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Conclusion from the Annual Meeting of the Society of Clinical Oncology 2012 in Chicago – Expert Opinions Revisited

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With more than 31,000 thousands participants, the Annual Meeting of the Society of Clinical Oncology 2012 June 1st–5th in Chicago was again both the largest meeting in oncology, but also overwhelming in the variety of scientific presentations as well as of educational and other sources of information. 25% of the all presentations were dedicated to breast cancer, by the far the most elaborate coverage of any cancer entity.

With almost 1,400 participants, Germans were the largest country group after US attendees. We asked 6 German experts about their bottom line of the ASCO 2012 meeting on 5 burning questions.

Question 1: What Was Your Highlight of the Annual Meeting of the Society of Clinical Oncology 2012 in Chicago?

Möbus: The EMILIA study, which showed superiority of trastuzumab-emtansine (T-DM1) in comparison with the established standard of capecitabine and lapatinib in HER2-positive patients who had failed on prior taxane and trastuzumab treatment. This is a breakthrough in the therapeutic options of breast cancer patients, who have failed first-line treatment. It is the first time that an antibody alone linked with a cytostatic drug (maytansine) shows superiority in comparison with a combination therapy of a cytostatic drug and antibody treatment.

Huober: A highlight of this year's ASCO was the presentation of the results of the EMILIA trial. In this randomized phase 3 study T-DM1 was compared to lapatinib and capecitabine in patients with HER2-positive metastatic breast cancer after progression on trastuzumab based therapy. Interestingly T-DM1 a conjugate of a tubulin inhibiting agent and trastuzumab was not only more effective in terms of increased PFS but also of better tolerability than lapatinib and capecitabine.

Thomssen: For me, it is not possible to define one single highlight. Actually, some topics made evident that, in general, further improvements are rather complex; on the other hand some topics showed huge steps forward and opened new options of treatment at least in the field of HER2 overexpressing disease. Dual blockade of HER2 signaling, e.g. by combination of lapatinib and trastuzumab again proved highest efficacy in the neoadjuvant situation (NSABP B-41) with pCR rates up to 70% as it has been shown previously in the NeoALTTO trial and also for the combination pertuzumab and trastuzumab in the NeoSPHERE trial; these results may be transformed also into higher cure rates. In addition, the data of the EMILIA trial showed that a new cytotoxic compound that was linked to a specific transporter antibody, T-DM1, was significantly and substantially more effective in first-line therapy of HER2 overexpressing metastatic breast cancer than the standard combination capecitabine and lapatinib.

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On the other hand two topics were less encouraging. Probably due to unsatisfactory management of side effects, the new and promising drugs lapatinib and nab-paclitaxel failed to show enhanced benefit for our patients although first data indicated high efficacy. As a further topic and important result, both, high level gene profiling and new targeted drugs demonstrated each interesting signals; however, the correlations between gene alterations and predicted effects were still disappointing. Thus, a substantial amount of research still has to be done.

von Minckwitz: No doubt, the EMILIA data were most overwhelming. Not surprisingly, I also found our own data on Ki67 very interesting, which could serve as a meaningful predictive marker on future neo-adjuvant studies.

Harbeck: This year, I do certainly agree with the ASCO organizers – the data of the EMILIA study as presented in the presidential plenary was certainly the breast cancer highlight of this year's ASCO. This T-DM1 registration trial not only presents a new option for HER2-positive breast cancer, it also demonstrates the efficacy of a new therapeutic concept, an antibody drug conjugate. As speculated already about 100 years ago by Paul Ehrlich, such 'magic bullets' may change cancer medicine by providing highly specific therapy without many systemic side effects.

Janni: The data on HER2 targeted treatment, like the EMILIA data, was spectacular. We are closer to cure HER2-positive disease than ever. However, many questions on sequencing and combinations remain to be answered in order to provide both targeted and personalized treatment.

Question 2: What Changes in the Primary Treatment of Breast Cancer Were Triggered by ASCO 2012?

