News from the San Antonio Breast Cancer Symposium 2018

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Question 1: According to the (subgroup) analysis of the efficacy of atezolizumab, what will be your procedure in accordance with your local pathologist regarding the treatment of metastatic triple-negative breast cancer (TNBC) in the near future?

André: Determination of programmed cell death ligand-1 (PD-L1) status by immunohistochemistry (IHC) assay.

Janni: We will determine the PD-L1 status on immune cells by the VENTANA SP142 IHC assay. I do not see any convincing signals to use atezolizumab outside of a positive immune cell PD-L1 status, such as BRCA-ness or presence of tumor-infiltrating lymphocytes. In my view, the implementation of atezolizumab in clinical practice will be largely determined by the establishment of predictive markers in our breast cancer centers.

Steger: Based on the data presented at ESMO 2018 and SABCS 2018, nab-paclitaxel + atezolizumab is already our first-line standard regimen for patients with TNBC. Reflex testing of the PD-L1 status on the immune cells by our pathologists is currently implemented for all fresh biopsy samples from metastatic lesions of these patients. PD-L1 testing from archival material is already done on request, and results are available within 5–7 working days.

Untch: The results of the IMpassion 130 study presented at ESMO 2018 in Munich and published online in the *New England Journal of Medicine* by Schmidt et al. were breathtaking and will change the standard of care in the first-line treatment of patients with metastatic TNBC. Obviously, the study has not clarified the role of platinum in patients with TNBC, who did not receive this drug during neoadjuvant or adjuvant therapy. Furthermore, results of the IMpassion 130 study were driven mainly, if not exclusively, by the patients who had PD-L1-overexpressing tumors. After ESMO 2018 and San Antonio 2018, our pathologists should be prepared to do PD-L1 subtyping in the primary tumor and also in the immune cells of patients with metastatic TNBC.

Since olaparib and talazoparib have also shown excellent results in patients with BRCA-mutated metastatic TNBC, the companion diagnostic algorithm should be: BRCA testing as well as PD-L1 subtyping, and after this the decision should be discussed with the patient whether one should start with one of the Parp inhibitors olaparib or talazoparib in BRCA-mutated patients, followed by atezolizumab, versus starting with atezolizumab in patients who have a PD-L1 overexpression. At the time, I personally favor the second option since we have seen a clear survival benefit with atezolizumab in PD-L1 overexpressors. The most challenging question is to combine these two drugs in patients with metastatic TNBC.

**Question 2: Does the option of TDM-1 (trastuzumab-
emtansine) after not reaching a pathologic
complete response (pCR) drive your decision
to use neoadjuvant treatment for early HER2-
positive breast cancer patients? How does adjuvant
pertuzumab impact on your decision?**

André: TDM-1 is the new standard of care.

Janni: Yes, definitely, I find the KATHERINE data very convincing and I strongly believe that in the studied indication this will become standard of care. I do not see any troubling data to show a decreased efficacy in patients who received a dual blockade as part of their neoadjuvant treatment. We do not have convincing data to combine TDM-1 and pertuzumab, however, so my choice will be TDM-1 in non-pCR cases.

Steger: Neoadjuvant chemotherapy with trastuzumab + pertuzumab is our standard for all patients with HER2-positive primary breast cancer. Thus, these favorable data of adjuvant TDM-1, as compared to adjuvant trastuzumab, do not influence the decision whether neoadjuvant therapy should be given or not. Up until now two adjuvant treatment regimens are proven to be superior to adjuvant trastuzumab alone, i.e. adjuvant trastuzumab + pertuzumab in node-positive disease and TDM-1 in patients without a pCR after neoadjuvant treatment. We can now further individualize the adjuvant treatment regimen based on significant results from clinical trials. However, due to the current absence of data from randomized studies comparing these two newly established adjuvant treatment approaches with or without the inclusion of neoadjuvant/adjuvant pertuzumab, an optimal standard treatment schedule for patients with early HER2-positive breast cancer warrants further trials.

Untch: The KATHERINE study is about to change the standard of care of patients with HER2-overexpressing primary breast cancer. For many years, the German AGO guideline has been favoring neoadjuvant chemotherapy and anti-HER2 treatment instead of surgery first followed by adjuvant chemotherapy with anti-HER2 therapy. St. Gallen has followed with their recommendation in the year 2017, also favoring neoadjuvant therapy in these patients. If we want to give our patients with HER2-overexpressing tumors the best chance to survive we have just one option: start with neoadjuvant therapy including anti-HER2 treatment (either trastuzumab or the combination of trastuzumab and pertuzumab), followed by TDM-1 after surgery in those patients who have residual disease in the breast or/and in the lymph nodes. The combination of trastuzumab and pertuzumab in the adjuvant therapy has shown no benefit in the APHINITY study in patients with node-negative disease and just a small but significant

difference in patients with node-positive disease. Therefore, irrespective of their nodal status, I personally prefer to treat patients with HER2-overexpressing tumors with neoadjuvant chemotherapy with anti-HER2 therapy followed by TDM-1 if there is residual tumor in the breast or/and in the lymph nodes.

