Highlights in breast cancer

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At ASCO 2018, the results of several anticipated studies were presented. While most of these studies were thought provoking, many results left practicing oncologists a little bit disoriented. How to translate these data in clinical practice?

EARLY BREAST CANCER

The Persephone study is a British non-inferiority trial investigating (again) the non-inferiority of a 6 months-long regimen of adjuvant trastuzumab, as compared to the current standard of care of 12 months.[1] While the 2 previously published trials (PHARE and HORG) failed to demonstrate the non-inferiority of the shorter duration of trastuzumab, this randomized phase III trial (N=4,089 patients), concludes at the non-inferiority of this regimen. In this study, non-inferiority was defined as as "no worse than 3% below" in disease-free survival (DFS). With a minimum follow-up of 5 years, the DFS rate at 4 years was 89.8% in the 12-months trastuzumab arm *vs.* 89.4% in the 6-months arm. This translated into a hazard ratio (HR) of 1.05 (95%CI: 0.93-1.24). As the upper margin of the confidence interval was below 1.31, the non-inferiority claim could be made from a statistical point of view. Cardiac safety was improved in the 6-months arm as compared to the 12-months arm, with 4% of patients having to stop trastuzumab in the 6-months arm, *vs.* 8% in the 12-months arm.[1]

However, very disturbingly, as pointed out by discussant Professor Martine Piccart (*Jules Bordet Institute, Brussels*) subgroup analyses suggest a superiority of the 12-months regimen in the patient population treated with today's most widely used regimens, i.e. patients treated with concomitant chemotherapy (47% of the patients in the trial, but most patients today), neoadjuvant chemotherapy (15% of the patients in the trial, but widely used today in HER2 positive disease), use of taxanes without anthracyclines (widely used in patients with small node-negative breast cancers, following the excellent results of the APT trial), and hormone receptor (HR) negative breast cancers (31% of patients in the trial). As such, the 6-months regimen will most likely not become the new standard of care, its use being probably limited to countries with scarce resources.

The much-anticipated results of the TAILORx study were presented at the plenary session of ASCO 2018.[2] The aim of the study was to investigate whether there was a benefit of adjuvant chemotherapy in patients with a mid-range Oncotype DX Recurrence Score (RS). In this trial a mid-range RS was set between 11 and 25, which is different from the traditional definition of 18-31. Patients with estrogen receptor (ER) or progesterone receptor (PgR) positive, HER2-negative, node-negative, early breast cancer, with a tumor size of 1.1-5.0 cm (or 0.6-1.0 cm and intermediate or high grade) and a mid-range RS (11-25) were randomized between endocrine therapy (ET) alone (3,399 patients) and chemotherapy (CT) + ET (3,312 patients). The HR margin for this non-inferiority trial was set at 1.322 for the primary endpoint of invasive disease-free survival (IDFS) with an anticipated IDFS rate of 90% in the chemotherapy arm and 87% in the non-chemotherapy arm. In the intent-to-treat (ITT) population, ET was non-inferior to CT + ET in terms of IDFS, with a HR of 1.08 (95%CI: 0.94-1.24) and a projected 9-year distant recurrence rate of 5% (*Figure 1*). ET alone was also non-inferior in terms of distant relapse-free interval, relapse-free interval (RFS),

