special article

Annals of Oncology 20: 1319–1329, 2009
doi:10.1093/annonc/mdp322
Published online 17 June 2009

Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009

A. Goldhirsch[1,2*], J. N. Ingle[3], R. D. Gelber[4], A. S. Coates[5], B. Thürlimann[6], H.-J. Senn[7] & Panel members[†]

[1]*International Breast Cancer Study Group, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland;* [2]*European Institute of Oncology, Milan, Italy;* [3]*Breast Cancer Research Program, Mayo Clinic Cancer Center, Rochester, MN, USA;* [4]*Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA;* [5]*International Breast Cancer Study Group, School of Public Health, University of Sydney, Sydney, New South Wales, Australia;* [6]*Breast Center, Kantonsspital, St Gallen, Switzerland and* [7]*Tumor and Breast Center ZeTuP, St Gallen, Switzerland*

Received 12 May 2009; accepted 12 May 2009

The 11th St Gallen (Switzerland) expert consensus meeting on the primary treatment of early breast cancer in March 2009 maintained an emphasis on targeting adjuvant systemic therapies according to subgroups defined by predictive markers. Any positive level of estrogen receptor (ER) expression is considered sufficient to justify the use of endocrine adjuvant therapy in almost all patients. Overexpression or amplification of HER2 by standard criteria is an indication for anti-HER2 therapy for all but the very lowest risk invasive tumours. The corollary is that ER and HER2 must be reliably and accurately measured. Indications for cytotoxic adjuvant therapy were refined, acknowledging the role of risk factors with the caveat that risk *per se* is not a target. Proliferation markers, including those identified in multigene array analyses, were recognised as important in this regard. The **threshold for indication** of each systemic treatment modality thus depends on different criteria which have been separately listed to clarify the therapeutic decision-making algorithm.

Key words: early breast cancer, St Gallen Consensus, therapies

introduction

The 11th St Gallen conference held in March 2009, which was attended by >4800 participants from 101 countries, incorporated incremental information but proposed a radically different treatment selection algorithm for the management of early breast cancer. The more we know about the tumour types underlying the heterogeneity of the disease, the greater the opportunity to refine treatment choice. It was recognised that clinical trials are very useful for identifying effective treatments, but fall short of defining the optimal treatment of individual patients. For example, local control is crucial to improve survival on average and especially in patients at low risk, but is overwhelmed by the risk of distant metastases in patients at high risk. Similarly, while cytotoxic chemotherapy improves outcome on average among patients with endocrine-responsive disease receiving endocrine therapy, subgroups can be defined by conventional pathology and by multigene analyses in which little or no additional benefit accrues from chemotherapy. Judgements must be made in the care of individual patients of whether to use or withhold each treatment modality. It is the intention of this report to assist in the rational application of evolving knowledge in reaching these judgements.

St Gallen 2009: news and progress

New information was presented in the areas of genetics, tumour biology, experimental therapeutics, surgery, radiation oncology, and adjuvant systemic therapy. Some of this new information is summarised in Table 1. In the light of this information, a Panel of 43 experts from around the world (see Panel members listed in the appendix) again considered specific questions to arrive at recommended principles for the selection of therapies in early breast cancer.

specific considerations for treatment choice

In distilling patient and tumour features to reach patient treatment decisions, the Panel has adopted a fundamentally different approach from that used in previous consensus reports [71, 72]. Clinical decisions in systemic adjuvant therapy

Correspondence to: Prof. A. Goldhirsch, International Breast Cancer Study Group, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. Tel: +39-02-57489439; Fax: +39-02-94379273; E-mail: aron.goldhirsch@ibcsg.org

[†]See appendix for members of the Panel.

Table 1. Recent research findings presented at the 11th 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 changes in breast cancer incidence	Decrease in breast cancer incidence in some countries is a result of recent changes in the use of hormone replacement therapy in postmenopausal women [1]. Thus, the increased incidence that might be attributed to the use of estrogen and progestin preparations (induced carcinogenesis? induced progression of subclinical breast cancer?) is to be considered at least partly reversible [2].
Genetic predisposition	The well-established high-penetrance *BRCA1* and *BRCA2* genes continue to demonstrate multiple mutations (roughly 2000 each) which make testing technically difficult. Founder mutations in *BRCA* in some geographical areas make the detection of mutations easier. Genome-wide association studies define an increased number of genes which carry a smaller increase in risk for breast cancer, but are relatively common in the population. These genes are of little value in counselling individuals, though they are of biological interest and can potentially identify women at slightly increased risk which might justify selective screening policies as public health resources are limited [3]. *BRCA1* mutations are associated with triple-negative phenotype, which require clinical evaluation of novel therapeutic approaches including poly (ADP-ribose) polymerase inhibitors and DNA-damaging agents [4, 5].
Selective estrogen receptor modulator (SERM) chemoprevention	Five-year results of lasofoxifene [6] involving >8000 postmenopausal women with osteoporosis were presented. Two doses of lasofoxifene were studied: the higher dose (0.5 mg daily) proving more effective with a significantly reduced incidence of estrogen receptor-positive breast cancer (the primary study end point), overall breast cancer, vertebral fracture, nonvertebral fracture, stroke, and major coronary heart disease [7]. These latter features suggest an improved therapeutic ratio compared with tamoxifen prevention. In particular, there was no increase in endometrial cancer, though there was an increased incidence of venous thromboembolism, similar to that seen with tamoxifen.
Whole-genome studies	A cistrome is a concept incorporating the complete set of interacting related factors across the entire genome. Advancing technology allowing us to take a more comprehensive overview of events, both genetic and epigenetic, which influence particular pathways, such as those involved in steroid receptors. Within the steroid receptor cistrome, these studies have identified FOXA1 as an important component [8, 9]. In experimental models, tamoxifen effectiveness requires HER2 suppression which is in turn regulated by the balance between PAX2 and AIB-1 [10].
Stem cells	Further support for the stem-cell hypothesis in breast cancer arises in preclinical studies in which a subpopulation of cells identified by aldefluor are uniquely capable of transplanting tumours in animal models and appear to have the characteristics of self-renewing stem cells [11]. Detection of such cells in clinical tissue microarrays identifies patients with a relatively poor prognosis [12].
microRNAs	MicroRNAs, particularly miR-335 and miR-206, affect metastases by blocking cell migration while miR-126 blocks cell proliferation. These microRNAs may be lost in highly metastatic cancers and this is associated with an oligogenic signature indicative of poor prognosis. The predictive potential is being investigated. Reintroduction of specific microRNAs has proved to be effective in suppressing metastases in animal models [13].
Networks in cellular systems	Evolution of cell survival mechanisms has required redundant network interactions rather than simple linear systems. This poses a more complex problem when attacking a cancer cell. Success is more likely to occur if two or more perturbations can be introduced, preferably at crucial early parts of the network [14]. An example is the epidermal growth factor receptor (EGFR) family, including HER2.
Circulating tumour cells	Circulating tumour cells have been increasingly studied as poor prognosis markers (though they are not yet ready for routine use). New technology allows the evaluation of phenotypic markers in individual circulating tumour cells and has demonstrated that these may differ from the gross characteristics of the parent tumour [15]. Thus, for example, HER2 overexpression in circulating tumour cells might justify targeted therapy even in the absence of conventional HER2 positivity of the primary tumour. This strategy is undergoing clinical investigation [16]. Current studies are examining the possibility that some circulating tumour cells may represent breast cancer stem cells.

