Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

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The 13th St Gallen International Breast Cancer Conference (2013) Expert Panel reviewed and endorsed substantial new evidence on aspects of the local and regional therapies for early breast cancer, supporting less extensive surgery to the axilla and shorter durations of radiation therapy. It refined its earlier approach to the classification and management of luminal disease in the absence of amplification or overexpression of the Human Epidermal growth factor Receptor 2 (HER2) oncogene, while retaining essentially unchanged recommendations for the systemic adjuvant therapy of HER2-positive and ‘triple-negative’ disease. The Panel again accepted that conventional clinico-pathological factors provided a surrogate subtype classification, while noting that in those areas of the world where multi-gene molecular assays are readily available many clinicians prefer to base chemotherapy decisions for patients with luminal disease on these genomic results rather than the surrogate subtype definitions. Several multi-gene molecular assays were recognized as providing accurate and reproducible prognostic information, and in some cases prediction of response to chemotherapy. Cost and availability preclude their application in many environments at the present time. Broad treatment recommendations are presented. Such recommendations do not imply that each Panel member agrees: indeed, among more than 100 questions, only one (trastuzumab duration) commanded 100% agreement. The various recommendations in fact carried differing degrees of support, as reflected in the nuanced wording of the text below and in the votes recorded in supplementary Appendix S1, available at Annals of Oncology online. Detailed decisions on treatment will as always involve clinical consideration of disease extent, host factors, patient preferences and social and economic constraints.

Key words: surgery, radiation therapy, systemic adjuvant therapies, early breast cancer, St Gallen Consensus, subtypes

introduction

The 2 years since the 2011 St Gallen Consensus [1] have seen substantial progress in evidence relevant to various aspects of the treatment of early invasive breast cancer. The genomic atlas of the disease [2] has emphasized its heterogeneity, and suggested that genomic studies may potentially inform treatment decisions such as the use of aromatase inhibitors [3, 4]. Further data became available reducing the necessity for axillary dissection [5, 6]. Studies presented at the 2012 ESMO meeting clarified the optimal duration of adjuvant trastuzumab in HER2-positive disease [7, 8]. The duration of adjuvant tamoxifen was addressed by the ATLAS study, which suggested a significant benefit for extending such treatment to 10 years rather than 5 years [9].

St Gallen 2013: news and progress

The 13th International Breast Cancer Conference held in St Gallen in March 2013 involved some 3700 participants from 95 countries and heard presentations from a faculty widely representative of disciplines and geographical areas. An Expert
Panel, which included 51 members from 21 countries, chaired by Aron Goldhirsch and Eric P. Winer met at the conclusion of the conference to review the new information presented and consider treatment recommendations for broad application over the next 2 years. As in the past, this conference included an explicit approach to management of conflicts of interest (see Appendix 2).

Table 1 summarizes the information presented during the conference.

Recent research in local therapy supports the continued trend towards less extensive procedures. Thus, axillary dissection can safely be omitted for patients with micrometastatic disease in sentinel nodes [65] and for those undergoing breast-conserving surgery and whole breast radiation therapy with up to two macroscopically positive sentinel nodes [66] (Table 1).

Two large studies [68, 69] support the safety and efficacy of shorter courses of whole breast radiation therapy (40 Gy in 15 or 42.5 Gy in 16 fractions), which offer advantages of convenience and cost over the previous standard of 50 Gy in 25 fractions.

New information became available for several aspects of systemic adjuvant therapy. The ATLAS trial reported superiority for 10 years compared with 5 years of adjuvant tamoxifen [9]. Further follow-up of the extended adjuvant study (MA.17) suggested particular benefit of letrozole for patients who were premenopausal at diagnosis but became postmenopausal by the time of letrozole administration [86].

The optimal duration of trastuzumab therapy in HER2-positive disease was clarified by results from two trials. The HERA trial [7] showed no additional benefit of 2 years trastuzumab compared with 1 year, while the PHARE trial [8] failed to show non-inferiority of 6 months trastuzumab compared with 1 year. Thus, the de facto standard of care remains 1 year of trastuzumab in patients with HER2-positive disease.

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of trials of chemotherapy versus no chemotherapy [18] failed to define any group for which chemotherapy did not offer an advantage. This conclusion is at odds with the results of individual trials and prospective/retrospective analyses of trials with assays such as the 21-gene recurrence score (RS). Furthermore, the control groups of trials included in the EBCTCG overview appear to exhibit much higher degrees of risk than that of patients with luminal disease seen in today’s practice who receive modern endocrine therapy as the backbone for their treatment. The EBCTCG report noted that ‘information was lacking about tumour gene-expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both’ [18]. Subsequent editorial comments [93, 94] drew differing interpretations of the EBCTCG conclusions.

breast cancer subtypes

The clinico-pathological surrogate definitions of subtypes as adopted by the Panel are summarized in Table 2, and their broad implications for systemic treatment selection are described in Table 3.

Further evidence has accrued in the last 2 years to support the use of multi-gene signatures to make distinctions among patients with luminal disease. Many different multi-gene assays provide prognostic information, primarily derived from their sampling of proliferation genes [97], which emphasizes the need for some measure of proliferation in any surrogate classification.

