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Adjuvant CDK4/6 inhibitors combined with endocrine therapy in HR-positive, HER2-negative early breast cancer: A meta-analysis of randomized clinical trials

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ABSTRACT

Background: The benefit of adjuvant cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with endocrine therapy (ET) in hormone receptor-positive, human epidermal growth factor 2 receptor-negative (HR+/HER2-) early breast cancer (EBC) is uncertain. Hence, we performed a meta-analysis to determine the efficacy and safety of adjuvant CDK4/6 inhibitors plus ET and to identify potential preferred subpopulations for this regimen.

Methods: A literature search was conducted in PubMed, Embase, Cochrane databases up to Jan 15, 2021. Hazard ratios (HRs) for invasive disease-free survival (IDFS) and risk ratios (RRs) for grade 3/4 adverse events (AEs) and treatment discontinuation were extracted. Analysis with predefined subgroup variables was done. Trial sequential analysis (TSA) was performed to assess the conclusiveness of survival outcomes.

Results: Three trials were eligible (N = 12647). Compared with ET, adjuvant CDK4/6 inhibitors with ET prolonged IDFS in patients with HR+/HER2- EBC (HR 0.87, 95% CI 0.76–0.98, p = 0.03, I^2 = 19%), with positive therapeutic responses observed in patients with N2/N3 nodal status (HR 0.83, 95% CI 0.71–0.97, p = 0.02, I^2 = 0%). None of the cumulative z-curves crossed the trial monitoring boundaries in TSA, and no reliable conclusion could be drawn. The combination treatment carried a higher risk of grade 3/4 AEs (RR 4.14, 95% CI 3.33–5.15, p < 0.00001) and an increase in treatment discontinuation due to AEs (RR 19.16, 95% CI 9.27–39.61, p < 0.00001).

Conclusions: Adjuvant CDK4/6 inhibitors with ET might provide survival benefit in HR+/HER2- EBC. A statistically significantly improved IDFS was only observed in N2/N3 subgroup. However, overall evidence favoring the use of this combination regimen was inadequate.

Contents

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Introduction

Approximately 70% of early breast cancer (EBC) are diagnosed as hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) [1–4]. Adjuvant endocrine therapy (ET) (aromatase inhibitors and/or antiestrogens with or without ovarian suppression) is a fundamental component of systemic therapy for standard treatment of HR+/HER2- EBC and has contributed to a significant decrease in risk of recurrence and death [5]. Still, up to 20% of patients may experience recurrence with/without distant metastases in the first 10 years [6]. Risk of recurrence is even higher for patients with high-risk clinicopathologic features, especially during the first several years of adjuvant ET [7]. Therefore, it is critical to optimize adjuvant therapy for these patients.

Recent studies have revealed an important role of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in endocrine-resistant breast cancer [8–13]. Cell cycle progression is strictly regulated by a wide range of pathways including the cyclin-dependent kinases (CDK)-retinoblastoma (RB)-E2F pathway [9,14]. The dysregulated CDK-RB-E2F pathways are associated with endocrine-resistance in HR + breast cancer [10,15]. The most relevant therapeutic improvement in this subset is represented by the introduction of CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) to standard ET. These drugs bind to CDK4/6 and inhibit their aberrant functioning, causing cell-cycle arrest and apoptosis [16]. Pivotal trials led to the approval of CDK4/6-inhibitors plus ET combinations after showing almost indistinguishable statistically significant and clinically meaningful improvements in progression-free survival (PFS) and/or overall survival in first/second-line setting of patients with HR+/HER2- metastatic breast cancer (MBC) [17–23]. Median PFS and overall response rates of all the intervention arms were roughly doubled compared to the comparison arms of standard ET [17–23].

Given the success of CDK4/6 inhibitors for HR+/HER2- MBC, there is great interest in determining whether the survival benefit translates into an adjuvant breast cancer setting [24]. All three CDK4/6 inhibitors are being studied in the adjuvant setting in phase III trial [25–28]. Three trials have completed enrollment. The monarchE trial (NCT03155997) explored the adjuvant use of abemaciclib. The PALLAS trial (NCT02513394) studied the addition of palbociclib to standard of care ET in stage II-III HR+/HER2- breast cancer. The PENELOPE-B trial (NCT01864746) investigated the combination of palbociclib with standard ET for patients with HR + residual disease after neoadjuvant chemotherapy. In contrast to the similar benefit observed in MBC, the three trials demonstrated inconsistent primary outcomes regarding the effectiveness of adjuvant CDK4/6 inhibitors in EBC. Thus, we performed this meta-analysis to evaluate the efficacy and safety of CDK4/6 inhibitors in combination with standard endocrine agents as compared to standard ET for the adjuvant treatment of HR+/HER2- EBC, and attempted to identify the potential candidates that may benefit most from this novel therapeutic regimen. Trial sequential analysis (TSA) was also applied to compute the required information size and evaluate the quality of information obtained from the conventional cumulative meta-analysis.

Materials and methods

This was a meta-analysis of randomized controlled trials investigating the efficacy and safety of adjuvant CDK4/6 inhibitors with ET in HR+/HER2- EBC patients. The study was registered on PROSPERO with registration number CRD42021231421.

Data sources and search strategy

A literature search in PubMed, Embase, and Cochrane Register of Controlled Trials with key words related to “palbociclib”, “ribociclib”, “abemaciclib”, “CDK4/6 inhibitors”, “adjuvant”, “endocrine therapy”, “early breast cancer”, and “randomized controlled trial” was conducted up to January 15, 2021. Conference proceedings of American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) were also consulted up to January 2021 to identify unpublished studies. No language restriction was applied. The citation lists of the relevant literature were reviewed for potentially eligible articles.

Study selection

Inclusion criteria were: (1) randomized-controlled trials of CDK4/6 inhibitors with ET for the adjuvant treatment of HR+/

HER2-early breast cancer; (2) trials reporting invasive disease-free survival (IDFS) as the primary outcome and hazard ratios (HRs) with 95% confidence intervals (CIs) for IDFS of the overall patients and the subgroups. Studies not fulfilling the inclusion criteria were excluded. Other exclusion criteria were as followed: (1) on-going trials with no results published or presented; (2) non-randomized, single-arm study; (3) other types of publication including review, trial protocol and report on patient characteristics.

Data extraction and risk of bias assessment

Two investigators (YYL and TZ) independently extracted the data and discrepancies were resolved by consensus. The following data from eligible studies were collected: trial name, design, treatment regimen, dose, population characteristics, the number of participants, median follow-up period, IDFS, number of grade 3/4 adverse events (AEs) and number of treatment discontinuation. The Cochrane Collaboration's tool [29] was used to assess the risk of bias of individual studies.

Statistical analysis

We used HR and 95% CI to evaluate IDFS, and risk ratios (RRs) to evaluate AEs and treatment discontinuation. The Cochran Q test and Higgins I^2 statistic were applied to assess statistical heterogeneity [30]. The pooled HR was calculated by inverse-variance-weighted method; the pooled RR was synthesized by Mantel-Haenszel method. When moderate heterogeneity was observed (p-value <0.10 or I^2 >30%), a random-effects model was employed; otherwise, a fixed-effects model was used. A p-value <0.05 was considered statistically significant. We conducted meta-analysis of IDFS, AEs and treatment discontinuation; and explored the effect of predefined subgroup variables (TNM stage, tumor stage, nodal stage, Ki-67, histologic grade, prior neoadjuvant chemotherapy [NAC], age, ethnicity, menopausal status, and type of CDK4/6 inhibitor) on IDFS. To resolve different subgroup categorizations in individual study, some subgroups were combined into a single group before the final analysis was done. Sensitivity analysis was applied to identify the source of heterogeneity when I^2 >75% in the analysis containing more than two studies. Publication bias was not assessed due to inadequate trials included in the analysis. Statistical analyses were carried out using Review Manager version 5.4 software (Cochrane Tech, London, UK).

