Review

Annals of Oncology 16: 1569–1583, 2005
doi:10.1093/annonc/mdi326
Published online 7 September 2005

Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005

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The ninth St Gallen (Switzerland) expert consensus meeting in January 2005 made a fundamental change in the algorithm for selection of adjuvant systemic therapy for early breast cancer. Rather than the earlier approach commencing with risk assessment, the Panel affirmed that the first consideration was endocrine responsiveness. Three categories were acknowledged: endocrine responsive, *endocrine non-responsive and tumors of uncertain endocrine responsiveness*. The three categories were further divided according to menopausal status. Only then did the Panel divide patients into *low-, intermediate- and high-risk* categories. It agreed that axillary lymph node involvement did not automatically define high risk. Intermediate risk included both node-negative disease (if some features of the primary tumor indicated elevated risk) and patients with one to three involved lymph nodes without additional high-risk features such as HER2/*neu* gene overexpression. The Panel recommended that patients be offered chemotherapy for endocrine non-responsive disease; endocrine therapy as the primary therapy for endocrine responsive disease, adding chemotherapy for some intermediate- and all high-risk groups in this category; and both chemotherapy and endocrine therapy for all patients in the uncertain endocrine response category except those in the low-risk group.

St Gallen 2005: news and progress

Since 1978, St Gallen (Switzerland) conferences have consistently focused on reaching expert consensus on the implications of evidence for patient treatment selection [1]. The ninth such meeting, in January 2005, attracted 4166 participants from 78 countries. Highlights reported here reflect information that has emerged since the last such meeting in 2003.

A Consensus Panel of experts (see Appendix), developed a series of guidelines and recommendations for selection of adjuvant systemic treatments in specific patient populations, modifying its previous guidelines and recommendations [1] based on the new evidence that has emerged since 2003. The declaration of consensus was based on best available evidence as presented at the St Gallen and other recent meetings and reflected by votes recorded at the Panel session. The manuscript was subsequently reviewed by all members of the Panel, and by other opinion leaders as acknowledged. The new treatment recommendations stress endocrine responsiveness and modify risk classification, since prognosis *per se* is now less of an issue influencing treatment choice.

This report concentrates on new aspects. Its recommendations are evidence-based to the extent possible, so recent evidence is critical, as summarized in Table 1. Breast cancer mortality is decreasing in many countries, despite a rising incidence. Care for patients with breast cancer is essentially multidisciplinary, and there is an important general trend to more selective interventions to minimize acute and late toxicity without compromising efficacy. Just as limited surgery allows conservation of the breast and unaffected lymph nodes and limited radiation therapy is being studied, so appropriate adjuvant systemic therapy involves choosing treatments tailored to individual patients according to assessment of endocrine responsiveness. This last aspect is perhaps the most important innovation for the 2005 conference.

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Table 1. Recent research findings presented at the 9th 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
Epidemiology and chemoprevention	Breast cancer incidence continued to rise worldwide even in countries where it is relatively low, such as India, Vietnam, Korea, Thailand, China and Gambia [2]. Breast cancer mortality is declining in many Western countries, reflecting increased awareness, early detection and better treatment. Deprivation and poverty are identified barriers to further improvements [3].
	Chemoprevention with raloxifene showed further reduction in invasive breast cancer incidence beyond 4 years of treatment in postmenopausal women with osteoporosis [4]. Adjuvant aromatase inhibitors showed significant reduction in contralateral breast cancer compared with tamoxifen or placebo [5].
Genetic susceptibility	Several founder mutations of *BRCA1* and *BRCA2* were identified recently in populations other than Ashkenazi Jews [6]. *BRCA1* tumors are typically ER, PgR and HER2/*neu* negative, often with basal-like phenotype [7], low expression of cyclin D1, p27 and AKT, high expression of cyclin E and high GMP, high acquired p53 mutation and frequent amplification of myc and EGF receptor genes [8]. *BRCA2* tumors typically express ER and PgR and tend to higher grade and less tubule formation.
	MRI appears more sensitive than mammography in detecting tumors in women at familial increased risk [9]. *BRCA1* and *BRCA2* mutation carriers benefit from prophylactic strategies including bilateral oophorectomy [10, 11], bilateral mastectomy with reconstruction [12] and chemoprevention, while the role of intensified surveillance is controversial [13]. Preclinical information strongly indicates that *BRCA1*-defective cells are hypersensitive to cisplatin while relatively resistant to doxorubicin and paclitaxel [14].
	Additional genes like *TP53*, *PTEN* and *CDH1*, confer an increased risk of breast cancer, but are rare [15].
Biology of cancer cells with special/unique metastatic potential: new targets for therapy	The hypothesis that a subset of tumor cells ('tumor stem cells') are responsible for invasion and metastases, while other tumor cells are not tumorigenic, is supported by experiments on human breast cancer cells in immunocompromised mice [16, 17]. A specific gene signature seems to characterize these cells and even specifically be associated with an organ specific metastatic potential [18]. Such stem cells might become a major target for tailored therapies.
ER and PgR: new information on resistance to selective estrogen receptor modulators and response to aromatase inhibitors	In premenopausal women tamoxifen induces increased estradiol levels, to 3000 pmol/l or more, which reduces the occupancy of ER by tamoxifen and metabolites. This increase is prevented by GnRH agonists, which might account for the observed superiority of the combination in advanced disease [19].
	In postmenopausal women, tamoxifen occupies 99.9% of ER. Its estrogen agonist effect can be dominant (as when tamoxifen is present with an aromatase inhibitor) [20]. Tamoxifen behaves as an estrogen agonist in breast cancer cells expressing high levels of the co-activator, AIB1 and HER2/*neu*, resulting in *de novo* tamoxifen resistance [21]. Absence of PgR is indicative of malfunctioning ER signaling, which is associated with tamoxifen resistance and perhaps with overexpression of growth factor receptors, like EGFR and HER2/*neu* [22–24].
DCIS	Although HER2/*neu* amplification and p53 mutation are often found in DCIS, their significance is unknown [25, 26]. Prognosis is associated with size, grade, distance to resection margins, degree of ER expression and age. Tamoxifen reduces recurrence of receptor positive DCIS, but shows little evidence of benefit in receptor negative disease [27]. Radiotherapy reduces *in situ* and invasive recurrence but is sometimes omitted, especially for small low-grade lesions [28, 26]. Sentinel node biopsy is generally superfluous in cases of DCIS, unless invasive cancer cannot be definitively excluded such as when microcalcifications are incompletely removed, or if mastectomy is planned due to extensive microcalcifications or multicentric disease [29].
Pathological findings: relevance of minimal lymph node involvement	Isolated tumor cells or small clusters of cells not larger than 0.2 mm may be detected in lymph nodes by H&E, IHC or molecular methods, usually without penetration of vascular or lymphatic sinus walls. While they have prognostic relevance, no data are available on how they should influence systemic therapy [30–32]. Such findings are common after incisional biopsies or large needle vacuum aspiration biopsy but their clinical relevance is unknown.
Prognostic and predictive factors: relevance for patient care	New data were presented on several factors but did not establish them as critical for treatment choice [33].
	Steroid hormone receptors (ERα, PgR) were overwhelmingly indicative of endocrine responsiveness, though not all tumors expressing detectable hormone receptors will have a clinically useful response. Tumors completely lacking such receptors were found to be particularly sensitive to preoperative cytotoxic agents, but despite a pathological complete remission rate exceeding 30%, survival of patients with this phenotype was shorter than for patients with receptor-positive tumors who obtained pathological complete remission significantly less frequently [34].
	Isolated tumor cells or micrometastases in bone marrow were shown to be prognostically important [35], even years after diagnosis [36], but the Panel thought examination for such cells was not standard, and their detection should not influence treatment.
	UPA and its inhibitor, PAI-1, was extensively discussed since high levels (as measured on tissue extracts using ELISAs) indicate dire prognosis [37]. In contrast, patients with low uPA/PAI-1 and ER showed a particularly good prognosis [38]. The practical value of this marker might increase if it could be more easily detected, such as by micro-ELISA or IHC on surgical tumor specimen or using tissue obtained by needle biopsy.
	Although p53 protein accumulation and gene mutation were implicated in resistance to chemotherapy, the clinical value of these findings remains controversial [39, 40].
	Gene profiling using cDNA microarrays was found to correlate with detailed clinico-pathological characteristics and clinical outcome [41, 42], yet this approach too was considered to require further prospective validation.
	Similarly, multi-gene assay (e.g. Oncotype DX for 16 genes) by RT–PCR was found to be useful for defining a group of patients with estrogen receptor positive disease who would benefit from chemotherapy added to tamoxifen [43], but further prospective validation of this method is required.

