News from the San Antonio Breast Cancer Symposium 2010

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Question 1: Which New Findings Concerning Chemotherapy Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: There has been an ongoing discussion whether capecitabine should be part of adjuvant treatment regimens. The data of two large trials presented at SABCS 2010 (FinXX and USON 01062) demonstrated that the addition of capecitabine to an anthracycline-taxane based treatment regimen did not improve the disease-free survival of primary breast cancer patients. Although there might be subgroups of patients (e.g. triple negative) which may benefit, capecitabine will not play a major role in the adjuvant setting in the future.

Liedtke/Kiesel: The FinXX trial is a randomized, multicenter phase III trial that was designed to examine whether the addition of capecitabine to a taxane-anthracycline containing combination chemotherapy regimen (T-CEF; docetaxel, cyclophosphamide, epirubicin, 5-fluorouracil) would improve recurrence free survival (RFS) in women with high-risk early breast cancer. High risk was defined as either node-positive disease or node-negative disease with additional risk factors, such as tumor size > 20 mm. An interim analysis that was triggered by 120 study events was initially presented at the 2008 annual San Antonio Breast Cancer Symposium (SABCS) and has recently been published [Joensuu H et al., Lancet Oncol 2009]. In this analysis, a significant benefit from the addition of capecitabine was observed for RFS and distant disease free survival but not for overall survival. At the 2010 SABCS, the final 5-year analysis of this study was presented. Surprisingly, no further benefit from the addition of capecitabine could be observed. RFS and OS analyses showed a

hazard ratio in favor of the combination including capecitabine; however, the observed differences were not found to be significant. Importantly, Joensuu et al. also mentioned the results of an exploratory analysis suggesting a significant benefit through the addition of capecitabine in subgroups of the study population, such as triple negative breast cancers (TNBC) and cancers with more than 3 axillary metastases. A subgroup analysis focusing on patients with TNBC (n = 202) was presented separately [Lindman et al., Proc SABCS 2010]. This subgroup analysis showed significant benefits in all end-points such as RFS, DFS and OS. The estimated risk reduction of relapse or death in patients with TNBC was around 50% in patients receiving combined chemotherapy with capecitabine in combination with anthracycline taxane chemotherapy. These results do not justify immediate incorporation of capecitabine into adjuvant chemotherapy regimens of patients with TNBC but build a basis for further clinical trials into this direction.

Loibl: Two trials dealing with the inclusion of capecitabine into adjuvant anthracycline/taxane containing regimens have been presented and demonstrated that the inclusion/addition does not add any benefit. The 5-year analysis of FinXX showed no reduction in risk of recurrence with addition of capecitabine to docetaxel plus cyclophosphamide and epirubicin in early breast cancer. Looking carefully at the dosing of the regimen shows that docetaxel was given only with 80 mg/m² and reduced in case of toxicity to 60 mg/m². There are some other data suggesting that the combination of docetaxel plus another agent which requires dose reduction of docetaxel will not lead to an improvement. Subgroup analysis of the FINXX trial suggested an additional benefit for TNBC

patients. However, numbers are small and the data do not lead to a change in the treatment of TNBC. The trial by the US oncology group (USON 01062) again demonstrated no benefit by adding capecitabine for DFS but OS in high-risk early breast cancer. Data had to be analyzed with less events than expected. By ‘squeezing’ the data it seems that patients with a higher Ki67 benefit from the addition. But again, this was only a subgroup analysis. In conclusion there is no need to change the current standard adjuvant regimens for primary breast cancer.

The SECRAB study was an interesting study demonstrating what we probably all knew already. Basically it does not make a difference how we give radiotherapy: in sequence or in combination with chemotherapy. The differences are absolutely negligible.

