Annals of Oncology 18: 1133–1144, 2007
doi:10.1093/annonc/mdm271

Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007

A. Goldhirsch[1]*, W. C. Wood[2], R. D. Gelber[3], A. S. Coates[4], B. Thürlimann[5], H.-J. Senn[6] & Panel Members[†]

[1]International Breast Cancer Study Group, Oncology Institute of Southern Switzerland, 6500 Bellinzona, Switzerland and European Institute of Oncology, 20141 Milan, Italy; [2]Department of Surgery, Emory University School of Medicine, N. E. Atlanta, GA 30322, USA; [3]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02115, USA; [4]International Breast Cancer Study Group and University of Sydney, Sydney, NSW 2006, Australia; [5]Division of Gynecologic Oncology, Kantonsspital, 9006 St Gallen, Switzerland; [6]Tumor-Center ZeTuP (Detection, Treatment, Prevention), 9006 St Gallen, Switzerland

Received 30 April 2007; accepted 2 May 2007

The 10th St Gallen (Switzerland) expert consensus meeting in March 2007 refined and extended a target-oriented approach to adjuvant systemic therapy of early breast cancer. Target definition is inextricably intertwined with the availability of target-specific therapeutic agents. Since 2005, the presence of HER2 on the cell surface has been used as an effective target for trastuzumab much as steroid hormone receptors are targets for endocrine therapies. An expert Panel reaffirmed the primary importance of determining endocrine responsiveness of the cancer as a first approach to selecting systemic therapy. Three categories were acknowledged: **highly endocrine responsive, incompletely endocrine responsive and endocrine non-responsive.** The Panel accepted **HER2-positivity** to assign trastuzumab, and noted that adjuvant trastuzumab has only been assessed together with chemotherapy. They largely endorsed previous definitions of risk categories. While recognizing the existence of several molecularly-based tools for risk stratification, the Panel preferred to recommend the use of high-quality standard histopathological assessment for both risk allocation and target identification. Chemotherapy, although largely lacking specific target information, is the only option in cases which are both endocrine receptor-negative and HER2-negative. Chemotherapy is conventionally given with or preceding trastuzumab for patients with HER2-positive disease, and may be used for patients with endocrine responsive disease in cases where the sufficiency of endocrine therapy alone is uncertain. Recommendations are provided not as specific therapy guidelines but rather as a general guidance emphasizing main principles for tailoring therapeutic choice.

introduction

Incremental rather than fundamental change in the approach to the management of early breast cancer was the hallmark of the 10th St Gallen conference held in March 2007, attended by more than 4700 participants from 95 countries. Successive St Gallen conferences since 1978 have brought into focus contemporary insights and produced general principles based upon available evidence and expert opinion to provide guidance for the therapy of early breast cancer outside clinical trials [1]. The publication in 2005 of trials of trastuzumab for HER2-positive disease [2–4] represented such an important advance as to necessitate an interim update in 2006 [5].

Some new information presented at the conference is summarized in Table 1. In light of this information, a Panel of 39 experts from around the world (see Appendix) considered specific questions to arrive at recommended principles for the selection of therapies in early breast cancer. Intrinsically different subtypes of breast cancer were clearly recognized based on genetic profile and immunohistochemical (IHC) demonstration of selected targets [18, 73]. Overall treatment strategy stressed the paramount importance of targeted therapies wherever possible, though acknowledging that supplementation with less target-specific chemotherapy may be required. An obvious corollary is the absolute importance of timely, accurate and reliable histopathological assessment including target identification and quantification; an ideal regrettably not yet universally attained. Enhanced partnership between clinicians and pathologists therefore offers the opportunity for substantially improved outcomes.

*Correspondence to: Dr A. Goldhirsch, International Breast Cancer Study Group, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy.
E-mail: aron.goldhirsch@ibcsg.org

[†]See Appendix for members of the Panel.

This is a corrected version of the original article. The corrected version was published on 25 October 2007.

Table 1. Recent research findings presented at the 10th 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
Genetic susceptibility and therapeutic implications	Overall, inherited genetic susceptibility accounts for only ~5-10% of breast cancer [6]. Discovered genes include BRCA1 (20-40% of hereditary breast cancers), BRCA2 (10-30%), TP53 (<1%), PTEN (<1%), ATM, CHK2, STK11 (~1%) and Fanconi's Anemia genes (~1%) [7]. BRCA1 tumors are typically poorly differentiated, ER, PgR and HER2/*neu* negative, often with basal-like phenotype, EGFR positive, cyclin E positive, express basal keratins and have little DCIS. BRCA1-deficient cells were found to be hypersensitive to platinum compounds and PARP.1 [poly(ADP-ribose) polymerase-1] inhibitors, which have shown efficacy in basal-like tumors [8]. Carriers of mutations of BRCA1 and BRCA2 were investigated for the effects of bilateral prophylactic salpingo-oophorectomy (BPSO) [9] or for bilateral or contralateral mastectomy [10] for reduction of the risk of breast and ovarian cancer. MRI is sensitive and cost effective for follow up of BRCA1 carriers (less so for BRCA2 carriers) [11]. The cost-effectiveness of adding MRI to mammography varies greatly by age.
Pathology of breast cancer	Pathological heterogeneity of breast cancer was substantially enhanced by the recognition of cellular markers through immunohistological and molecular classifications. These include lobular and ductal invasive cancers, but also basal-like cancers bearing various molecular markers of myoepithelial cells. Luminal types A, B, C, normal breast, HER2-positive, and basal-like phenotypes have been reproducibly separated [12-14]. Reliability of the pathological diagnosis [15], quality determination of the degree of endocrine responsiveness, through hormone receptors [16] and HER2/*neu* status for response to trastuzumab [17] are essential for a proper treatment allocation.
Endocrine therapies, estrogen and progesterone receptors and epithelial growth factors	Estrogen receptor positive breast cancer, although endocrine responsive, might develop resistance to endocrine therapies through altered transcription of progesterone receptors [18], through the presence of amplified epithelial growth factors [19], and through acquired resistance to aromatase inhibitors (AIs) by altered apoptosis, which might be reversed by the use of low-dose estrogens [20]. Overcoming resistance to AIs through the therapeutic association between endocrine therapies and epithelial growth factors or IGF inhibitors, MTor inhibitors, and antiangiogenesis has been described [21]. It is now recognized that the efficacy of tamoxifen might be compromised due to altered metabolism of this drug through altered transformation into its active metabolite due to constitutional or induced alteration of CYP2D6 [22]. Some selective serotonin reuptake inhibitor antidepressants can affect tamoxifen metabolism. Comparisons between AIs are being studied in randomized clinical trials. Indirect comparisons do not seem to demonstrate reasons to prefer one or other of the available agents [23]. Difference in the intensity of recording and grading undesirable effects may account for apparent differences in side effects [24]. More than 10 000 patients will be included in trials which directly compare different AIs (MA-27 and FACE) [23].
Chemotherapy regimens and their interaction with endocrine responsiveness	New information on the degree of responsiveness to chemotherapy of cohorts of patients selected according to the type of disease emerged as an important feature [25]. The effectiveness of chemotherapy advances may depend on estrogen receptor status [26]. Taxane combinations are effective in the adjuvant setting but especially in cohorts of patients with endocrine non-responsive or incompletely responsive tumors. Exploratory analyses to identify those for whom the addition of a taxane-containing regimen might be superfluous has not been attempted [27-29]. The question on how best to schedule taxanes seemed to favor the weekly administration of paclitaxel, or the three-weekly docetaxel, but must be best studied within the context of optimal ER, PgR and HER2 determination [27, 28, 30]. Microtubule binding protein Tau was identified as a new marker of response to paclitaxel. Its low expression was associated with increased sensitivity to paclitaxel in human breast cancers, while its down regulation increased their sensitivity to paclitaxel but not to anthracyclines [31]. Retrospective studies suggest that topoisomerase II alpha (topo II) gene amplification and protein overexpression predict anthracycline efficacy. Protein levels are however regulated by proliferation signals, independently of topo II gene status. It was suggested that studies on topo II gene amplification might be more useful if conducted in biologically more homogeneous populations (i.e. with similar proliferation, HER2 overexpression, and endocrine responsiveness patterns) [32]. Basal-like tumors, many of which are associated with BRCA1 mutation, were found to be particularly sensitive to DNA damaging chemotherapy such as platinum compounds or classical alkylating agents. This information is from small retrospective studies and thus controversial [33].
Immunity and vaccinations	Attempts at tumor immunotherapy have an unsuccessful history extending for more than a century. Current vaccines include HER2/*neu* protein, which has been shown to be immunogenic but has yet to demonstrate therapeutic efficacy [34].

