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REVIEW

CDK4/6 inhibitors as adjuvant treatment for hormone receptor-positive, HER2-negative early breast cancer: a systematic review and meta-analysis

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Background: The combination of cyclin-dependent kinases 4/6 inhibitors (CDK4/6is) and endocrine therapy (ET) is standard of care for patients with hormone receptor-positive (HR+), HER2-negative (HER2−) advanced breast cancer (BC). However, studies evaluating adjuvant CDK4/6is provided contradictory results thus far.

Materials and methods: We conducted a systematic review and meta-analysis to assess if the addition of CDK4/6is to adjuvant ET impacts on survival's outcomes and safety of patients with HR+/HER2− early BC (EBC). This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and was registered in the PROSPERO database (ID: CRD42020218597). A systematic review of PubMed, Cochrane and EMBASE databases and major conference proceedings was performed up to 15 December 2020. All randomized controlled trials including patients with HR+/HER2− EBC treated with CDK4/6is plus ET versus ET alone in the adjuvant setting were included. Pooled hazard ratios (HRs) and odds ratios (ORs) for survival and safety outcomes, respectively, were calculated with 95% confidence intervals (95% CIs) using random effect models.

Results: With data available from three studies ($N = 12\ 647$), the addition of CDK4/6is to adjuvant ET showed a trend for a benefit in terms of invasive disease-free survival (IDFS; HR 0.85, 95% CI 0.71-1.01; $P = 0.071$). No significant improvement in distant relapse-free survival was observed (HR 0.83, 95% CI 0.58-1.19; $P = 0.311$). The risk of all-grade toxicities and early treatment discontinuation increased significantly with the addition of CDK4/6is to ET (OR 9.36, 95% CI 3.46-25.33, $P < 0.001$, and OR 22.11, 95% CI 9.45-51.69, $P < 0.001$, respectively).

Conclusion: The administration of adjuvant CDK4/6is to patients with HR+/HER2− EBC showed a trend for an IDFS benefit and an increase in the risk of toxicities and treatment discontinuation. The role of adjuvant CDK4/6is remains controversial and a longer follow-up of these randomized controlled trials is needed before supporting a straightforward change in clinical practice.

Key words: breast cancer, HR-positive, adjuvant, CDK4/6 inhibitors, endocrine therapy, survival

INTRODUCTION

Breast cancer (BC) is the most frequent malignancy diagnosed among women worldwide with more than 400 000 estimated new cases in 2018 in the European Union.[1] Hormone receptor-positive/HER2-negative (HR+/HER2−) BC is the most frequent subtype, accounting for ∼70% of all BCs. More than 90% of patients with HR+/HER2− BC are diagnosed with early disease, which is potentially curable with available standard treatments.[2]

Although adjuvant endocrine therapy (ET) significantly reduces the risk of recurrence and death,[3] up to 20% of patients with early BC (EBC) will experience recurrences in the first 10 years after surgery, with either locoregional disease or distant metastases, becoming, in the latter scenario, incurable.[3] Hence, the development of new treatment strategies to further reduce the risk of recurrence and improve patient outcomes is of paramount importance.

The cyclin-dependent kinases (CDKs) are a family of molecules that play a key role in the control of cell division and constitute an important therapeutic target. CDK4/6 inhibitors (CDK4/6is) have been approved for the treatment of patients with HR+/HER2− locally advanced and

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metastatic BCs, and are now the standard of care in first line, and also a valid treatment option in second line, in combination with ET.[4,5]

With the aim to assess the efficacy of CDK4/6is at earlier treatment lines, several ongoing studies, focusing on different populations and with differing treatment strategies, are currently evaluating the addition of CDK4/6is to adjuvant ET for patients with HR+/HER2− EBC. Thus far, results from these studies have been heterogenous, and therefore the role of CDK4/6is in EBC has been the topic of an intense academic discussion.[6]

To further assess the efficacy and safety of CDK4/6is in the early disease setting, we conducted a systematic review and meta-analysis of the available results of randomized controlled studies that evaluated the combination of CDK4/6is with adjuvant ET in patients with HR+/HER2− EBC.

