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Impressions from the San Antonio Breast Cancer Symposium December 2012

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Question 1: Breast Cancer Surgery – Which New Findings with Clinical Implications Did You See?

Fehm: The role of sentinel lymph node biopsy (SNB) in patients receiving neoadjuvant chemotherapy (NAC) is still unclear. 2 abstracts investigated the feasibility and false negative rates of SNB in the neoadjuvant setting. The German SENTINA (SENTInel NeoAdjuvant) trial presented by Kühn et al. (S2–2) was a 4-arm prospective multicenter cohort study designed to evaluate a specific algorithm for the timing of a standardized sentinel lymph node (SLN) procedure in patients who undergo NAC and to provide reliable data for the detection rate (DR) and false negative rate (FNR) in different settings. 1,737 eligible patients from 103 institutions were enrolled in this trial. The DR for SNB was 99% before NAC in clinically node negative patients, 80% in clinically node positive patients receiving SNB after NAC, and 61% after prior SNB and NAC. The SNB was false negative in 14% of patients with cN1/ycNo and SNB after NAC and 52% in patients with re-SNB after NAC. The clinical consequences from these data are that SNB should be performed in cN0 patients before NAC. In cN1 patients who convert to ycN0, SNB is lacking accuracy and should not be performed.

The ACOSOG trial Z1071 presented by Boughey et al. (S2–1) investigated the role of SNB in 689 patients with clinically positive lymph nodes after NAC. 756 patients were enrolled from 136 institutions. SNB correctly identified the nodal status in 84% of the 695 patients and was associated with an FNR of 12.8%. The FNR could be reduced if at least 2 SN were removed and a dual tracer method was applied. However, the first suggestion to reduce the FNR cannot be implemented in clinical routine since in many cases patients have only 1 sentinel lymph node.

Kümmel: The timing of SNB in the neoadjuvant setting is still unclear. How useful could SLN surgery be in avoiding the more invasive formal axillary node dissection? The ACOSOG Z1071 trial, presented by Boughey et al., investigated the question, whether SNB after NAC is an accurate and feasible method. 689 patients with T0–4, histologically proven N1–2, M0 status were enrolled. Of 639 patients with identified SLN, the detection rate was 92.7% and 40% of the patients had a complete pathologic remission. The FNR with at least 2 SLN examined were 12.6%, for 1 SLN resected it was 31.5%. The conclusion of this important study: SNB will enable a reduction in the extend of axillary surgery if dual tracers are used and at least 2 SLN are examined after NAC. But the sentinel concept is not based on the model to resect a minimum of 2 SLN and for the FNR we should also take into consideration the rate of unidentified SLN of 7.3%.

The German SENTINA trial, presented by Kühn et al., is a 4-arm study with over 1,700 enrolled patients from 103 institutions. 50.8% of the enrolled patients were cN0 – after SNB 35.2% were pN1 prior to NAC. In the population of cN1 (41.2%) only 20% were histologically proven. The detection rate prior to any therapy was 99.1% – indicating the high quality of this multicenter surgical trial. However, after SNB and NAC the detection rate was only 60.8%; in patients with cN1 status without prior SNB it was 80.1%. For patients with pN1 (SNB = pN1 – NAC – Re-SNB – axillary lymph node dissection, ALND) the FNR was 51.6% – for patients with cN1 (no prior SNB – NAC – SNB – ALND) the FNR was 14.2%. Therefore it was concluded from this up to date largest prospective trial that in patients who convert under NACT from cN1 to cN0 SNB as a diagnostic procedure is not as reliable as SNB in primary surgery.

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Liedtke: To my opinion, the most important data regarding breast cancer surgery at this year's SABCS 2012 was that regarding axillary staging in the context of NAC. SLNB prior to NAC is associated with a reliable and accepted accuracy and a low false-negative rate, whereas SNB following NAC has the potential to spare patients who are downstaged from a positive to a negative lymph node status from further regional treatment.

