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16th St. Gallen BCC

St. Gallen International Breast Cancer Conference

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PEER-REVIEWED CONFERENCE REPORT

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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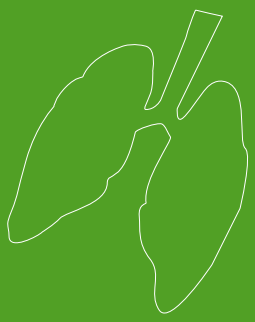

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Letter from the Editor

Dr Stefan Rauh

Dear Reader,

When oncologists hear the word St Gallen, they do not first think of a lovely Swiss town close to the Alps, they think of early breast cancer. St Gallen has become a brand, because it is here where maybe THE most important global forum on the treatment of early breast cancer started in 1987. Victim of its success and the ever-higher number of attendees, it has moved for logistic reasons to Vienna in recent years, but still holds the name of its origin.

The conference is also unique in its format: 4 days of intense debate of some of the globally most renowned experts in the field. Often passionate debates are an exquisite etude of dissecting study strengths, weaknesses and shortcomings in structures and outcomes, data analyzing and dialectic debating.

St Gallen's consensus statements will be the reference for decision-making for the 2 years to come. Looking for clear guideline – like algorithms, some attendees will be rather confused leaving the conference (and this Report will also give you a hint of an "attendee's experience"): Should you necessarily follow decisions based on a controversial vote of an expert panel? Which should be the threshold of a clear statement to follow? Full agreement, a 2/3 majority agreement, or a simple 51%?
I will leave this up to you, dear reader, to decide.

Yours, sincerely,
Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is Chair of the ESMO Practicing Oncologist's Working Group since 2015, member of the ESMO Quality Task Force, extended member of the ESMO Public Policy Committee, Assistant Editor of ESMO Cancer Horizons, and has been an ESMO Executive Board member in 2015-2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

Conflict of Interest Statement:
Nothing to declare.

Medical consensus is a public statement on a particular aspect of medical knowledge at the time the statement is made that a representative group of experts agree to be evidence-based and state-of-the-art (state-of-the-science) knowledge. Its main objective is to counsel physicians on the best possible and acceptable way to diagnose and treat certain diseases or how to address a particular decision-making area. It is usually, therefore, considered an authoritative, community-based expression of a consensus decision-making and publication process. Consensus statements differ from medical guidelines, another form of state-of-the-science public statements. According to the NIH, "Consensus statements synthesize new information, largely from recent or ongoing medical research, that has implications for reevaluation of routine medical practices. They do not give specific algorithms or guidelines for practice.

From: *Wikipedia.com, downloaded may 16, 2019*

St. Gallen Consensus

From March 20 to March 23, the Austrian capital Vienna hosted the 16th St. Gallen International Breast Cancer Conference. After three days of presentations that reviewed the recent developments in the primary treatment of early breast cancer, the meeting culminated in the traditional consensus session on the fourth day of the conference. In this session, a panel of 53 experts was asked to cast their vote on more than 135 (detailed) questions on the treatment of early breast cancer.

History of the consensus meeting

Established in 1978 in the Swiss town of St. Gallen, the St. Gallen International Breast Cancer Conference is now biannually organised in Vienna. This meeting is a global, multidisciplinary conference with over 2,000 representatives from multiple nations and every continent. The conference offers educational presentations that review recent developments in several areas of early breast cancer treatment. The highlight of the conference is the consensus panel meeting. This year, in a session chaired by Dr Giuseppe Curigliano (Instituto Europeo di Oncologica, Italy) and Prof. Eric Winer (Dana Farber Cancer Institute, Boston, USA), 53 experts discussed and casted their vote on specific areas of treatment with a focus on controversies and uncertainties in the management of early-stage breast cancer. The goal of this consensus process is to articulate important themes in management, and to provide guidance to clinicians around the world on how to think about and care for women with early-stage breast cancer. The 53 panellists were asked to cast their vote on more than 135 detailed questions, using 3 possible answers: yes / no / abstain. However, due to the complexity of some questions, more options were given in certain instances. 'Abstain' was to be used in case of insufficient data, no personal expertise on the particular issue, or a conflict of interest of a given panellist. After each vote, the answers were summarised in percentages.

Primary surgery: margins

The first topic of the consensus panel was the estimated clinical benefit of tumour-free margins after excision of the primary invasive tumour. At the St. Gallen Conference 2017, the panel suggested that "no ink on tumour" (meaning the tumour does not extend to the edge of excised tissue) provides adequate local control, i.e. an optimal local recurrence rate and/or lower rate of secondary surgery, in patients to receive standard radiotherapy [1]. This year, the panel zoomed in further on this topic. The majority of the panellists (86%) agreed that "no ink on tumour" also provides clinical benefit in patients with multifocal residual disease after neoadjuvant systemic therapy. In case of lobular cancer (no neoadjuvant systemic therapy!), 73% of the panellists accepted "no ink on tumour" to provide clinical benefit, and in case of the presence of extensive intraductal component, 63% of the panellists agreed "no ink on tumour" to provide clinical benefit. In addition, almost half of the panellists (46%) took the view that even 1 mm "ink on tumour" should require re-excision. In contrast, 38% of the panellists regarded 4 mm "ink on tumour" acceptable to forgo re-excision.

1. Curiglioane G, et al. Ann Oncol 2017; 28: 1700–1712.

Skin and nipple sparing surgery: still a matter of debate

A vast majority of the panel (83%) agreed that in patients with inflammatory breast cancer, , the risk of local recurrence when preserving the skin envelop (i.e. skin sparing mastectomy) outweighs the gains in cosmetics even with a clinical complete response to neoadjuvant systemic therapy and therefore should not be performed in these patients, whatever the extent of disease at the time of surgery. When asked for their opinion on the risks vs gains of preserving the skin envelope in patients without clinical signs of skin infiltrations, but tumours radiologically "reaching" the skin in preoperative imaging, the panellists did not reach any consensus: 38% of the panellists voted "yes", 40% voted "no". Can skin and nipple be preserved in cases were imaging suggests a centrally located tumour near the nipple? No consensus could be reached here, either: 38% of the panellists were of the opinion that skin and nipple sparing surgery should be avoided, 43% of the panellists were in favour of skin and nipple sparing surgery in these cases.

