REVIEW

Recent Progress in Breast Cancer Treatment

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Keywords: breast cancer, immunotherapy, antibody-drug conjugates, patient education

https://doi.org/10.36000/HBT.OH.2024.19.137

healthbook TIMES Oncology Hematology

Vol. 19, Issue 1, 2024

Breast cancer remains a significant global health concern and the leading cancer type amongst women worldwide. While significant progress has been made in the field of breast cancer therapy, there are still many unmet goals that require attention and innovation. Current breast cancer research aims to develop more precise and effective tailored treatments to improve cure rates in patients with early disease and prolong survival among patients with metastatic disease while maintaining quality of life and minimizing treatment-related side effects. Additionally, there is a growing need to optimize patient selection criteria and provide comprehensive patient education during therapy. The European Society for Medical Oncology (ESMO) Congress 2023, held in Madrid, Spain, from October 20 to 24, featured several important clinical trials evaluating novel therapeutic strategies for various subtypes of breast cancer. This review article summarizes the data from selected studies presented at the ESMO 2023 Congress, along with the valuable perspectives shared by key opinion leaders in the field of breast cancer during the ESMO 2023 Breaking Science in Breast Cancer Video Series.

PEER REVIEWED ARTICLE

Peer reviewers:
Dr Anna Durigova (Hospital Riviera Chablais Rennaz, Switzerland);
Dr Dario Trapani (European Institute of Oncology Milan, Italy)

Submitted on Feburary 9, 2024; accepted on March 19, 2024; published online on March 26, 2024.

Introduction

Breast cancer remains the most common cancer among women worldwide and the second leading cause of cancer-related deaths in women.[1] The heterogeneous nature of this disease, which encompasses numerous subtypes,

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each requiring individual treatment approaches, makes breast cancer a challenging disease to treat.[1] Current breast cancer research aims to develop more precise and effective tailored treatments to improve cure rates in patients with early disease and prolong survival among patients with metastatic disease while maintaining quality of life and minimizing treatment-related side effects.[1-5] In recent years, immunotherapies and antibody-drug conjugates (ADCs) have shown some promise in treating patients across various breast cancer subtypes/settings. This article summarizes data from the most relevant clinical trials presented at the ESMO 2023 Congress and offers insights from leading experts in the field of breast cancer who discussed the clinical significance of the data during the Breaking Science in Breast Cancer Video Series at ESMO 2023.

Early-stage high-risk ER+, HER2- breast cancer

KEYNOTE-756 (NCT03725059) is a phase III randomized study of neoadjuvant pembrolizumab or placebo plus chemotherapy, followed by adjuvant immune checkpoint inhibitor (ICI) pembrolizumab or placebo plus endocrine therapy (ET) for early-stage high-risk estrogen receptor-positive (ER+)/human epidermal growth factor receptor-negative (HER2-) early breast cancer (grade 3 T1c–T2 N1–2 or T3–T4 N0–2 disease).[6-8] This is one of the few studies to investigate the efficacy of immunotherapy in this disease subtype and the only study with two dual primary endpoints, including short-term pathological complete response (pCR) and long-term event-free survival (EFS).[9] At ESMO 2023, data on the pCR were presented, with patients displaying an improvement of 8.5% in the pCR rate when receiving pembrolizumab versus placebo.[6] Toxicity profiles aligned with those previously described for pembrolizumab, and no new safety signals were observed.[6] Neoadjuvant pembrolizumab treatment did result in increases in immune-mediated adverse events (AEs) (any grade, 32.8% vs 7.0%; grade 3–5, 7.1% vs 1.2%; led to drug discontinuation, 7.7% vs 1.6%), primarily hypo/hyperthyroidism.[6] The EFS data will be crucial to understanding if pembrolizumab has a role in this setting, as pCR cannot be considered as a surrogate for EFS or overall survival (OS) in neoadjuvant trials of ER+, HER2- early breast cancer.[10-12]

