SABCS 2024 Congress Report

Critical Coverage of Important Clinical Trials from SABCS® 2024

The San Antonio Breast Cancer Symposium (SABCS®) 2024 has showcased significant advancements in breast cancer research. This report provides a critical overview of key clinical trials presented at the conference, highlighting their potential impact on patient care.

Results of the Phase 3 EMBER-3 Trial Assessing the Efficacy of Imlunestrant for the Treatment of Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Advanced Breast Cancer (ABC)

Background

Hormone receptor-positive (HR+) breast cancer is typically treated with endocrine therapy (ET) as a first-line approach. For patients with ER+, HER2- ABC, the use of ER antagonists and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are essential. Suppression of ER and CDK4/6 using their antagonists is crucial for improving treatment outcomes in patients with ER+, HER2- advanced breast cancer. However, over time, patients often develop estrogen receptor mutations (ESR mutations) that reduce the effectiveness of endocrine therapy. Selective estrogen receptor degraders (SERDs) are innovative new drugs that target ESR mutations and restore the efficacy of ET.

Current treatment landscape

In the current treatment landscape, fulvestrant is the only approved SERD available. It can be used both as monotherapy and in combination with other therapies. However, despite its widespread use, fulvestrant has limitations. Its efficacy is limited in some patients, particularly those with ESR1 mutations (ESR1m). Additionally, since fulvestrant requires intramuscular injection, administration can be painful and burdensome for patients. To overcome these limitations, new oral SERDs are being developed. One such oral SERD called elacestrant has recently been approved for treating patients with ESR1m. Imlunestrant, a next-generation oral SERD, has shown significant promise in recent studies. In trials, imlunestrant has demonstrated potent brain penetration and as a pure ER antagonist, it is capable of continuous ER inhibition.

The EMBER-3 trial

The EMBER-3 trial was conducted to evaluate the efficacy of imlunestrant as monotherapy and in combination with abemaciclib in patients with ER+, HER2- ABC who had previously been treated with ET. This randomized trial included 874 participants divided into three groups in a 1:1:1 ratio: one group received imlunestrant as monotherapy, another received standard-of-care ET (either fulvestrant or exemestane), and the third group received a combination of imlunestrant and abemaciclib. The primary endpoint of the study was progression-free survival (PFS) while secondary endpoints included overall survival (OS), PFS assessed by blinded independent central review (BICR), objective response rate (ORR), and safety.

Key findings

Key findings from the EMBER-3 trial revealed that in the ESR1-mutant population, patients treated with imlunestrant monotherapy achieved a median PFS of 5.5 months, compared to 3.8 months for those receiving standard-of-care ET. This represents a 40% reduction in the odds of progression or death in the ESR1-mutant group. Further analysis showed that imlunestrant monotherapy demonstrated superior efficacy in specific subpopulations, including patients with visceral disease, those who had previously received CDK4/6 inhibitors, and patients with either wild-type or mutant phosphoinositide 3-kinase (PI3K) status. In the overall population, imlunestrant showed comparable efficacy to standard-of-care ET, with a median PFS of 5.6 months versus 5.5 months, respectively. These findings suggest that imlunestrant is a promising therapeutic option for patients with ER+, HER2- ABC, particularly those with ESR1 mutations.

Longer-Term Follow-Up of OlympiA Phase 3 for the Assessment of Adjuvant Olaparib After (Neo)Adjuvant Chemotherapy in Patients with Germline BRCA1/BRCA2 Pathogenic Variants and High-Risk HER2-Negative Primary Breast Cancer

Introduction

Patients with high-risk, HER2- primary breast cancer face a significant risk of recurrence despite receiving standard treatments, including the latest neoadjuvant chemotherapy. The risk of recurrence is even greater for patients with genetic predispositions — notably germline pathogenic variants (gBRCApv) in *BRCA1* and *BRCA2* genes — which impair the DNA damage repair mechanism. Novel targeted therapies such as poly ADP-ribose polymerase (PARP) inhibitors have emerged as a promising approach for improving treatment outcomes among high-risk patients, particularly those with BRCA1/BRCA2-related breast cancers.

Rationale for the OlympiA Study

BRCA1 and *BRCA2* proteins help repair double-strand DNA breaks, while the PARP1) enzyme repairs single-strand DNA breaks. PARP inhibitors block the ability of PARP1 to repair single-stranded breaks. When they persist, single-stranded breaks can become double-stranded breaks during DNA replication. While double stranded breaks normally get repaired by a mechanism involving *BRCA1* and *BRCA2*, this does not happen in individuals with *BRCA1/2* mutations. Therefore, genomic instability causes cell death in the mutant cells. The OlympiA study was designed based on this principle of synthetic lethality, which occurs when the inhibition of PARP1 becomes lethal in the context of a loss of function in BRCA1 and BRCA2 proteins.

