Highlights of the 16th St Gallen International Breast Cancer Conference, Vienna, Austria, 20–23 March 2019: personalised treatments for patients with early breast cancer

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Abstract

The 16th St Gallen International Breast Cancer Conference took place in Vienna for the third time, from 20–23 March 2019. More than 3000 people from all over the world were invited to take part in this important bi-annual critical review of the 'state of the art' in the primary care of breast cancer (BC), independent of political and industrial pressure, with the aim to integrate the most recent research data and most important developments in BC therapies since St Gallen International Breast Cancer Conference 2017, with the ultimate goal of drawing up a consensus for the current optimal treatment and prevention of BC.

This year, the St Gallen Breast Cancer Award was won by Monica Morrow (Memorial Sloan Kettering Cancer Center, USA) for her extraordinary contribution in research and practise development in the treatment of BC. She opened the session with the lecture 'Will surgery be a part of BC treatment in the future?' Improved systemic therapy has decreased BC mortality and increased pathologic complete response (pCR) rates after neoadjuvant chemotherapy (NACT). Improved imaging and increased screening uptake have led to detect smaller cancers. These factors have highlighted two possible scenarios to omit surgery: for patients with small low-grade ductal carcinoma in situ (DCIS) and for those who have received NACT and had a clinical and radiological complete response. However, considering that 7%-20% of 'low-risk' DCIS patients have co-existing invasive cancer at diagnosis, that surgery has become progressively less morbid and less toxic than some systemic therapies with a lower cost-effectiveness ratio, and that identification of pathologic complete response (pCR) without surgery requires more intensive imaging follow-up (more biopsies, higher cost and more anxiety for the patient), surgery still appears to be an essential treatment for BC.

The Umberto Veronesi Memorial Award went to Lesley Fallowfield (Brighton and Sussex Medical School, UK) for her important research and activity in the field of the development of patient outcome, of better communication skills and quality of life for women. In her lecture, she remarked on the importance of improving BC personalised treatments, especially through co-operation between scientists, always considering the whole woman and not just her breast disease. This award was given by Paolo Veronesi, after a moving introduction which culminated with the following words of Professor Umberto Veronesi:
‘It is not possible to take care of the people’s bodies without taking care of their mind. My duty, the duty of all doctors, is to listen and be part of the emotions of those we treat every day’.

**Keywords:** 16th St Gallen Consensus Conference 2019, early breast cancer, neoadjuvant, adjuvant, therapies, consensus

### News and research priorities since St Gallen 2017

Regarding new developments in surgery, Walter Paul Weber (University Hospital Basel, Switzerland) spoke about the de-escalation of surgery of axilla according to the results of the IBCSG 23-01 and Z0011 trials [1, 2]. The current indications for axillary dissection (AD) are: clinically node-positive disease in upfront surgery, residual disease after NACT, locally advanced breast cancer (BC) (>2 pos sentinel lymph node (SN), gross extranodal disease, cT3-4, inflammatory) and SN macrometastasis in patient undergoing mastectomy (if post-mastectomy radiation is not indicated by the positive SN or does not include the regional node). The EORTC-AMAROS trial demonstrated that AD and axillary radiotherapy (ART) after a positive SN provide excellent and comparable axillary control for patients with T1-2 primary BC and no palpable lymphadenopathy, but with less morbidity by performing ART [3]. There are ongoing studies whose results will allow the extension of the Z0011 criteria (SENOMAC, ERC/IPC). Currently, SN biopsy (SNB) after NACT in patients with initially positive nodes is accurate and reliable but requires patient selection and optimal surgical techniques [4–7]. The current ‘no ink on tumour’ for invasive BC was confirmed to be safe [8, 9].

Regarding radiotherapy (RT), Philip Poortmans (Institut Curie, France) underlined that the main research priorities are to adapt RT based on the individual patient’s risk factors: for low-risk women, use of a shorter treatment schedule (intra-operative RT) or only a few days of RT could be appropriate, on the contrary, for high-risk patients, fully locoregional RT should be considered. However, more research need to be done before speaking about truly personalised breast RT [10–13]. Something totally new appears to be the possibility of prophylactic irradiation of the contralateral breast for BRCA mutation carriers [14].

Martine Piccart-Gebhart (Institut Jules Bordet, Belgium) presented news about systemic therapies. In the adjuvant setting: ‘dose-dense’ chemotherapy reduces BC and all-cause mortality [15] and de-escalation chemotherapy with taxotere + cyclophosphamide (TC) × 6 could replace anthracycline-based regimens [16]. In luminal BC patients, de-escalation of chemotherapy (TAILORx - Trial Assigning Individualized Options for Treatment (Rx)) appears to be possible. In pre-menopausal high-risk patients who have received chemotherapy, aromatase inhibitor (AI) and ovarian function suppression (OFS) are effective in reducing distant relapse at 8 years [17]. Extension of endocrine therapy (ET) beyond 5 years with an AI in postmenopausal women modestly affects recurrences; for some of these patients at high risk but with low compliance, intermittent administration of AI might be feasible with an improved quality of life [18]. In HER2pos high-risk BC patients, dual blockade improves invasive disease-free survival (IDFS) [19, 20]. De-escalation of chemotherapy by omitting anthracycline remains safe after 7 years in small volume disease (results from the APT trial), while de-escalating trastuzumab duration from 12 to 6 months appears still controversial [21]. There are many neoadjuvant trials to be considered, for instance, in luminal BC results derived from adding phosphoinositide 3-kinase inhibitor (PI3Ki) (LORELEI NEO-ORB) or cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) (PALLET, NEOMONARCH) to AI are very interesting; in HER2pos BC, the high pCR using Trastuzumab emtansine (T-DM1) with or without ET (ADAPT) is noteworthy, and in another ADAPT trial, it is interesting that with pertuzumab + trastuzumab, the pathological complete response rate (pCR) is 36%, but adding docetaxel achieves a pCR of 90%. In triple negative breast cancer (TNBC), the role of platinum is still unclear. In the post-neoadjuvant setting, the KATHERINE trial should be mentioned: administration of T-DM1 (compared to trastuzumab) to patients with HER2pos BC showing residual disease at surgery following standard NACT and single or dual HER2-blockade revealed a striking 11% absolute improvement in IDFS. In TNBC and residual disease after NACT, the CREATE-X (Capecitabine for Residual Cancer as Adjuvant Therapy) trial demonstrated the benefit of post-neoadjuvant treatment with capecitabine.

Kathleen Pritchard (Sunnybrook Odette Cancer Center, Canada) stated that there are many research priorities in the treatment of BC women to better understand when and how to de-escalate or escalate treatments to guarantee the most accurate standard of care and the best quality of life for women.
Biology of breast cancer: risk stratification

Richard Gelber (Dana-Farber Cancer Institute, USA) spoke about the fundamental role of staging and pathology in evaluating BC patients’ risk of recurrence and therapy selection [22–24]. Moreover, the morphological assessment of tumour-infiltrating lymphocytes (TILs) has an important prognostic role, in particular, in TNBC [25, 26] and HER2pos disease [27, 28]. Furthermore, the absence of pCR after NACT has showed the ability to stratify population for escalating adjuvant treatment among those patients with greater risk of recurrence and, on the contrary, de-escalating therapy amongst those with the lowest risk [29, 30]. The role of TILs in residual disease may further improve risk stratification [31].

Christos Sotiriou (Institut Jules Bordet, Belgium) focussed on the genomic risk stratification of early relapse. Gene expression profile (GEP) assays (e.g. Prosigna, Endopredict and Oncotype) have an important role in Estrogen Receptor (ER)pos/HER2neg BC as they inform the physician and patient on the risk of early recurrence and to assist them to choose the best treatment option in order to avoid recurrences but also useless treatments, in fact, this group of BC is a very heterogeneous disease and GEP might help to provide tailored treatment [32]. Data derived from studies such as TAILORx and MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) may be able to assess a prognostic relevance and help clinicians to evaluate the best treatment for every patient [33, 34]. Moreover, there are many ongoing studies assessing the predictive value of GEP for chemotherapy benefit in N1-2 BC (e.g. RxPONDER, WSG-ADAPT).

