ASCO 2024: Highlights in Breast Cancer Research

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The theme of this year's American Society of Clinical Oncology (ASCO) Annual Meeting was 'The Art and Science of Cancer Care: From Comfort to Cure', with over 5,000 abstracts presented and over 200 educational sessions. The sun shone again in Chicago, USA, between May 31–June 4 for more than 40,000 attendees, reassuringly demonstrating that the appetite for in-person congresses with all the networking opportunities and other collaborative benefits brings us back to normal following the COVID-19 pandemic.

METASTATIC BREAST CANCER

First DESTINY-Breast06 Results

Perhaps the most anticipated results in the breast cancer track came from the Phase III DESTINY-Breast06 clinical trial.[1] The hall was packed for the early morning session for the late-breaking results of the study of trastuzumab deruxtecan (T-DXd) versus chemotherapy of physician's choice (TPC; capecitabine, paclitaxel, or nab-paclitaxel) as first-line cytotoxic therapy in estrogen receptor (ER)+ve HER2 low or ultra-low breast cancer, after progression on endocrine and targeted therapy in the metastatic setting.[1] Positive results have almost come to be expected from trials of T-DXd, and this was no exception. A total of 886 chemotherapy-naive patients were randomized, with the most common TPC option being capecitabine (60%); 17.5% were considered HER2 'ultra-low' and the median prior lines of therapy was two. Nearly 90% of patients had received prior CDK4/6 inhibitor therapy.

With a median duration of follow-up of 18 months the hazard ratio (HR) for progression-free survival (PFS) of 0.62 (0.51–0.74; p<0.0001), median PFS (mPFS) improved from 8.1 months with TPC to 13.2 months with T-DXd in the HER2 low cohort, with a 5-month improvement representing a similar magnitude of mPFS benefit to the DESTINY-Breast04 trial.[2] Subgroup analysis showed all groups benefited from T-DXd. The overall response rates were impressive, at 57.3% versus 31.2%. Rates of interstitial lung disease were slightly lower than in some prior DESTINY studies, at 11.3% for any grade, of which the majority was Grade 2 (8.3%); however, there were three deaths. No other new safety signals were seen, and rates of clinically significant cardiac impairment were low. Results from the HER2 ultra-low cohort alone were numerically consistent with the overall population. The overall survival (OS) data remains immature, with an HR of 0.81 (0.65–1.00), but 20.1% of patients in the TPC arm subsequently went on to receive T-DXd. These results confirm again the efficacy of T-DXd in this disease biology and will trigger debate on the optimal timing of use of T-DXd in this disease setting.

PostMONARCH Data

In a similar disease subtype, the postMONARCH study results were presented by Kevin Kalinsky.[3] This study randomized 368 patients with estrogen receptor positive (ER+) metastatic breast cancer to fulvestrant plus either abemaciclib or placebo in patients experiencing disease progression on CDK4/6 inhibitors (59% palbociclib, 34% ribociclib, and 8% abemaciclib) and an aromatase inhibitor. Approximately 60% of participants had documented visceral metastatic disease.

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This study met its primary endpoint of improving investigator-assessed PFS, with an HR of 0.73 (0.57–0.95; p=0.02), but the numerical mPFS was only 6.0 versus 5.3 months after 258 events triggered the primary analysis. The subgroup analysis showed a possible higher benefit in the patients who had received first-line palbociclib. However, the confidence intervals were wide for the other treatment groups, and this interaction was not statistically significant. In the exploratory biomarker studies, there were no signals suggesting that any specific molecular (PIK3CA/AKT1/ESR1/PTEN altered) subgroup benefited more from this approach, but the pre-specified subgroup without visceral metastases appeared to benefit most. This study is the first to show a statistically significant benefit of fulvestrant with continuation of CDK4/6 inhibition after progression on a CDK4/6 inhibitor and AI, although the benefits are modest. In discussion of the relevance of this study, single agent fulvestrant, the comparator arm, would only infrequently be considered a guideline-recommended therapeutic strategy in 2024, and is more usually reserved for patients with co-morbidities or another reason to choose a therapy with low risk of toxicity.

Germline Mutation-Associated Metastatic Breast Cancer

Poly-ADP ribose polymerase inhibitors are already firmly established as treatment in several germline *BRCA1/2*-associated solid tumors, but less data is available for the role of these agents in cancers associated with other mutations associated with homologous recombination repair deficiency. The TBCRC-048 study[4] was an investigator-initiated proof-of-principle study of olaparib in 30 patients with somatic *BRCA1/2* mutations (sBRCA) and 24 with germline *PALB2* (gPALB2) mutations. The results of these expansion cohorts were presented by Nadine Tung, reporting that in the gPALB2 cohort, 18 confirmed responses were seen for an impressive overall response rate of 75% (80% CI: 60.2–86.3), and a clinical benefit rate at 18 weeks of 83.3% (90% CI: 65.8–94.1). The median PFS was 9.6 months (90% CI: 8.3–12.4). In the sBRCA cohort, there were 11 confirmed responses for objective response rate of 36.7% (80% CI: 24.8–50). Clinical benefit rate was 53.3% (90% CI: 37–69.2) and median PFS was 5.6 months (90% CI: 3.0–8.3).