Positive results from meta-analysis of IDFS were examined with TSA. We set a two-sided 5% risk of type I error ($\alpha = 5\%$) and 20% risk of type II error ($\beta = 20\%$). Analyses were conducted with both a priori information size (APIS) and low-bias heterogeneity-adjusted information size (LBHIS) to estimate a realistic sample size [31,32]. APIS was computed for an a priori prespecified relative risk reduction (RRR) of 15%, the intervention effect seems relevant in most therapeutic area [31]. LBHIS was based on I^2 from all included studies [30] and the information size from trials with adequate allocation concealment [33]. Trial sequential monitoring boundaries (TSMB) using APIS ($TSMB_{APIS}$) and LBHIS ($TSMB_{LBHIS}$) were determined by O'Brien–Fleming α-spending function [34]. When $I^2 \leq 30\%$, a fixed-effects model was employed to calculate cumulative z-scores; otherwise, a random-effects model was used. We constructed a cumulative z-curve and assessed its crossing of $TSMB_{APIS}$ and $TSMB_{LBHIS}$ to ascertain the conclusiveness of the effectiveness of CDK4/6 inhibitor-based adjuvant regimen. TSA was performed using the metacumbounds command of Stata (version 16.0) [35].

Results

Characteristics of eligible studies

The literature search returned 115 records and three eligible phase III trials were identified (Fig. 1). Some data were retrieved from a later-published full article [36] and two latest conference proceedings [37,38]. A total of 12647 HR+/HER2- EBC patients were randomized to receive adjuvant CDK4/6 inhibitors in combination with ET (N = 6322; abemaciclib 44.4%, palbociclib 55.6%) versus adjuvant ET (N = 6325). The risk of bias was low for PENELOPE-B [27] and unclear for monarchE [25] and PALLAS [26] (Supplementary Figure 1). Main characteristics of the included studies are summarized in Table 1. Combination of subgroups was done for monarchE and PALLAS due to different subgroup categorizations (Supplementary Table 2).

Invasive disease-free survival

An overall pooled IDFS benefit was observed for adjuvant CDK4/6 inhibitors in combination with ET compared to standard ET (HR 0.87, 95% CI 0.76–0.98, p = 0.03, I^2 = 19%; Fig. 2).

Predefined subgroup analysis

Moderate heterogeneity was detected in six subgroups (stage IIB/III, stage T0/T1/Tis/TX, stage T3/T4, non-Asian, prior NAC, and premenopausal status) and a random-effects model was applied. Only one study reported the findings for Ki-67, and thus analysis was not conducted for this subgroup.

TNM stage

Two studies reported IDFS HR for patients with stage IIA (N = 1689). The pooled effect of adjuvant CDK4/6 inhibitors plus ET versus ET was not significant (HR 0.84, 95% CI 0.53–1.33, p = 0.46). Two studies reported the results for patient with stage IIB/III (N = 9468) and the cumulative effect was also statistically insignificant (HR 0.82, 95% CI 0.64–1.04, p = 0.10) (Fig. 3A). No significant subgroup differences were detected (p = 0.92).

Tumor stage

Two studies provided the findings for patients in stage T0/T1/Tis/TX (N = 2602), and the intervention effect of adjuvant CDK4/6 inhibitors plus ET in this subgroup was statistically insignificant (HR 0.81, 95% CI 0.47–1.39, p = 0.45). Two studies provided the findings for patients in stage T2 (N = 6027). The cumulative effect for the combination therapy was not significant (HR 0.84, 95% CI 0.67–1.04, p = 0.10). Results for patients in stage T3/T4 were also provided in two studies (N = 2685). The pooled result remained insignificant (HR 0.84, 95% CI 0.57–1.24, p = 0.39) (Fig. 3B). No significant subgroup differences were observed (p = 0.99).

Nodal stage

All the included studies reported IDFS for patients in stage N0/N1 (N = 6474) and N2/N3 (N = 6157). A statistically significant effect adjuvant CDK4/6 inhibitors plus ET was observed in stage N2/N3 (HR 0.83, 95% CI 0.71–0.97, p = 0.02), but not in stage N0/N1 (HR 0.87, 95% CI 0.71–1.07, p = 0.19) (Fig. 3C). Subgroup differences

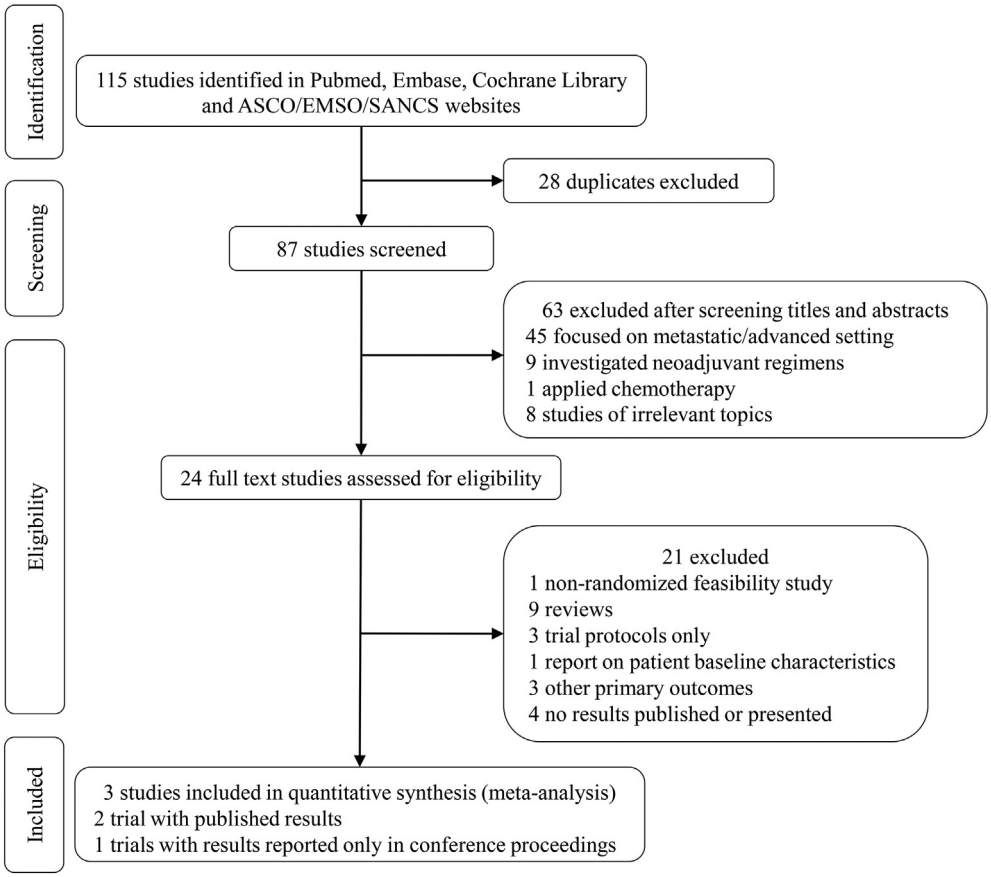

Fig. 1. Flow diagram of identifying eligible studies.

Table 1
Characteristics of included studies.

