Advances in Treatment for Oestrogen Receptor-Positive Breast Cancer

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THIS YEAR the European Society for Medical Oncology (ESMO) Congress was hosted in Barcelona, Spain from 13th–17th September. Among the many impactful sessions, a symposium titled 'Incorporating Novel Treatment Insights for Estrogen Receptor-Positive (ER+) Early Breast Cancer Patients' garnered particular attention. Featuring presentations by Stephen Johnston, Royal Marsden, London, UK; Nadia Harbeck, Ludwig Maximilian University of Munich, Germany; and Etienne Brain, Institut Curie in Paris & Saint-Cloud, France, the session provided a comprehensive overview of current advances in ER+ early breast cancer treatment. The speakers explored adjuvant endocrine therapies, prognostic and predictive factors for clinical decision-making, and the unique challenges of optimising treatment for older patients, underscoring the evolving landscape of personalised care in ER+ early breast cancer.

SPEAKER 1: STEPHEN JOHNSTON

Johnston began by describing the benefits of adjuvant endocrine therapies in postmenopausal ER+ early breast cancer, paying tribute to the late Virgil Craig Jordan widely known as the father of tamoxifen. Adjuvant endocrine therapy, particularly tamoxifen, has shown significant benefits, reducing the risk of recurrence by nearly 40%, while aromatase inhibitors offer a smaller additional gain.[1] Cyclin-dependent kinase (CDK) 4/6 inhibitors, crucial in managing hormone-resistant cancer, have been described as game-changers in advanced disease, but early breast cancer trials, especially with palbociclib, have yielded mixed results while managing toxicity remains a key challenge in treatment.

> **CDK 4/6 inhibitors, crucial in managing hormone-resistant cancer, have been described as game-changers in advanced disease**

Recent advancements in breast cancer treatment are highlighted by two pivotal clinical trials: monarchE[2] and NATALEE.[3] These studies focus on high-risk node-positive populations and a broader group of Stage II and III breast cancer patients, respectively. Both trials have shown promising results, demonstrating the efficacy of newer therapies that could significantly reduce recurrence rates.

monarchE Trial

The monarchE trial encompasses two cohorts. The first includes patients with high clinical risk features, such as having four or more positive nodes or large tumour sizes, while the second, added at the request of regulatory agencies, examines smaller tumours with one to three nodes that possess a high Ki-67 proliferation index.

Five-year data presented by Harbeck at ESMO 2023, indicated that, despite 95% of high-risk patients undergoing chemotherapy, one in four relapses in the control arm.[4] However, the addition of abemaciclib reduces this recurrence risk by

approximately 32%, significantly benefitting premenopausal women and patients with neoadjuvant therapy and large tumours. While distant relapse-free survival rates also reflect a positive trend, Johnston advised that it remains too early to draw meaningful conclusions from the overall survival data.

NATALEE Trial

NATALEE was designed as an open-label Phase III trial that includes a broader patient demographic, administering a 400 mg dose over 3 years. It also encompasses node-negative patients, particularly those classified as Stage IIa with either Grade III tumours or high-risk Grade II tumours based on Ki-67 or genomic features. The initial findings have indicated a 25% reduction in the risk of invasive disease-free survival and a 3.3% absolute difference at 27 months of follow-up.

Subgroup analyses reveal benefits across various categories, including node-negative patients, although the small sample size results in confidence intervals that cross one, indicating uncertainty in these findings.

Biomarker Research

Biomarker studies in monarchE have revealed that Ki-67 is a strong prognostic factor but does not predict treatment response. Furthermore, a more extensive exploratory biomarker analysis involving whole exome sequencing and RNA sequencing has identified intrinsic subtypes, Oncotype recurrence scores, and mutation profiles. Johnston noted that patients with a high Oncotype recurrence score showed no significant difference in benefit from abemaciclib treatment compared to those with a low score. This analysis underscores the complexity of treatment decision-making, as traditional pathology parameters may not reliably predict patient outcomes.

Additionally, circulating tumour DNA (ctDNA) detection has emerged as a promising prognostic marker, as patients with positive ctDNA after chemotherapy and before study enrolment have poorer outcomes, whereas those with negative ctDNA exhibit better prognosis. Monitoring ctDNA dynamics during treatment may further guide therapeutic decisions and identify patients who are not benefiting from their current regimen.

As Johnston concluded his presentation, he emphasised how vital it is to reflect on the significant developments in breast cancer treatment, particularly regarding the ongoing the ADAPTcycle trial.[5] This trial is exploring a preoperative selection strategy that integrates dynamic Ki-67 response to therapy and baseline Oncotype recurrence scores. The trial stratifies patients into three intermediate risk groups based on biological markers, enabling a randomisation between CDK inhibitor combined with endocrine therapy versus chemotherapy in the adjuvant setting. It is anticipated that this will provide crucial insights into whether patients with intermediate risk can achieve comparable outcomes with CDK inhibitor-based therapy instead of traditional chemotherapy.