The 21-gene RS is accepted as providing not only prognostic, but also predictive information regarding the utility of cytotoxic therapy in addition to endocrine therapy for patients with luminal disease. This and perhaps other multi-gene assays can help define a group of patients for whom chemotherapy is futile because the biological nature of the tumour is such that it is substantially unresponsive to such agents. Existing studies of the 21-gene RS involve retrospective analysis of previously conducted randomized clinical trials [75, 76], which included both HER2-positive and HER2-negative cohorts. A recent report demonstrated excellent 5-year outcome without chemotherapy for a ‘good prognosis’ 70-gene signature cohort [49].

In those areas of the world where multi-gene assays are readily available, clinical practice has developed to rely on the results to guide decisions about inclusion of chemotherapy in the treatment of patients with ER-positive, HER2-negative disease. The 70-gene assay returns a dichotomous result, while 21-gene RS is continuous. An unresolved question is the level of RS which should justify cytotoxic therapy: only high RS values (>31) were significantly associated with chemotherapy benefit in the prospective/retrospective studies [75, 76], while substantially lower values are being investigated in ongoing prospective trials and are being used in clinical practice. For many societies, the cost of these multi-gene assays remains prohibitive.

The possibility that multi-gene expression assays may become more widely available was discussed by some Panellists after the meeting during the preparation of this manuscript. Cost-effectiveness studies have been carried out in the United States [98, 99], Canada [100–104], Israel [105], the UK [106] and Germany [107, 108]. These studies have yielded varying estimates ranging from cost-saving to an incremental cost-effectiveness ratio (ICER) of US $60 000 per quality-adjusted life year (QALY). One Japanese study of the 70-gene assay [109] found an ICER of US $40 000 per QALY. Such assessments will be sensitive not only to the cost of the test, but to the net proportion of patients in whom testing leads to the omission of cytotoxic therapy, and to the cost of the cytotoxic regimen which would otherwise have been given. These reports have largely worked from the perspective of the health care system or third-party payer, and thus offer hope that such bodies may increasingly support multi-gene testing. It has recently been reported that the UK National Institute for Clinical Excellence, having reached a confidential pricing arrangement with the supplier, has issued a draft recommendation that the 21-gene RS be used for women with node-negative disease for whom the indication for chemotherapy is otherwise uncertain.

Meanwhile, in many settings patients can only access multi-gene testing by large personal out-of-pocket payments, and therefore, from a global perspective for the immediate future