Miller: The FinXX 5-year analysis showed no reduction in risk of recurrence with addition of capecitabine to docetaxel plus cyclophosphamide, and epirubicin in early breast cancer. USON 01062 showed that addition of capecitabine to adjuvant doxorubicin, cyclophosphamide, and docetaxel in high-risk early breast cancer does not improve DFS. Perhaps the main message with generic cytotoxic therapy is simple – ‘more is not better’. The addition of another active agent (capecitabine) or extension of therapy from 4 to 6 cycles does not improve outcome. In both cases, more therapy resulted in more toxicity so in the quest to do good, we have produced harm. These results should be especially sobering for those in the community who have arbitrarily extended the duration of therapy (a common trend with TC) to 6 cycles in the absence of any data.

The SECRAB study provides justification to individualize the sequencing of therapy based on patient considerations and the planned duration of therapy. For most patients receiving whole breast radiotherapy (RT), the current practice of completing chemotherapy, then proceeding to RT should continue. However, should patient circumstances intervene (for instance, the desire to delay chemotherapy-induced alopecia until after a daughter’s wedding), the opposite schedule could be used with little concern that this would alter the benefit. Similarly the current practice of completing partial breast radiotherapy prior to chemotherapy does not need to change.

Question 2: Which New Findings Concerning Bisphosphonates Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: In the past years, several studies have demonstrated that bisphosphonates (BP) may improve DFS and/or OS in premenopausal (e.g. ABCSG12) and postmenopausal patients (e.g. Z-FAST/ZOFAST). Moreover, the NeoAZURE

study indicated that patients receiving BP during neoadjuvant therapy have a higher rate of complete remissions underlining the anti-tumor activity of BP. Therefore, the data of the AZURE trial presented at this meeting were unexpected. Breast cancer patients with stage II/III disease receiving standard treatment and BP did not show any additional clinical benefit compared to those with standard treatment alone. Only the subgroup of postmenopausal patients (> 60 years or at least 5 years postmenopausal) had a better outcome in terms of DFS and OS. The role of BP in the adjuvant setting therefore has to be reevaluated.

Liedtke/Kiesel: The AZURE trial was designed to confirm the results of ABCSG-12 and ZOFAST regarding the significant effect of adjuvant treatment with zoledronic acid in patients with early breast cancer. However, the AZURE study did not meet its primary study endpoint, as there was no significant difference regarding DFS in patients treated with or without zoledronic acid [Coleman et al., Proc. SABCS 2010]. Of note, more than 90% of patients in this study were also treated with chemotherapy, which is significantly higher than in the two previous trials. Importantly, patients in the AZURE trial who had been postmenopausal for more than 5 years showed a significantly longer overall survival when they had received zoledronic acid. Overall, the authors reported 17 cases of confirmed and 9 cases of unconfirmed osteonecrosis of the jaw. Therefore, the role of bisphosphonates in the treatment of early breast cancer remains to be determined.

Loibl: The data presented from the AZURE trial were a little surprising given the results presented before by the ABCSG as well as the Z-FAST and ZOFAST data. However, it seems as if the endocrine environment plays a fundamental role and bisphosphonates might work only in the low endocrine environment of postmenopausal women because the bone turnover is low. We need to wait for the mature results and a metaanalysis. There is more behind it than we currently know.

Miller: We will struggle with the conflicting data regarding the benefit of adjuvant bisphosphonate therapy for some time. Did we so misunderstand the biology or have we simply not identified the proper patient population? Perhaps bisphosphonates only have an impact in a population with very low estrogen levels (a potential way to link the results of ABCSG12 and the post-menopausal subset in AZURE). In reality all the trials have individual flaws (low potency bisphosphonates given for short durations, highly selected patient populations, low event rates) so perhaps the inconsistent results should not be so surprising. Currently, use of bisphosphonates outside of trial settings is not justified although close attention to bone health remains important.

Question 3: Which New Findings Concerning Endocrine Therapy Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: Currently, 3 different aromatase inhibitors (AIs) are available for the adjuvant setting. The non-steroidal AIs anastrozole and letrozole are approved for use as front-line therapy. Anastrozole and the steroidal AI exemestane are approved for the use after 2–3 years of tamoxifen ('switch'). At this meeting, the first head-to-head comparison between the two AIs anastrozole and exemestane has been presented. No difference in terms of event-free survival could be observed. However, the side effects slightly differed between exemestane and anastrozole. These data indicate that exemestane may also be used in an upfront regimen.

