REVISTA PORTUGUESA DE **ONCOLOGIA**

Artigo de revisão narrativa

Best of ASCO 2024
Early Breast Cancer

Autores:
Leonor Matos [1]

Afiliação:
[1] Oncologia Médica – Centro Clínico Champalimaud

ORCID:
Leonor Matos – 0000-0001-9568-238X

Autor para correspondência:
Leonor Matos
Centro Clínico Champalimaud
Avenida Brasília
1400-038 Lisboa
analeonormatos9@gmail.com

Recebido/Received: 2024-08-05
Aceite/Accepted: 2024-10-19
Published/Publicado: 2024-11-25

Early Breast Cancer

Best of ASCO 2024

Introduction

At the 2024 ASCO Conference, several innovative works were presented in the field of Early Breast Cancer, that dive into old and new biomarkers and their potential to inform potential practice changing decisions. This review highlights four of the most relevant presentations in this disease setting.

A-BRAVE trial: A phase III randomized trial with avelumab in early triple-negative breast cancer with residual disease after neoadjuvant chemotherapy or at high risk after primary surgery and adjuvant chemotherapy

The A-BRAVE trial is an academic, phase III, randomized trial using avelumab in early triple-negative breast cancer (TNBC) with residual disease after neoadjuvant chemotherapy or at high risk after primary surgery and adjuvant chemotherapy. Contextualizing, this trial addresses the most aggressive breast cancer subtype, TNBC, for which neoadjuvant systemic treatment is currently considered standard of care for stage ≥ T1c or N+ disease. Important to state is that, at the time of this study (2015), chemotherapy was the only standard systemic therapy for patients with early TNBC and no effective therapy was available for patients with invasive residual disease after neoadjuvant therapy. However, not achieving a pathological complete response at the time of surgery after neoadjuvant treatment, is linked with a poor prognosis.[1,2]

Treatment options for TNBC have incorporated the use of immune checkpoint inhibitors (ICI) and several studies have bene conducted to explore the role of these therapies in the early disease setting. Avelumab, an anti PD-L1 antibody, has shown activity and an acceptable safety profile in a variety of solid tumors and immune biomarkers such as tumor-infiltrating lymphocyte (TILS) and PD-L1 expression have shown to be prognostic in this setting, while PD—L1 also predicts efficacy of immune-checkpoint inhibitors in metastatic breast cancer. Therefore, the A—BRAVE trial was designed to evaluate the role of escalating treatment with Avelumab in high risk early TNBC.

In this trial, high risk disease was defined according to two strata. A stratum A, in adjuvant setting, for patients that had disease staging of: pT2N1, pT3-4 N0-3, pN2—3 any T and a stratum B (post-neoadjuvant), defined as residual invasive carcinoma in the breast and/or axillary lymph nodes.

Patients in any strata had to receive anthracycline and taxane (neo)adjuvant chemotherapy. An important amendment in 2018 was performed to allow patients in stratum B to receive additional post-operative chemotherapy and were randomized at completion of treatment, which allowed for delivering treatment with adjuvant capecitabine. Patients, divided into stratum A or B, were randomized 1:1 to receive Avelumab 10mg/kg, iv, every 2 weeks for 52 weeks or for observation. The co-primary efficacy endpoints were disease-free survival (DFS) and disease-free survival in stratum B (post-neoadjuvant). Secondary efficacy endpoints were overall survival (OS) and disease-free survival in PD-L1 positive patients. The target effect for statistical analysis was a 13.6% improvement (from 60% to 73.6%) in 3-year DFS rate, which interestingly contrasts with the results of the landmark phase III registration KEYNOTE-522 trial, with an event-free survival at 3 months of 84.5% vs 76.8% in the control.[3]

A total of 477 patients were randomized. When analyzing overall patients' characteristics, it is worth pointing out that only 24% patients received adjuvant capecitabine in the stratum B, although all with residual disease, and most had a residual cancer burden of 2. Focusing on results, the primary endpoint of DFS was not met, since a non-statistically significant 5.1% improvement at 3-years DFS was observed, with HR 0.81, *p*-value=0.172. Similarly, DFS in stratum B was non-significant, with a 6.2% improvement and a HR 0.8 and *p*-value=0.170. Interestingly, the secondary endpoint of 3-year OS, showed an 8.5% additional benefit of adjuvant Avelumab, with an HR of 0.66 (*p*-value 0.035). Following these results, a post-hoc exploratory analysis was carried out to explore distant disease-free survival, showing also an improvement of 7.5% with HR 0.7 and *p*-value = 0.027. Focusing on safety, 27.9% patients discontinued treatment, mostly due to immune related adverse events (30.8%), the most frequent being hypothyroidism (13.2% any grade).

