RESEARCH HIGHLIGHT

The MonarchE trial: improving the clinical outcome in HR⁺/HER2⁻ early breast cancer: recent results and next steps

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Breast cancer (BC) is the most frequent cancer in women worldwide, and hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR⁺/HER2⁻) is the most frequent BC subtype. The adjuvant systemic treatment of HR⁺/HER2⁻ early-stage BC (eBC), based on prognostic factors [1], sometimes includes chemotherapy, and in most cases, it includes endocrine therapy (ET). In the past decade, advancements in ET, such as successive approvals of tamoxifen and aromatase inhibitors and the extension of ET duration to 10 years in high-risk patients, have shown promising results in improving their survival. However, ~20% of patients still relapse. In the metastatic setting, ET alone was the standard first-line treatment, but no progress in survival had been reported between 2008 and 2017. The recent results have recently improved with the approval of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i: palbociclib, ribociclib, abemaciclib) combined with ET, which doubled the progression-free survival.

Riding on these successes, several clinical research programs were developed to incorporate adjuvant CDK4/6is in eBC treatment (Table 1), i.e., palbociclib in the PALLAS [2] and PENEOPE-B trials [3], abemaciclib in MonarchE [4], and ribociclib in NATALEE [5]. MonarchE, initiated in 2017, enrolled 5,637 “high-risk” patients over 2 years. The “high-risk” status is defined as either ≥ 4 positive axillary lymph nodes (pN⁺) or 1 - 3 pN⁺ and either grade 3 or tumor size ≥ 5 cm. Patients were randomly assigned to receive standard-of-care ET for up to 10 years with or without abemaciclib (150 mg orally, twice daily) for 2 years. On April 2020, the pre-planned interim analysis of MonarchE reported positive results [6]. In the January issue of Lancet Oncology, Johnston et al. [4] reported the updated results with a 42-month follow-up (Figure 1A). The benefit of adjuvant abemaciclib was maintained for invasive disease-free survival (iDFS) and distant relapse-free survival (DRFS). Previously reported iDFS benefit was sustained with a 0.66 hazard ratio (HR, 95% confidence interval [CI] = 0.58–0.76, P < 0.001). The estimated 4-year iDFS rates were 85.8% (95% CI = 84.2%–87.3%) in the...
As abemaciclib + ET group versus 79.4% (95% CI = 77.5%–81.1%) in the ET alone group. Importantly, this absolute improvement continued to increase: 2.8% at 2 years, 4.8% at 3 years and 6.4% at 4 years, suggesting sustained benefit beyond the treatment period. The addition of abemaciclib to ET reduced the risk of DRFS event \( P < 0.001 \): the estimated 4-year DRFS rate was 88.4% (95% CI = 86.9%–89.7%) in the abemaciclib + ET group versus 82.5% (95% CI = 80.7%–84.1%) in the ET alone group. However, at this pre-specified overall survival (OS) analysis, the data were immature: 5.6% abemaciclib + ET patients died compared with 6.1% ET alone patients \( P = 0.500 \). Higher frequencies of grade \( \geq 3 \) adverse events (49.9% vs. 16.9%) and serious adverse events (15.5% vs. 9.1%) were observed with abemaciclib + ET versus ET alone, with the most common grade 3-4 adverse events being neutropenia, leukopenia, and diarrhea. These results marked another major milestone in the treatment of HR\(^+\)/HER2\(^-\) eBC, leading to the approval of adjuvant abemaciclib in patients with node-positive high-risk disease.

These MonarchE positive results are not supported by the published PALLAS [2] and PENELOPE-B trials [3] that assessed palbociclib (classical intermittent scheme: 3 weeks on/1 week off) for respective durations of 2 and 1 year. PALLAS [2] enrolled 5,761 stage II-III patients; with a 31-month median follow-up, the primary endpoint, 4-year iDFS, was not different between palbociclib + ET and ET alone groups \( P = 0.650 \). Similarly, in PENELOPE-B [3], which enrolled 1,250 patients with residual disease after neoadjuvant chemotherapy, no iDFS benefit was observed with palbociclib \( P = 0.520 \) after a 43-month median follow-up. The most recent NATALEE trial assessed the addition of 3 years of ribociclib to ET in “high-risk” patients and introduced a novel class of patients with stage II, N0, and grade 2 with Ki67 \( \geq 20\% \) or grade 2 with high metastatic risk according to prognostic gene expression signatures. A total of 5,101 patients were enrolled, and follow-up is ongoing.