Table 1. (*Continued*)

Field or Treatment	Status of research/Implications for patient care
Targeted biological therapies	Molecular testing may identify new features to aid therapeutic targeting [35]. Lapatinib has shown significant efficacy (together with capecitabine) in advanced breast cancer after failure of trastuzumab [36]. Its testing in the adjuvant setting is imminent [37]. Bevacizumab has shown efficacy when combined with capecitabine and taxanes in advanced breast cancer [38], and the drug will be tested in the adjuvant setting - E5103 Trial [39]. Combined bevacizumab with trastuzumab has shown efficacy in metastatic disease [39]. Other promising treatments include combination therapy with bevacizumab and a tyrosine kinase inhibitor and combining anti-VEGF therapy with metronomic chemotherapy [40].
Ductal carcinoma *in situ* (DCIS; DIN)	DCIS is more commonly diagnosed in the screening era. DCIS is treated with surgical excision, although mastectomy followed by proper reconstruction might be required in case of extensive disease [41]. Radiation therapy and/or tamoxifen are generally used following breast-conserving surgery except for some small, low grade lesions or in elderly patients [42-47]. Women with DCIS frequently overestimate their risk of recurrence and mortality and should be reassured accordingly [48]. There remains a need for predictors of which cases of DCIS are more likely to recur.
Surgical treatments: focus on sentinel node evaluations and surgery of the breast during course of metastatic disease	Sentinel node biopsy was accepted as reliable and safe even in elderly patients [49]. Avoidance of axillary dissection reduces morbidity of local regional therapy. Avoiding axillary dissection despite micrometastatic sentinel lymph node involvement is a subject of ongoing randomized clinical trial research [50]. Special problems arise with surgery in the setting of metastatic disease. There is a lack of evidence but in selected cases primary tumor resection or removal of accessible metastases may be considered [51, 52]. Prospective trials are required in patients with limited metastatic burden to formally assess the value of surgical excision plus or minus radiation therapy aimed at removal of all detectable disease [53].
Preoperative systemic therapy	The primary objective of this therapy is to improve resectability and cosmesis [54]. Assessment of responsiveness to preoperative therapy may in the future be useful in selection of postoperative adjuvant therapy.
Radiation therapy in early breast cancer	Treatments which achieved a reduction in local recurrence were also associated with a reduction in mortality after long-term follow up [55]. In practical terms this was felt to justify post-mastectomy radiation therapy for all patients with 4 or more involved lymph nodes, while the indication for such therapy with 1-3 nodes was less clear and patients with node-negative disease do not require post-mastectomy irradiation if not otherwise indicated (e.g. T4). Modern radiation therapy techniques allow reduction of normal tissue damage to heart and lungs [56]. Radiation therapy limited to the part of the breast closest to the site of the excised tumor (accelerated partial breast irradiation, APBI) was discussed but definitive results of ongoing trials are awaited [57].
Adjuvant therapies for older women with breast cancer	Review of patients with ER-poor disease in the EBCTCG overview revealed a benefit of chemotherapy which was substantial and similar in all age groups [58]. Similarly, a review of population based data from the SEER and Medicare databases suggested that the beneficial impact of chemotherapy on survival was best seen in patients with ER-negative disease [59]. Ongoing randomized trials in this population are investigating chemotherapy regimens selected for relatively low morbidity.
Staging and follow-up of patients after successful treatment of operable breast cancer	The benefits of extensive staging procedures in patients with early breast cancer have not been established. Similarly, during follow up the ASCO guidelines recommend history and physical examination, breast self examination, annual mammography and pelvic examination, and appropriate assessment of bone health. Other procedures such as blood tests, chest x-ray, bone scan, CT, MRI, PET and tumor markers are not recommended [60, 61].
Specific quality of life issues: cardiovascular side effects, cognitive function, fertility and menopausal symptoms	**Trastuzumab induced cardiac dysfunction** is largely reversible based on short observations. Prolonged oxidative stress associated with anthracyclines may lead to myocyte necrosis and irreversible cardiac dysfunction [62]. **Association between malignancy and thrombosis** is long established. Mechanisms include invasion of vessel walls and more recently specific anticancer agents and vascular access catheters. Risk of thrombosis may be reduced by selection of anticancer agents (e.g. aromatase inhibitors in place of tamoxifen and avoiding concurrent tamoxifen and cytotoxic therapy). Screening for increased thrombotic predisposition is not routinely recommended and antithrombotic prophylaxis should be limited to unusual cases with a history of idiopathic thrombosis who require relevant cancer therapies [63]. **Cognitive dysfunction after chemotherapy («chemo-brain»)** is frequently perceived by patients [64], though objective psychological testing correlates poorly with subjective experience [65]. Functional imaging documents variable areas of brain activation but their significance remains uncertain [66].