First, the Z1071 study of the American College of Surgeons Oncology Group (ACOSOG) analyzed data of 637 women with pathologically positive axillary nodes at primary diagnosis who underwent neoadjuvant chemotherapy. Patients then underwent SNB and secondary ALND. The authors stated that at least 2 SLN needed to be taken out. A detection rate of 92.7% (95% confidence interval (CI) 90.5–94.6) was reported. 40% of patients converted from pathologically positive lymph nodes prior to NAC to a histologically negative axilla (n = 255). Among the 382 patients (60%) who did show residual invasive tumor cells in the axillary nodes, 56 patients had a negative SNB but were found to be node positive upon ALND. This translated into an accuracy of 91.2% for SNB following NAC. Among patients who had at least 2 SLNs excised following NAC, an FNR of 12.6% was reported (95% CI 9.4–16.7%). However, an FNR of 31.5% was reported among patients who had only one SLN taken out at the time of axillary staging. The authors concluded that SNB following NAC would be a useful method for axillary staging provided that 2 SLN be taken out and a dual tracer (i.e. blue dye and radiolabelled colloid) be used.

These results are in contrast to the results from the German SENTINA trial. In this trial, patients undergoing axillary staging in the context of NAC were recruited to 4 study arms based on clinical nodal status before and after NAC. One arm containing 592 patients was largely similar to the study population of ACOSOG Z1071. In this trial a conversion rate of 52.3% from cN1 before NAC to pN0 following NAC was reported. In contrast to the results of Z1071 an FNR of 14.2% was reported in the study arm resembling ACOSOG Z1071 and an even higher rate of 51.6% was found among patients undergoing one SNB prior to and a second one after NAC. The authors of this trial concluded that the FNR for a repeated SNB after NAC would be unacceptable. Also the FNR for patients who are downstaged through NAC from a positive to a negative axillary status would appear less favorable compared to the FNR initially reported in the context of primary surgery. Therefore, in this study, SNB as a diagnostic procedure was not found to be a reliable tool in patients who convert under NAC from cN1 to cN0 compared to SNB in primary surgery and should therefore be omitted.

At this point we have to wait until further results and more details regarding the methodology of these trials are being reported before a final judgement can be made based on these data. Further trials evaluating this context are currently being conducted (see below). However, until the safety of axillary staging following NAC is undoubtedly demonstrated SNB following NAC should not applied as part of clinical routine.

Rack: The SENTINA trial evaluated nodal surgery in both clinically node-negative and node-positive disease. The usefulness of primary sentinel node excision in cN0 disease before the start of systemic treatment is confirmed by this trial. Both trials evaluate the optimal surgical procedure in cN1 patients. SNB after preceding lymph node surgery and systemic treatment in cN1 patients has an unacceptably high false negative rate of 51.6%, and is therefore no reasonable option. In cN1 patients only receiving preoperative chemotherapy but no previous SNB, the false negative rate is still higher than in patients with cN0: 14.2% (SENTINA) and 31.5% (ACOSOG). While Kühn et al. concluded that SNB is not a reliable diagnostic tool in cN1 patients, Boughey et al. considered SNB an option under special circumstances, i.e. in patients with good clinical response, using dye and a radioactive tracer, if > 3 lymph nodes are removed and a clip is placed at fine needle aspiration.

Steger: The results of 2 clinical trials dealing with the timing of sentinel node biospy in regard to NAC were presented. These prospective trials investigated mainly the detection rates and the FNRs of the sentinel node(s) and were similar in design though not identical. Of interest is the fact that even though the results were also rather similar with a false negative rate of 14% in the large German SENTINA trial (n = 1,737) und 12.8% in the ACOSOG Z1071 (n = 756), the conclusions drawn by the authors were exactly the opposite: while the German group concluded that this FNR of the SNB is too high after neoadjuvant treatment and cannot be recommended for routine use, the presenter of the ACOSOG trial did just that. I think that based on these results no clear and firm conclusions can be drawn at the moment and thus it is too early to recommend this procedure for the daily practice. Further clinical investigations should focus on modifications of the SNB procedure.