Table 1. (*Continued*)

Field or treatment	Status of research/implications for patient care
Angiogenesis	The benefits of current antiangiogenic treatment in metastatic disease are transitory. Drugs that target angiogenesis might, in the long run, induce angiogenesis as a rebound phenomenon and have been demonstrated in preclinical studies to induce tumour progression and metastases [17–19]. A possible mechanism for this tumour progression may be the release of increasing numbers of circulating endothelial cells following some types of chemotherapy. Importantly, this effect is not seen with metronomic chemotherapy [20]. Long-term treatment with antiangiogenic drugs together with metronomic chemotherapy was associated with dramatic and profound reduction of vascular endothelial growth factor (VEGF) and substantial clinical response in metastatic breast cancer [21]. The type of cancer vascularisation and the extent of VEGF targeting might be a crucial strategic issue in the treatment of malignancies [22]. Antiangiogenic treatments are under investigation in the adjuvant setting (but are not recommended for routine use outside clinical trials).
New opportunities for endocrine therapy	The mechanism of estrogen effect in cells resistant to estrogen deprivation is apoptosis, which is mediated by increased calcium influx [23]. Apoptosis is increased by G protein-coupled receptor 30 (GPR30). Which in turn can be induced by its agonist known as G-1 [24]. Antiangiogenic agents enhance the tamoxifen effect [25]. Cells which are resistant to this estrogen effect have high glutathione, and depletion of glutathione using buthionine sulphoximine (BSO) will restore full estrogen sensitivity [26].
Resistance to treatment by crosstalk	Further studies of the crosstalk between estrogen receptor and HER2 pathways show that each can act as resistance mechanism for the other. This logically led to studies combining antiestrogenic therapy with agents targeting receptors of the EGFR family. Examples included the combination of gefitinib with either tamoxifen or anastrozole and the combination of lapatinib with letrozole [27, 28].
Pharmacogenetics	The majority but not all studies have associated abnormalities of *CYP2D6* on genetic grounds or as a result of certain antidepressant drugs with poorer outcome among patients treated with tamoxifen [29]. It has been indicated that increased tamoxifen dosage may overcome less effective metabolic conversion to endoxifen in some of these patients [30].
Novel imaging	Functional imaging using targets of the hormone receptor [31] and HER2 is under development [32].
Multigene assays	Multigene assays are widely proposed to add to the prognostic information available from classical pathological markers and in some circumstances have been shown to identify groups which do or do not benefit from the addition of chemotherapy to endocrine adjuvant therapy. Surveys of clinical practice indicate that the information obtained from genetic assays lead to change in treatment decisions in ~30% of cases, mainly to avoid chemotherapy [33]. Trials to further validate this application are currently underway [34, 35]. No data are available regarding the applicability of these assays for patients with estrogen receptor-negative disease. Studies comparing the various genetic profiles indicate commonality in sampling groups of genes representing activation of the steroid hormone receptor pathway, the epidermal growth factor system, and markers of proliferation. While the former may be useful for specific treatment selection, the dominant prognostic information seems to reside within the proliferative marker set [36, 37].
Integrating molecular and other pathological features	Clinical, pathological, and molecular data may be integrated in more robust prognostic and predictive models. The best pathology and the most accurate assessment of established markers are key features for a choice of useful treatment, with appropriate integration of molecular assays [37] which add power to the model [38].
Surgery	Results of sentinel node biopsy after neoadjuvant chemotherapy are reliable as described in a meta-analysis [39] and supported by experience at a single institution [40]. The definition of adequate surgical margins remains controversial with a majority of North American radiation oncologists willing to accept a margin as negative if the tumour does not extend to the inked specimen surface, while surgeons and European radiation oncologists prefer a clearance of 2–5 mm in addition to this [41]. Invasive tumour found at the inked margin is associated with increased ipsilateral breast tumour recurrence [42]. Evidence was presented that a more generous margin was required in ductal carcinoma *in situ* (DCIS), perhaps reflecting the propensity of this disease to discontinuous spread [43]. Lobular carcinoma *in situ* (LCIS) at the margin is not regarded as an indication for reexcision [44]. Studies to investigate the necessity of axillary dissection for patients whose sentinel node biopsy contains only micrometastatic disease (<2 mm) are underway. Meanwhile, experience from a single institution suggests that the rate of axillary recurrence remains <2% at a median follow-up of 39 months [45]. The use of contralateral prophylactic mastectomy is clearly increasing in several series [46] though the rationale remains unclear, and evidence that this procedure improves survival is lacking [47].

Table 1. (*Continued*)

