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CDK4/6 Inhibitors Plus Endocrine Therapy vs Endocrine Monotherapy in HR+/HER2– Advanced Breast Cancer: A Patient-Level Meta-Analysis Using Reconstructed Data from Phase III Trials

Running title: *Meta-Analysis of CDK4/6i plus ET in HR+/HER2– advanced breast cancer*

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Research in context

Evidence before this study

We searched PubMed, Web of Science, the Cochrane Library, and Scopus from inception to June 2, 2025, using search terms related to “breast cancer”, “CDK4/6 inhibitors”, “abemaciclib”, “ribociclib”, “palbociclib”, “dalpiciclib”, and “endocrine therapy”, with no language or date restrictions. We included phase III randomized controlled trials comparing CDK4/6 inhibitors plus endocrine therapy (ET) with ET alone in patients with hormone receptor–positive, HER2-negative (HR+/HER2–) advanced breast cancer.

Previous meta-analyses demonstrated significant progression-free survival (PFS) benefits. However, they had several methodological limitations: most relied on aggregate summary statistics rather than patient-level data; several included early-phase or adjuvant trials; subgroup analyses stratified by endocrine-sensitivity status or by individual CDK4/6 agent were either absent or underpowered; and none assessed secondary endpoints such as chemotherapy-free survival (CFS), time to first chemotherapy (TFC), and duration of response (DOR).

For overall survival (OS), while individual phase III trials showed a clear OS benefit with ribociclib, abemaciclib had mixed results, and palbociclib did not reach statistical significance. Additionally, comparative pooled estimates across agents and relevant subgroups were not formally evaluated.

Added value of this study

To our knowledge, this is the most comprehensive meta-analysis to date assessing CDK4/6 inhibitors plus ET in HR+/HER2– advanced breast cancer. We reconstructed individual patient data (IPD) from 11 Phase III trials involving 6,035 patients treated with one abemaciclib, ribociclib, palbociclib, or dalpiciclib. Use of an IPD reconstruction approach enabled granular time-to-event analyses beyond the scope of prior meta-analyses.

Our results show that adding a CDK4/6 inhibitor to ET significantly improves PFS and OS across both endocrine-sensitive and endocrine-resistant populations, with consistent benefits across key subgroups, including age, ethnicity, progesterone receptor status, menopausal status, ECOG performance status, bone-only disease, and visceral metastasis. However, OS benefits were agent-specific: abemaciclib and ribociclib significantly improved OS, whereas palbociclib did not reach statistical significance, and data for dalpiciclib remain immature.

Implications of all the available evidence

Collectively, these findings confirm that CDK4/6 inhibitors plus endocrine therapy represent the standard of care for HR+/HER2– advanced breast cancer, providing meaningful improvements in both disease control and overall survival. The demonstration of consistent benefits across key clinical subgroups supports the broad applicability of these agents irrespective of age, menopausal status, or disease burden.

Importantly, our data confirm differences in long-term survival effects among individual CDK4/6 inhibitors. While all agents combined with endocrine therapy improved PFS, only ribociclib and abemaciclib showed statistically significant OS benefits; palbociclib did not, and data for dalpiciclib remain immature. These findings suggest that guideline recommendations may benefit from acknowledging ribociclib and abemaciclib as preferred first-line options, given their observed OS benefits, while palbociclib could be used primarily for disease control or when other agents are less suitable.

Future research should focus on head-to-head comparative trials, identifying biomarkers of response and resistance, clarifying optimal treatment sequencing strategies, and evaluating patient-reported outcomes and toxicity profiles to refine individualized care. Together, the evidence supports CDK4/6 inhibition as a cornerstone of modern management for HR+/HER2- advanced breast cancer, while emphasizing the need for precision in agent selection and sequencing.

Abstract

Background

CDK4/6 inhibitors have shown clinical benefits in patients with hormone receptor–positive, HER2–negative (HR+/HER2–) advanced breast cancer. However, their effects may vary across survival outcomes. This meta-analysis aims to clarify the variations in treatment effects on survival outcomes and to evaluate their impact across clinically relevant subgroups.