Question 2: Triple Negative Breast Cancer: Which New Aspects of Treatment Might Lead to Progress in the Clinical Management?

Fehm: Bevacizumab is an approved therapeutic option in HER2 negative metastatic breast cancer. A potential role was discussed for bevacizumab in the adjuvant setting for triple negative breast cancer (TNBC) patients. The BEATRICE trial was designed to test this hypothesis (S6–5). In this open-label randomized multinational phase III trial, patients with TNBC were randomized to receive ≥ 4 cycles of either chemotherapy (CT) alone or the same CT + 1 year of bevacizumab 5 mg/kg/wk equivalent. There was no statistically significant improvement in disease free survival (DFS) with the addition

of 1 year bevacizumab to adjuvant CT for TNBC, underlining the limited clinical role of bevacizumab in breast cancer (unless valid predictive biomarkers can be identified).

An important strategy to identify new targetable alterations in patients with TNBC may be the molecular profiling of residual tumor tissue after primary systemic therapy. Balko et al. (S3–6) demonstrated in their study that approximately 90% of these patients had aberrations in pathways (e.g. DNA repair, PI3K/mTOR, ras/MAPK9) which can already be targeted or for which targeted drugs are in development leaving hope for the optimization of treatment for TNBC patients.

Kümmel: The BEATRICE trial, presented by Cameron et al., evaluated in a phase III prospective setting the role of 1 year adjuvant bevacizumab in triple negative patients (centrally confirmed). In terms of primary endpoint – invasive disease free survival (IDFS) for the 2,591 randomly assigned patients, the 3-year rates were 82.7% for patients with anthracyline and/or taxan-based chemotherapy without bevacizumab vs. 83.7% with addition of bevacizumab. The subgroup analysis revealed no strong signal in any subpopulation. Another hope is to discriminate patients who benefit from an anti-angiogenesis strategy in the early phase of breast cancer. Therefore Carmeliet et al. presented the biomarker analysis of this study. Unlike other trials in the metastatic setting (AVADO, AVEREL), the baseline pVEGF A level showed no predictive value in the adjuvant microenvironment and only a small population of patients with high levels of baseline pVEGFR 2 had a benefit from the addition of bevacizumab. For this aggressive tumor biology there seems to be no additional therapy option to date.

Promising in vitro results were presented by Bhalla and colleagues indicating that pan-histone-deacetylase (HDAC) inhibitors can sensitize TNBC cells for poly-A-ribose polymerase (PARP) inhibitors and alkylating cytotoxic agents independent of BRCA mutation status. Another approach is to evaluate molecular alterations in patients with TNBC after NAC and residual disease. As known so far, these patients have a significantly poorer prognosis. Balko et al. demonstrated that 90% of these tumors had an aberration in PI3K/mTor, DNA repair (BRCA1/2), Ras/MAPK, cell cycle, or GFR pathways. The pathway which is affected could be the goal for additional targeted therapy.

Liedtke: As the use of bevacizumab seems to be beneficial for patients with TNBC in both the neoadjuvant and the metastatic setting, the results of the BEATRICE trial evaluating the use of bevacizumab among patients with TNBC in the adjuvant setting have long been awaited with interest. In this trial patients with TNBC having undergone primary curative breast and axillary surgery were randomized to either chemotherapy alone (4–8 cycles based on investigator's choice) or in combination with infusions of a 5 mg/kg body weight (BW) equivalent of bevacizumab (i.e. for instance 15 mg/kg BW 3-weekly). However, the primary endpoint of this study could not be reached as the IDFS rates in both study arms were not significantly different (82.7% (95% CI 80.5–85.0) vs. 83.7% (95% CI 81.4–86.0), respectively, hazard ratio (HR) 0.87, p = 0.18). Not surprisingly, there was no significant benefit as to overall survival in both arms. Toxicities were as can be expected in the context of combination chemotherapy and bevacizumab. Therefore, bevacizumab does not seem to be the optimal candidate for a novel adjuvant treatment option for patients with TNBC. Further trial results of bevacizumab in the adjuvant setting among patients with TNBC have to be awaited (e.g. NSABP-B46, *www.clinicaltrials.gov*).