Additionally, patients with gBRCApv in *BRCA1* and *BRCA2* mutation are predisposed to both ER+ breast cancer and triple-negative breast cancer (TNBC). This genetic vulnerability underscores the need for targeted interventions in these high-risk populations.

Study design

The OlympiA study evaluated the efficacy of olaparib, a PARP inhibitor, as adjuvant therapy for patients with gBRCApv and high-risk early HER2-negative primary breast cancer. The study included two patient groups: those who had received prior neoadjuvant therapy and those who were undergoing adjuvant treatment. All participants had gBRCA1 or gBRCA2 pathogenic variants and high-risk HER2-negative primary breast cancer. Patients were randomized in a 1:1 ratio to receive either olaparib or a placebo, allowing for a direct comparison of outcomes.

Key findings

Pre-specified analyses

Findings from pre-specified analyses demonstrated that olaparib significantly improved invasive disease-free survival (IDFS) and distant disease-free survival (DDFS) at the first interim analysis. At the second interim analysis, olaparib also showed a significant improvement in OS, reinforcing its potential benefit for this high-risk population.

Third pre-specified analysis

The third pre-specified analysis was conducted 10 years after the enrolment of the first patient, with a median follow-up of 6.1 years. At the time of this analysis, the 6-year IDFS rate showed an improvement of 9.4% for patients receiving olaparib compared to the placebo group. The difference in IDFS was consistent across various subgroups, including those who had received prior chemotherapy, prior platinum-based therapy, and across different hormone receptor (HR) statuses and BRCA statuses (*BRCA1, BRCA2*, or both). Additionally, IDFS analysis revealed an overall improvement of 7.8%, with consistent benefits observed across all subgroups. OS data also demonstrated significant improvements, further supporting the efficacy of olaparib.

Safety profile

The safety profile of olaparib was favorable, addressing previous concerns about potential adverse events. Specifically, cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) were low, with four events reported in the treatment arm compared to six in the placebo arm. Other safety concerns, such as pneumonitis and the occurrence of new primary malignancies, were also carefully monitored and found to be manageable.

Conclusion

Overall, the results from this analysis strongly support the use of adjuvant olaparib as the standard of care for patients with gBRCApv and high-risk HER2-negative primary breast cancer. The consistent benefits observed across various subgroups and the favorable safety profile reinforce its role as an effective therapeutic option in this high-risk population.

Additional Analysis of Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) vs Physician's Choice of Chemotherapy (TPC) from DESTINY-Breast06

Background

Hormone receptor–positive, HER2–low or HER2–ultralow metastatic breast cancer (mBC) presents significant challenges. This type of cancer is especially hard to treat after disease progression following endocrine-based therapies. To address this clinical need, the DESTINY-Breast06 phase 3 study was conducted to evaluate the efficacy and safety of T-DXd compared to TPC in patients with mBC. The study included patients with HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/*in situ* hybridization-negative) or HER2-ultralow (IHC 0 with membrane staining) mBC. Eligible patients were those who had progressed after at least one line of endocrine-based therapy and had not yet received chemotherapy for mBC.

Study design

The study enrolled 866 patients who were randomized in a 1:1 ratio to receive either T-DXd (5.4 mg/kg intravenously every 3 weeks) or TPC, which included capecitabine, nab-paclitaxel, or paclitaxel. To participate, patients were required to have received at least two prior lines of endocrine-based therapy for mBC or one prior line if progression occurred within 24 months of adjuvant ET or within 6 months of first-line (1L) ET combined with a CDK4/6i. Patients were stratified based on time to progression and endocrine resistance status. Key outcomes measured included PFS, confirmed objective response rate (ORR), duration of response (DOR), and safety.

Key findings

Efficacy outcomes

T-DXd significantly improved PFS compared to TPC, with a median PFS of 13.2 months versus 8.1 months, respectively. This benefit in PFS was consistent across all time to progression (TTP) subgroups, including those with rapid progression (<6 months), intermediate progression (6–12 months), and longer progression intervals (>12 months). Additionally, ORR and DOR were superior with T-DXd across all TTP subgroups. Efficacy was consistent regardless of whether patients had primary or secondary endocrine resistance, demonstrating the broad applicability of T-DXd in this patient population.