METHODS

Study objectives and endpoints

The primary objective of our study was to compare the outcomes of patients receiving CDK4/6is in combination with ET with those receiving ET alone as adjuvant treatment for HR+/HER2− EBC.

The primary endpoint was invasive disease-free survival (IDFS), defined according to the standardized definitions for efficacy end points in adjuvant breast cancer trials (STEEP) criteria[7] and measured from the date of randomization to the date of first event (ipsilateral or contralateral invasive in-breast or locoregional recurrence, distant recurrence, death from any cause, invasive contralateral BC, second primary non-breast invasive cancer).

Subgroup analyses were performed to evaluate IDFS according to patients' age, tumor size, nodal status, disease stage, tumor grade, proliferation index (Ki-67) and geographic region.

Secondary objectives included a further evaluation of the efficacy of the combination, and the evaluation of safety outcomes.

Secondary endpoints included (i) distant relapse-free survival (DRFS), defined as the time from the date of randomization to the date of distant recurrence or death from any cause, whichever occurred first; (ii) incidence of adverse events (AEs; overall and grade $\geq$3) in patients receiving CDK4/6is in combination with ET and in patients receiving ET alone and (iii) frequency of early treatment discontinuation (CDK4/6is and ET) due to toxicities in the two groups.

Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[8] and was registered in the international prospective register of systematic reviews (PROSPERO database; ID: CRD42020218597).

To identify all eligible records, a systematic review of the literature in PubMed, Cochrane and EMBASE databases, together with American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) Conference websites was performed up to 15 December 2020, with no date restrictions. Two authors (EA and LV) independently evaluated the titles and the abstracts of the identified studies to apply the eligibility criteria. A third author (RC) was invited to review search results to solve any disagreements regarding study eligibility. The references of interest in all the identified studies were tracked in order to search for additional studies.

The search strategy was developed using the patient, intervention, comparator and outcome (PICO) framework. The terms for the search strategy were related to the following keywords: 'breast cancer', 'HR-positive', 'HR+/HER2−', 'adjuvant', 'CDK 4/6 inhibitors', 'endocrine therapy', 'survival' and 'recurrence'. Boolean operators were used to connect specific search keywords for each database and other free-text terms. The specific rules and vocabulary of each database were used.

Study eligibility criteria

Studies that met all the following criteria were considered eligible and were included in this meta-analysis: (i) randomized controlled studies with published, presented or otherwise publicly available data, including conference proceedings, (ii) studies including patients with early HR+/HER2− BC treated with CDK4/6is in combination with ET versus ET alone in the adjuvant or postneoadjuvant settings, (iii) studies with available information for at least one of the objectives of this meta-analysis and (iv) studies published in English language. Conversely, studies that met at least one of the following criteria were excluded: (i) non randomized studies, (ii) studies evaluating treatments in other-than (post-neo)adjuvant setting and (iii) studies for which no or insufficient results were available at the time of the literature search.

Data extraction

For each eligible study, the following variables were extracted independently by two different investigators (EA and LV): first author, year of publication, sample size, type of study, type of CDK4/6i used, clinical–pathological characteristics of patients included in the studies, outcomes of patients treated with CDK4/6is + ET versus those treated with ET alone and safety data. In case there were multiple publications or presentations of the same trial, the one containing the longest follow-up period or the most comprehensive data was included. In case multiple publications of safety data with different follow-ups were available, the most updated data were collected for each AE.

Risk of bias assessment

Risk of bias for each study included in the meta-analysis was assessed by two independent investigators (EA and LV) using the Cochrane Risk of Bias tool version 2. Risk of bias was evaluated on five distinct domains regarding randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome and selection of the reported results. Based on these assessments, each study was classified as having a low, high or an unclear risk of bias.