Summarizing, the A-Brave study did not meet its primary endpoint, but did meet a key secondary endpoint of OS and the exploratory endpoint of DDFS, without new safety signals and rare grade 3 or higher immune—related adverse events (irAEs). It is to congratulate the effort of running this academic trial that, although leading to a non-statistically significant improvement in 3-yr DFS, improved significantly OS, leading to the hypothesis that Avelumab may play a role for patients with high risk early TNBC after surgery. However, additional limitations need to be pointed out: the trial did not use standard of care chemotherapy, that would include the addition of carboplatin, but mostly it does not reflect the current standard of treatment with the combination of Pembrolizumab for these patients, as per the Keynote-522 trial. In the light of the new recommended treatment regimen, where most patients with stage II-III disease will receive already ICI as part of the neoadjuvant treatment regimen, an option like the one studied in the A-BRAVE trial could eventually be reserved for the situations of clinical understaging that go for upfront surgery, although this represents an ever-bigger minority of patients.

For sure more granularity of data is needed, especially to understand who are the patients who derive more benefit from this treatment strategy. Findings from other trials, such as the Alexandra/Impassion030 phase 3 trial, presented at 2023 San Antonio Breast Cancer Symposium, do not support the addition of the PD-L1 immune checkpoint inhibitor to adjuvant chemotherapy following primary surgery for early TNBC, since adjuvant-only immunotherapy with Atezolizumab added to a standard chemotherapy backbone failed to improve invasive disease-free survival compared with chemotherapy alone in patients with early-stage triple-negative breast cancer.

Serum anti-Mullerian hormone levels refine identification of premenopausal patients with HR+, HER2-, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in SWOG S1007 (RxPONDER)

This study presentation brought to the discussion the need to refine who are the patients with early HR+/HER2- BC with 1 to 3 positive lymph nodes, who benefit from chemotherapy, using the fata from the RxPonder study and intending to go further on the definition of menopausal status. Refreshing the RxPonder trial design, this phase III trial enrolled women with HR+/HER2- early BC and 1 to 3 positive lymph nodes, without distant metastasis, and in all the oncotype dx study was performed. Patients with a recurrence score of 0 – 25 were further randomized to receive chemotherapy followed by endocrine therapy, or endocrine therapy alone. Out of the 5000 women included, 1/3 of these patients were classified as "pre-menopausal" and, according to the final study results, chemotherapy benefit differed according to menopausal status, with pre-menopausal women deriving benefit from chemotherapy, with a 5-year absolute difference in invasive disease-free survival of 5.2%. Thus, despite the positive trial results, the oncotype-dx test could not be of use in the decision to spare chemotherapy to these group of pre-menopausal patients.

When dissecting these results, it is however interesting to realize that amongst the "premenopausal" patient subgroup, the older premenopausal, i.e. women with more than 50 years but still classified as premenopausal, seemed to derive less benefit from chemotherapy, leading to questioning how to better refine what are the premenopausal patients who derive more or less benefit from chemotherapy in an accurate manner?

The authors of this study thus postulated that anti-müllerian hormone (AMH) could be a useful serum marker to determine chemotherapy benefit if < 55 years. Indeed, lower AMH reflects fewer growing follicles, and AMH is more stable and reliable during menstrual cycle than estradiol and Follicular stimulating hormone (FSH). A total of 1016 patients from the

RxPonder trial were included in this analysis, of which 14-19% of "premenopausal" women < 55 years had traditional serum hormone levels in postmenopausal range and 21% had serum AMH in postmenopausal range (<10 pg/mL). Multivariable Cox models adjusted for confounders and testing the interaction of the variable and treatment for significance, found that pre-treatment serum AMH predicts chemotherapy benefit in "premenopausal" women < 55 years and that while patients with Low AMH seem to derive no benefit from chemotherapy, with no difference seen in 5-year IDFS, patients with medium/high AMH had a 7.8% improvement in 5-year IDFS with chemotherapy and a 4.4% improvement in DRFS.

It is thus possible to conclude that, in the RxPONDER trial, "premenopausal" women < 55 years with 1-3 Lymph nodes positive and a recurrence score < 25, 20.6% have low pre-treatment serum AMH levels < 10 pg/ML by traditional ELISA assay and did not benefit from adding chemotherapy to ET, making AMH a better indicator of adjuvant chemotherapy benefit than reported menopause status, age, or other serum hormone levels. Ongoing analyses include assessing serum hormones in ~300 UNICANCER pts <55 years since low serum AMH could classify who can safely forego adjuvant chemotherapy in women whose menopausal status is unclear.