Table 1. (*Continued*)

Field or Treatment	Status of research/Implications for patient care
	Maintaining fertility: women who wish to maintain fertility may prefer to avoid systemic adjuvant therapy in situations in which it is only marginally indicated. Ongoing research is investigating a possible protective role for LHRH agonists during chemotherapy especially for patients with endocrine non-responsive tumors in whom no benefit could be anticipated from therapy induced ovarian suppression [67]. Cryopreservation of ovarian tissue, oocytes or embryos may be considered [68].
	Avoiding premature menopause: even in patients who do not become immediately amenorrheic, menopause occurs earlier following chemotherapy, particularly in patients aged 40 years or older who received prolonged cytotoxic regimens [68].
	Breast cancer diagnosed during pregnancy: breast cancer diagnosed during pregnancy poses therapeutic problems particularly requiring delay in radiation therapy until after delivery and delay of chemotherapy at least until completion of organogenesis [69, 70]. Several cytotoxics and endocrine agents are contraindicated throughout pregnancy.
	Safety of pregnancy after the diagnosis of breast cancer: most observational studies of pregnancy following treatment for breast cancer are reassuring and do not suggest that this carries a danger of breast cancer recurrence [71, 72].

A subtle but important clarification of terminology was introduced relative to endocrine responsiveness. The three categories described in 2005 remain essentially unchanged but can more clearly be described as: (i) **highly endocrine responsive** [high expression of both estrogen receptor (ER) and progesterone receptor (PgR) in a majority of tumor cells]; (ii) **incompletely endocrine responsive** (lower expression of ER and or PgR); and (iii) **endocrine non-responsive** (complete absence of both ER and PgR). The degree of endocrine responsiveness varies quantitatively, and will contribute, together with an assessment of the level of risk of relapse, to a decision about whether endocrine therapy alone may be sufficient. While no absolute threshold can be defined, highly endocrine responsive tumors in patients with low risk (Table 2) may be suitable for endocrine therapy alone, while supplementary chemotherapy may be required for patients with highly endocrine responsive tumors in the presence of intermediate- or high-risk factors, and for patients with incompletely endocrine responsive tumors.

The risk categories as defined in 2005 [1] remained essentially unchanged (Table 2), except that (i) peritumoral vascular invasion should be extensive (i.e. neoplastic emboli seen in two or more blocks of the tumor) to justify incremental risk; (ii) some small tumors and histological types might be at low risk despite the absence of steroid hormone receptors (e.g. medullary carcinoma, apocrine carcinoma, etc.); and (iii) the level of steroid hormone receptor expression and overexpression or amplification of HER2 constitute risk factors as well as therapeutic targets.

The resulting algorithms (Table 3) should serve to assist selection of optimal therapy in the immediate future.

St Gallen 2007: news and progress

St Gallen conferences typically concentrate on breast cancer therapeutics, but various other aspects deserve to be mentioned for completeness, including epidemiology of breast cancer in various geographical areas and across socio economic strata. Reduced breast cancer incidence has been attributed to reduced prescribing of hormone replacement therapies [75]. Adherence to therapeutic guidelines is affected by affordability of systemic therapies in various geographic settings. Table 1 displays selected news in several of these areas.

categories of endocrine responsiveness

Three endocrine responsiveness categories were defined. (i) **Highly endocrine responsive** (previously referred to as endocrine responsive): tumors express high levels of both steroid hormone receptors in a majority of cells (identified with proper immunohistological methods). (ii) **Incompletely endocrine responsive** (previously referred to as endocrine response uncertain): some expression of steroid hormone receptors but at lower levels or lacking either ER or PgR. (iii) **Endocrine non-responsive:** tumors having no detectable expression of steroid hormone receptors. While this group is clearly defined in terms of lack of responsiveness to endocrine therapies, it includes tumors of diverse phenotype [76].

HER2-positivity

Two technologies are recognized for the determination of HER2-positivity. Either strong IHC staining (3+) of >30% of the tumor cells, or, alternatively, determination of gene amplification by FISH (fluorescence *in situ* hybridization: ratio of HER2 gene copies to chromosome 17 centromers > 2.2) or CISH (chromogenic *in situ* hybridization: more than six HER2 signals per cell) [77] is sufficient. The presence of strong IHC staining (3+) is associated with response to trastuzumab in several clinical trials. Theoretically, weaker staining (1+ or 2+) even in the presence of amplification could be associated with a lesser degree of efficacy of trastuzumab. The preliminary data from the N9831 trial are consistent with this hypothesis [78], indicating the urgent need for more research on correlation between specific biological markers and response to anti HER2 agents. It

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**, AND Absence of extensive peritumoral vascular invasion[b], AND ER and/or PgR*** expressed[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**, OR Presence of extensive peritumoral vascular invasion[b], OR ER and PgR absent[c], OR HER2/*neu* gene overexpressed or amplified[d], OR Age <35 years **Node positive (1-3 involved nodes)** AND ER and/or PgR expressed, AND HER2/*neu* gene neither overexpressed nor amplified[d]
High risk	**Node positive (1-3 involved nodes)** AND ER and PgR absent, OR HER2/*neu* gene overexpressed or amplified[d] **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]Extensive peritumoral vascular invasion (i.e. neoplastic emboli seen in two or more blocks of the tumor) was recognized 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 [74].
[c]Some cases such as medullary carcinoma and apocrine carcinoma may be regarded as low risk despite the absence of steroid hormone receptor expression.
[d]HER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or FISH 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); **histologic and/or nuclear grade; ***ER, estrogen receptor; PgR, progesterone receptor.