Statistical analysis

For efficacy analyses, pooled hazard ratios (HRs) were calculated for the comparison of CDK4/6is + ET versus ET. For the safety analysis, the odds ratio (OR) for each AE was calculated by comparing the frequency of events occurring in the CDK4/6is + ET versus ET groups. The OR for early treatment discontinuation was calculated by comparing the frequency of early treatment discontinuation (of CDK4/6is/placebo and of ET) in each group. For each OR or HR estimates, 95% confidence intervals (CIs) were computed. Pooled ORs or HRs using the random-effects model were computed with the method of DerSimonian and Laird.

The Higgins' I^2 index was used to obtain a quantitative measure of the degree of inconsistency in the results of the included studies. To assess whether the pooled OR/HR estimates were stable or strongly dependent on one or few studies, sensitivity analyses were conducted by interactively recalculating the pooled OR/HR estimates after exclusion of each single study. All reported *P* values were two-sided and considered significant if $\leq$0.05.

Egger's test was performed to exclude potential publication bias.

All analyses were performed using STATA software version 14 (StataCorp, College Station, TX).

RESULTS

The PRISMA flowchart with the study selection process is reported in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100091. From the 123 records initially identified, 120 remained after duplicate removal and were screened, with 117 being excluded for the following reasons: 55 were subanalyses of randomized controlled trials, 21 were reviews, 20 included patients with advanced BC, 14 were articles about tumors other than breast and 7 were preclinical studies. The screening process led to three eligible studies that enrolled a total of 12 647 patients, which were included in the present meta-analysis.

Characteristics of the included studies are reported in Table 1. All studies were phase III trials. Two studies (PALLAS and PENELOPE-B) evaluated the addition of the CDK4/6i palbociclib to ET,[9,10] and one (monarchE) the addition of abemaciclib.[11,12] The duration of the adjuvant therapy with CDK4/6is was 2 years in the PALLAS and monarchE trials, and 1 year in the PENELOPE-B trial. Two studies (PALLAS and monarchE) evaluated CDK4/6is in the adjuvant setting, whereas one study (PENELOPE-B) in the postneoadjuvant setting, namely on patients with residual disease after neoadjuvant treatment.

Invasive disease-free survival

With data available from three studies ($N = 12\,647$), CDK4/6is use in the adjuvant setting showed a trend for an IDFS benefit (HR 0.85, 95% CI 0.71-1.01; $P = 0.071$; Figure 1). No heterogeneity was observed ($I^2 = 53.8\%$, $P_{\text{heterogeneity}} = 0.115$) in this analysis. These findings were consistent across all subgroups, according to tumor size, nodal status, disease stage, grading, proliferation index (Ki-67), age and geographic region. Figure 2 reports pooled HR according to subgroups (including HR for those subgroups based on the results of one study only, which are not discussed in the present review). In the sensitivity analysis for IDFS, the pooled HR estimates were stable, with minimal variations when excluding each study sequentially (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100091). No publication bias was observed after Egger's test ($P = 0.440$).

Distant relapse-free survival

With data available from two studies (PALLAS and monarchE) ($N = 11\,397$), we observed no statistically significant improvement in terms of DRFS (HR 0.83, 95% CI 0.58-1.19; $P = 0.311$; Figure 3). Significant heterogeneity was observed ($I^2 = 79.9\%$, $P_{\text{heterogeneity}} = 0.026$).

Frequency of adverse events

With data available from three studies ($N = 12\,578$), adjuvant CDK4/6is were significantly associated with an overall increased incidence of AEs of any grade (OR 9.36, 95% CI 3.46-25.33, $P < 0.001$) and of grade $\geq$3 (OR 11.06, 95% CI 5.38-22.74, $P < 0.001$; Figure 4). Significant heterogeneity was observed in these analyses ($I^2 = 87.5\%$, $P_{\text{heterogeneity}} < 0.001$ and $I^2 = 98.3\%$, $P_{\text{heterogeneity}} < 0.001$, respectively). The sensitivity analyses for incidence of AEs (any grade and grade $\geq$ 3) are reported in Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2021.100091, and show that heterogeneity disappears after removal of the PALLAS study in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100091, and after removal of the monarchE study in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100091, yet with pooled OR remaining consistent with the main findings. Egger's test did not show evidence of publication bias ($P = 0.988$ and 0.816, respectively).