Another interesting topic was the role of CYP2D6 in predicting therapy response to tamoxifen. Several studies have demonstrated that patients with poor-metabolizing CYP2D6 variants do not respond to tamoxifen and may therefore initially be treated with an AI. In the last year, a large pooled analysis by Goetz et al. questioned these results since this correlation could not be approved in their data set consisting of more than 4,800 patients. Now, the CYP2D6 phenotype of postmenopausal patients treated within the BIG 1-98 trial comparing tamoxifen versus letrozole upfront in the adjuvant setting was correlated to clinical outcome. No significant association between CYP2D6 phenotype and breast cancer free interval could be observed, indicating that CYP2D6 testing should still not be implemented in clinical routine due to conflicting results.

Liedtke/Kiesel: The comparison of tumor phenotype between primary tumor and corresponding metastases has been a matter of debate for some time and many scientific groups including ours have contributed to the current body of scientific data. At the 2010 SABCS, data were presented confirming significant discordance regarding the expression of estrogen and progesterone receptors (ER/PR) and HER2 in primary and recurrent disease [Lindström et al., Proc SABCS 2010]. However, the biological and most importantly clinical consequence of these findings remains uncertain. The accuracy of immunohistochemistry-based analysis of hormone receptor and HER2 status is often unknown, given the lack of an accepted gold standard as comparator [Pusztai et al., Oncologist 2010]. Current methods are far from being perfect and differences in tissue fixation, antigen retrieval, and staining methods can have profound influence on staining results. It has been estimated that false-negative rates for ER status (when compared with values from a reference laboratory) may be as high as 60% [Rüdiger et al., Am J Surg Pathol 2002]. Therefore, relying exclusively on the staining results of a re-biopsy when deciding on a given patient's systemic therapy may carry a potential risk of harm to the patient through a false-negative result. It has been argued that in

patients with clinical courses consistent with hormone responsiveness, or with prior positive hormone receptor results, continuation of endocrine therapy may be reasonable even if the most current hormone receptor determination resulting from a metastatic biopsy yielded a negative result [Pusztai et al., Oncologist 2010].

Loibl: The results from NCIC CTG MA.27 showed no difference between exemestane and anastrozole in postmenopausal women with hormone receptor positive breast cancer. Did we learn anything? We finally got the confirmation that exemestane is as effective as anastrozole as endocrine therapy. Did we expect anything else?

TEAM pathology sub-study: After all AIs are not better than tamoxifen in HER2 positive breast cancer. Did we really believe that AIs work better in HER2 positive disease?

The results from ATAC and BIG1-98 showed that we do not need CYP2D6 to decide if we should use tamoxifen or an aromatase inhibitor. Two retrospective analyses from large adjuvant prospectively randomized trials clearly demonstrated that there is no indication for testing the CYP2D6 profile. Previous results suggesting a role for CYP2D6 were from smaller trials that were undertaken in heterogeneous cohorts.

Changes in receptor expression between primary and metastatic breast cancer may affect clinical outcomes. The data confirm that, as the AGO guidelines for metastatic breast cancer suggest, whenever possible a biopsy of the metastases should be performed.

In the adjuvant setting the decision which endocrine agent to use should be based on the risk profile and the endocrine responsiveness as well as the general condition of the women and in the metastatic setting on the hormone receptor status and previous endocrine agents. In the metastatic setting it could be demonstrated that fulvestrant 500 mg, but not 250 mg, is superior to an AI.

Miller: Another lesson in caution when interpreting subsets! As has been stated before, subset analyses are *only* useful to formulate hypotheses to be tested in subsequent trials. Changing practice based on subsets plays into our biases in many ways... and can lead to improper treatment. To be clear about the implications of these data:

- The association of CYP2D6 was based on small subsets and should never have been used to select or alter endocrine therapy. It still shouldn't.
- The suggestion that tamoxifen was less effective in HER2+ patients than AIs was based on subsets with inconsistent results across trials. Don't do it.
- Receptor status might change, in some cases the change is real and in some artifactual due to inaccuracies in testing. What isn't clear is which results should drive therapy. The safe choice: if there is an option for targeted therapy based on any test result – take it.