Methods

On June 2, 2025, we searched PubMed, Web of Science, the Cochrane Library, and Scopus for Phase III trials that compared CDK4/6 inhibitors plus endocrine therapy (ET) to ET monotherapy in patients with HR+/HER2– advanced breast cancer. Kaplan-Meier (KM) curves were reconstructed using a time-to-event algorithm to estimate survival. A series of pooled analyses for the reconstructed IPD were conducted using a stratified Cox regression model. A pairwise random-effects meta-analysis was also conducted. Outcomes included progression-free survival (PFS; time to progression or death), overall survival (OS; time to death from any cause), chemotherapy-free survival (CFS; time to chemotherapy initiation or death), time to first chemotherapy (TFC), and duration of response (DOR; time from response to progression or death). Patients were stratified by endocrine sensitivity into endocrine-sensitive (de novo disease or relapse ≥ 12 months after completing adjuvant ET, without prior systemic therapy for advanced disease) and endocrine-resistant (relapse within 12 months during adjuvant ET or progression within 6 months of ET for advanced disease).

Findings

Eleven phase III trials, including 6,035 patients and four agents—abemaciclib, ribociclib, palbociclib, and dalpiciclib—were included. CDK4/6 inhibitors plus ET significantly improved PFS in both endocrine-sensitive (HR 0.57, 95% CI 0.52–0.63; $p < 0.0001$) and endocrine-resistant settings (HR 0.51, 95% CI 0.45–0.57; $p < 0.0001$). OS was also prolonged in both subgroups: endocrine-sensitive (HR, 0.83; 95% CI, 0.74–0.92; $p = 0.0005$) and endocrine-resistant (HR, 0.77; 95% CI, 0.67–0.89; $p = 0.0003$). CFS (HR 0.69, 95% CI: 0.63–0.75; $p < 0.0001$), TFC (HR 0.68, 95% CI: 0.63–0.74; $p < 0.0001$), and DOR (21.4 months for CDK4/6 inhibitors plus ET; 16.6 months for ET alone) also showed improvement.

Across individual agents, all combined with ET showed PFS benefits: abemaciclib (HR 0.53, 95% CI 0.46–0.61; $p < 0.0001$), ribociclib (HR 0.60, 95% CI 0.52–0.68; $p < 0.0001$), palbociclib (HR 0.56, 95% CI 0.49–0.65; $p < 0.0001$), and dalpiciclib (HR 0.49, 95% CI 0.40–0.61; $p < 0.0001$). However, for OS, only abemaciclib (HR 0.79, 95% CI 0.67–0.92; $p = 0.0031$) and ribociclib (HR 0.73, 95% CI 0.64–0.84; $p < 0.0001$) showed significant benefits, whereas palbociclib did not reach statistical significance (HR 0.89, 95% CI 0.77–1.02; $p = 0.0920$), and data for dalpiciclib remain immature.

Other clinically relevant subgroups, including age, ethnicity, progesterone receptor status, menopausal status, ECOG status, bone-only disease, and visceral metastasis, showed PFS benefits in both endocrine-sensitive and endocrine-resistant settings. These subgroups also showed OS benefits.

Interpretation

CDK4/6 inhibitors plus ET significantly improved PFS and other key endpoints in HR+/HER2– advanced breast cancer. Benefits in PFS and OS were consistent across major clinical subgroups. While all agents

improved PFS, only ribociclib and abemaciclib showed statistically significant OS benefits; palbociclib did not, and data for dalpiciclib remain immature. Further head-to-head comparisons and assessments of toxicity profiles, as well as patient-reported outcomes, are needed.

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Keywords

Advanced; metastatic; breast cancer; CDK4/6 inhibitors; endocrine therapy

Introduction

Metastatic breast cancer is the second leading cause of cancer-related death among women in the US and has an incidence of 7.9 per 100,000 in 2021 ¹. About 71.1% of breast cancers are hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-), according to a large US population-based analysis that also reported a 1.9% annual increase in HR+/HER2- cases between 2010 and 2019 ².

Endocrine therapy (ET) is a standard treatment for advanced breast cancer, and it inhibits tumour growth by targeting estrogenic receptor (ER) signalling. However, its effectiveness is limited by acquired resistance, leading to poor clinical outcomes and disease progression ³.

Targeted therapy has become a crucial strategy for overcoming endocrine resistance. In recent years, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have emerged as a key treatment for advanced breast cancer. Several Phase III clinical trials have evaluated the efficacy of CDK4/6 inhibitors in combination with endocrine therapies in patients with HR+/HER2- advanced breast cancer ⁴⁻⁷. These trials demonstrated survival benefits; however, differences in their effects on outcomes such as overall survival (OS) were observed, with variability among individual drugs in this class.