A few potential reasons explaining the different results observed between adjuvant abemaciclib and palbociclib have risen. They include the different CDK inhibition potency, the continuous versus intermittent administration scheme that might be more critical in the adjuvant versus advanced setting, more drug stoppage intervals with palbociclib, and the lesser efficacy of palbociclib in the metastatic setting. Another potential explanation is the difference in patients’ selection. In MonarchE, “high-risk” was defined as either \( \geq 4 \) pN+, or 1-3 pN+ and grade 3 or tumor size \( \geq 5 \) cm. PALLAS selected patients with stage II-III disease; however, subgroup analysis showed no benefit in both “high-risk” and “low-risk” patients defined according to the MonarchE criteria [2]. In PENELOPE-B, patients were eligible in case of no complete response after neoadjuvant chemotherapy and with a Clinical-Pathologic Scoring system incorporating Estrogen receptor status and Grade (CPS-EG) score \( \geq 3 \) or \( \geq 2 \) with residual cancer cells in lymph nodes (ypN+).

Another key question is which patients may benefit from adjuvant CDK4/6i. In MonarchE [4], analysis per
pre-specified subgroups showed consistent abemaciclib benefit. Unexpectedly, the magnitude of benefit was higher in subgroups with better prognoses, such as patients with small pathological tumor size (pT1), low stage (IIA), or post-menopausal status. We thus investigated whether patients with “low-risk” eBC, excluded from MonarchE, might also benefit from adjuvant abemaciclib. We analyzed our gene expression database (Supplementary Table S1) containing 8,689 HR+/HER2− eBCs [7] comprising 5,711 “low-risk” and 1,143 “high-risk” patients, as defined according to MonarchE. Their characteristics are summarized in Supplementary Table S2, with significant differences between groups regarding pathological grade, tumor and lymph node status but no difference in terms of molecular subtype. Since no data were available regarding response to CDK4/6i, we compared the predicted sensitivities to CDK4/6i and ET according to published expression signatures: Rbsig [8] and E2Fregulon [9] for CDK4/6i and E2F4-activation [10] for ET. With a 77-month median follow-up, the 5-year DFS rate was 86% (95% CI = 85%-87%) and 74% (95% CI = 71%-77%) in the “low-risk” and “high-risk” groups, respectively. The “low-risk” patients, as compared to “high-risk” patients, were more often predicted as sensitive to CDK4/6i (59% vs. 54%, P = 0.003 according to E2Fregulon signature and 59% vs. 55%, P = 0.021 according to Rbsig signature) and more often predicted as sensitive to ET (59% vs. 55%, P = 0.011) (Figure 1B). Similar results were observed with expression analysis of other potential biomarkers such as RB1, FAT1 and FGFR1 (Supplementary Figure S1). The difference in the percentage of potentially sensitive patients was small (4%-5%) but significant between both groups and clearly suggested that the so-defined “low-risk” patients should not be excluded from adjuvant CDK4/6i. Our results are hypothesis-generating. Such hypothesis of sensitivity of the “low-risk” group can be tested in “low-risk” versus “high-risk” patients enrolled in NATALEE and MonarchE cohort 2. If this sensitivity to CDK4/6i is confirmed in the “low-risk” group, it might lead to wider use of adjuvant CDK4/6i. However, in this context, and given the related morbid and financial costs.
(> 300,000 US dollars for abemaciclib), identification of markers predictive of benefit is crucial and will benefit from omics profiling of tumor and liquid biopsies collected in adjuvant trials and interaction analyses.

Besides the predictive biomarkers issue, numerous other issues persist for more precisely defining the place of adjuvant CDK4/6i in the treatment algorithm of eBC (Figure 1C): i) the eventual impact on OS that needs a longer follow-up in both PALLAS and MonarchE; ii) the results in terms of efficacy and toxicity of ribociclib in NATALEE; iii) the optimal duration of treatment; and iv) the benefits of CDK4/6i after poly-ADP ribose polymerase (PARP) inhibitor in germline BRCA-mutated patients.

In conclusion, MonarchE results provide “high-risk” patients with a new treatment able to improve their outcomes. A major issue is the identification of clinical and/or biological markers predictive of benefit, which will authorize a rationale and cheaper use of CDK4/6i in eBC.

DECLARATIONS

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Concept and design: François Bertucci; Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: François Bertucci; Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: Pascal Finetti, François Bertucci. Validation: all authors; Supervision: François Bertucci.

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ETHICS IN APPROVAL AND CONSENT TO PARTICIPATE
Our *in-silico* analysis is based upon public data from published studies in which the informed patient’s consent to participate and the ethics and institutional review board were already obtained by the authors. The study was approved by our institutional review board (the Institut Paoli-Calmettes (IPC) “Comité de Recherche de Transfert, n°2023-014) according to good clinical practices and applicable laws and regulations.

CONSENT FOR PUBLICATION
Not applicable.

DATA AVAILABILITY STATEMENT
All datasets analyzed during the current study are publicly available, and the respective sources are indicated in Supplementary Table S1.

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REFERENCES


SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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