJ, Polyak K, Wong JS et al. Ductal carcinoma *in situ* of the breast. N Engl J Med 2004; 350: 1430–1441.
2. Wapnir IL, Dignam JJ, Fisher B et al. Long-term outcome of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011; 103: 478–488.
3. Morrow M, Van Zee KJ, Solin LJ et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma *in situ*. J Clin Oncol 2016; 34: 4040–4046.
4. Forbes JF, Sestak I, Howell A et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma *in situ* (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016; 387: 866–873.
5. Margolese RG, Cecchini RS, Julian TB et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma *in situ* undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet 2016; 387: 849–856.
6. Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014; 32: 1507–1515.
7. De La Cruz L, Moody AM, Tappy EE et al. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol 2015; 22: 3241–3249.
8. Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305: 569–575.
9. Ataseven B, Lederer B, Blohmer JU. Impact of multifocal or multicentric disease on surgery and locoregional, distant and overall survival of 6,134 breast cancer patients treated with neoadjuvant chemotherapy. Ann Surg Oncol 2015; 22: 1118–1127.
10. Santoro S, Loreti A, Cavaliere F. Neoadjuvant chemotherapy is not a contraindication for nipple sparing mastectomy. Breast 2015; 24: 661–666.
11. Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013; 14: 609–618.
12. Boughey JC, Suman VJ, Mittendorf EA. 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.
13. Boileau JF, Poirier B, Basik M et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 2015; 33: 258–264.
14. Mamtani A, Barrio AV, King TA et al. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? Results of a prospective study. Ann Surg Oncol 2016; 23: 3467–3474.
15. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg 2016; 212: 969–981.
16. Whelan TJ, Pignol JP, Levine MN et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513–520.
17. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract Rad Oncol 2017; 7: 73–79.
18. Bartelink H, Maingon P, Poortmans P et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 2015; 16: 47–56.
19. Vrieling C, van Werkhoven E, Maingon P et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs no boost trial: a randomized clinical trial. JAMA Oncol 2017; 3: 42–48.
20. Whelan TJ, Olivotto IA, Parulekar WR et al. MA.20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015; 373: 307–316.
21. Poortmans PM, Collette S, Kirkove C et al. EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 2015; 373: 317–327.
22. Harris LN, Ismaila N, McShane LM et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34: 1134–1150.
23. Sparano JA, Gray RJ, Makower DF et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 2015; 373: 2005–2014.
24. Gluz O, Nitz UA, Christgen M et al. West German Study Group Phase III PlanB Trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol 2016; 34: 2341–2349.

25. Cardoso F, van't Veer LJ, Bogaerts J et al. MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016; 375: 717–729.
26. Gnant M, Filipits M, Greil R et al. Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 risk of recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol 2014; 25: 339–345.
27. Filipits M, Rudas M, Jakesz R et al. EP Investigators. A new molecular predictor of distant recurrence in ER-positive, *HER2*-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011; 17: 6012–6020.
28. Gnant M, Sestak I, Filipits M et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and intrinsic subtype. Ann Oncol 2015; 26: 1685–1691.
29. Early Breast Cancer Trialists Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomized trials. Lancet 2012; 379: 432–444.
30. Sgroi DC, Sestak I, Cuzick J et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 2013; 14: 1067–1076.
31. Dubsky P, Brase JC, Jakesz R et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/*HER2*- breast cancer patients. Br J Cancer 2013; 109(12): 2959–2964.
32. Francis PA, Regan MM, Fleming GF et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015; 372: 436–446.
33. Pagani O, Regan MM, Walley BA et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014; 371: 107–118.
34. Gnant M, Mlineritsch B, Stoeger H et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Ann Oncol 2012; 6: 313–320.
35. Burstein HJ, Temin S, Anderson H et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of clinical oncology clinical practice guideline focused update. J Clin Oncol 2014; 32: 2255–2269.
36. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015; 386(10001): 1341–1352.
37. Metzger Filho O, Giobbie-Hurder A, Mallon E et al. Relative effectiveness of letrozole compared With tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial. J Clin Oncol 2015; 33(25): 2772–2779.
38. Goss PE, Ingle JN, Pritchard KI et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016; 375(3): 209–219.
39. Tjan-Heijnen VC, Van Hellemond IE, Peer PG et al. First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2–3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S1-03).
40. Blok EJ, van de Velde CJH, Meershoek-Klein Kranenbarg EM et al. Optimal duration of extended letrozole treatment after 5 years of adjuvant endocrine therapy; results of the randomized phase III IDEAL trial (BOOG 2006-05). In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S1-04).