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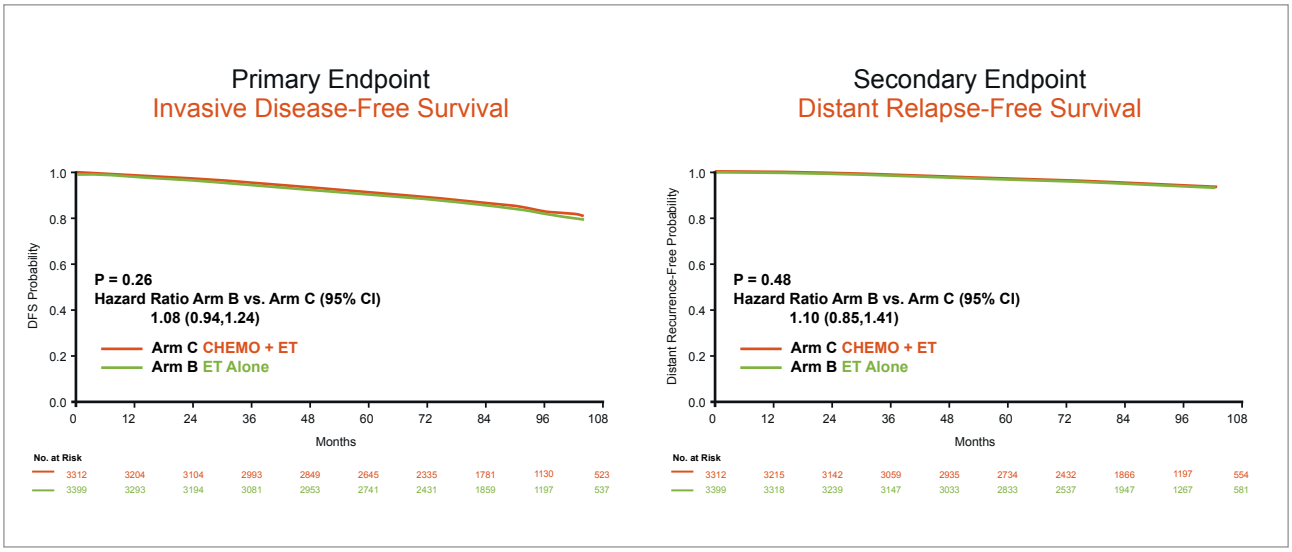

FIGURE 1. IDFS and distant RFS in RS 11-25 patients enrolled in the TAILORx trial.[2]

and overall survival (OS). However, in an unplanned post-hoc subgroup analysis, the investigators did find some chemotherapy benefit in pre-menopausal women younger than 50 years with a RS between 15 and 25. This effect was most pronounced in patients with a RS between 21 and 25, where there was a 6% difference in favor of chemotherapy in terms of (mainly distant) IDFS events. Thus, the main findings of the study were that the OncotypeDX RS could be used as a dichotomous test, the benefit of chemotherapy being limited to the patient population with a RS of 25 and above (or 21 and above in premenopausal patients).[2]

There is a debate however on the optimal use of this genomic assay. In the TAILORx study, 74% of the patients were considered clinically low-risk. In this setting, the Mindact trial recently showed the absence of benefit of adjuvant chemotherapy, independently of the results of a genomic test. Much work remains to be done in order to correctly identify the patient population that will benefit from the addition of a genomic test to the standard clinical criteria.

Updated results from the SOFT and TEXT trials were also presented.[3] Among premenopausal patients with HR-positive, HER2-negative cancers, the magnitude of absolute improvement in 8-year freedom from distant recurrence varied widely according to the risk of recurrence, as shown by a Subpopulation Treatment Effect Pattern Plot (STEPP) analysis. While the patients at the highest risk of recurrence (based on age, nodal status, tumor size, magnitude of ER and PgR expression, tumor grade and Ki-67) experienced a 10-15% improvement with exemestane (E) + ovarian function suppression (OFS) *vs.* tamoxifen (T) + OFS or T alone, improvement with E + OFS may be 4-5% for patients at intermediate risk (most of whom also received chemotherapy) and minimal for those at low-risk (given that >97% of these women treated with T alone were without distant recurrence at 8 years).[3]

Two trials investigated the use of denosumab in the adjuvant setting. As a reminder, the EBCTCG meta-analysis had shown a reduction in the rate of breast cancer recurrence in the bone and an improvement in breast cancer survival limited to women who were postmenopausal at treatment initiation, which triggered the question of the use of other bone-modifying agents in this setting.

