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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 PENELOPE-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

Abbreviations: BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CPS-EG, Clinical-Pathologic Scoring system incorporating Estrogen receptor status and Grade; CI, confidence interval; DRFS, distant relapse-free survival; eBC, early-stage breast cancer; ET, endocrine therapy; g*BRCA*, germline BReast CAncer gene; HR, Hazards Ratio; HR$^+$/HER2$^-$, hormone receptor-positive/human epidermal growth factor receptor 2-negative; iDFS, invasive disease-free survival; OS, overall survival; PARP, poly-ADP ribose polymerase; pN, pathological lymph nodes; ypN+, residual cancer cells in lymph nodes.

TABLE 1 Summary of the clinical trials of adjuvant CDK4/6 inhibitors.

Variables	Trial			
	PALLAS [2]	**PENELOPE-B [3]**	**MonarchE [4]**	**NATALEE [5]**
CDK4/6 inhibitor	Palbociclib	Palbociclib	Abemaciclib	Ribociclib
	125 mg daily	125 mg daily	150 mg daily	400 mg daily
	3 weeks on/1 week off	3 weeks on/1 week off	continuous	3 weeks on/1 week off
Number of patients	5,761	1,250	5,637	5,101
Patients' characteristics	Stage II–III	High risk after neoadjuvant chemotherapy	High risk	Stage II–III
Duration of CDK4/6i treatment	2 years	1 year	2 years	3 years
Median follow-up	31 months	43 months	42 months	Ongoing
Primary endpoint	iDFS	iDFS	iDFS	iDFS
HR for iDFS	HR = 0.96, 95% CI, 0.81–1.14	HR = 0.93, 95% CI, 0.74–1.17	HR = 0.66, 95% CI, 0.58–0.76	-
	$P = 0.650$	$P = 0.525$	$P < 0.001$	
HR for OS	HR = 1.32, 95% CI, 0.98-1.78	HR = 0.87, 95% CI, 0.61 -1.23	HR = 0.93, 95% CI, 0.75-1.15	-
	Not reported	$P = 0.420$	$P = 0.500$	

Abbreviations: CDK4/6i, cyclin-dependent kinases 4/6 inhibitors; iDFS, invasive disease-free survival; OS, overall survival; HR, hazards ratio; CI, confidence interval.

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 (HR = 0.66, 95% CI = 0.57–0.77; $P < 0.001$): 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 (HR = 0.93, 95% CI = 0.75–1.15; $P = 0.500$). Higher frequencies of grade ≥ 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 intermittence 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 ≥ 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 ≥4 pN+, or 1-3 pN+ and grade 3 or tumor size ≥ 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 ≥ 3 or ≥ 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

