News from ASCO 2018

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Question 1: In the plenary session at the ASCO Annual Meeting 2018, Joseph A. Sparano has presented results of the TAILORx trial of chemo-endocrine therapy versus endocrine therapy alone in hormone receptor(HR)-positive/HER2-negative node-negative breast cancer and intermediate prognosis based on 21-gene recurrence score (RS). Does this data impact the daily practice and how do they compare to previous data, particularly the MINDACT trial?

Dedic: There is a lot of interest for systemic treatment toxicity avoidance, so the results of the TAILORx trial are very important for the majority of early breast cancer (EBC) patients. It is important to put the results in perspective of daily practice in my country where genomic assays are not reimbursed despite their endorsement by most guidelines. These guidelines are being widely accepted in the USA.

The lack of evidence for treatment recommendation in the intermediate RS group was the main reason why I was not feeling comfortable with recommending some of my patients to pay for the Oncotype DX[®] test by themselves.

After ASCO 2018 we have better data for adjuvant treatment of HR-positive/HER2-negative node-negative patients with intermediate RS, especially for patients older than 50 years. For those 50 years of age or younger, who are predominantly premenopausal according to exploratory analyses, there is still some benefit of adjuvant chemotherapy. It remains unclear whether this represents the ovarian suppression effect of chemotherapy or different disease biology in the premenopausal setting. Further, it remains unclear whether the chemotherapy would still be beneficial if most of the premenopausal intermediate RS patients randomized to endocrine therapy alone were treated with a gonadotropin-releasing hormone

(GnRH) agonist. Suppression of ovarian function was used in only 13% of premenopausal women in the TAILORx trial.

The MINDACT trial also confirmed excellent results with endocrine therapy in patients with low RS prospectively. The primary endpoint differed a little, with MINDACT focusing on important distant metastasis-free survival in clinical high-risk but genomic low-risk patients who were assigned to receive no adjuvant chemotherapy. In contrast, almost three quarters of the TAILORx participants are considered as low risk according to clinical criteria used in the MINDACT trial.

I am looking forward to the results of the RxSPONDER trial to help us deal with adjuvant therapy of HR-positive/HER2-negative node-positive disease.

From the perspective of a health care practitioner from a middle income country, I am a little bit concerned about the overall costs of implementation of genomic tests in routine practice. The earlier real-world data showed that, despite lower rates of chemotherapy use, the 21-gene assay test results in an overall incremental cost to the healthcare system in the short term under most assumptions [1]. Maybe with the greater proportion of patients omitting the chemotherapy, including most of the patients with intermediate RS, this balance could be changed.

De Mattos Arruda: The results of the phase III TAILORx trial showed that endocrine therapy alone was non-inferior to endocrine therapy plus chemotherapy for women with estrogen receptor(ER)-positive/HER2-negative node-negative breast cancer with a mid-range risk score as measured by the Oncotype DX Breast RS gene expression assay, for which the benefit of adding chemotherapy to endocrine therapy has been unsure in the past.

The gene expression assay for ER-positive/HER2-negative node-negative breast cancer has been prognostic for patients with a low RS (0–10) – these patients have a very low risk of recurrence

with endocrine therapy alone. However, patients with a high RS (26–100) demonstrated poorer outcomes with higher event rates despite the addition of chemotherapy to endocrine therapy.

The results of the TAILORx trial are expected to be practice-changing. It indeed *tailors* treatment of those ER-positive/HER2-negative node-negative breast cancers as it confirms the very good outcome without chemotherapy in very low RS and now supports sparing chemotherapy in small node-negative disease with RS up to 25 (particularly in women older than age 50, and one third of women less than age 50).