Table 3. Choice of treatment modalities 2007 (see text)

	Highly endocrine responsive[a]	Incompletely endocrine responsive[a]	Endocrine non-responsive[a]
HER2-negative	ET[b] (consider adding CT according to risk)[c]	ET[b] (consider adding CT according to risk)[c]	CT
HER2-positive	ET + Trastuzumab[d,e] + CT[e]	ET + Trastuzumab[d,e] + CT[e]	Trastuzumab[d,e] + CT

ET, endocrine therapy; CT, chemotherapy.
[a]Responsiveness to endocrine therapies is defined in the text.
[b]Endocrine therapy is effective for prevention and DCIS and therefore might be considered even for very low risk invasive breast cancer.
[c]Within the highly and incompletely endocrine responsive categories, addition of chemotherapy may be based on degree of steroid hormone receptor expression and level of risk (see text).
[d]Trastuzumab should not be viewed as a standard treatment in women with a primary tumor <1 cm of size and with no axillary node involvement. This is particularly true in patients with highly and perhaps also incompletely endocrine responsive disease.
[e]Trastuzumab should be given concurrently and after chemotherapy or following completion of all chemotherapy according to clinical trial evidence available at present, though a majority of the Panel agreed that trastuzumab without prior or concurrent chemotherapy may become appropriate for some patients in the future.

is recognized that these are arbitrary thresholds in a biological continuum, but a pragmatic decision needs to be made particularly because of the high cost of trastuzumab therapy, and the definitions used in the clinical trials upon which such therapy is based.

risk categories

The Panel in 2007 recognized few changes for the risk classification (Table 2). Peritumoral vascular invasion was considered to elevate risk category only if it was extensive [74].

Total absence of steroid hormone receptors and amplification or overexpression of HER2 were each considered sufficient to exclude low risk assignment except for rare tumors such as medullary or apocrine carcinoma (which usually lack any of these receptors). Again, the Panel did not accept the molecularly based tools such as Oncotype Dx™ or gene expression profiling by MammaPrint™ as sufficiently established to define risk categories. Both methods are being currently tested within prospective clinical trials [79, 80].

specific considerations for treatment choice

local and regional treatments

Surgical considerations presented during the conference included reaffirmation of breast conservation, sentinel node technology to avoid unnecessary axillary surgery, and the challenging role of surgical treatment in the presence of metastatic disease (see Table 1). These aspects were not subsequently considered by the Panel.

Several aspects of radiation therapy were discussed. In general, recommendations of the American Society for Clinical Oncology (ASCO) or European Society of Mastology (EUSOMA) might be used to guide radiation treatment choice [81, 82]. Current standards for proper irradiation include CT scan simulation for all left-sided cancers, and use of techniques to minimize cardiac irradiation [83]. There was strong agreement to avoid postmastectomy radiation therapy for patients with node-negative disease and T1–T2 tumors, while a slender majority would restrict such treatment to those with 4 or more involved axillary lymph nodes. Publication of the findings from the EBCTCG presented in San Antonio in December 2006 showing an advantage for postmastectomy radiation in women with 1–3 positive nodes is awaited with interest. Postmastectomy irradiation volume should include chest wall and supraclavicular fossa for those with axillary nodes involved. It was agreed that in general axillary radiation should be avoided if proper axillary clearance had been performed. Even following breast conservation, a majority of the Panel would avoid radiation therapy in elderly patients who would receive endocrine therapy. It was the opinion of some of the Panel members, however, that elderly patients should not be denied standard radiation therapy if indicated. No other radiation therapy question commanded majority support among the Panel. These included questions regarding concurrent chemo–radio therapy, delay of endocrine therapy until completion of radiation therapy, partial breast irradiation and shortened courses with hypofractionation.

the systemic adjuvant therapy program

As in 2005, the first consideration is the use of appropriately targeted therapy. For highly and incompletely endocrine responsive disease the selection of endocrine therapy will depend upon menopausal status of the patient. This may be difficult to determine in patients who have recently received cytotoxic chemotherapy, a matter of particular importance if an aromatase inhibitor is being considered: the Panel insisted on ensuring a postmenopausal status *before* and *during* the use of an aromatase inhibitor. Other host-related factors governing selection of therapy may include a history of thromboembolic disease contraindicating tamoxifen. Likewise, host factors such as the existence of concomitant cardiac disease might influence the choice of particular chemotherapy agents or the suitability of treatment with trastuzumab. Patient age or co-morbid conditions may further restrict the feasibility of more intensive cytotoxic regimens. Different patterns of expected adverse events may influence patient preference for one or other treatment strategy.

endocrine therapy in postmenopausal patients

Clearly the availability of third generation aromatase inhibitors (AIs) [24, 84–88] has added substantially to the available treatment choice after a quarter century of successful use of tamoxifen. Nevertheless, a clear majority of the Panel felt that 5 years of tamoxifen alone was still a viable option for certain patient categories. Among strategies for the use of AIs, the Panel expressed a clear preference for a switch from tamoxifen to an AI after 2–3 years of tamoxifen, with a substantial minority also supporting an initial use of an AI and very few in favor of a prospective policy of 5 years of tamoxifen followed by an AI. For patients who have completed 5 years of tamoxifen, the majority of the Panel would support the addition of an AI for a further period of time only for patients with node-positive disease. Initial AI was more acceptable in patients at higher risk or with HER2-positive disease. A slim majority also favored initial AIs in patients receiving SSRI anti-depressants.

The Panel clearly preferred sequential rather than concurrent administration of cytotoxic and endocrine therapies. The total duration of optimal adjuvant endocrine treatment was seen as between 5 and 10 years.

Most Panelists considered it wise to check for ovarian function suppression in younger postmenopausal women receiving an AI, though the timing of such an assessment was uncertain.

The Panel supported evaluation of bone mineral density prior to commencement of an AI and the use of calcium, vitamin D and especially physical exercise to reduce the risk of bone loss and treatment-related symptoms.

endocrine therapy for premenopausal patients

The Panel accepted either tamoxifen plus ovarian function suppression or tamoxifen alone as standard endocrine therapies in this group. Ovarian function suppression alone was considered a possibility if subsequent pregnancy is planned, although avoiding tamoxifen for this reason may not be completely justified.

The Panel strongly endorsed a GnRH analogue as a means of ovarian function suppression and a substantial majority also regarded surgical oophorectomy as an appropriate option with the choice of method depending upon disease type and circumstances. Ovarian radiation was overwhelmingly rejected. It is important to recognize that in some patients GnRH analogue alone may not suppress ovarian function completely [89].

While admitting that evidence was lacking about the optimal duration of ovarian function suppression by GnRH analogue for women with hormone receptor positive breast cancer, a clear majority favored a period of 5 years, especially in patients at higher risk of relapse and/or with HER2-positive disease [90]. It was recognized that individual patients would exercise choice regarding the type and duration of ovarian function suppression.