However, despite these disappointing data, several translational and basic science analyses were presented that provided a rationale for the use of anti-myc-targeted agents (Goga et al.) or a combination approach of inhibitors of the HDAC together with inhibition of PARP function (Bhalla et al.). Balko et al. presented results of a systematic analysis of tumor tissue derived from 114 clinically defined TNBC patients who presented with residual tumor burden following NAC. These tumors were analyzed using immunohistochemistry (112/114), next generation sequencing (81/114) and gene expression (89/114). The authors hypothesized that at least 5 targetable signaling pathways were present among these tumors, i.e. PI3K/mTOR inhibition, receptor tyrosine kinase inhibitors, DNA repair targeting agents, cell cycle/mitotic spindle inhibitors, and RAF/MEK inhibitors. The authors regard their results as a 'targetable catalogue' of the alterations present in the residual disease of TNBC after NAC. As to how these results may be translated into clinical practice remains to be demonstrated.

Rack: Of interest, albeit negative, were the results from the BEATRICE trial: there is no benefit for TNBC patients from the addition of bevacizumab to adjuvant anthracycline and taxane based chemotherapy in the whole study population or in any subgroup. Also the results from the LEA trial were negative: the investigators found no benefit from the addition of bevacizumab to letrozole or fulvestrant in the first-line treatment of metastatic patients. Therefore unfortunately no progress has been made so far for triple negative patients.

Steger: I am afraid, no practice-changing results were presented! The negative results of the large adjuvant BEATRICE trial showing no significant benefit for patients receiving chemotherapy and adjuvant bevacizumab for 1 year are very disappointing. Even though there was a small numerical reduction in events during the bevacizumab treatment with maybe a short 'carry over effect', this trial has to be judged to be negative. From a biostatistical point of view there might still be a small chance for the secondary study endpoint 'overall survival' to come up with a positive result, but this chance is very small and it is projected that these results are maybe available at the ASCO meeting 2013. As always, data from

several preclinical studies were presented which might give new insights for the treatment of basal-like or TNBC but it does not appear that these data will lead to a change in the clinical management soon.

Question 3: Which New Developments in Targeted Therapies of Breast Cancer Will Find Their Way Into Practice?

Fehm: PD 0332991 is an oral, highly selective inhibitor of cyclin dependent kinase (CDK)4/6 activity and prevents cellular DNA synthesis by inhibiting progression of cell cycle from G1 to S phase. Preclinical data revealed that PD 0332991 may be particularly effective in the luminal subtype of breast cancer. Finn et al. (S1–6) presented the results of a phase II study comparing letrozole alone versus letrozole in combination with PD 0332991 for first-line treatment of estrogen receptor (ER)+/HER2– advanced breast cancer. The combination showed a statistically significant improvement in median progression-free survival (PFS) (26.1 vs. 7.5 months). The combination was well tolerated with uncomplicated neutropenia as the most common adverse event. Due to the promising results, a randomized phase III study is planned to start in 2013.

Kümmel: Cyclin dependent kinases play their role in regulating cell cycle progression. The orally given PD 0332991 is a highly selective inhibitor of CDK4/cyclin D1 and CDK6/cyclin D2 as recently presented at the SABCS meeting by Finn et al. Their results of a phase II study revealed promising data in patients with ER+/HER2– metastatic breast cancer. In combination with letrozole (n = 84) the median PFS was 26.1 months vs. 7.5 months for letrozole given alone (n = 81) with a clinical benefit rate of 70% vs. 44%. These important data will be further investigated in phase III trials and should then be translated as soon as possible into trials for treatment of early breast cancer patients.