Gampenrieder: The TAILORx trial is the second of a few large phase III trials reporting results about the value of a multigene assay in HR-positive/HER2-negative node-negative EBC. The trial used the 21-gene RS (Oncotype DX) to classify the biologic risk into three categories: low risk, intermediate risk, and high risk. Data from the low-risk group (RS ≤ 10) were already reported earlier. All these patients were treated with endocrine therapy alone and showed an excellent prognosis with an invasive disease-free survival (iDFS) rate of 93.8% at 5 years. This year, the results from the much more interesting intermediate-risk group (RS 11–25) were reported. These patients were randomized between chemotherapy plus endocrine therapy or endocrine therapy alone irrespective of their clinical risk defined by tumor size, age, menopausal status, extent of HR expression, or grading. The intermediate-risk group as a whole did not benefit from the addition of adjuvant chemotherapy – with a hazard ratio for iDFS of 1.08 (95% confidence interval (CI) 0.94–1.24; $P = 0.26$). The chemotherapy benefit varied, however, in dependence of age, with some benefit of chemotherapy found in women 50 years of age or younger with an RS of 16–25 (up to 6.5 absolute percentage points of difference in the distant recurrence rate at year 9).

The most important information for interpreting these results is from my point of view the fact that 74% of patients in the intermediate-risk group according to Oncotype DX fell into the ‘clinical low-risk’ group defined by tumor size and histologic grade. In the MINDACT trial, which investigated the value of the 70-gene signature MammaPrint®, patients with a low clinical risk, did not benefit from the use of the multigene assay because the addition of chemotherapy did not improve the outcome even in the case of a high-risk MammaPrint result. Unfortunately, the subgroup analysis of TAILORx for low and high clinical risk has not been presented yet, and therefore the direct comparison with MINDACT and definitive conclusions are difficult.

In daily practice, most of the patients included in TAILORx would not have needed an expensive multigene assay, because there was no indication for chemotherapy based on their clinical risk. In contrast, for the small group of patients with node-negative, HR-positive EBC with clinical high-risk features, the use of a multigene assay like Oncotype DX or MammaPrint is of value, because about half of these patients does not need adjuvant chemotherapy because of low-risk molecular features.

Problematic are the costs for such a test which range between EUR 2,700 for MammaPrint and USD 3,500 for Oncotype DX,

which is currently not available in Europe. Several other tests like EndoPredict®, Prosigna®, or Breast Cancer Index® have been retrospectively validated in randomized trials and are commercially available. Since no prospective phase III trial data are available, the level of evidence and therefore the recommendation for these tests are weaker though compared to Oncotype DX and MammaPrint.

In conclusion, the results of the TAILORx trial do not directly influence our daily practice, because we still do not see an indication for a multigene assay in patients with low clinical risk. Based on the results of MINDACT, we will continue to use a multigene assay in patients with high clinical risk only, in order to spare them adjuvant chemotherapy.

Question 2: What was in your opinion the most clinically relevant study in metastatic breast cancer (MBC) presented at the ASCO 2018 and why?

Dedic: We heard some new data on drugs we are familiar with, like CDK4/6 inhibitors and everolimus (MONALEESA-3, peri- and premenopausal patients from MONARCH-2, BOLERO-6) but also some data on novel agents like taselisib in *PIK3CA* mutated tumors (phase III SANDPIPER trial) and Akt inhibitors from two phase II trials (LOTUS and PAKT). The reason why the results of LOTUS and PAKT are interesting is an overall survival (OS) benefit in the triple-negative breast cancer (TNBC) population, as metastatic TNBC represents a high unmet clinical need. Both trials with Akt inhibitors (ipatasertib and capivasertib) in combination with paclitaxel showed intriguing results in TNBC with an OS benefit in the combination arm, despite only modest improvement in progression-free survival (PFS). Despite more toxicities, both Akt inhibitors warrant to wait for further phase III study results and final OS results of LOTUS in 2019. I was expecting to see the results of BOLERO-6 with special interest because in Croatia everolimus is not reimbursed (neither are the CDK4/6 inhibitors, but we are expecting them in a few months). That is the reason why in some clinical situations we use capecitabine instead of CDK4/6 combinations or everolimus after the progression on aromatase inhibitors. It was interesting to see how capecitabine is performing, despite the open-label design, limited sample size, and various baseline characteristics (median PFS 9.6 months with capecitabine was longer than in previous studies).