Table 1. (*Continued*)

Field or treatment	Status of research/implications for patient care
Preoperative systemic therapy	Systemic therapy is indicated before tumor removal in patients with locally advanced disease or if tumor shrinkage might lead to better local disease control and to potential breast conservation [44, 45]. Treatment choice depends upon potential endocrine responsiveness although most studies have used chemotherapy, frequently containing anthracyclines and taxanes. In a small randomized study (42 patients) neo-adjuvant trastuzumab plus chemotherapy yielded a higher pathologic complete response rate than chemotherapy alone for patients with HER2-positive disease [46]. These data require confirmation.
	Endocrine neoadjuvant therapy has also been successful [47, 48]. Remaining questions include combined chemotherapy with endocrine treatments (e.g. aromatase inhibitors) and duration of systemic therapy for best timing of surgery [34].
Surgery for invasive breast cancer	Surgical research has continued to evaluate less radical procedures in order to minimize morbidity while maintaining local disease control. Confidence in this approach has increased [49]. Exclusion of multifocal disease by MRI may improve selection for conservative surgery. Conservation of the nipple-areola complex during mastectomy, with immediate breast reconstruction, while well accepted by patients [50], requires careful patient selection and patient information on limited long-term experience.
Radiation therapy in early breast cancer	Breast radiation reduces relapses in the breast and chest wall. On average, for patients at high risk of local relapse, radiation therapy was also shown to improve survival [51]. Radiation therapy is clearly indicated after breast conserving surgery including a boost in younger patients. It remains uncertain whether radiation therapy may be omitted for women above the age of 70 years with clear margins who also receive adjuvant endocrine therapy [52].
	The balance between beneficial and harmful effects of post-mastectomy radiation therapy depends on the risk of local recurrence, the age of the patient, the efficacy of systemic therapies (especially endocrine agents) and competing causes of morbidity and mortality. Two recent updated postmastectomy adjuvant radiation therapy trials were presented. The Danish Group showed in a retrospective analysis for the cohort of patients with 1–3 positive lymph nodes, that radiotherapy reduced the overall 15-year locoregional failure rate even more than for those with 4 or more positive nodes [53]. The British Columbia study was updated at a median of 20 years and concluded that for patients with high-risk breast cancer radiation therapy and adjuvant chemotherapy yielded better survival than chemotherapy alone [54]. Despite methodological concerns on adequacy of systemic treatments employed, these findings stress the need for trials which investigate the role of postmastectomy radiation therapy, especially for those patients at moderate risk with 1–3 axillary nodes involved.
	Radiation therapy limited to the part of the breast closest to the site of the excised tumor (accelerated partial breast irradiation, APBI) has shown promising early results [55, 56]. Long-term safety, efficacy and issues about treatment of regional nodes remain to be defined.
	A retrospective review indicated some increased risk of local disease reappearance with delay of radiation therapy, although the general applicability of this finding is controversial [57].
Biological therapies, antibodies and metronomic (low-dose) cytotoxics	Adjuvant trastuzumab is currently being tested in four large randomized trials, including more than 13 000 patients with either overexpression or amplification of HER2/*neu*[a] [58]. Promising results in the neoadjuvant setting [46] require confirmation. Vaccines against various parts of the HER2 receptors are being tested [59].
	There is a significant controversy on the interaction between functioning steroid hormone receptors and HER2/*neu*, as well as between trastuzumab and tamoxifen [60].
	Preoperative trastuzumab was found to enhance antibody dependent cellular cytotoxicity [61]. Further research in this area might require the use of trastuzumab combinations with other therapeutic agents including taxanes and anthracyclines [62].
	Bevacizumab, an anti-VEGF monoclonal, was tested in patients with advanced disease together with chemotherapy. The initial study with capecitabine did not show increased time to progression despite an increased remission rate [63].[b]
	On the basis of a postulated effect on angiogenesis and/or stroma, low-dose, metronomic chemotherapy has been studied in advanced disease [64, 65]. It is currently being tested in the adjuvant setting for women with endocrine non-responsive disease, but cannot be recommended outside clinical trials.
Endocrine therapies	Initial adjuvant endocrine therapy with the aromatase inhibitors anastrozole or letrozole was tested in large trials against tamoxifen and found to significantly reduce relapse among postmenopausal women with endocrine responsive disease [66, 67]. Sequential adjuvant endocrine therapy using exemestane or anastrozole after 2–3 years of tamoxifen to complete 5 years of endocrine therapy significantly improved treatment outcome [68, 69]. Letrozole was tested against placebo after completion of about 5 years of adjuvant tamoxifen. A significant advantage in disease-free survival was observed. Overall survival was also significantly better in the subgroup of patients with node-positive disease at diagnosis, but not for the cohort with node-negative disease [70]. Several issues of safety (bone fractures, cardiac and vascular disease as well as changes in blood lipids) require further study [71]. The most recent revision of the ASCO Technology Assessment concluded that optimal hormonal therapy for a postmenopausal woman with ER-positive breast cancer should include an aromatase inhibitor [72]. Whether aromatase inhibitors should be offered initially (replacing tamoxifen), or at some time after completion of 2–5 years of tamoxifen, remains uncertain [73]. For patients at low risk of relapse or with co-morbidity raising concern on the safety of aromatase inhibitors, adjuvant tamoxifen alone remains a reasonable alternative, and may be the only economically viable option in many situations.
	For premenopausal women with endocrine responsive disease, combined ovarian function suppression (goserelin) and tamoxifen appeared to be as effective as CMF chemotherapy [74, 75]. Addition of tamoxifen after chemotherapy reduced relapse in premenopausal women with endocrine-responsive tumors but the same study found a detrimental impact of tamoxifen on disease-free survival in endocrine non-responsive disease [76].
	Quality of life issues related to endocrine therapies influence their acceptance. Patients treated with aromatase inhibitors experience arthralgia, and estrogen deprivation effects including vaginal dryness, dyspareunia, lowered libido and hot flushes. Research is required to reduce these side-effects and thus improve tolerance [77].