Previous meta-analyses evaluating CDK4/6 inhibitors in HR+/HER2- advanced breast cancer were limited by the small number of included studies, the absence of subgroup analyses for individual CDK4/6 inhibitors, or the absence of subgroup analyses of clinically important subgroups by endocrine-sensitivity status ⁸⁻¹¹.

To clarify these differences, we conducted a meta-analysis using reconstructed individual patient data (IPD). The analysis focused on key outcomes, including progression-free survival (PFS) and OS in patients with HR+/HER2- advanced breast cancer. Subgroup analyses were performed based on the specific CDK4/6 inhibitor used, endocrine resistance status, and other clinically relevant factors.

Methods

Search strategy and selection criteria

This reconstructed-IPD meta-analysis was conducted in accordance with the PRISMA guidelines for IPD meta-analyses (**appendix p 3**). The protocol was prospectively registered in PROSPERO (**CRD420251073444**).

An electronic search was conducted in PubMed, Cochrane Library, Web of Science, and Scopus from inception to June 2, 2025. Keywords related to *breast cancer*, *endocrine therapy*, and *CDK4/6 inhibitors*

were used. No language, region, or time restrictions were applied. The detailed search strategy is provided in the **appendix (p 6)**.

Each article was independently screened by two authors (AF, RHS, AFA, AA) at both the title/abstract and full-text stages, using the Covidence platform (Covidence.org, Melbourne, Australia). The senior authors resolved any discrepancies (MSB and ME). Duplicate records were removed using Covidence's built-in duplicate removal tool.

We included phase III randomized controlled trials (RCTs) that evaluated the use of CDK4/6 inhibitors in combination with ET and compared them to ET monotherapy in patients with HR+/HER2- advanced breast cancer. Exclusion criteria were: trials investigating early-stage breast cancer; studies involving hormone receptor-negative tumours (lacking both estrogen and progesterone receptors); studies with a control group other than endocrine therapy as monotherapy; phase II or lower trials; studies that included HER2-positive breast cancers; and studies that included patients who had progressed after prior CDK4/6 inhibitor use.

Only Phase III randomized trials were included to ensure sufficient sample sizes, well-defined endpoints, and consistent trial design and reporting. While Phase II trials may provide useful preliminary evidence, their smaller sample sizes and very small subgroups could lead to some unreliable estimates.

Data were extracted into a standardized Excel sheet comprising three sections: (1) study characteristics (e.g., region, design, interventions, and treatment line), (2) participants' baseline data (e.g., age, race, menopausal status, hormone receptor status, and metastasis), and (3) study outcomes.

Data analysis

Survival data from Kaplan-Meier (KM) curves were reconstructed using the *IPDfromKM* workflow described by Liu et al.¹². This involved a two-stage process: first, extracting time points and corresponding survival probabilities from the published KM curves using WebPlotDigitizer (version 5.2; developed by Ankit Rohatgi); second, combining these data with the number-at-risk tables and number of events reported in the trials to reconstruct the IPD using RStudio. To assess the quality of the reconstructed IPD, we performed a Cox regression analysis and compared the hazard ratios and confidence intervals with those reported in the original studies. A visual comparison of the KM curves was also conducted to confirm the accuracy of the reconstruction. A comparison between the reconstructed and original HRs is provided in the **appendix (p 7)**.

For the studied outcomes, a one-step pooled analysis was conducted using the reconstructed IPD. Hazard ratios were estimated using a stratified Cox regression model, with stratification by study to account for between-study heterogeneity. The proportional hazards assumption was assessed using the Grambsch-Therneau test, and a p-value < 0.05 indicates a violation. If the assumption was violated, Restricted Mean Survival Time (RMST) was used to evaluate survival data from the pooled IPD. Sensitivity analyses using RMST were performed for all pooled outcomes. To support the primary findings and assess secondary subgroups, a conventional pairwise meta-analysis was conducted using published hazard ratios and a random-effects model. Heterogeneity was evaluated using the Q-test and I-squared statistics. Publication bias was assessed using Egger's test and the funnel plots. All analyses were conducted in RStudio (version 4.4.2) using the following packages: *IPDfromKM*, *survival*, *survRM2*, and *meta*.

The risk of bias assessment was conducted using the Cochrane Risk of Bias tool for randomized clinical trials (**RoB2; appendix, p. 23**). Two reviewers (AF, RHS, AFA, AA) independently assessed each study, and any discrepancies were resolved through discussions.

