special article

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

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The 12th St Gallen International Breast Cancer Conference (2011) Expert Panel adopted a new approach to the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes within the breast cancer spectrum. For practical purposes, these subtypes may be approximated using clinicopathological rather than gene expression array criteria. In general, systemic therapy recommendations follow the subtype classification. Thus, 'Luminal A' disease generally requires only endocrine therapy, which also forms part of the treatment of the 'Luminal B' subtype. Chemotherapy is considered indicated for most patients with 'Luminal B', 'Human Epidermal growth factor Receptor 2 (HER2) positive', and 'Triple negative (ductal)' disease, with the addition of trastuzumab in 'HER2 positive' disease. Progress was also noted in defining better tolerated local therapies in selected cases without loss of efficacy, such as accelerated radiation therapy and the omission of axillary dissection under defined circumstances. Broad treatment recommendations are presented, recognizing that detailed treatment decisions need to consider disease extent, host factors, patient preferences, and social and economic constraints.
Key words: adjuvant therapies, early breast cancer, St Gallen Consensus, subtypes

introduction

It is no longer tenable to consider breast cancer as a single disease. Subtypes can be defined by genetic array testing [1–3] or approximations to this classification using immunohistochemistry [4–7]. These subtypes have different epidemiological risk factors [8, 9], different natural histories [10–12], and different responses to systemic and local therapies [13–17]. These differences imply that clinicians managing breast cancer should consider cases within the various distinct subtypes in order to properly assess the relevant evidence and arrive at appropriate therapeutic advice.

St Gallen 2011: news and progress

The 12th International Breast Cancer Conference in March 2011 brought together some 4300 participants from 96 countries and a worldwide faculty representing all relevant disciplines. After presentation of recent research findings, a 51-member Expert Panel (see Appendix 1) considered a number of questions in order to arrive at treatment recommendations for the immediate future. As in previous St Gallen conferences [18], the Panel was charged with assessing the evidence, but also advising on the basis of expert opinion on those questions where the evidence was ambiguous or lacking. For the first time, this conference included an explicit approach to management of conflicts of interest (see Appendix 2).

Evidence was presented to support a less aggressive approach to axillary surgery in defined circumstances and the use of more convenient equally effective approaches to radiation therapy. For systemic therapy, the emphasis of this year's consensus was to reach recommendations within each of the biological subtypes, since these already incorporate many of the risk factors and response predictors previously considered separately. Disease extent, host factors, patient preferences, and economic and social factors inevitably impact the choice and delivery of care. In general, the recommendations are intended to guide therapy considerations outside clinical trials in

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communities with reasonable levels of available resources, but noting where possible the availability of alternatives, which might be only marginally less effective but less expensive.

This report will first review the new findings presented at the meeting (Table 1) and then proceed to summarize the deliberations of the Panel, bringing these together to form broad therapy recommendations.

local therapies

New results from clinical trials supported the safety of omitting axillary dissection not only in patients with a negative sentinel node biopsy [19] but also in patients with a clinically node-negative axilla but pathological macrometastatic involvement of one or two sentinel nodes in the context of breast-conserving surgery with tangential field radiation therapy [20]. This continues a trend of reduced surgical extent without loss of efficacy, which dates back to the breast-conserving approaches pioneered by Veronesi [74] and Fisher [75].

Similarly, recent studies in radiation therapy have demonstrated the safety and efficacy of abbreviated schedules for improved patient convenience and the use of partial breast irradiation (PBI) under certain defined circumstances. These findings are summarized in Table 1.

breast cancer subtypes

Analysis of gene expression arrays has resulted in the recognition of several fundamentally different subtypes of breast cancer [1]. Because it is not always feasible to obtain gene expression array information, a simplified classification, closely following that proposed by Cheang et al. [7], has been adopted as a useful shorthand. Subtypes defined by clinicopathological criteria are similar to but not identical to intrinsic subtypes and represent a convenient approximation. As summarized in Table 2, this approach uses immunohistochemical definition of estrogen and progesterone receptor, the detection of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2) oncogene, and Ki-67 labeling index, a marker of cell proliferation, as the means of identifying tumor subtypes.