In the ABCSG-18 trial, 3,425 post-menopausal women with ER or PR positive early breast cancer on an adjuvant aromatase inhibitor were randomly assigned to either denosumab at a low dose of 60 mg or placebo every 6 months for a total of 7 doses.[4] The updated results, after a median follow-up of 73 months, show an improved DFS (the secondary endpoint) in favor of the denosumab arm in the ITT population, with a HR at 0.82 (95%CI: 0.69-0.98). However, this improvement in DFS was mainly driven by a reduction in contralateral breast cancer cases and other non-breast primary carcinomas rather than recurrences in the bone or other metastatic sites. This raises the question of the physiopathology of these findings. Of note, the treatment at that dose was considered safe, with no adjudicated case of osteonecrosis of the jaw (ONJ).[4]

In the D-CARE study, 4,509 stage II or III breast cancer patients at high risk of relapse, scheduled to receive (neo)-adjuvant chemotherapy, were randomly assigned to denosumab at a higher dose of 120 mg or placebo every 3-4 weeks for 6 doses, followed by injections at the same dose level every 3 months for 54 months.[5] There was no difference between the 2 treatment arms in terms of bone metastasis free sur-

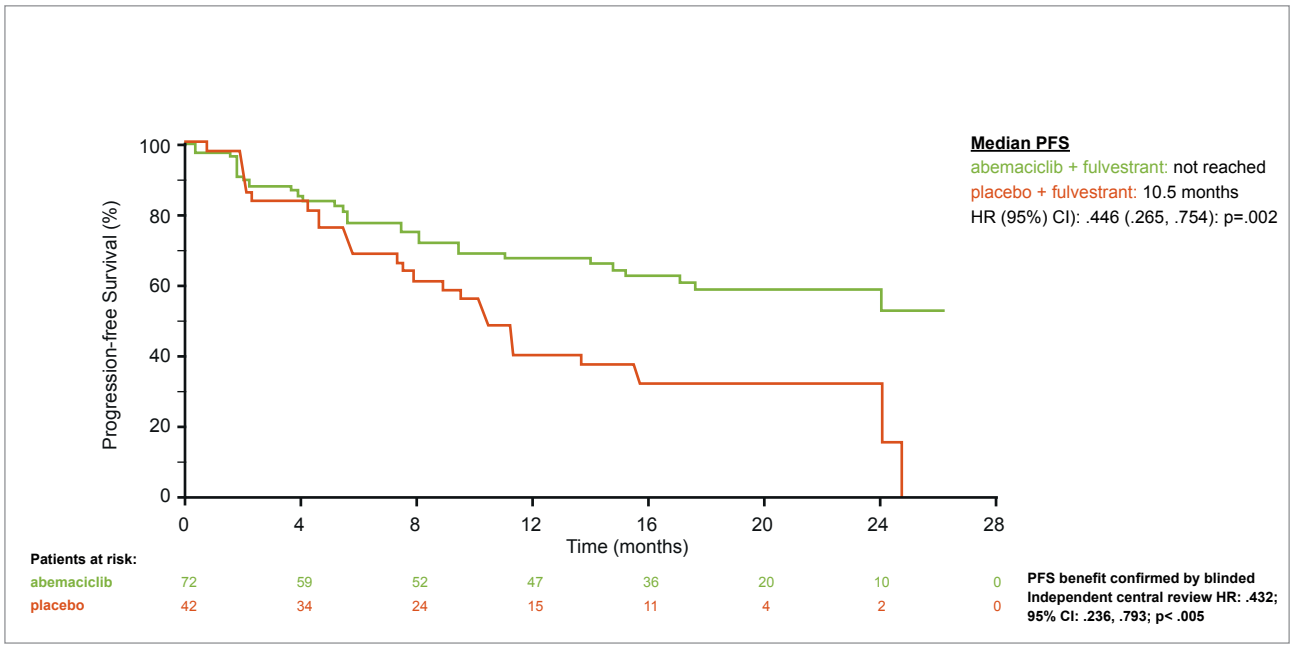

FIGURE 2. PFS in pre/perimenopausal women enrolled in MONARCH-2.[8]

vival (BMFS) after a median follow-up of 67 months. While the value of this endpoint can be debated, there was also no difference in terms of DFS and OS. However in 5% of the denosumab treated patients, ONJ was seen.[5]

