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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Panel Members of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017

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Abstract

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 which 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 for 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.

Introduction

The fifteenth 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 ≥ 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 option 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 afford adequate cosmesis. The Panel reiterated the "no ink on tumor" rule for surgical margins for 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 node dissection with macrometastases affecting 1 or 2 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 affords a de-escalation of 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 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 dissection to be appropriate and favored sentinel dissection 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 dissection, as opposed to axillary dissection, to be adequate if at least 3 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 1 or 2 negative sentinel nodes were identified. The Panel recommended that patients with a clinically positive axilla or with macro-metastases 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 neo-adjuvant 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, 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 for regional nodal irradiation (RNI) for women with node positive and high risk node negative breast cancers [20, 21]. The Panel recommended RNI in patients with pN1 (1 to 3 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 4 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 4 or more positive lymph nodes and/or pT3 tumors. For women with pT1/pT2 pN1 cancers, the Panel recommended PMRT when adverse clinical factors (above) were present. 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 loco-regional 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 towards 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 Fluorescence in situ hybridization (FISH) status. In addition, tumors are characterized by grade and proliferation, factors that may affect the recommendation for chemotherapy in ER positive tumors (Table 3). 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 proliferation scores. Luminal-B-like tumors are ER positive but may have variable degrees of ER/PR expression, are higher grade, and have higher rates of proliferation. The Panel acknowledged that these classifications based on routine histopathology were clinically valuable, and could be used to influence adjuvant treatment decisions. Specifically, the panel agreed that either grading or Ki-67 could be used to distinguish between the Luminal –A-like 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 ascertained. 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 1-3 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].

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 [29-31]. 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.

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 2/3 positive lymph nodes, and intermediate proliferation scores. 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 that demonstrated that ovarian function suppression (OFS) can lower the risk of breast cancer recurrence in higher risk cancers [32]. The Panel identified age ≤ 35 and/or involvement of 4 or more lymph nodes as factors arguing for inclusion of ovarian function suppression. 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 (FSH), or luteinizing hormone (LH) 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 aromatase inhibitor is administered (Table 4).

Adjuvant Endocrine Therapy: Postmenopausal Women

A vast literature supports the use of tamoxifen or aromatase inhibitors in the adjuvant treatment of postmenopausal women. Large randomized trials have shown that initial treatment with aromatase inhibitors may reduce recurrence risk and improve survival compared to tamoxifen alone. The Panel noted that tamoxifen alone is still appropriate for some patients. Slightly more than half of the panelists believed that an aromatase inhibitor should be used at some point during the course of adjuvant therapy. Factors that favored the use of an aromatase inhibitor 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 aromatase inhibitor as initial therapy. The panel acknowledge the importance of patient preference and tolerability of therapy, particularly given the modest differences between tamoxifen and aromatase inhibitors 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 five years of tamoxifen and then switching to an AI. The benefits of extended therapy include reductions in risk of local-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 cancers. 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 yield only modest benefits in terms of preventing breast cancer recurrence, especially in those 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) [42].

Which Patients Should Receive Adjuvant Chemotherapy?

Triple-negative breast cancer (TNBC). The Panel recommended adjuvant chemotherapy for TNBC stage T1b pN0 and higher; it 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 cancers (Table 5).

The Panel recommended a duration of one year of adjuvant trastuzumab (Table 5). 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, acknowledging that data on the role of adjuvant pertuzumab are expected in 2017.
The Panel endorsed adjuvant use of adequately evaluated biosimilar trastuzumab.
There is evidence from a single randomized trial that extended adjuvant therapy with neratinib after one 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 immunohistochemistry / pathology or by gene expression signatures. The Panel identified traditional pathological factors as relative indications for adjuvant chemotherapy including node-positive stage, extensive lympho-vascular invasion, high Ki-67, and low hormone-receptor expression (Table 6). 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 luminal-B-like tumors with low genomic risk scores on the 21-gene and 70-gene signatures when presenting with limited nodal involvement [23-25]. 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.