Question 4: Which New Findings Concerning HER2 Inhibitors Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: Currently, trastuzumab and lapatinib are approved for the use in HER2 positive breast cancer. Pertuzumab and trastuzumab-DM1 are still under investigation. Numerous clinical trials are investigating the efficacy and safety of these targeted therapies in combination with each other or with standard treatment. This year, 3 neoadjuvant studies (GeparQuinto, Neo-ALTTO and NeoSphere) were presented investigating the clinical benefit of HER2 targeted therapies with neoadjuvant chemotherapies. In the GeparQuinto trial, lapatinib was less effective than trastuzumab based on the pCR rates (21.7% vs. 31.3%, $p < 0.05$). However, more than 34% of patients discontinued their treatment with lapatinib due to toxicity.

In the Neo-ALTTO trial, the efficacy of lapatinib (1,500 mg), trastuzumab (4 mg/m² loading dose, 2 mg/m²) and the combination of both (lapatinib reduced to 1,000 mg) added to chemotherapy was evaluated. The pCR rate was 51.3% in the lapatinib + trastuzumab arm compared to 29.5% and 24.7% in the trastuzumab and lapatinib arm, respectively. These results indicate that the dual HER2 blockade may be a valid concept for treatment of HER2 positive early breast cancer. However, treatment discontinuation was observed in 19% in the lapatinib arm, 22% in the combination arm and only 2% in the trastuzumab arm.

Pertuzumab is a humanized antibody which inhibits HER2-HER3 heterodimerization. The NeoSphere trial is a randomized phase II study with 4 neoadjuvant treatment arms: doxetacel + trastuzumab, doxetacel + trastuzumab + pertuzumab, doxetacel + pertuzumab, and trastuzumab + pertuzumab. The pCR rates were 29, 45.8, 24 and 16.8%, respectively. In concordance with the other two trials, these data indicate that a dual blockade of HER2 receptor when combined with neoadjuvant chemotherapy increases the pCR rates. However, before we change clinical practice, it will be necessary to demonstrate whether the increase of the pCR

rates results in a longer DFS and OS for HER2 positive patients.

Liedtke/Kiesel: Results from the GeparQuinto Study showed that trastuzumab is significantly superior to lapatinib in achieving a pCR in patients undergoing neoadjuvant combined HER2 targeted and chemotherapy. However, these results have to be put into perspective with the increased number of patients discontinuing treatment with lapatinib. Although these studies suggest a clear advantage of trastuzumab over lapatinib, further analyses including secondary endpoints, such as disease-free and overall survival endpoints will be necessary. The results of the NeoALTTO trial also showed a numerically higher number of patients achieving pCR from trastuzumab compared to lapatinib. However, this difference was not statistically significant. Importantly, the results confirmed results observed in the preclinical and metastatic setting. The combination of both agents resulted in a significantly higher pCR rate of 51.3% than either agent given alone (24.7 vs. 29.5% for lapatinib and trastuzumab, respectively). In the NeoSphere trial, pertuzumab was added to trastuzumab and/or docetaxel and compared to both agents alone in neoadjuvant therapy of patients with HER2 positive breast cancer. The combination of all three agents was associated with a pCR rate as high as 45.8% and significantly superior to all other doublet combinations. Importantly, pertuzumab therapy was not associated with an excess of high-grade toxicity (including changes in LVEF) and showed excellent tolerability.