Table 1. (*Continued*)

Field or treatment	Status of research/implications for patient care
Chemotherapy regimens and their interaction with endocrine responsiveness	New information on the degree of responsiveness to chemotherapy of cohorts of patients selected according to expression of steroid hormone receptors in their tumors came from a 10-year analysis of the SWOG 8814/Intergroup 0100 trial in postmenopausal women with ER- and/or PgR-positive, node-positive breast cancer. Six courses of CAF prior to tamoxifen improved disease-free and overall survival compared with tamoxifen alone [78, 79]. An exploratory analysis showed little benefit for the chemoendocrine combination over tamoxifen alone in the group of patients with high ER scores [80].
	Another retrospective evaluation emphasized the importance of endocrine responsiveness in selection of patients for addition of chemotherapy. Three CALGB/ Intergroup trials, each had a more 'intensive' compared with 'standard dose' chemotherapy. While each trial showed a significant benefit for the experimental (typically more intense) treatment regimen in the groups overall and 'overwhelmingly' in the subgroups classified as estrogen receptor negative, the difference between the two treatment arms was negligible in patients with estrogen receptor positive cancers who also received tamoxifen [81].
	Postmenopausal patients with ER-poor disease in trials unconfounded with tamoxifen in the Oxford overview obtained substantial benefit similar to that which was seen in younger women with similar tumor characteristics [82].
Adjuvant therapies for very young women with breast cancer	Very young patients have a worse prognosis compared to older premenopausal women presenting with otherwise similar cancer [83, 84]. Three high priority trials are specifically investigating ovarian function suppression (SOFT), an aromatase inhibitor (TEXT), and the need for chemotherapy (PERCHE) in adjuvant therapy for endocrine responsive breast cancer in young women [74, 75].
Adjuvant therapies for older women with breast cancer	Co-morbidity and life expectancy are critical to treatment of elderly patients [85]. Even one year of endocrine therapy with tamoxifen and prednisone yielded a significant, long-term improved disease-free and overall survival in women aged over 65 years [86]. A French trial showed a significant disease-free survival benefit for low-dose epirubicin plus tamoxifen with tamoxifen alone (3 years). About 20% of these patients had negative or unknown hormone receptors [87]. A tailored, well-tolerated chemotherapy regimen is being tested in older women with endocrine non-responsive disease, who although too frail to receive a standard cytotoxic regimen, have a reasonable life expectancy [88].
Follow-up of patients after successful treatment of operable breast cancer	Treatment of advanced disease is not known to be favorably influenced by early detection of overt disease. After completion of local and systemic adjuvant therapies, standard follow-up limits routine tests in asymptomatic women to regular clinical examination and imaging of the breast, avoiding other elective imaging [89, 90].

[a]Since the St Gallen meeting three of these trials have reported results based on protocol-defined early stopping. The HERA trial showed a highly significant and substantial improvement in disease-free survival (hazard ratio 0.54). A pooled analysis of the NSABP and NCCTG trials showed a similar improvement in disease-free survival (hazard ratio 0.48) and significantly improved overall survival (hazard ratio 0.67) (Piccart-Gebhart M, First results of the HERA/BIG 01-01 trial; Romond E et al., for the joint analysis of NSABP-B-31 and NCCTG-N9831; Perez E et al., for the NCCTG-N9831 collaboration; all presented at ASCO Meeting, Orlando, FL, USA, 16 May 2005).

[b]Since the St Gallen meeting the combination of bevacizumab with paclitaxel was shown to improve survival compared with paclitaxel alone in patients with metastatic breast cancer (Miller K et al., E2100: a phase III trial of paclitaxel versus paclitaxel-bevacizumab for metastatic breast cancer. ASCO Meeting, Orlando, FL, USA, 16 May 2005).