41. Mamounas EP, Bandos H, Lembersky BC et al. A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. San Antonio Breast Cancer Symposium 2016, 2016 Dec 6–10, San Antonio, TX (abstr S1-05)
42. Masuda N, Lee SJ, Ohtani S et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017; 376(22): 2147–2159.
43. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015; 386(10001): 1353–1361; Erratum *Lancet* 2016; 387(10013): 30.
44. Gnant M, Pfeiler G, Dubsky PC et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015; 386: 433–443.
45. Nangia JR, Wang T, Niravath PA et al. Scalp cooling alopecia prevention trial (SCALP) for patients with early stage breast cancer. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S5-02).
46. Kurian AW, Hare EE, Mills MA et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol 2014; 32(19): 2001–2009.
47. Strnad V, Ott OJ, Hildebrandt G et al. Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-Year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016; 387(10015): 229–238.
48. Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015; 33(1): 13–21.
49. Rugo HS, Olopade OI, DeMichele A et al. I-SPY 2 Investigators. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med 2016; 375(1): 23–34.
50. Untch M, Jackisch C, Schneeweiss A et al. German Breast Group (GBG), Arbeitsgemeinschaft Gynäkologische Onkologie—Breast (AGO-B) Investigators. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol 2016; 17(3): 345–356.
51. Gianni L, Mansutti M, Anton A et al. ETNA (Evaluating Treatment with Neoadjuvant Abraxane) randomized phase III study comparing neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) both followed by anthracycline regimens in women with *HER2*-negative high-risk breast cancer: a MICHELANGO study. J Clin Oncol 2016; 34(suppl): abstr 502.
52. Gianni L, Pienkowski T, Im YH et al. 5-Year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage *HER2*-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol 2016; 17(6): 791–800.
53. Hurvitz SA, Martin M, Symmans WF et al. Pathologic complete response (pCR) rates after neoadjuvant trastuzumab emtansine (T-DM1 [K]) + pertuzumab (P) vs docetaxel + carboplatin + trastuzumab + P (TCHP) treatment in patients with *HER2*-positive (*HER2*+) early breast cancer (EBC) (KRISTINE). J Clin Oncol 2016; 34(suppl): abstr 500.
54. Park JW, Liu MC, Yee D et al. I-SPY 2 Investigators. Adaptive randomization of neratinib in early breast cancer. N Engl J Med 2016; 375(1): 11–22.
55. Curigliano G, Gómez Pardo P, Meric-Bernstam F et al. Ribociclib plus letrozole in early breast cancer: a presurgical, window-of-opportunity study. Breast 2016; 28: 191–198.
56. Ma CX, Gao F, Luo J et al. NeoPalAna: neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor positive breast cancer. Clin Cancer Res 2017 [epub ahead of print], pii:clincanres.3206.2016, doi: 10.1158/1078-0432.CCR-16-3206.
57. Hurvitz S, Abad MF, Rostorfor R et al. Interim results from neoMONARCH: a neoadjuvant phase II study of abemaciclib in postmenopausal women with HR +/*HER2*- breast cancer (BC). Ann Oncol 2016; 27(suppl_6): LBA13.

58. Bear HDD, Wan W, Robidoux A et al. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: a multicenter trial. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr P2-10-04).
59. Blum JL, Flyn PJ, Yothers G et al. Interim joint analysis of the ABC (anthracyclines in early breast cancer) phase III trials (USOR 06-090, NSABP B-46I/USOR 07132, NSABP B-49 [NRG Oncology]) comparing docetaxel + cyclophosphamide (TC) v anthracycline/taxane-based chemotherapy regimens (TaxAC) in women with high-risk, *HER2*-negative breast cancer. J Clin Oncol 2016; 34: (suppl; abstr 1000).
60. Bell R, Brown J, Parmar M et al. Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer. Ann Oncol 2016; 28(4): 754–760.
61. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R et al. Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide for early breast cancer: the randomized clinical FinXX trial. JAMA Oncol 2017; 3(6): 793–800.
62. Del Mastro L, De Placido S, Bruzzi P et al. Gruppo Italiano Mammella (GIM) investigators. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2×2 factorial, randomised phase 3 trial. Lancet 2015; 385(9980): 1863–1872.
63. Foukakis T, von Minckwitz G, Bengtsson NO et al. Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-free survival among women with high-risk early breast cancer: a randomized clinical trial. JAMA 2016; 316(18): 1888–1896.
64. Piccart-Gebhart M, Holmes E, Baselga J et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol 2016; 34(10): 1034–1042.
65. Chan A, Delaloge S, Holmes FA et al. ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with *HER2*-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; 17(3): 367–377.
66. van Ramshorst MS, van der Heiden-van der Loo M, Dackus GM et al. The effect of trastuzumab-based chemotherapy in small node-negative *HER2*-positive breast cancer. Breast Cancer Res Treat 2016; 158(2): 361–371. Erratum in Breast Cancer Res Treat 2016;159(2): 393.
