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Breast cancer panel: summary of 5 key studies

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At the Best of ASCO 2025 meeting hosted by the Portuguese Society of Oncology, five studies were presented in the Breast Cancer panel, all considered relevant to present clinical practice. One focused on early-stage breast cancer (NeoCARHP), while the remaining studies addressed advanced breast cancer (aBC), including two on luminal human epidermal growth factor receptor (HER2)-negative subtypes (inavolisib [INAVO]120 and SERENA-6), one on triple negative breast cancer (ASCENT-04/KEYNOTE-D19), and one on HER2-positive disease (DESTINY-Breast09).

Below is a summary of each of these studies:

De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): a multicenter, open-label, randomized, phase 3 trial

Phase III non-inferiority trial, which aimed to evaluate the efficacy and safety of de-escalating treatment in HER2-positive early breast cancer. The study compared taxane (docetaxel, paclitaxel, or nab-paclitaxel) given every 3 weeks for six cycles, trastuzumab, and pertuzumab (THP), with or without carboplatin, in the neoadjuvant setting. A total of 774 previously untreated patients with stage II-III tumors (77% being stage II) were included. The primary endpoint, pathological complete response (pCR), met the non-inferiority criteria, with a difference of only 1.8% between arms: 64.1% in the arm without carboplatin and 65.9% in the arm with carboplatin. When stratified by hormone receptor (HR) status, the difference in pCR was just 0.4% in HR-negative tumors (77.8 and 78.2% with and without carboplatin, respectively) and 3% in HR-positive tumors (58.8 vs. 55.8%, with and without carboplatin, respectively). The group treated with carboplatin had a higher number of partial and complete responses (364 vs. 351). The rate of adverse events (AEs) was also higher in the carboplatin group, especially hematologic toxicity, with twice as many cases of febrile neutropenia. The overall AE profile was also more common with carboplatin. Despite demonstrating that THP without carboplatin is non-inferior in terms of pCR, this study has limitations, including the use of taxanes every 3 weeks (less effective than weekly paclitaxel) and the fact that only about one-quarter of patients had stage III tumors. Therefore, further follow-up (FUP) is needed for more robust evidence supporting this de-escalation strategy in stage III disease.

INAVO120: phase III trial final overall survival (OS) analysis of first-line (1L) INAVO/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, HR-positive (HR+), HER2-negative (HER2–), endocrine-resistant aBC

The INAVO120 trial evaluated the use of INAVO or PBO, in combination with PALBO and FULV, as 1L

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treatment for advanced, endocrine-resistant breast cancer with *PIK3CA* mutations. Patients with fasting glucose above 126 mg/dL or HbA1c above 6% were excluded. The trial included 325 patients and the primary endpoint, progression-free survival (PFS), had been previously reported, showing a median of 15 months in the INAVO arm versus 7.3 months in the PBO arm (hazard ratio 0.43; 95% confidence interval [CI] 0.32-0.59; p < 0.0001), with a median FUP of 21 months. At ASCO 2025, final OS results were presented: 34 months in the INAVO group versus 27 months in the PBO group (hazard ratio 0.67; 95% CI 0.48-0.94; p = 0.0190), with a median FUP of 34.2 months. Updated PFS was 17.2 months in the triplet group versus 7.3 months in the PBO group (hazard ratio 0.42; 95% CI = 0.32-0.55). The objective response rate and duration of response were significantly higher with the INAVO combination (62.7 vs. 28%; 95% CI 24.5-44.8; p < 0.0001; duration of 19.2 vs. 11.1 months, respectively). INAVO also delayed the time to chemotherapy by approximately 2 years (35.6 vs. 12.6 months; hazard ratio 0.43; 95% CI = 0.30-0.60). Grade 3-4 AEs occurred in 90.7% of patients in the INAVO arm and 84.7% in the PBO arm, with more treatment discontinuations (6.8 vs. 0.6%) and more grade 5 AEs (6 vs. 2) in the INAVO group. Common toxicities of INAVO included hyperglycemia, stomatitis, and dry eye. Notably, few control-arm patients received PI3K inhibitors after progression, which may have impacted OS results. Other limitations include the exclusive use of PALBO rather than other CDK4/6 inhibitors, such as ribociclib or abemaciclib, and the low proportion of patients who had received adjuvant CDK4/6 inhibitors, which may limit the study's applicability to present clinical practice.

Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent ESR1 mutations during 1L endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2–aBC: phase 3, double-blind ctDNA-guided SERENA-6 trial

The SERENA-6 trial investigated whether switching from an aromatase inhibitor to camizestrant upon the emergence of ESR1 mutations (detected in circulating tumor DNA) and before progression of disease, would improve PFS in patients with HR-positive HER2-negative metastatic breast cancer receiving 1L endocrine therapy plus CDK4/6 inhibitors. A total of 315 patients were randomized. All were on a combination of aromatase inhibitor and CDK4/6 inhibitor for at least 6 months, with over 70% on PALBO—a choice that may not reflect present clinical practice. Median PFS was 16 months in the camizestrant arm versus 9.2 months in the aromatase inhibitor arm (hazard ratio 0.44; 95% CI 0.31-0.60; p < 0.00001), with this benefit observed across nearly all subgroups. Camizestrant also significantly extended time to quality-of-life deterioration (23 vs. 6.4 months; hazard ratio 0.53; 95% CI 0.33-0.82, p < 0.001). Notably 10% more patients in the experimental arm received chemotherapy after disease progression (45.6 vs. 22.9%) when compared to the control arm. Camizestrant was associated with more grade ≥ 3 AEs (60 vs. 46%), but not with higher rates of treatment discontinuation (1.3 vs. 1.9%). A typical side effect of camizestrant, photopsia, did not impact daily activities and it didn't impair vision or eye structure. Since cross-over was not permitted in the trial, it remains unclear whether switching therapy upon ESR1 mutation detection leads to better outcomes than switching only at disease progression (i.e., using camizestrant as a second-line therapy).

Sacituzumab govitecan (SG) + pembrolizumab (pembro) versus chemotherapy (chemo) + pembro in previously untreated PD-L1-positive advanced triple-negative breast cancer (TNBC): primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study

The *ASCENT-04/KEYNOTE-D19* study was a phase III trial evaluating SG plus pembrolizumab versus chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine with carboplatin) plus pembrolizumab in 1L treatment of PD-L1-positive (CPS ≥ 10; 22C3 assay) advanced TNBC. Patients needed to have completed prior curative treatment at least 6 months earlier, and prior use of anti-PD-(L)1 agents was allowed. Of the 443 randomized patients, most had visceral disease, 34% in each arm had *de novo* metastatic disease, and 48% had a disease-free interval of over 12 months; 18% had recurrence within 6-12 months. Only 20 patients had previously received an anti-PD-(L)1 therapy. With a median FUP of 14 months, the primary endpoint of PFS was 11.2 months in the SG + pembrolizumab arm versus 7.8 months in the chemotherapy + pembrolizumab arm (hazard ratio 0.65; 95% CI 0.51-0.84; p = 0.0009), with benefits observed across nearly all subgroups. OS data remain immature. Notably, 81% of

patients in the control arm who received further treatment after discontinuation were treated with SG. The duration of response was substantially longer in the SG+pembrolizumab arm (16.5 vs. 9.2 months). Diarrhea, nausea, and vomiting were more frequent with SG + pembrolizumab, but the incidence of grade ≥ 3 AEs was similar between arms. The combination of SG and pembrolizumab did not lead to more treatment discontinuations or dose reductions compared to chemotherapy with pembrolizumab.

Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) versus taxane + trastuzumab + pertuzumab (THP) for 1L treatment of patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC): interim results from DESTINY-Breast09:

Finally, the DESTINY-Breast09 trial evaluated trastuzumab deruxtecan (T-DXd) with pertuzumab versus taxane plus trastuzumab and pertuzumab (THP) as 1L treatment for HER2-positive advanced or metastatic breast cancer. A total of 1157 patients were randomized. Eligible participants had to have completed curative-intent treatment at least 6 months prior, and one prior line of hormone therapy for metastatic disease was allowed. Although the study had three arms (T-DXd with PBO, T-DXd with pertuzumab, and THP), only the latter two were presented in this analysis. T-DXd was administered until disease progression, while the taxane was given for at least six cycles. In the event of T-DXd discontinuation due to AEs, patients could receive trastuzumab (with pertuzumab or with PBO) depending on their original assignment. Endocrine therapy was permitted in HR-positive tumors after six T-DXd cycles or upon taxane discontinuation, but it was used in only 13.5% of patients in the T-DXd arm and 38.3% in the THP arm. Anti-HER2 therapy usage in early disease was relatively low: 56.6% had received trastuzumab, 14.3% pertuzumab, and 1.8% T-DM1. With a median FUP of 29.2 months, PFS was significantly improved in the T-DXd plus pertuzumab arm (40.7 vs. 26.9 months; hazard ratio 0.56; 95% CI 0.44-0.71; $p < 0.00001$), with benefit observed across nearly all subgroups. The rate of complete responses nearly doubled (15.1 vs. 8.5%), and the median duration of response exceeded 3 years. In the control arm, 10% later received T-DXd and 12% received T-DM1. Second PFS2 showed a hazard ratio of 0.60. OS data are still immature. Grade 3-4 AE rates were similar between arms and T-DXd-related pneumonitis occurred in 12% of patients, mostly grade 1-2, with two grade 5 events.

Clinicians are left with unanswered questions regarding optimal treatment duration, sequencing, and patient selection, as it remains unclear who truly benefits from this strategy versus those who may have durable responses to the present standard of care without the added potential toxicities of T-DXd.

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