Regarding risk assessment of late recurrence from ERpos BC, Ivana Sestak (Wolfson Institute of Preventive Medicine, UK) reported that clinico-pathological parameters, especially nodal status and tumour size, are important for prediction of late recurrences. In some patients, extended ET can reduce recurrences but given the side effects of ET to define optimal patient selection for extended treatment is crucial. Many web-based risk calculators incorporating clinico-pathological and epidemiological parameters providing information on the risk of late recurrence have been developed, for example, the CTS5 calculator. Even if GEP have been developed to predict early recurrence, some of them have shown clinical validity for late recurrence too (e.g. BC Index, Prosigna and EndoPredict).

Fabrice André (Institut de Cancérologie Gustave Roussy, France) presented the argument ‘identifying research priorities in risk stratification of patients with BC’. Molecular tests could have the clinical utility to better decide which patients should receive chemotherapy or not, patients who can avoid ET with the rationale of not reducing quality of life unnecessarily [35], women at high risk even when optimally treated who are eligible for new (expensive) drugs and predict which patients will present outlier toxicity in order to substitute conventional treatments with new drugs. Regarding new tools for risk stratification, it should be taken into consideration that some genomic alteration could predict the outcome of BC patients—for instance, it has been reported in several studies that 8p11 amplification identifies a group of patients with poor outcome, in contrast, mutations on MAP3KA have been associated with better outcome [36]. Detection of circulating tumour DNA (ctDNA) after NACT and surgery could be associated with the worst prognosis [37], this tool could be important because we can detect micro metastases before to give local therapies. Testing pharmacodynamic of the drug in vivo [38] can also be relevant. Intratumour heterogeneity (genetic distance, lethal sub-clones in the primary tumour and genome instability) and genome evolution are going to give us information about the risk of relapse. Interestingly, there also appears to be a possible application for artificial intelligence and machine learning in this field of prediction [39].

Biology of breast cancer: prediction of response

Aleix Prat (Hospital Clinic of Barcelona, Spain) reported in his presentation on the heterogeneity in treatment response in patients with HER2pos BC and the importance of combinations of clinical and biomarker data with well-designed trials in order to successfully escalate or de-escalate therapy. At the DNA level, the two most relevant somatic mutations within HER2pos disease are TP53 and PIK3CA; interestingly, these mutations tend to be mutually exclusive. PIK3CA mutant/HER2pos tumours had lower pCR in the neoadjuvant setting compared with wild-type tumours [40]. HER2-enriched intrinsic subtype, which represents 50%–60% of all HER2pos tumours, is an important biomarker tracking HER2-addition and chemotherapy sensitivity [41]. Tumour microenvironment is also important, in particular, TILs in the stroma is a consistent biomarker of better outcome [42]. TILs seem to be interesting also as an on-treatment biomarker, in fact, there is a correlation between increasing TILs during therapy and pCR [43].
Matthew J Ellis (Lester and Sue Smith Breast Center, USA) presented the difference in treatment response in luminal BC related to genomic complexity with extremely marked intra- and inter-tumoural heterogeneity. While many patients follow a benign clinical course, others manifest a lethal systemic disease with resistance to current ET which may due to: single-strand break repair defects which give adaptive evolution and drug resistance, specific DNA repair defects such as MutL defects (which, however, could be used to direct adjuvant CDK4/6i inhibitors) [44, 45] and specific gene mutation such as NF1 [46]. Interestingly, ESR1 fusion transcripts drive ET resistance and metastatic disease progression although CDK4/6i inhibitors are predicted to be effective [47]. Since the progression of ERpos BC is related to increased somatic mutation rates, immunotherapy approaches should be aggressively pursued.

Carsten Denkert (Charité University Hospital Berlin, Germany) stated that in the TNBC, there is heterogeneity of treatment response based on: high level of TILs which increase neoadjuvant response and improve prognosis [48], and PD-L1 (programmed death-ligand 1) which is a predictive biomarker expressed on the tumour cells, as well as on TILs in a subset of TNBC and has been shown to be predictive for response to a combination of immunotherapy and chemotherapy in the metastatic setting [49]. The current research challenges are the translations of biomarkers to early BC (e.g. GeparNuevo), integration of PD-L1 as a new marker for neoadjuvant and adjuvant clinical trials and selection of patients for additional therapeutic strategies.

Lisa A Carey (Lineberger Comprehensive Cancer Center, USA) underlined the research priorities in the prediction of response in early BC. HER2pos low-risk BC has excellent outcomes with paclitaxel + trastuzumab alone (APT trial) while a different situation appears in higher clinical risk HER2pos BC. Research priorities are the identification and the evaluation of biomarkers that could allow the best treatment for the patient [50–54]. In hormone receptor (HR)pos BC, it should be considered that pCR is meaningful but rare with treatments. The ALTERNATE trial (Estrogen Receptor positive breast cancer NeoAdjuvant. TrEatment) could provide the opportunity to prospectively validate a biomarker-driven strategy for treatment of ERpos postmenopausal women. MINDACT and TAILORx may clarify which patients can have benefits from chemotherapy. Moreover, multigene signatures (MGSs) can estimate the risk of late distant recurrence and this might help to choose the most appropriate treatments, such as, for instance, chemotherapy and/or extended ET for high-risk ERpos BC [55].

**Risk stratification and prevention in ductal carcinoma in situ**

William F Symmans (MD Anderson Cancer Center, USA) presented the argument ‘risk stratification in patients with ductal carcinoma in situ’. It appears almost clear that women with higher grade ductal carcinoma in situ (DCIS), HRneg, larger size, have a significant risk of recurrence and even risk of invasive recurrence and require surgery associated with radiotherapy [56]. In ERpos DCIS, tamoxifen reduced the rate of ipsilateral and contralateral events [57].

Shelley Hwang (Duke University Hospital, USA) highlighted some current prospective randomised clinical trials regarding women with grade 1-2 DCIS with the challenge to reduce over-treatment (LORD, LORIS, COMET). Moreover, it is necessary to encourage effective communication between patients and their physicians about the pros and cons of treatment versus surveillance. Emerging molecular tools offer the potential to tailor treatment according to biology. Numerous efforts have evaluated the role of biomarkers in discriminating high from low-risk DCIS. Both genomic and proteomic approaches have been developed and appear promising, the results that will come from the PRECISION project seem to be very interesting in this area.

Andrea De Censi (Galliera Hospital, Italy) underlined a phase III trial, TAM01, which explores the role of low dose of tamoxifen ‘babytam’ (5 mg/day) in women who had been treated with surgery for breast intraepithelial neoplasia; this trial has demonstrated comparable risk reduction and significantly lower toxicity compared with data derived from trials of tamoxifen given at 20 mg/day (NSABP B-24, NSABP-P1). The expression of 23 genes involved in cell cycle progression (CCP score, Myriad Genetics) may provide prognostic and predictive markers to identify patients who can derive the greatest benefits from low dose of tamoxifen in terms of recurrences.

**Special lectures I**

The first special lecture of the second day of the congress was held by Sharon H Giordano (MD Anderson Cancer Center, USA), who spoke about the necessity to extrapolate data from clinical trials to applying them in real life. It is very important to carefully select the study design, statistical techniques and also be aware of the limitations of trial data.
New pathways with potential impact in the treatment of early breast cancer

Andrew Tutt (The Institute of Cancer Research, UK) stated that homologous recombination (HR) deficiency deserves a lot of attention, in fact, it is significant both in family BC and in sporadic TNBC and it leaves a pathognomonic 'scar' on the genome and it may have important clinical benefits. Targeting this is now approved for two poly ADP ribose polymerase inhibitor (PARPi) for BRCA1-2 metastatic BC (EMBRACA, OLYMPIAD) while its role in adjuvant therapy will be clarified by the ongoing OlympiA trial. Moreover, it appears to be important to target HR in order to understand the mechanism of resistance and how treatment affects the evolution of resistance mechanisms. ATR inhibition can increase response and inhibit resistance to PARPi [58]. New strategies using combinations of PARPi with ATRi or Wee1i in advance TNBC may increase response and reduce resistance to treatment (VIOLETTE trial).

Nicholas C Turner (Royal Marsden Hospital, UK) focussed on the role of CDK4/6i and their important role in metastatic ER pos BC, both in association with AI (PALOMA2, MONALEESA2, MONARCH3) and with Fulvestrant (PALOMA3, MONARCH2). They have also demonstrated high activity (not really any evidence yet of efficacy improving outcomes) also in early BC, for instance when CDK4/6i are used preoperatively (POP, NeoPalAna, neoMONARCH, PALLET). Adjuvant studies (Penelope B, PALLAS, monarchE, NATALEE) have completed patient enrolment and we are awaiting the data and results from the follow up, in fact, early relapse in the first 2 years is not the main problem in ER pos/HER2 neg BC and longer follow up of all the studies will be critical. These studies between them are starting to help us to understand the most correct duration of treatment with CDK4/6i. Currently, emerging clinical biomarkers may predict the response to these drugs (e.g. mutations in RB1 and FAT1) but none of these are ready for clinical implementation.