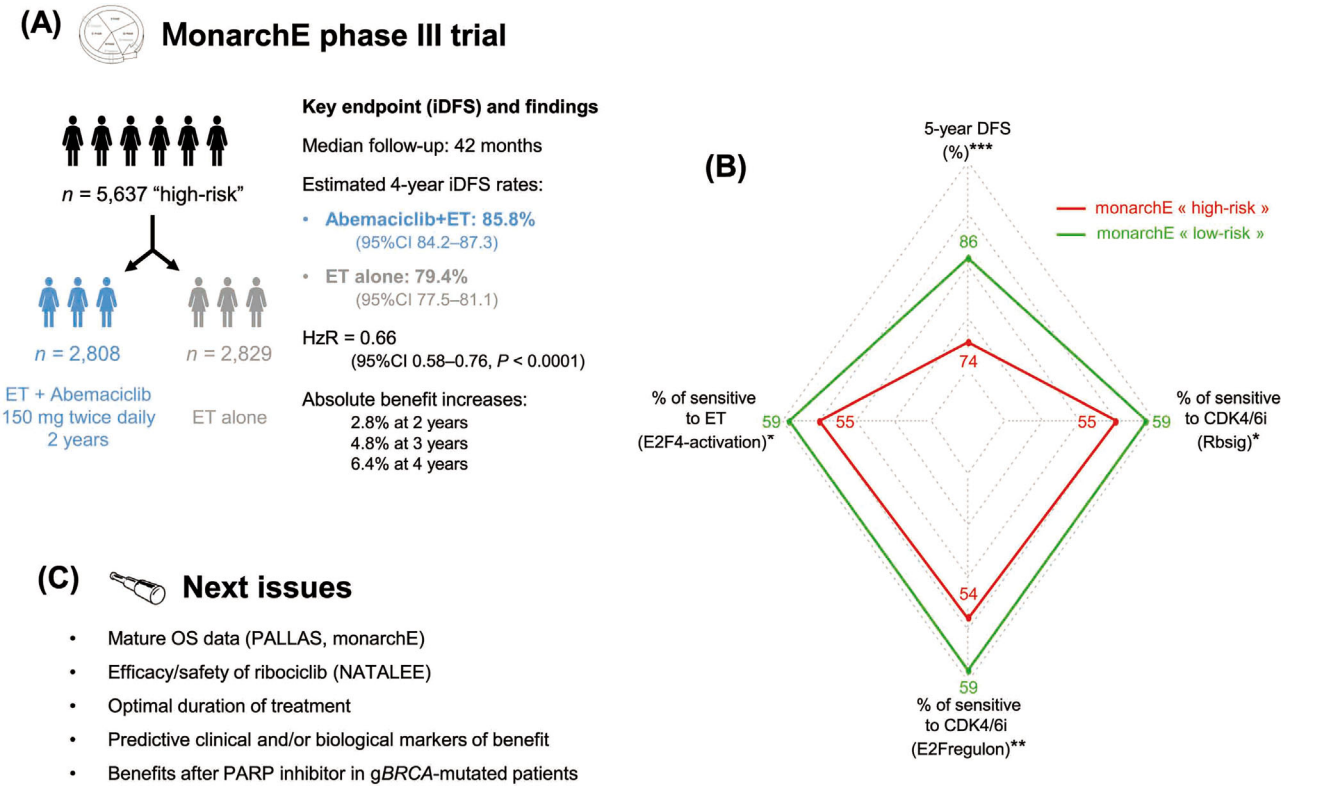

FIGURE 1 MonachE results, DFS and sensitivity profiles of patients with HR$^+$/HER2$^-$ eBC according to "low-risk" and "high-risk" defined by MonarchE clinical criteria and next issues.

(A) MonarchE results. (B) Results Radar chart showing the 5-year DFS and the percentage of patients predicted as sensitive to CDK4/6i (RBsig and E2Fregulon signatures) and ET (E2F4-activation signature) in the "low-risk" patients (green line) and the "high-risk" patients (red line) as defined by MonarchE clinical criteria. The radar chart scale axes range from 40 to 60%, except for the 5-year DFS axis, which ranges from 70 to 100%. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$. (C) Several issues of research are still required in this setting.

Abbreviations: eBC: early-stage breast cancer; CDK4/6i, cyclin-dependent kinases 4/6 inhibitors; ET, endocrine therapy; DFS, disease-free survival; iDFS, invasive disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

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 BReast CAncer gene (g*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

AUTHOR CONTRIBUTIONS

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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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

Alexandre de Nonneville declares consulting fees by Gilead, Seagen, Lilly, and Novartis, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events by Gilead, Daiichi Sankyo, and MSD, Support for attending meetings and/or travel by Gilead, Lilly, and Daiichi Sankyo. The other authors declare no competing interests.

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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

1. Garutti M, Griguolo G, Botticelli A, Buzzatti G, De Angelis C, Gerratana L, et al. Definition of high-risk early hormone-positive HER2-negative breast cancer: A consensus review. Cancers. 2022;14(8):1898.
2. Gnant M, Dueck AC, Frantal S, Martin M, Burstein HJ, Greil R, et al. Adjuvant palbociclib for early breast cancer: The PALLAS trial results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2022;40(3):282-93.
3. Loibl S, Marme F, Martin M, Untch M, Bonnefoi H, Kim SB, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer-the penelope-b trial. J Clin Oncol. 2021;39(14):1518-30.
4. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): Results from a pre-planned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023;24(1):77-90.
5. Slamon DJ, Fasching PA, Patel R, Verma S, Hurvitz SA, Chia SKL, et al. NATALEE: Phase iii study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) early breast cancer (ebc). J Clin Oncol. 2019;37:TPS597–TPS597.
6. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarche). J Clin Oncol. 2020;38(34):3987-98.
7. Bertucci F, Finetti P, Simeone I, Hendrickx W, Wang E, Marincola FM, et al. The immunologic constant of rejection classification refines the prognostic value of conventional prognostic signatures in breast cancer. Br J Cancer. 2018;119(11):1383-91.
8. Malorni L, Piazza S, Ciani Y, Guarducci C, Bonechi M, Biagioni C, et al. A gene expression signature of retinoblastoma

loss-of-function is a predictive biomarker of resistance to palbociclib in breast cancer cell lines and is prognostic in patients with er positive early breast cancer. Oncotarget. 2016;7(42):68012-22.

9. Turner NC, Liu Y, Zhu Z, Loi S, Colleoni M, Loibl S, et al. Cyclin E1 expression and palbociclib efficacy in previously treated hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2019;37(14):1169-78.
10. Guerrero-Zotano AL, Stricker TP, Formisano L, Hutchinson KE, Stover DG, Lee KM, et al. ER(+) breast cancers resistant to prolonged neoadjuvant letrozole exhibit an e2f4 transcriptional program sensitive to CDK4/6 inhibitors. Clin Cancer Res. 2018;24(11):2517-29.

SUPPORTING INFORMATION

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

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