1http://guidance.nice.org.uk/DT/4 accessed 3 May 2013
Table 1. Recent research findings presented at the 13th 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                                                                                                                                                                                                                           |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Targeted treatments                                     | Proof of concept of mTOR pathway inhibition in metastatic disease was provided by the Bolero study [10]. The PI3K-alpha inhibitors, such as GDC-0032, have shown strong interaction with ER signalling in laboratory studies. Another PI3K-alpha inhibitor, BYL719, showed preclinical evidence of synergy with fulvestrant. The strong preclinical evidence for favourable interaction between endocrine therapy and various inhibitors of the PI3 kinase pathway (AKT inhibitors or MEK inhibitors) points to the need for clinical trials of such combinations [11]. In triple-negative breast cancer, PI3K inhibition impairs BRCA1/2 expression, thus sensitizing cells to PARP inhibition [12, 13]. A frequently mutated gene is TP53, which is abnormal in the majority of cases of HER2 overexpressing and triple-negative disease [2, 14]. Although, p53 has been studied for decades, its clinical utility remains limited due to the absence of standardization and the heterogeneity of the studies. Wild-type p53 activity impairs the preclinical response to anthracyclines [15], and there is an interaction with ER such that ER prevents p53-dependent apoptosis [16]. However, p53 was not predictive of preferential sensitivity to an anthracycline-based versus a taxane-based chemotherapy in a large phase III neoadjuvant study [17]. |
| Messages from the EBCTCG                                 | The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis showed efficacy of adjuvant chemotherapy compared with no chemotherapy, superiority of anthracycline-based regimens over CMF and of taxane-containing regimens over those based on anthracycline. The relative magnitude of benefit from anthracycline or anthracycline-taxane combinations resulted in similar reductions of breast cancer mortality irrespective of age, stage, histopathological grade and ER status, although the absolute gain for a low disease burden Luminal A-type of cancer will be very small [18, 19]. |
| Overview                                                 | Detailed analysis of the entire genome of breast cancers offers the potential for more precisely personalizing therapy [20]. Application is currently limited by the availability of suitably targeted therapeutic agents and by limited understanding of the roles and functions of many of the identified abnormalities, and clarification of which genomic alterations are functional and which are merely passenger mutations. |
| Personalizing treatment                                  | Analytic validity, clinical (or biologic) validity, and clinical utility are all required for optimal clinical application of tumour biomarkers [21].                                                                                                                                 |
| Intrinsinc subtypes                                      | Identification of intrinsic subtypes is most precise using molecular technologies [22]. Where such assays are unavailable, surrogate definitions of subtype can be obtained by IHC measurements of ER, PgR, Ki-67 and HER2 with in situ hybridization confirmation, where appropriate [23]. Moderate or strong expression of PgR has been proposed as an additional restriction in the surrogate definition of ‘Luminal A-like’ disease [24]. Ki-67 level as a marker of proliferation is also important for this distinction [23]. Both of these markers require quality control. In particular, Ki-67 measurement is not currently standardized among laboratories [25–27] (see panel deliberations below). |
| Lifestyle issues                                         | Epidemiological evidence suggests that a ‘Mediterranean’ diet is associated with a modest reduction in the risk of the occurrence of breast cancer [28]. Several recent meta-analyses have confirmed the association of physical activity with reduced breast cancer incidence and improved prognosis [29].                                                                                                                                 |
| Hormonal influences                                      | Sex hormones, particularly estrogens, are recognized as important in defining the risk of occurrence of breast cancer, and may be important in particular treatment situations, such as the use of aromatase inhibitors. However, analytical issues still limit the measurement of estrogen at low but clinically relevant levels [30, 31].                                                                                                                                 |
| Hereditary breast cancer                                 | Factors to be considered regarding recommendation for genetic testing include known mutation in the family, patient or close relative with breast cancer diagnosis <35, patient or close relatives with ovarian or fallopian tube cancers, multiple pancreatic cancers, and some pathological features. However, intrinsic subtype cannot safely be used to exclude the need for genetic testing [32].                                                                                                                                 |
| Obesity and fat                                          | Obesity is widely recognized as a risk factor for both occurrence and worsened prognosis of breast cancer [33]. Obesity is not clearly predictive of AI (versus Tam) benefit in postmenopausal women [34–36], but may be predictive of reduced AI benefit in premenopausal women [37]. Evidence exists that adipose tissue contains pluripotent stem cells, which might be responsible for tumour angiogenesis [38, 39]. Such cells have been shown to promote breast cancer growth in preclinical models [40], raising the hypothetical concern that use of adipose tissue in breast reconstruction might increase the risk of recurrence. |
| Metastasis, microenvironment, bone and bisphosphonates    | Metastasis is a complex event governed by host interactions. Characteristics of the microenvironment are important in the metastatic process. In preclinical models, tenascin C promotes the aggressiveness of metastasis [41] and autocrine tenasin C is required for early colonization [42]. Bisphosphonates may have beneficial effects in estrogen-deprived women [43–45]. This benefit, which remains uncertain, does not appear to be limited to the inhibition of bone metastases.                                                                                                                                 |
| Metronomic chemotherapy                                  | Metronomic chemotherapy demonstrates activity in the neoadjuvant setting [46] and in preclinical studies is effective in combination with anti-angiogenic treatments [47].                                                                                                                                 |

Continued
Radiation therapy
Clinical trial evidence supports the validity of hypofractionated radiotherapy such as 40 Gy in 15 or 42.5 Gy in 16 fractions in

Immunity and vaccines
Therapeutic vaccination remains elusive because of tumour heterogeneity and immune escape mechanisms. Agents, such as

Surgery of the primary
Although the risk of local regional relapse is related to the biological aggressiveness of the disease as reflected in its intrinsic

Surgery of the axilla
Substantial new data were presented about the role of and necessity for completion axillary dissection after positive sentinel

Radiation therapy
Clinical trial evidence supports the validity of hypofractionated radiotherapy such as 40 Gy in 15 or 42.5 Gy in 16 fractions in many patients [68–70]. Such short course whole breast radiation therapy has obvious advantages in terms of patient convenience and cost.

Adjuvant chemotherapy
A major unresolved question is the threshold for use of adjuvant cytotoxic chemotherapy for patients with Luminal A or Luminal B disease. In prospective/retrospective studies, the 21-gene recurrence score (RS) identifies groups who do not benefit from the addition of chemotherapy in node-negative [75] or node-positive [76] disease. In both these studies based on randomised trials, chemotherapy benefit was confined to the group with high 21-gene RS. Another series using the 70-gene signature noted excellent 5-year distant recurrence free interval for the ‘good prognosis’ group without chemotherapy [49]. PAM50 classification showed no benefit of anthracycline-based chemotherapy (CEF) compared with CMF chemotherapy in patients with either Luminal A or Luminal B disease [77]. For patients with triple-negative disease, optimal chemotherapy regimens have not been defined, but evidence supports the inclusion of anthracyclines and taxanes, but not bevacizumab, platinumus, capecitabine, or gemcitabine [78]. No standard duration of adjuvant chemotherapy has yet been identified for patients with endocrine non-responsive disease [79].
multi-gene testing remains inaccessible for the majority of women with early breast cancer. It is for these women that the Panel believed that the approach adopted by successive St Gallen Panels based on the available clinico-pathological testing, and now expressed in the surrogate IHC-based classification shown in Table 2 will be more widely applicable at lesser cost, notwithstanding its limited validation.