ER, estrogen receptor; PgR, progesterone receptor; EGF, epidermal growth factor; DCIS, ductal carcinoma *in situ*; H&E, hematoxylin and eosin; IHC, immunohistochemistry; uPA, urokinase-type plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; VEGF, vascular endothelial growth factor; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; CAF, cyclophosphamide, adriamycin and 5-fluorouracil.

Endocrine responsiveness

Three disease responsiveness categories were defined:

(i) *Endocrine responsive:* the cells express steroid hormone receptors (diagnosed with proper immunohistological or biochemical methods) and for which it is probable that endocrine therapies are effective in improving disease-free and overall survival.

(ii) *Endocrine response uncertain:* some expression of steroid hormone receptors either quantitatively low or qualitatively insufficient to indicate a substantial chance for response to endocrine therapies alone, thus suggesting the need for chemotherapy. The exact boundary between 'endocrine responsive' and 'endocrine response uncertain' is undecided, and may well be different in different clinical settings (e.g. according to number of involved axillary lymph nodes or menopausal status).

(iii) *Endocrine non-responsive:* cells have no detectable expression of steroid hormone receptors.

The value of this primary classification is that endocrine therapies may be offered alone to selected patients with clearly endocrine responsive disease, while chemotherapy alone is offered to patients with endocrine non-responsive disease. The newly defined category of uncertain endocrine responsiveness is suited to combinations of chemotherapy and endocrine therapy.

Features indicative of uncertainty of endocrine responsiveness include low levels of steroid hormone receptor immunoreactivity (usually considered as <10% of cells positive), lack of progesterone receptors (PgR) [irrespective of the expression of estrogen receptors (ER)], features suggesting potential resistance to particular endocrine therapies (e.g. HER2/*neu* overexpression and tamoxifen), a high number of involved lymph nodes, high tumor levels of urokinase-type plasminogen activator/plasminogen

activator inhibitor type 1 (uPA/PAI-1) [91] and increased proliferation markers. Since any detectable steroid hormone receptor indicates some degree of endocrine responsiveness, such patients should receive endocrine therapy, but the doubtful adequacy of such treatment alone suggests a need also for adjuvant chemotherapy.

As biological understanding of factors influencing treatment response improves, it is likely that the language used to describe various aspects of discussion on treatment choice will evolve. Currently, the terms *endocrine responsive*, *uncertain endocrine response* (see text), and *endocrine non-responsive* refer to the groups of tumors that are responsive to endocrine therapies alone, chemotherapy and endocrine therapy combinations, and chemotherapy alone, respectively. Endocrine responsiveness may not in future be the most precise way to describe the continuum of therapeutic targets against which new biological agents are effective.

Research findings summarized in Table 1 bring together and interpret recent data, and lead to re-interpretion of some older observations according to newer hypotheses (generated by clinical observations). While much useful information will come from new technologies, there is also a valuable resource of information in data from current and past studies. Subset analysis is extremely helpful as we try to tailor treatment to individual patients. Such analysis is statistically proper provided sufficient numbers of patients are available and provided hypotheses generated in one dataset can be independently confirmed [92]. An important finding from this approach was the large benefit of chemotherapy alone for postmenopausal women with endocrine non-responsive disease [93], which was confirmed by an analysis of patients with ER-poor tumors enrolled in randomized trials unconfounded by tamoxifen [information derived from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overview] [82]. Retrospective, exploratory analysis of the SWOG 8814/Intergroup 0100 trial similarly indicated little additional benefit from CAF (cyclophosphamide, adriamycin and 5-fluorouracil) chemotherapy among patients with high ER levels who also received tamoxifen [78, 94, 95], in contrast to the benefit of CAF in sequence with tamoxifen in patients with low and intermediate levels of ER expression. Similarly, although more intensive chemotherapy (compared with a less intensive 'standard') is reproducibly more effective across trials in cohorts of patients with endocrine non-responsive disease, this effect is almost imperceptible in the cohorts with endocrine responsive disease [81].

Risk categories

Nodal status remains the most important feature for defining risk category. Node-negative status, including sentinel node negative, was accepted overwhelmingly to be the major condition defining low risk [96]. Although nodal micrometastases were prognostically relevant in several studies [31, 32], the Panel considered that neither they nor isolated tumor cells in lymph nodes should influence risk allocation and treatment choice. Involvement of four or more nodes in the axilla by itself indicated high risk, but patients with one to three nodes involved required significant HER2/*neu* overexpression or amplification [58] to be included in the high-risk group, with other patients with one to three nodes included in the intermediate-risk category. The reproducibility of HER2/*neu* testing was recognized as a significant methodological problem [97], but was not directly addressed by the Panel. Fluorescence *in situ* hybridization (FISH) testing was viewed as more reliable if HER2/*neu* was to dictate risk group or treatment choice.

Tumors larger than 2 cm (measured as the invasive component on the pathological specimen), indicated intermediate- or high-risk allocation, even in the absence of other adverse prognostic features. The risk allocation of tumors below 1 cm in size and negative nodes remained controversial. Some but not all Panel members viewed all such patients as having an excellent prognosis regardless of any additional feature (i.e. despite high-grade histology or the absence of steroid hormone receptor expression) [98]. Recent observations indicate that treatment choice for patients with very small tumors (but not including microinvasive disease) should be based upon endocrine responsiveness [99].

While tumor (histological or nuclear) grade was accepted as useful for risk allocation, quantitative Ki67 expression was not. Other tumor features (Table 1) were not viewed by the panelists as sufficiently established to guide responsiveness or prognosis.

Gene expression profiling studies of several types were reviewed (Table 1). The Panel overwhelmingly endorsed the need for further prospective studies of gene profiling both for prognostic estimation, and especially to aid treatment choice. Such trials are being discussed and hopefully will soon be activated [33, 100].

The Panel modified classification of risk, defining three categories: low-, intermediate- and high-risk groups (Table 2). Risk is a continuum, so distinction between risk categories is inevitably arbitrary and indeed less important now that endocrine responsiveness is the primary consideration in treatment choice. The new risk groups departed from the traditional node-positive/node-negative boundary, by including some patients with node-negative, low-grade disease but with features conferring a worse prognosis and patients with one to three involved axillary lymph nodes but no other adverse features in an intermediate-risk group (Table 2).