CheckMate 7FL (NCT04109066) is a randomized, double-blind trial of ICI nivolumab, a programmed cell death protein 1 (PD-1) inhibitor, versus placebo with neoadjuvant chemotherapy followed by adjuvant ET with or without nivolumab in patients with newly diagnosed, high-risk, ER+, HER2- early breast cancer (grade 3 [or grade 2 if ER expression was 1–10%]; T1c–T2 N0–2 or T3–4 N0–2).[13,14] The primary endpoints in this study were pCR and EFS; however, due to problems with patient recruitment the protocol was amended and EFS is now an exploratory endpoint.[14] Programmed death-ligand 1 (PD-L1)-positive or high immune filtration groups had high pCR rates (44.3% vs 24.2%). This highly significant result shows the pCR benefit

of PD-1 inhibitors in this subset of patients; however, long-term follow-up is needed.[14,15] A similar trial on pembrolizumab further supports these results.[15] Importantly, neoadjuvant therapy with ADCs such as trastuzumab deruxtecan (T-DXd) did not result in improved pCR rates,[16] highlighting the potential benefit of neoadjuvant anti-PD-L1 treatment in this subset of patients.[14,15]

monarchE (NCT03155997) is a phase III study assessing the efficacy of adjuvant CDK4/6 inhibitor abemaciclib plus ET in ER+, HER2-, high-risk, early breast cancer.[17,18] The primary endpoint for monarchE was invasive disease-free survival (iDFS).[19] At ESMO 2023, landmark 5-year data were presented, showing sustained iDFS benefit in patients receiving abemaciclib plus ET versus ET alone (83.6% vs 76.0%), corresponding to a 32% reduction in event risk (**Figure 1**).[18] No new safety signals were observed. A subpopulation treatment effect pattern plot (STEPP) analysis showed no differential impact of Ki-67, ER or progesterone receptor expression status on abemaciclib benefit.[20] These results confirm the long-term efficacy of CDK4/6 inhibitors in this breast cancer subtype in what concerns PFS. However, it will be crucial to know the proportion of patients in the control arm who received CDK4/6 inhibitors upon metastatic relapse (in theory, close to 100% since it is the current standard of care [SoC]). If this proportion is low, it could bias the assessment of a potential OS benefit, as observed in the first-line trials of CDK4/6 inhibitors in the metastatic setting.

Furthermore, attention should also be paid to the censoring in both arms to determine if it is informative (i.e., if it differs between the two arms), which could lead to an overestimation of iDFS and OS benefit if patients with a higher risk of relapse or death stop the study treatment due to toxicity and are excluded from the analyses.

The use of CDK4/6 inhibitors in the adjuvant setting also opens the question of how to treat patients diagnosed with metastatic disease while on adjuvant CDK4/6 inhibitor treatment. Trial data to support decisions in this setting is non-existent. As such, it can be argued that patients should be treated with regimens validated in the metastatic setting as second line. For instance, a selective estrogen degrader in association with a targeted therapy (e.g., another CDK4/6 inhibitor, everolimus, PIK3CA inhibitor), according to the molecular characteristics of the disease and the expected patient tolerability. Ongoing trials in the context of progression on CDK4/6 inhibitor with novel selective estrogen degraders (e.g., imlunestrant) may establish new options for these patients.

NATALEE (NCT03701334) is a phase III study assessing the efficacy and safety of ribociclib plus ET as adjuvant treatment versus ET alone in patients with stage II and III HR+, HER2- early breast cancer (a lower risk group than that recruited in the monarchE trial).[21,22] As in monarchE, the primary