Sherene Loi (Peter MacCallum Cancer Centre, Australia) spoke about target immunity in BC. TILs have shown strong prognostic value in early-stage TNBC treated with adjuvant chemotherapy [26]. High levels of TILs correlate with high level of PD-1, which is the predominant checkpoint present on both CD8+ and CD4+ T cells, whilst CTLA-4 is present on T regulatory cells. In contrast, the quantity of TILs in metastatic lesions is extremely low, indicating why advanced BC patients did not have high response rates to immune checkpoint PD-(L)1 inhibitors. Combinations of immunotherapy with chemotherapy have been investigated in the advanced setting (e.g. Impassion130). Checkpoint inhibitors are currently being investigated in the early stage setting in a number of phase II/III trials in TNBC with different anti-PD-1, PD-L1 and CTLA-4 agents. Trastuzumab resistance in HER2pos BC could be mediated by immune mechanism, adding pembrolizumab to trastuzumab showed a clinical benefit in HER2pos advance BC patients with PD-L1-pos, trastuzumab-resistant (PANACEA trial). In early-stage ERpos/HER2neg BC, TILs are associated with adverse biology, and in these patients, adding pembrolizumab seems to have an increase in pCR (I-SPY2). Further studies are necessary but target immune pathway in BC appears promising.

Fatima Cardoso (Champalimaud Cancer Centre, Portugal) presented on how the recent data from advanced BC (aBC) trials inform us on treatment opportunities for patients with early BC (eBC). It should be considered that surrogate endpoints do not consistently correlate with long term endpoints [59]. Moreover, when the benefit seen in aBC is substantial and includes overall survival (OS), usually the treatment is also useful in eBC, differently to when the benefit is moderate and/or only progression-free survival (PFS) is achieved, a substantial benefit in eBC is very rarely seen. What can we expect from the latest drugs approved for aBC and evaluated for eBC? Regarding CDK4/6i, a substantial PFS benefit was shown in the first line, a moderate PFS benefit in the second line, OS not statistically significant in the second line but probably because the trials were not sufficiently powered—it is likely that they have a future role in eBC. Regarding mammalian target of rapamycin inhibitor (mTORi)—moderate PFS benefit was demonstrated, OS not statistically significant (maybe also because the trials were not powered), with toxicity now better managed with the use of steroid mouth wash for stomatitis—they probably do not have a future role in eBC. This is likely to be the same for PI3Ki, currently only one of which has showed a moderate PFS benefit and all of these drugs showed too much toxicity. The role of Histone deacetylase inhibitor (HDACi) still remains uncertain: chidamide has a moderate PFS benefit but some toxicity and we are still waiting to hear about entinostat. Hopefully, PARPi, which currently shows small PFS benefit but important benefit...
in QoL, will have a future role in eBC. Regarding checkpoint inhibitors, we cannot conclude based on aBC trials the benefit for eBC because aBC and eBC are totally different in the immune setting.

Treatment tailoring according to pathology and biology

Stefan Aeby (Luzerner Kantonsspital, Switzerland) presented the role of MGS. There isn’t a need for MGS for all patients (e.g. Oncotype Dx, Mammaprint, Endopredict and Prosigna), such as patients with an excellent prognosis based on conventional criteria and patients for whom management decisions will not be influenced by the results of MGS. For other patients, MGS scores may have a role in prognostication and prognosis models. TAILORx and MINDACT are examples of prediction prospective trials. Future studies may establish MGS to guide the choice of drug therapies with benefits for patients and also for health care systems avoiding unnecessary and costly treatments.

Hope S Rugo (University of California, San Francisco, USA) presented the treatment selection for patients with low and equivocal ER status. According to ASCO/CAP guidelines, if ER ≥ 1%, the term equivocal should not be used based on data, suggesting response to ET even in low ERpos (1%–9%). These groups of BC are relatively uncommon and heterogeneous by gene expression profiling. Low HR expression is associated with higher Ki67, higher grade and less progesterone receptor (PR) positivity, higher recurrence score and higher chemo-sensitivity. Regarding treatment recommendations, chemotherapy should be given following guidelines for TNBC [60]. Currently, the benefit of ET is unknown, but in general, it should be recommended despite the likely extremely small benefit, especially for lowest ERpos disease (<5%).

Giuseppe Viale (Istituto Europeo di Oncologia, Italy) focussed on the controversial treatment of patients with HER2 status. According to ASCO/CAP 2013 guideline recommendations, HER2 status is equivocal if both immunohistochemistry (IHC) (score 2+) and in situ hybridisation test for HER2 (4–6 copies of the gene and the ratio less than 2) are equivocal. ASCO/CAP 2018 recommended that these cases must be considered HER2neg due to the lack of evidence for any benefit from HER2-targeted therapy in these groups of patients as the results of the B-47 trial suggest. It is important to consider the intra- and inter-tumoural heterogeneity and the fact that there is no correlation between IHC and gene expression profiling. Knowing this is important, for example, in order to de-escalate therapy, in fact, in the neoadjuvant setting without chemotherapy we may have: in HER2pos/HRneg with dual blockade, 20%–30% of pCR, in HER2pos/HRpos with lapatinib + trastuzumab + letrozole, 21% of pCR (TBCRC006 trial) and 32% of pCR with lapatinib + trastuzumab + ET (PAMELA). In the adjuvant setting, however, the larger benefit from trastuzumab in HRneg compared to HRpos disease has not been observed and all the intrinsic subtypes did benefit similarly from trastuzumab. Also, with adjuvant T-DM1 for residual disease after neoadjuvant therapy, there is evidence of interaction between HR status although there is likely better response of HER2pos/HRpos disease to extended therapy with neratinib (ExteNET - Extended Adjuvant Treatment of Breast Cancer with Neratinib). In the advanced setting, expression of ER > 30% of tumour cells is associated with reduced probability of response to chemotherapy and trastuzumab, maintenance ET is associated with a significant reduction in the risk of progression and dual blockade of HER2 with an AI is effective for treatment of HER2pos/ERpos disease in the first line (PERTAIN trial). Possible new treatment options include: triple blockade of ER, HER2 and CDK4/6 both in the neoadjuvant setting (NAPHER 2) and in the advanced setting (PATRICIA) and anti-immune checkpoint agent in the neoadjuvant setting (APTneo, neoHIP trial).

Judy E Garber (Dana-Farber Cancer Institute, USA) spoke about treatment selection for patients with BRCA mutations that are more predisposed to BC by impairing HR and causing genomic instability. HR also repairs DNA lesions caused by platinum agents and PARPi, thus these groups of patients have increased sensitivity to them. According to the results of the POSH trial, BRCA status should not be viewed as an independent poor prognostic factor. Some studies demonstrated major sensitivity to carboplatin [61] but in others, it is less evident (GeparSixto). Additional prospective studies stratified by BRCA1 and BRCA2 mutation status are needed to better understand the effect of carboplatin in polychemotherapy regimens. It should be considered in fact, that the BRCA mutation carriers make the tumour more sensitive to killing by chemotherapy that induces DNA damage [62]. PARPi were approved for treatment of metastatic BC with BRCA mutations (OlympiAD, Abrazo, EMBRACA). Lurbinectedin is another drug that targets DNA repair, it showed an interesting activity in patients with BRCA mutation [63]. There are ongoing studies evaluating combination therapies such as PARPi with immunotherapy (MEDIOLA). The phase III study BRCA-P will determine if denosumab may have a role in the prevention of BC in BRCA1 mutation carriers.
Surgery of early breast cancer

Paolo Veronesi (Istituto Europeo di Oncologia, Italy) started the surgical session with a presentation based on standards and controversies in SN, making a quick historical explanation from the initial surgical approach to the axilla with the AD for all patients with BC, passing on the SNB, to the current management. Nowadays, the axilla treatment does not require AD for all BC patients, for example women who are candidates for BC conservative surgery macrometastases in 1-2 SN (Z0011 trial), patients undergoing mastectomy with micrometastatic SN (IBCSG 2301) and patients who underwent NACT and shifted from a status of cN1 to cN0. Moreover, data derived from the SOUND trial will indicate whether it may avoid SNB in patients with clinical and radiological negative axilla. Data derived from ongoing studies (SENOMAC) may further reduce axillary surgery in the future, but nowadays even if medical treatment recommendations depend mostly on primary tumour biology rather than on axillary status, information about axillary status given by SNB still remains important.