The studied endpoints were progression-free survival (PFS; time from randomization to progression or death), overall survival (OS; time from randomization to death from any cause), chemotherapy-free survival (CFS; time from randomization to chemotherapy initiation or death), time to first chemotherapy (TFC; time from randomization to initiation of first chemotherapy after trial treatment discontinuation), and duration of response (DOR; the first documented objective response to progression or death). Patients were stratified by endocrine sensitivity into endocrine-sensitive (de novo advanced disease or relapse ≥ 12 months after completing adjuvant ET, without prior systemic therapy for advanced disease) and endocrine-resistant (relapse within 12 months during adjuvant ET or progression within 6 months of ET for advanced disease).

Other clinically relevant subgroups, including progesterone receptor status, menopausal status (premenopausal/perimenopausal vs. postmenopausal), age, ethnicity, bone-only disease, liver metastases, visceral metastases, and ECOG performance status, were also evaluated using a random effects conventional meta-analysis.

Role of the funding source

This study did not receive any funding. The authors had full responsibility for the study design, data collection, analysis, interpretation, and writing of the report.

Results

After the database search, 7,760 articles were identified. Eighteen reports from 11 trials were deemed eligible for data extraction and analysis ^{4-7,13-26}. A detailed illustration of the selection process is presented in the **appendix (p 10)**. All included studies were phase III, double-blind, placebo-controlled, and enrolled 6,035 patients. Each trial evaluated a CDK4/6 inhibitor in combination with ET versus ET monotherapy, and all have excluded patients who had previously progressed on a CDK4/6 inhibitor. Six trials were conducted in the endocrine-sensitive setting ^{5,7,14,15,19,26}, and three in the endocrine-resistant setting ^{4,13,24}. The MONALEESA-3 ¹⁷, MONALEESA-7 ¹⁹, and MONARCH-plus ²² trials included a mixed population of endocrine-sensitive and endocrine-resistant patients. We extracted data in line with the endocrine sensitivity definitions prespecified in the Methods. Details of how the sensitivity status was handled for those trials are provided in the **appendix (p 2)**. A detailed overview of the included studies is provided in **Table 1**.

[Table 1. Overview of the included studies]

One-stage reconstructed IPD meta-analyses of pooled CDK4/6 inhibitors were conducted according to endocrine sensitivity status (**Table 2a**). For progression-free survival (PFS), in the endocrine-sensitive setting, CDK4/6 inhibitors combined with ET significantly reduced the risk of progression or death (HR 0.57, 95% CI 0.52–0.63, $p < 0.0001$; 7 studies; $n = 3,294$; **Figure 1A**). A similar benefit was observed in the endocrine-resistant setting (HR 0.51, 95% CI 0.45–0.57, $p < 0.0001$; 5 studies; $n = 2,054$; **Figure 1B**). Overall survival (OS) was also significantly prolonged in endocrine-sensitive (HR 0.83, 95% CI 0.74–0.92, $p = 0.0005$; 5 studies; $n = 2,532$; **Figure 1C**) and endocrine-resistant (HR 0.77, 95% CI 0.67–0.89, $p < 0.0003$; 3

studies; $n = 1,536$; **Figure 1D**). The proportional hazards assumption was valid for all (Grambsch–Therneau $p > 0.05$).

When stratified by endocrine backbone, CDK4/6 inhibitors combined with NSAs in endocrine-sensitive disease significantly improved PFS and OS. Similarly, combinations with fulvestrant in endocrine-resistant disease also showed significant PFS and OS benefits. These analyses are summarized in **Table 2a**, and the figures are presented in the appendix (**p. 11**).

Other time-to-event endpoints also favoured CDK4/6 inhibitors plus ET (**appendix p 12**). TFC showed a significant improvement with CDK4/6 inhibitors plus ET compared with ET alone (HR 0.68, 95% CI: 0.63–0.74; $p < 0.0001$). Similarly, CFS showed benefits with the combination therapy (5 trials; HR 0.69, 95% CI: 0.63–0.75; $p < 0.0001$). DOR showed longer median duration in the combination arm (3 trials; 21.4 months, 95% CI: 20.1–not reached) than ET monotherapy (16.6 months, 95% CI: 13.5–20.6). These analyses are summarized in **Table 2a**.