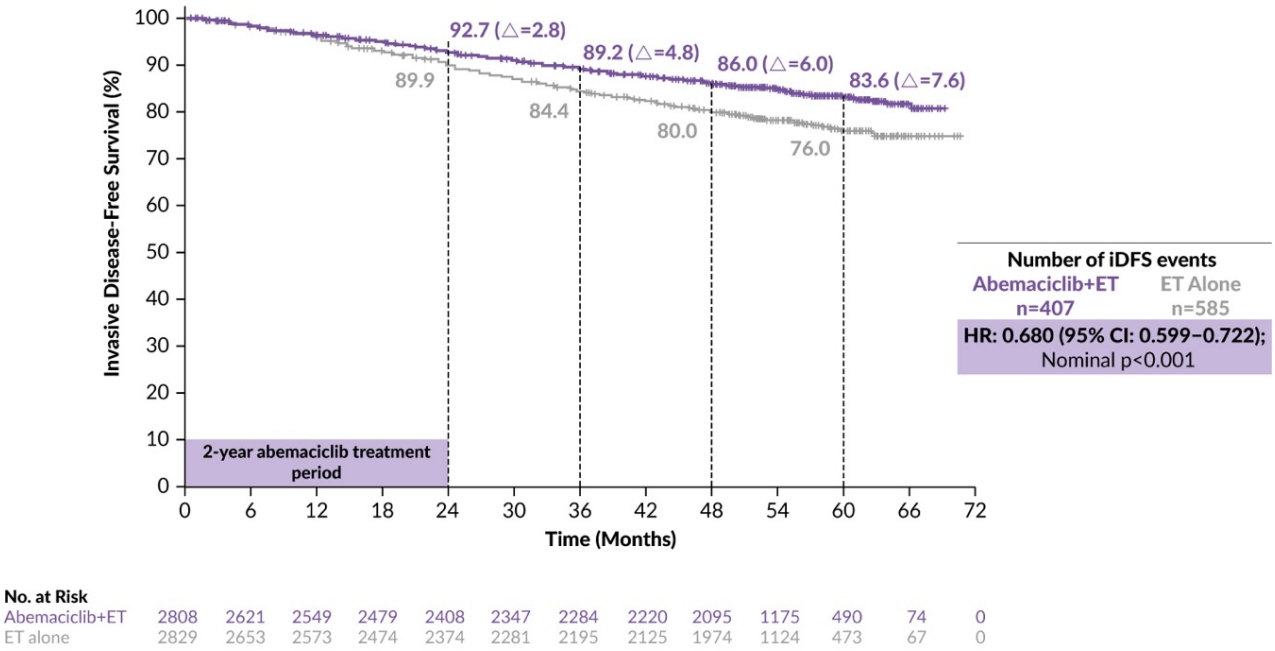

Figure 1. monarchE 5-year data show that treatment with abemaciclib plus endocrine therapy (ET) versus ET alone improves invasive disease-free survival (iDFS) in patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–), node-positive, high-risk, early breast cancer.

Adapted from Harbeck et al. 2023.[18]

endpoint was iDFS.[22] In NATALEE, treatment duration was 3 years compared with 3 years in monarchE and ribociclib posology was 400 mg/day (vs 600 mg/day in the metastatic setting). Data presented at ESMO show a benefit in iDFS, independently of the disease stage. The current results from the NATALEE study support the role of CDK4/6 inhibitors in the early-stage setting.[23] Further updates will help clinicians understand if the magnitude of benefit is different according to nodal status and stage and how to tailor the prescription of adjuvant ribociclib.

If approved and further updates confirm the current NATALEE data, ribociclib will become an alternative to abemaciclib in high-risk patients, with the choice being guided by patient and clinician preference concerning treatment duration and side effect profile.[23] In intermediate-risk patients, the adoption of adjuvant ribociclib will probably be dictated by the observed absolute benefit in iDFS. Ongoing and future studies will determine if CDK4/6 inhibitor-containing adjuvant ET could allow forgoing chemotherapy in lower/intermediate-risk patients. This includes the German multicenter ADAPTcycle trial assessing adjuvant ET plus 2 years of ribociclib versus adjuvant chemotherapy followed by standard ET in 1,684 patients with HR+, HER2- early breast cancer good response to neoadjuvant.[23, 24] Importantly, the investigators will take into account genomic risk and response to neoadjuvant ET to identify patients at intermediate recurrence risk who will be included in the trial. Additional trials that are more

pragmatic, not requiring genomic risk determination nor the assessment of the efficacy of neoadjuvant ET and focusing on chemotherapy de-escalation in the same population, are expected in the future.