Möbus: Primary Treatment should not be changed! Some colleagues may argue that we should stop giving chemotherapy to patients with a low number of positive nodes who have luminal A breast cancer subtype. However the declining breast cancer mortality rate observed over the last two decades is, at least in part, due to the widespread use of adjuvant chemotherapy. In our intention to personalize breast cancer care, we must be careful not to dilute the impressive results of today's standard of adjuvant treatment. Evidence supporting the theory of chemotherapy resistance in luminal A cancers is mainly based on retrospective subgroup analyses. I recommend routine administration of adjuvant chemotherapy, until the results of prospective randomized trials, such as TAILOR-X, MINDACT, and RxPONDER have been reported.

von Minckwitz: I agree, there should be no changes to the primary treatment of breast cancer based on the ASCO 2012 data.

Müller: In my opinion, no practice-changing trials were presented. Swain et al. (LBA 1000) showed results from the NSBP-38 trial that was not able to find a relevant difference between 3 different chemotherapy regimens, one including gemcitabine as additional drug. This indicates that further improvements in chemotherapy for unselected patient cohorts cannot be expected and that treatment has to be adapted for individual patients. With the approach of neoadjuvant therapy, big improvements in the understanding of the tumor biology were gained. In this context, the results of von Minckwitz and coworkers are of relevance (abstract 1023). They examined proliferation by immunohistochemistry for Ki-67 in patients treated in the neoadjuvant Gepartrio trial. Post-treatment Ki-67 adds independent and additional prognostic information on the outcome after surgery. Therefore, post-treatment Ki-67 identifies groups of patients at high risk for relapse, for which additional post-surgical treatment options could be developed.

Huober: Adjuvant treatment after this year's ASCO will basically remain the same. Taxanes have been established in the adjuvant setting also in node-negative patients, and targeted treatment with anti-HER2 agents is standard in the adjuvant and neoadjuvant setting in patients with HER2-positive tumors. We may have to rethink the strategy of dose dense therapy which was not superior to conventionally dosed anthracyclin taxane based adjuvant chemotherapy in the NSABP 38 study, enrolling almost 5,000 patients. The regimen with 4 × AC/EC followed by weekly paclitaxel (also a kind of dose dense treatment) remains one of our most valuable regimens in the adjuvant treatment of primary breast cancer.

Thomssen: In metastatic disease, the new combinations and compounds for the treatment of HER-2 overexpressing breast cancer will enter our panel of therapeutic tools, very soon. Modern neoadjuvant trials do not work with single anti-HER2 medication anymore; and the APHINITY trials looks at the combination pertuzumab-trastuzumab in the adjuvant therapy of HER2-positive breast cancer.

Harbeck: As already stated by my colleagues, there will be no change in practice after ASCO 2012 in therapy for early breast cancer. The data of 2012 showed that we will not get any better by adding more therapy (and in particular chemotherapy) to unselected patient collectives. New studies need to show which new therapy concepts are important based on tumor biology. We will certainly move towards more neoadjuvant therapy in order to be able to tell our patients early about excellent response but also in order to introduce new therapy concepts in non-pCR (pathologic complete response) patients. Last but not least, the critical appraisal of adjuvant bisphosphonate therapy showed that most evidence across trials is available for postmenopausal patients.

Question 3: What, in Your Opinion, Will Be the Development in the Treatment of HER2-Positive Breast Cancer?

Möbus: Regarding primary systemic treatment – independent of adjuvant or neoadjuvant administration – we strongly move towards a cure for HER2 positive breast cancer patients. Dual blockade of the HER2 receptor will become the accepted standard of care. But we also must develop strategies to 'deescalate' the treatment, e.g. the duration of therapy in patients with pCR after neoadjuvant treatment. Regarding metastatic disease the clinical application of new targeted drugs like pertuzumab and T-DM1 will further improve overall survival and optimize the patients' quality of life.

Müller: With the presentation of the EMILA trial (abstract LBA 1) comparing T-DM1 with capecitabine and lapatinib in HER2-positive metastatic breast cancer, Blackell et al. showed results with a relevant improvement by the novel approach of T-DM1 over the currently approved standard. Together with data on targeting of HER2 with trastuzumab combined either with the novel antibody pertuzumab or the tyrosine kinase inhibitor lapatinib, the perspective of further big improvements also in the adjuvant setting is open.

