The Breast Cancer community witnessed the presentation of several important studies though 2018. From molecular evaluation of primary breast tissue to predict chemotherapy benefit, to major advances in systemic therapy in the metastatic setting, clinical trials highlighted in this BJO especial edition have truly major impact in current clinical practice for breast cancer patients.

**Keywords:** Breast Neoplasms. Review. Combined Modality Therapy.
PERSEPHONE

Twelve months of adjuvant Trastuzumab (T) remains standard care since 2005 pivotal trials. No reduced-duration trial to date has demonstrated non-inferiority (N-I).

PERSEPHONE was a randomised phase 3 N-I trial comparing 6 to 12m T, the largest reduced-duration N-I trial internationally¹. Stratification was by ER status, chemotherapy (CT) type, and CT and T timing. The primary endpoint was DFS from diagnosis. 4089 pts randomized from 152 UK sites (1:1) enabled the trial to assess the N-I of 6m as “no worse than 3% below the 12m arm. ER+ 69%; CT - 41% anthracycline (A)-based / 49% A and taxane (Tax)-based / 10% Tax-based; adjuvant CT 85%; sequential T 54%. At 4.9 yrs, median follow-up the of DFS rate was 89% and OS 94% in both arms, calculated HR for DFS was 1.05 (95%CI 0.88 – 1.25 demonstrating N-I (HR < 1.29) of 6m T (p = 0.01). Cardiac events were reduced in 6m pts (4% v 8% of 12m (p < 0.0001)). PERSEPHONE has demonstrated 6m of T as N-I to 12m. The authors recommended a reduction of standard T duration to 6 m. Those results were not published yet.

Heterogeneity was observed in some stratification variables suggesting that TAX- base CT, concomitant T, neoadjuvant CT and ER negative patients derives better results with 12 m of T. Brazilian Society of Clinical Oncology made a statement about this topic available in www.sboc.org.br/posicionamentos/item/1330-duracao-do-tratamento-adjuvante-do-cancer-de-mama-her2-positivo.

PALOMA 3 OVERALL SURVIVAL RESULT

A synergistic effect is observed upon CDK4/6 and estrogen receptor pathway targeting. The PALOMA-3 Phase III trial explored the combination of fulvestrant (F) with aCDK4/6 inhibitor, palbociclib (P) in advanced hormone receptor positive (HR+) HER2 negative breast cancer (BC) patients, who have previously progressed on endocrine therapy². Those patients were randomized to F alone or F plus P. The results were updated at ESMO 2018, with a median follow up of 44.8 months and 60% of data maturity.² Patients enrolled to receive combination therapy experienced a PFS of 11.2 months, contrasting with 4.6 months for those receiving F alone [HR=0.49 95% CI (0.39- 0.62) p<0.000001]. Additionally, OS was numerically improved among the cohort of patients who received P+F, namely 34.9 months versus 28 months for F alone [HR=0.79 95% CI (0.62-0.9) p=0.0246]¹. A subgroup analysis revealed that the magnitude of benefit with CDK4/6i was more pronounced in individuals with previous sensitivity to endocrine therapy. Importantly, the PALOMA-3 study was powered for the primary endpoint, PFS, but was not optimized for the secondary endpoint, OS. Although not statistically significant, the benefit in OS for patients managed with CDK4/6i plus F is clearly clinically meaningful. Also, patients randomized to combination therapy experienced a delay to post-progression chemotherapy initiation.

Quality of life evaluation from the studies evaluating the addition of CDK4/6i to hormone therapy also favors combination therapy, with a longer period to quality of life scores deterioration in the group receiving CDK4/6i. Altogether, this data reinforces the benefit of this combination, with substantial benefit for HR+, HER2 negative breast cancer patients.

TAILOR X

The use of genetic signatures, like Oncotype DX (ODX) and Mammmaprint, potentially helps treatment decisions for many patients with ER+ HER2 negative early breast cancers (EBC). Tailor X is a phase 3 clinical trial designed to provide an evidence-based support whether hormone therapy (HT) alone is not inferior to HT plus chemotherapy (CT) based on recurrence scores (RS) derived from the expression of 21 genes in the molecular test ODX in patients with ER+, HER2 negative, node negative EBC.

The ODX RS ranges from 0 to 100, and previous reports demonstrated that low scores (0-10) should receive only HT and to higher scores (higher than 26 or 31) CT should be included in treatment plan².

Results from the intermediate scores (11 to 25) were presented at ASCO of 2018 and already published³. Of the 10.273 patients from the entire study, 6711 were in the mid-range score (11-25) and randomly assigned to receive either HT alone or HT and CT. At nine years of follow up the rate of DFS was similar for both groups, indicating no benefit from CT But an exploratory analysis indicated that women aged 50 years or less may benefit from CT But the ODX in patients with ER+, HER2 negative, node negative EBC.

Based on the results of ODX it is proposed that CT could be avoided in women with ER+, HER2 negative, node negative EBC if older than 50 and with a RS of 11-25, at any age for those with a RS of 0-10 and for those aged 50 years or younger with a RS of 11-15. For the remaining patients, consider CT at any age with a RS of 26-100 and for those 50 years or younger with a RS between 16 and 25³.