Clearly, this clinicopathological classification requires the availability of reliable measurements of its individual components. Guidelines have been published for estrogen and progesterone receptor determination [76] and for the detection of HER2 positivity [77]. For clinical decision making, the Panel supported using the US Food and Drug Administration definition of HER2 positivity based on the eligibility criteria for HER2 status determination from the pivotal clinical trials [80, 81]. It was noted that clarifications to the ASCO/CAP guidelines were in preparation, and these have subsequently been published [82]. Ki-67 labeling index presents more substantial challenges, but important guidelines for this test are under development [7, 83–85]. In the proposed classification, Ki-67 labeling index is chiefly important in the distinction between 'Luminal A' and 'Luminal B (HER2 negative)' subtypes. If reliable Ki-67 labeling index assessment is not available, some alternative measure of proliferation such as a histological grade may be used in making this distinction.

panel deliberations

More than 100 questions were circulated and agreed among Panel members before the meeting. These were presented during the final session of the conference. Panel members had the opportunity to comment, and then voted electronically either yes or no on each question, with the option to abstain if they felt uninformed or conflicted. The detailed votes are not presented here: Rather, verbal descriptions of the extent of agreement or disagreement are given in the following sections.

axillary surgery

The Panel was clearly of the view that the routine use of immunohistochemistry to look for low-volume metastatic disease in sentinel nodes was not indicated, since metastases shown only by immunohistochemistry would not alter management. Furthermore, isolated tumor cells, and even metastases up to 2 mm (micrometastases) in a single sentinel node, were not considered to constitute an indication for axillary dissection regardless of the type of breast surgery carried out. The Panel accepted the option of omitting axillary dissection for macrometastases in the context of lumpectomy and radiation therapy for patients with clinically node-negative disease and 1–2 positive sentinel lymph nodes as reported from ACOSOG trial Z0011 with a median follow-up of 6.3 years [20]. The Panel, however, was very clear that this practice, based on a specific clinical trial setting, should not be extended more generally, such as to patients undergoing mastectomy, those who will not receive whole-breast tangential field radiation therapy, those with involvement of more than two sentinel nodes, and patients receiving neoadjuvant therapy.

radiation therapy

The Panel considered accelerated whole-breast radiotherapy to be an acceptable option in select patients: In particular, the Panel was divided about the use of this approach in the presence of extensive vascular invasion.

Partial breast irradiation (PBI) as definitive treatment in selected patients was supported by almost half of the Panel and by a strong majority for patients above the age of 70. There was considerable uncertainty about its use in lymphoma survivors who had previously undergone mantle field irradiation, where out-of-quadrant second cancers' risks are considerable and for any patient groups different from the current eligible population in PBI trials. The Panel generally accepted PBI as an alternative to conventional external beam boost to the tumor bed.

Post-mastectomy radiation therapy was strongly supported for patients with four or more axillary lymph nodes involved. While not in general favoring irradiation for those with lesser nodal involvement, the Panel by a slim majority favored post-mastectomy radiation for patients younger than 45 years with 1–3 positive nodes and for patients at any age with extensive vascular invasion in two or more blocks in conjunction with 1–3 positive nodes.

A majority of the Panel supported radiation after complete excision of ductal carcinoma *in situ* (DCIS) but was prepared to

Table 1. Recent research findings presented at the 12th International Conference on Primary Therapy of Early Breast Cancer and their implications for patient care