Field or treatment	Status of research/implications for patient care
Radiation therapy	Partial breast irradiation is being studied in several clinical trials but remains experimental. One application might be the treatment of patients who have already received radiation to part of the breast in the course of treatment for a previous lymphoma [48]. Recent studies of postmastectomy radiation therapy have attempted to dissect the average survival ratio of one death prevented for every four local recurrences avoided [49]. In patients at very high risk of relapse, distant metastases predominate and local control is a less critical determinant of survival. Conversely, in low-risk cohorts, the ratio may be more favourable and has been reported to approach one death prevented for each local recurrence avoided [50]. Accelerated partial breast irradiation is being investigated in ongoing trials, but a consensus statement from the American Society for Therapeutic Radiology and Oncology [51] provides guidance on patients who might be considered suitable for this technique outside of a study.
Endocrine therapies	Either tamoxifen or tamoxifen plus ovarian function suppression, both for the duration of 5 years, is acceptable standards for premenopausal women with endocrine-responsive disease [52, 53]. Recent results from trials continue to support the benefit of aromatase inhibitors in postmenopausal women with receptor-positive breast cancer [54, 55], though others have questioned the extent of benefit [56]. Benefit may be particularly marked for women at higher risk of relapse. For the women at very low risk of recurrence, there appears to be little benefit from the use of aromatase inhibitors as compared with tamoxifen during the first 5 years [57]. For such patients, it may be wise to choose the best tolerated agent that maximises adherence and minimises impact on quality of life and health status. The duration of aromatase inhibitor therapy, supported by trial results, is 2–5 years [57].
HER2-targeted therapy	There is some evidence that HER2 positivity carries an adverse prognostic significance even in patients with tumours <1 cm [58], but the relationship to steroid hormone receptor status and adjuvant endocrine or cytotoxic therapies remains unclear in this group [59, 60].
Chemotherapy	There is a lack of specific predictive markers for response to individual chemotherapeutic agents. Many different regimens are used and no clear indications for a particular regimen exist. Low estrogen receptor, HER2 overexpression, and increased proliferation predict response to chemotherapy in general, rather than being agent specific [61].
Neoadjuvant systemic therapy	Preoperative cytotoxic therapy is less effective for tumours with higher levels of estrogen receptor expression [62].
Treatment of triple-negative disease	Triple-negative breast cancer is associated with an improved pathological complete response rate with neoadjuvant chemotherapy [63], but despite this there is an inferior overall survival in comparison to other breast cancer types [64]. New approaches undergoing clinical trial evaluation for treatment of triple-negative disease include new agents such as ixabepilone [65] and DNA-damaging agents such as platinum compounds, anthracyclines, and poly (ADP-ribose) polymerase (PARP) inhibitors [66].
Novel systemic treatments	Early clinical investigations are underway to evaluate several promising compounds including new anti-HER2 therapies, HSP-90 inhibitors, mTor inhibitors, anti-IGF1R mAbs, PI3K inhibitors, and antiangiogenesis drugs [67].
Follow-up after treatment for breast cancer	All the randomized trials on follow-up were conducted before availability of targeted therapies and molecular markers. A revisiting of early diagnosis of metastases to permit earlier application of targeted therapies is warranted. Intensive follow-up does not have clinical relevance. Beyond the randomized trials, new technologies including positron emission tomography scans and the detection of circulating tumour cells require further evaluation [68].
Specific news from trials	**BIG 1-98**: Neither the conventional sequence of tamoxifen followed by letrozole nor the reverse sequence of letrozole followed by tamoxifen proved superior to 5 years of letrozole monotherapy. Early relapses were more frequent among patients commencing treatment with tamoxifen, particularly in those at higher risk for such events. Despite substantial crossover among patients assigned tamoxifen monotherapy, the updated comparison suggested that letrozole monotherapy produced superior survival, though this did not attain conventional significance in the intent-to-treat analysis ($P = 0.08$) [55]. **FinHER update**: Updated results of the HER2-positive component in the FinHER study confirmed the benefit of a 9-week duration treatment with trastuzumab especially if given with docetaxel (at reduced dose). Exploratory analyses suggested that the trastuzumab benefit was particularly seen among patients receiving docetaxel rather than vinorelbine during trastuzumab therapy. A prospective study is comparing this short regimen with a conventional 1-year trastuzumab regimen (SOLD trial) [69]. **HERA**: Updated analyses to 4-years median follow-up confirmed the value of one year of trastuzumab in improving disease-free survival, but the overall survival analysis on an intent-to-treat basis has been complicated by substantial crossover to late use of trastuzumab in the control arm after publication in 2005 of initial study results. The 2-year treatment group remains blinded [70].

Table 2. Thresholds[a] for treatment modalities

Treatment modality	Indication	Comments
Endocrine therapy	Any ER staining[b]	ER negative and PgR positive are probably artefactual [73]
Anti-HER2 therapy	ASCO/CAP HER2 positive [>30% intense and complete staining (IHC) or FISH >2.2+][b]	May use clinical trial definitions
Chemotherapy		
In HER2-positive disease (with anti-HER2 therapy)	Trial evidence for trastuzumab is limited to use with or following chemotherapy[b]	Combined endocrine therapy + anti-HER2 therapy without chemotherapy in strongly ER-positive, HER2-positive is logical but unproven
In triple-negative disease	Most patients[b,c]	No proven alternative; most at elevated risk
In ER-positive, HER2-negative disease (with endocrine therapy)	Variable according to risk[b]	See Table 3

[a]Most factors are continuous but a binary decision needs to be made at some level.
[b]Patients with tumours of <1 cm in size without axillary nodal involvement and without other features indicating increased metastatic potential (e.g. vascular invasion) might not need adjuvant systemic therapy. If the tumour is, however, endocrine responsive, endocrine therapy should be considered.
[c]Medullary carcinoma, apocrine carcinoma, and adenoid cystic carcinoma do not require chemotherapy due to low risk despite being triple negative (provided that, as is usually the case, they have no axillary node involvement and no other signs of increased metastatic risk).
ER, estrogen receptor; PgR, progesterone receptor; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry.

of early breast cancer must address three distinct questions: (i) what justifies the use of endocrine therapy, (ii) what justifies the use of anti-HER2 therapy, and (iii) what justifies the use of chemotherapy. Because these decisions are based on quite separate criteria, the previous attempt to produce a single-risk categorization and a separate therapy recommendation are no longer considered appropriate. The new algorithm is summarised in Table 2. As before, the Panel recognised that adherence to therapeutic guidelines is affected by affordability of certain genetic and imaging tests and the costs of some systemic therapies in various geographic settings.

endocrine therapy

The Panel recommends the inclusion of adjuvant endocrine therapy in almost all patients whose tumours show evidence of endocrine responsiveness, now defined as the presence of any detectable estrogen receptor (ER). It questioned the validity of reports of positive progesterone receptor (PgR) in the absence of ER and suggested that such cases be submitted for further pathological review. Whereas previous categories of highly endocrine responsive and incompletely endocrine responsive are not relevant to the decision to use or withhold endocrine therapy, such consideration remains important for the selection of patients with ER-positive disease to receive chemotherapy.

anti-HER2 therapy

Anti-HER2 therapy is indicated in patients with HER2-positive disease as defined by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines [74]. The Panel noted that the existing trials used a slightly less restrictive definition of HER2 positivity and acknowledged that patients satisfying the inclusion criteria used in the trials might also be considered for anti-HER2 treatment.

chemotherapy

The threshold for use of cytotoxic chemotherapy is the most difficult to define. Patients receiving anti-HER2 therapy conventionally also receive chemotherapy either preceding or concurrent with the anti-HER2 treatment. Although considered logical by some of the Panel members, the use of adjuvant anti-HER2 therapy without chemotherapy remains unsupported by evidence. Chemotherapy is the mainstay of adjuvant treatment of patients with triple-negative disease who are at sufficient risk of relapse to justify its utilisation. Some rare histological types of breast cancer that fall into the category of triple negative and are diagnosed neither with axillary node involvement nor with other signs of increased metastatic potential do not require adjuvant treatment (e.g. medullary, apocrine, and adenoid cystic breast cancers). Patients with small primary tumours (pT1a pN0 and ER negative) might be spared adjuvant systemic therapy.