The main reason for attempting distinction between ‘Luminal A-like’ (more endocrine sensitive, indolent, better prognosis) and ‘Luminal B-like’ (less endocrine sensitive, more aggressive, worse prognosis) tumours was recognized to be the differing implications for the utility or futility of adjuvant cytotoxic therapy between these groups. Evidence was presented that the clarity of distinction between ‘Luminal A-like’ and ‘Luminal B-like’ tumours could be improved by the requirement for substantial PgR positivity in the definition of ‘Luminal A-like’ disease [24]. Adding this restriction will have the effect of reducing the number of patients classified as ‘Luminal A-like’ and thus increasing the number for whom cytotoxic therapy is generally recommended. Recognizing that high-quality pathology and quality assurance programmes are important for the interpretation of these tests, it was noted that the absolute values of each IHC parameter/cut-point may vary between laboratories, and that pending improved standardization local experience might best define the locally useful cut-points between ‘high’ and ‘low’ Ki-67 and PgR.

### panel deliberations

The Panel reviewed a series of questions developed by iterative consultation over the months preceding the conference. Voting on most questions was in the format yes, no or abstain, where abstaining was recommended if the Panel member felt a conflict of interest in the question, that there was insufficient evidence to support an opinion either way or that he or she lacked the relevant expertise. Detailed voting records for each of the questions put to the Panel are provided in the supplementary Appendix S1, available at Annals of Oncology online.

### surgery of the primary

The Panel found very few absolute contraindications to breast-conserving therapy. Margins involved with invasive carcinoma or DCIS after repeated resection were one such absolute contraindication. The minimal acceptable surgical margin was felt to be ‘no ink on invasive tumour’ (i.e. margins free of tumour) by nearly three quarters of the Panellists and most of the others would accept a minimum clearance of 1 mm. The Panel was almost unanimous that breast-conserving surgery should not be carried out unless postoperative radiation (if indicated, as described below in the radiation therapy section) could be delivered.

A majority of the Panel considered that relative but not absolute contraindications to breast-conserving therapy included very young age (<35 years), extensive or diffuse
Luminal A-like:
c- all of:
- ER and PgR positive
- HER2 negative
- Ki-67 ‘low’
- Recurrence risk ‘low’ based on multi-gene-expression assay (if available) 

Luminal B-like (HER2 negative):
- ER positive
- HER2 negative
- and at least one of: Ki-67 ‘high’
- PgR ‘negative or low’
- Recurrence risk ‘high’ based on multi-gene-expression assay (if available) 

Luminal B-like (HER2 positive):
- ER positive
- HER2 over-expressed or amplified
- Any Ki-67
- Any PgR 

Erb-B2 overexpression:
- HER2 positive (non-luminal):
  - HER2 over-expressed or amplified
  - ER and PgR absent

‘Basal-like’:
- Triple negative (ductal):
  - ER and PgR absent
  - HER2 negative 
  
There is an 80% overlap between ‘triple-negative’ and intrinsic ‘basal-like’ subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. ‘Triple negative’ also includes some special histological types such as adenoid cystic carcinoma.

A majority of the Panel voted that a threshold of ≥20% was indicative of ‘high’ Ki-67 status. Others, concerned about the high degree of inter-laboratory variation in Ki-67 measurement [26] and the possibility for undertreatment of patients with luminal disease who might benefit from chemotherapy, would use a lower (local laboratory specific) cut-point to define Ki-67 ‘high’ or use multi-gene-expression assay results, if available.

This factor was added during Panel deliberations after circulation of the first draft of the manuscript, to reflect a strong minority view. Although neither the 21-gene RS nor the 70-gene signature was designed to define intrinsic subtypes, a concordance study noted that over 90% of cases with a low RS and almost 80% of those with a 70-gene low-risk signature were classified as Luminal A [95].

microcalcifications where the presence of malignancy cannot be reliably excluded without complete excision; multicentric disease; tumour location near the nipple and mutations of the BRCA1 or BRCA2 genes. Substantial minority support added multifocal disease, extensive vascular invasion and an extensive intraductal component to this list of relative contraindications. Positive family history and unfavourable biology based on genomic profiling were not considered to be contraindications to breast-conserving therapy.

Nipple-sparing surgery was considered acceptable, provided the margin close to the nipple was not involved. The vast majority of Panel members thought magnetic resonance imaging should not be routinely used in the assessment of newly diagnosed breast cancer.

surgery of the axilla
The Panel believed that axillary dissection could be safely omitted in patients with one or two positive sentinel nodes following breast-conserving surgery when whole breast radiation therapy is planned. The Panel was nearly equally divided whether this recommendation also applied to mastectomy followed by radiotherapy, but was almost unanimous in the need for axillary dissection if no radiotherapy was planned.

The Panel also considered that axillary dissection was required with three or more involved sentinel nodes or if nodes were clinically involved before surgery and confirmed by biopsy.

radiation therapy
The Panel strongly agreed that ‘short course’ radiotherapy, such as 40 Gy in 15 or 42.5 Gy in 16 fractions, could be offered as a standard for at least some patients, with a slim majority thinking that this would be suitable for almost all patients. The Panel agreed that short course radiotherapy was an option whether or not a boost to the tumour bed was planned. A large majority of Panel members thought that there were definable
groups of patients not requiring radiotherapy following breast-conserving surgery, and that these might include the elderly and those with substantial comorbidity. The Panel could not reach a majority view regarding the current acceptability of the various techniques for partial breast radiation as definitive treatment.