We also conducted one-stage reconstructed IPD meta-analyses stratified by individual CDK4/6 inhibitors (**Table 2b**). For abemaciclib, PFS showed significant improvement in the overall population (HR 0.53, 95% CI 0.46–0.61, $p < 0.0001$), and in both the endocrine-sensitive (HR 0.54, 95% CI 0.43–0.68, $p < 0.0001$) and endocrine-resistant settings (HR 0.52, 95% CI 0.43–0.63, $p < 0.0001$). OS showed a modest survival benefit in the overall population (HR 0.79, 95% CI 0.67–0.92, $p = 0.0031$), and CFS was markedly prolonged (HR 0.67, 95% CI 0.58–0.77, $p < 0.0001$). The proportional hazards assumption was valid in all (Grambsch–Therneau $p > 0.05$). KM curves for the abemaciclib analyses are provided in the **appendix (p 13)**.

Combining ribociclib with ET significantly improved PFS (HR 0.60, 95% CI 0.52–0.68, $p < 0.0001$) and OS (HR 0.73, 95% CI 0.64–0.84, $p < 0.0001$). These survival benefits were also consistent in the endocrine-sensitive setting, with HRs of 0.56 (95% CI 0.47–0.68, $p < 0.0001$) for PFS and 0.73 (95% CI 0.62–0.87, $p = 0.0005$) for OS (**appendix p 14**). TFC (HR 0.71, 95% CI 0.63–0.81, $p < 0.001$) and CFS (HR 0.70, 95% CI 0.63–0.78, $p < 0.0001$) also showed significant benefits (**Table 2b; appendix p 14**). The proportional hazards assumption was valid in all analyses, except for TFC (Grambsch–Therneau $p = 0.03$).

Palbociclib plus ET significantly improved PFS in the overall population (HR 0.56, 95% CI 0.49–0.65, $p < 0.0001$; **Figure 2A**) and in the endocrine-sensitive subgroup (HR 0.61, 95% CI 0.52–0.72, $p < 0.0001$; **Figure 2B**). Regarding OS, although a numerical reduction in the risk of death was observed, the improvement did not reach statistical significance in the overall (HR 0.89, 95% CI 0.77–1.02, $p = 0.0920$; **Figure 2C**) and the endocrine-sensitive subgroup (HR 0.94, 95% CI 0.79–1.12, $p = 0.4784$; **Figure 2D**). TFC had significant improvement with palbociclib (HR 0.66, 95% CI 0.57–0.76, $p < 0.0001$; **appendix p 15**). The proportional hazards assumption was valid in all analyses.

Dalpiciclib plus ET also significantly improved PFS (HR 0.49, 95% CI 0.40–0.61, $p < 0.0001$) and TFC (HR 0.62, 95% CI 0.47–0.80, $p = 0.0003$) compared to ET alone (**appendix p 16**). While OS data remain immature, preliminary results showed 52 deaths (9.6%) among 544 patients in the dalpiciclib group compared to 30 deaths (11%) among 273 patients in the ET alone group across the DAWNA-1 and DAWNA-2 trials.

[Table 2. One-stage reconstructed IPD meta-analyses of pooled CDK4/6 inhibitors]

We performed a conventional meta-analysis to evaluate the effects of CDK4/6 inhibitors overall and across subgroups based on age (<65 vs ≥ 65 years), ethnicity (Asian vs White), and endocrine sensitivity status

(sensitive vs resistant). The analyses showed significant survival benefits for both PFS and OS across these subgroups (**Tables 3 and 4; appendix, pp. 18 and 21**). Subgroup analyses by individual CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib, and dalpiciclib) also showed consistent PFS benefits (**appendix p 17**). For OS, both abemaciclib and ribociclib showed survival benefits, whereas the OS improvement for palbociclib did not reach statistical significance (**appendix p 17**). The HRs for OS were as follows: abemaciclib (HR 0.78, 95% CI 0.66–0.91, $p = 0.0023$), ribociclib (HR 0.74, 95% CI 0.64–0.84, $p < 0.0001$), and palbociclib (HR 0.89, 95% CI 0.76–1.05, $p = 0.1716$).

Other clinically relevant subgroups, including progesterone receptor status (PR-positive or PR-negative), menopausal status (pre/perimenopausal or postmenopausal), ECOG performance status, and metastasis site (bone-only disease, liver, or visceral), were also evaluated. For PFS, the analyses were stratified by endocrine sensitivity (sensitive vs. resistant), and all subgroups showed benefit in both the sensitive and resistant groups (**Table 3; appendix p 19-20**). For OS, survival benefits were observed across these subgroups, including those based on progesterone receptor status, menopausal status, ECOG performance status, and metastasis site (bone-only or visceral) (**Table 4; appendix p 22**).