Trial	Design	Population characteristics	Regimen	Dose	ITT N	Median age, year	Median follow-up, mo	Primary endpoint	IDFS HR (95% CI) of overall patients
monarchE	Open label, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, high risk[a], stage II or III, node positive, with or without NACT	Abemaciclib + ET vs ET alone	Abemaciclib 150 mg bid × 2 years; standard adjuvant ET[d]	5637 (2808/2829)	51; 51	15.5; 15.5	IDFS	0.75 (0.60–0.93)
PALLAS	Open label, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, low risk or high risk[b], stage II or III, node positive or negative, with or without NACT	Palbociclib + ET vs ET alone	Palbociclib 125 mg once daily, d1-21 in a 28-day cycle × 2 years; standard adjuvant ET[d]	5760 (2883/2877)	52; 52	23.7; 23.7	IDFS	0.93 (0.76–1.15)
PENELOPE-B	Double blind, randomized (1:1), phase III	HR + HER2-, pre- or post-menopausal, high risk[c], early BC, node positive or negative, no pCR after NACT	Palbociclib + ET vs placebo + ET	Palbociclib 125 mg once daily, p.o., d1-21, q28d for 13 cycles; Placebo d1-21, q28d for 13 cycles; ET according to local standard	1250 (631/619)	49; 48	42.8; 42.8	IDFS	0.93 (0.74–1.17)

ITT intention-to-treat; *IDFS* invasive disease-free survival; *HR* hazard ratio; *95% CI* 95% confidence interval; *TNM* tumor, node, metastasis; *ET* endocrine therapy (aromatase inhibitors and/or antiestrogens with or without ovarian suppression); *NACT* neoadjuvant chemotherapy; *BC* breast cancer; *pCR* pathologic complete remission.

[a] Defined as patients with four or more positive pathologic axillary lymph nodes or one to three positive axillary lymph nodes and at least one of the following: tumor size≥5 cm, histologic grade 3, or centrally assessed Ki-67 ≥ 20%.

[b] Defined as patients with≥4 nodes involved (≥N2), or 1–3 nodes with either T3/T4 and/or G3 disease.

[c] Defined as patients with CPS-EG (Clinical-Pathologic Scoring System incorporating estrogen receptor-negative disease and nuclear grade 3 tumor pathology) score≥3, or 2 with ypN+.

[d] Consist of tamoxifen or an aromatase inhibitor (letrozole, anastrozole exemestane), with or without an LHRH agonist.

between these groups were insignificant (p = 0.69).

Histologic grade

Two studies reported the results for patients with G1/G2 histologic grade (N = 7085), and patients with G3 histologic grade (N = 3759). The cumulative estimates of adjuvant CDK4/6 inhibitors plus ET versus ET in both subgroups were statistically insignificant (HR 0.82, 95% CI 0.66–1.01, p = 0.07; and HR 0.82, 95%

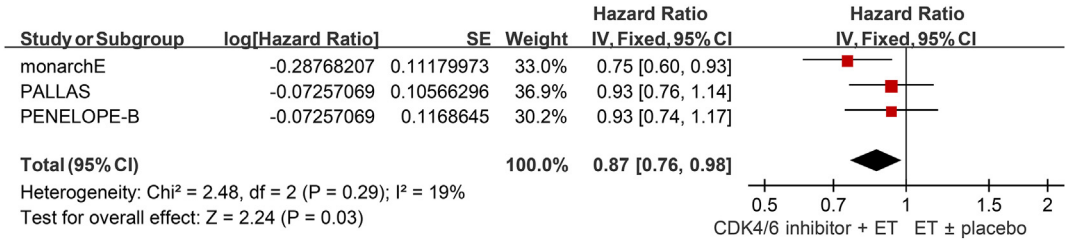

Fig. 2. Forest plot of pooled hazard ratio for invasive disease-free survival of CDK4/6 inhibitors plus endocrine therapy versus ET in the overall patients. ET endocrine therapy.

CI 0.65–1.03, p = 0.09, respectively) (Fig. 3D). There were no significant subgroup differences (p = 0.48).

Prior NAC

Survival outcomes for patients with prior NAC (N = 3306) were reported in two studies. The cumulative result of adjuvant CDK4/6 inhibitors plus ET was statistically insignificant (HR 0.76, 95% CI 0.51–1.14, p = 0.19). One study reported the outcome for patients without prior NAC or adjuvant chemotherapy (N = 1005) and the effect was also insignificant (HR 0.71, 95% CI 0.39–1.29, p = 0.26) (Fig. 3E). Differences between the two subpopulations were insignificant (p = 0.85).

Ethnicity

Two studies reported IDFS HR for non-Asians (N = 5366). The pooled estimate of adjuvant CDK4/6 inhibitors plus ET was not remarkable (HR 0.83, 95% CI 0.64–1.07, p = 0.15). Two studies reported the results for Asians (N = 1439), and the intervention effect was also unremarkable (HR 0.82, 95% CI 0.54–1.26, p = 0.37) (Fig. 3F). No significant subgroup differences were detected (p = 0.99).

Age

Results for patients ≤50 (N = 3314) and >50 years old (N = 3759) were provided in two studies. No statistically significant effect of adjuvant CDK4/6 inhibitors plus ET was observed in both subgroups (HR 1.01, 95% CI 0.81–1.25, p = 0.96, and HR 0.86, 95% CI 0.70–1.07, p = 0.18, respectively) (Fig. 2G). There were no significant differences between the two groups (p = 0.33).

Menopausal status

Two studies reported the subgroup findings for premenopausal patients (N = 3069), and one study reported the finding for postmenopausal patients (N = 3184). The treatment effects of adjuvant CDK4/6 inhibitors combined with ET in both subgroups were statistically insignificant (HR 0.78, 95% CI 0.52–1.17, p = 0.23; and HR 0.82, 95% CI 0.62–1.08, p = 0.16, respectively) (Fig. 3H).

Type of CDK4/6 inhibitor

The pooled HR for abemaciclib and palbociclib was 0.75 (95% CI 0.60–0.93, p = 0.01) and 0.93 (95% CI 0.80–1.08, p = 0.35), respectively. There were no statistically significant discrepancies between the two types of CDK4/6 inhibitor regarding clinical efficacy (p = 0.12).

Trial sequential analysis

TSA of two meta-analyses of IDFS was conducted using fixed-effects models. We found lack of evidence for an overall favorable effect of adjuvant CDK4/6 inhibitors with ET over standard endocrine agents in HR+/HER2- EBC. The cumulative z-curve only touched the $TSMB_{APIS}$ and $TSMB_{LBHIS}$, with the accumulated information size exceeding APIS (Fig. 4A), but not LBHIS (Fig. 4B), implying a potential weaker intervention effect than anticipated from a prespecified 15% RRR and more trials should be included in the analysis to provide substantial evidence for an intervention effect of 13% RRR. Likewise, evidence for the superiority of the combination therapy over standard ET in patients with stage N2/N3 was inconclusive. The cumulative z-curve just crossed $TSMB_{APIS}$ before APIS and did not cross $TSMB_{LBHIS}$ despite accruing adequate information size (Fig. 4C and D), suggesting this meta-analysis was underpowered to detect a 17% RRR suggested by studies with low-bias risk and future studies were warranted to confirm the prespecified 15% RRR.

Grade 3/4 adverse events

All the studies provided the incidence of total grade 3/4 AEs. The pooled RR was 4.14 with significant heterogeneity emerged (95% CI 3.33–5.15, p < 0.00001, I^2 = 91%; Fig. 5A). After excluding PALLAS, I^2 for heterogeneity dramatically reduced from 91% to 0% (Supplementary Table 3). Subgroup analysis with type of CDK4/6 inhibitor demonstrated no statistically significant differences between abemaciclib and palbociclib in total grade 3/4 AEs (p = 0.08; Supplementary Fig. 2A).