Bahadir Gulluoglu (Marmara University School of Medicine, Turkey) focussed his presentation on the impact of older age on local treatment decisions. Systematic analyses showed that both ET alone and surgical approach plus adjuvant ET provided similar OS rates, but without surgery, there is a higher local recurrence (LR) rate [64]. The surgical option remains the standard in physiologically fit elderly patients with all subtypes of BC, but in fragile HRpos BC patients with limited life expectancy, it may be possible to consider primary ET, with AI being preferable over tamoxifen [65]. Controversy also remains regarding the utility of whole breast irradiation (WBI). WBI reduces LR rate but does not improve OS, and therefore it can be omitted in unfit patients or in fit patients with clinical low-risk BC [66, 67]. SNB can possibly be omitted in unfit patients and in fit patients with clinical low risk or in those in which SN information will not change surgical management [68, 69]. In summary, it is not the age which governs the outcome of BC but the biology of disease (which is often more favourable in elderly patients), however, in this group of patients, it is necessary to assess multiple considerations to decide the best treatment.

Emiel JT Rutgers (The Netherlands Cancer Institute, The Netherlands) presented the controversial argument of prophylactic mastectomy in women without BRCA mutation. In this group of patients, a possible contralateral prophylactic mastectomy (CPM) should be a shared decision between women and their physicians. CPM has not shown any survival benefit, the annual risk of contralateral BC (second primary) is only 0.3%–0.5%, breast conservative surgery is as oncologically safe as mastectomy and CPM may have side effects that can lead to further surgery or adverse effects on body image and quality of life [70–74]. Moreover, in women < 40 years, with an extensive family history and a germline mutation in CHEK2 (11000delC), it is important to intensify screening with an annual mammography starting from 35 years [75]. In some case, CPM could be justified, especially in patients < 30 years or < 40 years with very dense breasts or extensive family history, CHEK2 mutation and high levels of anxiety and fear.

Florian Fitzal (Medical University Vienna, Austria) stated that breast conservative surgery is safe in new borders after NACT but care should be taken with large or multifocal disease and luminal subtype with more possibility of residual scatter cells over original tumour volume [76]. There is no difference in terms of LR comparing different mm of R0 resection after NACT, the gold standard is ‘no ink on tumour’ [77]. The resection of the whole residual microcalcification is still necessary after NACT [78]. Currently, omitting surgery after NACT is still not possible, but there are many ongoing trials that will perhaps lead to a change in this approach. The optimal time after last NACT and surgery is 21 days: surgery within 21 days was associated with an improved OS [79]. There are many ongoing trials that will clarify the standard of care of axillary surgery (Alliance A11202, SAKK 23/16, IBCSG 57-18 and ABCSG-53).

Radiotherapy for early breast cancer

Timothy J Whelan (McMaster University, Canada) remarked that breast irradiation in some patients may be omitted. Nowadays, there are many trials evaluating the omission of RT in patients at low biological risk based on biomarker assessment (e.g. LUMINA, PAM50, PRIME-TIME). These trials will help to quantify the risk of LR and select patients for whom RT may be omitted. There are also trials evaluating the elimination of regional nodal radiotherapy in patients with limited node-positive disease and low biological risk (e.g. MA.39).
Harry Bartelink (The Netherlands Cancer Institute, The Netherlands) presented the clinical benefit of regional node irradiation (RNI) for BC. Meta-analyses showed that post-mastectomy RT is effective and reduced both LR and BC mortality in women with SNpos [80]. Three recently published prospective trials (DBCG, EORT and MA.20) showed a reduction in BC mortality and recurrences with RNI. RNI after AD is recommended in high-risk patients with N1-3 positive nodes and if positive nodes are more than 3. In the AMAROS trial, both AD and ART provide a comparable LR in SNpos patients but the lymphoedema was doubled after AD compared to ART. The IBCSG 23-01 [1] showed that there is no need for extra treatment of the axilla after micro-metastases in SN. New data are expected from ongoing trials about SNpos after NACT (Alliance A011202, NSABP B-51/RTOG 1304).

Boon H Chua (Prince of Wales Hospital, Australia) focussed attention on the individualization of RT after surgery. Whole breast radiotherapy (WBRT) after breast-conserving surgery improves local control and BC survival. However, hypofractionated WBI (HF-WBI) also showed equivalent tumour control (START-P, START-A, START-B, OCOG); the use of HF-WBI in under-represented patient subgroups (e.g. very young patients) remains controversial. There are randomised clinical studies of HF-WBI involving a 1-week period (FAST, FAST-forward) that may well improve the balance of local control and side effects. Tumour bed boost (TBB) is especially used in higher-risk patients and improved local control but also increased breast fibrosis (EORTC, Budapest, Lyon). The IMPORT HIGH trial compared sequential TBB and simultaneous integrated TBB given during WBRT and it showed similar toxicity but efficacy data are still pending. There are many trials involving partial breast irradiation (PBI), some of these, such as IMPORT LOW and RAPID, showed that PBI resulted in low absolute LR rates similar to WBI but higher rates of late toxicity and adverse cosmetic outcome. Other PBI trials, however, have highlighted higher LR rate compared to WBI [81]. Current data support PBI use for selected low-risk patients but longer-term safety data are essential for definitive evaluation. Regarding clinical trials demonstrating the efficacy of PMRT: results derived from trials suggest that chest wall is an important target volume, while current evidence does not enable the distinction of relative contributions of nodal target sub-volumes to treatment efficacy, routine RT of internal mammary chain is controversial but ASCO-guidelines recommend that internal mammary chain (IMC) should be included in patients with SNpos BC receiving PMRT.

The use of hypofractionated-PMRT currently remains unclear. Patients with breast reconstruction are at increased risk of late fibrosis and adverse cosmetic outcome after RT but there are no current guidelines for target volume definition after reconstruction.

John H Maduro (University Medical Centre Groningen, The Netherlands) spoke about the potential role of proton irradiation compared to conventional photon irradiation. Protons are charged particles able to deliver the dose to a specified depth where they stop, with a reduction of cardiac and pulmonary toxicity [82]. Patients who could benefit from this technique for excellent local control, good cosmetic results and low dose given to mediastinal organs are: young patients, bilateral BC, patients with cardiac risk factor or special anatomy (pectus excavatum) and patients who need IMC irradiation [83]. Nowadays, however, even if there has been a clear increase in proton facilities in recent years, the availability remains scarce and the costs high.

**Special lecture II**

In his lecture, Eric P Winer (Dana-Farber Cancer Institute, USA) presented principles and practical considerations about systematic treatments. The goals of adjuvant therapy are: eradicate micrometastatic disease, improve OS, and delay recurrence resulting in a better overall quality of life. The goals of neoadjuvant therapy are: eradicate micrometastatic disease, improve OS, decrease extent of surgery, provide prognostic information, select candidates for additional treatment, test de-escalation trials and strategies and conduct tissue-intensive trials. Adjuvant chemotherapy with upfront surgery should be preferred, dependent on the anatomic extent of disease and when it is impossible to follow disease during NACT. Neoadjuvant treatment should be preferred in stage II/III TNBC or HER2pos disease, in stage II/III ERpos, if it is clear that chemotherapy will be administrated and if optimal surgery treatment will be facilitated by NACT. Even neoadjuvant ET should sometimes be considered, for instance: women who are not considered to have chemotherapy sensitive BC, to optimise breast conservation in stage II/III disease, to assess prognosis through assessment of Ki67 or other markers and determine the need for chemotherapy (but this is still being investigated). pCR is important but is a strong predictor for individual patients and a poor predictor of the long term success of regimen in terms of OS and DFS [84]. It is time for a new approach for clinical trials in the neoadjuvant setting which can lead to individualization therapy and improved outcomes (COMPASS trial).
Primary and adjuvant systemic therapy of early breast cancer: estimating the magnitude of clinical benefit

Angelo Di Leo (Azienda USL Toscana Centro, Italy) discussed chemotherapy in luminal BC. This group of BCs has generally favourable prognosis, but sometimes of them have a poor prognosis. In the future, we could benefit from the clinical use of circulating tumour cells (CTC) to assess prognosis [85, 86]. Circulating tumour DNA (ctDNA) methylation in serum and plasma has been shown to be effective for diagnostic or prognostic biomarkers detection in different tumour types and in the future will be useful in clinic. DNA methylation alterations across the different tumour types, in fact, may occur more frequently than genomic alterations on ctDNA and apparently could be a more sensitive technology with respect to gene mutations on ctDNA, moreover, some DNA methylation seems to be less dependent on BC subtypes compared to gene mutations [87]. There is emerging evidence that metabolomic profiling may have the ability to further stratify risk within existing genomic assay determined risk categories [88, 89]. Integrating standard pathology and genomics of primary tumour with tools detecting ‘signals’ of active micro-metastatic disease (blood, serum and plasma) is a challenge for new prospective designed studies in the attempt to produce better prognostic stratification of eBC.