Again without specific evidence, most Panelists preferred to defer GnRH analogue until completion of chemotherapy.

The use of AIs as the sole endocrine therapy for premenopausal patients is not appropriate. The use of AIs together with ovarian function suppression is currently being tested in clinical trials but might be considered outside trials when tamoxifen is contraindicated. Patients who were premenopausal at diagnosis and became postmenopausal after chemotherapy or during adjuvant endocrine therapy may receive AIs [85], but loss of ovarian endocrine function should be verified *prior* to and *during* exposure of these drugs, which typically stimulate endocrine ovarian function [91].

trastuzumab

The Panel was prepared to accept strong IHC staining as justifying trastuzumab therapy with only a small minority demanding FISH testing in all cases. The opinion of several Panelists was that, considering the absence of relevant data from randomized trials trastuzumab cannot be viewed as a standard treatment in women with a primary tumor <1 cm of size and with no axillary node involvement. This is particularly true in the setting of endocrine responsive disease. The role of trastuzumab in patients with small, endocrine responsive tumors and no axillary node involvement has not been adequately evaluated.

The standard duration of trastuzumab therapy was accepted as 1 year. A shorter duration (9 weeks) as used in the FinHER study [92] was not generally accepted.

A majority of the Panel found both the sequential HERA model (trastuzumab commencing after completion of all chemotherapy) [2] and the concurrent model (trastuzumab commencing concurrently with a taxane following anthracycline) [3, 4] as equally acceptable. A slim majority found the use of carboplatin and docetaxel administered concurrently with trastuzumab without anthracycline [4] to be an acceptable alternative.

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. The Panel thought it important to avoid trastuzumab in patients with low LVEF (<50%).

chemotherapy

Perhaps the most difficult decision in current adjuvant therapy is selection of patients with highly or incompletely endocrine responsive disease for whom additional chemotherapy should be given. Features that raise doubt about the adequacy of endocrine therapy alone include relatively lower expression of steroid hormone receptor, involvement (and particularly extensive involvement) of axillary lymph nodes, higher grade or proliferative markers, larger tumor size and extensive peri-tumoral vascular invasion. Molecular-based technologies have been proposed to assist in this discrimination (OncotypeDX™, Mammaprint™) but were not regarded by the Panel as yet sufficiently reliable to make a definitive contribution to the therapeutic decision.

A wide variety of chemotherapy regimens was considered acceptable with little agreement on any particular favorite. Most Panelists supported the use of anthracyclines for all patients and an even greater majority supported anthracycline use for patients with HER2-positive disease. For treatment of patients with triple negative tumors, the Panel was careful to include DNA damaging compounds [33]. Combinations of cyclophosphamide, 5-fluorouracil and an anthracycline (variously abbreviated as CAF, CEF, FEC, FAC [93–96]), commanded relatively wide support, as did the sequence of anthracycline and cyclophosphamide followed by paclitaxel or docetaxel. There was only minority support for dose-dense therapy, while high-dose therapy requiring peripheral blood stem cell support was rejected overwhelmingly.

In general, the Panel was prepared to accept less intensive chemotherapy such as four courses of doxorubicin and cyclophosphamide or six courses of classical CMF in patients with highly (but at high risk of relapse) or incompletely endocrine responsive HER2-negative disease. Other regimens considered suitable for this group included CAF and the combination of docetaxel and cyclophosphamide. Preference for various chemotherapy regimens was geographically heterogeneous, a fact which explains the large range of therapies considered by the Panelists.

The majority of the Panel considered that a shorter duration of chemotherapy (12–16 weeks) might be suitable for elderly patients and that an early initiation of such therapy was important for patients with steroid hormone receptor negative disease. Panel members noted the importance of offering standard chemotherapy to fit elderly patients with sufficient life expectancy. While a clear majority of the Panel supported a role for hematopoietic growth factors in patients with a clinical indication, only a minority supported their routine use. An excess of MDS and acute leukemia has been reported in older recipients of hematopoietic growth factors during adjuvant chemotherapy [97], but this finding is derived from non-randomized series, and no similar excess is evident in prospective randomized trials.

choice of systemic adjuvant treatment modalities 2007

Bringing together these various concepts, Table 3 presents a summary in terms rather simpler than on previous occasions. In 2007 we have two therapeutic targets. Risk plays a minor role and is not a first order consideration in treatment selection, though it may guide selection of patients with endocrine responsive tumors for addition of chemotherapy. All patients receiving trastuzumab should also receive prior or concurrent chemotherapy according to available clinical trial evidence. Patients with triple negative disease are limited to

chemotherapy. Thus, the only ambiguity arises in the two boxes describing treatment for patients with HER2-negative disease and at least some degree of endocrine responsiveness. Those with highly endocrine responsive tumors, particularly in the absence of other adverse factors (**those at low or intermediate risk of relapse and no indication for trastuzumab**), might well receive only endocrine adjuvant therapy, while others may also require at least some chemotherapy. The judgment required in advising such patients on the addition of chemotherapy will involve many factors of risk assessment, degree of endocrine responsiveness, and patient preference. No absolute rules can be defined for this decision which remains a matter for discussion between each patient and her treating clinician. Appendix Table 4 is provided to illustrate treatment decision algorithms incorporating information on therapeutic target and risk category. Current trials on the role of gene profiling in defining efficacy of adjuvant chemotherapy for patients with endocrine responsive disease might provide clinically relevant information [79, 80].

preoperative systemic therapy

Apart from the routine use of such treatment for large tumors, a majority of the Panel supported preoperative systemic therapy to improve resectability and thus cosmesis, while a minority also considered that the assessment of responsiveness constituted a reason to employ this treatment approach. A clear majority supported the inclusion of trastuzumab in the preoperative treatment program for patients with HER2-positive disease.

special considerations

Presentations covered at the conference addressed the specific needs of very young patients with particular reference to the preservation of fertility, the avoidance of premature menopause, the safety of pregnancy after the diagnosis of breast cancer and the special therapeutic problems when breast cancer is diagnosed during pregnancy (Table 1). Although not discussed by the Panel, other presentations canvassed the question of cognitive impairment after breast cancer therapy, and the prevention of cancer associated thromboembolic disease (Table 1).

Particular problems recognized in elderly patients included the presence of co-morbidities which might limit the feasibility of particular therapeutic options.

commentary

Clearly there has been continued progress in definition of effective systemic adjuvant therapies for early breast cancer. Future studies should define the molecular basis for treatment selection and in particular the definition of patients who might not require chemotherapy [98].