Huober: The number of available anti-HER2 agents increases. The challenge for the future will be the optimal use of these agents in the metastatic setting and to select and successfully transfer the most effective agents to the adjuvant setting. Several trials showed that dual blockade of the HER2 receptor with two different anti-HER2 agents is a very promising treatment strategy and this may give us the opportunity to delay chemotherapy in many patients with HER2-positive metastatic breast cancer. This important topic will be investigated in an international first-line trial (SAKK 22/10). Patients will be randomized to receive pertuzumab and trastuzumab versus the same treatment in combination with chemotherapy. Endocrine treatment will be added if hormone receptors are positive, which appreciates the different nature of the HER2- and estrogen receptor (ER)-positive disease. In case of progression all patients will be treated with T-DM1 in second line.

Another important challenge in the treatment of HER2 positive disease will be reliable HER2 testing. We presented at ASCO data from the neoadjuvant GeparQuattro trial where in 27% of patients the locally determined HER2-positive result could not be confirmed by central testing. This was clinically relevant since the response rate to trastuzumab plus chemotherapy was significantly lower in these centrally HER2-negative tumors.

von Minckwitz: I agree, it is the increasing number of HER2 targeted agents. Pertuzumab and T-DM1 will only stay temporarily in the metastastic setting. Lapatinib will probably remain in second line. HER2-positive disease will develop into the most favorable entity in terms of prognosis. However, it remains unclear whether triple positive disease needs a different treatment strategy.

Thomssen: In terms of therapy, the neoadjuvant approach seems to be most adequate in HER2 overexpressing breast cancer. I assume that in the near future combined therapies consisting of two compounds that interact with the HER2 receptor in combination with an anthracycline-taxane chemotherapy sequence will be standard for this purpose. This refers to antibody-TKI-combinations (trastuzumab-lapatinib) as well as to antibody-antibody combinations (trastuzumab-pertuzumab). The chemotherapy loaded antibody T-DM1 will be introduced into first-line therapy of metastatic breast cancer very soon; however, the logical next step in this situation might be the combination of pertuzumab and T-DM1. Another relevant option is the development of mTOR-inhibitors (e.g. everolimus) that interact also in the HER2 signalling cascade and may be helpful in resistance to anti-HER2 directed therapy. Minimizing side effects of treatment will be another issue of therapy development.

In terms of prediction, additional markers, e.g. alterations in the PI3K-pathway, will be studied. Also neoadjuvant therapy might be used as a dynamic predictive marker. In non-responders the use of T-DM1 is discussed and will be studied. As a further point, also ER-expression has a predictive impact, indicating fewer responses to neoadjuvant therapy in HER2 overexpressing tumors, thus suggesting trials on alternative therapy combinations.

Harbeck: Together with the data for T-DM1 and pertuzumab already mentioned by my colleagues, we will see HER2-positive advanced breast cancer to move towards becoming a chronic disease. When these two drugs are registered, we will have – together with trastuzumab and lapatinib, four registered options. Moreover, a phase III registration trial for the irreversible panHER inhibitor afatinib is currently on the way. We now need to learn how to optimally use these drugs in combination or in sequence. It is very good that we will be able to use all of these new compounds in further trials, also in primary breast cancer, such as in the WSG-ADAPT trial, here in Germany.

Question 4: Do You See Any Meaningful Improvements in the Treatment of Triple-Negative Breast Cancer?

Möbus: I'm afraid that 'no' is the correct answer. Even after ASCO 2012, targeted treatment of triple-negative breast cancer based on genotype, biologically distinct molecular subtypes or other markers of heterogeneity is rather unlikely. Triple-negative breast cancer is a heterogeneous disease and

its diversity hinders detection of therapeutically competent markers. To further complicate matters, each metastasis may have a molecular signature that differs from other metastases or the primary cancer.