The threshold for recommending chemotherapy for patients with ER-positive, HER2-negative disease is particularly difficult to define. These patients include a spectrum from those at low risk [75, 76] for whom there is little evidence supporting the addition of chemotherapy to endocrine therapy and to those with high risk disease and limited ER expression where chemotherapy appears clearly justified. Table 3 summarises the

Table 3. Chemoendocrine therapy in patients with ER-positive, HER2-negative disease

	Relative indications for chemoendocrine therapy	Factors not useful for decision	Relative indications for endocrine therapy alone
Clinicopathological features			
ER and PgR	Lower ER and PgR level		Higher ER and PgR level
Histological grade	Grade 3	Grade 2	Grade 1
Proliferation	High[a]	Intermediate[a]	Low[a]
Nodes	Node positive (four or more involved nodes)	Node positive (one to three involved nodes)	Node negative
PVI	Presence of extensive PVI		Absence of extensive PVI
pT size	>5 cm	2.1–5 cm	≤2 cm
Patient preference	Use all available treatments		Avoid chemotherapy-related side-effects
Multigene assays			
Gene signature[b]	High score	Intermediate score	Low score

[a]Conventional measures of proliferation include assessment of Ki67-labelling index (e.g. low, ≤15%; intermediate, 16%–30%; high, >30%) [77] and pathological description of the frequency of mitoses. The reliability of these measures will vary in different geographic settings. First-generation genetic signatures contain genes sampling the ER, HER2, and proliferative pathways [78, 79]. Meta-analysis indicates that much of the prognostic information in these signatures resides in their sampling of proliferative genes [80], but their respective total scores may be the only form in which information is provided at present and could be used in this component of assessment of relative indications for chemotherapy.

[b]The Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers.

ER, estrogen receptor; PgR, progesterone receptor; pT, pathological tumour size (i.e. size of the invasive component); PVI, peritumoral vascular invasion.

characteristics which favour the use of chemotherapy, those that might justify endocrine therapy alone, and those which are not useful for making this decision. Features indicating increased risk of recurrence and thus indirectly supporting the value of adding chemotherapy to endocrine therapy in such patients include lower expression of steroid hormone receptors, grade 3 tumours, high proliferation as measured by conventional or multigene assays, and the risk factors of four or more axillary lymph nodes involved, extensive peritumoral vascular invasion, and tumour size >5 cm. Emerging data presented but not published indicate that the overall scores from multigene assays may identify patients in these high-risk categories who do not gain benefit from the addition of chemotherapy to endocrine therapy. This represents an important area of research that will likely be clarified over the next several years. Patients with high expression of ERs and PgRs (e.g. >50%), grade 1 tumours, low proliferation, negative axillary lymph nodes, no peritumoral vascular invasion, and tumour size ≤2 cm may be considered for endocrine therapy alone. We note that some features individually provide little guidance in reaching a decision to use chemotherapy. In particular, histological grade 2, intermediate scores on multigene assays, tumour size between 2 and 5 cm, and low numbers of involved lymph nodes (one to three) do not provide definitive indications to either give or withhold chemotherapy. However, if all these intermediate criteria are present, it usually tips the balance towards the use of chemotherapy. The Panel considered the available multigene assays in this context and concluded that a validated assay should be taken into account as an adjunct to high-quality pathology phenotyping if doubt about the indication for chemotherapy persists after consideration of other factors. Considerations of availability and cost determine the current usefulness of multigene assays. The Panel noted that patients with pT1a pN0 and ER-positive disease should be offered endocrine therapy alone even if features which usually indicate chemotherapy are present.

endocrine responsiveness

Based on the philosophy of defining categories according to their implications for treatment selection, the previous three categories of endocrine responsiveness have been simplified so that endocrine therapy is considered indicated if any ER staining is present in the tumour. The majority of Panellists were in favour of indicating the percentage of stained cells on pathology reports rather than merely using scores. Staining for hormone receptors of ≥50% of tumour cells was viewed as indicating highly endocrine-responsive tumours.

HER2 positivity

Two technologies are recognised for the determination of HER2 positivity. These have recently been addressed by a joint working party of the ASCO/CAP [74]. Either immunohistochemical analysis showing uniform, intense membrane staining of >30% of the tumour cells or, alternatively, determination of gene amplification by fluorescence *in situ* hybridisation (FISH) (ratio of *HER2* gene

copies to chromosome 17 centromers >2.2) or chromogenic *in situ* hybridisation (CISH) (more than six HER2 signals per nucleus) is sufficient to define HER2 positivity. Although the definitions used in the pivotal trials of trastuzumab were less restrictive [81–84], a substantial minority of the Panellists preferred to use 30% intense and complete staining as a threshold for recommendation of anti-HER2 therapy.

pathological evaluation of characteristics of the disease

In addition to reporting the presence and type of tumour, the Panel considered various additional pathological parameters. Markers of proliferation, and specifically Ki-67-labelling index, were considered important for the determination of prognosis and, importantly, to indicate the potential value of the addition of chemotherapy to patients with receptor-positive disease. Ki-67 specifically was not accepted as the basis for choosing aromatase inhibitors rather than tamoxifen in postmenopausal patients with receptor-positive disease [85] as further validation of findings in this regard was felt to be necessary [86]. Reporting of ER generated considerable discussion. The Panel strongly endorsed the reporting of percentage of stained cells but was evenly divided on whether other scoring methods should also be reported. PgR was considered valuable for prognosis, but less important for predicting response to treatment (e.g. tamoxifen).

The majority of the Panel considered that high grade was a sufficient indication for chemotherapy and that genomic grade could be considered as an adjunct to histological grade if readily available. Gene expression signatures are likely to indicate a prognostically relevant dichotomy (low grade versus high grade), though the implications of this observation for therapy require further study [87, 88]. uPA/PAI-1 was not accepted by a majority of the Panel as a useful prognostic factor.

In an important change from the previous St Gallen conference and after a long debate, the Panel supported the use of a validated multigene-profiling assay, if readily available, as an adjunct to high-quality phenotyping of breast cancer in cases in which the indication for adjuvant chemotherapy remained uncertain.

local and regional treatments

The aspects considered by the Panel included surgical margins, indications for sentinel node biopsy, and the role of prophylactic mastectomy. Re-excision was considered mandatory if invasive cancer or DCIS is present at the inked surgical margin, but is not required for lobular carcinoma *in situ* (LCIS). The Panel was divided about the need for surgical margins greater than ''not on ink'' in DCIS, although no detailed specific recommendation was given beside avoiding the need to insist on a large (e.g. 1 cm) free margin. The use of surgical procedures developed to allow a wide excision with satisfactory results (oncoplastic surgery) was also endorsed. The Panel considered that sentinel node biopsy is the standard of care for patients with a clinically negative axilla and that axillary node dissection could be avoided in all patients with a negative sentinel node and in selected patients with micrometastatic disease or isolated tumour cells in the sentinel node. A trend to increasing use of prophylactic contralateral mastectomy was reported, though it was acknowledged that this procedure was not associated with any proven survival advantage.