Post-mastectomy radiotherapy was considered indicated by almost all Panel members for patients with four or more positive nodes, while the majority would not advise post-mastectomy irradiation for those with one to three positive nodes, except in the presence of adverse tumour pathology. The Panel was content to omit post-mastectomy radiotherapy with pathologic uninvolved nodes even when fewer than eight nodes had been examined and if the tumour was \( \leq 5 \) cm. Two-thirds felt that radiation therapy should be given after mastectomy if positive sentinel nodes were not followed by axillary dissection.

Other indications recommended by the Panel for post-mastectomy radiotherapy included positive deep margins and, for two-thirds of the Panel, tumours greater than 5 cm regardless of the nodal status. However, the Panel strongly rejected needing radiotherapy solely based on Grade 3, lymphovascular invasion, HER2-positive status or triple-negative disease.

Areas to be irradiated following mastectomy and axillary dissection should not be influenced by any neoadjuvant systemic therapy or by the intrinsic subtype of the tumour. There was no clear agreement about the necessity to include the supraclavicular fossa, though trials have routinely included this area. Most Panel members would not include the internal mammary nodes and a strong majority felt that the axilla should not be radiated after dissection.

**pathology**

The Panel recognized substantial progress in the pathological characterization of tumour subtypes. There was little change in the classification of HER2-positive or triple-negative disease. The majority of the Panel accepted that a useful surrogate definition of Luminal A-like as distinct from Luminal B-like disease could be made using a combination of ER, PgR and Ki-67, without requiring molecular diagnostics. Ki-67 has been used for more than two decades as a prognostic marker in early breast cancer [110–118]. The Panel did not accept that distinction between Luminal A-like and Luminal B-like tumours could be made with ER and PgR alone, and a clear majority voted that grade 3 could not be used as a substitute for high Ki-67 for this purpose. The Panel noted that standardized cut-offs for Ki-67 have not been established and laboratory specific values should be used, but the majority of the Panel voted that a threshold of \( \geq 20\% \) was clearly indicative of ‘high’ Ki-67 status. A minority questioned the role of Ki-67 in breast...
cancer treatment decisions. The Panel stressed the need for standardization, and that laboratories should participate in quality assurance programmes.

The Panel was strongly of the opinion that intrinsic subtypes, including those defined by the clinico-pathological surrogates, should influence whether or not chemotherapy was used, but not the choice of the cytotoxic regimen. After clinico-pathological assessment, a slim majority of the Panel was in favour of requesting a multi-gene assay in node-negative, ER-positive and HER2-negative cases. The Panel considered that only the 21-gene RS was predictive of chemotherapy responsiveness, though a substantial minority would also endorse PAM50 or the 70-gene signature for this purpose. This led to a recommendation that selection of patients who might forego chemotherapy could be based on the 21-gene RS, but the Panel did not offer majority endorsement for PAM50, the 70-gene signature or EPIClin as yet established for this purpose.

For patients with ER-positive, HER2-negative disease, the use of molecular diagnostics was felt to be unnecessary in low-risk patients such as those with a tumour size of ≤1 cm in the setting of negative lymph nodes, since chemotherapy would be unlikely to be given anyway. Similarly, patients with a higher risk such as those with a tumour size >5 cm, inflammatory breast cancer, those with four or more involved nodes, or a very low ER positivity (e.g. 5%) might not benefit from molecular diagnostics because chemotherapy would be likely to be offered in any case. Patients in whom chemotherapy was thought to be of uncertain indication and who might, therefore, benefit from molecular diagnostics were felt to include selected patients with node-negative disease, those with one to three positive nodes, and patients aged <35.

In the determination of HER2 status for treatment purposes, the Panel did not believe that polysomy of chromosome 17, or heterogeneity of expression of HER2 need to be considered.

**adjuvant endocrine therapy in premenopausal women**

The large majority of the Panel said that tamoxifen alone was the default adjuvant endocrine therapy for premenopausal patients. In light of recent trial evidence, it was felt that at least some patients should have a treatment duration of 10 years, although this may not be needed by all patients. Most Panellists thought ovarian suppression need not be added to tamoxifen, but Panellists were evenly divided for patients <40 years of age. Most of the Panel regarded both ovarian suppression alone without tamoxifen and its combination with aromatase inhibitors as inappropriate unless tamoxifen was contraindicated.

**adjuvant endocrine therapy in postmenopausal women**

The Panel strongly believed that some postmenopausal women could be treated with tamoxifen alone. If an aromatase inhibitor were included in the regimen, Panellists were equally divided whether treatment should start with the aromatase inhibitor, although this strategy was strongly preferred for patients at high risk. Most Panellists believed that initial aromatase inhibitor therapy could be replaced by tamoxifen after 2 years, if there were a reason to do so. Extension of aromatase inhibitor therapy beyond the first five years for patients with node-positive, but not node-negative disease was strongly supported, for patients whose initial treatment was tamoxifen or whose initial therapy was <5 years of an aromatase inhibitor. The Panel was equally divided concerning an extended duration of aromatase inhibitor therapy beyond 5 years of treatment with these agents. Extended adjuvant endocrine therapy using tamoxifen is a consideration after a 5-year course of an aromatase inhibitor, though this approach has not been directly studied.