Overall, it can be said that the benefit of adjuvant denosumab was not clearly demonstrated by any of these abstracts.[4,5]

In the neoadjuvant setting, the GeparNuevo study investigated the addition of durvalumab to a taxane-anthracycline containing chemotherapy regimen in triple negative breast cancer (TNBC).[6] In total, 174 patients were treated with nab-paclitaxel followed by epirubicin/cyclophosphamide (EC), +/- the PD-L1 antibody durvalumab. The primary endpoint of pathological complete response (pCR), defined as ypT0, ypN0, was presented during the meeting. The pCR rate was 53.4% in the durvalumab-containing arm, and 44.2% in the placebo arm (p=0.287). Of note, 117 patients took part in a window study in which durvalumab (or placebo) was administered alone for 2 weeks before the start of chemotherapy. In this cohort, 61.0% of patients reached a pCR at the end of the chemotherapy in the durvalumab-containing arm, as opposed to 41.4% in the placebo arm (p=0.052). In summary, there was a numerically higher rate of pCR in the patients treated with a combination of chemotherapy and immunotherapy, especially in the subgroup of patients treated with induction immunotherapy. The addition of durvalumab to chemotherapy was generally well tolerated.[6]

METASTATIC BREAST CANCER

The MONALEESA-3 trial added to the overwhelming literature concerning CDK4/6 inhibitors in HR-positive/HER2-negative breast cancers. In this trial, 726 postmenopausal women or men with no or ≤1 line of prior ET for advanced breast cancer (ABC), and no prior treatment with chemotherapy in this disease setting, were randomly assigned to fulvestrant + ribociclib or fulvestrant + placebo. There was a statistically significant improvement in the primary endpoint of investigator-assessed progression-free survival (PFS) in the group of patients receiving ribociclib (20.5 months *vs* 12.8), with a HR of 0.593 (95%CI: 0.480–0.732) (p<0.0001). None of the studied subgroups showed a disadvantage of ribociclib over placebo. Adverse events were in line with prior ribociclib trials: grade 3/4 adverse events consisted mainly of neutropenia (53.4% *vs.* 0%) and increased ALT/AST (8.5% *vs.* 6.0%). Post-baseline QTcF > 480ms occurred in 5.6% of patients in the ribociclib arm as compared to 2.5% in the placebo arm. This trial establishes the combination of fulvestrant + ribociclib as a new treatment option in the first- or second-line treatment of postmenopausal women with HR- positive HER2-negative ABC.[7]

Efficacy and safety data of the MONARCH 2 study for pre/perimenopausal women with HR-positive, HER2-negative ABC were presented by *Professor Patrick Neven (University Hospital Leuven).*[8] Out of a total of 669 patients included in MONARCH-2, 114 pre/perimenopausal patients with ET-resistant breast cancer (defined as relapsed on neoadjuvant or on/within 1 year of adjuvant ET, or who had progressed on first-line ET, with no chemotherapy for metastatic breast cancer, and no more than 1 ET for metastatic breast cancer) were

randomized 2:1 between fulvestrant + GnRH agonist + abemaciclib and fulvestrant + GnRH agonist + placebo. Median PFS was not reached in the abemaciclib arm and was 10.5 months in the placebo arm (HR[95%CI]: 0.446[0.264-0.754]; p=0.002) (*Figure 2*). The overall response rate (ORR) was 43.1% in the abemaciclib arm and 19.0% in the placebo arm. The safety profile was consistent with other studies (mainly diarrhea). The addition of a GnRH agonist did not add any additional toxicity.[8]

The BOLERO-6 study was conducted to fulfill post-approval regulatory commitments to the FDA and EMA. It randomized 309 postmenopausal women with ER+ HER2- ABC who had recurred or progressed on anastrozole or letrozole to either everolimus (EVE) + exemestane (EXE), EVE alone, or capecitabine (CAP). The primary endpoint of PFS was higher in the EVE+EXE arm than in the EVE arm (8.4 *vs.* 6.8 months), with a HR of 0.74 (90%CI: 0.57-0.94). The key secondary objective of PFS showed no statistically significant difference between the EVE+EXE arm and the CAP arm (8.4 *vs.* 9.6 months), with a HR at 1.26 (90%CI: 0.96-1.66). Of note, the CAP arm may have been favored by baseline imbalances and potential informative censoring.[9] The benefit-risk profile of EVE+EXE was consistent with the previously published BOLERO-2 trial.