Field or Treatment	Status of research/implications for patient care
Surgery—axillary nodes	Several studies have underlined the safety of more conservative approaches to the surgery of the axilla. If sentinel lymph nodes are clear, axillary dissection can be omitted [19]. The ACOSOG trial Z0011 for patients with a clinically node-negative axilla who underwent lumpectomy and tangential whole-breast irradiation showed at a median follow-up of 6.3 years that axillary dissection can be omitted without adversely affecting prognosis even in the presence of one or two positive sentinel nodes [20].
Radiation therapy—partial breast irradiation	A randomized trial of targeted intraoperative radiotherapy yielded results closely similar to conventional whole-breast irradiation [21]. It is noteworthy that in this study, 14% of the targeted intraoperative radiotherapy group also received external beam radiotherapy and the median follow-up in the study is ∼2.5 years. A single institution series of 1822 patients treated with breast-conserving surgery has documented excellent local control with intraoperative electron beam therapy in selected patients [22].
Radiation therapy—abbreviated (hypofractionated or accelerated) whole breast	Long-term results of the Canadian randomized trial in pT1,2 N0 patients largely treated without adjuvant chemotherapy at a median follow-up of 12 years show similar locoregional control, survival, tolerability, and cosmesis for a 16 fraction regimen compared with a 25 fraction conventionally fractionated whole-breast radiotherapy delivered without external beam boost [23]. Similar results have been reported from the UK START trial at a median follow-up of 6 years using a 15 fraction regimen [24].
PARP inhibition	In the presence of tumor defects in homologous recombination DNA repair, inhibition of the PARP enzyme system may result in 'synthetic lethality' and increased cell kill [25]. This is particularly well seen in carriers of BRCA1 and BRCA2 mutations. In such patients, single-agent PARP inhibitors, such as olaparib, produce substantial tumor responses. Other cases of triple-negative disease seldom respond to single-agent PARP inhibition [26]. In such patients, DNA disrupting cytotoxic agents are being investigated in combination with PARP inhibitors.
Anti-HER2 (Human Epidermal growth factor Receptor 2) therapies	Double inhibition of HER2 by agents with differing mechanisms of action has been shown to be superior to single-agent therapy in neoadjuvant studies [27, 28], a concept being tested in the postoperative adjuvant setting in the ongoing ALTTO study. The further study of the mechanism of action of trastuzumab has clarified a role for antibody-dependent cell-mediated cytotoxicity [29].
Endocrine therapy in postmenopausal patients	Direct comparison between 5 years of adjuvant exemestane and anastrozole yielded comparable results, suggesting that exemestane provides an alternative aromatase inhibitor for up-front use [30].
Bisphosphonates	Adjuvant use of zoledronic acid did not improve disease-free survival in a broad population in the AZURE trial [31]. Subset analysis of this study showed an apparent benefit in postmenopausal patients and no benefit in premenopausal women. By contrast, the ABCSG 12 trial showed a disease-free survival benefit associated with the use of zoledronic acid among premenopausal patients, all of whom received GnRH analog [32]. These data raise the hypothesis that an antitumor effect of bisphosphonates might depend upon a low estrogen environment. This hypothesis remains to be tested in further clinical trials.
Intrinsic breast cancer subtypes	Definition of intrinsic subtypes has proved efficient in defining prognosis for breast cancer patients [33]. Currently, there are no data from phase III trials on their role as predictive tools for chemotherapy benefit. Gene expression arrays are reproducible and quantitative, but cost considerations limit their wide availability. An approximation of gene expression array results is now possible using formalin-fixed paraffin-embedded material [7].

Table 1. (*Continued*)