Loibl: GeparQuinto study: lapatinib as sole anti-HER2 agent in combination with chemotherapy as we give it currently, is not able to increase the pCR rate compared to trastuzumab. However, it looks as if the combination of two anti-HER2 agents is giving better results. For daily clinical practice there will be no changes. The application of 24 weeks of chemotherapy and trastuzumab results in a pCR rate of the breast which is comparable to that achieved with the double anti-HER2 treatment plus paclitaxel (table 1). Pertuzumab is

Table 1. Study results of NeoSphere, Neo-ALTTO and GeparQuinto

Study	Arm	pCR (breast) %	pCR breast N- %	pCR breast HR+ %	pCR breast HR- %
NeoSphere (n = 417)	DocH	29	21.5	20	36.8
	DocHP	45.8	39.3	26	63.2
	HP	16.8	11.2	5.9	29.1
	DocP	24	17.7	17.4	30
Neo-ALTTO (n = 450)	PacL	24.7	20.0	16.2	33.8
	PacH	29.5	27.6	22.7	36.5
	PacHL	51.3	46.9	41.6	61.3
pCR (ypT0, ypN0)					
GeparQuinto (n = 620)	ECH-DocH	50.4	45.0	31.3	
	ECL-DocL	35.2	29.9	21.7	

pCR: Pathological complete remission; N-: node negative; HR: hormone receptor; Doc: docetaxel; H: trastuzumab; P: pertuzumab; Pac: paclitaxel; L: lapatinib; E: epirubicin; C: cyclophosphamid.

a very promising new agent, which is currently under further investigation.

Miller: Trastuzumab achieves a higher pCR rate compared to lapatinib in preoperative treatment of large primary tumors (GeparQuinto). Adding pertuzumab to trastuzumab improves the pCR rate in HER2 positive breast cancer (NeoShpere). Clinical study confirms preclinical synergy between trastuzumab and lapatinib. The combination of both resulted in a significantly higher pCR rate than either agent given alone (NeoALTTO). Clearly the bright spot of the meeting – a wealth of new options with important activity. The overarching message, combination HER2 blockade is superior to single agent inhibition, making the results of the GeparQuinto study irrelevant shortly after the presentation. The biobanks from these studies are likely to yield important insights for years.

Question 5: Which New Findings Concerning Triple Negative Breast Cancer Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: In TNBC patients the epidermal growth factor receptor (EGFR) expression contributes to the oncogenesis and may play an important role as therapeutic target. This year, the efficacy and safety results of a phase II study (BALI-1 trial) adding the anti-EGFR monoclonal antibody cetuximab to cisplatin in metastatic TNBC patients was presented. The overall response rate in the combination arm was 20% versus 10% in the control arm but the difference between response rates did not exceed the expected 20%. Nevertheless, these data indicate that the EGFR targeted therapy may be a step towards improved treatment strategies in TNBC patients.

Liedtke/Kiesel: Data presented in San Antonio did not provide a basis for altering current treatment decisions in patients with TNBC. However, a number of analyses provided new insight into novel therapeutic concepts in this breast cancer subtype. The phase II clinical trial Bali I was initiated based on the preclinically observed synergy between cisplatin and anti-EGFR monoclonal antibodies and analyzed the impact of cisplatin with or without cetuximab in patients with metastatic breast cancer as first- or second-line chemotherapy option. Adding cetuximab to cisplatin in metastatic TNBC resulted in a doubling of the overall response rate (ORR) (20.0% vs. 10.3%) with a chance for response twice as high for patients receiving cetuximab plus cisplatin (odds ratio = 2.13). However, these results did not meet the primary objective since the overall response rate in the cetuximab plus cisplatin group did not exceed 20%. Furthermore, adding cetuximab to cisplatin also led to a significantly longer progression free survival (PFS).

Another interesting insight into the biology of TNBC was provided by Rody et al. He and his colleagues combined

publicly available gene expression datasets into a single meta-dataset containing data points from 579 patients with TNBC. Two metagenes mirroring interleukin-1 (IL-1) signaling and a B-cell phenotype were associated with event-free survival in 3 independent data subsets. The authors concluded that TNBC consists of distinct disease subsets which may show differences with regard to clinical behavior (such as prognosis). Metagenes associated with immune phenotype are one example.