Surgery of the axilla: indications decrease

Next, the panel zoomed in on the benefit of (omitting) axillary surgery. Referring to the - recently updated - results of the AMAROS trial [1], suggesting equal outcomes between axillary surgery and axillary radiotherapy in terms of recurrence and/or disease-free survival but with less

morbidity after radiotherapy, the majority of the panellists voted for omitting complementary axillary surgery as long as radiotherapy of the axilla and positive sentinel nodes was planned. This was the case both for patients (T1-2 with 1 or 2 positive sentinel nodes) who had undergone breast-conserving surgery (73% of the panellists voted for omitting axillary surgery) and patients who had a mastectomy (83% of the panellists voted for omitting axillary surgery). However, in case of patients with 1 or 2 positive sentinel nodes undergoing mastectomy and for whom no regional node irradiation was planned, 66% of the panellists voted against omitting axillary surgery. In addition, a majority (61%) of the panellists voted against omitting axillary surgery in patients with tumours greater than 5 cm with 1 or 2 positive sentinel nodes undergoing breast-conserving therapy and whole breast irradiation.

Almost all panellists (92%) were in favour of omitting axillary surgery in patients who had lymph node-positive disease before neoadjuvant systemic therapy, who were downstaged to cN0 after neoadjuvant systemic therapy, and who had at least 3 negative sentinel nodes after the neoadjuvant therapy. Exactly the same percentage of the panellists voted for omitting axillary surgery in patients had lymph node-positive disease before neoadjuvant systemic therapy, who were downstaged to cN0 after neoadjuvant systemic therapy, and who had 1 clipped lymph node-negative or 1 or 2 negative sentinel nodes after the neoadjuvant therapy.

1. Rutgers EJ, et al. SABCS 2018; abstr GS4-01.

DCIS: de-escalation of (adjuvant) therapy

De-escalation of therapy for patients with ductal carcinoma *in situ* (DCIS) was surveyed in 4 questions. Almost all panellists (98%) agreed that screening-detected, small DCIS with favourable biological features (e.g. G1-2, or other low risk features) has a better prognosis and therefore may require less intensive treatment. In line with this, 84% of the panellists found it a reasonable option to omit radiotherapy for patients with DCIS with favourable features and a clear tumour-free surgical margin (≥ 5 mm). Only a small majority of the panellists (56%) found it a reasonable option to omit endocrine therapy in these patients, while 66% of the panellists found it a reasonable option to omit both radiotherapy and endocrine therapy.

Gene expression signatures

The use of gene expression signatures is becoming increasingly important in risk stratification and treatment decision-making for patients with early breast cancer. At the St. Gallen Conference 2017 a majority of the panellists took the view that results of gene expression signature tests like Oncotype DX and MammaPrint are prognostic for recurrence of disease within 5 years after surgery. In recent years, the results of MINDACT [1], TAILOR-X [2] and the PLAN-B trial [3] have been published. Based on the results of these trials, almost all panellists (94%) were in favour now of using these gene expression signatures as a decision aid for adjuvant systemic therapy in patients with ER+/Her2-, T1/T2, N0 breast cancer. In case of ER+/Her2-, T3, N0 breast cancer, 75% of the panellists found gene expression signatures to be valuable for determining whether to recommend adjuvant systemic chemotherapy. Also in case of patients with ER+/Her2- (any T) and 1 to 3 positive lymph nodes, a majority (80%) of the panellists was in favour of using a gene expression signature.

In case of a low risk MammaPrint in patients with 1 or 2 positive lymph nodes, 80% of the panellists voted against an indication for adjuvant chemotherapy, irrespective of age. In line with this, 80% of the panellists voted against an indication for adjuvant chemotherapy in patients (older than 50 years) with 1 or 2 positive nodes and an Oncotype DX Recurrence Score <11. Remarkably, 51% of the panellists took the view that patients younger than 50 years, with node-negative disease and an Oncotype DX Recurrence Score of 21 to 25 should be advised adjuvant chemotherapy. This is in contrast with the results of TAILOR-X, which showed little benefit of adjuvant chemotherapy for patients younger than 50 years, node-negative disease and an Oncotype DX Recurrence Score <25. With regard to postmenopausal, node-negative patients having an Oncotype DX Recurrence Score >26, 57% of the panellists agreed that these patients should be offered adjuvant chemotherapy depending on (unfavourable) histopathological parameters and patients preferences, while 39% of the panellists voted that these patients should be offered adjuvant chemotherapy routinely.

1. Cardoso F, et al. N Engl J Med 2016; 375:717-729.
2. Sparano JA, et al. N Engl J Med 2018; 379:111-121.
3. Nitz U, et al. J Clin Oncol. 2019; 37: 799-808.

Neoadjuvant therapy and residual disease

Just as it was 2 years ago, almost all panellists (98.5%) endorsed neoadjuvant systemic treatment for patients with stage 2 or stage 3 triple-negative breast cancer, or with Her2-positive breast cancer. In addition, the panel this year voted about which type of neoadjuvant should be preferred in some specified subtypes of breast cancer. For

example, in case of a postmenopausal patient with a luminal A subtype based on immunohistochemistry (or equivalent based on gene expression testing), 81% of the panellists preferred endocrine neoadjuvant therapy over neoadjuvant chemotherapy. This opinion means a clear shift in advantage of neoadjuvant endocrine therapy. Asked for their opinion on the appropriate duration of the endocrine neoadjuvant therapy in postmenopausal patients with a luminal A type tumour, 47% of the panellists preferred to continue endocrine neoadjuvant therapy until optimal reduction in tumour size is reached however long it takes, while 33% of the panellists preferred 6 month of endocrine neoadjuvant therapy.