**Question 3: Which of your patients are going to
receive just 5 years of antihormonal treatment by
aromatase inhibition? Who needs longer treatment,
and for how long?**

André: Node-negative: 5 years; node-positive: longer, with a maximum of 10 years.

Janni: I still go with the pragmatic premises: to decide based on the remaining risk for recurrence, tolerability of the endocrine treatment so far, and bone health. Obviously, the optimal patient for extended endocrine therapy is the high-risk patient who tolerated the endocrine treatment well and has good bone mineral density. I will recommend 7 years – the data beyond that duration become less convincing, in my view.

Steger: For patients with lower risk characterized by negative nodal status, low tumor grade, and low proliferation not necessitating chemotherapy, 5 years of antihormonal therapy suffices in the majority of patients. Higher-risk premenopausal patients should receive tamoxifen up to 10 years. In postmenopausal patients, at least 7 years should be recommended based on the ABC-SG-16 data. 10 years of antihormonal treatment should only be reserved for selected patients with good tolerability of the treatment.

Untch: Patients who receive 5 years of antihormonal treatment are especially those with node-negative disease. Patients with a negative biomarker profile (tested by one of the multigene assays) or those with involved axillary lymph nodes are candidates for longer antihormonal treatment.

**Question 4: When is the best time to test for PI3K
mutations? Are there some patients who should
receive PI3K inhibitors in the first line?**

André: First line: patients resistant to endocrine therapy + CDK4 given adjuvant; best time for genotyping: at the time of PD after CDK4.

Janni: In the SOLAR-1 study, the majority of tissue was obtained on the primary tumor. Obviously, the PI3K

mutational status does not frequently change over the course of time so that testing the distant metastases might not be warranted for this reason. However, in the SABCS analysis, circulating tumor DNA in plasma was even more convincing than tissue so that I believe that liquid biopsy will play an increasingly important role in treatment prediction, especially in the context of PI3K inhibition.

Steger: For the time being, it appears that it is sufficient to test on an individual basis, and archival tumor material can be used since PI3K mutations develop rather early in the course of cancerogenesis. Based on the data available, it is currently not possible to seriously define patients who might benefit from PI3K inhibitors as compared to the current standard of care with CDK4/6 inhibitors.

Untch: The best time to test for PIK3 mutations is when a patient has HER2-negative, hormone receptor-positive metastatic disease and is primary or secondary resistant to endocrine-based therapy. The data from the SOLAR-1 study have shown that these patients have a significant benefit from alpelisib, a PIK3 inhibitor, if they have PIK3CA mutations. In the SOLAR-1 trial, postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer were randomized if they had recurrence or progression on or after aromatase inhibitor treatment. The PIK3CA mutation was tested in archival of fresh tumor tissue. Patients were randomized either to the combination fulvestrant + alpelisib versus fulvestrant + placebo. The median progression-free survival was 11 months for the alpelisib/fulvestrant combination versus 5.7 months in the fulvestrant/placebo arm. The hazard ratio was 0.65 and the p-value was highly significant. Central review of progression-free survival was even better in the PIK3CA mutant cohort: 11.1 versus 3.7 months with a hazard ratio of 0.48. In the non-mutant cohort there was no significant difference, although there was a trend in favor of the alpelisib/fulvestrant arm with a hazard ratio of 0.85, but crossing the one in the confidence interval.

Question 5: Thinking of efficacy and cardiovascular function in patients with breast cancer, is lifestyle modification ready for prime time? What do you tell your patients?

André: Lifestyle modification is good for everyone, not only breast cancer patients; this is what I tell them. The problem of survivorship studies is that most of what they tell us is also true for the general population.

Janni: In my opinion, there is increasing data to support that lifestyle modification, especially increased physical activity, can not only significantly contribute to reduce cardiovascular morbidity and metabolic disorders but can also play a positive role in the context of anti-tumor treatment. We recommend at least 3–5 h of increased physical activity per week in order to improve prognosis and to reduce adverse effects of treatment.

Steger: I think that there are now enough data to prove that some lifestyle modifications should be routinely included in our treatment recommendations, and we try to do so in our patients. However, since this task is not easily done or implemented by doctors, nurses, and other medical staff in addition to their already existing workload and as this also requires specific knowledge and training, we should think about developing and establishing a new professional group for this task.

Untch: Lifestyle modifications for patients with breast cancer are ready for primetime. Many studies have shown that physical activity, weight loss, and healthy lifestyle are influencing disease-free and overall survival of our breast cancer patients both in the adjuvant and in the metastatic setting. Therefore, we should approach this topic when we talk to our breast cancer patients. The magnitude of benefit is similar to the best drugs we have available on the market, and this should be a major driver for cost providers, insurance companies, as well as physicians and treating nurses to give this information to the patients.

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