ADCs in advanced breast cancer

HER2-low, unresectable and metastatic breast cancer

In the randomized phase III **DESTINY-Breast04** study (NCT03734029), the efficacy of T-DXd versus treatment of physician's choice (TPC) was assessed in patients with HER2-low unresectable and/or metastatic breast cancer.[25,26] The primary endpoint was progression-free survival (PFS) in the ER+ cohort. At ESMO 2023, updated OS data at a 32-month follow-up and PFS by investigator assessment were presented.[26] Data for PFS by investigator assessment were similar to PFS by blinded independent central response (BICR), showing a benefit for treatment with T-DXd versus TPC in both the ER+ cohort (9.6 months vs 4.2 months; HR: 0.37 [95% CI: 0.30–0.46]) and in all patients (8.8 months vs 4.2 months; HR: 0.36 [95% CI: 0.29–0.45]). The overall safety profile was consistent with those reported in the primary analysis and other T-DXd trials, with grade 1–2 nausea and fatigue as the most commonly reported AEs.[26,27] Lung toxicity is the most important AE of special interest with T-DXd (occurred in 12% of patients), and the object of careful monitoring in routine clinical practice.[26] Importantly, no new grade 3–4 events of lung toxicity have been recorded since the last update. In summary, the extended follow-up data of the trial continue to support T-DXd as SoC after one line of chemotherapy in patients with HER2-low metastatic breast cancer.

HER2+ metastatic breast cancer with brain metastases

At ESMO 2023, the results from a pooled analysis assessing the benefit of T-DXd in patients with HER2-positive (HER2+), metastatic breast cancer and brain metastases (BMs) from **DESTINY-Breast-01, -02, and -03** (NCT03248492, NCT03523585 and NCT03529110, respectively) were reported.[28-31] The primary endpoint in this exploratory pooled analysis was intracranial (IC) objective response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors version 1.1. (RECIST v1.1). Other endpoints included duration of response (DoR), PFS and safety.[28] The T-DXd brain metastases pool showed a higher IC ORR (~46%) than the comparator pool. A trend towards longer IC PFS was observed with the T-DXd brain metastases versus comparator pool (treated/stable BMs, 12.3 months vs 8.7, HR: 0.59; untreated/active BMs, 18.5 months vs 4.0 months, HR: 0.19).[32] While this was a post hoc analysis and not a prespecified analysis based on a subgroup, such as in the HER2CLIMB trial, T-DXd shows a similar IC ORR to that reported for tucatinib and is a good alternative to the

latter for patients with stable or active BMs. The mechanism allowing T-DXd to penetrate the blood-brain barrier remains elusive and should be the focus of future studies.

The phase III **TULIP** trial (NCT03262935) assessed trastuzumab duocarmazine versus TPC in pretreated, HER2+, metastatic breast cancer after ≥2 lines of therapy.[33,34] The primary endpoint was centrally assessed PFS.[34] Updated OS data were reported at ESMO 2023; unfortunately, no statistically significant improvement in OS was observed in patients receiving trastuzumab duocarmazine versus TPC (21.0 months vs 19.5 months, HR: 0.87 [95% CI: 0.68–1.12]; p=0.236).[34] Moreover, treatment with trastuzumab duocarmazine had marked toxicity, relative to TPC. For instance, grade ≥3 ocular toxicity, such as conjunctivitis and keratitis, was observed in 21% of patients, leading to dose reductions and interruptions in 22% and 21% of patients, respectively.[32,34]

BEGONIA, a phase Ib/II study (NCT03742102), assessed datopotamab deruxtecan (Dato-DXd) plus durvalumab, an anti-PD-L1 antibody, as a first-line treatment for patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC).[35,36] Dato-DXd targets tumor-associated calcium signal transducer 2 (Trop-2), a common antigen in TNBC. The primary endpoints of BEGONIA were safety and tolerability. An updated analysis of secondary endpoint data (ORR, PFS and DoR) was reported at ESMO 2023.[36] The ORR was 79% (49/62, 6 complete and 43 partial responses) for patients receiving Dato-DXd. The median PFS was 13.8 months and the median DoR was 15.5 months. Most patients had PD-L1-low tumors (<10% expression), 60% had visceral disease and >40% were treatment-naïve.