IMPASSION130

Results of the IMpassion130 were presented at ESMO 2018 and this is the first phase 3 randomized trial to show significant benefit of immunotherapy for triple negative PD-L1 positive breast cancer⁴.

IMpassion130 trial is an international, randomized, double-blind, placebo-controlled trial of first-line atezolizumab plus nab-paclitaxel, as compared with placebo plus nab-paclitaxel, in patients with locally advanced or metastatic triple-negative breast cancer. Pd-L1 expression was defined in this study by PD-L1 greater than or equal to 1% tumor-infiltrating immune cells.
Patients received atezolizumab at a dose of 840 mg or placebo, IV, on days 1 and 15, and nab-paclitaxel at a dose of 100 mg/m², IV, on days 1, 8, and 15 of every 28-day cycle. The two primary end points were progression-free survival (PFS), in the intention-to-treat population and PD-L1-positive subgroup, and overall survival (OS). Each group included 451 patients (median follow-up, 12.9 months). Patients were eligible to receive taxane monotherapy and had received no previous chemotherapy or targeted therapy for metastatic triple-negative breast cancer. Radiation therapy and previous chemotherapy (including taxanes) in the context of curative therapy (if treatment was completed ≥12 months before randomization) were allowed. Exclusion criteria included untreated central nervous system (CNS) disease (patients with asymptomatic treated CNS metastases were permitted), PD-L1 was evaluated according to immunohistochemical testing (<1% [PD-L1 negative] vs. ≥1% [PD-L1 positive]).

In the intention-to-treat analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio [HR] for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002); among patients with PD-L1-positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (HR, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (HR for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08); among patients with PD-L1-positive tumors, the median OS was 25.0 months and 15.5 months, respectively (HR, 0.62; 95% CI, 0.45 to 0.86 - first interim analysis).

**EMBRACA**

OlympiAD was the first trial with PARP inhibitor in patients with metastatic breast cancer HER2 negative and germline BRCA mutated, demonstrating longer median progression-free survival and lower risk of disease progression or death with olaparib monotherapy compared to chemotherapy7.

Talazoparib is a new PARP inhibitor, with a dual-mechanism both inhibiting the PARP enzyme and effectively trapping DNA breaks in the context of curative therapy (if treatment was completed ≥12 months before randomization) were allowed. Exclusion criteria included untreated central nervous system (CNS) disease (patients with asymptomatic treated CNS metastases were permitted), PD-L1 was evaluated according to immunohistochemical testing (<1% [PD-L1 negative] vs. ≥1% [PD-L1 positive]).

In the intention-to-treat analysis, the median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio [HR] for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002); among patients with PD-L1-positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (HR, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (HR for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08); among patients with PD-L1-positive tumors, the median OS was 25.0 months and 15.5 months, respectively (HR, 0.62; 95% CI, 0.45 to 0.86 - first interim analysis).

Patients were randomized to receive talazoparib (287 patients) or standard therapy (144 patients). The median progression-free survival was significantly longer in the talazoparib group (8.6 months vs. 5.6 months; hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.41 to 0.71; P=0.001) and objective response rate was higher in the talazoparib group (62.6% vs. 27.2%; P<0.001). The hematologic (primarily anemia) and nonhematologic toxicities grade 3–4 occurred in 55% x 38% and 32% x 38% of the patients who received talazoparib and the standard therapy, respectively. In the patient-reported outcomes, talazoparib showed significant overall improvements and significant delays in the time to clinical deterioration.

The single agent talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival Therefore, talazoparib is a new option of PARP inhibitors for treatment of metastatic breast cancer with germline BRCA mutation, and already approved by the FDA.

**MODERATE HYPOFRACTIONATION**

This new guideline issued by ASTRO expands the population of patients eligible to receive a shorter radiation treatment known as moderate hypofractionation (HF). HF whole breast irradiation (WBI) is recommended independently of age, breast side and size, tumor stage, previous chemotherapy, use of transtuzumab or endocrine therapy. In invasive breast cancer HF, WBI may include the low axila to a dose of 40Gy in 15 fractions or 42.5Gy in 16 fractions; other regional nodes should not be targeted. In these patients, boost could be omitted in women older than 70, with low-to- intermediate-grade, hormone-positive tumors and widely negative margins. For DCIS, hypofractionated WBI may be applied and boost to tumor bed should be considered in women younger than 50, with high-grade tumors and/or those with positive or close margins (<2mm).

**RADIOTHERAPY AND DCIS**

This is a prospective randomized phase III trial to evaluate the effect of whole breast radiation (WBRT) versus observation (OBS) in 636 ductal carcinoma in situ (DCIS) patients who underwent breast conservation surgery with low risk of recurrence disease (clinically occult DCIS, diagnosed by mammogram or incidental finding at surgery, size ≤ 2.5 cm, surgical margins ≥3 mm, nuclear grade 1 and 2)10. The use of tamoxifen for 5 years was optional. The 12-year cumulative incidence of local relapse was 2.8% versus 11.4% for WBRT and OBS groups, respectively (p=0.0001). Similarly, the 12-year cumulative incidence of invasive local recurrence was 1.5% with WBRT and 5.8% (p=0.016).
REFERENCES