Radiation therapy after local excision of DCIS was considered to be standard by the Panel members, though most members considered that it could be avoided in elderly patients and those with low-grade DCIS and clearly negative margins. For patients with invasive cancer, postmastectomy radiation therapy was indicated for those with four or more involved axillary lymph nodes, but indications for its use in patients with one to three nodes were considered more restricted and particularly applicable for young patients and those with other poor prognostic features. The majority of the Panel considered that accelerated whole-breast radiation after conservative surgery was an acceptable option for patients aged ≥60 with cancers with favourable patterns, but that partial breast radiation should still be considered experimental. The Panel considered that endocrine therapy without radiation might be considered in elderly patients with small tumours, clinically node-negative and -positive ERs.

adjuvant systemic therapies

The Panel considered targeted therapies against the steroid hormone receptors and overexpressed HER2 as of prime importance. In patients whose tumours lack these targets or in those at higher risk despite the presence of steroid hormone receptors, the use of chemotherapy requires consideration as set out in Tables 2 and 3.

endocrine therapy for premenopausal patients

The Panel accepted either tamoxifen or tamoxifen plus ovarian function suppression as standard endocrine therapies in this group. Ovarian function suppression alone or ovarian ablation was considered a possibility only in extraordinary circumstances. Aromatase inhibitors alone are contraindicated in premenopausal patients. In case tamoxifen is contraindicated, aromatase inhibitors may be administered to premenopausal women together with ovarian function suppression. Verification of ovarian function suppression to postmenopausal levels is important also in patients under the age of 60 who are receiving aromatase inhibitors.

Pharmacogenetic determination of tamoxifen metabolism status as influenced by *CYP2D6* was not considered ready for routine application in selecting patients for tamoxifen therapy by the majority of the Panellists.

endocrine therapy in postmenopausal patients

A majority of the Panel considered that an aromatase inhibitor should form part of standard endocrine therapy for postmenopausal women with receptor-positive breast cancer, though acknowledging that there were certain patients for whom tamoxifen alone can be considered adequate. There was division about the proper duration of treatment with aromatase inhibitors, though it was pointed out that safety data beyond 5 years are not yet available. The majority of the Panel preferred aromatase inhibitors as up-front endocrine treatment particularly in patients at higher risk of early relapse.

anti-HER2 therapy

Updated results from two of the trastuzumab trials were presented continuing to demonstrate the value of this therapy for patients with HER2-positive disease. The FinHER trial evaluated a short course of trastuzumab, which is currently being compared with a conventional 1-year duration. Meanwhile, the standard duration of trastuzumab therapy remains 1 year. The Panel noted that no results are yet available from the 2-year trastuzumab group in the HERA trial. Interestingly, a majority of the Panel was prepared, for selected women, to contemplate trastuzumab with endocrine therapy but without chemotherapy despite the absence of clinical trial evidence to support this approach. Finally, the limited evidence of increased risk among patients with HER2-positive tumours <1 cm in size without axillary nodal involvement does not allow definitive recommendation regarding anti-HER2 therapy in this group.

adjuvant chemotherapy

Two situations were recognised in which the decision to use adjuvant chemotherapy was relatively clear-cut. First, adjuvant systemic therapy for patients with triple-negative disease is essentially limited to chemotherapy, and most such patients are at sufficient risk to justify this treatment. Secondly, as noted above, chemotherapy is conventionally given with or preceding trastuzumab for patients with HER2-positive invasive breast cancer. The remaining patients—those with ER-positive, HER2-negative disease—are the group in whom decisions about adjuvant chemotherapy are most difficult (Table 3). The Panel recognised that patients whose tumours contained high levels of ER derived less benefit from addition of chemotherapy to endocrine therapy. There was no agreement about the definition of a standard chemotherapy regimen for any disease subset. Taxane-containing regimens were discussed and combinations containing docetaxel and cyclophosphamide as well as dose-dense doxorubicin and cyclophosphamide followed by paclitaxel were viewed as standard therapies among several other regimens.

neoadjuvant systemic therapy

Neoadjuvant systemic therapy was considered justified primarily to enhance the possibility of breast-conserving surgery. If indicated, the majority of the Panel considered that the neoadjuvant chemotherapy regimen should include both a taxane and an anthracycline and (for HER2-positive disease) an anti-HER2 drug. Thus, the choice of a regimen for adjuvant or neoadjuvant chemotherapy might be made using similar criteria. Neoadjuvant endocrine therapy without chemotherapy was considered reasonable for postmenopausal patients with strongly receptor-positive disease. If used, such treatment should be considered for a duration of 5–8 months or until maximum tumour response.

preservation of fertility

Pregnancy after diagnosis of breast cancer has not been shown to negatively impact prognosis. Women should be counselled about options for preserving fertility. The Panel did not consider that any currently available methods for preservation of fertility following chemotherapy were of proven value, though gonadotropin-releasing hormone agonists are used occasionally. These are being tested in an ongoing clinical trial for women with endocrine nonresponsive disease who are receiving alkylating agents. Cryoconservation and retransplantation of ovarian tissue are also experimental.

use of bisphosphonates

Emerging information on bone protection from demineralisation and tumour by bisphosphonates was viewed as interesting, but the Panel did not consider that routine use of bisphosphonates was indicated for women with normal bone health receiving adjuvant endocrine therapy.

male breast cancer

The Panel considered that adjuvant tamoxifen was standard therapy and did not endorse the use of adjuvant aromatase inhibitors in men with breast cancer.

commentary

The present report proposes a new approach to the separate selection of each treatment modality according to its most relevant indications. We look forward to future studies more accurately defining the value of various high-throughput technologies in assessing the level of risk and likelihood of response to specific therapies. Meanwhile, careful application of the presently available therapies described in this report offers great value to women with early breast cancer.

appendix and acknowledgements

Members of the Panel are listed below. All had a significant input to the discussion and manuscript. John Forbes and Stella Kyriakides were unable to attend the Panel session, but provided input for the planning of the meeting and reviewed and approved the manuscript.