Field or Treatment	Status of research/implications for patient care
Molecular mechanisms predicting chemotherapeutic response	Proliferative or immune signatures are associated with good chemotherapy response [34–37]. In neoadjuvant therapy, a stromal signature is associated with a reduced response, while a lymphocytic infiltrate predicts for a higher response rate [38, 39].
Multiple targets for successful treatments	The large and growing number of agents targeting specific mutations suggests the eventual need for individual mutational analysis of each tumor to select a combination of agents to block multiple pathways [40].
Overcoming resistance to endocrine therapies	An improved understanding of the mechanisms of endocrine therapy resistance includes the role of growth factors, integrins, stress kinases, and molecular pathways including PI3K/AKT and MEK/MAPK [41]. Overcoming endocrine therapy resistance may, therefore, require inhibition of multiple escape pathways selected by biopsy of resistant tumors to confirm the mechanisms of resistance, which are active in each.
Treatment of germline genetic predisposition	Of the 394 genes, which have been causally implicated in human cancer, some 10% are transmitted in the germline leading to increased susceptibility [42]. Of these, the BRCA1 and BRCA2 have been best studied, but others include TP53, PTEN, and CDH1, all of which can increase the risk of breast cancer. BRCA1- and BRCA2-associated breast cancer is sensitive to cross-linking agents such as cisplatin [43], but data from randomized comparisons with standard chemotherapy agents are awaited.
Host factors and cancer risk	Host factors including obesity and hyperinsulinemia are associated with increased risk of breast cancer and recurrence of breast cancer. Retrospective studies indicate that diabetic patients receiving metformin have a lower incidence of cancer compared with diabetic patients not receiving this agent [44].
Vitamins and antioxidants	Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential role of vitamin C and selenium on mortality remains inconclusive [45]. Fenretinide showed reduced breast cancer incidence in young women [46]. The relationship between vitamin D levels and breast cancer risk or prognosis is controversial [46].
Endocrine effects of cytotoxic drugs	A recent analysis of the NSABP B-30 [47] confirmed previous observations from IBCSG 13-93 [48] that amenorrhea following chemotherapy was associated with substantial benefit in disease-free survival. On reanalysis of the NSABP trial using the landmark method, as in the IBCSG study, this effect was limited to the subset of patients with estrogen receptor-positive disease [49].
Modulation of angiogenesis	The early promise of the use of bevacizumab in metastatic breast cancer seen in the E2100 study has not translated into a survival benefit in subsequent studies: A synthesis of these results suggests no overall survival benefit [50]. This has led the US Food and Drug Administration to reconsider its accelerated approval of bevacizumab in breast cancer. Studies of lipotransfer have demonstrated the potential for a stromal interaction to stimulate vessel formation, raising the possibility that obesity might have an adverse prognostic impact in cancer patients via a similar stromal interaction [51].
Stem cells	Studies of mammary stem cells suggest a synergistic role for progesterone and RANK ligand in tumor formation [52]. This raises the possibility of an additional mechanism of action of clinically available RANK ligand antagonists such as denosumab [53]. Further studies of mouse mammary stem cells demonstrated that they are highly responsive to steroid hormone signaling though they lack both estrogen and progesterone receptors. This is thought to be mediated through paracrine signaling involving RANK ligand [54].
Micro RNAs and their influence on tumor growth and inhibition	Micro RNAs are involved in different biopathological features of breast cancer. MER221 and MER222 are involved in resistance and response to endocrine agents, while MER205 is an oncosuppressor able to interfere with response to tyrosine kinase inhibitors of the HER family [55].

Table 1. (Continued)