Grade 3/4 hematologic AEs were more commonly observed in CDK4/6 intervention arm in the three studies (RR 45.96, 95% 13.57–155.70, p < 0.00001). The RRs were 67.39 (95% CI 19.56–232.17, p < 0.0001) for neutropenia, 86.69 (95% CI 20.52–366.23, p = 0.0005) for leukopenia, 4.17 (95% CI 2.37–7.32, p < 0.00001) for anemia, 11.12 (95% CI 7.20–17.18, p < 0.00001) for lymphopenia, and 8.26 (95% CI 2.33–29.34, p = 0.001) for thrombocytopenia. The pooled estimate of grade 3/4 non-hematologic AEs in the three studies was statistically insignificant (RR 2.23, 95% CI 0.77–6.44, p = 0.14). The RRs were 5.86 for fatigue (95% CI 1.64–20.93, p = 0.006), 2.73 for nausea (95% CI 0.70–10.68, p = 0.15), 5.24 for diarrhea (95% CI 0.30–92.27, p = 0.26), and 0.62 for arthralgia (95% CI 0.31–1.25, p = 0.18) (Fig. 5B, Supplementary Fig. 2B and C). The results of sensitivity analysis are presented in Supplementary Table 4–9.

Treatment discontinuation

Pooled analysis of the three included studies revealed an insignificant increase in patients discontinuing treatment in the combination arm (RR 2.07, 95% CI 0.55–7.77, p = 0.28, I^2 = 100%; Fig. 6A). Sensitivity analysis identified PALLAS as the major source of heterogeneity (Supplementary Table 10).

The incidence of treatment interruption due to AEs was markedly higher in the intervention group than the control group. The pooled RR was 19.14 (95% CI 9.25–39.58, p < 0.00001, I^2 = 81%; Fig. 6B), and 27.64 (95% CI 17.95–42.55, p < 0.00001, I^2 = 52%; Supplementary Table 11) after excluding PENELOPE-B. Two studies provided the number of patients discontinuing treatment due to

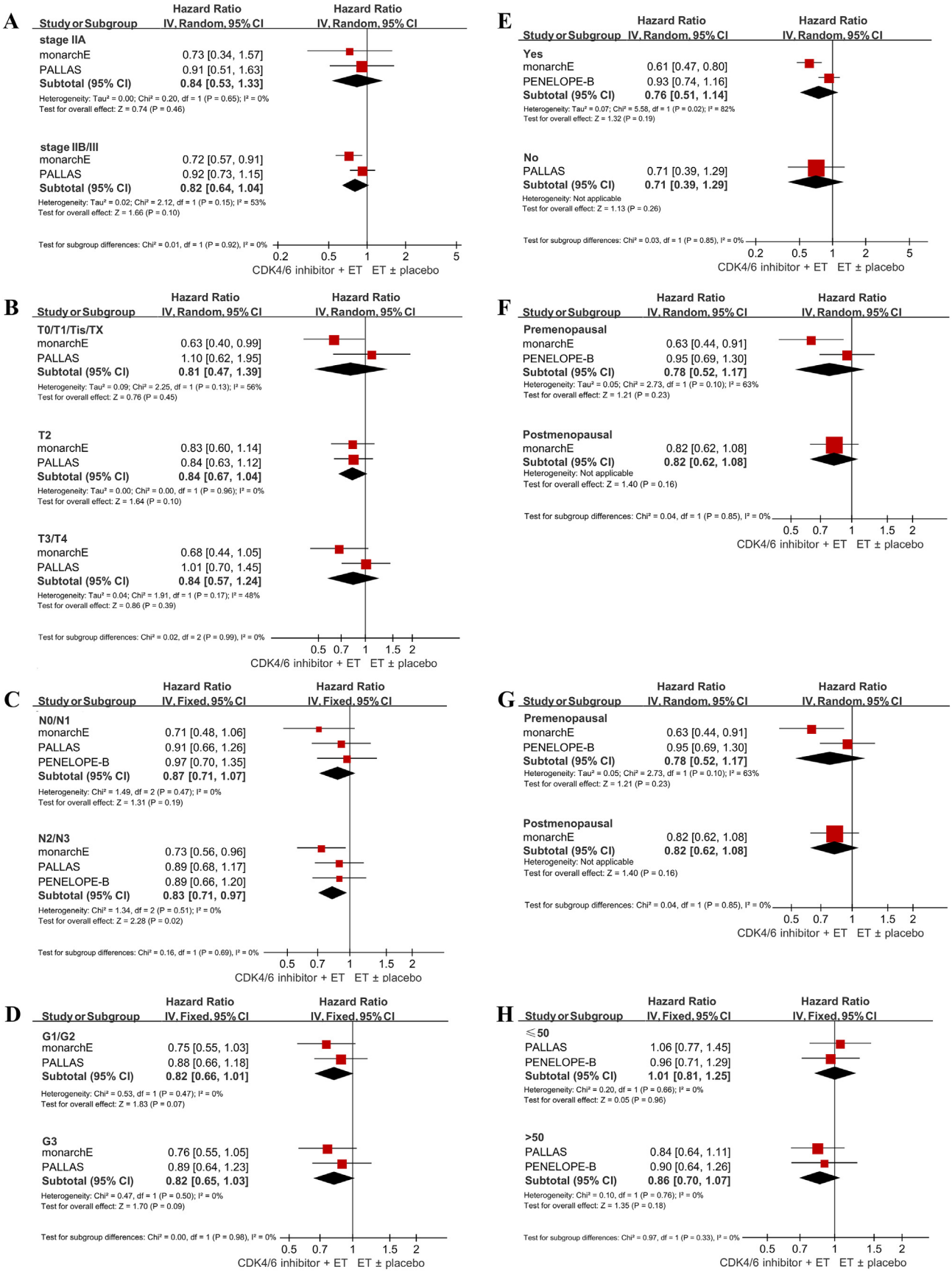

Fig. 3. Forest plot of pooled hazard ratios comparing invasive disease-free survival in stage IIA and stage IIB/III subgroups (A); in stage T0/T1/Tis/TX, stage T2 and stage T3/T4 subgroups (B); in N0/N1 and N2/N3 subgroups (C); in G1/G2 and G3 subgroups (D); in patients with or without prior neoadjuvant chemotherapy (E); in non-Asians and Asians (F); in patients ≤50 years old and patients >50 years old (G); in premenopausal and postmenopausal patients (H). ET endocrine therapy.

development of recurrent disease or secondary malignancy, and the cumulative result was statistically insignificant (RR 0.91, 95% CI 0.45–1.83, p = 0.78, I^2 = 85%; Supplementary Fig. 3A). The pooled estimate of treatment interruption owing to death was also insignificant (RR 1.36, 95% CI 0.77–2.43, p = 0.29, I^2 = 0%; Supplementary Fig. 3B).

Discussion

Optimizing adjuvant therapy for HR+/HER2- EBC is imperative to preventing early recurrence and metastases. Three large-scale, randomized, phase III trials reported inconsistent primary outcomes regarding the efficacy of adjuvant CDK4/6 inhibitors with ET in EBC. The present study is the first meta-analysis with TSA that summarizes the association between CDK4/6 inhibitor-based adjuvant therapy and survival outcomes in HR+/HER2- EBC. Results showed a potential favorable effect of adjuvant CDK4/6 inhibitors combined with ET over standard ET in HR+/HER2- EBC, and patients in stage N2/N3 were the only subpopulation that could derive statistically significant survival benefit from the combination treatment. However, overall evidence favoring the use of this novel regimen was inadequate. Future trials are needed to establish firm evidence for these findings.