The Panel added two features not previously accepted as sufficiently reliable to define risk category. The first was overexpression or amplification of the HER2/*neu* gene. Despite issues related to reproducibility of immunohistochemistry staining or FISH testing for HER2/*neu*, it was felt that HER2/*neu* status should be regarded as useful for patient care, with overexpression indicating a worsened prognosis [101]. Overexpressed or amplified HER2/*neu* may also have predictive value. It may indicate a lower probability of response to tamoxifen [21] and perhaps suggest treatment with taxanes or anthracyclines [102], rather than CMF (cyclophosphamide, methotrexate and 5-fluorouracil).

The second new adverse prognostic feature was peritumoral vessel invasion [103–105], especially lymphovascular invasion

Table 2. Definition of risk categories for patients with operated breast cancer

Risk category	
Low risk[a]	*Node negative* AND *all* of the following features:
	pT ≤2 cm, AND
	Grade 1,[b] AND
	Absence of peritumoral vascular invasion,[c] AND
	HER2/*neu* gene neither overexpressed nor amplified,[d] AND
	Age ≥35 years
Intermediate risk[e]	*Node negative* AND *at least one* of the following features:
	pT >2 cm, OR
	Grade 2–3,[b] OR
	Presence of peritumoral vascular invasion,[c] OR
	HER2/*neu* gene overexpressed or amplified,[d] OR
	Age <35 years
	Node positive (1–3 involved nodes) AND
	HER2/*neu* gene neither overexpressed nor amplified[4]
High risk	*Node positive (1–3 involved nodes)* AND
	HER2/*neu* gene overexpressed or amplified[4]
	Node positive (4 or more involved nodes)

[a]Some Panel members view pT1a and pT1b (i.e. pT <1 cm) tumors with node-negative disease as representing low risk even if higher grade and/or younger age.
[b]Histologic and/or nuclear grade.
[c]Peritumoral vascular invasion was considered controversial as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease.
[d]HER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or fluorescence *in situ* hybridization analysis.
[e]Note that the intermediate-risk category includes both node-negative and node-positive 1–3 disease.
pT, pathological tumor size (i.e. size of the invasive component).

Table 3. Choice of treatment modalities 2005 (see text)

Risk category[a]	Endocrine responsive[b]	Endocrine response uncertain[b,c]	Endocrine non-responsive[b]
Low risk	ET Nil[d]	ET Nil[d]	Not applicable
Intermediate risk	ET alone, or CT → ET (CT + ET)[e]	CT → ET (CT + ET)[e]	CT
High risk	CT → ET (CT + ET)[e]	CT → ET (CT + ET)[e]	CT

[a]See Table 2 for definitions of risk categories.
[b]Responsiveness to endocrine therapies is defined in the text.
[c]High levels of urokinase-type plasminogen activator (uPA) and its inhibitor, plasminogen activator inhibitor type 1 (PAI-1) as measured on tissue extracts using ELISA, are associated with increased uncertainty of endocrine responsiveness (Table 1).
[d]Indicates alternative treatment option in case of medical contraindications, preference of patient or of physician.
[e]Clinical trial evidence suggests that chemotherapy and tamoxifen should be delivered sequentially but no such data exist for aromatase inhibitors or ovarian function suppression/ablation. Hence, the option to deliver concurrent chemotherapy and some forms of endocrine therapy must be included. Specifically, concurrent GnRH analog given with chemotherapy for premenopausal women is acceptable [111, 112].
ET, endocrine therapy; Nil, no adjuvant systemic therapy; CT, chemotherapy.

[106]. This proved somewhat controversial, but was accepted by the majority of panelists for patients with node-negative disease [107]. Its value in patients with one or few positive axillary lymph nodes was considered uncertain, and insufficient at the present time to influence the hierarchical risk allocation (e.g. a patient with one positive axillary node, no HER2/*neu* overexpression should remain in the intermediate-risk category despite peritumoral vascular invasion).

Several instruments are available to help estimate the risk of breast cancer-related events and the reduction of these risks by given therapies, as well as their costs in terms of side-effects [108, 109]. *Adjuvant! On line* was independently validated by Olivotto et al. [110] and provides simplified (average) estimates for various clinical scenarios allowing graphical presentation of risks and benefits during consultations. The appeal of these instruments lies in their simplified and averaged format, but this is also their major drawback.

The historical evolution of thinking about risk and responsiveness may be summarized as follows: in 2001 multiple categories of risk were based upon nodal status (three risk categories for node-negative and a fourth for the node-positive group); 2003 added endocrine responsiveness to define both risk and treatment choice leading to only two categories of risk for node-negative disease plus one for node-positive; in 2005 endocrine responsiveness is removed from determination of risk since it is the primary factor determining treatment choice (Table 3). The 2005 edition defines three risk categories including a group merging higher risk node-negative disease and lower risk node-positive disease into an intermediate-risk group 'across nodal status'.

Panel recommendations and guidelines

This section and Tables 3 and 4 summarize the recommendations and guidelines for post-operative adjuvant systemic therapies of early breast cancer as updated by the International Consensus Panel during the St Gallen Conference, 2005. The Panel emphasized that these guidelines are based on evidence from clinical trials demonstrating that various adjuvant therapies can reduce the risk of relapse and increase survival duration, and include expert interpretation of the implications of this evidence

Table 4. Adjuvant systemic treatment regimens for patients with operable breast cancer[a]