[Table 3. Hazard ratios for PFS in clinically relevant prespecified subgroups (pairwise meta-analysis).]

[Table 4. Hazard ratios for OS in clinically relevant prespecified subgroups (pairwise meta-analysis).]

Sensitivity analyses for all pooled outcomes were conducted using the RMST, and the results were consistent with the main findings (**appendix, p. 9**). Similarly, using the conventional pairwise random-effects meta-analysis, the pooled results for CDK4/6 inhibitors overall, by endocrine status, and by individual CDK4/6 inhibitors for both PFS and OS were consistent with the primary analyses.

For risk of bias assessment, all included trials were judged to be at low risk (**appendix p 23**). Publication bias assessment was conducted for both PFS and OS (**appendix, p. 24**). For PFS, Egger's test suggested potential funnel plot asymmetry ($p = 0.024$). A leave-one-out sensitivity analysis showed that this signal persisted after excluding all studies except the smallest cohort (MONARCH-plus Cohort B, $n = 157$). After its exclusion, statistical significance was lost ($p = 0.117$; **appendix p 24**), suggesting that the initial asymmetry was primarily driven by a single small study rather than by systematic publication bias. For OS, both the funnel plot and Egger's test did not indicate asymmetry.

Discussion

In this systematic review and meta-analysis, CDK4/6 inhibitors combined with ET in HR+/HER2- advanced breast cancer showed survival benefits for both OS and PFS in endocrine-sensitive and endocrine-resistant populations. Secondary outcomes, including TFC, CFS, and DOR, were also significantly improved compared with ET alone.

Subgroup analyses by individual CDK4/6 inhibitor showed consistent PFS benefits across all agents (abemaciclib, ribociclib, palbociclib, and dalpiciclib). OS benefits, however, varied by agent: abemaciclib and ribociclib showed survival benefits, whereas palbociclib did not reach statistical significance, and OS data for dalpiciclib are not yet available. Other clinically relevant subgroups, including age, ethnicity, endocrine sensitivity, progesterone receptor status, menopausal status, ECOG performance status, bone-only disease, and visceral metastasis, all demonstrated survival benefits for both PFS and OS.

Several prior systematic reviews and meta-analyses have evaluated CDK4/6 inhibitors in combination with ET for HR+/HER2- advanced breast cancer ⁸⁻¹¹. However, these analyses were limited by the number of included studies, the trial phase, or the lack of detailed subgroup analyses. Earlier analyses reported improvements in PFS and OS but were limited by small numbers of trials, inclusion of phase II studies, or the absence of detailed subgroup and agent-specific analyses ^{9,27}. More recent meta-analyses confirmed survival benefits and highlighted increased adverse events with CDK4/6 inhibitors ^{10,11}; however, they focused primarily on safety outcomes, and did not stratify results by endocrine sensitivity or individual CDK4/6 inhibitor.

In contrast, the present analysis applied strict inclusion criteria, excluding trials with beyond-progression status with prior CDK4/6 inhibitor use, and phase II or lower studies. We included only phase III trials with updated results to ensure adequate power for time-to-event outcomes. Reconstruction of Kaplan–Meier curves enabled more granular estimation of treatment effects, which was further supported by secondary analyses using RMST and conventional meta-analysis.

Importantly, we evaluated clinically relevant subgroups and stratified them by endocrine sensitivity status, which enhances the clinical applicability of the findings. We also stratified CDK4/6 inhibitor by agent, as their survival outcomes can vary, and relying solely on pooled analyses could obscure these differences. Overall, this meta-analysis provides the most up-to-date evidence and addresses key limitations of previous studies.

In our analysis of individual CDK4/6 inhibitors, their effects on OS varied. Palbociclib demonstrated a clear and consistent PFS benefit, but did not show a statistically significant OS benefit in either the overall or the endocrine-sensitive group. In contrast, both abemaciclib and ribociclib demonstrated significant improvements in both PFS and OS. A recent large real-world retrospective study from the US (Flatiron Health database) by Rugo et al. ²⁸ analysed patients with HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors plus NSAI. It included 6,831 patients on palbociclib, 1,279 on ribociclib, and 1,036 on abemaciclib. No significant OS differences were observed among the three agents, and results were consistent across sensitivity and subgroup analyses.