Our meta-analysis demonstrated survival benefit of adjuvant CDK4/6 inhibitors with ET in EBC (IDFS HR 0.87, 95% CI 0.76–0.98, p = 0.03). The cumulative z-curve did not cross the TSMB in TSA, indicating that the current meta-analysis is of insufficient evidence to substantiate the result, and the overall intervention effect of the combination therapy may be around 13% RRR, which awaits validation by including more trials in the analysis to accrue ample information size. We further focused our meta-analysis on predefined subgroups of clinical relevance. The combinatorial regimen did not significantly prolong IDFS in most subgroups irrespective of TNM stage (stage IIA vs stage IIB/III), tumor stage (T0/T1/Tis/TX, T2 vs T3/T4), histologic grade (G1/G2 vs G3), prior NAC (yes vs no), ethnicity (non-Asian vs Asian), age (≤50 years old vs > 50 years old), or menopausal status (premenopausal vs postmenopausal). A statistically significant treatment effect was only observed in patients with stage N2/N3 (HR 0.83, 95% CI 0.71–0.97, p = 0.02). Results from TSA suggested a possible therapeutic effect of 15% RRR without reaching the required information size, which also calls for an update analysis involving more studies. Lymph node involvement is one of the most important risk factors for disease recurrence in HR + EBC. Unlike positive hormonal status, no statistical correlation between node infiltration and strong cyclin D1 protein expression and gene amplification was heretofore established [39–41]. Therefore, the mechanisms underlying the prognostic value of advanced nodal status in HR+/HER2- EBC patients receiving adjuvant CDK4/6 inhibitors plus standard ET is still unclear. Recent updates of subgroup analyses in PENELOPE-B

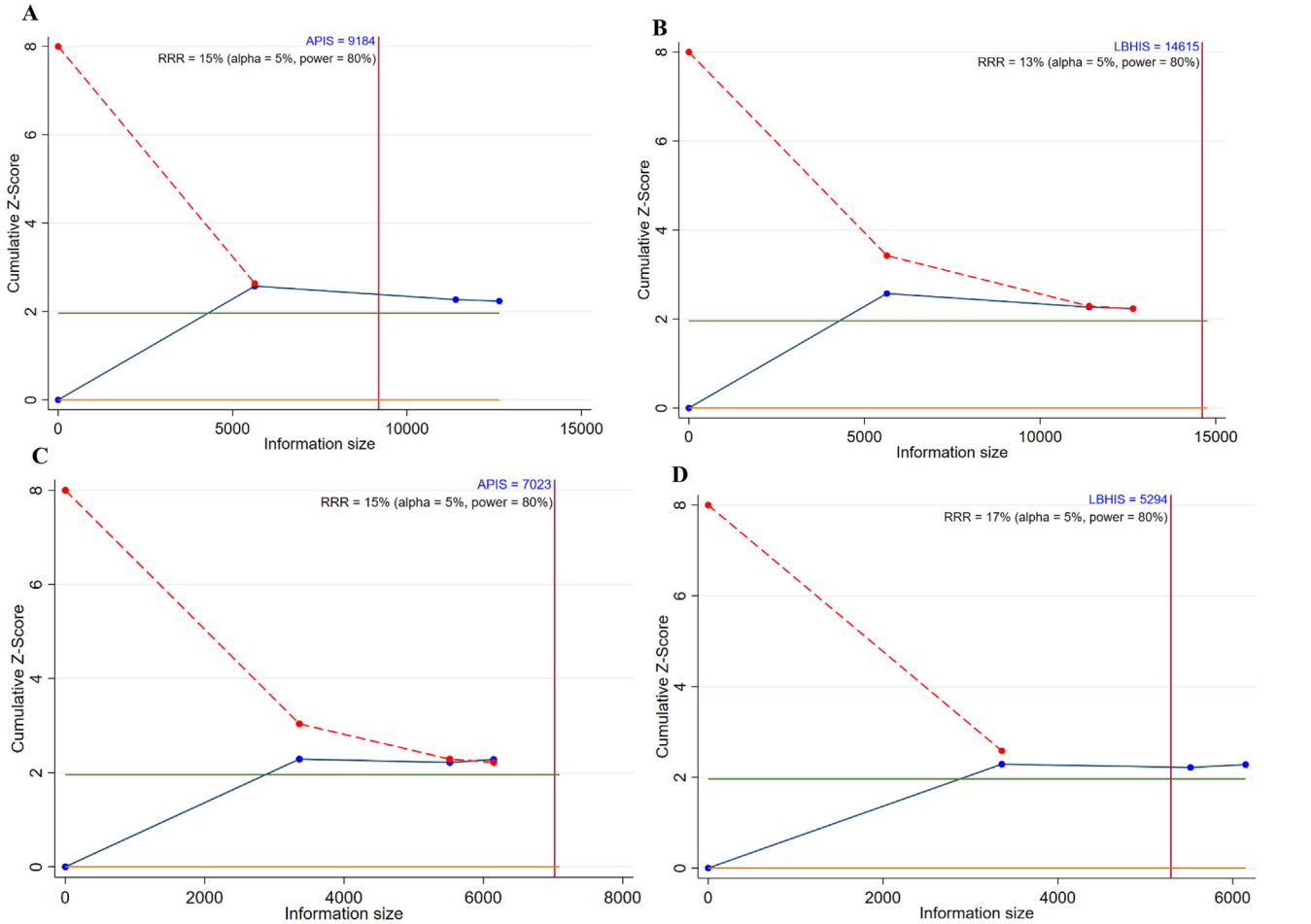

Fig. 4. Trial sequential analyses of meta-analysis of adjuvant CDK4/6 inhibitor-endocrine therapy in overall patients (A, B) and patients with stage N2/N3 (C, D) HR+/HER2-early breast cancer. The blue full line represents the cumulative z-curve; the green full line represents the conventional boundary for statistical significance (p = 0.05); the red dotted line represents the trial monitoring boundary; and the red full line represents the required information size determined by APIS (A, C) and LBHIS (B, D). APIS a priori information size; LBHIS low-bias heterogeneity-adjusted information size; RRR relative risk reduction; alpha risk of type I error; power statistical power to reject type II error.