67. Tolaney SM, Barry WT, Dang CT et al. Adjuvant paclitaxel and trastuzumab for node-negative, *HER2*-positive breast cancer. N Engl J Med 2015; 372(2): 134–141.
68. Ribi K, Luo W, Bernhard J et al. Adjuvant tamoxifen plus ovarian function suppression versus tamoxifen alone in premenopausal women with early breast cancer: patient-reported outcomes in the suppression of ovarian function trial. J Clin Oncol 2016; 34(14): 1601–1610.
69. Smith I, Yardley D, Burris H et al. Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor-positive, node-positive early breast cancer: final results of the randomized phase III femara versus anastrozole clinical evaluation (FACE) trial. J Clin Oncol 2017; 35(10): 1041–1048.
70. Rugo HS, Klein P, Melin SA et al. Association between use of a scalp cooling device and alopecia after chemotherapy for breast cancer. JAMA 2017; 317(6): 606–614.
71. Henry NL, Unger JM, Schott AF et al. Randomized, placebo-controlled trial of duloxetine for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS) in early stage breast cancer (SWOG S1202). In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S5-06).
72. Nanda R, Chow LQ, Dees EC et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. J Clin Oncol 2016; 34(21): 2460–2467.
73. Dirix LY, Takacs I, Nikolinakos P et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase Ib JAVELIN solid tumor trial. In San Antonio Breast Cancer Symposium 2015, 8–12 December 2015, San Antonio, TX (abstr S1-04).
74. Adams S, Diamond JR, Hamilton EP. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). J Clin Oncol 2016; 34: (suppl; abstr 1009).
75. Finn RS, Martin M, Rugo HS et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016; 375(20): 1925–1936.
76. Turner NC, Ro J, André F et al. PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015; 373(3): 209–219.
77. Hortobagyi GN, Stemmer SM, Burris HA et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016; 375(18): 1738–1748.
78. Perez EA, Barrios C, Eiermann W et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. J Clin Oncol 2017; 35(2): 141–148.
79. Urruticoechea A, Rizwanullah M, Im SA et al. PHEREXA: a phase III study of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the *HER2*-positive metastatic breast cancer (MBC) setting. J Clin Oncol 2016; 34: (suppl): abstr 504.
80. Arpino G, Ferrero J-M, de la Haba-Rodriguez J et al. Primary analysis of PERTAIN: a randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with *HER2*-positive and hormone receptor-positive metastatic or locally advanced breast cancer. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S3-04).
81. Fribbens C, O'Leary B, Kilburn L et al. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer. J Clin Oncol 2016; 34(25): 2961–2968.
82. Tutt A, Ellis P, Kilburn L et al. TNT: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or *BRCA1/2* breast cancer (CRUK/07/012). In San Antonio Breast Cancer Symposium 2014, 9–13 December 2014, San Antonio, TX (abstr S3-01).
83. Diéras V, Han HS, Robson MEE et al. Evaluation of veliparib (V) and temozolomide (TMZ) in a phase 2 randomized study of the efficacy and tolerability of V+TMZ or carboplatin (C) and paclitaxel (P) vs placebo (Plc)+C/P in patients (pts) with *BRCA1* or *BRCA2* mutations and metastatic breast cancer. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr P4-22-02).
84. Baselga J, Im S-A, Iwata H et al. PIK3CA status in circulating tumor DNA (ctDNA) predicts efficacy of buparlisib (BUP) plus fulvestrant (FULV) in postmenopausal women with endocrine-resistant HR+/*HER2*– advanced breast cancer (BC): First results from the randomized, phase III BELLE-2 trial. San Antonio Breast Cancer Symposium 2015, 8–12 December 2015, San Antonio, TX (abstr S6-01).
85. Di Leo A, Seok Lee K, Ciruelos E et al. BELLE-3: A phase III study of buparlisib+fulvestrant in postmenopausal women with HR+, *HER2*–, aromatase inhibitor-treated, locally advanced or metastatic breast cancer, who progressed on or after mTOR inhibitor-based treatment. In San Antonio Breast Cancer Symposium 2016, 6–10 December 2016, San Antonio, TX (abstr S4-07).
86. Krop IE, Mayer IA, Ganju V et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016; 17(6): 811–821.
87. Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009; 360: 679–691.
88. Polley MY, Leung SC, Gao D et al. An international study to increase concordance in Ki67 scoring. Mod Pathol 2015; 28: 778–786.
89. Polley MY, Leung SC, McShane LM et al. An international ki67 reproducibility study. J Natl Cancer Inst 2013; 105: 1897–1906.
90. von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant pertuzumab and trastuzumab in early *HER2*-positive breast cancer. N Engl J Med 2017; 377(2): 122–131.