The best way to achieve optimal treatment of today's patients is to ensure the availability of reliable and timely pathological assessment in routine practice including treatment target identification.

appendix and acknowledgements

Members of the Panel are listed below. All had a significant input to the discussion and manuscript. Drs A. Costa and L. Norton were unable to attend the Panel session, but provided input for the planning of the meeting and reviewed and approved the manuscript. Profs H. Mouridsen and A. Wallgren were also unable to attend, but maintained significant input throughout the process and were represented by B. Ejlertsen and P. Karlsson, respectively, senior members of their research teams. For the first time, a patient representative, I. Kössler, joined the Panel.

- M. Aapro, Clinique de Genolier, 1245 Genolier, Switzerland
- K. S. Albain, Loyola University Medical Center, Cardinal Bernardin Cancer Center, Maywood, IL 60153, USA
- J. Bergh, Department of Oncology, Radiumhemmet, Karolinska Institute and Hospital, 17176 Stockholm, Sweden
- H. Burstein, Department of Medical Oncology/Solid Tumor Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA
- R. Carlson, Division of Oncology and Stanford Medical Informatics, Stanford University, Stanford, CA 94305-5826, USA
- M. Castiglione-Gertsch, International Breast Cancer Study Group Coordinating Center, 3008 Bern, Switzerland
- A. S. Coates, International Breast Cancer Study Group and University of Sydney, Sydney, NSW 2006, Australia
- M. Colleoni, Division of Medical Oncology, European Institute of Oncology, 20141 Milan, Italy
- A. Costa, Maugeri Foundation Breast Unit, Pavia, Italy, and Cantonal Breast Unit, Lugano & Bellinzona, Ospedale San Giovanni, 6500 Bellinzona, Switzerland (Absent)
- J. Cuzick, Cancer Research, UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary College, University of London, London EC1M 6BQ, UK
- N. Davidson, Sidney Kimmel Cancer Center of Johns Hopkins, Baltimore, MD 21231-1000, USA
- A. Di Leo, «Sandro Pitigliani» Medical Oncology Unit, Department of Oncology, Hospital of Prato, 59100 Prato, Italy
- B. Ejlertsen, Department of Oncology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
- J. F. Forbes, Department of Surgical Oncology, University of Newcastle, NSW 2310, Australia
- R. D. Gelber, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02115, USA
- J. H. Glick, University of Pennsylvania Cancer Center, Philadelphia, PA 19104-4283, USA
- J. Gligorov, Medical Oncology, CancerEst, Tenon Hospital, 75970 Paris Cedex 20, France
- A. Goldhirsch, International Breast Cancer Study Group, Oncology Institute of Southern Switzerland, 6500 Bellinzona, Switzerland, and European Institute of Oncology, 20141 Milan, Italy (**Chairman**)

- P. Goss, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
- J. Harris, Department of Radiation Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA
- J. N. Ingle, Mayo Clinic, Rochester, MN 55905, USA
- R. Jakesz, University of Vienna, Department of General Surgery, 1090 Wien, Austria
- J. Jassem, Medical University of Gdansk, Department of Oncology & Radiotherapy, 80-211 Gdansk, Poland
- P. Karlsson, Sahlgrenska University Hospital, Department of Oncology, 413 45 Göteborg, Sweden
- M. Kaufmann, Department of Gynecology and Obstetrics, Goethe University, 60596 Frankfurt am Main, Germany
- I. Kössler, President Europa Donna, Bröstcancerföreningarnas Riksorganisation-BRO, 172 27 Sundbyberg, Sweden
- L. Mauriac, Institute Bergonié, 33076 Bordeaux, France
- M. Morrow, Chairman, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111-2497, USA
- H. T. Mouridsen, Department of Oncology 5074, Rigshospitalet, 2100 Copenhagen, Denmark (Absent)
- M. Namer, Centre Antoine Lacassagne, 06189 Nice Cedex, France
- L. Norton, Director of Breast Cancer Programs, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA (Absent)
- M. J. Piccart-Gebhart, Department of Medicine, Institut Jules Bordet, 1000 Brussels, Belgium
- K. Possinger, Universitätsklinikum Charité, Onkologie/ Hämatologie, 10098 Berlin, Germany
- K. I. Pritchard, Toronto-Sunnybrook Regional Cancer Center, Head Clinical Trials & Epidemiology, Toronto, ON M4N 3M5, Canada
- E. J. T. Rutgers, The Netherlands Cancer Institute, Department of Surgery, 1066 CX Amsterdam, The Netherlands
- V. F. Semiglazov, Petrov Research Institute of Oncology, Pesochny-2 197758 St Petersburg, Russia
- I. Smith, Department of Medicine, Royal Marsden Hospital, London SW3 6JJ, UK
- B. Thürlimann, Medizinische Onkologie, Haus 06, Kantonsspital St. Gallen, 9007 St Gallen, Switzerland
- G. Viale, Department of Pathology, European Institute of Oncology and University of Milan, 20141 Milan, Italy
- A. Wallgren, Sahlgrenska University Hospital, Department of Oncology, 413 45 Göteborg, Sweden (Absent)
- T. Watanabe, Department of Medicine, Hamamatsu Oncology Center, Hamamatsu, Shizuoka, Japan
- E. P. Winer, Breast Oncology Center, Dana-Farber Cancer Institute, Boston, MA 02115, USA
- W. C. Wood, Department of Surgery, Emory University School of Medicine, N.E. Atlanta, GA 30322, USA (**Chairman**)

The authors thank the Participants in the 10th 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 Dr Giuseppe Curigliano, Mrs Shari Gelber and Mrs Sabina Briner. We also thank Professor Umberto Veronesi for his guidance and Dr Franco Nolè for his thoughtful remarks. This work is dedicated to the memory of Dr John Bryant who, as senior statistician with the National Surgical Adjuvant Breast and Bowel Project, made significant contributions to the conduct and interpretation of early breast cancer clinical trials.