**adjuvant cytotoxic chemotherapy**

The Panel was clearly of the opinion that factors arguing for the inclusion of chemotherapy were histological grade 3 tumours, high Ki-67, low hormone receptor status, HER2 positivity or triple-negative status, high 21-gene RS, high-risk 70-gene signature and the involvement of more than three lymph nodes. Most felt that nodal positivity per se was not an indication for chemotherapy but very few would forego chemotherapy for patients with four or more positive nodes. Lymphovascular invasion was not recognized as an indication, while the Panel was equally divided whether young age (<35 years) was an indication.

The Panel was of the strong opinion that patients with Luminal A-like disease were ‘less responsive to chemotherapy’, but this treatment could be added to endocrine therapy based on the large tumour volume, assessment of risk or patient preference. The Panel did not select a specific chemotherapy regimen for these patients and expressed the view that any of the standard regimens, including the first- and second-generation regimens (CMF, AC, TC), could be considered.

For patients with Luminal B (HER2-negative) disease, the majority of the Panel considered chemotherapy to be indicated. Chemotherapy regimens for Luminal B (HER2-negative) disease should generally contain anthracyclines and (by a slim majority) taxanes. Half the Panel agreed that such chemotherapy should be delivered for at least six cycles, but the Panel did not endorse the exclusive use of a dose dense regimen.

For patients with HER2-positive disease, the Panel strongly believed, while there was no specifically preferred regimen, chemotherapy should include a taxane and, for most Panel members, also an anthracycline.

For patients with ‘basal-like’ (triple-negative ductal) disease, the Panel strongly endorsed both anthracyclines and taxanes, and did not believe that platinum, or regimens emphasizing alkylating agents were specifically required. There was no clear consensus on the role of dose dense regimens, though a substantial minority expressed support for such treatment.

General considerations influencing the choice of chemotherapy regimen were thought to include a desire to preserve fertility, the avoidance of alopecia and the presence of co-morbidities, but not intrinsic subtype or the presence of BRCA1 or BRCA2 mutation. Older chronological age should not necessarily influence the choice of regimen [119], but assessment of co-morbidities and general health was considered, especially important in older patients.
anti-HER2 therapies
For patients whose tumours show amplification or overexpression of HER2, the Panel considered that trastuzumab therapy was indicated for patients with tumours >5 mm, while some Panellists would treat patients with such tumours of any size. Most felt that trastuzumab should be given concurrently with a taxane, but not with an anthracycline. The Panel was prepared to endorse trastuzumab (with endocrine therapy, if indicated) without chemotherapy only if chemotherapy were contraindicated. The Panel was unanimous that the duration of treatment of trastuzumab should be 1 year.

neoadjuvant cytotoxic chemotherapy
The Panel was split about whether neoadjuvant chemotherapy had benefits beyond local downstaging. The Panel did not support additional postoperative adjuvant chemotherapy following a full course of neoadjuvant chemotherapy, whether or not pCR were achieved. Most believe when neoadjuvant therapy is given outside of a clinical trial, the full course of chemotherapy should be completed before surgery. In the unusual situation in which a surgery is carried out after less than a full course of neoadjuvant chemotherapy most Panel members would complete the course postoperatively.

neoadjuvant anti-HER2 therapy
For patients with HER2-positive disease, the Panel was strongly of the opinion that neoadjuvant treatment should include anti-HER2 drugs, and the majority recommended the use of chemotherapy plus trastuzumab alone (without additional anti-HER agents).

neoadjuvant endocrine therapy
The Panel strongly endorsed endocrine therapy alone as neoadjuvant treatment for postmenopausal patients with strongly positive hormone receptors and low proliferating disease, and most thought that such treatment should be continued until maximal response.

bisphosphonates
The Panel considered several situations in which bisphosphonates might be used with the aim of improving disease-free survival, but did not endorse such treatment for this purpose in any group, though a substantial minority felt that premenopausal patients receiving an LHRH agonist plus tamoxifen or clearly postmenopausal patients might derive benefit from such treatment. Denosumab was not endorsed for adjuvant use.

follow-up
The majority of the Panel believed that regular follow-up after the completion of immediate treatment (excluding long-term endocrine therapy) was appropriate, but that this could be supervised by a nurse specialist, rather than a surgeon or oncologist. The majority of the Panel also believed that follow-up should be done in person and not by telephone.

summary of treatment recommendations
The conference endorsed recent trial evidence supporting less extensive local therapies. It refined and re-iterated the value of clinico-pathological surrogate definitions resembling intrinsic subtypes to guide selection of systemic adjuvant therapies. The Panel recognized the superior accuracy and reproducibility of multi-gene molecular assays, but recognized that these assays are not available in all parts of the world. The Panel also noted the variability in the current levels of evidence to support the use of the individual multi-gene assays. Ongoing trials will prospectively define the value of chemotherapy in addition to endocrine therapy in patients with luminal disease in the node-negative (TAILORx, MINDACT) and node-positive (MINDACT, RxPONDER) cohorts. It is therefore to be hoped that a future St Gallen Consensus conference will be able to provide more robustly supported recommendations for treatment of such patients.