Safety outcomes

The incidence of treatment-emergent adverse events of grade 3 and above was comparable between T-DXd and TPC across each TTP subgroup. Importantly, the safety profile of T-DXd was consistent with the overall study population and was considered manageable.

Conclusion

T-DXd demonstrated a statistically significant and clinically meaningful benefit in PFS, ORR, and DOR compared to TPC, particularly in patients with rapid progression (<6 months TTP). These results highlight the potential of T-DXd as an effective early-line treatment option after at least one line of endocrine-based therapy in patients with hormone receptor–positive, HER2-low, or HER2-ultralow mBC.

Results of the Phase 3 PATINA Trial Assessing the Efficacy of Palbociclib for the Treatment of HR+/HER2+ mBC

Background

HR+/HER2+ mBC presents significant treatment challenges, especially after disease progression following induction chemotherapy and anti-HER2 therapy. To address this clinical need, the Phase III PATINA trial was conducted to evaluate the efficacy and safety of adding palbociclib to anti-HER2 therapy and ET in patients with HR+/HER2+ mBC.

Study design

The PATINA trial enrolled 518 patients who had completed 6-8 cycles of induction chemotherapy plus trastuzumab plus pertuzumab (HP) or trastuzumab (H) without evidence of progression. Participants were randomized to receive either palbociclib (125 mg orally daily for 21 days followed by 7 days off) in combination with anti-HER2 therapy (H or HP) plus ET or anti-HER2

therapy plus ET alone. ET options included aromatase inhibitor (AI) or fulvestrant, with ovarian suppression required for premenopausal patients. The primary endpoint of the study was PFS, while secondary endpoints included OS, ORR, and safety.

Key findings

The addition of palbociclib significantly improved PFS compared to the control arm. Median PFS was 44.3 months in the palbociclib arm versus 29.1 months in the control arm, with a hazard ratio (HR) of 0.74. Confirmed ORR was 29.2% in the palbociclib arm compared to 22.2% in the control arm. The clinical benefit rate (CBR) was 89.3% in the palbociclib arm compared to 81.3% in the control arm.

Safety outcomes

The most frequent adverse event in the palbociclib arm was grade 3 neutropenia. Additionally, grades 2 and 3 fatigue, stomatitis, and diarrhea occurred more frequently in the palbociclib arm. The incidence of grade ≥4 adverse events was similar across both study arms. No treatment-related deaths were reported.

Conclusion

The PATINA Phase III trial demonstrated a statistically significant and clinically meaningful improvement in PFS with palbociclib added to anti-HER2 therapy plus ET, with a manageable toxicity profile. This combination may represent a new standard of care for patients with HR+ HER2+ advanced breast cancer.

Findings from the SOLTI VALENTINE Study Assessing HER3-DXd in High-Risk HR+/HER2- Early Breast Cancer

Background

Despite the efficacy of chemotherapy and ET in treating high-risk HR+/HER2- early breast cancer (EBC), recurrence rates remain significant, highlighting the need for more effective treatment options. HER3-DXd, a HER3-directed antibody-drug conjugate, has shown promise in improving treatment success across multiple breast cancer subtypes. Previous studies have demonstrated its ability to increase CelTIL (tumor-infiltrating lymphocytes) and improve clinical response in HR+/HER2- EBC, making it a potential targeted therapy for this high-risk population.

Study design

The SOLTI VALENTINE trial was designed to evaluate the efficacy and safety of HER3-DXd, with or without letrozole (LET), compared to standard chemotherapy in patients with operable stage II-III high-risk HR+/HER2- EBC. This randomized open-label neoadjuvant study aimed to explore whether HER3-DXd could provide comparable efficacy with a more favorable safety profile than traditional chemotherapy. In the study, patients were randomized into three treatment arms: Arm A received HER3-DXd monotherapy, Arm B received HER3-DXd in combination with LET, and Arm C received standard chemotherapy. The primary endpoint of the study was the pathological complete response (pCR) rate at surgery. The

secondary endpoints included residual cancer burden (RCB), overall response rate, changes in CelTIL score, safety, invasive DFS , and OS.

Key findings

Efficacy outcomes

The efficacy outcomes revealed that pCR rates were low and comparable across all three arms: 4.0% in Arm A, 2.1% in Arm B, and 4.2% in Arm C. However, RCB0/1rates favored Arm C (30.4%) over Arms A (18.4%) and B (12.5%). Despite these findings, the overall response rate was high across all groups, with 72.0% in Arm A, 81.3% in Arm B, and 70.8% in Arm C. Notably, the HER3-DXd arms demonstrated significant increases in CelTIL scores from baseline. Additionally, HER3-DXd led to reductions in Ki-67 (a marker of cell proliferation) and desirable shifts in the Prediction Analysis of Microarray 50 (PAM50) risk of recurrence profile from high/medium to low and from luminal B to luminal A/normal-like subtypes. These results indicate a favorable impact on tumor biology and potential long-term benefits of HER3-DXd.