Liedtke: To my opinion, the most striking results in the context of novel therapies was the study of PD 0332991, as mentioned by Drs. Fehm and Kümmel. Also, several analyses of the CLEOPATRA study, a randomized, double-blind, placebo-controlled phase III study of first-line treatment with pertuzumab, trastuzumab, and docetaxel in patients with HER2+ metastatic breast cancer (MBC) showed that the use of pertuzumab resulted in a statistically significant and clinically highly meaningful improvement of overall survival (OS) with a HR of 0.66 (95% CI 0.52–0.84). The median OS in the standard arm was 37.6 months whereas for patients in the experimental arm it has not yet been reached (Swain et al.). In another analysis, a benefit of pertuzumab in the subgroup of patients aged ≥ 65 years was investigated. A PFS benefit in this subgroup of patients could clearly be reached: median PFS was 10.4 months in the placebo arm and 21.6 months in the pertuzumab arm (HR = 0.52; 95% CI 0.31–0.86; p = 0.0098 (Miles et al.). In a first translational analysis of the expression / function of HER2 pathway components predicting particular benefit from pertuzumab, no clear predictive biomarker could be identified (Baselga et al.). These results underscore the therapeutic importance of pertuzumab in the treatment of HER2+ breast cancer.

Rack: The ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) study showed a benefit from 5 vs. 10 years of tamoxifen in a large randomized trial with long follow-up. These results should be translated into clinical practice in premenopausal patients or in case of contraindications against aromatase inhibitors. A confirmatory analysis of the CLEOPATRA trial shows an advantage in PFS and OS for patients treated with first-line pertuzumab + trastuzumab + docetaxel for MBC. The combined HER2 blockade will become the new standard of care. 1 year of trastuzumab in early breast cancer was confirmed as best standard of care by several trials. Also the oral CDK46 inhibitor PD 0332991 shows very promising results in postmenopausal ER+HER2– in an interim analysis of a small phase II trial with very limited side effects. However, confirmatory trials are needed.

Steger: The pertuzumab data from the CLEOPATRA trial showing a significant survival benefit for HER2+ patients will for sure change our way to treat these patients in the clinical routine. It is expected that pertuzumab will be available soon for this indication. Also, the adjuvant evaluation is still ongoing (APHINITY trial) which might also lead to a change in clinical practice when positive. Also the data from the trastuzumab-emtansine (T-DM1) trials are very promising that the possibilities to treat HER2+ breast cancer in advanced disease might change to even more effective treatments with a good and low toxicity profile. Moreover, results from a randomized phase II trial with the CDK 4/6 inhibitor PD0332991 in ER+/HER2– patients show that this approach may also influence overall survival and thus phase III trials are urgently needed and are already set up.

Question 4: Which of the Presented Data on Adjuvant and Neoadjuvant Chemotherapy Will Be Applied in Your Clinical Routine?

Fehm: The 10-year survival follow-up of the AGO trial IDD-ETC presented by Moebus et al. (S3–4) confirmed the role of intense dose-dense (IDD) regimens in high-risk breast cancer patients with at least 4 positive nodes. In the experimental arm, patients were assigned to receive 3 courses each of epirubicin (150 mg/m^2), paclitaxel (225 mg/m^2) and cyclophosphamide (2,500 mg/m^2) at 2-week intervals with G-CSF support. In the standard arm 4 courses of conventionally dosed epirubicin / cyclophosphamide (90/600 mg/m^2) followed by 4 courses

of paclitaxel (175 mg/m^2) were given (EC → T, q3w). The survival rate was 69% in the IDD arm versus 59% in patients treated with standard chemotherapy. The application of epoetin alfa in the IDD-ETC arm had no impact on DFS and OS.