Furthermore, the GEICAM group is conducting the CARABELA trial, which compares neoadjuvant treatment with letrozole and abemaciclib against chemotherapy in high and intermediate risk patients is providing head-to-head comparisons in early breast cancer treatments, which echo similar efforts seen in metastatic settings.[6]

SPEAKER 2: NADIA HARBECK

Harbeck provided a comprehensive overview of treatment indications for ER+, HER2- early breast cancer, highlighting the significance of biomarkers, prognostic factors, and predictive factors, especially considering the recently published ESMO early breast cancer guidelines.[7] Unlike HER2+and triple-negative breast cancers, which have more defined treatment pathways, hormone receptor-positive cases present diverse therapeutic options, and this variability necessitates careful consideration in determining treatment indications. Emphasising the critical role of validated biomarkers in guiding treatment decisions, Harbeck quoted former ASCO President Den Hayes, University of Michigan, USA when he stated: "A bad biomarker is as bad for a patient as a bad drug." She underscored the risks associated with unvalidated biomarkers, which could either withhold effective treatments or lead to unnecessary therapies. Understanding a patient's risk profile, whether low-risk (luminal A-like) or high-risk (luminal B-like), is essential for informing therapy choices.

Assessing the Need for Chemotherapy

One of the most pressing questions from patients is whether chemotherapy is necessary in addition to endocrine therapy. For patients with 0–3 positive lymph nodes, gene expression assays can assist in making this determination. Harbeck noted that only two assays, TAILORx and the recently reported results, have been prospectively validated in clinical settings.[8] The TAILORx trial found that patients with intermediate-risk recurrence scores (11–25) do not benefit from chemotherapy, while premenopausal patients show some uncertainty, with marginal benefits for recurrence scores of 16–20 and clearer benefits for scores of 21–25. This highlights the need for careful evaluation of cutoff scores when utilising genomic testing.

Insights From Recent Clinical Trials

Harbeck discussed findings from studies such as MINDACT[9] and RxPONDER,[10] which suggested that postmenopausal women with low genomic risk scores and high clinical risk do not require chemotherapy. However, the data for younger women remain ambiguous, with indications of a potential 5% benefit from chemotherapy. She expressed concern over the ASCO committee's decision not to recommend gene expression assays for node-positive young women, arguing that many of these patients might not need chemotherapy.

Furthermore, she highlighted that recent data from the RxPONDER trial revealed the influence of ovarian function on determining chemotherapy necessity for younger women. Specifically, patients with low AMH levels showed no significant differences in outcomes between chemotherapy and endocrine therapy, whereas those with preserved ovarian function appeared to benefit from chemotherapy.

Harbeck reiterated the complexity of treatment decisions for ER+ and HER2-

early breast cancer and concluded her presentation by underscoring the importance of addressing the specific needs of younger patients and the necessity for further investigation into treatment strategies to ensure appropriate care without unnecessary interventions.