Prudence Francis (Peter McCallum Cancer Centre, Australia) spoke about adjuvant ET in premenopausal BC patients. According to the data, the use of adjuvant tamoxifen (T) for 5 years in these women determines substantial reductions in recurrence with an important improvement of OS. Updated results from the suppression of ovarian function trial (SOFT) and tamoxifen and EXemestane trial (TEXT) have helped to identify the differential value of different adjuvant ET strategies in high-risk and low-risk premenopausal women but longer follow-up remains fundamental. With a median follow-up of 8 years in SOFT, there is a significant improvement in DFS for patients assigned to receive T + OFS for 5 years as compared with T alone for 5 years. Further improvement in DFS was observed for those assigned 5 years’ of exemestane + OFS (AI + OFS). While these results applied to the overall randomised SOFT premenopausal population, larger absolute improvements in DFS were observed with ET escalation in the premenopausal cohort who had received prior chemotherapy due to the perceived risk of recurrence, while smaller absolute improvements in DFS were observed in women who did not receive chemotherapy. Despite some improvements in DFS in the lower risk no-chemotherapy cohort, the SOFT 8-year results for that cohort continue to demonstrate a low risk of recurrence or death with the use of adjuvant tamoxifen alone. Small OS advantages from the addition of OFS to T have now emerged in SOFT, which appear more clinically meaningful in the cohort who received prior chemotherapy. In the joint analysis of the SOFT and TEXT trials, there is currently no OS improvement at 8 years for those assigned AI + OFS versus those assigned T + OFS despite a significant reduction in distance recurrences with AI + OFS. In women < 35 years if AI + OFS are not tolerated, may be consider T + OFS before T alone in fact, in the SOFT trial after median 8 years, among those patients assigned T more than 1/3 had an invasive BC and more than 1/4 had a distant recurrence. There is evidence to support 5 years of OFS + AI/T but, according to the ATLAS (Adjuvant Tamoxifen Longer Against Shorter) trial, continuing tamoxifen up to 10 years produces an addition to a statistically significant improvement of OS and reduction of recurrence and BC-specific mortality. In choosing the duration of ET, the following should be considered: baseline tumour risk, age, tolerance to ET, and fertility.

Harold J Burstein (Dana-Farber Cancer Institute, USA) focussed attention on adjuvant ET in postmenopausal women. The current treatment options include T, AI or a sequence of these. Individual trials and meta-analysis suggest that AI treatment, such as either initial or sequential therapy, reduces recurrence risk compared to 5 years of T alone and it appears to be better, especially for women with higher risk tumours and lobular carcinomas (BIG 1-98, ABCSG 8). Extending ET (NSABP B-42, MA.17, DATA) reduces the risk of recurrence. It is important to consider that ET also have side effects which can be reduced by switching a type of ET with another one or, for example, regarding arthralgia, using omega-3 fatty or acupuncture [90, 91]. The aim for better therapeutic management is to identify patients with intermediate-high risk of recurrences that could potentially benefit from the extension of ET. Genomic signature has been shown to be prognostic in term of the risk of recurrences [92]. Currently, we should consider the extension of ET in women with high stage BC, especially patients who have tolerated the treatment and are willing to continue, and patients who started with T [93].

Robert Coleman (Weston Park Hospital, UK) focussed on the clinical benefit of bisphosphonates, which should be part of routine treatment in the adjuvant setting in postmenopausal women with early BC at significant risk for disease recurrence. In fact, as highlighted, for example, in the EBCTCG Meta-analysis, bisphosphonates reduce the development of bone metastases and improve survival and should be given to postmeno-
Nadia Harbeck (Comprehensive Cancer Center of the Ludwig-Maximilians-University, Germany) underlined emerging strategies in the neoadjuvant treatment of HER2pos BC. Future research need to focus on avoiding over-treatment of patients with pCR which is a prognostic factor for both DFS and OS in HER2pos BC (TECHNO). De-escalation therapeutic strategy should involve reducing the chemotherapy component while optimising anti-HER2 therapy; on the contrary, escalation should take into consideration immunotherapy and novel HER2-targeting drugs.

Ian E Krop (Dana-Farber Cancer Institute, USA) presented the optimisation treatment for HER2pos BC. With the use of HER2 directed therapies, outcomes for patients with early-stage HER2pos BC are now favourable for all but the highest risk women (APHINITY, APT). These favourable outcomes increase the importance of risk stratification to minimise over and under treatment, and de-escalation strategies to potentially further reduce the toxicities of therapy. Tumour size, lymph node status and HR status have well-established prognostic value in HER2pos BC, and these can be utilised to risk stratify patients. However, one of the strongest prognostic markers in HER2pos BC is pCR after NACT (I-SPY). Thus, treating patients in the neoadjuvant setting provides prognostic data and can identify patients who may benefit from a change in therapy, just think of T-DM1 for patients without pCR (KATHERINE). Currently, there are no data comparing T-DM1 to trastuzumab + pertuzumab in the adjuvant setting. However, given the large benefit seen in KATHERINE compared to the relatively small benefit of the addition of pertuzumab in APHINITY, it would seem unlikely that adjuvant T-DM1 would be inferior to the other treatment. The ExteNET study demonstrated a benefit to a year of neratinib in ERpos/HER2pos BC completing a year of (neo)adjuvant HER2 directed therapy. Is there a role for neratinib in patients who received T-DM1 after neoadjuvant therapy? As there are no data on adjuvant neratinib after T-DM1 or pertuzumab, it is difficult to recommend neratinib in patients after T-DM1. However, in the absence of such data, neratinib can be considered in rare cases with extremely high-risk ERpos BC patients after a year of T-DM1. In patients with low clinical risk HER2pos BC, 12 weekly doses of paclitaxel with a year of trastuzumab demonstrate very good outcomes: in this subgroup of women neoadjuvant treatment can be avoided (APT).

Javier Cortes (Vall d’Hebron Institute of Oncology, Spain) spoke about neoadjuvant and adjuvant chemotherapy in TNBC. TNBC is a very heterogeneous group of tumours in terms of genetic profile and in histology. Clinical trials (CALGB 40603, GeparSixto) evaluated the addition of platinum compounds in the neoadjuvant setting and demonstrated an increase of pCR but not a statistical improvement of DFS or OS. For some patients at high risk, platinum may be taken into consideration. The role of adding nab-paclitaxel is still unclear with different results from the data (GeparSepto, ETNA). Instead, using both nab-paclitaxel and platinum without anthracyclines in the neoadjuvant setting produces 50% pCR and may be considered in clinic, for example, in patients with allergic reactions (ADAPT trial). The role of PARPi is uncertain, in fact, in I-SPY2 (which resulted in higher rates of pCR compared to standard therapy), but veliparib and carboplatin have been added to standard therapy. Interesting data derived from the use of talazoparib alone in advanced BC with germline BRCA1/2 mutation, with a significant benefit over standard chemotherapy [96]. Immunotherapy shows promising activity with upcoming trials such as KEYNOTE-522 and GeparDouze. In the adjuvant setting, chemotherapy should be started as soon as possible after surgery; however, delayed treatment has a big negative impact on TNBC [97]. In the post-neoadjuvant setting, capectabim for high-risk patients with residual disease after NACT should be considered (CREATE-X), maybe also for patients pre-treated with platinum compounds. The results which will come from ECOG-ACRIN EA1131 will be interesting, a phase III trial that investigates the role of adjuvant platinum in patients with no pCR after NACT. Biology-driven clinical trials in residual tumours will be key to optimise new strategies in TNBC.