Safety outcomes

In terms of safety, HER3-DXd demonstrated a more favorable profile compared to standard chemotherapy. The incidence of treatment-emergent adverse events of grade 3 or above was lower in the HER3-DXd arms (18.0% in Arm A, 16.7% in Arm B) compared to Arm C (54.2%). The most common treatment-emergent adverse events in the HER3-DXd arms were nausea, alopecia, fatigue, and diarrhea, with side effects generally more frequent when combined with LET. Importantly, the safety outcomes suggest that HER3-DXd is better tolerated than conventional chemotherapy, potentially improving the quality of life for patients undergoing treatment.

Conclusion

In conclusion, HER3-DXd, with or without LET, demonstrated similar pCR rates to chemotherapy but with a more favorable safety profile. The significant correlations between CelTIL changes and radiological responses suggest that HER3-DXd has unique immunomodulatory effects, which may contribute to its therapeutic efficacy. These findings underscore the potential of HER3-DXd as a targeted treatment strategy for high-risk HR+/HER2-negative early breast cancer, warranting further investigation in future clinical trials.

Exploratory Biomarker Analysis in the Phase 3 KEYNOTE-522 Trial

Introduction

The KEYNOTE-522 trial investigated the effectiveness of neoadjuvant pembrolizumab (pembro) combined with chemotherapy (chemo), followed by adjuvant pembro, in patients with high-risk, early TNBC. This approach was evaluated to determine whether the addition of pembrolizumab could improve outcomes compared to chemotherapy alone. Results from the trial demonstrated significant improvements in pCR, event-free survival (EFS), and OS with the combination of pembro and chemo. To further understand the underlying mechanisms driving these benefits, an exploratory biomarker analysis was conducted to assess the association of tumor mutational burden (TMB), T-cell–inflamed 18-gene expression profile (TcellinfGEP), and non-TcellinfGEP signatures with pCR and EFS.

Study design

Eligible patients included those with newly diagnosed, high-risk, early TNBC who provided pretreatment tumor samples. The study utilized whole-exome sequencing (WES) and RNA sequencing (RNAseq) to evaluate relevant biomarkers. The primary objective of the biomarker analysis was to determine the associations, if any, between TMB, TcellinfGEP, and non-TcellinfGEP signatures with pCR and EFS. These associations were assessed using logistic regression and Cox proportional hazards models. Additionally, secondary objectives included evaluating RNAseq-based molecular subtypes, BRCA/HRD status, HER2 gene expression, and PTEN loss signature.

Key findings

The key findings from the analysis revealed several important associations. First, TcellinfGEP was positively associated with both pCR and EFS in both treatment arms, highlighting its potential as a consistent prognostic biomarker in TNBC. This suggests that tumors with higher T-cell–inflamed gene expression are more likely to respond to therapy, resulting in improved survival outcomes. The study also found that TMB was associated with better pCR and EFS in the pembro + chemo arm but showed no association in the placebo + chemo arm. This finding suggests that TMB may be prognostic biomarker when the treatment combines the use of pembro with chemotherapy.

The study also found that non-TcellinfGEP signatures, such as proliferation and glycolysis were associated with pCR but not EFS. This indicates that tumors with higher proliferative activity and glycolytic metabolism may initially respond to treatment but do not necessarily lead to long-term survival benefits.

Further evaluation of secondary biomarkers showed positive associations between PTEN loss signature, BRCA/HRD status, and pCR in both treatment arms, indicating that these genetic alterations may influence treatment response. In contrast, HER2 gene expression showed no association with pCR or EFS after adjusting for TcellinfGEP, suggesting that HER2 expression alone is not a reliable biomarker for predicting outcomes in TNBC treated with immunotherapy and chemotherapy.

Conclusion

In conclusion, the exploratory biomarker analysis from the KEYNOTE-522 trial identified TcellinfGEP as a consistent prognostic biomarker for pCR and EFS across both treatment arms, emphasizing its potential role in guiding treatment decisions for TNBC. TMB was found to be predictive of improved EFS specifically in patients receiving pembro + chemo, supporting its use as a predictive biomarker for immunotherapy benefit. Overall, pembro + chemo demonstrated efficacy benefits over chemo alone, regardless of biomarker-defined subgroups.