There was no consensus at all on the issue of the use of a platinum-based regimen – in addition to an anthracycline/taxane based regimen – as neoadjuvant chemotherapy in patients with triple-negative breast cancer; 57% of the panellists voted against a platinum-based regimen, 35% agreed with a platinum-based regimen. On the other hand, platinum-based neoadjuvant chemotherapy was endorsed by 67% of the panellists for a patient with triple-negative breast cancer and a *BRCA* mutation. This prompted one of the panellists to say this is not in line with the scientific data showing that non-*BRCA* mutation carriers benefit most from platinum because *BRCA* mutation carriers are so chemosensitive that the addition of platinum on top of anthracycline/taxane does not add much extra benefit.

Adjuvant chemotherapy after neoadjuvant chemotherapy? Going beyond EMA/FDA

At the time of the St. Gallen Conference 2017, there was still a lack of scientific data to decide for which patients adjuvant systemic therapy should be recommended after neoadjuvant systemic therapy. However, recently, the results of the CREATE-X trial [1] and the KATHERINE trial [2] have been published. In patients with a Her2-negative tumour who had residual disease after neoadjuvant chemotherapy, the CREATE-X trial showed a clinical benefit (e.g. a reduction in recurrence and longer overall survival) of adjuvant treatment with capecitabine. In the KATHERINE trial, patients with a Her2-positive tumour who had residual disease after Her2-targeted neoadjuvant therapy had more clinical benefit from adjuvant treatment with TDM-1 compared to adjuvant treatment with trastuzumab. In line with these data, 83% of the panellists endorsed adjuvant treatment with capecitabine in patients with triple-negative breast cancer and residual disease (>1 cm residual tumour in the breast and/or positive axillary lymph nodes) following neoadjuvant chemotherapy (anthracycline/taxane). Only 6% of the panellists endorsed no further therapy. In case of residual disease less than 1 cm (and no positive axillary lymph nodes) the panellists were less in favour of adjuvant chemotherapy with capecitabine; 51% of the panellists endorsed adjuvant therapy with capecitabine vs 39% of the panellists who were in favour of no further therapy. In Her2-positive tumours and residual disease in the breast (>1 cm) or in the axillary lymph nodes following a Her2-targeted neoadjuvant therapy, 94% of the panellists endorsed adjuvant chemotherapy with TDM-1. This prompted one panellist to remark that **momentarily TDM-1 is not (yet) approved for this indication by EMA and/or FDA**. In case of no residual disease (e.g. a pathological complete response) following neoadjuvant therapy with polychemotherapy plus trastuzumab/pertuzumab in lymph node-positive patients with a Her2-positive tumour, 38% of the panellists endorsed adjuvant therapy with trastuzumab vs 48% of the panellists preferring dual Her2-blockade adjuvant therapy with trastuzumab plus pertuzumab. In patients benefitting from a complete remission following neoadjuvant treatment with combined polychemotherapy and trastuzumab/pertuzumab in patients with a Her2-positive lymph node-negative tumour, 52% of the panellists endorsed adjuvant therapy with trastuzumab vs 26% of the panellists preferring a dual Her2-blockade adjuvant therapy with trastuzumab plus pertuzumab.

1. Masuda N, et al. N Engl J Med 2017; 376: 2147-2159.
2. von Minckwitz G, et al. N Engl J Med 2019; 380: 617-628.

Endocrine therapy in premenopausal patients

The first question the panel had to answer on this topic was the ideal cut-off – in terms of percentage of ER-positive tumour cells – to prescribe endocrine therapy. There was no clear consensus on this topic: 30% of the panellists voted for >1%, 4% voted for >5%, 39% voted for >10%, while 25% took the view that there is no clear answer. Recently, updates were presented of the SOFT and TEXT trial [1] showing that among premenopausal women with breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of both disease-free and overall survival than tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. Based on these results, a majority of the panellists (68%) took the view that premenopausal patients with an ER-positive tumour who are getting adjuvant chemotherapy are candidate for ovarian function suppressive (OFS) therapy. Also in line with the SOFT and TEXT trials, 85% of the panellists

agreed that an age <35 years should lower the threshold to prescribe OFS therapy. There was no consensus on the question whether premenopausal ER-positive patients with a moderate risk and no adjuvant chemotherapy are candidate for OFS: 46% voted "yes", 42% voted "no." A small majority of the panellists (60%) was of the opinion that an adverse result of a gene expression test should lower the threshold for OFS therapy in premenopausal ER-positive patients. Half of the panellists (52%) was of the opinion that Her2-positive status should not lower the threshold for OFS therapy. Asked for their opinion on the duration of OFS, a small majority of the panellists (55%) favoured 5 years of OFS, which was the duration of OFS in the SOFT and TEXT trial (24% voted for 2-3 years of OFS). A majority of the panellists endorsed OFS during chemotherapy for women who want a future pregnancy. This was the case for patients with HR-negative breast cancer (92% voted "yes"), and for patients with HR-positive breast cancer (80% voted "yes").

With regard to preferred endocrine therapy for patients who remain premenopausal after 5 years of tamoxifen therapy, a small majority of the panellists recommended to stop further treatment with tamoxifen, while 37% of the panellists recommended to continue to 10 years of treatment with tamoxifen. However, in case the patient – who remained premenopausal after 5 years of tamoxifen – was at high risk at presentation (e.g. stage 2, node positivity), 80% of the panellists would recommend continuing tamoxifen treatment to 10 years.