The Sandpiper trial included 480 postmenopausal women with ER-positive, HER2-negative metastatic or locally ABC who had recurred or progressed during or after treatment with an aromatase inhibitor.[10] No more than one chemotherapy regimen for metastatic breast cancer was allowed, and prior treatment with fulvestrant or a PI3K or mTOR inhibitor was prohibited. All patients carried PIK3CA mutant tumors. They were randomly assigned (2:1) to either taselisib (a mutant-selective next-generation PI3K inhibitor) + fulvestrant or placebo + fulvestrant. The primary endpoint of investigator-assessed PFS was 7.4 months in the taselisib arm and 5.4 months in the placebo arm, with a HR at 0.70 (95%CI: 0.56-0.89) and a p-value at 0.0037. Grade ≥ 3 AEs were more frequent in the taselisib arm (49.5% *vs.* 16.4%), mainly diarrhea (11.5%), hyperglycemia (10.8%), rash (3.8%) and stomatitis (3.6%). Though statistically significant, the difference in outcomes does not seem clinically significant, especially given the toxicity profile.[10] The results of this trial do not bode well for the future of PI3K inhibitors in luminal breast cancer.

The efficacy of sacituzumab govitecan, an anti-Trop-2-SN-38 antibody-drug conjugate which had previously shown activity in triple negative breast cancer, was assessed in 54 patients with treatment-refractory HR-positive, HER2-negative metastatic breast cancer included in a phase I/II basket trial.[11] These were heavily pretreated patients, with a median number of prior metastatic treatment lines of 5 (2-17). The most frequent grade 3/4 adverse event was neutropenia, observed in 42% of patients. The objective response rate was 31%, with a clinical benefit rate of 48% (including complete response, partial response and stable disease ≥ 6 months). The estimated median duration of response was 7.4 months (95%CI: 4.4-18.3) and the estimated median PFS was 6.8 months (95%CI: 4.6-8.9).[11]

The TOPACIO/Keynote-162 trial is a phase 1/2 trial evaluating the combination of niraparib, a PARP inhibitor, and pembrolizumab, an anti-PD1 antibody, in metastatic triple negative breast cancer patients who recurred or progressed following (neo)-adjuvant therapy, treated with ≤ 2 prior lines of cytoxic treatment for advanced disease.[12] Prior platinum was allowed in the metastatic setting, provided there was no progression while or within 8 weeks of the last dose. Fifty-five patients were included, with an overall response rate of 28% and a disease control rate (including complete response, partial response and stable disease) of 50%. Clinical activity was observed in both patients with and without tumor *BRCA* mutations, and the addition of pembrolizumab did not add any immune-mediated adverse events.[12]

In the randomized, placebo-controlled phase II PAKT trial, investigators evaluated the added benefit of capivasertib (AZD5363), a highly selective, oral, small molecule AKT inhibitor (*vs.* placebo) to paclitaxel as first-line therapy for metastatic triple-negative breast cancer. One hundred and forty patients were randomized one to one, with a significantly longer median PFS in the patients treated with capivasertib (5.9 months *vs.* 4.2 months, HR 0.74). Of note, the addition of capivasertib also resulted in a significantly longer median OS (19.1 months *vs.* 12.6 months, HR 0.61). Subgroup analyses demonstrated more pronounced benefits in patients with *PIK3CA/AKT1/PTEN*-altered tumors. The most common observed grade 3 and worse adverse events were diarrhea, infection, neutropenia, rash and fatigue.[13]

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