Antonio C Wolff (Johns Hopkins University, USA) concluded with a presentation that remarked on the advances in adjuvant therapies and greater access to care which have resulted in a steady improvement in survival outcomes for BC patients across the world. However, it is necessary to consider the short-term toxicities, as well as the long-term ones, which determine a worsening of quality of life [98]. In these terms, the correct management of therapy and also integrative therapies which can help to reduce the impact of the side effects assume great importance [99]. Non-medical factors, like underemployment, socioeconomic status and ‘financial toxicity’ can also negatively impact on health outcome and quality of life [100]. Nowadays, it is important to reduce barriers to care as much as possible. Therapies should be effective, offer value, result in meaningful outcomes and be available.
Conclusions

The 16th St Gallen International Breast Cancer Conference did not disappoint the delegates’ high expectations. The presentations of major international experts in the different fields of therapeutic application gave the impression of more curable BC with increasing optimism for the future through the integration of strategies of care.

References

1. Galimberti V, Cole BF, and Viale G, et al (2018) Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial Lancet Oncol 9(10) 1385–1393 https://doi.org/10.1016/S1470-2045(18)30380-2

2. Giuliano V, Ballman KV, and McCall L, et al (2017) Effect of axillary dissection versus no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial JAMA 318(10) 918–926 https://doi.org/10.1001/jama.2017.11470 PMID: 28898379 PMCID: 5672806

3. Donker M, van Tienhoven G, and Straver ME, et al (2014) Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial Lancet Oncol 15(12) 1303–1310 https://doi.org/10.1016/S1470-2045(14)70460-7 PMID: 25439688 PMCID: 4291166

4. Tee SR, Devane LA, and Evoy D, et al (2018) Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer Br J Surg 105(12) 1541–1552 https://doi.org/10.1002/bjs.10986 PMID: 30311642

5. Simons JM, van Nijnatten TJ, and van der Pol CC, et al (2016) Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment Eur J Surg Oncol 42(3) 361–368 https://doi.org/10.1016/j.ejso.2015.11.019 PMID: 26746091

6. Nguyen TT, Hoskin TL, and Day CN, et al (2018) Decreasing use of axillary dissection in node-positive breast cancer patients treated with neoadjuvant chemotherapy Ann Surg Oncol 25(9) 2596–2602 https://doi.org/10.1245/s10434-018-6637-9 PMID: 29978369

7. Havel L, and Landercasper J (2019) ASO author reflections: rapid uptake of the SSO ASTRO margin guideline and decreased reoperations after lumpectomy: a success story Ann Surg Oncol https://doi.org/10.101257/10434-012-07289-9 PMID: 30850902

8. Poortmans PMP, Arenas M, and Livi L (2017) Over-irradiation Breast 31 295–302 https://doi.org/10.1016/j.breast.2016.07.022

9. Marta GN, Barrett J, and Porfirio GJM, et al (2019) Effectiveness of different accelerated partial breast irradiation techniques for the treatment of breast cancer patients: Systematic review using indirect comparisons of randomized clinical trials Rep Pract Oncol Radiother 24(2) 165–174 https://doi.org/10.1016/j.rpor.2019.01.009 PMID: 30814916 PMCID: 6378667

10. Wang SL, Fang H, and Song YW, et al (2019) Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial Lancet Oncol 20(3) 352–360 https://doi.org/10.1016/S1470-2045(18)30813-1 PMID: 30711522

11. Lighttowlers SV, Boersma LJ, and Fourquet A, et al (2017) Preoperative breast radiation therapy: indications and perspectives Eur J Cancer 82 184–192 https://doi.org/10.1016/j.ejca.2017.06.014
14. Evron, E., Ben-David, A.M., and Goldberg, H., et al (2019) Prophylactic irradiation to the contralateral breast for BRCA mutation carriers with early-stage breast cancer Ann Oncol 30(3) 412–417 https://doi.org/10.1093/annonc/mdy515

15. EBCTG (2019) Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials Lancet [doi:10.1016/S0140-6736(18)33137-4]

16. Caparica, R., Bruzzone, M., and Poggio, F., et al (2018) Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials Breast Cancer Res Treat 174(1) 27–37 https://doi.org/10.1007/s10549-018-5055-9 PMID: 30465156

17. Francis, P.A., Pagani, O., and Fleming, G.F., et al (2018) Tailoring adjuvant endocrine therapy for premenopausal breast cancer N Engl J Med 379(2) 122–137 https://doi.org/10.1056/NEJMoa1803164 PMID: 29863451 PMCID: 6193457

18. Colleoni, M., Luo, W., and Karlsson, P., et al (2018). Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial Lancet Oncol 19(1) 127–138 https://doi.org/10.1016/S1470-2045(17)30715-5

19. Von Minckwitz, G., Proctor, M., and de Azambuja, E., et al (2017) Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer N Engl J Med 377(2) 122–131 https://doi.org/10.1056/NEJMoa1703643 PMID: 28581356 PMCID: 5538020

20. Martin, M., Holmes, F.A., and Ejlertsen, B., et al (2017) Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncol 18(12) 1688–1700 https://doi.org/10.1016/S1470-2045(17)30717-9 PMID: 29146401

21. Pondè, N., Gelber, R.D., and Piccart, M. (2019) PERSEPHONE: are we ready to de-escalate adjuvant trastuzumab for HER2-positive breast cancer? NPI Breast Cancer 5 1 https://doi.org/10.1034/s41523-018-0098-y PMID: 5679819

22. Chavez-MacGregor, M., Mittendorf, E.A., and Clarke, C.A., et al (2017) Incorporating tumor characteristics to the American joint committee on cancer breast cancer staging system Oncologist 22(11) 1292–1300 https://doi.org/10.1016/S1470-2045(17)30717-9 PMID: 29146401

23. Cuzick, J., Dowsett, M., and Pineda, S., et al (2016) Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer J Clin Oncol 29(32) 4273–4278 https://doi.org/10.1200/JCO.2010.31.2835

24. Viale, G., Regan, M.M., and Dell’Orto, P., et al (2011) Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial Ann Oncol 22(10) 2201–2217 https://doi.org/10.1093/annonc/mdq738 PMID: 21335417 PMCID: 3179413

25. Salgado, R., Denkert, C., and Demaria, S., et al (2015) The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014 Ann Oncol 26(2) 259–271 https://doi.org/10.1093/annonc/mdu450

26. Loi, S., Drubay, D., and Adams, S., et al (2019) Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers J Clin Oncol 37(5) 559–569 https://doi.org/10.1200/JCO.2018.30.0004 PMID: 5679819

27. Dieci, M.V., Conte, P., and Bisagni, G., et al (2019) Association of tumor-infiltrating lymphocytes with distant disease-free survival in the ShortHER randomized adjuvant trial for patients with early HER2+ breast cancer Ann Oncol 30(3) 418–423 https://doi.org/10.1093/annonc/mdz007 PMID: 30675511 PMCID: 6320365

28. Denkert, C. (2018) Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy Lancet Oncol 19(1) 40–50 https://doi.org/10.1016/S1470-2045(17)30904-X

29. Symmans, W.T., Wei, C., and Gould, R., et al (2017) Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype J Clin Oncol 35(10) 1049–1060 https://doi.org/10.1200/JCO.2015.63.1010 PMID: 28135148 PMCID: 5455352
30. Masuda N, Lee SJ, and Ohtani S, et al (2017) Adjuvant capecitabine for breast cancer after preoperative chemotherapy N Engl J Med 376(22) 2147–2159 https://doi.org/10.1056/NEJMoa1612645 PMID: 28564564

31. Kurozumi S, Inoue K, and Matsumoto H, et al (2019) Prognostic utility of tumor-infiltrating lymphocytes in residual tumor after neoadjuvant chemotherapy with trastuzumab for HER2-positive breast cancer Sci Rep 9(1) 1583 https://doi.org/10.1038/s41598-018-38272-1 PMID: 30733496 PMCID: 6367461

32. Sestak I, Buus R, and Cuzick J, et al (2018) Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: a secondary analysis of a randomized clinical trial JAMA Oncol 4(4) 545–553 https://doi.org/10.1001/jamaoncol.2017.5524 PMID: 29450494 PMCID: 5885222

33. Sparano JA, Gray RJ, and Makower DF, et al (2018) Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer N Engl J Med 379(2) 111–121 https://doi.org/10.1056/NEJMoa1804710 PMID: 29860917 PMCID: 6172658