1. Francis PA, et al. N Engl J Med 2018; 379: 122-137.

Endocrine therapy in postmenopausal patients: a graded approach

At the St. Gallen Conference 2017, a small majority of the panellists (55%) took the view that for most postmenopausal patients an aromatase inhibitor (AI) should be considered at some point in the course of treatment. This year, almost all panellists (96%) were of this opinion. Parameters that favour the inclusion of an AI at some point in the course of treatment of postmenopausal patients are grade 3 or high Ki67 (83% of the panellists voted "yes") and Her2 positivity (68% of the panellists voted "yes"). Upfront therapy with an AI should be considered in all postmenopausal patients of high risk by stage or tumour volume (94% of the panellists voted "yes") but not in all postmenopausal patients (59%% of the panellists voted against upfront AI in all postmenopausal patients). In postmenopausal patients, the historical duration of endocrine therapy is 5 years. Recently, Gray at al. presented a meta-analysis of studies that explored the benefit of extended endocrine therapy [1]. At the St. Gallen Conference 2019 the panellists were asked in which particular situations the endocrine therapy should be extended beyond 5 years of duration. For patients with stage 1 breast cancer who had 5 years of tamoxifen, a majority of the panellists (72%) would not recommend extending the endocrine therapy beyond 5 years. One of the panellists remarked that this result contradicts the earlier statement of 96% of the panel that treatment with an AI should be considered for all postmenopausal patients at some point in the course of treatment. A majority of the panellists (78%) also would not recommend extension of endocrine therapy for patients with stage 1 breast cancer who had 5 years of AI treatment. For a postmenopausal patient who has stage 2 node-negative breast cancer and who had 5 years of tamoxifen, 68% of the panellists would recommend extended endocrine therapy beyond 5 years. However, for a postmenopausal patient who has stage 2 node-negative breast cancer and who had 5 years of AI treatment, 35% of the panellists would recommend extended endocrine therapy while 59% of the panellists would not.

For postmenopausal patients with stage 2 node-positive breast cancer, a vast majority of the panel was in favour of extended endocrine therapy beyond 5 years: 98% of the panellists recommended extended endocrine therapy after 5 years of tamoxifen; 81% of the panellists recommended extended endocrine therapy, after 5 years of AI treatment. Asked their opinion on the optimal duration of the extended endocrine therapy 38% of the panellists voted for a total duration of the endocrine therapy of 7-8 years, while 59% of the panellists voted for 10 years. A majority of the panellists (60%) took the view that for postmenopausal patients at very high risk (10 or more positive nodes), extended endocrine therapy should not routinely be recommended but should be considered on a case by case basis.

1. Gray R, et al. SABCS 2018, abstract GS3-03.

Adjuvant Her2-targeted therapy

For patients with Her2-positive early breast cancer, the standard management includes adjuvant chemotherapy plus Her2-targeted therapy. At the St. Gallen Conference 2019, the panel zoomed in on specific subtypes of Her2-positive early breast cancer. A small majority of the panellists (55%) took the view that Her2-targeted therapy is not required for patients with Her2-positive, T1a, node-negative breast cancer, while 43% of

the panellists voted in favour of Her2-targeted therapy for these patients. A majority of 62% of the panellists stated that ER-status does not affects this opinion, while 28% of the panellists stated that ER-status will affect their decision on Her2-targeted adjuvant therapy. In line with the previous questions, 52% of the panellists indicated that for patients with ER-positive, Her2-positive breast cancer, addition of pertuzumab to the adjuvant treatment is not a standard therapy.

The preferred regimen for adjuvant therapy in patients with stage 1 Her2-positive breast cancer is, according to 74% of the panellists, taxane plus trastuzumab. Based on the results from the APHINITY trial [1], 77% of the panellists endorsed adding pertuzumab to the adjuvant Her2-targeted therapy for all patients with Her2-positive breast cancer (stage 2 or stage 3, but not in stage 1 patients). This prompted one panellist to remark that the approval for adjuvant therapy with pertuzumab is, according to the results of the APHINITY trial, for (Her2-positive) patients with positive nodes or ER-negative breast cancer.

With regard to the duration of adjuvant therapy with trastuzumab, the vast majority of the panellists (90%) was in favour of 12 months of therapy. A duration of 6-month adjuvant therapy with trastuzumab might be an acceptable option for patients with stage 1 Her2-positive breast cancer, according to 29% of the panellists.

Recently, 1 year of adjuvant therapy with neratinib (after neoadjuvant or adjuvant treatment with trastuzumab) proved to significantly reduce the proportion of clinically relevant breast cancer relapses in patients with Her2-positive, stage 2 or 3 early breast cancer [2]. However, the panellists did absolutely **not** reach any consensus for which patients adjuvant therapy with neratinib should be recommended both after (neo)adjuvant therapy with trastuzumab and after (neo)adjuvant therapy with trastuzumab plus pertuzumab. About one third of the panellists voted "abstain" on both questions.

1. von Minckwitz G, et al. N Engl J Med 2017; 377:122-131.
2. Holmes MM, et al. Lancet Oncol. 2017; 18: 1688-1700.

Adjuvant therapy in triple-negative breast cancer

The panellists voted about several questions regarding recommendations for adjuvant chemotherapy in patients with triple-negative breast cancer. All panellists agreed that for patients with pT1a, pN0 (tumour <6 mm), triple-negative breast cancer, chemotherapy is not always indicated; 35% of the panellists took the view that chemotherapy for these patients is never indicated, 65% of the panellists were of the opinion that chemotherapy for these patients is sometimes indicated. In general, the preferred chemotherapy regimen for patients with stage 1 triple-negative breast cancer should contain anthracyclines, alkylators, and taxanes, according to 78% of the panellists, while 50% of the panellists preferred chemotherapy with only alkylators and taxanes in case a stage 1 triple-negative breast cancer patient has a tumour with a size ≤1 cm. For patients with stage 2 triple-negative breast cancer, almost all panellists (94%) were in favour of a chemotherapy regimen containing anthracycline, alkylator, and taxane.