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disclosure
The full COI statements of all authors are included in appendix 2.

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appendix 1

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| Adami, Kathy       | GHU  | Roche/GeneTech                     | < $10k |            |       |          |        |            |       |
|                    |      | Pfizer                             | < $10k |            |       |          |        |            |       |
|                    |      | Novartis                           | < $10k |            |       |          |        |            |       |
| Andrea, Fabrice    | Novartis | Roche                           | < $10k | < $10k |       |          |        |            |       |
| Baselga, Jose      | Roche          | Bavarian                           | < $10k | < $10k |       |          |        |            |       |
|                    |               | Janssen                             | < $10k | < $10k |       |          |        |            |       |
|                    |               | Merck                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Novartis                           | < $10k | < $10k |       |          |        |            |       |
|                    |               | Roche                               | < $10k | < $10k |       |          |        |            |       |
| Bergh, Morgan       | none          | ESRCA                               |        |            |       |          |        |            |       |
| Berry, Don         | none          | Barry Consultants LLC              |       |            |       |          |        |            |       |
| Bertheau, Philippe  | none          |                                    |       |            |       |          |        |            |       |
| Bertoni, Francesco  | none          |                                    |       |            |       |          |        |            |       |
| Bonnetto, Herve     | none          |                                    |       |            |       |          |        |            |       |
| Breule, Dominique   | none          |                                    |       |            |       |          |        |            |       |
| Burenhult, Harald   | none          |                                    |       |            |       |          |        |            |       |
| Cadozo, Fatima      | Novartis       | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
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|                    |               | Genentech                          |        |            |       |          |        |            |       |
| Castagnone, Monica  | none          |                                    |       |            |       |          |        |            |       |
| Chelisowska, Rowan T | none      | Angen                              | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
|                    |               | Novartis                           | < $10k | < $10k |       |          |        |            |       |
| Coates, Alan       | none          |                                    |       |            |       |          |        |            |       |
| Coleman, Robert     | none          |                                    |       |            |       |          |        |            |       |
| Vollrath, Marco      | none          |                                    |       |            |       |          |        |            |       |
| Costa, Alberto      | DUNE          | Roche                               | < $10k | < $10k |       |          |        |            |       |
| Cuglazione, Giuseppe | none        | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Merck                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
| Davidec, Nancy      | none          |                                    |       |            |       |          |        |            |       |
| De Leo, Angelo      | AstraZeneca   | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Novartis                           | < $10k | < $10k |       |          |        |            |       |
|                    |               | Merck                               | < $10k | < $10k |       |          |        |            |       |
| Dowsett, Mitch      | AstraZeneca   | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Novartis                           | < $10k | < $10k |       |          |        |            |       |
| Edelsten, Bent      | Novartis       | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Merck                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
| Els, Matthew       | Novartis       | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
| Fortes, John F      | Sanofi-Aventis | Roche                             | < $10k | < $10k |       |          |        |            |       |
| Frulli, Vincenzo    | none          |                                    |       |            |       |          |        |            |       |
| Glangheli, Viviana  | none          |                                    |       |            |       |          |        |            |       |
| Gamble, Judy        | none          |                                    |       |            |       |          |        |            |       |
| Gebauer, Richard    | none          |                                    |       |            |       |          |        |            |       |
| Gerard, Michael     | Angen          | Roche                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | AstraZeneca                         | < $10k | < $10k |       |          |        |            |       |
|                    |               | Genentech                          | < $10k | < $10k |       |          |        |            |       |
|                    |               | Merck                               | < $10k | < $10k |       |          |        |            |       |
|                    |               | Novartis                           | < $10k | < $10k |       |          |        |            |       |
|                    |               | Pfizer                             | < $10k | < $10k |       |          |        |            |       |
|                    |               | Roche                               | < $10k | < $10k |       |          |        |            |       |
| Goodwin, Alan       | none          |                                    |       |            |       |          |        |            |       |
| Goodman, Pamela J   | none          |                                    |       |            |       |          |        |            |       |
| Gosse, Paul         | none          | Pfizer                             | < $10k | < $10k |       |          |        |            |       |
| Gruber, Günter      | none          | Genentech                          |        |            |       |          |        |            |       |