In particular, adjuvant CDK4/6i was significantly associated with an increased risk of AEs of any grade and grade $\geq$3 for neutropenia, anemia, thrombocytopenia, diarrhea, upper respiratory infections and fatigue. An increased risk of nausea (any grade) was also observed. Figure 4 shows OR according to each AE (including OR for those AEs reported in one study only, which are not discussed in this review).

Table 1. Characteristics of the studies included in the meta-analysis

Study characteristics	PALLAS[9]		MonarchE[11,12]		PENELOPE-B[10]	
	Palbociclib + ET	ET alone	Abemaciclib + ET	ET alone	Palbociclib + ET	ET alone
N	2883	2877	2808	2829	631	619
Median follow-up (months)	23.7		19.1		42.8	
CDK4/6i duration (years)	2		2		1	
Age, years, median (range)	52 (25-90)	52 (22-85)	51 (23-89)	51 (22-86)	49 (22-76)	48 (19-79)
Stage, *n* (%)						
IA	—	—	2 (0.1)	1 (0)	—	—
IIA	504 (17.5)	509 (17.7)	323 (11.5)	353 (12.5)	—	—
IIB	968 (33.6)	951 (33.1)	389 (13.9)	387 (13.7)	—	—
III	1402 (48.6)	1408 (48.9)	2081 (74.1)	2077 (73.4)	—	—
Pathologic tumor size, *n* (%)						
T0, T1, Tx, Tis	557 (19.3)	500 (17.4)	780 (27.8)	765 (27.0)	238 (37.7)	208 (33.7)
T2	1603 (55.6)	1636 (56.9)	1369 (48.8)	1419 (50.2)	368 (58.3)	389 (62.9)
T3, T4	722 (25.0)	741 (25.8)	610 (21.7)	612 (21.6)	25 (4.0)	21 (3.4)
Nodal status, *n* (%)						
N0/1	1794 (62.2)	1798 (62.5)	—	—	310 (49.1)	310 (50.1)
N2/3	1088 (37.8)	1079 (37.5)	—	—	321 (50.9)	309 (49.9)
Grade, *n* (%)						
G1	300 (10.4)	313 (10.9)	209 (7.4)	215 (7.6)	—	—
G2	1622 (56.3)	1658 (57.6)	1373 (48.9)	1395 (49.3)	—	—
G3	836 (29.0)	767 (26.7)	1090 (38.8)	1066 (37.7)	294 (46.7)	297 (48.1)
Ki-67[a], *n* (%)						
Low	—	—	953 (33.9)	973 (34.4)	—	—
High	—	—	1262 (44.9)	1233 (43.6)	161 (25.5)	158 (25.5)
Prior CT, *n* (%)	2384 (82.7)	2370 (82.4)	2681 (95.5)	2695 (95.3)	631 (100)	619 (100)
Adjuvant ET, *n* (%)						
Tamoxifen	923 (32.0)	949 (33.0)	857 (30.7)	898 (32.1)	314 (49.8)	308 (49.8)
Tamoxifen + ovarian suppression	—	—	192 (6.9)	232 (8.3)	—	—
AI, *n* (%)	1954 (67.8)	1918 (66.7)	1928 (69.1)	1891 (67.5)	—	—
AI + ovarian suppression, *n* (%)	—	—	410 (14.7)	386 (13.8)	—	—
Ovarian suppression (any time), *n* (%)	532 (18.5)	604 (21.1)	606 (21.7)	627 (22.4)	108 (17.1)	113 (18.3)
IDFS events	351 events		395 events		308 events	
IDFS	HR 0.93 (0.76-1.15), $P = 0.51$		HR 0.71 (0.58-0.87), $P = 0.0009$		HR 0.93 (0.74-1.17), $P = 0.525$	
DRFS events, *n*	271		324		227	
DRFS	1.00 (0.79-1.27)		0.69 (0.55-0.86)		No difference (HR not reported)	
Early CDK4/6i discontinuation, *n* (%)	1199 (42.2)		773 (27.7)		123 (19.5)	
Early CDK4/6i discontinuation due to AEs, *n* (%)	772 (26.7)		481 (17.2)		33 (5.2)	

AEs, adverse events; AI, aromatase inhibitor; CDKi, cyclin dependent kinase inhibitors; CT, chemotherapy; DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival.