Bisphosphonates and denosumab

At the St. Gallen Conference 2017, the panel was inconclusive about the use of bisphosphonates during adjuvant endocrine therapy to improve disease-free survival – irrespectively of bone mineral density – in premenopausal patients on ovarian function suppression therapy (plus tamoxifen or aromatase inhibitor) (53% yes, 37% no, 10% abstain). Now, 2 years later, there was still no consensus; the panellists voted in exactly the same way. However, the support for the use of bisphosphonates during endocrine therapy to improve disease-free survival in postmenopausal patients has increased: 2 years ago, 76% of the panellists endorsed the use of bisphosphonates for these patients while this year 84% of the panellists was in favour of the therapy. Remarkably, when asked whether the panellists prescribe bisphosphonates in their own daily practice, like they just recommended, only 43% of the panellists voted for "yes" (40% voted "no", 17% abstained). The opinion of the panellists on the use of denosumab (60 mg twice a year) instead of bisphosphonates was crystal clear, however: 75% of the panellists were not in favour of the use of denosumab, echoing the results of the recently presented data of the D-CARE trial [1].

1. Coleman RE, et al. J Clin Oncol 2018; 36 (supp) abstract 105.

Germ-line mutations

Like 2 years ago, the panellists were asked to vote on the advisability of genetic testing for high risk (germ-line) mutations after counselling for several subtypes of patients with early breast cancer. In general, the panellists were more inclined to advise genetic testing compared to 2 years ago. There was absolute consensus (100% of the panellists voted "yes") that all patients with a strong family history should be offered genetic testing. In addition, almost all panellists (96%) endorsed genetic testing in all patients who are younger than 35 years. A vast majority of the panellists (85%) was in favour of genetic testing in all patients with triple-negative breast cancer who are 60 years or younger at the time of diagnosis. However, only 39% of

the panellists endorsed genetic testing in all patients with triple-negative breast cancer (regardless of their age); 33% of the panellists endorsed genetic testing in all patients with breast cancer who are younger than 50 years and 29% of the panellists took the view that all patients with breast cancer (regardless of age and/or type of breast cancer) should be offered genetic testing. One of the panellists who was in favour of offering genetic testing to all patients with breast cancers argued that all guidelines about genetic testing are aiming on a moving target: the number of mutations that are of clinical importance in breast cancer is still rising and genetic testing is becoming increasingly broader and cheaper. As a result, the threshold for genetic testing is lowering.

Pregnancy after breast cancer

Many young breast cancer survivors retain a project of childbearing, but both patients and their physicians have concerns that a pregnancy, with its associated hormone-amplified milieu, will increase the risk for breast cancer recurrence, especially if the disease is hormone-sensitive, i.e., ER–positive. Recently published data showed reassuring data on the long-term safety of pregnancy in breast cancer survivors, including those with ER-positive disease [1]. Whether a break in adjuvant endocrine therapy will compromise breast cancer outcomes is the subject of a large international cooperative group study (POSITIVE; NCT02308085). At the St. Gallen Conference 2019, the panellists were asked to give their opinion on the minimal duration of endocrine therapy before interrupting to allow pregnancy. A majority of 80% took the view that this is allowed after 18 months. A majority of 60% of the panellists endorsed restaging prior to attempted conception. According to the panellists, there is no reason to discourage pregnancy after breast cancer in all non-high-risk situations, irrespective of ER-status.

1. Lambertini M, et al. J Natl Cancer Inst 2018; 110: 426-429

Life style

The final topic of the consensus session was about exercise and diet. First, the panellists were asked whether they think patients with breast cancer should be recommended to avoid weight gain. Not surprisingly, the vast majority of the panellists (83%) agreed that patients should avoid weight gain. Almost exactly the same proportion of the panellists (84%) therefore endorsed an exercise regimen to be part of the standard care.

Finally, the panellists were asked whether or not they agreed that patients should be informed about the magnitude of benefit (in terms of overall survival) of interventions with a known small-to-marginal benefit, and be offered no treatment as a reasonable alternative. Predictably, in the present era of "shared decision-making", 92% of the panellists voted "yes" on this last question.

Special Lectures

Extrapolating data from clinical trials as we treat patients in real life

Randomised clinical trials are the gold standard for assessing the efficacy of an intervention. However, their results are not always generalisable to real-world populations. Prof. Sharon Giordano (MD Anderson, Houston, USA) sketched how real-world data sometimes can fill this gap.

Although being the gold standard, randomised clinical trials have a couple of shortcomings that challenge the application of the outcomes of the trials when treating real-world patients, Giordano said. First of all, clinical trials don't include (all) representative populations. In general, patients who participate in clinical trials are younger than the average real-world patient, have less comorbidities, have a better performance status, have a higher social-economic status, and often more late-stage cancer. As a consequence, it is not clear whether or not results of the clinical trial are also applicable to patient populations who where excluded from the trial, in particular patients who are older and/or have more advanced disease than the trial participants, patients who have comorbidities, or female patients who are pregnant (or even males with breast cancer!). Effectiveness also depends on many additional issues like comorbidities, adherence, and side effects. In addition, Giordano said, randomised studies are not always feasible, such as for rare tumors, are sometimes considered unethical, and sometimes fail because doctors and/or patients are unwilling to support randomisation. Finally, randomised clinical trials often do not study patient-centred outcomes, do not follow patients for sufficient duration to assess the late effects of therapy, and have insufficient numbers to study rare outcomes.

In these situations, data from observational studies may be used to help fill in the gaps in knowledge, according to Prof. Giordano. For example, results from one observational study showed a much higher rate of hospitalisation during chemotherapy in patients older than 65 years than was reported in clinical trials [1]. However, the major threat to the validity of observational studies are several types of bias: selection bias, performance bias, detection bias, attrition bias, selective outcome-reporting bias. For example, selection bias can result in patients with a poorer prognosis getting the treatment under investigation, resulting in a worse survival among treated patients. Or the other way around: patients with better underlying health are selected to receive the treatment under investigation, resulting in better survival. Therefore, it is of utmost importance to assess and address the risks of bias in observational studies, in order to estimate whether the observational study is likely to produce valid results, Giordano emphasised. There are statistical tools to address these biases, like multivariate regression models and propensity score analysis, but these techniques will never be able to completely take the biases away. As illustration, Giordano showed the results of an observational study that suggested that treatment for prostate cancer decreases the chance of dying of heart disease or diabetes [2].