De Mattos-Arruda: Results of the phase III MONALEESA-3 trial (Abstract 1000 [2]) in postmenopausal women with ER-positive/HER2-negative advanced breast cancer showed a significant improvement in PFS for those who received ribociclib plus fulvestrant (median PFS 20.5 months) compared with fulvestrant alone (12.8 months), representing a 41% reduction in the risk of disease progression. The study is distinctive in that eligible patients were those who did not receive endocrine therapy, as well as those in the first- or second-line setting. Therefore, patients received the combination of ribociclib and fulvestrant earlier in their lines of treatment. Ribociclib combined with fulvestrant represents a new first-

or second-line treatment option for postmenopausal women with ER-positive/HER2-negative advanced breast cancer. This is the first study that shows the benefit of this combination in patients with de novo advanced breast cancer which relapse over 12 months after the completion of neoadjuvant endocrine therapy.

Results of the phase I/II study evaluating sacituzumab govitecan (Trop-2 antibody-drug conjugate) for refractory HR-positive/HER2-negative MBC demonstrated significant clinical activity as single agent (Abstract 1004 [3]). Among 54 patients, 17 (31%) had a partial response, and the clinical benefit rate was 48%. The median time to disease progression was almost 7 months. Common adverse effects included grade 3 or 4 neutropenia in 42% and grade 3 diarrhea in 4%. The drug received fast-track designation 2 years ago and was given breakthrough status for TNBC more recently.

Gampenrieder: From my point of view, MONALEESA-3 is the only study in MBC presented at ASCO 2018 directly influencing daily practice. In this multicenter phase III trial, 726 postmenopausal women with HR-positive MBC were randomly assigned to receive fulvestrant plus the CDK4/6 inhibitor ribociclib or fulvestrant alone. As expected based on the results of previous studies with CDK4/6 inhibitors, the addition of ribociclib significantly improved the PFS, the primary endpoint of the study. Interestingly, in contrast to the PALOMA-3 trial (fulvestrant ± palbociclib), MONALEESA-3 included about half of the patients in the first line, therefore providing the first evidence for fulvestrant, the most potent endocrine therapy, plus a CDK4/6 inhibitor in this setting. Confirming the results of the FALCON trial, fulvestrant alone resulted in the longest median PFS in first-line patients when compared with the control arms of the three pure first-line studies (18.3 months vs. 16 months in MONALEESA-2, 14.5 months in PALOMA-2, and 14.7 months in MONARCH-3). The median PFS of the ribociclib plus fulvestrant arm is not yet reached; however, since the hazard ratio is comparable to the other trials (0.58), the combination of fulvestrant and a CDK4/6 inhibitor suggests to be the most effective treatment available for ER-positive/HER2-negative MBC. If this combination will receive approval by the Food and Drug Administration and/or the European Medicines Agency based on the results of this trial remains to be seen.

Question 3: In most of the cancers, therapy with immune checkpoint inhibitors has already impacted the clinical management of metastatic patients. In breast cancer, interesting trials have suggested a role of immune checkpoint inhibitors in certain subtypes of MBC, particularly triple-negative and HER2-positive subtype. Were there some important insights with regard to immunotherapy in breast cancer presented at ASCO 2018?

Dedic: Despite the fact that we are still waiting for progress in immunotherapy for MBC (results of ongoing trials: Impassion 120, 131, 132, etc.), we have heard some interesting results. I was curi-

ously waiting for ASCO 2018 to hear the first results of the TONIC trial [4] where some old therapies (radiation, low dose of cyclophosphamide, cisplatin and doxorubicin) were used to turn the so-called ‘cold’ into the ‘hot’ tumor. The intention of the trial was to ‘pick the winner’ and expand the selected cohort into the stage II, based on clinical and translational endpoints in previously pretreated patients. Safety data was presented earlier at ESMO 2017. Final response data of stage I and first translational data of this phase II study were presented, where nivolumab was given after the induction treatment in TNBC patients. The TONIC trial was trying to address questions on how to improve anti-programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) efficacy for TNBC and how to combine anti-PD-1/PD-L1 with standard therapies. More T cells and more clonal T cells were identified in responders in biopsies, and induction treatment with cisplatin and doxorubicin were shown to likely result in increased response to nivolumab and upregulation of ‘responding’ gene signatures. The cohort with doxorubicin as an ‘immune inductor’ will be expanded in stage II of the trial.