Although real-world data complement clinical trials and offer valuable insights for cancer care, patient selection bias and the lack of randomization remain key limitations. The absence of significant OS differences among CDK4/6 inhibitors in this real-world study does not establish their equivalence, given its observational nature. A head-to-head randomized trial may provide more definitive answers to these questions.

Additional real-world studies by Brufsky et al. evaluated first-line palbociclib in patients aged ≥75 years (n=961) and those with cardiovascular disease (n= 469), populations often underrepresented in phase III trials ^{29,30}. These studies were associated with improved effectiveness and a favourable safety profile of palbociclib. It is worth noting that emerging real-world evidence has revealed disparities between trial participants and routine clinical practice. Pilehvari et al. found that patients receiving first-line CDK4/6 inhibitors were more likely to be younger, White, and have better performance status with fewer comorbidities than those on ET alone ³¹. Black patients had lower odds of receiving CDK4/6 inhibitors than White patients, and patients with Medicare-only were less likely to receive CDK4/6 inhibitors than those with commercial and Medicaid insurance. These disparities may limit access to optimal cancer care and adversely affect health outcomes.

In our analysis, adding CDK4/6 inhibitors to ET improved survival across all clinical subgroups, including those stratified by endocrine-sensitivity. Survival benefits were observed in patients with bone-only, liver, and visceral metastases. Similarly, a published pooled analysis of the MONALEESA trials reported benefits with ribociclib in patients with liver and multiple visceral metastases³², and a meta-analysis in bone-only disease showed superior outcomes with CDK4/6 inhibitors plus ET³³.

TFC and CFS were not primary endpoints in the included trials. These were exploratory secondary endpoints, reported in subsequent overall survival publications. Thus, our analyses of TFC and CFS for CDK4/6 inhibitors should be considered exploratory, though the consistent effect across studies supports the clinical relevance of delaying chemotherapy.

We could not assess other clinicopathological factors that may identify patients who would or would not benefit from CDK4/6 inhibitors. Moreover, data remain limited for specific subgroups such as patients with brain metastases, the very elderly, or those with significant comorbidities. These patients are often excluded from trials, and real-world evidence and prospective studies are warranted to better inform optimal management in these populations.

The optimal sequencing of CDK4/6 inhibitors remains an area of active investigation. Ongoing and recently completed studies suggest that treatment order, duration, and patient selection may influence toxicity and long-term outcomes. Detailed discussion of sequencing strategies is provided in the **appendix (p 2)**. Further work is needed to refine sequencing strategies in routine clinical practice.

For adverse events, Zhang et al. found higher rates of leukopenia, neutropenia, nausea, and diarrhea with CDK4/6 inhibitors compared with ET alone¹⁰. A more recent review assessed the risk of QTc prolongation and major cardiovascular adverse events associated with CDK4/6 inhibitors³⁴. QTc prolongation was reported only in ribociclib and palbociclib trials, with an overall increased risk (RR 1.83, 95% CI 1.23–2.74). In agent-specific analyses, this increased risk was observed only with ribociclib. QTc prolongation was not reported in abemaciclib trials. For cardiovascular adverse events, using a composite of venous thromboembolism (VTE), heart failure, ischemic events, hypertension, arrhythmias, or sudden death, no significant increase was observed overall or by agent. When individual cardiac outcomes were evaluated separately, only VTE and arrhythmias showed an increased risk with abemaciclib; although arrhythmia data were limited. Balancing these risks at baseline and offering a pre-treatment cardiac evaluation, especially for those at higher risk, would be beneficial.

Future research should focus on biologically and genetically guided treatment strategies, as well as comparative analyses of toxicity profiles and patient-reported outcomes, including health-related quality of life (HRQoL) and patient-reported outcome measures (PROMs), to further personalize care.

Survival data, integrated with toxicity and HRQoL considerations, will inform clinical practice and can support shared decision-making between patients and clinicians. Moreover, if a specific CDK4/6 inhibitor is not tolerated, substitutions can be made with confidence that treatment efficacy will not be compromised, which enables a more individualized treatment approach in HR+/HER2- advanced breast cancer.

Our meta-analysis has several limitations. Most notably, we lacked access to the original trial data and therefore relied on reconstructed IPD from published KM curves. While this allows time-to-event analyses, it does not replace a true IPD-MA, particularly for exploring treatment-effect heterogeneity using

multivariable models or unreported baseline covariates. In addition, we were unable to further assess certain subpopulations, such as patients with high burden disease or specific molecular subtypes. Although we closely matched the reconstructed IPD HRs to the original trial HRs through multiple quality checks, minor differences remained, likely due to variations in censoring or other unaccounted factors. These differences were minimal, and the reconstructed curves closely matched the published ones. We further supported our primary findings with conventional meta-analyses and an RMST, which yielded similar conclusions.