Risk group	Treatment according to responsiveness to endocrine therapies[b]				
	Endocrine responsive		Endocrine response uncertain		Endocrine non-responsive
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Premenopausal or postmenopausal
Low risk	Tam or Nil[c] or GnRHa[c]	Tam or AI or Nil[c]	Tam or Nil[c] or GnRH analog[c]	Tam or AI or Nil[c]	Not applicable
Intermediate risk[d]	Tam (± OFS)[e] (± CT[f]), or CT[f] → Tam[e] (±OFS), or Tam alone, or OFS[g]	Tam, or AI, or CT[f] → Tam,[e] or CT[f] → AI Indication for switch to an AI after Tam: exemestane or anastrozole after 2–3 years, and letrozole after 5 years.	CT[f] → Tam[e] (± OFS), or Tam[e] ± OFS (± CT[f]), or CT[f] → (AI + OFS)[c] OFS[g]	CT[f] → AI; or CT[f] → Tam[e] Indication for switch to an AI after Tam: exemestane or anastrozole after 2–3 years, and letrozole after 5 years.	CT Regimens: AC[d], CMF[d]; AC or A → CMF; FEC (day 1 every 21 days); (Taxane-containing regimens: AC or A → paclitaxel, FEC_{100} → docetaxel, TAC)
High risk	CT[f] → Tam,[e] or CT[f] → Tam[e] + OFS, or CT[f] → (AI + OFS)[c]	CT[f] → Tam,[e] or CT[f] → AI Indication for switch to an AI after Tam: Exemestane or anastrozole after 2–3 years, and letrozole after 5 years.	CT[f] → Tam,[e] or CT[f] → Tam[e] + OFS, or CT[f] → (AI + OFS)[c]	CT[f] → AI; or CT[f] → Tam[e] Indication for switch to an AI after Tam: exemestane or anastrozole after 2–3 years, and letrozole after 5 years.	CT Regimens: AC or A → CMF; CEF or CAF (days 1 & 8 every 28 days); FEC (day 1 every 21 days); Taxane-containing regimens: AC or A → paclitaxel, FEC_{100} → docetaxel, TAC; (Dose dense regimen)

This table does not include information on the adjuvant treatment with trastuzumab of patients with overexpressed or amplified HER2/*neu* breast cancer. Such treatment should be discussed with these patients based upon information from trials presented at the ASCO meeting (May 2005; see footnote to Table 1), and according to availability of trastuzumab for use in the adjuvant setting.

Parentheses indicate questions pending answers from ongoing clinical studies.

[a]See Table 1 for discussions concerning surgery, radiation therapy, preoperative systemic therapy, biological therapies, and specific chemotherapy regimens.

[b]See text for definitions of responsiveness to endocrine therapies.

[c]Indicates alternative treatment option in case of medical contraindications, preference of patient or of physician.

[d]Some panelists recommended that all patients with node-positive disease (irrespective of number of positive nodes) should be treated according to the guidelines for high-risk patients, and that AC and CMF should be eliminated from the list of acceptable chemotherapy regimens.

[e]Patients receiving chemotherapy should not start tamoxifen until the completion of chemotherapy.

[f]The threshold for considering addition of chemotherapy to endocrine therapies may depend on the degree of confidence in endocrine responsiveness. Considerations about a low relative risk, age, toxic effects, socioeconomic implications and information on the patient's preference might justify the use of endocrine therapy alone.

[g]If ovarian function suppression is considered, adding tamoxifen may improve outcome at least after chemotherapy. The use of GnRH analog alone was shown to be as effective as chemotherapy and may be taken as an adjuvant treatment option in case tamoxifen is not indicated or not desired.

Tam, tamoxifen; AI, aromatase inhibitor (anastrozole, exemestane, letrozole); CT, chemotherapy (A, anthracycline: either adriamycin or epirubicin; epirubicin mentioned also as E in CEF and FEC regimens); GnRH, gonadotropin releasing hormone (research was conducted using goserelin); OFS, ovarian function suppression or ablation; AC, doxorubicin or epirubicin plus cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; FEC_{100}, 5-fluorouracil, epirubicin 100 mg/m^2 and cyclophosphamide; TAC, docetaxel, doxorubicin, cyclophosphamide; CAF, cyclophosphamide, adriamycin and 5-fluorouracil.

for clinical decision making. Clinical trial evidence applies only on average for a patient population. Selection of treatment for an individual typically involves attempts to relate clinical trial findings to specific subgroups, despite the uncertainties inherent in this step.

Patient preferences will frequently influence treatment choice. A thorough discussion of the potential benefits and risks of each therapeutic option is required for each patient. Therefore, these recommendations are not intended as prescriptive for all patients, since circumstances, attitudes toward treatment and availability of resources may vary both among individuals and across health care systems in different parts of the world.

Emerging evidence on postoperative radiation therapy, preoperative systemic therapy, biological therapies, choice, timing and duration of endocrine treatments and chemotherapy regimen are also described within sections of Table 1.

Systemic treatment regimens

Choice of modalities

Treatment allocation follows considerations related to endocrine responsiveness, which are summarized in Table 3. Patients with tumors that express some level of steroid hormone receptors but with characteristics indicating a potential clinically relevant (slight to substantial) benefit from adding chemotherapy to endocrine therapy were defined as having an uncertain degree of endocrine responsiveness. While such patients should receive endocrine therapy, adding four to six courses of chemotherapy to the adjuvant program was viewed as appropriate. The endocrine components of these therapies should be tailored according to menopausal status.

Low-risk group. In the low-risk category there are by definition no endocrine non-responsive cancers. Patients with endocrine responsive low-risk disease should be offered an endocrine treatment according to menopausal status (Table 3). If endocrine treatment is contra-indicated (e.g. known intolerance, co-morbid condition) or rejected, the alternative of no adjuvant systemic treatment is a reasonable option.

Intermediate-risk group. Intermediate-risk (Table 3) includes patients with endocrine responsive disease for whom endocrine therapy alone is reasonable, as well as patients with endocrine non-responsive disease for whom chemotherapy alone is indicated. Between these extremes, some patients with endocrine responsive disease or disease of uncertain endocrine responsiveness should receive chemotherapy in addition to endocrine treatment. Experimental and clinical experience has shown that tamoxifen, and probably other selective estrogen receptor modulators (e.g. toremifene), should not be administered concurrently with chemotherapy, especially for patients in whom the disease is of uncertain endocrine responsiveness [78, 113]. It is not known whether concurrent use of chemotherapy and other types of endocrine therapies (e.g. GnRH analog for premenopausal patients) should be similarly avoided, though concurrent treatment works well in advanced disease [111] and in the preoperative treatment setting [112].

High-risk group. Most patients in the high-risk group (Table 3) are likely to receive chemotherapy unless it is contraindicated (owing to a co-morbid condition) or rejected by patient preference. Elderly patients at high risk of relapse and without significant co-morbidity should be offered chemotherapy. EBCTCG Overview analyses for the ER-poor cohort in trials not confounded by tamoxifen show that the benefits of adjuvant chemotherapy are substantial and unrelated to age in such patients. Elderly patients with co-morbidities, but with a sufficiently long life expectancy, require difficult individualized decisions about adjuvant systemic therapy outside clinical trials.