The Impact of Adjuvant Endocrine therapy omission in ER-low Early stage Breast Cancer

At the meeting, Grace Mei Yee Choong, an oncologist at the Mayo Clinic, presented results of a retrospective analysis of patient outcomes from the National Cancer Database that examined the effect of adjuvant endocrine therapy (AET) use or omission in ER-positive breast cancer patients. The main research focus of this study was the population with ER-low tumors. ER positivity is strongly predictive of response to endocrine therapy in breast cancer. ER status is typically gauged based on the percentage and intensity of immunohistochemical staining of cancer cells. However, in a small number of patients, ER status is neither clearly negative, nor clearly positive, but instead shows very weak positivity, in the range of 1 to 10 percent of cells, indicating there is heterogeneity within the tumor. Patients with such ER-low breast cancer typically respond to chemotherapy similarly to ER-negative patients, but the benefits of endocrine therapy are less clear for those patients. Currently, there are no universal guidelines covering adjuvant endocrine therapy for ER-low breast cancer, and while patients with ER-low breast cancer are typically offered endocrine therapy, to date there has been little evidence of benefit for them. Choong and colleagues identified 1032 patients with stage I-III ER-low breast cancer, of which nearly 7,000 received neoadjuvant or adjuvant chemotherapy between 2018 and 2020, and compared outcomes for those who also received adjuvant endocrine therapy versus those who did not. Median age was 55 years, 73% with PR-negative BC and 65% HER2-negative disease. Of these, 42% patients omitted adjuvant endocrine therapy. Factors associated with AET were PR-, HER2-, Ki67≥20%, higher grade, cN0 status and receipt of neoadjuvant chemotherapy.

After a median follow-up of three years, 586 patients had died. The researchers found that omission of adjuvant endocrine therapy was associated with significantly worse overall survival compared to those who received it (HR 1.25, 95% CI 1.05-1.48, p=0.01). Further, that effect was similar regardless of progesterone receptor status, HER2 status, or the cellular proliferation marker Ki-67. At follow-up, omission of endocrine therapy was associated with a 25 percent higher risk of death compared to those who received it. Of note, patients with residual disease after neoadjuvant chemotherapy in particular had worse overall survival when endocrine therapy was omitted.

These results contrast with other studies, as the Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis of randomized trials published in 2011,[4] that showed that for ER-poor primary BC, tamoxifen did not significantly reduced overall recurrence rate and did not seem to reduce the incidence of contralateral breast cancer, despite limitations of the ligand—binding ER assay method used in the evaluated trials. Although the obvious limitations related with a retrospective analysis and the short follow-up, this study is clinically meaningful, and patients with ER-low breast cancer should be recommended endocrine therapy until further studies can be performed to identify those that are most likely to benefit.

Prognostic utility of ctDNA detection in the monarchE trial of adjuvant abemaciclib plus endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk early breast cancer (EBC)

The global monarchE trial showed that 2-years of adjuvant abemaciclib, a CDK4/6 inhibitor, significantly improved invasive disease-free survival when added to endocrine therapy, for patients with HR+/HER2-, node-positive, high-risk early BC. This treatment Is now globally approved and category 1 and ESMO-Magnitude of Clinical Benefit Score A rating.[5]

At the 2024 ASCO Meeting, Dr. Sherene Loi reported the prognostic utility of circulating tumor DNA (ctDNA) in a subset of 910 patients from the monarchE trial. These patients were cross-treatment arms, and this group was enriched for invasive disease events, in order to look at the sensitivity of the assay. The assay was tumor-informed, which means whole exome sequencing was performed on the primary tumor, and then each assay was designed specifically for the individual patient using that information. Patients had blood samples taken pre-study treatment, and at 3, 6 or 24 months of treat-

ment. The detection of ctDNA positivity at baseline occurred in about 8% of patients. However, despite this low-frequency and despite a high-risk population, this serial sampling was very informative. This exploratory analysis showed that patients that had detectable ctDNA (ctDNA-positive) at the start of the study experienced worse outcomes. Those who remained persistently ctDNA-positive or became positive after treatment were more likely to experience a recurrence event compared to those who persistently had no detectable ctDNA (ctDNA-negative). Those who became ctDNA-negative after treatment also had more favorable outcomes, regardless of treatment. Importantly, lead time from first ctDNA detection to IDFS event was relatively short

In summary, although the detection of ctDNA was relatively infrequent, ctDNA positivity seemed to be an important prognostic factor for increased risk of an iDFS event. These findings suggest that ctDNA clearance could become a non-invasive surrogate to monitor response to neoadjuvant (pre-surgery) therapy and for evaluation of future therapies in the future. These data suggest that patients who are positive for ctDNA at baseline and remain positive have very aggressive disease and are resistant to treatment and in the future will need some sort of rethink or different types of therapy quite early on. Nevertheless, proof of principle that patients will live longer and/or better if earlier action is taken is still warranted.+

References

1. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–72.
2. Hamy AS, Darrigues L, Laas E, De Croze D, Topciu L, Lam GT, et al. Prognostic value of the residual cancer burden index according to breast cancer subtype: Validation on a cohort of bc patients treated by neoadjuvant chemotherapy. PLoS One. 2020;15(6 June):1–17.
3. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb;382(9):810–21.
4. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet (London, England). 2011 Aug;378(9793):771–84.
5. Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard J-Y, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol Off J Eur Soc Med Oncol. 2017 Oct;28(10):2340–66.