Matti Aapro, Clinique de Genolier, 1 Route du Muids, 1245 Genolier, Switzerland; **Kathy S. Albain,** Loyola University Medical Center, Cardinal Bernardin Cancer Center, 2160 S First Avenue, Room 109, Maywood, IL 60153, USA; **Jonas Bergh,** Department of Oncology, Karolinska Institute and University Hospital, 17176 Stockholm, Sweden; **Harold Burstein,** Department of Medical Oncology/Solid Tumor Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA; **Robert Carlson,** Medical Oncology, Stanford University, 875 Blake Wilbur Drive, Stanford, CA 94305-5826, USA; **Monica Castiglione-Gertsch,** MHA ISPM/RGT University of Geneva, Boulevard de la Cluse 55, 1205 Geneva, Switzerland; **Alan S. Coates,** International Breast Cancer Study Group and University of Sydney, Sydney, 40 Cook Road, Centennial Park NSW 2021, Australia; **Marco Colleoni,** Research Unit Medical Senology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy;

Alberto Costa, European School of Oncology, Via del Bollo 4, 20123 Milan, Italy; **Jack Cuzick,** Cancer Research, UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary College, University of London, Charterhouse Square, London EC1M 6BQ, UK; **Nancy Davidson,** Director, University of Pittsburgh Cancer Institute, 5150 Centre Avenue, UPMC Cancer Pavilion, 5th Floor, Suite 500, Pittsburgh, PA 15232, USA; **Angelo Di Leo,** Sandro Pitigliani Medical Oncology Unit, Department of Oncology, Hospital of Prato, Piazza dell'Ospedale, 59100 Prato, Italy; **John F. Forbes,** ANZ Breast Cancer Trials Group, University of Newcastle, Locked Bag 7, Hunter Region Mail Centre, NSW 2310, Newcastle, Australia (Absent); **Richard D. Gelber,** Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA; **John H. Glick,** University of Pennsylvania, Abramson Cancer Center, 16 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104-4283, USA; **Joseph Gligorov,** APHP Tenon, Cancer Est, 4 Rue de la Chine, 75020 Paris, France; **Michael Gnant,** Department of Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Wien, Austria; **Aron Goldhirsch,** International Breast Cancer Study Group, Oncology Institute of Southern Switzerland, 6500 Bellinzona, Switzerland and European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy (Chairman); **Paul E. Goss,** Director, Breast Cancer Research, MGH Cancer Center, 55 Fruit Street, Boston, MA 02114, USA; **Jay Harris,** Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Room 1622, 44 Binney Street, Boston, MA 02115, USA; **James N. Ingle,** Mayo Clinic Cancer Center, Breast Cancer Research Program, 200 First Street, S.W., Rochester, MN 55905, USA (Chairman); **Jacek Jassem,** Department of Oncology & Radiotherapy, Medical University of Gdansk, Debinki Street 7, 80-211 Gdansk, Poland; **Per Karlsson,** Department of Oncology, Sahlgrenska University Hospital, 41345 Göteborg, Sweden; **Manfred Kaufmann,** Director, Department Gynecology, Obstetrics and Breast Unit, J.W. Goethe University Hospital, Theodor Stern Kai 7, 60596 Frankfurt a. M., Germany; **Stella Kyriakides,** Europa Donna Cyprus, 28 Prodromou Street, 2406 Nicosia, Cyprus (Absent); **Louis Mauriac,** Institute Bergonié, Regional Cancer Center, 229 Cours d'Argonne, 33076 Bordeaux, France; **Gunter von Minckwitz,** GBG Forschungs GmbH, Schleussnerstrasse 42, 63263 Neu Isenburg, Germany; **Monica Morrow,** Breast Surgery Service, Anne Burnett Windfohr Chair of Clinical Oncology, Memorial Sloan-Kettering Cancer Center, Department of Surgery, 1275 York Avenue MRI 1026, New York, NY 10065, USA; **Henning T. Mouridsen,** Department of Oncology, Finsen Center 5074, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark; **Moise Namer,** Head, Medical Oncology, Centre Antoine Lacassagne, 33 Avenue de Valombrose, 06189 Nice Cedex 2, France; **Larry Norton,** Director of Breast Cancer Program, Memorial Sloan-Kettering Cancer Center, Room H 901, 205 East 64th Street, Concourse Level, New York, NY 10021-6007, USA; **Soonmyung Paik,** National Surgical Adjuvant Breast and Bowel Project, 4929 Bayard Street, Pittsburgh, PA 15213, USA; **Martine J. Piccart-Gebhart,** Internal Medicine, Oncology, Institut Jules Bordet, Rue Héger-Bordet 1, 1000 Brussels, Belgium; **Kurt Possinger,** Universitätsklinikum Charité Campus Mitte, Centrum 14, M.S. Onkologie/ Hämatologie, Charitéplatz 1, 10117 Berlin, Germany; **Kathleen I. Pritchard,** Sunnybrook Odette Cancer Centre, Ontario Clinical Oncology Group, 2075 Bayview Avenue, Toronto, Ontario M4N 1H6, Canada; **Emiel J.T. Rutgers,** The Netherlands Cancer Institute, Department of Surgery, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; **Vladimir F. Semiglazov,** N.N. Petrov Research Institute of Oncology, 68 Leningradskaya Street, Pesochny-2, 197758 St. Petersburg, Russia; **Ian Smith,** Department of Medicine, Royal Marsden Hospital and Institute of Cancer Research, Fulham Road, London, SW3 6JJ, UK; **Beat Thürlimann,** Breast Center, Kantonsspital St Gallen, 9007 St Gallen, Switzerland; **Giuseppe Viale,** Department of Pathology, European Institute of Oncology and University of Milan, Via Ripamonti 435, 20141 Milan, Italy; **Toru Watanabe,** Department of Medicine, Hamamatsu Oncology Center, 3-6-13 Chuo Naka-Ku, 430-0929 Hamamatsu, Japan; **Eric P. Winer,** Breast Oncology Center, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA, 02115, USA; **William C. Wood,** Department of Surgery, Suite B 206, Emory University Hospital, 1364 Clifton Road, Atlanta, GA 30322, USA.