Field or Treatment	Status of research/implications for patient care
Immunity and autoimmunity	Tumor-infiltrating regulatory T cells stimulate mammary cancer metastases through receptor activator (RANKL-RANK) signaling [56]. Tumor FOXP3$^+$ T$_{reg}$ cells are a major source of RANKL, which stimulates the metastatic progression of HER2-positive RANK-expressing breast cancer cells [52].
Gene-based testing	The commercial scores from assays such as Oncotype DX® [57] and Mamma Print® [58] have been used to determine prognosis. Oncotype DX® has been shown to predict chemotherapy benefit among patients with hormone receptor-positive disease. An interesting STEPP analysis [59] from the adjuvant trastuzumab NSABP B-31 trial examined the degree of HER2 mRNA expression and corresponding trastuzumab benefit separately for patients with estrogen receptor-positive and estrogen receptor-negative disease. The striking finding was that among patients with estrogen receptor-positive disease, trastuzumab benefit in terms of 8-year disease-free survival was entirely confined to those with the higher levels of HER2 mRNA expression. In contrast, patients with estrogen receptor-negative disease derived some benefit from trastuzumab at all levels of mRNA expression, though the quantitative benefit was greater among those with higher levels of HER2 [60].
Timing of adjuvant trastuzumab	The North Central Cancer Treatment Group adjuvant trastuzumab study (N9831) included a randomization between trastuzumab administered either concurrently with or following chemotherapy. Analysis presented at the SABCS 2009 suggested a superior disease-free survival with concurrent administration [61].
Targeted therapy in the neoadjuvant setting	The NOAH study [62] showed clear improvement in breast pathological complete remission (bpCR) rate and event-free survival at 3 years with neoadjuvant trastuzumab for patients with HER2-positive disease.
Anti-HER2 therapy without chemotherapy	Studies in metastatic breast cancer and in the neoadjuvant setting have demonstrated activity of trastuzumab and other anti-HER2 agents without chemotherapy [63] albeit usually less than the activity seen for the combination with chemotherapy. There are no corresponding data in the adjuvant setting. However, it may be logical to propose that anti-HER2 therapy, alone or with endocrine therapy if appropriate, may be effective in patients who for various reasons cannot receive cytotoxic therapy [64, 65].
Neoadjuvant platinums in triple-negative (ductal) disease	Triple-negative breast cancer includes cases susceptible to DNA-damaging agents such as cisplatin. Neoadjuvant studies including cisplatin have produced pCR rates between 22% and 40% among unselected triple-negative cases [66, 67], while 10 of 12 cases with BRCA1 mutations achieved pCR with single agent cisplatin [68].
End points in neoadjuvant therapy	Failure to achieve pCR among patients with rapidly proliferating tumors identifies a group with a poor prognosis, which may be suitable for early trials of investigational agents [11].
Patients with small tumors in the absence of other risk factors	A historical cohort of patients, who did not receive adjuvant systemic therapy in the Danish Breast Cancer Group, were compared with the general Danish population to ascertain mortality ratios associated with the diagnosis of breast cancer. In the absence of other risk factors, patients aged 50 years and older with small (1–10 mm) breast cancers had a risk of death comparable to the background population. By contrast, younger patients with similar tumors had a significantly higher risk of death than the unaffected population [69].
Young patients with endocrine-responsive disease	The ABCSG Trial 12 shows that premenopausal women with endocrine-responsive disease who receive ovarian function suppression plus either tamoxifen or anastrozole continue to experience a low risk of relapse [32].
Older patients and systemic chemotherapy	The EBCTCG reported similar benefit to systemic chemotherapy in all age groups with estrogen receptor poor disease [70]. The CALGB 49907 study showed inferior results for single-agent chemotherapy compared with standard first generation combination regimens [71]. The SWOG 8814 trial demonstrated an overall benefit to CAF followed by tamoxifen versus tamoxifen alone in postmenopausal patients with endocrine-responsive disease [72], though this was seen primarily among those with adverse biologic features such as quantitatively lower estrogen receptor levels, involvement of four or more lymph nodes, or high 21 gene RS [14].

Table 1. (*Continued*)

Field or Treatment	Status of research/implications for patient care
Special histological types of breast cancer	Review of special histological types in a large institutional series suggested that endocrine-responsive types such as tubular and cribriform carcinomas may be suitable for observation without therapy or for endocrine therapy alone. Rare variants of lobular carcinomas (e.g. pleomorphic) and apocrine carcinomas require treatment according to their biological features in a manner analogous to that used for ductal carcinoma. The heterogeneous 'Triple negative' subtype includes adenoid cystic, juvenile secretory (good prognosis), medullary (intermediate prognosis), and metaplastic (either low grade, with good prognosis; or high grade, with poor prognosis) carcinomas, for which no generalizations can be proposed [73].

countenance its omission for some elderly patients and those with low-grade low-risk DCIS.

definition of biological subtypes

The Panel strongly supported the clinicopathological determination of estrogen receptor, progesterone receptor, HER2, and Ki-67 as useful for defining subtypes, but did not support the incorporation of tests for cytokeratin 5/6 or epidermal growth factor receptor/HER1 for the determination of 'basal-like' tumors for clinical decision making. The endorsed clinicopathological criteria define a convenient alternative to formal subtyping and are likely to be refined in the future. The Panel did not require multigene array definition of tumor subtype, although there was acceptance of such assays for certain indications (see below). However, the Panel did recommend that the clinicopathological markers described above were generally sufficient to guide therapeutic choices.