34. Cardoso F, van’t Veer LJ, and Bogaerts J, et al (2016) 70-gene signature as an aid to treatment decisions in early-stage breast cancer N Engl J Med 375(8) 717–729 https://doi.org/10.1056/NEJMoa1602253 PMID: 27557300

35. Esserman LJ, Yau C, and Thompson CK, et al (2017) Use of molecular tools to identify patients with indolent breast cancers with ultralow risk over 2 decades JAMA Oncol 3(11) 1503–1510 https://doi.org/10.1001/jamaoncol.2017.1261 PMID: 28662222 PMCID: 5710197

36. Luen SJ, Asher R, and Lee CK, et al (2018) Association of somatic driver alterations with prognosis in postmenopausal, hormone receptor-positive, HER2-negative early breast cancer: a secondary analysis of the BIG 1-98 randomized clinical trial JAMA Oncol 4(10) 1335–1343 https://doi.org/10.1001/jamaoncol.2018.1778 PMID: 29902286 PMCID: 6233777

37. Garcia-Murillas I, Schiavon G, and Weigelt B, et al (2015) Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer Sci Transl Med 7(302) 302ra133 https://doi.org/10.1126/scitranslmed.aab0021 PMID: 26311728

38. Ellis MJ, Tao Y, and Luo J, et al (2008) Outcome prediction for estrogen-receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics J Natl Cancer Inst 100(19) 1380–1388 https://doi.org/10.1093/jnci/djn309 PMID: 18812550 PMCID: 2556704

39. Zou J, Huss M, and Abid A, et al (2018) A primer on deep learning in genomics Nat Genet 51(1) 12–18 https://doi.org/10.1038/s41588-018-0295-5 PMID: 30478442

40. Loi S, Majewski I, and Guarnieri V, et al (2016) PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab Ann Oncol 27(8) 1519–1525 https://doi.org/10.1093/annonc/mdw197 PMID: 27177864 PMCID: 6279074

41. Llombart-Cussac A, Cortés J, and Paré L, et al (2017) HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial Lancet Oncol 18(4) 545–554 https://doi.org/10.1016/S1470-2045(17)30021-9 PMID: 28238593

42. Salgado R, Denkert C, and Campbell C, et al (2015) Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the NeoALTO trial JAMA Oncol 1(4) 448–454 https://doi.org/10.1001/jamaoncol.2015.0830 PMID: 26181252 PMCID: 5551492

43. Nuciforo P, Pascual T, and Cortés J, et al (2018) A predictive model of pathologic response based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-positive breast cancer treated with chemo-free dual HER2 blockade Ann Oncol 29(1) 170–177 https://doi.org/10.1093/annonc/mdx647

44. Haricharan S, Punturi N, and Singh P, et al (2017) Loss of MutL disrupts CHK2-dependent cell-cycle control through CDK4/6 to promote intrinsic endocrine therapy resistance in primary breast cancer Cancer Discov 7(10) 1168–1183 https://doi.org/10.1158/2159-8290.CD-16-1179 PMID: 28801307 PMCID: 5733075
45. Ma CX, Gao F, and Luo J, et al (2017) NeoPalAna: neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer Clin Cancer Res 23(15) 4055–4065 https://doi.org/10.1158/1078-0432.CCR-16-3206 PMID: 28270497 PMCID: 5555232

46. Griffith OL, Spies NC, and Anurag M, et al (2018) The prognostic effects of somatic mutations in ER-positive breast cancer Nat Commun 9(1) 3476 https://doi.org/10.1038/s41467-018-05914-x PMID: 28270497 PMCID: 5555232

47. Lei JT, Shao J, and Zhang J, et al (2018) Functional annotation of ESR1 gene fusions in estrogen receptor-positive breast cancer Cell Rep 24(6) 1434–1444.e7 https://doi.org/10.1016/j.celrep.2018.07.009 PMID: 30089255 PMCID: 6171747

48. Denkert C, von Minckwitz G, and Darb-Esfahani S, et al (2018) Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy Lancet Oncol 19(1) 40–50 https://doi.org/10.1016/S1470-2045(17)30904-X

49. Emen LA (2018) Breast cancer immunotherapy: facts and hopes Clin Cancer Res 24(3) 511–520 https://doi.org/10.1158/1078-0432.CCR-16-3001

50. Veeraraghavan J, De Angelis C, and Mao R, et al (2019) A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer Ann Oncol https://doi.org/10.1093/annonc/mdy547

51. von Minckwitz G, Huang CS, and Mano MS, et al (2019) Trastuzumab emtansine for residual invasive HER2-positive breast cancer N Engl J Med 380(7) 617–628 https://doi.org/10.1056/NEJMoa1814017

52. Blum JL, Flynn PJ, and Yothers G, et al (2017) Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology) J Clin Oncol 35(23) 2647–2655 https://doi.org/10.1200/JCO.2016.71.4147 PMID: 28398846 PMCID: 5549453

53. Luen SJ, Salgado R, and Dieci MV, et al (2019) Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy Ann Oncol https://doi.org/10.1093/annonc/mdy547

54. Masuda N, Lee SJ, and Ohtani S, et al (2017) Adjuvant capecitabine for breast cancer after preoperative chemotherapy N Engl J Med 376(22) 2147–2159 https://doi.org/10.1056/NEJMoa1612645 PMID: 28564564

55. Sestak I, Buus R, and Cuzick J, et al (2018) Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: a secondary analysis of a randomized clinical trial JAMA Oncol 4(4) 545–553 https://doi.org/10.1001/jamaoncol.2017.5524 PMID: 29450949 PMCID: 5885222

56. Grimm LJ, Ryser MD, and Partridge AH, et al (2017) Surgical upstaging rates for vacuum assisted biopsy proven DCIS: implications for active surveillance trials Ann Surg Oncol 24(12) 3534–3540 https://doi.org/10.1245/s10434-017-6018-9 PMID: 28795370 PMCID: 6414216

57. Cuzick J, Sestak I, and Pinder SE, et al (2011) Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial Lancet Oncol 12(1) 21–29 https://doi.org/10.1016/S1470-2045(10)70266-7 PMID: 3018565

58. Yazindki SA, Comaills V, and Buisson R, et al (2017) ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells Genes Dev 31(3) 318–332 https://doi.org/10.1101/gad.290957.116

59. Haslam A, Hey SP, and Gill J, et al (2019) A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology Eur J Cancer 106 196–211 https://doi.org/10.1016/j.ejca.2018.11.012