The authors thank the Participants in the 11th International Conference on Primary Therapy of Early Breast Cancer for many useful remarks and for substantial contributions to the process. We acknowledge the substantial contributions of Giuseppe Curigliano, Shari Gelber, and Sabina Briner. We also thank Professor Umberto Veronesi for his guidance and Franco Nolè for his thoughtful remarks.

references

1. Chlebowski RT, Kuller LH, Prentice RL et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009; 360: 573–587.
2. Ravdin PM. The changes in breast cancer incidence: a result of recent changes in hormone use by postmenopausal women? Breast 2009; 18 (Suppl 1): S1 (Abstr S3).
3. Brody LC. Current knowledge on genetic predispositions for breast cancer. Breast 2009; 18 (Suppl 1): S4 (Abstr S9).
4. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434: 917–921.
5. Rottenberg S, Jaspers JE, Kersbergen A et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A 2008; 105: 17079–17084.
6. Powles T, Neven P, Osborne C et al. Five year results of a randomised placebo controlled trial of lasofoxifene (PEARL) on the incidence of ER positive breast cancer in postmenopausal women with osteoporosis. Breast 2009; 18 (Suppl 1): S5 (Abstr S12).
7. Powles T, Neven P, Osborne C et al. Effects of 5 years of treatment with lasofoxifene on incidence of breast cancer in older women by baseline estradiol levels. Breast 2009; 18 (Suppl 1): S26 (Abstr 0033).
8. Krum SA, Miranda-Carboni GA, Lupien M et al. Unique ERalpha cistromes control cell type-specific gene regulation. Mol Endocrinol 2008; 22: 2393–2406.
9. Lupien M, Eeckhoute J, Meyer CA et al. FoxA1 translates epigenetic signatures into enhancer-driven lineage-specific transcription. Cell 2008; 132: 958–970.

10. Brown M. Mining the steroid receptor cistrome for novel targets, biomarkers and risk alleles. Breast 2009; 18 (Suppl 1): S3 (Abstr S6).
11. Charafe-Jauffret E, Ginestier C, Iovino F et al. Breast cancer cell lines contain functional cancer stem cells with metastatic capacity and a distinct molecular signature. Cancer Res 2009; 69: 1302–1313.
12. Wicha MS, Ginestier C, Dontu G et al. Breast cancer stem cells: getting to treat the core. Breast 2009; 18 (Suppl 1): S7 (Abstr S17).
13. Tavazoie SF, Alarcón C, Oskarsson T et al. Endogenous human microRNAs that suppress breast cancer metastasis. Nature 2008; 451: 147–152.
14. Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol 2006; 7: 505–516.
15. Ignatiadis M, Kallergi G, Ntoulia M et al. Prognostic value of the molecular detection of circulating tumor cells using a multimarker reverse transcription-PCR assay for cytokeratin 19, mammaglobin A, and HER2 in early breast cancer. Clin Cancer Res 2008; 14: 2593–2600.
16. Cristofanilli M. The biological information obtainable from circulating tumor cells. Breast 2009; 18 (Suppl 1): S6 (Abstr S13).
17. Ebos JM, Lee CR, Cruz-Munoz W et al. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 2009; 15: 232–239.
18. Loges S, Mazzone M, Hohensinner P et al. Silencing or fueling metastasis with VEGF inhibitors: antiangiogenesis revisited. Cancer Cell 2009; 15: 167–170.
19. Pàez-Ribes M, Allen E, Hudock J et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 2009; 15: 220–231.
20. Kerbel RS. Modulation of angiogenesis: clinical impact (in breast cancer). Breast 2009; 18 (Suppl 1): S6 (Abstr S14).
21. Dellapasqua S, Bertolini F, Bagnardi V et al. Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. J Clin Oncol 2008; 26: 4899–4905.
22. Bertolini F, Mancuso P, Curigliano G et al. The (last?) word about biomarkers for angiogenesis. Breast 2009; 18 (Suppl 1): S6 (Abstr S15).
23. Prossnitz ER, Arterburn JB, Smith HO et al. Estrogen signalling through the transmembrane G protein-coupled receptor GPR30. Annu Rev Physiol 2008; 70: 165–190.
24. Bologa CG, Revankar CM, Young SM et al. Virtual and biomolecular screening converge on a selective agonist for GPR30. Nat Chem Biol 2006; 2: 207–212.
25. Aesoy R, Sanchez BC, Norum JH et al. An autocrine VEGF/VEGFR2 and p38 signaling loop confers resistance to 4-hydroxytamoxifen in MCF-7 breast cancer cells. Mol Cancer Res 2008; 6: 1630–1638.
26. Lewis-Wambi JS, Kim HR, Wambi C et al. Buthionine sulfoximine sensitizes antihormone-resistant human breast cancer cells to estrogen-induced apoptosis. Breast Cancer Res 2008; 10: R104.
27. Arpino G, Wiechmann L, Osborne CK et al. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev 2008; 29: 217–233.
28. Osborne K, Schiff R. Combined ER and HER-targeted therapy in breast cancer treatment. Breast 2009; 18 (Suppl 1): S8 (Abstr S20).
29. Ntukidem NI, Nguyen AT, Stearns V et al. Estrogen receptor genotypes, menopausal status, and the lipid effects of tamoxifen. Clin Pharmacol Ther 2008; 83: 702–710.
30. McLeod HL. Pharmacogenetics to drive breast cancer treatments. The Breast 2009; 18 (Suppl 1): S8 (Abstr S18).
31. Hospers GA, Helmond FA, de Vries EG et al. PET imaging of steroid receptor expression in breast and prostate cancer, Curr Pharm Des 2008; 14: 3020–3032.
32. de Vries E, Oude Munnink T, Nagengast W et al. Molecular imaging of breast cancer. Breast 2009; 18 (Suppl 1): S8 (Abstr S21).
33. Albain KS. Should genomic profiles be used to determine who should receive adjuvant chemotherapy? Breast 2009; 18 (Suppl 1): S17 (Abstr S40).
34. Bogaerts J, Cardoso F, Buyse M et al. Gene signature evaluation as a prognostic tool: challenges in the design of the MINDACT trial. Nat Clin Pract Oncol 2006; 3: 540–551.
35. Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). Clin Breast Cancer 2006; 7: 347–350.
36. Wirapati P, Sotiriou C, Kunkel S et al. Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. Breast Cancer Res 2008; 10: R65.
37. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med 2009; 360: 790–800.
38. Viale G. Integrating molecular profiling, histologic type and other variables: defining the fingerprint of responsiveness to treatment. Breast 2009; 18 (Suppl 1): S3 (Abstr S8).
39. Xing Y, Foy M, Cox DD et al. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg 2006; 93: 539–546.
40. Veronesi P, Rodriguez J. Breast conservation and sentinel lymph node biopsy after neoadjuvant systemic therapy. Breast 2009; 18 (Suppl 1): S11 (Abstr S27).
41. Morrow M, Wu S. Breast conservation and clear margins: invasive or in situ involvement. Breast 2009; 18 (Suppl 1): S12 (Abstr S28).
42. Kreike B, Hart AA, van de Velde T et al. Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. Int J Radiat Oncol Biol Phys 2008; 71: 1014–1021.
43. Dunne C, Burke JP, Morrow M et al. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. J Clin Oncol 2009; 27: 1615–1620.
44. Ciocca RM, Li T, Freedman GM et al. Presence of lobular carcinoma in situ does not increase local recurrence in patients treated with breast-conserving therapy. Ann Surg Oncol 2008; 15: 2263–2271.
45. Galimberti V. Axillary sentinel lymph node: how low can you go? Breast 2009; 18 (Suppl 1): S12 (Abstr S29).
46. Tuttle TM, Jarosek S, Habermann EB et al. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol 2009; 27: 1362–1367.
47. Brekelmans CT, Seynaeve C, Menke-Pluymers M et al. Survival and prognostic factors in BRCA1-associated breast cancer. Ann Oncol 2006; 17: 391–400.
48. Kraus-Tiefenbacher U, Bauer L, Scheda A et al. Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy. BMC Cancer 2007; 7: 178.
49. Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087–2106.
50. Kyndi M, Overgaard M, Nielsen HM et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol 2009; 90: 74–79.
51. Smith BD, Arthur DW, Buchholz TA et al. Accelerated partial breast irradiation consensus statement from the American Society of Therapeutic Radiology and Oncology. Int J Radiat Oncol Biol Phys 2009; doi:10.1016/j.ijrobp.2009.02.031.
52. Higgins MJ, Davidson NE. What is the current status of ovarian suppression/ablation in women with premenopausal early-stage breast cancer? Curr Oncol Rep 2009; 11: 45–50.
53. Davidson NE. Adjuvant therapies for premenopausal women with endocrine-responsive disease. Breast 2009; 18 (Suppl 1): S15 (Abstr S35).
54. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Forbes JF, Cuzick J et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008; 9: 45–53.
55. Mouridsen HT, Giobbie-Hurder A, Mauriac L et al. BIG 1–98: a randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. In San Antonio Breast Cancer Symposium, San Antonio, TX. 2008; (Abstr 13).
56. Seruga B, Tannock IF. Up-front use of aromatase inhibitors as adjuvant therapy for breast cancer: the emperor has no clothes. J Clin Oncol 2009; 27: 840–842.
57. Winer E. Treatment of postmenopausal women with hormone responsive breast cancer. Breast 2009; 18 (Suppl 1): S16 (Abstr S39).