selection of endocrine therapy in premenopausal women

The Panel accepted tamoxifen alone or ovarian function suppression plus tamoxifen as reasonable, though expressing a preference for tamoxifen alone. In patients with a contraindication to tamoxifen, ovarian function suppression alone was accepted as a treatment, while the combination of ovarian function suppression plus an aromatase inhibitor was also considered reasonable.

selection of endocrine therapy in postmenopausal women

The Panel was exactly equally divided about whether all postmenopausal patients should receive an aromatase inhibitor (if available and not contraindicated) at some point in treatment, but was more supportive of aromatase inhibitors in the presence of involved lymph nodes. A large majority felt that selected patients could be treated with tamoxifen alone, and that patients could be switched to tamoxifen if intolerant to aromatase inhibitors. The Panel stressed the need to ensure that patients receiving an aromatase inhibitor were indeed postmenopausal, whether by clinical or biochemical criteria.

The Panel considered that 5 years of an aromatase inhibitor was a sufficient duration and a majority opposed extension even in the presence of node-positive disease or among younger

postmenopausal patients (<55 years of age). The Panel was almost unanimous in rejecting CYP2D6 testing to dictate choice of endocrine therapy type.

chemotherapy

The Panel agreed that factors arguing for the inclusion of chemotherapy were high histological grade, high proliferation as measured by Ki-67, low hormone receptor status, positive HER2 status, and 'Triple negative' status in invasive ductal carcinoma of usual forms. These factors are largely captured in the tumor subtype definitions summarized in Table 2. There was a lack of complete consensus on the threshold indication for inclusion of chemotherapy for patients with 'Luminal A' or 'Luminal B (HER2 negative)' disease. In terms of disease extent, the Panel did not believe that node positivity *per se* was an indication for use of chemotherapy, though a strong majority would use it if more than three lymph nodes were involved.

Several tests are available which define prognosis [57, 58, 86]. These may indicate a prognosis so good that the doctor and patient decide that chemotherapy is not required. A strong majority of the Panel agreed that the 21-gene signature (Oncotype DX®) [57] may also be used where available to predict chemotherapy responsiveness in an endocrine-responsive cohort where uncertainty remains after consideration of other tests, but the majority agreed that the chemopredictive properties of the 70-gene signature (MammaPrint®) [58] were not yet sufficiently established. Trials are ongoing to clarify this role for both tests. The majority of the Panel did not support lymphovascular invasion as a sufficient indication for chemotherapy, and less than a quarter of the Panel supported uPA/PAI1 [86] as a predictive marker for the use of chemotherapy.

chemotherapy in subtypes

The Panel strongly agreed that the 'Luminal A' subtype was less responsive to chemotherapy; that chemotherapy was less useful in such patients; and that no preferred chemotherapy regimen could be defined for treatment of 'Luminal A' disease.

For 'Luminal B' disease, the Panel considered that both anthracyclines and taxanes should be included in the chemotherapy regimen. While the Panel could not define a single preferred chemotherapy regimen for 'HER2 positive' disease, the majority again favored the inclusion of both anthracyclines and taxanes. For 'Triple negative' disease of the usual ductal type, the

Table 2. Surrogate definitions of intrinsic subtypes of breast cancer (4, 7)

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive(76) HER2 negative (77) Ki-67 low (<14%)[*]	This cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping (7). Local quality control of Ki-67 staining is important.
Luminal B[**]	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays (78). If reliable Ki-67 measurement is not available, some alternative assessment of tumor proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.
	'Luminal B (HER2 positive)' ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Both endocrine and anti-HER2 therapy may be indicated.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence. Staining for basal keratins (79) although shown to aid selection of true basal-like tumors, is considered insufficiently reproducible for general use.