Giordano concluded her lecture by briefly addressing two other issues that make it challenging to apply data from a clinical trial to real-world patients. Sometimes in a clinical trial, an intervention shows a statistically significant, but (very) small, benefit. For example, in the APHINITY trial, the absolute benefit after 3 years was only 0.9% and the number needed to treat (with adjuvant pertuzumab) was 112 [3]. Likewise, the ExteNET trial reported an absolute benefit after 2 years of adjuvant therapy with neratinib of 2.3% (number needed to treat of 44) [4]. In these cases, it is difficult to balance the pros and cons of applying treatment to an individual patient, Giordano remarked. Finally, applying outcomes from clinical studies to daily practice can be difficult when the standard of care has been changed by the time the results of the trial are presented. For example, the KATHERINE trial showed clinical benefit from adjuvant treatment with TDM-1 compared to adjuvant treatment with trastuzumab in patients with Her2-positive breast cancer and residual disease after neoadjuvant therapy [5]. However, less than 20% of the patients in KATHERINE were treated with dual anti-Her2 neoadjuvant therapy, which is the standard now. So, this makes it difficult to estimate the benefit of TDM-1 adjuvant therapy for patients who have residual disease after dual anti-Her2 neoadjuvant therapy. In these areas of uncertainty, shared decision-making becomes critical, Giordano said.

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3. von Minckwitz G, et al. N Engl J Med 2017; 377:122-131.
4. Holmes MM, et al. Lancet Oncol. 2017; 18: 1688-1700.
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What is the clinical benefit of treatment of patients with early breast cancer?

Prof. Ann Partridge (Dana-Farber Cancer Institute, Boston, USA) addressed the relevance of clinical benefit, clinical meaningfulness, and shared decision-making in the treatment of patients with early breast cancer.

Due to improvements in local and systemic treatments, the age-adjusted breast cancer mortality rate has gradually dropped in the last decades: from about 70 per 100,000 women (40-84 years) in the 1970's to <40 per 100,000 women now. In light of the improved outcomes of the treatment, the definition of clinical benefit of a treatment has also evolved, Partridge said. In the 1970's, clinical benefit meant that a patient had an objective response to the treatment. In the 1980's, overall survival, quality of life, and physical functioning became objective parameters to define benefit. Since the 1990's, the definition is mainly related to surrogate parameters like progression-free survival, overall response rates, durability of responses (in particular in metastatic disease setting), and disease-free survival (in adjuvant setting). Translated to the individual patient, this means that the patient lives longer, feels better (has less symptoms), and/or functions better, Partridge said. To measure all these parameters, several types of assessment are needed: clinician-reported outcomes, observer-reported outcomes, performance outcomes, and – probably most important – patient-reported outcomes.

The concept of clinical benefit has also incorporated the concept of value, Partridge explained. The approval of so many new (and expensive) cancer drugs has shifted focus beyond the statistical improvements of the therapies. Increasingly, the focus is on the clinical value of therapy, both for the individual patient as well as for society. Both ASCO and ESMO recently have developed frameworks to calculate the added clinical value of (new) cancer drugs in a transparent and objective way. ASCO has developed the Net Health Benefit (NHB) scale [1], and ESMO has developed the ESMO Magnitude of Clinical Benefit Scale (MCBS) [2]. Both frameworks factor in outcomes of clinical trials like survival, toxicity, and other symptoms, but also the price of the drug. In the ASCO NHB scale, the added value of the drug is expressed in a number theoretically ranging from -20 to 180 (the higher the score, the greater the added value). In the ESMO MCBS, added clinical value can range from C (lowest added value) to A (highest added value) for potentially curative therapies and from grade 4 (lowest added value) to grade 1 (highest added value) for therapies that are not likely to be curative.

However, therapies that have a high ASCO NHB score or a high ESMO MCBS, e.g. therapies that have clinical benefit, are not necessarily also clinically meaningful, Partridge emphasised. Clinical meaningfulness also depends on individual patient parameters like age, performance status, comorbidities, and personal goals and values. Therefore, thresholds for a therapy being clinically meaningful may be higher or lower for each individual patient (or society). So, in order to define the meaningfulness of an intervention for an individual patient, it is essential to explore the patients' preferences and personal goals, Partridge said. This is particularly important in situations where there is more than one treatment option (e.g. systemic interventions with different potential therapeutic effects and toxicities, mastectomy vs breast-conserving surgery, or different radiotherapeutic strategies).

Patients' preferences for the required benefit of an intervention - e.g. the absolute increase of survival or the acceptable treatment toxicity - show a wide range of variation, Partridge illustrated with results from a recent review [3]. In addition, there is a difference between patients and physicians with regard to their definition of a meaningful treatment, and what survival benefit is needed to make adjuvant chemotherapy worthwhile [4]. Physicians, on average, put the bar higher than patients for adjuvant chemotherapy to be worthwhile. However, this study showed that also between physicians' opinions there is a wide range of variation. Therefore, in every single case it is important to find out what matters to the patient, Partridge concluded. Shared decision-making is a critical factor and, according to the Three-Talk Model of Shared Decision-Making [5], includes talking with the patient, describing the choices, offering support, and asking about their goals. All the options have to be described, including the risks and benefits of every option in the context of what matters to the patient. Finally, the treatment decision is made together with the patient.

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3. Hamelinck VC, et al. Cancer Treat Rev. 2014; 40:1005-1018.
4. Vaz-Luis I, et al. Cancer 2017; 123: 2821–2828.
5. Elwyn G, et al. J Gen Intern Med. 2012; 27: 1361-1367.

Adjuvant and neoadjuvant therapy: principles and practical considerations

Prof. Eric Winer (Dana-Farber Cancer Institute, Boston, USA) compared the goals, merits, and surgical advantages of adjuvant and neoadjuvant therapy for patients with early breast cancer. He also discussed the clinical meaning of a complete pathological response after neoadjuvant therapy.