[a] Ki-67 was categorized as low or high according to the following cut-offs: 20% (low < 20%, high ≥ 20%) for the monarchE trial, 15% (low ≤ 15%, high > 15%) for the PENELOPE-B trial.

There was a significant association with early treatment discontinuation due to AEs (OR 22.11, 95% CI 9.45-51.69, $P < 0.001$). Significant heterogeneity was observed ($I^2 = 86.6\%$, $P_{heterogeneity} < 0.001$) in this analysis. The sensitivity analysis is reported in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100091. No publication bias was detected after Egger's test ($P = 0.352$).

We observed no significant differences in terms of early ET discontinuation due to AEs or due to any cause (OR 3.31, 95% CI 0.48-22.92, $P = 0.225$, $I^2 = 96.6\%$ and OR 0.97, 95% CI 0.67-1.38, $P = 0.849$, $I^2 = 49.5\%$, respectively).

Risk of bias assessment

Risk of bias was assessed for the three studies included in the meta-analysis and is reported in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100091. Two studies (PALLAS and monarchE) had an unclear risk of bias, due to their open-label design which could not prevent outcome assessment from being influenced by knowledge of the intervention received. The remaining study (PENELOPE-B) was considered as having a low risk of bias. A detailed risk of bias assessment for each study is reported in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100091.

DISCUSSION

Three studies (PALLAS, monarchE and PENELOPE-B) evaluating CDK4/6i in the adjuvant setting have become available thus far, showing discordant findings. This meta-analysis aimed to shed further light on the role of these agents in

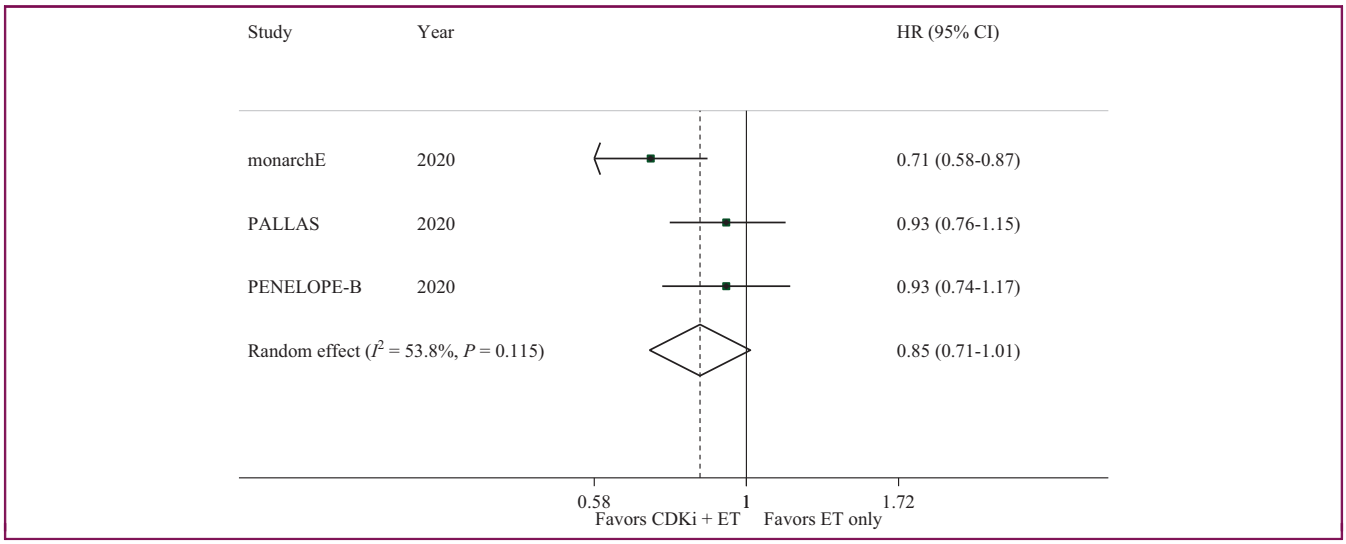

Figure 1. Forest plot for invasive disease-free survival.
CI, confidence interval; CDKi, cyclin dependent kinase inhibitors; ET, endocrine therapy; HR, hazard ratio.