Loibl et al. (S3–1) presented the results of the pooled analysis of neoadjuvant trials for the subgroup of very young patients (age ≤ 35 years). The pCR rate was significantly higher in the very young than in the group > 35 years (23.6% vs. 15.7.%; p < 0.0001). This effect was mainly seen in the triple negative group. Interestingly, in comparison to other analyses, very young patients with luminal subtype benefit from a pathological complete response and should therefore be considered for neoadjuvant treatment

Kümmel: In the adjuvant setting, Moebus et al.; presented the 10-year DFS and OS analysis for high-risk early breast cancer patients with ≥ 4 positive LN. In this randomized phase III trial with 1,284 patients with a median number of 8 involved lymph nodes, the 6-cycle IDD-ETC regimen showed a significant overall survival advantage (69% vs. 59%) for patients treated with 8 cycles of EC followed by paclitaxel 3-weekly. In accordance with these data IDD-ETC should be considered as a standard regimen for high-risk breast cancer patients with node positive disease (≥ 4 involved LN).

In patients with local and regional recurrences, Aebi and colleagues presented an intergroup study (CALOR – Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer). This is the first randomized study that shows that patients benefit from adjuvant or extended adjuvant chemotherapy, a clinically widely accepted routine, with the main effect in the ER– situation (5-year OS 88% CT vs. 76% no CT, p 0.02). Unfortunately, the trial was closed prematurely with only 162 randomized patients because of a low accrual rate. In the neoadjuvant situation, Loibl et al. presented the data from the AGO-B, GBG neoadjuvant metaanalysis (overall n = 8,949) for the subgroup of very young patients ≤ 35 years (n = 704). The more aggressive biology and poorer survival is known but in contrast to further analysis for all patients, very young patients with ER+/HER2– tumors benefit from a pCR and these patients should be considered for (neo)adjuvant chemotherapy.

Liedtke: With regard to adjuvant chemotherapy, to my opinion the most important results were those of extended adjuvant tamoxifen therapy (10 instead of 5 years) among patients with hormone receptor-positive breast cancer. The ATLAS study is a randomized phase III trial of 6,846 women that have been randomized to receive an additional 5 years of tamoxifen following 5 years of adjuvant tamoxifen therapy vs. none. After a median follow-up of 8 years, the authors demonstrated a significant improvement regarding all 3 survival endpoints, i.e. disease recurrence (617 vs. 711, p = 0.002), breast cancer mortality (331 vs. 397, p = 0.01) and overall mortality (639 vs. 722, p = 0.01). This benefit was observed particularly more than 10 years after initiation of adjuvant therapy. The relative risk of breast cancer mortality was 0.97 (95%CI 0.79–1.18) after 5–9 years and 0.71 (95%CI 0.58–0.88) after more than 10 years. If these results are added to the results seen after 5 years of adjuvant tamoxifen one may summarize that 10 years of tamoxifen lead to a reduction in breast cancer mortality of 30% within the first decade and of about 50% in the second decade following initiation of therapy. The German national guidelines have not yet commented on these results. Also, the results have to be seen in the context of extended adjuvant therapy with 5 years of tamoxifen followed by 5 years of aromatase inhibition, which may result in a higher therapeutic index given a change in the toxicity spectrum. However, up to this point, extended adjuvant therapy may be an option particularly in the context of contraindications against the use of aromatase inhibitors.

Rack: The data from the IDD-ETC trial are confirmatory and show clinical benefit for dose-dense treatment in high-risk patients. This should be translated into clinical practice.