First results of the TOPACIO phase I/II study with combination of the poly (ADP-ribose) polymerase (PARP) inhibitor niraparib and anti PD-1 antibody pembrolizumab in unselected metastatic TNBC patients are also interesting. This combination was well tolerated, and durable clinical benefit was demonstrated beyond patients with tumor *BRCA* mutations (*tBRCAmut*) tumors. Homologous recombination repair (HRR) mutations may enrich activity in tumor *BRCA* wild-type (*tBRCAwt*) patients. Nevertheless, unlike some other diseases, in breast cancer we are still waiting for improvements in immunotherapy based on better selection of patients with novel biomarkers and rational new combinational strategies based on preclinical data in order to make progress with immunotherapy in this indication.

De Mattos Arruda: In the TOPACIO/Keynote-162 study (Abstract 1011 [4]), half of the patients with metastatic TNBC achieved disease control with a treatment combination of the PARP inhibitor niraparib and an anti-PD-1 agent, i.e. pembrolizumab. Median duration of response has not been reached; objective response rate and disease control rate to treatment with niraparib and pembrolizumab were seen in 28% and 50% of the patients, respectively. Clinical activity was observed in patients with *tBRCAmut* and *tBRCAwt*.

The TONIC trial (Abstract 1011 [4]), an innovative basket study exploring combination therapy, provides data on the effect of chemotherapy and radiotherapy in priming the immune system, while adopting strategies to render the tumor microenvironment more susceptible to anti-PD1 nivolumab. Short-term induction with chemotherapy or radiation followed by nivolumab showed promising response rates as to its translational data (upregulation of gene signatures, and modulation of T cell number and clonality).

Gampenrieder: The most important trial in this regard was the German GeparNuevo study. In this phase II trial, patients with

early TNBC (n = 174) were treated with 12 cycles of neoadjuvant nab-paclitaxel followed by 4 cycles of epirubicin/cyclophosphamide and were randomly assigned to either concomitant durvalumab (anti-PD-L1 antibody) or placebo. The primary endpoint was pathologic complete response (pCR) (ypT0 ypN0). The addition of the checkpoint inhibitor did not add significant toxicity to the chemotherapy regimen. Only the rate of thyroid dysfunction was higher in the experimental arm (14 vs. 2%). 64 and 59% of patients in the durvalumab and in the placebo arm, respectively, completed all therapies. There was a numerically higher rate of pCR in the durvalumab arm compared to the control arm; however, without reaching statistical significance (53.4 vs. 44.2%, odds ratio 1.53, 95% CI 0.82–2.85; P = 0.182). The subgroup analysis suggested that patients who were treated with a run-in phase of durvalumab or placebo without chemotherapy for 2 weeks before the study design was amended (n = 117), derived more benefit from the addition of the checkpoint inhibitor (pCR 61.0 vs. 41.4%, P = 0.052). The GeparNuevo study confirms the results of the I-SPY2 trial by showing that the addition of a checkpoint inhibitor to standard neoadjuvant chemotherapy is feasible and improves – at least numerically – the pCR rate. If this effect on the response rate, however, translates into a better long-term outcome remains to be explored in larger trials.

Question 4: Do we have to include any novel biomarkers in the diagnostic workup of breast cancer? Did the importance for incorporating genomics from tissue and liquid biopsies in MBC increase after the ASCO 2018 and why?

Dedic: After ASCO 2018 we have better data based on results of TAILORx for further improvement in predicting EBC prognosis and tailoring systemic treatment according to the predicted clinical outcome based on tumor aggressiveness. I hope that genomic assays like Oncotype DX will be finally reimbursed in my country and become part of the standard diagnostic workup for EBC patients, especially postmenopausal. The 21-gene assay would help to spare more patients with ER-positive/HER2-negative tumors from chemotherapy.

I maybe expected that in the future selection of patients in MBC for targeted agent treatment by single assessment will not be enough, and serial biomarker assessments will be needed to guide treatment in dynamic breast cancer tumor environment and monitor evolution of cancer genetics. Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) offer promise in improving prognostication and tailoring systemic therapy. ASCO 2018 provided new data to further support the *clinical validity* of using liquid biopsies in the MBC setting. Before liquid biopsies may be routinely adopted into clinical practice, demonstrations of *clinical utility* are needed. Novel results that validate the correlation between CTCs and clinical outcomes in MBC, independent of molecular subtype, disease location, and line of therapy, were presented. A threshold of 5 CTCs could predict indolent metastatic

disease. Liquid biopsies could also help us to predict treatment resistance, not only to deal with resistance but also not to waste time on treatment that will not work.