the adjuvant setting, evaluating their efficacy as well as their safety profile, while discussing a potential forthcoming change in clinical practice.

In our analysis, the addition of CDK4/6is to adjuvant ET showed a trend toward a benefit in terms of IDFS, whereas no benefit in terms of DRFS was observed. Our results

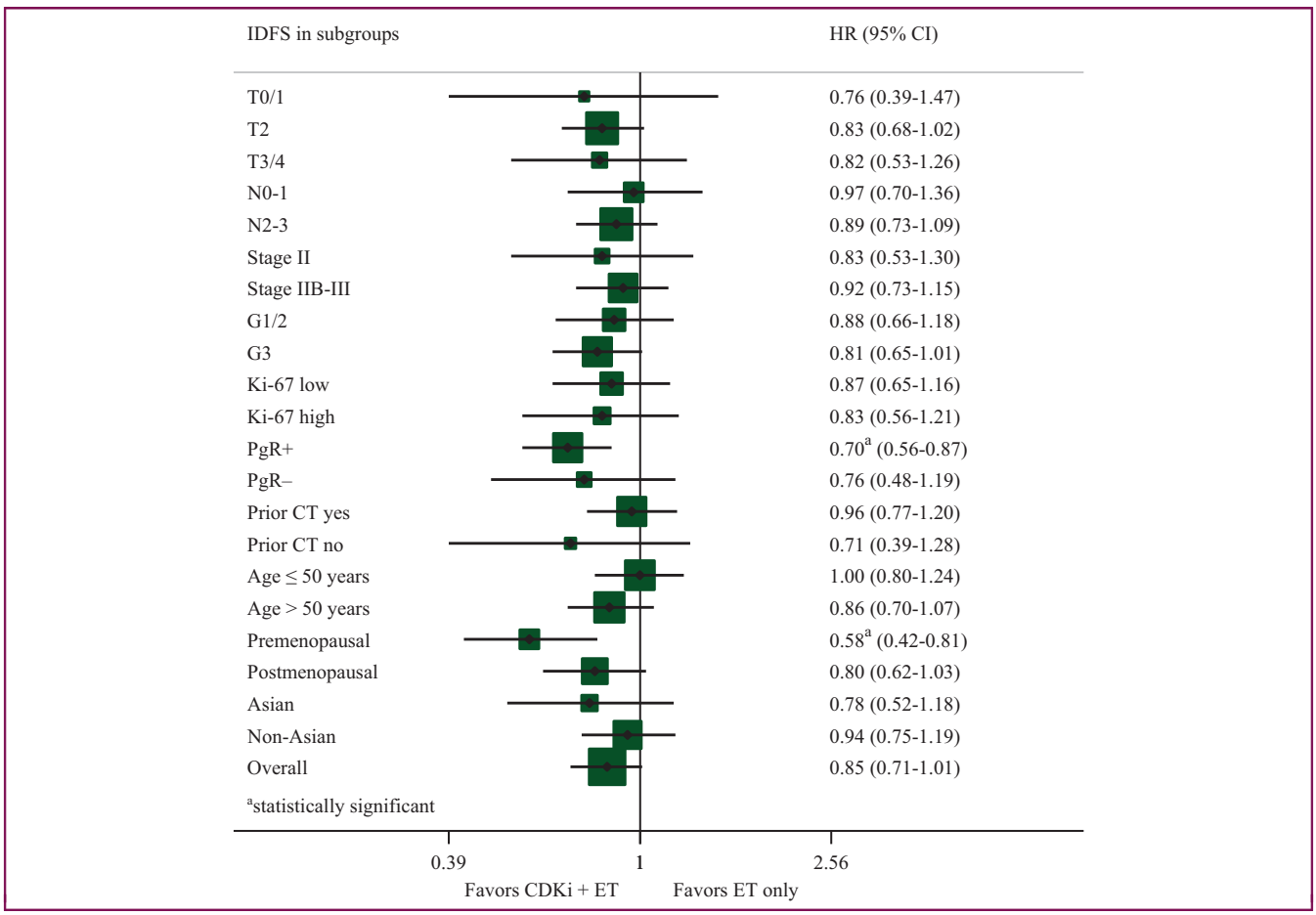

Figure 2. Pooled hazard ratios for invasive disease-free survival according to subgroups.
Hazard ratios for the following subgroups were reported based on the results of one study only: N0-1, stage IIB-III, G1/2, Ki-67 low, PgR+/−, prior CT yes/no, pre/postmenopausal, non-Asian. CDK, cyclin-dependent kinase; CI, confidence interval; CT, chemotherapy; G, grade; HR, hazard