<u>Neoadjuvant Therapy and Post-neoadjuvant Therapy</u>

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 pathological response. At this juncture, there are no published data that additional therapy – beyond "standard" treatment – reduces recurrence risk in women with residual disease [43]. 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, nor which treatment might be preferred. A recent trial used capecitabine in this setting with very encouraging results, but the panelists noted the absence of a published manuscript and, ideally, some additional confirmation. 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 for postmenopausal women with breast cancer [88, 89]. 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 ovarian function suppression. 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 [44, 45].

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 [46].

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) 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 to 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 aromatase inhibitor could be an alternative.

Testing for Hereditary Breast Cancer. The Panel endorsed genetic testing for patients with strong family history of breast cancer regardless of age; for women diagnosed at age ≤ 40 regardless of tumor subtype, or for women with triple-negative breast cancer age ≤ 60.

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-like 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.

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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 [47].
Surgery of ductal carcinoma *in situ*	Meta-analysis and expert panel recommends ≥ 2mm 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, anastrozole, against tamoxifen as treatment for estrogen receptor (ER) positive DCIS showed that the aromatase inhibitors (AI) was at least as effective as tamoxifen, with differences in side effect profiles [4,5].
Surgery of the axilla after neo-adjuvant therapy	Randomized 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 [48].
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 pathological 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 [49]. In an adaptive randomized trial, the addition of carboplatin and the PARP inhibitor, veliparib, improved the rate of pCR in TNBC [50]. There were inconsistent findings for the use of nab-paclitaxel instead of paclitaxel as neoadjuvant chemotherapy [51, 52].
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 [53]. The antibody-drug conjugate, ado-trastuzumab emtansine paired with pertuzumab was less effective at achieving pCR than the chemotherapy-trastuzumab-pertuzumab TCHP [54]. An adaptive randomized trial suggested that the dual tyrosine kinase inhibitor neratinib, might improve rates of pCR compared to trastuzumab-based regimens though this awaits confirmation [55].

Neoadjuvant therapy - endocrine therapy.	The addition of the cyclin D-cyclin-dependent kinase (CDK) 4/6 inhibitors to aromatase inhibitor treatment dramatically suppresses tumor cell proliferation [56-58]. Among women with low genomic scores, neoadjuvant endocrine therapy is associated with high rates of clinical response [59].
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 [43].
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 [60]. The addition of bevacizumab to chemotherapy did not improve long term outcomes for triple-negative breast cancer [61]. Adjuvant capecitabine may reduce recurrence in TNBC when added to anthracycline- and taxane- based chemotherapy [62], and may reduce recurrence in women with residual cancer after neoadjuvant chemotherapy [43]. “Dose-dense” chemotherapy scheduling is validated for reducing cancer recurrence while 5-fluorouracil was shown to not affect recurrence risk [63, 64].
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 [65]. 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 [66]. Trastuzumab reduced risk even in small, sub-centimeter, node-negative breast cancers [67]. Paclitaxel and trastuzumab is an effective regimen for stage I breast cancers with low rates of recurrence [68]. Preliminary reports suggest that adding pertuzumab to chemotherapy and trastuzumab reduces recurrence risk, especially in higher risk, HER2 positive breast cancers.
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, 69]. 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 [70].
Gene Expression Profiling for Early	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

Stage Breast Cancer: Prospective Studies	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].
Bone modifying therapy	A meta-analysis of adjuvant bisphosphonate therapy trials demonstrated reduced risk of recurrence in postmenopausal women [44]. Denosumab can reduce the risk of bone fracture and may reduce recurrence risk in postmenopausal women [45].
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 [71, 46]. Interventions including exercise or duloxetine may reduce aromatase inhibitor-associated arthralgias [72].
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 [73, 75].
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 [76-78].
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 [79]. Adding pertuzumab to second-line chemotherapy in patients not previously treated with pertuzumab yielded small clinical benefit [80]. In the PERTAIN trial, adding pertuzumab to first-line trastuzumab and endocrine therapy improved progression free survival [81].
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 [82].
BRCA-associated metastatic breast cancer	BRCA mutated tumors show preferential benefit for carboplatin based chemotherapy in palliative of metastatic disease [83]. The addition of veliparib to carboplatin and paclitaxel chemotherapy did not meaningfully improve outcomes in BRCA-associated advanced breast cancer [84]. Preliminary data from the Olympia trial suggest that olaparib is a more effective treatment for 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 [85-87]. There may be more activity with more alpha-selective agents in tumors with PI3K mutations.