Appendix Table 4. Treatment allocation by therapeutic target and risk categories. Treatment options in each cell are listed in the order of preference (see text and footnotes)

HER2/*neu* gene overexpression and/or amplified			HER2 negative					HER2 positive				
Endocrine responsiveness[a]			highly responsive		incompletely responsive		non-responsive	highly responsive		incompletely responsive		non-responsive
Menopausal status			pre	post	pre	post	pre and post	pre	post	pre	post	pre and post
Risk category	Low	Node negative and **all** of the following features: pT ≤2 cm, Grade 1, no vascular invasion, HER2(−), ER and/or PgR expressed, Age ≥35 years	E[b]	E[b]	E[b]	E[b]						
	Intermediate	Node negative and **at least one** of the following features: pT >2 cm, Grade 2−3, vascular invasion, HER2(+), ER and PgR absent, Age <35 years	E C → E	E C → E	C → E E	C → E E	C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr
		1–3 nodes positive AND ER and/or PgR expressed and HER2(−)	E C → E	E C → E	C → E E	C → E E						
	High	1–3 nodes positive AND ER and PgR absent OR HER2(+)					C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr
		>4 nodes positive	C → E	C → E	C → E	C → E	C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr

[a]Responsiveness to endocrine therapies is defined in the text.

[b]Endocrine therapy is effective for prevention and DCIS and therefore might be considered even for very low risk invasive breast cancer.

C, chemotherapy; E, endocrine therapy (selected according to menopausal status); **Tr, trastuzumab** (note 1: trastuzumab should not be viewed as a standard treatment in women with a primary tumor <1 cm of size and with no axillary node involvement. This is particularly true in patients with highly and perhaps also incompletely endocrine responsive disease; note 2: trastuzumab should be given concurrently and after chemotherapy or following completion of all chemotherapy according to clinical trial evidence available at present, though a majority of the Panel agreed that trastuzumab without prior or concurrent chemotherapy may become appropriate for some patients in the future).

references

1. 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.
2. 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.
3. 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.
4. Slamon D. BCIRG 006 II interim analysis. San Antonio Breast Cancer Symposium. 2006 http://www.bcirg.org/Internet/BCIRG+at+SABCS+2006/default.htm.
5. Goldhirsch A, Coates AS, Gelber RD et al. First select the target: better choice of adjuvant treatments for breast cancer patients. Ann Oncol 2006; 17: 1772–1776.
6. Yang X, Lippman ME. BRCA1 and BRCA2 in breast cancer. Breast Cancer Res Treat 1999; 54: 1–10.
7. Walsh T, King MC. Ten genes for inherited breast cancer. Cancer Cell 2007; 11: 103–105.
8. De Soto JA. Deng CX. PARP-1 inhibitors: are they the long-sought genetically specific drugs for BRCA1/2-associated breast cancers? Int J Med Sci 2006; 3: 117–123.
9. Domchek SM, Friebel TM, Neuhausen SL et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 2006; 7: 223–229.
10. Rebbeck TR, Friebel T, Lynch HT et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2004; 22: 1055–1062.
11. Plevritis SK, Kurian AW, Sigal BM et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA 2006; 295: 2374–2384.
12. Sorlie T. Molecular classification of breast tumors: toward improved diagnostics and treatments. Methods Mol Biol 2007; 360: 91–114.
13. Rodriguez-Pinilla SM, Sarrio D, Honrado E et al. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res 2006; 12: 1533–1539.
14. Fan C, Oh DS, Wessels L et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006; 355: 560–569.
15. Viale G. Pathological definitions of invasion, metastatic potential and responsiveness to targeted therapies. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
16. Viale G, Regan M, Dell'Orto P et al. Central review of ER, PgR and HER-2 in BIG 1-98 evaluating letrozole vs. tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Breast Cancer Res Treat 2005; 94 (Suppl 1): S13 Abstract 44.
17. Perez EA, Suman VJ, Davidson NE et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. J Clin Oncol 2006; 24: 3032–3038.
18. Regan MM, Viale G, Mastropasqua MG et al. Re-evaluating adjuvant breast cancer trials: assessing hormone receptor status by immunohistochemical versus extraction assays. JNCI Cancer Spectrum 2006; 98: 1571–1581.
19. Ariazi EA. Crosstalk between estrogen receptor and growth factor receptor pathways as a cause for endocrine therapy resistance in breast cancer. Clin Cancer Res 2005; 11: 865s–870s.
20. Ariazi EA. Emerging principles for the development of resistance to antihormonal therapy: implications for the clinical utility of fulvestrant. J Steroid Biochem Mol Biol 2006; 102: 128–138.
21. Goss P. Application of aromatase inhibitors in endocrine responsive breast cancer. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
22. Goetz MP. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007; 101: 113–121.
23. Smith I. The evolution of adjuvant endocrine therapy: Developments since St Gallen 2005. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
24. Coates AS, Keshaviah A, Thurlimann B et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 2007; 25: 486–492.
25. Albain KS. Chemotherapy for endocrine responsive disease: An evolving story. Breast 2007; 16 (Suppl 1): S9 Abstract S30.
26. Berry DA, Cirrincione C, Henderson IC et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006; 295: 1658–1667.
27. Martin M. Benefit with adjuvant taxanes and endocrine responsiveness in breast cancer. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
28. Hudis C. Taxing the taxanes in adjuvant therapy. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
29. Hayes DF, Thor A, Dressler L et al. HER2 predicts benefit from adjuvant paclitaxel after AC in node-positive breast cancer: CALGB 9344. J Clin Oncol 2006; 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition; June 20 Suppl) 24: 510.
30. Dang D, Hudis C. Adjuvant taxanes in the treatment of breast cancer: no longer at the tip of the iceberg. Clin Breast Cancer 2006; 7: 51–58.
31. Rouzier R, Rajan R, Wagner P et al. Microtubule-associated protein tau: a marker of paclitaxel sensitivity in breast cancer. Proc Natl Acad Sci USA 2005; 102: 8315–8320.
32. Di Leo A. Using specific cytotoxics with a targeted mind. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
33. James CR, Quinn JE, Mullan PB et al. BRCA1, a potential predictive biomarker in the treatment of breast cancer. Oncologist 2007; 12: 142–150.
34. Curigliano G, Spitaleri G, Pietri E et al. Breast cancer vaccines: a clinical reality or fairy tale? Ann Oncol 2006; 17: 750–762.
35. Sledge GW. The evolution of targeted biologic therapies. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
36. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2783–2785.
37. Piccart-Gebhart M. The evolution of treatment strategies. Aiming at the target. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
38. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005; 10 (Suppl 3): 20–29.
39. Hayes D. Angiogenesis as targeted therapy for breast cancer. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
40. Burstein H, Spigel D, Kindsvogel K et al. Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: a randomized phase II study. Breast Cancer Res Treat 2005; 94 (Suppl 1): S6 abstract 4.
41. Cataliotti L, De Wolf C. Holland R et al, for EUSOMA. Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. Eur J Cancer 2007; 43: 660–675.
42. Fisher B, Land S, Mamounas E et al. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol 2001; 28: 400–418.
43. EORTC. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006; 24: 3381–3387.
44. Mokbel K, Cutuli B. Heterogeneity of ductal carcinoma in situ and its effects on management. Lancet Oncol 2006; 7: 756–765.
45. Wong JS, Kaelin CM, Troyan SL et al. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006; 24: 1031–1036.
46. Katz SJ, Hofer TP, Hawley S et al. Patterns and correlates of patient referral to surgeons for treatment of breast cancer. J Clin Oncol 2007; 25: 271–276.
47. Daly MB. Tamoxifen in ductal carcinoma in situ. Semin Oncol 2006; 33: 647–649.
48. Rakovitch E, Franssen E, Kim J et al. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat 2003; 77: 285–293.
49. Forbes J. Controversies in the use of sentinel nodes in elderly women. St. Gallen 2007. Breast 2007; 16 (Suppl 1): S5 Abstract S19.
50. Galimberti V. International Breast Cancer Study Group Trial of sentinel node biopsy. J Clin Oncol 2006; 24: 210–211.
51. Wood WC. Breast surgery in advanced breast cancer: Local control in the presence of metastases. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
52. Rapiti E, Verkooijen HM, Vlastos G et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006; 24: 2743–2749.