Müller: For triple-negative breast cancer, relatively few new results were shown, in my view none of them promising a relevant improvement. Gucalp et al. (abstract 1006) showed a study that targeted the androgen receptor (AR) in women with AR+ ER–/progesterone receptor negative (PR–) metastatic breast cancer. They found that 12% of ER–/PR– patients are AR+. They stated (based on preliminary results from a small clinical study) that for these patients, AR inhibition with the AR antagonist bicalutamide is feasible, well tolerated, and has activity based on pre-specified criteria. Several presentations tried to improve the understanding of the heterogeneous biology of triple-negative breast cancer. As an example, Shapiro and coworkers (abstract 1007) used microRNA (miR) expression profiling to identify distinct subclasses of triple-negative breast cancers. They stated that miR expression profiling identifies and discriminates five subclasses, which do not coincide with those identified as basal and non-basal by immunohistochemistry. However, none of the currently described classifiers has led to relevant improvements in the treatment of patients.

Huober: There are still many open questions in triple-negative disease. We know that this subgroup is not as homogeneous as initially thought. The significance of platinum based treatment is still under discussion and new neoadjuvant data from the Spanish SOLTI Group showed good tolerability of olaparib with paclitaxel, however, similar pCR rates compared to paclitaxel alone. The results of the Beatrice trial will show us in the future whether adjuvant bevacizumab will improve outcome.

Thomssen: Optimal treatment of triple-negative breast cancer is still not known. At ASCO 2012 many researchers focused on better characterization of triple-negative breast cancer. However, today we have to treat triple-negative breast cancer with the same drugs as non- triple-negative cancers.

von Minckwitz: For the moment, I don't see any light at the horizon. Maybe in future, androgen receptor inhibitors might prove to be helpful.

Harbeck: I certainly agree with my colleagues that the advances in triple-negative disease are slow. After getting our hopes up maybe too high with the exciting data on PARP inhibitors, we have now learned that triple-negative breast cancer is quite heterogeneous. There are functional tests under development for impaired DNA repair mechanisms which would be clinically useful for indicating DNA damaging therapeutics. PARP inhibitors are also further explored. Yet, we should not forget that at least in early breast cancer, about 40% of triple-negative breast cancers respond extremely well to standard anthracycline-taxane-based chemotherapy. Recently, adding bevacizumab has further improved pCR rates in triple-negative breast cancer. As mentioned by Jens Huober, the results of BEATRICE are eagerly awaited in order to address the role of VEGF inhibition in primary triple-negative breast cancer.

Question 5: What Do You Expect of ASCO 2013?

Möbus: Modern endocrine and chemotherapeutic treatment will remain the cornerstone of adjuvant therapy. ASCO should focus on translational and clinical research which deals with better defined targets. Only such an approach can avoid the problems of the last decade, where large clinical trials have failed because so-called 'targeted therapy' was based on limited preclinical data or inappropriate definition of the target.

Müller: I think one of the most important clinical challenges is the improvement of treatment for triple-negative patients. An additional challenge is the increasing number of brain metastases, with currently little progress in the clinical management.

Huober: I expect more data about potential predictive factors especially for the increasing number of new drugs.

Thomssen: Research focusing on HER2 overexpressing disease has shown huge successes. However, most breast cancers are HER2-negative, and for many of these cancers we do not have adequate therapies. In anti-angiogenic therapy, we still do not treat specifically enough, such that I wish that in the next 12 months a predictive marker may be found. In addition, facing the new technologies of genome and mutation profiling, I hope that more insights will lead to more targeted and more effective therapy approaches which was not convincing at ASCO 2012.

von Minckwitz: For now, I focus on the SABCS 2012, which will provide very interesting data: the Beatrice study, the HERA study, more survival data on the EMILIA and Cleopatra studies and maybe more on bevacizumab and endocrine treatment. This will be exciting.

Harbeck: I would love to see new study concepts and results that help us in daily clinical practice with tumor biology based treatment decisions. Moreover, it would be nice to see more trail data from our own German trials which will then be able to impact our guidelines (AGO, S3) as well.

Janni: In my opinion, the next step beyond targeted treatment of the tumor should be personalized treatment, with more predictive tools to guide length, combination, and sequence of treatment. Whether these tools will be molecular tests, circulating tumor cells or other markers probably remains not only for ASCO 2013 but also 2023.

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