Other highlights include patient-reported outcomes from the TROPION-1[5] and INAVO120[6] studies, in addition to the largest study of real-world data comparing first-line CDK4/6 inhibitor therapy, PALMARES-2,[7] in over 1,800 patients across 18 Italian cancer centers. There was also a small Phase II study of patients receiving tucatinib, trastuzumab, and capecitabine for metastatic HER2 positive breast cancer with leptomeningeal disease, which is the first prospective study to show clinically meaningful benefit signals (response, symptom improvement, quality of life, and survival) with systemic therapy in HER2 positive leptomeningeal disease.[8]

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EARLY BREAST CANCER

Predicting the Benefit of Chemotherapy in Pre-menopausal Patients

Moving to early breast cancer (EBC), further prospectively-collected data from the RxPONDER study was presented.[9] This study had already reported that in pre-menopausal females, chemo-endocrine therapy (ET) had an invasive disease-free survival (iDFS) improvement compared to ET alone (HR: 0.60; 95% CI: 0.43–0.83) in patients with Oncotype Dx recurrence scores of <25. This sub-study sought to further refine which measure of pre-menopausal status best predicted benefit from the addition of chemotherapy. Patients with baseline serum anti-Müllerian hormone (AMH) levels ≥10 pg/mL showed significant benefit from chemo-ET compared to patients with AMH levels <10 pg/mL, with an absolute improvement of 7.8% in 5-year iDFS. AMH levels were shown to be a superior tool for selecting patients for chemotherapy benefit than self-reported menopause status, age, or estradiol/luteinizing hormone/follicle-stimulating hormone levels. This simple measure could be used to more accurately select patients for the addition of adjuvant chemotherapy to ET.

Omission of Adjuvant Endocrine Therapy in Estrogen Receptor Low Early Breast Cancer

Although not a new therapy, there remains debate and some equipoise about the role of adjuvant ET in low ER (defined as ER 1–10%) EBC. The US National Cancer Database between 2018–2020 was interrogated for outcomes among an initial population of over 350,000 patients. Of these, 7,956 were identified as having Stage I–III low ER EBC and had received chemotherapy.[10] Adjuvant ET was omitted in 41% of patients, and this was associated with worse overall survival. In an unadjusted analysis, omission of ET

was associated with worse OS (HR: 1.40; 95% CI: 1.19–1.65; p<0.001), with similar effects regardless of PR, HER2, or Ki67 (each interaction test p>0.3). The adjusted hazard after sensitivity analysis of ET omission on OS was 1.24 (95% CI: 1.02–1.51; p=0.03). Although retrospective and non-randomized, given the size of the study, these data strongly suggest that patients with ER-low EBC should be counseled regarding the benefit of adjuvant ET, and practice guidelines should continue to recommend ET in this setting.

Utility of Circulating Tumor DNA in High-Risk ER+ HER2 Negative Early Breast Cancer

Important biomarker data from the monarchE trial[11] of adjuvant abemaciclib in high-risk ER+ HER2 negative EBC was presented, focusing on the serum ct-DNA results. Patient characteristics and treatment effects were similar between the overall trial population and the biomarker cohort, but the biomarker group (n=910) was enriched with more patients with an invasive DFS event (27% versus 18%). At baseline, 92% of patients had no detectable circulating tumor DNA (ctDNA), but 10% subsequently did develop detectable ctDNA during the study period. Conversely, of the 8% of patients who were ctDNA positive at baseline, 59% of these remained persistently elevated, and 41% subsequently had negative results. Despite enrolling a high-risk population, it is notable that overall, the incidence of ctDNA detection was relatively low, with only 17% of patients having detectable ctDNA at any time.

Baseline ctDNA detection was associated with significantly worse outcomes, with the 4-year iDFS rate being 79% in the baseline negative cohort, versus 20% in the baseline positive group (nominal p<0.0001). In patients with baseline negative ctDNA results, only 23% experienced an iDFS event (recurrence), in contrast to 80% in the baseline positive group. The predictive value of the test was improved with serial testing, and those who remained persistently negative on serial testing had the best outcomes, with 14% experiencing recurrence versus those who had baseline positive results that subsequently became negative (n=24; 42% iDFS recurrence rate) and those who became positive on treatment or were persistently positive (93% and 100%, respectively).

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These data suggest that ctDNA detection is highly prognostic of worse outcomes, and although to date there is no data that treatment of molecular relapse improves outcomes, ctDNA clearance may be a useful outcome measure for the evaluation of efficacy and intensification of adjuvant therapy in the future. There are several ongoing clinical trials evaluating early treatment for clinically undetectable molecular relapse, which will be awaited with great interest.

NATALEE Node Negative Cohort Results

Initial results of the NATALEE trial[12] of adjuvant ribociclib in ER+ HER2 negative EBC were presented in December 2023, and an update was presented regarding the node-negative cohort involving 613 patients. A total of 71% had received prior chemotherapy, and the discontinuation rate was 24%. After 38.7 months of follow-up, there was a reported non-significant trend to improvement (iDFS HR: 0.73 [0.412–1.368], with a 3-year iDFS rate of 93.2% versus 90.6%) in favor of the ribociclib arm. Safety data was reassuring in this curative cohort, but longer follow-up will be important to gain a better understanding of the magnitude of benefit in this setting.

Adjuvant PD-L1 Inhibition in Triple Negative Breast Cancer

Other highlights included the A-BRAVE clinical trial,[13] another study investigating a PD-L1 inhibitor, on this occasion, avelumab, in 466 patients with high-risk early triple negative breast cancer. This study did not demonstrate a significant improvement in 3-year DFS (HR: 0.81 [0.61–1.09] in the overall population; 0.80 [0.58–1.10] in the post-neoadjuvant cohort), but intriguingly there was a reported 8.5% overall survival improvement (HR: 0.66 [0.45–0.97]). This study further strengthens the argument that the standard of care should continue to be checkpoint blockade for early triple negative breast cancer starting in the neoadjuvant setting.

CONCLUSION

The above summary represents selected highlights and are only a small snapshot of the breadth of data presented at ASCO 2024, an undoubted key congress for professionals working in the field of breast cancer research and/or care.

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