53. Babiera GV, Rao R, Feng L et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006; 13: 776–782.
54. Kaufmann M, Hortobagyi GN, Goldhirsch A et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006; 24: 1940–1949.
55. Early Breast Cancer Trialists' Collaborative Group (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.
56. Harris JR. Post-mastectomy radiation therapy: translating local benefits into improved survival. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
57. Orecchia R. Partial breast irradiation: ready for routine? St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
58. Pritchard K, Piccart M. for the Early Breast Cancer Trialists' Collaborative Group (manuscript in preparation), 2007.
59. Giordano SH, Duan Z, Kuo Ye et al. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol 2006; 24: 2750–2756.
60. Khatcheressian JL, Wolff AC, Smith TJ et al. for the American Society of Clinical Oncology. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006; 24: 5091–5097.
61. Winer E. Follow-up care of patients with breast cancer. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
62. Timolati F, Ott D, Pentassuglia L et al. Neuregulin-1 beta attenuates doxorubicin-induced alterations of excitation-contraction coupling and reduces oxidative stress in adult rat cardiomyocytes. J Mol Cell Cardiol 2006; 41: 845–854.
63. Levine MN. Adjuvant therapy and thrombosis: how to avoid the problem? St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
64. Phillips KA, Bernhard J. Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. J Natl Cancer Inst 2003; 95: 190–197.
65. Burstein H. Cognitive side-effects of adjuvant treatments. St. Gallen. Breast 2007; 16 (Suppl): in print.
66. Tannock IF, Ahles TA, Ganz PA et al. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. J Clin Oncol 2004; 22: 2233–2239.
67. Partridge A. Fertility and adjuvant treatment in young women with breast cancer. St. Gallen 2007. Breast 2007; 16 (Suppl): in print.
68. Oktay K, Sonmezer M. Fertility preservation in young women undergoing breast cancer therapy. Oncologist 2006; 11: 422–434.
69. Ring AE, Smith IE, Ellis PA. Breast cancer and pregnancy. Ann Oncol 2005; 16: 1855–1860.
70. Loibl S, von Minckwitz G, Gwyn K et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer 2006; 106: 237–246.
71. Gelber S, Coates AS, Goldhirsch A et al. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. J Clin Oncol 2001; 19: 1671–1675.
72. Kroman N, Jensen MB, Wohlfahrt J. Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 2000; 320: 474–478.
73. Sorlie T, Perou CM, Tibshirani R et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001; 98: 10869–10874.
74. Colleoni M, Rotmensz N, Peruzzotti G et al. Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. Ann Oncol 2007 (accepted for publication).
75. Clarke CA, Glaser SL. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 2006; 24: 49.
76. Sorlie T, Tibshirani R, Parker J et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100: 8418–8423.
77. Wolff AC, 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. Arch Pathol Lab Med 2007; 131: 18.
78. Perez E. Combining adjuvant chemotherapy with biologicals. St. Gallen 2007. Breast 2007; 16 (Suppl 1): S10 Abstract S34.
79. Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). Clin Breast Cancer 2006; 7: 347–350.
80. 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.
81. Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol. 19. 2001; 1539–1569.
82. Kurtz J, Working Party EUSOMA. The curative role of radiotherapy in the treatment of operable breast cancer. Eur J Cancer 2002; 38: 1961–1974.
83. Korreman SS, Pedersen AN, Aarup LR et al. Reduction of cardiac and pulmonary complication probabilities after breathingadapted radiotehrapy for breast cancer. Int J Radiot Oncol Biol Phys 2006; 65: 1375–1380.
84. Coombes RC, Kilburn LS, Snowdon CF et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007; 369: 559–570.
85. Goss PE, Ingle JN. Martino S et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. JNCI Cancer Spectrum 2005; 97: 1262–1271.
86. Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005; 365: 60–62.
87. Jakesz R, Jonat W, Gnant M et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005; 366: 455–462.
88. Winer EP, Hudis C, Burstein HJ et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005; 23: 619–629.
89. Jimenez-Gordo AM, De Las Heras B, Zamora P et al. Failure of Goserelin ovarian ablation in premenopausal women with breast cancer: two case reports. Gynecol Oncol 2000; 76: 126–127.
90. Mauriac L, Keshaviah A, Debled M et al. Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial. Ann Oncol 2007; 18: 859–867.
91. Barroso G, Menocal G, Felix H et al. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertil Steril 2006; 86: 1428–1431.
92. 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.
93. Pritchard KI, Shepherd LE, O'Malley FP et al. HER2 and Responsiveness of Breast Cancer to Adjuvant Chemotherapy. N Engl J Med 2006; 354: 2103–2111.
94. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001; 19: 602–611.
95. Martin M, Villar A, Sole-Calvo A et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. Ann Oncol 2003; 14: 833–842.
96. Wood WC, Budman DR, Korzun AH et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994; 330: 1253–1259.
97. Hershman D, Neugut AI, Jacobson JS et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst 2007; 99: 196–205.
98. www.toptenresearch.org.