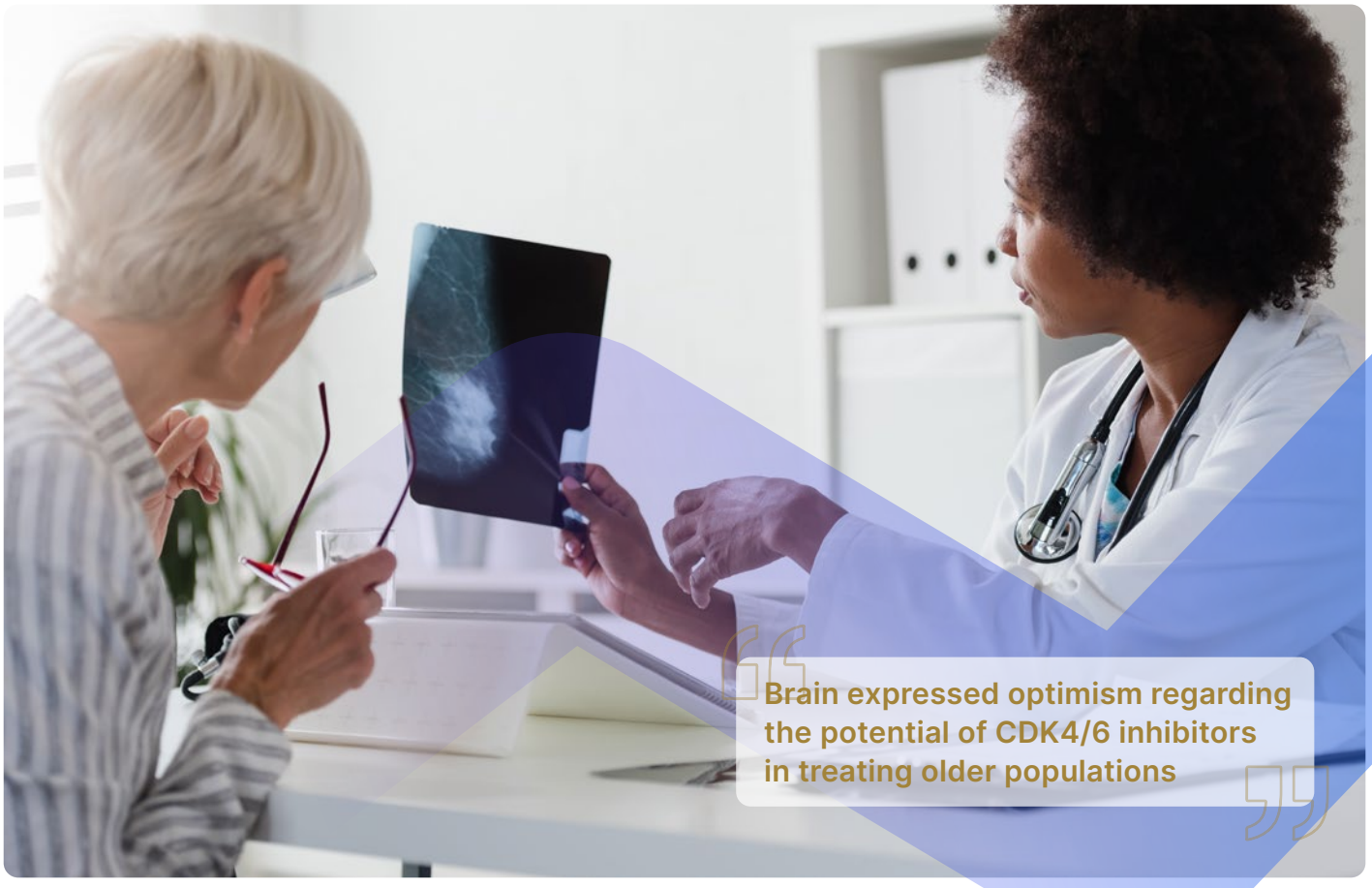
SPEAKER 3: ETIENNE BRAIN

The third, and final, speaker, Brain, addressed the challenges and considerations in optimising treatment for older patients diagnosed with ER+ early breast cancer. His discussion highlighted the unique needs of this patient demographic, emphasising the importance of tailoring treatment strategies to account for the complexities associated with ageing.

Future Directions: Combination Therapies and New Strategies

In light of these challenges, Brain expressed optimism regarding the potential of CDK4/6 inhibitors in treating older populations. He referenced ongoing trials that, despite mixed results, indicate that the benefits observed with these agents do not significantly differ across age groups. However, he cautioned that older patients often experience higher rates of treatment discontinuation and dose adjustments, which could influence the overall effectiveness of these therapies. Furthermore, Brain pointed out that efforts are underway to explore chemo-free regimens combining aromatase inhibitors with CDK4/6 inhibitors as a viable alternative for older patients. Such regimens aim to mitigate the toxicities associated with chemotherapy while maintaining treatment efficacy.

Finally, Brain addressed the emerging interest in neoadjuvant strategies as a way to better assess treatment efficacy and safety before surgical interventions, stressing that patient-centred care must take precedence and acknowledging the unique values older patients prioritise, such as safety, quality of life, and active participation in their treatment decisions.



ER+ Breast Cancer in Older Women

Brain noted a critical misconception in cancer statistics: it is often stated that one in eight women will develop breast cancer in their lifetime. While there is a preconceived notion that this regards young womens' risk, he clarified that this statistic is based on a model where all women live to the age of 71 years. This statistic underscores the significance of older populations in breast cancer care, as the majority of cases diagnosed in women over 65 years are ER+.

Despite the prevalence of ER+ cases in older women, Brain pointed out a notable lack of specific data regarding this population in clinical trials. He lamented that while older patients often represent a significant portion of breast cancer cases, they are underrepresented in clinical research. For instance, only about 5% of participants in registration trials for CDK4/6 inhibitors were aged 75 years and older, indicating a clear gap in data that could inform treatment guidelines.

Brain emphasised the importance of understanding competing risks for older patients. Many individuals over the age of 70 years do not die from cancer but rather from other health conditions, highlighting the necessity for an integrated approach to treatment. He argued in favour of the integration of geriatric assessments in the treatment decision-making process, noting that such evaluations can significantly influence management strategies.

Brain stated that integrating geriatric assessments can lead to treatment modifications in up to 40% of cases, often resulting in de-escalation of treatment and his presentation as a whole underscored the need for a more nuanced understanding of treatment strategies for older patients with ER+ early breast cancer. He advocated for a tailored approach that takes into account the complexities of ageing, emphasising the importance of geriatric assessments and individualised treatment plans.

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