Therapeutic agents for post-T-DXd remain an unmet need, and ADCs may replace chemotherapy in the future, even in earlier lines. However, it is worth mentioning that while the introduction of ADCs to the first line of treatment of multiple subtypes is an almost forgone conclusion (obviously, depending on positive results from phase III trials), some may argue that they still constitute cytotoxic chemotherapy. Understanding how first-line ADC treatment impacts patients' quality of life will be key to their adoption. Moreover, since most ADCs currently in clinical practice or later stages of development have a topoisomerase 1 inhibitor with a payload, their sequencing may not yield significant clinical benefit.

Early-stage TNBC

The **NeoTRIP Michelangelo** (NCT02620280) randomized study assessed the benefit of neoadjuvant chemotherapy with or without the ICI atezolizumab in high-risk TNBC.[37,38] The primary endpoint of EFS at 54 months demonstrated no significant difference between the two arms (70.6% vs 74.9%; HR: 1.076 [95% CI: 0.67–1.73]; p=0.76).[38] No additional

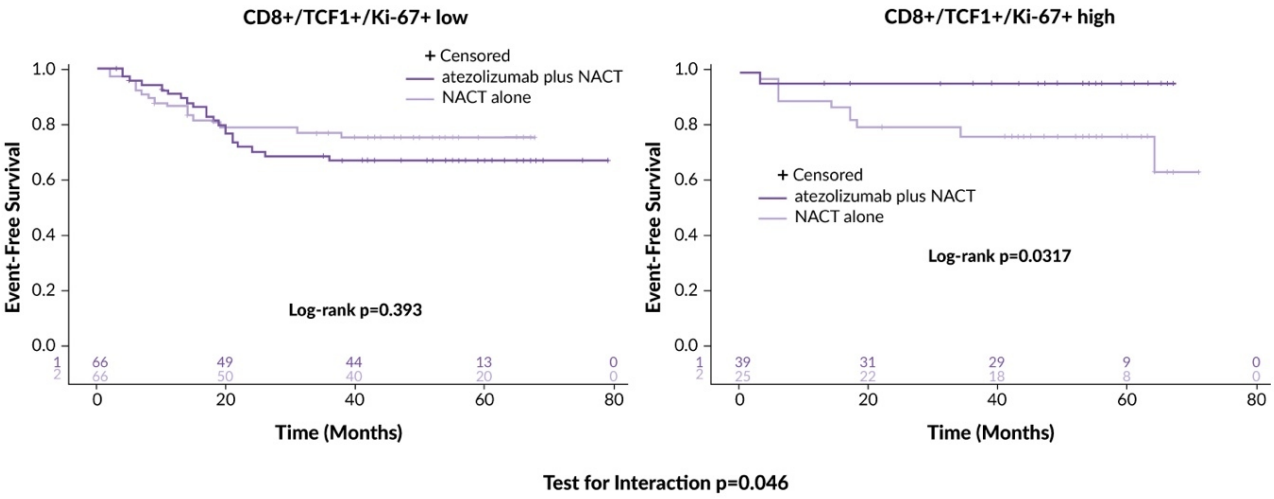

Figure 2. In patients with high-risk triple-negative breast cancer (TNBC), an immune cell signature predicts increased event-free survival (EFS) with the addition of atezolizumab to neoadjuvant chemotherapy (NACT).

CD8, cluster of differentiation 8; TCF1, T-cell factor-1. Adapted from Gianni et al. 2023.[38]

toxicity was observed with atezolizumab. A subgroup analysis also showed no benefit with atezolizumab across key patient subgroups, including pCR status, disease stage, PD-L1 status and age. An exploratory analysis was performed using Image Mass Cytometry (IMC)[39] to identify spatial predictors of ICI efficacy. This thorough analysis showed that a high density of a specific immune cell population (CD8+/TCF1+/Ki-67+) predicts an increased EFS benefit to neoadjuvant atezolizumab (p=0.0317) (**Figure 2**).[38] While exploratory, the presented data showcased how digital pathology approaches could help refine the identification of patients with an early-stage TNBC that will have increased benefit from neoadjuvant ICI in TNBC.[40]