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 (2mm 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 3 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	Consider whole breast irradiation for all others

		receiving adjuvant endocrine therapy	
	Boost	Omit boost in patients ≥ 60 years, low grade, or favourable biological profile	Consider boost in other patients
	Post-mastectomy radiation therapy	Consider omit ting radiotherapy in women with pT1-pT2, pN1 (1-3) and favourable 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

Molecular subtype according to clinical pathological features and to genomic score	**Definition**
Ductal Triple negative	Negative ER, PgR and HER2
Basal like breast cancer	Genomic assay
Hormone receptor-negative & HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive & HER2-positive	ASCO/CAP guidelines ER and/or PgR positive >= 1%[1]
HER2-enriched subtype	Genomic assay
Hormone receptor-positive & HER2-negative – luminal disease as a spectrum typically defined by ASCO/CAP guidelines ER and/or PgR positive >= 1%[1]	
• Luminal like-A subtype : high ER, high PgR, low proliferative index[2], low grade	The panel agreed that there was no role for genomic testing in clinical pathological low risk cases (pT1a, pT1b, G1, ER high, N0)
• Luminal A/B like breast cancer	
• Unclassified luminal breast cancer: low-intermediate hormone receptor, intermediate grade, grey zone for proliferative index	The Panel agreed that genomic classifiers are valuable to refine the prognosis for node-negative breast cancers. However, it did not uniformly endorse their use for prognosis in node-positive breast cancer.
• Luminal B-like subtype: Low receptors, high proliferative index, high grade	Multigene signature “high risk”

[1] ER values between 1% and 9% were considered equivocal. Thus endocrine therapy alone cannot be relied upon for patients with these values.
[2] Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.

Table 4. 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 5 year Consider AI as an option if tamoxifen is contraindicated or not tolerated	No role for extended adjuvant tamoxifen or AI 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 alone according to menopausal status plus adjuvant chemotherapy in many cases		
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

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
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 some cases		Bisphosphonates
Postmenopausal “intermediate/high genomic risk” and intermediate/high “clinical risk” (node positive)	Chemotherapy AI up front		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-pathological 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 the preferred initial treatment approach. Chemotherapy should include anthracycline and taxanes	Dose-dense adjuvant chemotherapy not as necessarily preferred treatment approach.	No consensus on post-neoadjuvant treatment in case of residual disease, nor which treatment might be preferred. 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 one year trastuzumab without anthracyclines	*Data about dual blockade with pertuzumab and trastuzumab are pending*
Higher T or N stage	Neoadjuvant therapy for stage II or III is the preferred initial treatment approach.	Patients may be treated with TCH regimen	Dual anti-HER2 therapy with pertuzumab and trastuzumab with chemotherapy as the

Subtypes according to clinical-pathological and genomic risk assessment	**Treatment recommendation**	**De-escalation**	**Escalation**
	Anthracycline/taxane with concurrent trastuzumab continued to 12 months		preferred option in the neoadjuvant setting *Data with dual blockade in the adjuvant setting are pending* *Extended adjuvant*
ER positive & HER2-positive	As above plus endocrine therapy appropriate to menopausal status		*Therapy with neratinib after one year of trastuzumab may reduce recurrence in ER positive subgroup.*

Table 6. Factors affecting indication to chemotherapy in patients with ER-positive, HER2-negative disease

Relative Indications for chemotherapy in addition to endocrine therapy	**Area of uncertainty for indication to chemotherapy in addition to endocrine therapy**	**Relative Indications for endocrine therapy alone**
Histological Grade 3 High or intermediate "genomic risk"	Histological Grade 2 Intermediate "genomic risk"	Histological Grade 1 Low "genomic risk"
High proliferation[a]	Intermediate proliferation[a]	Low proliferation[a]
Lower ER and PgR level	High/Intermediate degree of ER and PgR expression	Higher ER and PgR level
Node positive (4 or more involved nodes)	Node positive (1-3 involved nodes)	Node negative
Presence of extensive peritumoral vascular invasion		Absence of extensive peritumoral vascular invasion
pT > 5 cm	pT 2.1 – 5 cm	pT ≤ 2cm

[a]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.