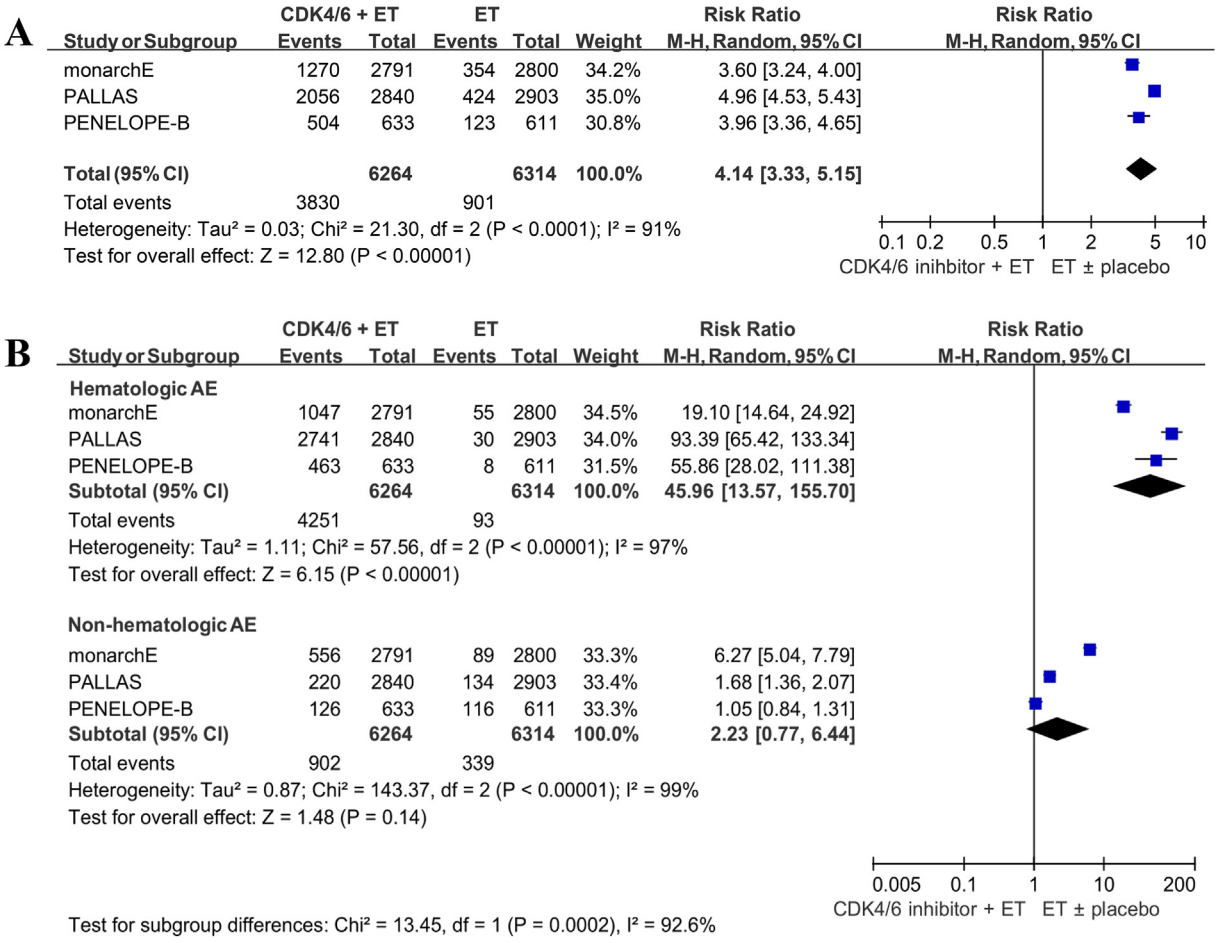

Fig. 5. Forest plot of pooled risk ratio for grade 3/4 adverse events in the overall patients (A); forest plot of pooled risk ratio for grade 3/4 hematologic and non-hematologic adverse events (B). ET endocrine therapy.

revealed that numerically significant benefit from palbociclib was seen in a small group of patients (N = 64) with a luminal-B tumor assessed by Absolute Intrinsic Molecular Subtyping (IDFS HR 0.50, 95% CI 0.24–1.05), and a small subgroups of premenopausal patients (N = 119) receiving tamoxifen and gonadotropin-releasing hormone analogue as adjuvant ET (HR 0.52, 95% CI 0.27–1.02) [38,42]. Given the limited number of patient cohort, these results are mainly hypothesis generating and merit confirmation by examining the corresponding subgroup outcomes in other parallel clinical trials. Overall, our findings suggest the lack of definitive clinicopathologic features indicative of preferred therapeutic responses to adjuvant CDK4/6 inhibitors treatment. Combined with the fact that there are no available genomic signatures or validated predictive biomarkers to adequately select patients for CDK4/6 inhibitors [43,44], introduction of adjuvant CDK4/6 inhibitors to ET in HR+/HER2- EBC warrants deliberation.

The efficacy of the three CDK4/6 inhibitors abemaciclib, palbociclib, and ribociclib in combination with ET for HR+/HER2- MBC is almost parallel across different clinical trials. In the adjuvant setting, the effectiveness of abemaciclib and palbociclib contradicts one another (HR 0.75 [95% CI 0.60–0.93] vs. 0.93 [95% CI 0.80–1.08]), despite a statistically insignificant test for subgroup differences (p = 0.12). Possible explanations for the conflicting findings can be encapsulated in three aspects. One consideration is the differences in study population. Both monarchE and PENELOPE-B specifically enrolled EBC patients with high-risk of recurrence. In contrast, only 58.7% of patients in PALLAS were of high clinical risk disease. Enrollment of low-risk patients may have contributed to the negative results of PALLAS. A substantial proportion of patients in the intervention group in PALLAS discontinued treatment prematurely (42.2% versus 16.6% in monarchE and 19.5% in PENELOPE-B), which may also precipitate the observed lack of benefit from palbociclib. Additionally, even though both monarchE and PENELOPE-B exclusively included high-risk patients, the two trials applied different eligibility criteria, possibly making the positive results of monarchE irreproducible in PENELOPE-B. There are also concerns with the discrepancies in trial design. The course of treatment varied across studies. Both monarchE and PALLAS adopted a two-year treatment schedule, whereas PENELOPE-B only adopted a one-year treatment schedule. It is not impossible that positive results could be obtained in PENELOPE-B with continuation of therapy beyond one year. The duration of follow-up also raises attention. The median follow-up was 15.5 months for monarchE, 23.7 months for PALLAS, and 42.8 months for PENELOPE-B. Some researchers suggested that the follow-up in PALLAS was inadequate and might obscure potential significant delayed effect of palbociclib; and for monarchE, HR interpretation might be confounded by temporal fluctuations given the shortest period of follow-up period among the three trials [45]. The latest updates in monarchE partly addressed such concern, and showed that with an extended period of follow-up to over 24 months, the IDFS improvement for HR+/HER2- EBC who received prior NAC remained statistically significant (HR 0.61, 95% CI 0.47–0.80) [37], suggesting a lasting treatment benefit from adjuvant abemaciclib.

Results of grade 3/4 toxicity profiles in the present study mirrored those observed in the metastatic setting (RR 4.14, 95% CI

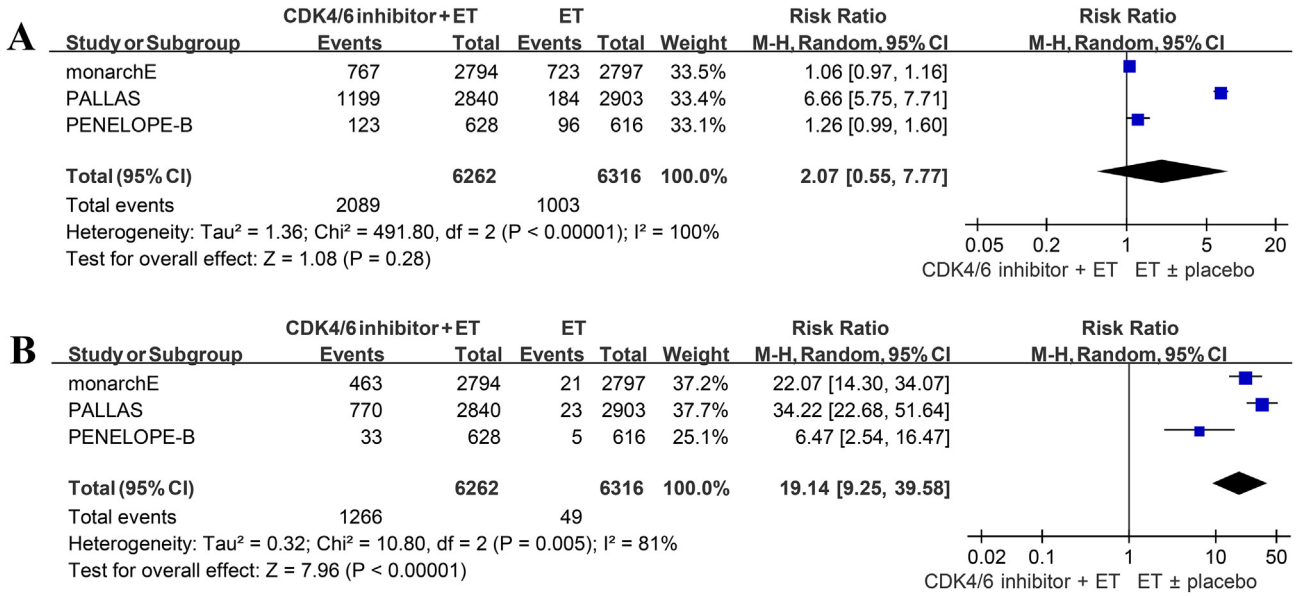

Fig. 6. Forest plot of pooled risk ratio for treatment discontinuation (A); forest plot of pooled risk ratio for treatment discontinuation due to adverse events (B). ET endocrine therapy.