The phase III **KEYNOTE-522** study (NCT03036488) assessed the benefit of neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo for early stage TNBC.[41,42] In this sixth prespecified interim analysis, updated EFS results were reported.[42] At the 5-year follow-up, the EFS benefit was maintained (81.3% vs 72.3%; HR: 0.63 [95% CI: 0.49–0.81]), regardless of key baseline characteristics such as PD-L1 status, node status or disease stage (**Figure 3**). While the eagerly awaited OS data is reported as not yet being mature, the 5-year distant recurrence rates are promising (84.4% vs 76.8%; HR: 0.64 [95% CI: 0.49–0.84]). This interim analysis showed that in patients achieving a pCR, there was a trend for better EFS in the pembrolizumab group. Yet, the absolute difference was 4% (92.2% vs 88.2%) and not significant (HR: 0.65 [95% CI: 0.39–1.08]). In the final analysis, a clearer picture of the potential difference between the treatment groups in patients achieving pCR will be of particular interest. Furthermore, at least two large trials will address the question of whether pembrolizumab should be continued as an adjuvant treatment if pCR is achieved (OptimICE-PCR and OPT-

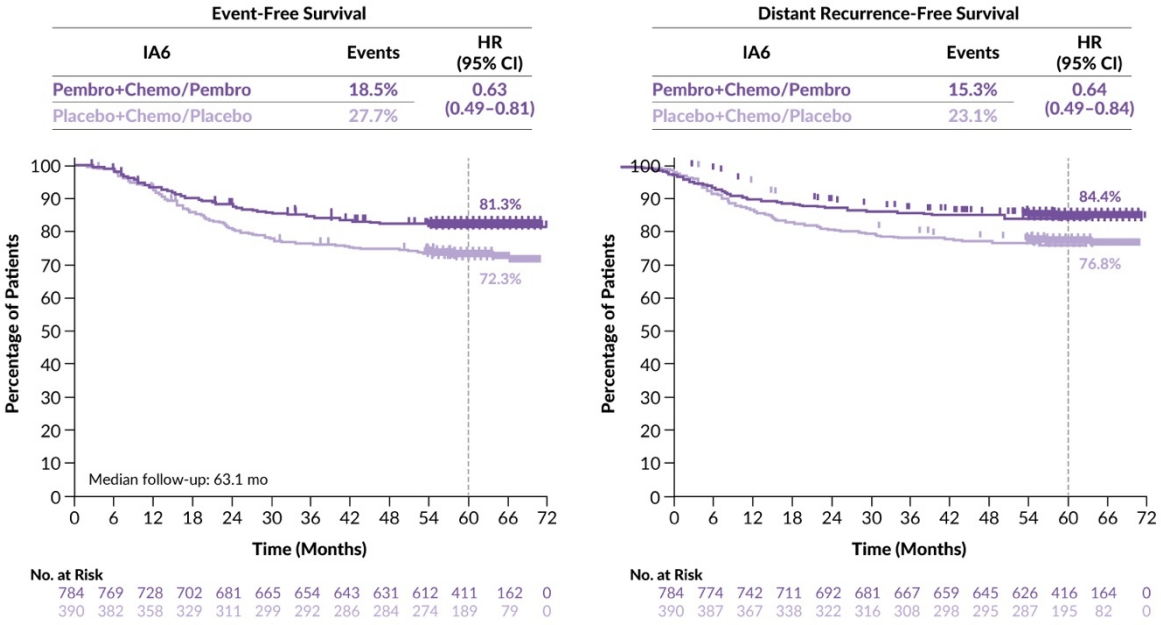

Figure 3. KEYNOTE-522: Five-year follow-up of event-free survival and distant recurrence-free survival in patients with early stage triple-negative breast cancer (TNBC) who received pembrolizumab plus chemotherapy/pembrolizumab versus placebo plus chemotherapy/pembrolizumab.

Chemo, chemotherapy; IA6, 6th prespecified interim analysis; mo, months; Pembro, pembrolizumab. Adapted from Schmid et al. 2023.[42]

Pembro), which could confirm (or not) what is observed in KEYNOTE-522. It is worth noticing that this subgroup includes most patients, and the adjuvant pembrolizumab part of the treatment protocol is associated with higher patient and financial toxicity. The safe de-escalation of adjuvant pembrolizumab could improve patients' quality of life and reduce healthcare costs. On the other hand, patients with residual disease were shown to do substantially better when they received immunotherapy (5-year EFS rate, 62.6% vs 52.3%; HR: 0.72 [95% CI: 0.54–0.96]).[42] Tailoring the indication, treatment duration and adjuvant phase composition in the presence or absence of pCR is the focus of several ongoing clinical trials.