In the metastatic setting, according to results of the IMPACT trial (Initiative for Molecular Profiling and Advanced Cancer Therapy), the impact of personalized therapy selection based on molecular testing of tumors is clinically relevant. MBC patients were among other solid tumors in that trial. Matched targeted therapy was found to be an independent factor predicting longer OS in multivariate analysis.

De Mattos Arruda: At ASCO 2018, an array of potential biomarkers was presented, particularly *tissue and liquid biopsies* (ctDNA and CTCs in MBC) *genotyping*. Vidula et al. (Abstract 1020 [5]) evaluated the impact of *tissue genotyping* or ctDNA on the selection of matched therapy and clinical outcomes in MBC patients and showed that matched therapy was associated with a better OS in ctDNA-profiled patients (hazard ratio 0.41, p = 0.002).

Davies et al. (Abstract 1019 [6]) identified an indolent subset of patients in MBC, stage IV_{indolent}, using CTC counts. ctDNA and CTCs hold promise to improve prognostication and tailoring systemic therapy. However, clinical utility and validity need to be well established before they are routinely adopted in clinical practice for breast cancer.

The genetic landscape of resistance to CDK4/6 inhibition in ctDNA analysis of the PALOMA-3 study identified mutations that emerged in a longitudinal analysis of samples obtained from patients treated with palbociclib and fulvestrant or placebo and fulvestrant (Abstract 1001 [7]). Results of genomic analysis of ctDNA in plasma showed that acquired *RB1* mutations are selected by the palbociclib and fulvestrant arm, although infrequently. *PIK3CA* and *ESR1* Y537S mutations were likely to contribute to fulvestrant resistance.

Furthermore, promising research addressing the integration of the genomic and immune landscapes among multiregional metastases of MBCs for uncovering tumor heterogeneity (also incorporating ctDNA from body fluids bathing the analyzed organ sites) were presented (Abstract 1009 [8]). The translational research while characterizing the genomics, neoantigen and T cell receptor landscapes of the heterogeneous metastases offer new therapeutic avenues in boosting effective anti-tumor immune responses in breast cancer patients.

Gampenrieder: Several educational sessions and one oral presentation addressed the topic of liquid biopsy in breast cancer. Nowadays, the rapid progress in polymerase chain reaction (PCR) techniques does not only allow detection of ctDNA in the neoadjuvant and adjuvant setting but also screening of mutation panels without prior knowledge of tumor mutations. Ultra-deep sequencing like CAPP-Seq (cancer personalized profiling by deep sequencing) reaches an analytic sensitivity ranging from 0.0021 to 0.00025%.

A retrospective analysis of the prospective randomized phase III trial PALOMA (palbociclib and fulvestrant vs. placebo and fulvestrant in second-line HR-positive, HER2-negative MBC) investi-

gated the genetic landscape of resistance to CDK4/6 inhibition in ctDNA. Plasma samples at baseline and at end of treatment were available from 193 (out of 521) patients. Amplicon error-corrected sequencing of 17 targetable driver and CDK4/6 related genes was performed. Additionally, whole exome sequencing was possible in 14 patients where enough DNA was available. To shortly summarize the results, driver mutations in genes like *PIK3CA* and *ESR1* were acquired in both treatment arms, while mutations in the retinoblastoma gene (*RB1*), known to provide resistance against CDK4/6 inhibition, were acquired in the palbociclib arm only. The frequency, however, was very low (4.8%). The study shows the feasibility of detecting emergent genomic alterations in liquid biopsies during treatment. In the future, a larger mutation panel could provide hints how to modify therapy dependent on emerging mutations and clarify the mechanism of resistance to endocrine therapy and CDK4/6 inhibition in an individual patient. Today, ctDNA still remains experimental and should not influence the management of patients with EBC or MBC.

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