**Note:** COI = Conflict of Interest; Sp/Bur = Support for Burden; Consultant = Financial Relationships with Consulting Companies; Stock = Financial Relationships with Companies; Travel = Financial Relationships with Travel Expenses; Employment = Employment Relationships with Companies; Other = Other Financial Relationships.
| Name                      | None | Company                        | Stock | Research | Travel | Employment | Other                                      |
|---------------------------|------|--------------------------------|-------|----------|--------|------------|--------------------------------------------|
| Henki, Moutzaphs          | none |                                |       |          |        |            | My private institution has a research contract with Siemens concerning the investigation of homoyruth. There is no personal salary for me as head investigator. The research is sponsored by Siemens. |
| Harris, Jay R             | none |                                |       |          |        |            |                                            |
| Hayes, Daniel             | none | Oncoimmune LLC                 | x     |          |        |            |                                            |
| Stockbrokers              |      |                                 |       |          |        |            |                                            |
| Ixchel, William           | none |                                |       |          |        |            |                                            |
| Janssen, Marie            | none |                                |       |          |        |            |                                            |
| Jekel, Alexander          | none |                                |       |          |        |            |                                            |
| Jia, James                | none |                                |       |          |        |            |                                            |
| Jiang, Zefei              | none |                                |       |          |        |            |                                            |
| Korf, Paulo               | none |                                |       |          |        |            |                                            |
| Kaufmann, Manfred         | none |                                |       |          |        |            |                                            |
| Kerbel, Robert S          | none | Pfizer                          |    10k|          |        |            |                                            |
| Kitchen, Robert           | none |                                |       |          |        |            |                                            |
| Kuttles, Shilpa           | none |                                |       |          |        |            |                                            |
| Luba, Sylvia              | none |                                |       |          |        |            |                                            |
| Macher, Geoffrey          | none |                                |       |          |        |            |                                            |
| Manne, Marzena            | none |                                |       |          |        |            |                                            |
| Merkatz von, Gunter       | none |                                |       |          |        |            |                                            |
| Mihale, Elke              | none |                                |       |          |        |            |                                            |
| Oliver, Ingrid Vinsen     | none |                                |       |          |        |            |                                            |
| Oore, Robba               | none |                                |       |          |        |            |                                            |
| Osborn, Darrell H         | none |                                |       |          |        |            |                                            |
| Odkersen, Thaddeus        | none |                                |       |          |        |            |                                            |
| Pardilla, Ann H           | none |                                |       |          |        |            |                                            |
| Pensa, Luise, Frederic    | none |                                |       |          |        |            |                                            |
| Perez, Charles            | none |                                |       |          |        |            |                                            |
| Peschke, Karlheinz F      | none |                                |       |          |        |            |                                            |
| Picart, Martine           | none |                                |       |          |        |            |                                            |
| Possinger, Kurt           | none |                                |       |          |        |            |                                            |
| Pritchard, Kathleen F     | none |                                |       |          |        |            |                                            |
| Rutgers, Emil             | none |                                |       |          |        |            |                                            |
| Schirmer, Felix           | none |                                |       |          |        |            |                                            |
| Sampath, Vatsana          | none |                                |       |          |        |            |                                            |
| Name               | None | Company    | Spk Bur | Consultant | Stock Research | Travel | Employment | Other                                      |
|--------------------|------|------------|---------|------------|----------------|--------|------------|--------------------------------------------|
|enn, Hae-Jong      | Novartis |            | <10k    |            |                |        |            | Co-inventor of an immune related gene-expression signature |
| Shao, Zhiming     |none         |            | <10k    |            |                |        |            |                                            |
| Scharnagel, David |none         |            |         |            |                |        |            |                                            |
| Smith, Ian         | Lilly | yes        | <10k    | <10k       |                |        |            |                                            |
| Stroh, Christian   | Novartis |            | 50k     |            |                |        |            |                                            |
| Thuermann, Beat    | Roche |            | >50k    | <10k       |                |        |            |                                            |
| Ueda, Masaharu    | Lilly | <10k       |         |            |                |        |            |                                            |
|       | Taiko Pharmaceutical |              | <10k    |            |                |        |            |                                            |
|       | Chugai Pharmaceutical |          | >10k    |            |                |        |            |                                            |
|       | Toyama Pharmaceutical |          | <10k    |            |                |        |            |                                            |
|       | Otsuka Pharmaceutical |          | <10k    |            |                |        |            |                                            |
| Tu, Andrew         | Astrazeneca | <10k      | <10k    |            |                |        |            |                                            |
|       | Clavir | <10k       |         |            |                |        |            |                                            |
|       | E mesa | <10k       |         |            |                |        |            |                                            |
|       | Bae | <10k       |         |            |                |        |            |                                            |
|       | Pfizer | <10k       |         |            |                |        |            |                                            |
|       | Astellas | <10k      | <10k    |            |                |        |            |                                            |
| Uehara, Michael    | Novartis |            | >10k    | <10k       |                |        |            |                                            |
| Viale, Giuseppe    | Diver | 50 K       |         |            |                |        |            |                                            |
| Watanabe, Tatsuo   | Taiko Pharmaceutical |          | >10k    |            |                |        |            |                                            |
| Nikken, Nicholas   | Roche | yes        | >10k    | <10k       |                |        |            |                                            |
|       | Taiko | yes        |         | <10k       |                |        |            |                                            |
|       | Novartis | yes       | <10k    |            |                |        |            |                                            |
|       | Astrazeneca | yes      | <10k    |            |                |        |            |                                            |
|       | Argen | yes        |         | <10k       |                |        |            |                                            |
|       | Roche | yes        |         | <10k       |                |        |            |                                            |
|       | Pfizer | yes        |         | <10k       |                |        |            |                                            |
| Winer, Eric        | Genetech | none      | No compensation | None | 50k | All travel | none                                      |
| Wood, William C    |none         |            |         |            |                |        |            |                                            |