PARP inhibitors have recently become a potential new means to treat TNBC and/or breast cancer associated with mutations of the BRCA-1/BRCA-2 gene. At the SABCS 2010, Veeck et al. presented data showing that methylation of the promoter of the BRCA-1 gene in breast cancer cell lines was associated with sensitivity against PARP inhibition in vitro. The authors hypothesize that BRCA-1 promoter methylation may help to identify patients who benefit from PARP inhibition in the clinical setting.

von Minckwitz et al. provided new insight into the future value of angiogenesis inhibition in patients with TNBC. The authors presented results of the GeparQuinto clinical trial, examining the effect of adding bevacizumab to standard anthracycline-taxane neoadjuvant chemotherapy. Whereas in the total study population no significant benefit from the addition of bevacizumab was observed (pCR rates 15.0% vs. 17.5%), the authors presented results of a subgroup analysis suggesting a benefit of the addition of bevacizumab in patients with TNBC.

Loibl: The data on TNBC are interesting but not practice changing. The addition of cetuximab to cisplatin was better than cisplatin alone, but both regimens performed low. This is not an alternative to the currently existing strategies. The gene expression set presented by Rody et al. seems interesting but these are reanalyzed data from the web and a reconfirmation in a prospective trial is necessary.

The data on promoter methylation of BRCA1 predicting sensitivity to PARP inhibitors presented by Veeck et al. is an academically interesting finding which has so far no clinical relevance, but might become interesting at a later stage.

Question 6: Which Additional Important Findings Have You Learned of that May/Will Affect Your Clinical Decisions?

Fehm: In the metastatic setting, circulating tumor cells (CTCs) are an independent prognostic factor for PFS and OS. The role of CTCs in the adjuvant setting, however, is still not defined. The SUCCESS-A trial has prospectively investigated the prognostic relevance of CTCs in 2,026 primary breast cancer patients before starting adjuvant treatment. The interim analysis has been presented at this year's meeting. The positivity rate was 21.5%. The detection of one CTC was associ-

ated with shortened DFS, DDFS and OS. The multivariate analysis revealed the presence of CTCs as an independent prognostic factor. Therefore, the presence of CTCs is also of clinical relevance in the adjuvant setting.

Liedtke/Kiesel: The TAMRAD trial analyzed whether treatment with the mTor inhibitor RAD001/everolimus in combination with tamoxifen was associated with an increased clinical benefit rate (CBR) compared to tamoxifen alone in patients with hormone receptor-positive, HER2-negative metastatic breast cancer with prior exposure to an AI. All patients had been treated with an AI previously. The authors showed that the combination of RAD001 with tamoxifen was in fact associated with an increased CBR compared to tamoxifen alone (61.1% vs. 42.1%, $p = 0.045$) and significantly delayed time to progression (TTP) (8.6 vs. 4.5 months, $p = 0.0026$). Similarly, a significant benefit regarding OS was observed (HR 0.32, $p = 0.0019$). The effect regarding PFS was limited to patients with secondary resistance against AI defined as either late relapse (≥ 6 months) or prior response and subsequent progression on AI treatment in the metastatic setting. These results show that combination of RAD001 with endocrine agents such as tamoxifen is effective.

Loibl: Results of the prospective and retrospective registry of the GBG-20 and BIG02-03 studies show that patients with breast cancer during pregnancy can be safely treated with standard chemotherapy regimens. There is no need for premature delivery with the risk to harm the fetus. Premature delivery bears a higher risk for the fetus than chemotherapy during pregnancy.

CTCs in the primary as well as the metastatic setting give prognostic information. In the metastatic setting they might be used for monitoring therapy. We need to be aware that only the test systems which are officially licensed should be

used, because they have been investigated in a prospective fashion. The recent sentinel node trials (e.g. NSABP B-32) raise the question in how far we really need axillary clearance. Sentinel node biopsy is clearly the preferred option and there is no need to fear missing involved lymph nodes as there is no difference in survival. Another interesting point is that it could be proven in a randomized trial that the addition of lymph massage does not add any benefit to physical activity in terms of preventing a lymph edema.

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