Endocrine therapies for premenopausal women

Published EBCTCG Overview results indicated a beneficial effect of tamoxifen [114] and of ovarian ablation [115], the latter only in trials without chemotherapy [116]. Ovarian ablation and tamoxifen yielded results similar to those obtained with chemotherapy, while the need for both modalities in women with endocrine responsive disease remains unclear [117].

The 2005 Panel again viewed tamoxifen as a standard adjuvant treatment for premenopausal women with endocrine responsive disease who have an indication for endocrine therapy alone. Ovarian function suppression (OFS) was accepted as an alternative where tamoxifen was contraindicated [118]. While admitting the lack of conclusive data favoring the combination of tamoxifen plus ovarian function suppression, this was accepted as reasonable for very young patients, especially in intermediate- and high-risk groups, and for premenopausal patients of any age at high risk, especially if chemotherapy did not induce OFS. The lack of evidence on the combination of OFS and tamoxifen in patients with intermediate risk and those for whom endocrine therapy alone is prescribed emphasizes the strategic importance of the ongoing trials such as SOFT and TEXT [75]. The Panel was reluctant to recommend the use of aromatase inhibitors plus GnRH analog for premenopausal patients outside clinical trials, although the majority accepted the combination as an option for women with contraindications to adjuvant tamoxifen especially for those with node-positive disease. Tamoxifen should be avoided in pregnancy owing to its teratogencity [119].

Optimal duration of ovarian function suppression is unknown. Patients with tumors overexpressing HER2/*neu* [120] may benefit if the entire period of tamoxifen were covered with a GnRH analog.

Most panelists agreed that tamoxifen should be given sequentially after adjuvant chemotherapy, but timing of OFS in relation to chemotherapy was less clearly defined. Sequential use of any indicated chemotherapy before OFS allows assessment of chemotherapy-induced amenorrhea [121].

Patients who received adjuvant tamoxifen when they were premenopausal for node positive, endocrine responsive disease, might consider later continuation of the adjuvant endocrine treatment with letrozole if they become postmenopausal in the

interim. Almost 14% of the patients in the MA-17 trial were premenopausal at diagnosis and postmenopausal before randomization [122].

Endocrine therapies for postmenopausal women

Several trials comparing aromatase inhibitors either versus standard tamoxifen or versus placebo after completion of about 5 years of tamoxifen have reported results during the past 2 years. The ATAC trial results indicated that 5 years of anastrozole increased disease-free though not overall survival compared with tamoxifen [66]. Joint, muscle and bone pain, especially bone fractures, were more frequent with anastrozole, while gynecological and vascular events were more frequent with tamoxifen. In the BIG 1-98 trial, letrozole was shown to improve disease-free survival, especially systemic disease-free survival [67], as compared with tamoxifen. Cardio- and cerebro-vascular events, as well as bone fractures, were more frequent with letrozole, while gynecological and venous thromboembolic complications were more frequent with tamoxifen.

Five trials have examined a switch to an aromatase inhibitor after 2–3 years of adjuvant tamoxifen compared with continuing tamoxifen alone to complete 5 years. The first trial (380 patients) tested low-dose aminogluthethimide and resulted in comparable event-free survival, but longer overall survival [123]. In an Italian trial (426 patients), switch to anastrozole after 2 years of tamoxifen yielded a significant reduction in recurrences [124]. A joint analysis combined an Austrian and a German trial (total of 3123 patients) of anastrozole treatment after 2 years of tamoxifen. The group treated with anastrozole had significantly improved relapse-free survival compared with continuing on tamoxifen, regardless of nodal status [69]. IES, the largest such trial (4742 patients), tested switch to the aromatase inhibitor exemestane after 2–3 years of tamoxifen. There was a significant improvement of disease-free survival, but not survival within the first 30 months of follow-up [68]. The MA-17 trial compared letrozole with placebo after completion of about 5 years of tamoxifen in 5157 women. Letrozole improved disease-free and overall survival in patients with node-positive disease at diagnosis. Patients with node-negative disease at diagnosis experienced improved disease-free but not overall survival compared with placebo [122].

The ASCO Technology Assessment report recently recommended that 'optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer should include an aromatase inhibitor either as initial therapy or after treatment with tamoxifen. Of course, women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options' [72]. Is tamoxifen alone still an acceptable therapy? Cost and side-effects are important issues when choosing a treatment for an individual patient. Adjuvant tamoxifen has a long-lasting ('carry-over') benefit well beyond 5 years after its cessation, while no information is available on similar long-term follow up of patients after aromatase inhibitor therapy. Treatment with aromatase inhibitors compared with tamoxifen is associated with a decreased risk of endometrial cancer and thromboembolic events, but with increased cardiovascular events as well as bone fractures, muscle and osteoarticular pain. Knowledge of long-term side-effects of aromatase inhibitors is much less extensive than that for tamoxifen, an issue of concern for several panelists.

In summary, recent trials support several options for postmenopausal women who require endocrine therapy, while lacking evidence to choose between them: (i) an aromatase inhibitor (anastrozole, letrozole) alone for 5 years; (ii) tamoxifen for 2–3 years followed by an aromatase inhibitor (exemestane, anastrozole) to complete 5 years of therapy; or (iii) switch to an aromatase inhibitor (letrozole) after completing 5 years of tamoxifen. (iv) Finally, selected patients at low risk or with comorbid musculo-skeletal or cardiovascular risk factors may be considered suitable for tamoxifen alone, and this may be the only option available on economic grounds in many cases [125, 126].

An additional area of uncertainty was whether adjuvant chemotherapy should be given concurrently with aromatase inhibitors. The majority of the panelists supported sequential use, but data directly addressing this question are lacking.