Steger: The data which will for sure change daily clinical practice immediately are those for the long-term use of tamoxifen in patients with hormone-sensitive tumors. The presented data of the very large ATLAS trial show very clearly that tamoxifen for 10 years instead of only 5 years leads to a significant reduction of risk for all 3 clinically relevant endpoints, i.e. DFS, breast cancer specific survival, and OS. To me it is of note that these results were seen particularly in women who were premenopausal at the time of diagnosis and that this benefit occurred as late as during the third quinquennium of follow-up, showing how important long-term observation is for clinical trials as well as for our routine patients in order to detect late recurrences. The metaanalysis of the German neoadjuvant trials clearly show how bad the prognosis of young women (≤ 35 years at diagnosis) really is; but the results also show how well these patients respond to neoadjuvant treatment. This higher rate of complete pathological responses was not only seen in patients with triple-negative but also in patients with hormone-sensitive disease. For me these data are very valuable since they show that neoadjuvant chemotherapy in young patients with tumors of the luminal subtype really does make sense and should therefore been offered to these patients if neoadjuvant treatment is indicated.

Question 5: 'Trials in Progress' Session: What Are Important Breast Cancer Trials Currently Recruiting?

Fehm: In this year, several ongoing trials were presented investigating the clinical role of circulating tumor cells (CTCs) in the metastatic setting. The *German DETECT III trial (www.detect-studien.de)* (OT1–1–10) is a randomized, open-

label, 2-arm phase III study comparing standard treatment alone vs. standard treatment plus HER2-targeted therapy with lapatinib in HER2-negative metastatic breast cancer patients with HER2-positive CTCs. Choices of chemotherapy and endocrine therapy include: docetaxel, paclitaxel, capecitabine, vinorelbine, non-pegylated liposomal doxorubicin, letrozole, exemestane, and anastrozole. The aim of the *French STIC trial* (OT3–4–06) is to evaluate the use of CTCs to determine the disease aggressiveness and the choice of first-line treatment in potentially hormone sensitive MBC. First-line MBC patients will be randomized between the clinician's choice and CTC count-driven choice. In the CTC arm, patients with ≥ 5 CTC/7.5 ml will receive chemotherapy whereas patients with < 5 CTC/7.5 ml will receive endocrine therapy as first-line treatment. In the *CirCe01 trial* (OT3–4–05) 304 metastatic breast cancer patients will be randomized between the standard arm, in which the treatment management is made following the current standard of care, and the CTC-driven arm, in which the 'response' after every first cycle of any new chemotherapy line is assessed by CTC count before the second cycle.

Kümmel: The most interesting trials are studies with focus on personalized treatment strategy: The *ADAPT* (Adjuvant Dynamic marker-Adjusted Personalized Therapy) trial optimizes risk assessment and therapy response prediction in early breast cancer as an umbrella program for all tumor subtypes and *GeparSepto* in the neoadjuvant setting compares nanoparticle-based paclitaxel with solvent-based paclitaxel and the use of pertuzumab in combination with trastuzumab in the HER2+ subgroup. In metastatic breast cancer a focus is on the *DETECT III* study, which randomizes HER2+ CTCs to treat these patients with chemotherapy ± lapatinib.

Liedtke: It is difficult, if not impossible to single out one or two clinical trials from the plethora of studies presented at this year's SABCS. As could be expected a large number of trials focused on the optimal use of HER2 targeted agents evaluating the optimal agents or combinations thereof, optimal duration and optimal scheduling / sequence. One trial I would like to point out in this context is the NSABP B43 trial which was presented by Cobleigh et al. and which is currently being conducted among patients with HER2+ DCIS. The Investigators evaluate whether radiotherapy in combination with trastuzumab decreases ipsilateral breast cancer recurrence, ipsilateral skin cancer recurrence, or ipsilateral DCIS recurrence. The target accrual is set at 2,000 patients. Also, given the controversial results of the German SENTINA study and the American ACOSOG Z1071 study, the results of the French GANEA II study are awaited with interest. This study largely resembles the ACOSOG Z1071 trial and will accrue 858 patients (Classe et al.).

Rack: Most interesting in my opinon are the DETECT study for MBC and the ADAPT study for early breast cancer.

Steger: Many trials have been presented which are currently ongoing or will be opened within 2013. I think that most of them are interesting and promising but we will only know which ones are really important once the results are presented!

Question 6: Did You Find Further Aspects of Relevance?