The goals of adjuvant and neoadjuvant therapy are somewhat overlapping, Winer demonstrated. For both therapies, eradicating micrometastatic disease and prolonging survival are the primary goals. In addition, the goal of adjuvant therapy is to improve disease-free and/or distant disease-free survival given that these parameters are good surrogates for overall survival or a better quality of life. Additional goals of neoadjuvant therapy are: to decrease the extent of surgery, to provide prognostic information, to identify candidates for additional treatment approaches, and – from a scientific point of view – to test de-escalation strategies and to conduct tissue-intensive trials. Referring to the results of the NSABP B-18 and NSABP B-27 trials, Winer concluded that – so far – there is no difference in (disease-free and/or overall) survival between patients with early breast cancer who had neoadjuvant treatment vs patients who had adjuvant treatment [1]. However, there are circumstances where adjuvant therapy is preferred. For example, if the decision about therapy depends on the anatomic extent of disease (stage 1 Her2-positive disease, T1 triple-negative breast cancer), or if it is impossible to follow the disease (e.g. by imaging or palpation) during neoadjuvant treatment. On the other hand, where it is clear that chemotherapy will be the treatment (e.g. patients with stage 2/3 ER-positive disease) this therapy could as well be given up front, Winer stated. Neoadjuvant therapy is also preferred in case optimal surgery will be facilitated by neoadjuvant treatment. In addition, endocrine neoadjuvant therapy is preferable in patients who are not considered to be candidates for (adjuvant) chemotherapy. However, to successfully administer neoadjuvant therapy an experienced multidisciplinary team is indispensable, Winer cautioned.

One goal of neoadjuvant therapy is to reduce the tumor size. This, theoretically, should increase the number of women who are eligible for (and eventually get) breast-conserving surgery. However, this is not the case, Winer demonstrated with the results of 4 neoadjuvant trials. Although in all studies the experimental neoadjuvant regimens induced a higher pathological complete response (pCR) rate, the rate of breast-conserving surgery only modestly increased [2]. Winer put forward several possible explanations: patient or physician anxiety and bias, multifocal disease at presentation, diffuse calcifications that can not be cleared by conservative surgery, and less than perfect imaging. On the other hand, studies like the ACOSOG Z1071 trial showed that neoadjuvant therapy is able to downstage 40% of cN1 patients to pN0 and that in these patients sentinel node biopsies correctly identified the axillary nodal status ≥90%. This raises the question whether axillary surgery is still necessary after an excellent response to neoadjuvant therapy. This question is now subject of several trials.

In the last part of his lecture, Winer zoomed in on the meaning of a pCR after neoadjuvant therapy. The main question on this topic he addressed was "Is there a consistent correlation between pCR and outcome?" It turned out that this depends on whether we look at the level of clinical trials or on the level of an individual patient. Referring to a review of 12 clinical trials that tested several neoadjuvant regimens in several subtypes of early breast cancer, Winer showed that pCR rates depend both on type of treatment and subset of breast cancer [3]. However, in 3 clinical trials, the magnitude of improvement in pCR did not at all correlate with improvement in event-free or overall survival. Recently, also in the NEO-ALTTO and APHINITY trials, an increase in pCR was not or hardly translated into an increase in survival [4,5]. In contrast to this lack of correlation between pCR and survival in trials, pCR can be a very powerful biomarker in individual patients, Winer illustrated with results from the same review of 12 trials and results from the I-SPY2 trial [6]. Both event-free, distant relapse-free, and overall survival were substantially longer for patients who had a pCR.

Summarised, pCR seems a good predictor for individuals but a poor predictor for the long-term success of a regimen. The explanation for this paradox is, according to Winer, that pCR is related to a better outcome but the relationship between pCR and favourable outcome is not causal. In other words, not all patients with a pCR achieve a favourable outcome and not all patients without a pCR achieve a worse outcome. Therefore, new trials should not aim to increase pCR but instead use pCR on an individual level to test escalation or de-escalation of therapies, Winer concluded.

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4. Piccart-Gebhart M, et al. J Clin Oncol 2016; 34: 1034-1042.
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Selected Posters

Discordance of biomarkers in multifocal and lymph node positive breast cancer

Histological, molecular, and genetic characterisation of the tumour can guide tailored adjuvant treatment of breast cancer. However, characteristics can differ between different foci in multifocal cancers [1].

Tailored adjuvant therapy according to histological grade, biomarkers ER, PR, and Her2, and proliferative indicators like Ki67 has been one of the most important factors improving survival in breast cancer. However, a number of reports show that in a small proportion of cases characteristics differ between primary tumour and lymph node metastasis and between different foci in multifocal cancers. Usually, assessment of biomarkers is performed on one primary only. This might lead to some patients receiving suboptimal treatment.

In Sweden, about 9,000 women are diagnosed with breast cancer each year, Dr Marie Sundquist (Kalmar County Hospital, Sweden) and colleagues showed. About 20% have more than one primary tumour and approximately 30% have lymph node metastases. Sundquist et al. explored concordance regarding tumour biology between different primary foci and between lymph node metastases and primary tumour in these patients. From 3 Swedish breast units, they included all consecutive breast cancer patients with more than one primary tumour and/or lymph node metastasis. In these patients, assessments of ER, PR, Her2, and Ki67 were performed with immunohistochemistry and *in situ* hybridisation on at least two lesions in multifocal cases and on one to two metastatic lymph nodes.

Dr Sundquist presented interim results of the study (74 patients with more than one primary tumour and 58 patients with lymph node metastases). In about 17% of cases there was discordance in tumour biology between foci. In 8 cases, Ki67 scored high in one lesion and low in another. Five of those also differed in histological grade between Nottingham histological grade 3 and 1–2. Three had different ER/PR status, two had Her2 amplification in one foci while the other was normal. In metastatic lymph nodes, the biology differed between primary and metastases in 5 of 58 cases (8,6%). ER/PR nodal status was different from the primary in two cases. One triple-negative tumour had an ER/PR-positive metastasis and one ER/PR-positive primary had an ER/PR-negative metastasis. In three cases, Her2 normal primaries had an amplified lymph node metastasis.