60. Fuji T, Kogawa T, and Dong W, et al (2017) Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer Ann Oncol 28(10) 2420–2428 https://doi.org/10.1093/annonc/mdx397 PMID: 28961844 PMCID: 5834134
61. Tutt A, Tovey H, and Cheang MC, et al (2018) Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCA1ness subgroups: the TNT Trial Nat Med 24(5) 628–637 https://doi.org/10.1038/s41591-018-0009-7 PMID: 29713086 PMCID: 6372067
62. Hahnen E, Lederer B, and Hauke J, et al (2017) Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the gepaSixto randomized clinical trial JAMA Oncol 3(10) 1378–1385 https://doi.org/10.1001/jamaoncol.2017.1007 PMID: 28715532 PMCID: 5710508
63. Cruz C, Llop-Guevara A, and Garber JE, et al (2018) Multicenter phase II study of lurbinectedin in BRCA-mutated and unselected metastatic advanced breast cancer and biomarker assessment substudy J Clin Oncol 36(31) 3134–3143. https://doi.org/10.1200/JCO.2018.78.6558 PMID: 30240327 PMCID: 6209089
64. Morgan JL, Reed MW, and Wyld L, et al (2014) Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings Eur J Surg Oncol 40(6) 676–684 https://doi.org/10.1016/j.ejso.2014.02.224 PMID: 24703110
65. Matuschek C, Bölke E, and Haussmann J, et al (2017) The benefit of adjuvant radiotherapy after breast conserving surgery in older patients with low risk breast cancer: a meta-analysis of randomized trials Radiat Oncol 12(1) 60 https://doi.org/10.1186/s13014-017-0796-x PMID: 28335784 PMCID: 5364687
66. Wickberg A, Liljegren G, and Killander F, et al (2018) Omitting radiotherapy in women ≥ 65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe Eur J Surg Oncol 44(7) 951–956 https://doi.org/10.1016/j.ejso.2018.04.002 PMID: 29709338
67. Welsh JL, Hoskin TL, and Day CN, et al (2017) Predicting nodal positivity in women 70 years of age and older with hormone receptor-positive breast cancer to aid incorporation of a society of surgical oncology choosing wisely guideline into clinical practice Ann Surg Oncol 24(10) 2881–2888 https://doi.org/10.1245/s10434-017-5932-1 PMID: 28766197
68. Liang S, Hallet J, and Simpson JS, et al (2017) Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: a systematic review and meta-analysis J Geriatr Oncol 8(2) 140–147 https://doi.org/10.1016/j.jgo.2016.12.003
69. Wong SM, Freedman RA, and Sagara Y, et al (2017) Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer Ann Surg 265(3) 581–589 https://doi.org/10.1097/SLA.0000000000001698 PMID: 28169929
70. Elshof LE, Schaapveld M, and Schmidt MK, et al (2016) Subsequent risk of ipsilateral and contralateral invasive breast cancer after treatment for ductal carcinoma in situ: incidence and the effect of radiotherapy in a population-based cohort of 10,090 women Breast Cancer Res Treat 159(3) 553–563 https://doi.org/10.1007/s10549-016-3973-y PMID: 27624164 PMCID: 5021731
71. Carbine NE, Lostumbo L, and Wallace J, et al (2018) Risk-reducing mastectomy for the prevention of primary breast cancer Cochrane Database Syst Rev 4 CD002748 [doi:10.1002/14651858.CD002748.pub4] PMID: 29620792
72. Van Mareen MC, de Munck L, and de Bock GH, et al (2016) 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study Lancet Oncol 17(8) 1158–1170 https://doi.org/10.1016/S1470-2247(16)30067-5
73. Van Mareren MC, de Munck L, and de Bock GH, et al (2016) 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study Lancet Oncol 17(8) 1158–1170 https://doi.org/10.1016/S1470-2247(16)30067-5
74. Parker PA, Peterson SK, and Shen Y, et al (2018) Prospective study of psychosocial outcomes of having contralateral prophylactic mastectomy among women with nonhereditary breast cancer J Clin Oncol 36(25) 2630–2638 https://doi.org/10.1200/JCO.2018.78.6442 PMID: 30044955 PMCID: 6118404
75. Adank MA, Verhoef S, and Oldenburg RA, et al (2013) Excess breast cancer risk in first degree relatives of CHEK2-1100delC positive familial breast cancer cases Eur J Cancer 49(8) 1993–1999 https://doi.org/10.1016/j.ejca.2013.01.009 PMID: 23415889

76. Lander casper J, Bennie B, and Parsons BM, et al (2017) Fewer reoperations after lumpectomy for breast cancer with neoadjuvant rather than adjuvant chemotherapy: a report from the national cancer database Ann Surg Oncol 24(6) 1507-1515 https://doi.org/10.1245/s10434-016-5760-8 PMID: 28062931 PMCID: 5413581

77. Choi J, Laws A, and Hu J, et al (2018) Margins in breast-conserving surgery after neoadjuvant therapy Ann Surg Oncol 25(12) 3541-3547 https://doi.org/10.1245/s10434-018-7602-4 PMID: 30128902

78. Feliciano Y, Mamtani A, and Morrow M, et al (2017) Do calcifications seen on mammography after neoadjuvant chemotherapy for breast cancer always need to be excised? Ann Surg Oncol 24(6) 1492-1498 https://doi.org/10.1245/s10434-016-5741-y PMID: 28058550 PMCID: 5485840

79. Omarini C, Guaitoli G, and Noventa S, et al (2017) Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients Eur J Surg Oncol 43(4) 613-618 https://doi.org/10.1016/j.ejso.2016.09.020

80. EBCTCG (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials Lancet 383(9935) 2127-2135 https://doi.org/10.1016/S0140-6736(14)60488-8 PMID: 24656685 PMCID: 5015598

81. Marta GN, Macedo CR, and Carvalho Hde A, et al (2015) Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials Radiother Oncol 114(1) 42–49 https://doi.org/10.1016/j.radonc.2014.11.014

82. Dasu A, Flejmer AM, and Edvardsson A, et al (2018) Normal tissue sparing potential of scanned proton beams with and without respiratory gating for the treatment of internal mammary nodes in breast cancer radiotherapy Phys Med 52 81–85 https://doi.org/10.1016/j.ejmp.2018.06.639 PMID: 30139613

83. Langendijk JA, Lambin P, and De Ruysscher D, et al (2013) Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach Radiother Oncol 107(3) 267–273 https://doi.org/10.1016/j.radonc.2013.05.007 PMID: 23759662

84. Prowell TM, Beaver JA, and Pazdur R (2019) Residual disease after neoadjuvant therapy - developing drugs for high-risk early breast cancer N Engl J Med 380(7) 612–615 https://doi.org/10.1056/NEJMp1900079 PMID: 30763188

85. Rack B (2014) Circulating tumor cells predict survival in early average-to-high risk breast cancer patients J Natl Cancer Inst 106(9) [doi/10.1093/jnci/dju273] https://doi.org/10.1093/jnci/dju066 PMID: 24832787 PMCID: 4112925

86. Garcia-Murillas I (2015) Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer Sci Transl Med 7(302) 302ra133 https://doi.org/10.1126/scitransmed.aab0021 PMID: 26311728

87. Tenori L (2015) Serum metabolomic profiles evaluated after surgery may identify patients with oestrogen receptor negative early breast cancer at increased risk of disease recurrence. Results from a retrospective study Mol Oncol 9(1) 128–139 https://doi.org/10.1016/j.molonc.2014.07.012

88. Oakman C (2011) Identification of a serum-detectable metabolomic fingerprint potentially correlated with the presence of micrometastatic disease in early breast cancer patients at varying risks of disease relapse by traditional prognostic methods Ann Oncol 22(6) 1295–1301 https://doi.org/10.1093/annonc/mdq606 PMID: 21199886

89. Hershman DL, Unger JM, and Greenlee H, et al (2015) Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor-induced musculoskeletal pain: SWOG S0927 J Clin Oncol 33(17) 1910–1917 https://doi.org/10.1200/JCO.2014.59.5595 PMID: 25940724 PMCID: 4451174

90. Hershman DL, Unger JM, and Crew KD, et al (2015) Effect of acupuncture versus Sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial JAMA 320(2) 167–176 https://doi.org/10.1001/jama.2018.8907 PMID: 29998338
92. Laenkholm AV, Jensen MB, and Eriksen JO, et al (2018) PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer J Clin Oncol 36(8) 735–740 https://doi.org/10.1200/JCO.2017.74.6586 PMID: 29369732

93. Burstein HJ, Lacchetti C, and Anderson H, et al (2019) Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update J Clin Oncol 37(5) 423–438 https://doi.org/10.1200/JCO.18.01160

94. Wilson C, Martin C, and Winter MC (2019) Compliance and patient reported toxicity from oral adjuvant bisphosphonates in patients with early breast cancer. A cross sectional study J Bone Oncol 15 100226 https://doi.org/10.1016/j.jbo.2019.100226 PMID: 30937280 PMCID: 6429539

95. Coleman RE, Collinson M, and Gregory W, et al (2018) Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04) J Bone Oncol 13 123–135 https://doi.org/10.1016/j.jbo.2018.09.008 PMID: 30591866 PMCID: 6303395

96. Litton JK, Rugo HS, and Ettl J, et al (2018) Talazoparib in patients with advanced breast cancer and a germline BRCA mutation N Engl J Med 379(8) 753–763 https://doi.org/10.1056/NEJMoa1802905 PMID: 30110579

97. Chavez-MacGregor M, Clarke CA, and Lichtensztajn DY, et al (2017) Delayed initiation of adjuvant chemotherapy among patients with breast cancer JAMA Oncol 2(3) 322–329 [doi:10.1001/jamaoncol.2015.3856] https://doi.org/10.1001/jamaoncol.2015.3856

98. Tao JJ, Visvanathan K, and Wolff AC (2015) Long term side effects of adjuvant chemotherapy in patients with early breast cancer Breast 24(2) S149–S153 https://doi.org/10.1016/j.breast.2015.07.035 PMID: 26299406 PMCID: 4743500

99. Lyman GH, Greenlee H, and Bohlke K, et al (2018) Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline J Clin Oncol 36(25) 2647–2655 https://doi.org/10.1200/JCO.2018.79.2721 PMID: 29889605

100. Carrera PM, Kantarjian HM, and Blinder VS (2018) The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment CA Cancer J Clin 68(2) 153–165 https://doi.org/10.3322/caac.21443 PMID: 29338071