[*]This cut-point is derived from comparison with gene array data as a prognostic factor [7]. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.

[**]Some cases over-express both luminal and HER2 genes.

Panel again supported the inclusion of anthracyclines and taxanes and an alkylating agent (typically cyclophosphamide), but did not support the routine use of cisplatin or carboplatin. A slim majority agreed that dose-dense chemotherapy [87] should be considered for such patients, and the Panel was strongly opposed to the inclusion of antiangiogenic therapies at this time, while noting that further trials are ongoing.

trastuzumab

The Panel unanimously supported the use of 1 year of trastuzumab as standard adjuvant treatment for patients with 'HER2 positive' disease, and the majority were willing to extend this to patients with pT1b, but not pT1a pN0 disease. Trastuzumab administered for <1 year [88] was regarded as suboptimal if 1 year of therapy was feasible, but better than no trastuzumab if limited resources prevented its full duration use. While awaiting data from the ongoing HERA trial, the Panel did not support continuation of adjuvant trastuzumab beyond 1 year. While preferring that trastuzumab be initiated concurrently with chemotherapy, the Panel also accepted its sequential use. The Panel did not support the use of trastuzumab without chemotherapy if chemotherapy could be given, but was prepared to countenance such treatment in circumstances where chemotherapy could not be delivered.

neoadjuvant cytotoxic therapy

A majority of the Panel considered that neoadjuvant cytotoxic therapy was of value beyond its role in facilitating conservative surgery and noted the improved prognostic information

associated with pathological complete response to such therapy, particularly in patients with 'HER2 positive' and 'Triple negative (ductal)' tumors [89], which may allow earlier change from an ineffective regimen.

The Panel considered that the choice of neoadjuvant chemotherapy should be made on the same basis as applied in the selection of postoperative adjuvant treatments. The Panel supported the incorporation of an anti-HER2 drug in the neoadjuvant therapy for patients with 'HER2 positive' disease, but did not support dual HER2 targeting at this point in time. The Panel did not support cytotoxic neoadjuvant therapy for tumors with low proliferation or high endocrine responsiveness.

neoadjuvant endocrine therapy

The Panel was almost unanimous in supporting the use of neoadjuvant endocrine therapy as an option for postmenopausal patients with highly endocrine-responsive disease. If given, the Panel considered that such treatment should be continued until maximal response or for a minimum of 4–8 months.

bisphosphonates

The Panel did not support the use of bisphosphonates for antitumor effect in either pre- [32] or postmenopausal [90] patients.

male breast cancer

Adjuvant tamoxifen was strongly supported, but only a slim majority would consider aromatase inhibitors in patients with

Table 3. Systemic treatment recommendations for subtypes

'Subtype'	Type of therapy	Notes on therapy
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy	Inclusion and type of cytotoxics may depend on level of endocrine receptor expression, perceived risk and patient preference.
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'[*]		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonresponsive	Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

[*]Special histological types: Endocrine responsive (cribriform, tubular, and mucinous); Endocrine nonresponsive (apocrine, medullary, adenoid cystic and metaplastic).

contraindications to tamoxifen, such as thrombosis. The Panel did not support extended endocrine treatment beyond 5 years for male breast cancer. The lack of any evidence on these latter two points was acknowledged.

summary of systemic treatment recommendations

The approach to treatment within breast cancer subtypes greatly simplifies the definition of therapy indications, since the subtypes themselves incorporate many of the risk and predictive factors used in previous consensus recommendations. The broad recommendations are summarized in Table 3 and essentially indicate endocrine therapy alone for patients with clinicopathologically classified 'Luminal A' disease (except in defined high-risk cases), chemo-endocrine therapy for 'Luminal B', the addition of anti-HER2 therapy in the presence of 'HER2 positivity', and a reliance on chemotherapy for most patients with 'Triple negative' disease (e.g. those with invasive ductal carcinoma).

disclosure

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Appendix 2

Note: details of the declared conflicts of interest are available at http://www.oncoconferences.ch