3.33–5.15, p < 0.0001) [17,18,20,23]. Administration of CDK4/6 inhibitors was associated with a significantly higher risk of grade 3/4 hematologic AEs (RR 45.96, 95% 13.57–155.70, p < 0.00001) compared to non-hematologic AEs (RR 2.23, 95% CI 0.77–6.44, p = 0.14), and an increase in early treatment discontinuation caused by AEs (RR 19.14, 95% CI 9.25–39.58, p < 0.00001). No significant differences between the two types of CDK4/6 inhibitor regarding the incidence of total grade 3/4 AEs was found (p = 0.08). PALLAS was the primary source of heterogeneity in the pooled analysis for grade 3/4 AEs and early treatment discontinuation. It is possible that such findings are attributed to the relatively high proportion of low-risk patients included in the study.

Our study has several limitations. First, the aggregated data were from published articles instead of individual patient data. Second, subgroup characterizations differed across the included studies, making it unfeasible to extract all the primary results for each predefined subgroup. Third, the inclusion of two different CDK4/6 inhibitors (abemaciclib and palbociclib) might introduce heterogeneity to the analysis.

A recent meta-analysis has also evaluated CDK4/6 inhibitors as adjuvant treatment for HR+/HER2- EBC. Similarly to our results, it has showed that administration of adjuvant CDK4/6 inhibitors was associated with a trend toward an IDFS benefit and an increase in the risk of toxicities and treatment discontinuation [46]. However, in this meta-analysis, two out of the three included trials had unpublished data, possibly undermining the accuracy of results. Comparatively, our study collected the latest data from published articles and conference proceedings of the three trials. In addition, we further ascertained the quality of information obtained from the conventional meta-analysis by performing TSA. We found that patients with N2/N3 disease had a tendency to benefit from adding CDK4/6 inhibitors to standard adjuvant treatment, and future analysis renewed with data from the currently ongoing studies (NCT03701334 and NCT03820830) is essential to help determine the ultimate role of CDK4/6 inhibitors in the adjuvant setting. Translation analyses from the included studies are also eagerly awaited to elucidate the relationship between high-risk clinicopathologic features, such as receiving prior NAC, advanced nodal status and luminal-B tumors, and therapeutic responses to CDK4/6 inhibitors. In short, adjuvant use of CDK4/6 inhibitors is not suitable for all HR+/HER2- EBC patients. Careful decision making is required in better tailoring patients' treatments.

Conclusions

Adjuvant CDK4/6 inhibitors with ET may provide survival benefit in HR+/HER2- EBC. A statistically significant IDFS benefit was only observed in patients with N2/N3 disease. However, overall evidence favoring the use of this combination regimen was inadequate, and future trials are warranted to substantiate the results. Compared with ET, the addition of CDK4/6 inhibitors to ET carries a higher risk of grade 3/4 AEs and early treatment discontinuation. These results highlight the imperative to identify predictive biomarkers to select patients for whom adjuvant CDK4/6 inhibitors constitute effective treatment, and to investigate the correlation between tumor biology and the pharmacodynamics of different CDK4/6 inhibitors to guide adjuvant therapeutic strategy for HR+/HER2- EBC.

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Data availability statement

The data underlying this study will be shared on reasonable request to the corresponding author.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.07.002.

References

[1] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. Epub 2014/04/30 J Natl Cancer Inst 2014;106(5). https://doi.org/10.1093/jnci/dju055. PubMed PMID: 24777111; PubMed Central PMCID: PMC4580552.

[2] Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, et al. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015). Epub 2018/04/22 Breast 2018;39:131–8. https://doi.org/10.1016/j.breast.2018.03.002. PubMed PMID: 29679849.

[3] Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Epub 2009/05/26 Breast Cancer Res 2009;11(3):R31. https://doi.org/10.1186/bcr2261. PubMed PMID: 19463150; PubMed Central PMCID: PMC2716499.

[4] Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Epub 2009/07/04 Clin Med Res 2009;7(1–2):4–13. https://doi.org/10.3121/cmr.2009.825. PubMed PMID: 19574486; PubMed Central PMCID: PMC2705275.

[5] National Comprehensive Cancer Network. Breast cancer (version 1.2021). 2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

[6] Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386(10001):1341–52. https://doi.org/10.1016/S0140-6736(15)61074-1.

[7] Mamounas EP, Tang G, Paik S, Baehner FL, Liu Q, Jeong JH, et al. 21-Gene Recurrence Score for prognosis and prediction of taxane benefit after adjuvant chemotherapy plus endocrine therapy: results from NSABP B-28/NRG Oncology. Epub 2017/11/13 Breast Canc Res Treat 2018;168(1):69–77. https://doi.org/10.1007/s10549-017-4550-8. PubMed PMID: 29128898; PubMed Central PMCID: PMC5996978.

[8] Murphy CG, Dickler MN. Endocrine resistance in hormone-responsive breast cancer: mechanisms and therapeutic strategies. Epub 2016/07/14 Endocr Relat Canc 2016;23(8):R337–52. https://doi.org/10.1530/ERC-16-0121. PubMed PMID: 27406875.

[9] Hamilton E, Infante JR. Targeting CDK4/6 in patients with cancer. Epub 2016/03/28 Canc Treat Rev 2016;45:129–38. https://doi.org/10.1016/j.ctrv.2016.03.002. PubMed PMID: 27017286.

[10] Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. Epub 2016/02/10 Breast Cancer Res 2016;18(1):17. https://doi.org/10.1186/s13058-015-0661-5. PubMed PMID: 26857361; PubMed Central PMCID: PMC4746893.

[11] Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. Epub 2006/04/11 J Clin Oncol 2006;24(11):1770–83. https://doi.org/10.1200/JCO.2005.03.7689. PubMed PMID: 16603719.

[12] Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Canc Therapeut 2004;3(11):1427–38. Epub 2004/11/16. PubMed PMID: 15542782.

[13] Gelbert LM, Cai S, Lin X, Sanchez-Martinez C, Del Prado M, Lallena MJ, et al. Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. Epub 2014/06/13 Invest N Drugs 2014;32(5):825–37. https://doi.org/10.1007/s10637-014-0120-7. PubMed PMID: 24919854; PubMed Central PMCID: PMC4169866.

[14] Johnson J, Thijssen B, McDermott U, Garnett M, Wessels LF, Bernards R. Targeting the RB-E2F pathway in breast cancer. Epub 2016/03/01 Oncogene 2016;35(37):4829–35. https://doi.org/10.1038/onc.2016.32. PubMed PMID: 26923330; PubMed Central PMCID: PMC4950965.

[15] Baker SJ, Reddy EP. CDK4: a key player in the cell cycle, development, and cancer. Epub 2013/05/02 Genes Cancer 2012;3(11–12):658–69. https://doi.org/10.1177/1947601913478972. PubMed PMID: 23634254; PubMed Central PMCID: PMC3636745.

[16] Schettini F, De Santo I, Rea CG, De Placido P, Formisano L, Giuliano M, et al. CDK 4/6 inhibitors as single agent in advanced solid tumors. Epub 2019/01/12 Front Oncol 2018;8:608. https://doi.org/10.3389/fonc.2018.00608. PubMed PMID: 30631751; PubMed Central PMCID: PMC6315195.