58. Chia S, Norris B, Speers C et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol 2008; 26: 5697–5704.
59. Curigliano G, Viale G, Bagnardi V et al. Clinical relevance of HER-2 overexpression/amplification in patients with small tumor size (pT1a-b) and node-negative breast cancer. J Clin Oncol 2009 in press.
60. Smith IE. Targeting HER2 in the adjuvant setting: dealing with new standards and open questions. Breast 2009; 18 (Suppl 1): S17 (Abstr S41).
61. Hayes D. Is there a standard type and duration of adjuvant chemotherapy? Breast 2009; 18 (Suppl 1): S15 (Abstr S37).
62. Colleoni M, Viale G, Zahrieh D et al. Expression of ER, PgR, HER1, HER2, and response: a study of preoperative chemotherapy. Ann Oncol 2008; 19: 465–472.
63. von Minckwitz G, Kaufmann M, Kümmel S. Integrated meta-analysis on 6402 patients with early breast cancer receiving neoadjuvant anthracycline-taxane +/− trastuzumab containing chemotherapy. In San Antonio Breast Cancer Symposium, San Antonio, TX. 2008; (Abstr 79).
64. Liedtke C, Mazouni C, Hess KR et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26: 1275–1281.
65. Baselga J, Zambetti M, Llombart-Cussac A et al. Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer. J Clin Oncol 2009; 27: 526–534.
66. Perez EA. Adjuvant therapy of triple negative breast cancer. Breast 2009; 18 (Suppl 1): S17 (Abstr S42).
67. Baselga J. Review of new targeted drugs: crawling towards the adjuvant setting. Breast 2009; 18 (Suppl 1): S17 (Abstr S43).
68. Smith IE. The follow-up of women at high risk for breast cancer relapse. Breast 2009; 18 (Suppl 1): S9 (Abstr S22).
69. Joensuu H, Bono P, Kataja V et al. Update of the FINHER trial based on 5 years of follow-up. Breast 2009; 18 (Suppl 1): S10 (Abstr S24).
70. Gianni L, Goldhirsch A, Gelber RD et al. Update of the HERA trial and the role of 1 year trastuzumab as adjuvant therapy for breast cancer. Breast 2009; 18 (Suppl 1): S11 (Abstr S25).
71. Goldhirsch A, Glick JH, Gelber RD et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16: 1569–1583.
72. Goldhirsch A, Wood WC, Gelber RD et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007; 18: 1133–1144.
73. Ibrahim M, Dodson A, Barnett S et al. Potential for false-positive staining with a rabbit monoclonal antibody to progesterone receptor (SP2): findings of the UK National External Quality Assessment Scheme for Immunocytochemistry and FISH highlight the need for correct validation of antibodies on introduction to the laboratory. Am J Clin Pathol 2008; 129: 398–409.
74. Wolff A, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118–145.
75. Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009; 360: 679–691.
76. Thürlimann B, Price KN, Gelber RD et al. Is chemotherapy necessary for premenopausal women with lower-risk node positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11–93. Breast Cancer Res Treat 2009; 113: 137–144.
77. Jalava P, Kuopio T, Juntti-Patinen L et al. Ki67 immunohistochemistry: a valuable marker in prognostication but with a risk of misclassification: proliferation subgroups formed based on Ki67 immunoreactivity and standardized mitotic index. Histopathology 2006; 48: 674–682.
78. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006; 24: 3726–3734.
79. van de Vijver MJ, He YD, van't Veer LJ et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347: 1999–2009.
80. Wirapati P, Sotiriou C, Kunkel S et al. Meta-analysis of gene expression profiles in breast cancer: toward a unified understanding of breast cancer subtyping and prognosis signatures. Breast Cancer Res 2008; 10: R65.
81. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673–1684.
82. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659–1672.
83. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354: 809–820.
84. Slamon D, Eiermann W, Robert NJ. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in Her2neu positive early breast cancer patients. In Presented at the 2006 San Antonio Breast Cancer Symposium. San Antonio: Texas, 14–17 December 2006.
85. Dowsett M, Dunbier AK. Emerging biomarkers and new understanding of traditional markers in personalized therapy for breast cancer. Clin Cancer Res 2008; 14: 8019–8026.
86. Viale G, Giobbie-Hurder A, Regan MM et al. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine responsive breast cancer. Results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol 2008; 26: 5569–5575.
87. Ivshina AV, George J, Senko O et al. Genetic reclassification of histologic grade delineates new clinical subtypes of breast cancer. Cancer Res 2006; 66: 10292–10301.
88. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med 2009; 360: 790–800.