Stratified analyses by endocrine sensitivity were not possible for OS. For daltapiclib, OS data are not yet available; therefore, its effects on OS remain unknown. Adverse events were not analysed. Finally, Egger's test suggested possible funnel asymmetry for PFS; however, the funnel plot appeared symmetrical, and excluding the smallest study ($n = 157$) rendered the test non-significant, suggesting a probable small-study effect.

In conclusion, this reconstructed IPD meta-analysis shows that adding CDK4/6 inhibitors to ET significantly improved PFS and OS in HR+/HER2- advanced breast cancer. Exploratory endpoints, including TFC, CFS, and DOR, also showed improvements. PFS and OS benefits were consistent across key subgroups, including age, ethnicity, endocrine sensitivity, progesterone receptor status, menopausal status, ECOG performance status, bone-only disease, and visceral metastasis. Although all CDK4/6 inhibitors showed consistent PFS benefits, OS effects varied by agent: ribociclib and abemaciclib showed statistically significant OS benefits, whereas palbociclib did not, and OS data for daltapiclib are immature.

Further studies, including head-to-head comparisons, assessments of toxicity profiles, and patient-reported outcomes such as HRQoL and other PROMs, are needed to support personalized treatment strategies and optimize care for HR+/HER2- advanced breast cancer.

Contributors

MSB, AF, and ME conceptualised the study. MSB, AF, AA, AFA, and ME developed the methodology. MSB, AF, RHS, AA, and AFA curated the data. MSB, AF, and ME performed the formal analysis. MSB, AF, RHS, and ME conducted the software implementation and statistical analyses. AV, ML, LC, HAA, MEA, AE, MA, and ME validated the study methods and findings. AF, RHS, AA, AFA, MEA, AE, and MA conducted the investigation. MSB, AF, and RHS were responsible for data visualisation. MSB, AF, RHS, AV, ML, LC, GV, and ME drafted the original manuscript. All authors contributed to manuscript review and editing, critically reviewed the content, and approved the final version. AV, ML, LC, GV, and ME supervised the study. ME administered the project. All authors had full access to all the data reported in the study. MSB and ME accessed and verified the data and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

ML reports advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini, Nordic Pharma and Exact Sciences; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Ipsen, Menarini and AstraZeneca; receiving travel grants from Gilead, Roche, and Daiichi Sankyo; receiving research funding (to his institution) from Gilead; and having nonfinancial interests as a member of the national council of the Italian Association of Medical Oncology (AIOM). HA reports the following: Speaker's bureau for AstraZeneca and NewBridge; Honorarium for Roche; Consultant/Advisory roles for Servier, PEP-Therapy, Linkinrax, Traverse Biotech, Nanoligent, Ferring Pharmaceuticals, and Guardant Health. GV reports receiving honoraria from Pfizer, Novartis, Eisai, Lilly,

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Data sharing

All data used in this meta-analysis are publicly available from the included studies. The analysis code can be obtained from the corresponding author upon request. After publication, reconstructed individual patient-level datasets may be shared upon reasonable requests from the corresponding author.

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Figures legend

Figure 1. Pooled analysis of CDK4/6 inhibitors: (A) PFS in endocrine-sensitive disease, (B) PFS in endocrine-resistant disease, (C) OS in endocrine-sensitive disease, and (D) OS in endocrine-resistant disease

Figure 2. Pooled analysis of palbociclib: (A) Overall PFS, (B) PFS in endocrine-sensitive disease, (C) Overall OS, and (D) OS in endocrine-sensitive disease

Abbreviations

HR+: hormone receptor-positive
HER2-: human epidermal growth factor receptor 2-negative
CDK4/6: cyclin-dependent kinase 4/6
ET: endocrine-therapy
NSAIs: non-steroidal aromatase inhibitors
PFS: progression-free survival
OS: overall survival
CFS: chemotherapy-free survival
TFC: time to first chemotherapy
DOR: duration of response
ECOG: Eastern Cooperative Oncology Group
KM: Kaplan-Meier
HR: hazard ratio
RMST: Restricted Mean Survival Time
ORR: objective response rate
HRQoL: health-related quality of life
PROMs: patient-reported outcome measures

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