[17] Sledge Jr GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. Epub 2017/06/06 J Clin Oncol 2017;35(25):2875–84. https://doi.org/10.1200/JCO.2017.73.7585. PubMed PMID: 28580882.

[18] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Epub 2016/03/08 Lancet Oncol 2016;17(4):425–39. https://doi.org/10.1016/S1470-2045(15)00613-0. PubMed PMID: 26947331.

[19] Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Epub 2018/05/29 Lancet Oncol 2018;19(7):904–15. https://doi.org/10.1016/S1470-2045(18)30292-4. PubMed PMID: 29804902.

[20] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. Epub 2016/12/14 N Engl J Med 2016;375(20):1925–36. https://doi.org/10.1056/NEJMoa1607303. PubMed PMID: 27959613.

[21] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Epub 2018/05/03 Ann Oncol 2018;29(7):1541–7. https://doi.org/10.1093/annonc/mdy155. PubMed PMID: 29718092.

[22] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. Epub 2018/06/05 J Clin Oncol 2018;36(24):2465–72. https://doi.org/10.1200/JCO.2018.78.9909. PubMed PMID: 29860922.

[23] Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. Epub 2017/10/03 J Clin Oncol 2017;35(32):3638–46. https://doi.org/10.1200/JCO.2017.75.6155. PubMed PMID: 28968163.

[24] Mayer EL, DeMichele A, Rugo HS, Miller K, Waks AG, Come SE, et al. A phase II feasibility study of palbociclib in combination with adjuvant endocrine therapy for hormone receptor-positive invasive breast carcinoma. Ann Oncol : official journal of the European Society for Medical Oncology 2019;30(9):1514–20. https://doi.org/10.1093/annonc/mdz198.

[25] Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR1, HER22, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38(34):3987–98. https://doi.org/10.1200/JCO.20.02514.

[26] Mayer EL, Dueck AC, Martin M, Rubovszky G, Burstein HJ, Bellet-Ezquerra M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2021;22(2):212–22. https://doi.org/10.1016/S1470-2045(20)30642-2.

[27] Sibylle Loibl FM, Martin Miguel, Untch Michael, Bonnefoi Hervé, Kim Sung-Bae, Bear Harry, Mc Carthy Nicole, Olivé Mireia Melé, Gelmon Karen, et al., editors. Phase III study of palbociclib continued with endocrine therapy in patients with hormone-receptor-positive, HER2-negative primary breast cancer and high relapse risk after neoadjuvant chemotherapy: first results from the PENELOPE-B. San Antonio Breast Cancer Symposium Virtual Meeting; December 8-11; 2020.

[28] 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. https://doi.org/10.1200/JCO.2019.37.15-suppl.TPS597.

[29] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Epub 2011/10/20 BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928. PubMed PMID: 22008217; PubMed Central PMCID: PMC3196245.

[30] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Epub 2002/07/12 Stat Med 2002;21(11):1539–58. https://doi.org/10.1002/sim.1186. PubMed PMID: 12111919.

[31] Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Epub 2007/12/18 J Clin Epidemiol 2008;61(1):64–75. https://doi.org/10.1016/j.jclinepi.2007.03.013. PubMed PMID: 18083463.

[32] Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Epub 2008/04/16 J Clin Epidemiol 2008;61(8):763–9. https://doi.org/10.1016/j.jclinepi.2007.10.007. PubMed PMID: 18411040.

[33] Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Epub 1995/02/01 J Am Med Assoc 1995;273(5):408–12. https://doi.org/10.1001/jama.273.5.408. PubMed PMID: 7823387.

[34] O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials.

Biometrics 1979;35(3):549–56. Epub 1979/09/01. PubMed PMID: 497341.
[35] Miladinovic B, Hozo I, Djulbegovic B. Trial sequential boundaries for cumulative meta-analyses. 2013 STATA J 2013;13(1):77–91. Available from: http://ageconsearch.umn.edu/record/241329/files/sjart_st0284.pdf.
[36] Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim S-B, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer—the penelope-B trial. J Clin Oncol 2021;20:03639. https://doi.org/10.1200/JCO.20.03639. JCO.
[37] Martin M, Hegg R, Kim S-B, Schenker M, Grecea D, García-Sáenz JA, et al. Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). J Clin Oncol 2021;39(15_suppl):517. https://doi.org/10.1200/JCO.2021.39.15_suppl.517.
[38] Marmé F, Martin M, Untch M, Bonnefoi HR, Kim S-B, Bear HD, et al. Palbociclib combined with endocrine treatment in breast cancer patients with high relapse risk after neoadjuvant chemotherapy: subgroup analyses of premenopausal patients in PENELOPE-B. J Clin Oncol 2021;39(15_suppl):518. https://doi.org/10.1200/JCO.2021.39.15_suppl.518.
[39] Ortiz AB, Garcia D, Vicente Y, Palka M, Bellas C, Martin P. Prognostic significance of cyclin D1 protein expression and gene amplification in invasive breast carcinoma. Epub 2017/11/16 PloS One 2017;12(11):e0188068. https://doi.org/10.1371/journal.pone.0188068. PubMed PMID: 29140993; PubMed Central PMCID: PMC5687747.
[40] Elsheikh S, Green AR, Aleskandarany MA, Grainge M, Paish CE, Lambros MBK, et al. CCND1 amplification and cyclin D1 expression in breast cancer and their relation with proteomic subgroups and patient outcome. Breast Canc Res Treat 2008;109(2):325–35. https://doi.org/10.1007/s10549-007-9659-8.
[41] Ahlin C, Lundgren C, Embretsen-Varro E, Jirstrom K, Blomqvist C, Fjallskog M. High expression of cyclin D1 is associated to high proliferation rate and increased risk of mortality in women with ER-positive but not in ER-negative breast cancers. Epub 2017/05/22 Breast Canc Res Treat 2017;164(3):667–78. https://doi.org/10.1007/s10549-017-4294-5. PubMed PMID: 28528450; PubMed Central PMCID: PMC5495873.
[42] Denkert C, Marmé F, Martin M, Untch M, Bonnefoi HR, Witkiewicz AK, et al. Subgroup of post-neoadjuvant luminal-B tumors assessed by HTG in PENELOPE-B investigating palbociclib in high risk HER2-/HR+ breast cancer with residual disease. J Clin Oncol 2021;39(15_suppl):519. https://doi.org/10.1200/JCO.2021.39.15_suppl.519.
[43] Schoninger SF, Blain SW. The ongoing search for biomarkers of CDK4/6 inhibitor responsiveness in breast cancer. Mol Canc Therapeut 2020;19(1):3. https://doi.org/10.1158/1535-7163.MCT-19-0253.
[44] Kwa M, Makris A, Esteva FJ. Clinical utility of gene-expression signatures in early stage breast cancer. Nat Rev Clin Oncol 2017;14(10):595–610. https://doi.org/10.1038/nrclinonc.2017.74.
[45] Di Cosimo S, Porcu L, Cardoso F. CDK 4/6 inhibitors mired in uncertainty in HR positive and HER2 negative early breast cancer. Epub 2020/12/23 Breast 2020;55:75–8. https://doi.org/10.1016/j.breast.2020.12.006. PubMed PMID: 33352521; PubMed Central PMCID: PMC7758367.
[46] Agostinetto E, Vian L, Caparica R, Bruzzone M, Ceppi M, Lambertini M, et al. CDK4/6 inhibitors as adjuvant treatment for hormone receptor-positive, HER2-negative early breast cancer: a systematic review and meta-analysis. Epub 2021/03/21 ESMO Open 2021;6(2):100091. https://doi.org/10.1016/j.esmoop.2021.100091. PubMed PMID: 33743330; PubMed Central PMCID: PMC8010395.