Based on these (interim) results, Sundquist et al. concluded that biomarker status is relatively consistent between foci in multifocal tumours and between lymph node metastases and primaries. However, the results indicate that there is a risk of suboptimal treatment that might have important consequences on the outcome for this subgroup.

1. Sundquist M, et al. The Breast 2019; 44 (suppl 1): abstract P225.

New prognostic biomarkers for survival breast cancer

Tailored therapy of patients with breast cancer - to avoid overtreatment as well as undertreatment - is dependent on the availability of prognostic and predictive biomarkers. Dr Jasmin Zeindler (University Hospital Basel, Switzerland) and colleagues presented two new prognostic biomarkers associated with survival: nectin-4 expression on triple-negative breast cancer cells and tumour infiltration by myeloperoxidase neutrophilic cells [1,2].

Triple-negative breast cancer represents about 10–20% of all invasive breast cancers and is associated with a poor prognosis. The nectin cell-adhesion protein 4 (nectin-4) is a junction protein involved in the formation and maintenance of cell junctions. Nectin-4 has previously shown to be expressed in about 60% of triple-negative breast cancer cells as well as in triple-negative breast cancer metastases, but to be absent in normal breast tissue, which makes it a potential specific target for triple-negative breast cancer therapy. Previous studies have shown an association of nectin-4 protein expression with worse prognosis in triple-negative breast cancer in a small patient cohort.

To further explore the role of nectin-4 in triple-negative breast cancer and confirm its impact on survival, Zeindler et al. now performed immunohistochemical staining for nectin-4 on tumour tissue of 112 triple-negative breast cancer cases with detailed clinical annotation and outcomes data. A high expression of nectin-4 was present in 86 (76.8%) of the

triple-negative breast cancer cases. In univariate survival analysis, high expression of nectin-4 was associated with a significantly worse overall survival when compared with low expression of nectin-4 (hazard ratio 0.022; P<0.0001). No correlation of nectin-4 expression with any other clinicopathological features could be found. The authors concluded that these results confirm the role of nectin-4 as a prognostic biomarker in triple-negative breast cancer.

Myeloperoxidase (MPO) is an enzyme secreted by neutrophil granulocytes as a result of phagocytosis during inflammation. In colorectal cancer, tumour infiltration by MPO-expressing cells has been shown to be independently associated with a favourable prognosis.

To explore the role of MPO-positive cell infiltration and its prognostic significance in invasive breast cancer, Zeindler et al. performed immunohistochemical staining for MPO on tumour tissue of 928 human breast cancer samples. MPO-positive cell infiltration (≥5 cells/tissue punch) was found in 150 (16%) of the 928 evaluable breast cancer cases. In univariate survival analyses, infiltration by MPO-positive cells was associated with a significantly better overall survival (P<0.001). In subset univariate analyses, the infiltration by MPO-positive cells was associated with significantly better overall survival in the Luminal B Her2-negative subtype (P=0.005), the Her2 subtype (P=0.011), and the basal-like subtype (P<0.001). In multivariate analysis, MPO expression proved to be an independent prognostic factor for improved overall survival (P<0.001). Based on these results, Zeindler et al. conclude that infiltration of MPO-positive cells is an independent prognostic biomarker for improved overall survival in human breast cancer.

1. Zeindler J, et al. The Breast 2019; 44 (suppl 1): abstract P243.
2. Zeindler J, et al. The Breast 2019; 44 (suppl 1): abstract P241.

Selection of patients for neoadjuvant chemotherapy treatment based on oncotype recurrence score in luminal breast cancer

Multigene signatures, e.g. the Oncotype DX Breast Recurrence Score, are increasingly used to guide adjuvant treatment decisions in patients with early breast cancer. Dr Ariadna Gasol Cudos (Hospital Universitari Arnau de Vilanova de Lleida, Spain) explored the possible use of the Oncotype DX Breast Recurrence Score to select patients with luminal breast cancer to receive neoadjuvant chemotherapy [1].

Neoadjuvant chemotherapy is considered an optimal option in early breast cancer specially in Her2-positive and triple-negative phenotypes, but in luminal ones remains controversial, so a more accurate selection is necessary. Oncotype Recurrence Score (RS) is a validated test to select luminal patients to receive adjuvant chemotherapy.

In 77 consecutive with breast cancer considered candidates to receive chemotherapy (based on clinical variables such as initial tumour size or lymph node involvement), Gasol Cudos et al. performed an Oncotype DX test and analysed the score results and its correlation with response. Median age of the patients was 55 (range 32–84), median tumour size was 36.78 mm (20–100), and 44 tumours (55.7%) had initial node involvement. Median oestrogen expression was 259 histoscore, progesterone 111, and median Ki67 was 32%. Obtained median Oncotype RS was 23 (6–76); 6 (7.8%) of low risk (RS <11), 52 (67.5%) of intermediate risk (RS 11–30), and 19 (24.7%) of high risk (RS >31).

Using a threshold of 25; 48 (62%) patients were of low risk and 29 (38%) patients were of high risk. Final neoadjuvant chemotherapy was administered in 50 patients (63%); the 27 other patients underwent surgery. However, 5 patients received adjuvant chemotherapy due to major node involvement. Pathologic response after neoadjuvant chemotherapy in 46 patients was: 5 with RCB-0 (9.8%); 8 RCB-I (15.7%); 13 RCB-II (25.5%), and 20 RCB-III (39.25). Highest histological response (RCB-0 + RCB-I) was observed in 10/26 (38.5%) patients of RS >25 and 15% (3/20) patients of RS <25.

Based on these results, Gasol Cudos et al. concluded that the Oncotype DX RS could be a useful tool to select neoadjuvant chemotherapy in luminal breast cancer. Neoadjuvant chemotherapy could be avoided in 37% of patients, but few patients will still need adjuvant chemotherapy because of nodal involvement despite of low risk RS. Major responses are observed in patients with RS >25.

1. Gasol Cudos A, et al. The Breast 2019; 44 (suppl 1): abstract P166.