Fehm: Two important studies have to be mentioned. The ATLAS trial (S1–2) demonstrated that the clinical outcome of patients receiving 10 years tamoxifen is improved compared to those with 5 years tamoxifen. Therefore, particularly in premenopausal patients 10 years tamoxifen might be an important option as extended adjuvant treatment. The data of the CALOR trial (S3–2) presented by Aebi et al. demonstrated that chemotherapy should be offered to hormone receptor negative patients with local recurrence since this subgroup of patients showed a significant benefit from systemic cytotoxic treatment.

Kümmel: Hypofractionated postsurgery radiation (40 Gy in 15 fractions vs. conventional 50 Gy in 25 fractions) to treat early breast cancer patients was investigated in the UK in the START B trial, presented by Haviland et al., with a follow up of 10 years (n = 2,215). They conclude that the 15-fraction (3 weeks) radiotherapy is gentler on normal tissue and non-inferior to a conventional 25-fraction (5 weeks) schedule and therefore standard of treatment in UK for all patients with invasive breast cancer. Earlier trials did not show a benefit of longer administration of tamoxifen. Davies and colleagues on behalf of the ATLAS trial group showed in ER+ disease an overall benefit of extending tamoxifen from 5 to 10 years (6,846 patients who had completed 5 years of tamoxifen were randomized; RR 0.79, p 0.01). Patients who are still premenopausal after 5 years of tamoxifen and are not candidates for an AI according to the MA.17 trial, have a benefit from a longer duration of tamoxifen treatment.

Liedtke: Several researchers analyzed the value of gene expression profiling indices in the context of prediction of late metastases among patients with hormone receptor positive breast cancer (Dubsky et al.; Sgroi et al.). These authors could demonstrate that several genomic tools designed to predict disease recurrence within 5 years do also predict late recurrence between 5 and 10 years after primary results. These results not only add to the body of evidence supporting the use of genomic tools in risk stratification of patients of hormone receptor positive breast cancer but also suggest that late metastases may not be that biologically distinct from early metastases as we have thought. Another interesting study was the CALOR trial (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer). Many clinicians tend to use an adjuvant chemotherapy regimen for patients with locore-

gional recurrence, however, a clear benefit of this approach has not yet been demonstrated. Aebi et al. randomized 162 women to either adjuvant chemotherapy or none upon diagnosis and resection of locoregional recurrence. Thereby, the authors could demonstrate an improvement of 5-year DFS rate from 57 to 69% (p = 0.0455). The authors of this study should be congratulated for demonstrating these clinically highly relevant results, however, additional studies will be needed analyzing which regimens best be used in this setting (Aebi et al.).

Rack: The CALOR trial could show that patients with isolated local or regional recurrence benefit from chemotherapy, especially if they are ER–. This finding is clinically very relevant, however, the trial accrued only a limited number of patients and had to be closed early. An updated analysis of the TARGIT A trial after a median follow up of 5 years showed that more local recurrences occurred with intraoperative radiotherapy, however, more deaths due to other cancers and cardiovascular events with external beam radiotherapy. The START B trial could show that hypofractionated irradiation (15 fractions) is equivalent to 25 fractions.

Steger: The Austrian data on the value of a genomic assay for the prediction of late recurrences in patients with hormone-sensitive breast cancer are really interesting, in particular in the context of the results of the ATLAS trial showing the benefits from tamoxifen use over 10 years. This assay may also give important information about adjuvant aromatase inhibitors but the results from these studies are not available yet. The results of the CALOR trial dealing with adjuvant chemotherapy after local recurrences are for sure very important. Even though this trial is small and took a long time for recruitment, the data show a clear DFS benefit at 5 years for those patients having received the adjuvant intervention. I really do think that these results must lead to a large international study to clarify this important question. I think, for the time being, patients after local recurrences should be offered appropriate systemic therapy including chemotherapy based on the results of the CALOR trial.

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