Chemotherapy regimens

The Panel recognized several types and levels of chemotherapy regimens, but acknowledged the possibility that the higher the degree of endocrine responsiveness, the lower the likely benefit from adding chemotherapy. For patients with endocrine responsive high-risk disease, chemotherapy in addition to endocrine therapy was considered indicated by most panelists. In such cases, however, the more intensive regimens (i.e. adding taxanes to the regimen or using a dose-dense schedule) may not be more effective than 'basic', once every 3 weeks anthracycline-based regimens like AC (doxorubicin or epirubicin plus cyclophosphamide), FEC_{100} (5-fluorouracil, epirubicin 100 mg/m^2 and cyclophosphamide) or CAF (Table 1). The degree of perceived benefit led to the various categories of chemotherapy displayed in Table 4.

Recent references describe current use of chemotherapy in clinical practice. Less intensive regimens like AC or classical CMF [127, 128] are typically used for node-negative disease, while more intensive regimens such as AC or A followed by CMF [129], Canadian CEF [130], the CAF regimen [131, 132], dose-dense cyclophosphamide, doxorubicin and paclitaxel [133], FEC_{100} followed by docetaxel [134], tailored FEC [135], FEC_{100} [136] and TAC (docetaxel, doxorubicin, cyclophosphamide) [137] are more frequently offered to patients with node-positive disease. These have been shown in comparative trials to yield superior results, though at the cost of greater complexity, cost or toxicity.

For patients with endocrine responsive disease and an indication for chemotherapy, treatment with four courses of AC was considered to be appropriate. Most panelists did not support taxane-containing treatments in this population regardless of their nodal status.

The Panel favored anthracycline-containing regimens for patients with endocrine non-responsive disease and intermediate risk. Duration was controversial, with roughly equal Panel support for 4 or 6 months for patients with node-negative disease. Six courses of 3 or 4 weeks duration were clearly favored for

patients at higher range of risk of relapse. Most but not all Panel members agreed that chemotherapy should start within 3–4 weeks from operation for patients with endocrine non-responsive disease [138]. Taxanes were supported for patients at higher risk. Most Panel members did not advocate dose-dense regimens even for patients with endocrine non-responsive disease notwithstanding results from one large study [133]. Panel members could not agree on the use of hematopoietic growth factors to avoid dose reduction or delay.

Radiation therapy

The Panel members reviewed recent changes in practice related to the developments described in Table 1. Radiation therapy, whether after breast conservation or mastectomy, should follow chemotherapy. Concurrent chemotherapy and radiation therapy might be feasible with CMF, perhaps requiring alteration to the schedule or dose of radiation [139, 140]. Concurrent radiation with anthracycline-based regimes or taxanes is not recommended since it increases the risk of symptomatic radiation-induced damage to normal tissue. Tamoxifen and radiotherapy can be given concurrently without significant altered efficacy or increased toxicity [141, 142].

Radiation therapy may not be necessary after conservative surgery in selected elderly patients (over 70 years) with small endocrine responsive cancer whose tumor excision was complete and who receive tamoxifen, although long-term follow up is not yet available [143, 144]. Thus, for example, an 80-year-old patient with significant co-morbid conditions and a small endocrine responsive breast cancer, endocrine therapy alone following proper local tumor excision is appropriate. However, for a healthy 70 year old patient (with life expectancy that might exceed 15 years), radiation therapy to the conserved breast might be preferred.

Radiotherapy variations

A boost may be particularly useful in premenopausal patients [145]. Accelerated partial breast irradiation (APBI) lacks data from phase III trials. Outside trials, the Panel recommended that APBI should be limited to defined patient groups (e.g. older age, low or intermediate risk, negative margins) with informed consent on lack of data on long-term outcome [55].

Although shorter radiotherapy fractionation schemes are popular due to logistical and patient convenience [146], data are lacking on long-term efficacy and toxicity.

Indications for radiation therapy after mastectomy are unchanged from previous St Gallen Meeting highlights [1], although computed tomography scan-based simulation, especially for left-sided cancers, may ensure that the heart is not included in the radiation fields [1, 147, 148].

Specific aspects of treatments

Patient preferences and quality of life considerations

Quality of life during treatment is important, but not the dominant factor for patients with operable breast cancer since the adverse effects of treatments are transient [149, 150]. Patients' preferences assessed *post hoc* were found to support this attitude [151, 152]. Long-term effects may be important. Special considerations may apply to underserved minority groups, younger women, elderly women, those in difficult relationships or who are rendered prematurely menopausal by adjuvant chemotherapy [153]. Endocrine-related symptoms usually worsened initially and recovered partially during 2 years [1].

Commentary

The Panel tried to apply answers derived from randomized clinical trials. Trials are usually designed to test the value of one or more treatments in a defined group, but tailoring treatment for an individual patient requires an additional step. Extrapolation of information from clinical trials, focusing upon patterns of response of different subpopulations, yielded important answers for several groups, especially contrasting those with endocrine responsive and endocrine non-responsive disease. Panel members were convinced that increased participation in clinical trials would increase knowledge about the disease and improve patient care [154]. International trial cooperation should be focused on questions relevant for patient care and biological principles, rather than regulatory requirements for the marketing of a new drug. Substudies focusing on safety, quality of life and subjective side-effects, and on economic and personal costs should be routinely incorporated in cooperative group trials.

Definition of appropriate niches for tailored research is perhaps the key achievement of this St Gallen Conference. Such an approach brings clinical research closer to the individual patient. Women with breast cancer deserve no less.

Appendix

Members of the Panel are listed below. All had a significant input to the discussion and manuscript. Professor Alan S. Coates was unable to attend the conference, but had a major impact on the planning of the meeting and on the final manuscript. Professor Martine Piccart also was unable to attend, but maintained a significant input and was represented by a senior member of her institution.

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Acknowledgements

The authors thank the Participants of the 9th International Conference on Primary Therapy of Early Breast Cancer for many useful remarks. They acknowledge substantial contribution of Dr. Marco Colleoni, Dr. Giuseppe Curigliano, Dr. Eric Winer, and Mrs. Shari Gelber. They also thank Professor Umberto Veronesi, Dr. Anne Hamilton, Dr. Franco Nolè, and Dr. Filippo de Braud for their thoughtful remarks. Partial support was provided by grant number CA-75362 from the United States National Cancer Institute. This work is dedicated to the memories of Joan Coates, Harold Frankel and Carlo Stucchi.

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