Patient selection for immunotherapy in early breast cancer

In TNBC, the indication for combination therapy is based on the **KEYNOTE-522** trial,[43] where patients were selected using disease stage (computed tomography scan >2 cm or node-positive disease), and this should not change based on the latest update.[44] PD-L1 expression is key for selecting patients for immunotherapy in the metastatic setting; however, PD-L1 expression is not predictive of achieving pCR with immunotherapy.

In early-stage ER+, HER2- breast cancer, **KEYNOTE-756** (NCT03725059) showed a pCR benefit for immunotherapy in patients with tumors receiving pembrolizumab plus chemotherapy versus placebo (24.3% vs 15.6%)[44]; long-

term EFS follow-up data will add more clarity to the benefit of pembrolizumab in this setting. Interestingly, patients with ER-low tumors (1–10% expression) had a significantly higher probability of achieving pCR with pembrolizumab when compared to those with tumors with ER >10%. Similar results were observed in the CheckMate 7FL study. It is reassuring that these patients show a pCR benefit of immunotherapy similar to that observed in TNBC, which further reinforces the choice of a cut-off of 10% to classify tumors according to ER positivity in future clinical trials.

Impact of patient education and coaching in breast cancer

The importance of patient education and coaching to improve health literacy and treatment compliance is increasingly being recognized as fundamental to achieving the best possible outcomes in breast cancer care. New portable and wearable connected technologies have enabled novel interventions focused on patient education and coaching.

The **DISCO** study (NCT03529383) was a randomized trial of therapeutic patient education to promote physical activity in women with localized breast cancer.[31,45,46] Patients received either a web-based connected device, therapeutic patient education (two sessions), a combination of both interventions or usual care.[45] The primary endpoint was the proportion of patients who reached physical activity recommendations at 6 months based on the Recent Physical Activity Questionnaire in each intervention compared to patients who did not receive it. Unfortunately, no statistically significant difference was found for either intervention, probably due to other barriers to patients becoming physically active outside the healthcare sector.

The **IMPACT** trial (NCT04030728) compared patient coaching with the MASCC Oral Agent Teaching Tool (MOATT) versus local routine patient coaching (LC) in patients with HR+, HER2- advanced breast cancer, receiving abemaciclib plus ET.[47,48] Persistence probability after 24 weeks was 71% with LC and 82% with MOATT (HR: 0.59 [95% CI: 0.32–1.07]; p=0.078).[48] The probability for permanent therapy discontinuations was reduced by ~40% during the first six months of therapy following coaching with MOATT.[46,48] A slight numerical improvement was observed in the PFS rate at 24 weeks (87% vs 81%), and future updates will allow us to understand if the higher persistence probability translates into improved patient outcomes.

Conclusions

- Immunotherapies such as pembrolizumab and nivolumab improve pCR rates in patients with high-risk HR+, HER2- early breast cancer.

- The results from the monarchE trial confirm the long-term PFS efficacy of CDK4/6 inhibitors in HR+, HER2-, high-risk, early breast cancer.
- The currently available data support T-DXd as the SoC in patients with HER2-low metastatic breast cancer who have received one line of chemotherapy.[26]
- CD8+/TCF1+/Ki-67+ high signature may help select patients with benefit from neoadjuvant ICI therapy and could be explored in future trials.
- T-DXd, together with tucatinib, is a good option for treating patients with brain metastases.
- Interventions that use connected technology to improve patient treatment compliance and well-being are an increasing research focus.

Conflict of interest

José Luis Sandoval received travel and accommodation grants from Pfizer and consulting fees from Eli Lilly and Company. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

Funding

The author has declared that no financial support was received from any organization for the submitted work.

Author contributions

The author has created and approved the final manuscript.

Submitted: February 09, 2024 CEST. Accepted: March 19, 2024 CEST. Published: March 26, 2024 CEST.

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