ratio; IDFS, invasive disease-free survival; N, nodal stage; PgR; progesterone receptors; T, tumor stage.

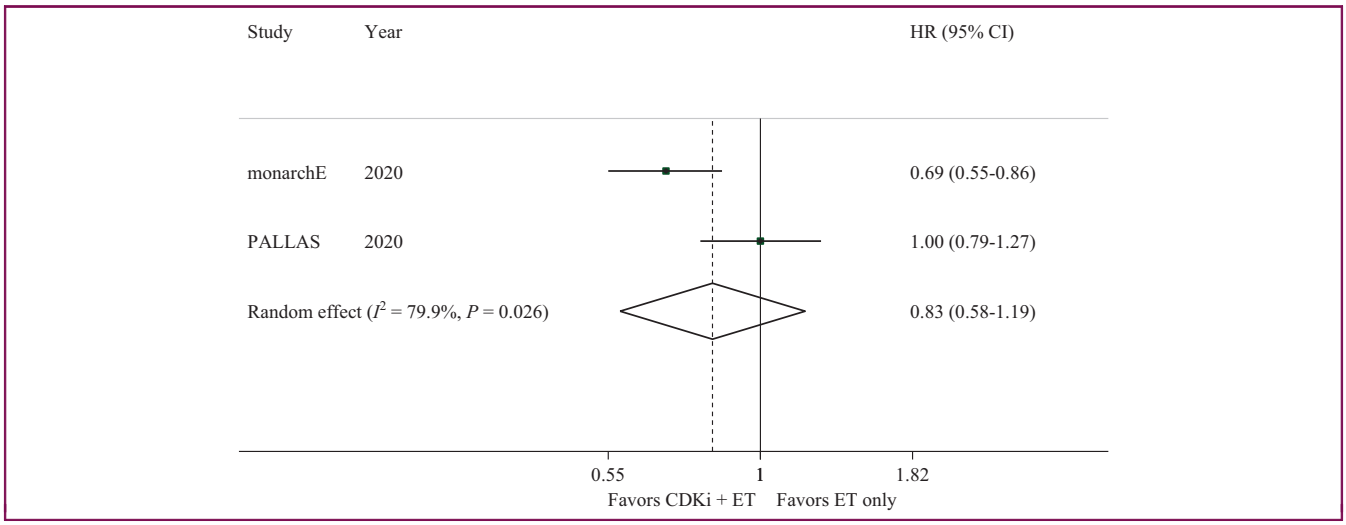

Figure 3. Forest plot for distant relapse-free survival.
CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio.

could not confirm the benefit of CDK4/6is in adjuvant setting, underscoring the need for a longer follow-up before supporting a straightforward change in clinical practice based on the results of a single trial. Indeed, the benefit in terms of IDFS was mainly driven by the results of the monarchE trial, in which a median follow-up of 19.1 months may be insufficient to drive solid conclusions. Importantly, the absolute improvement in 2-year IDFS rate

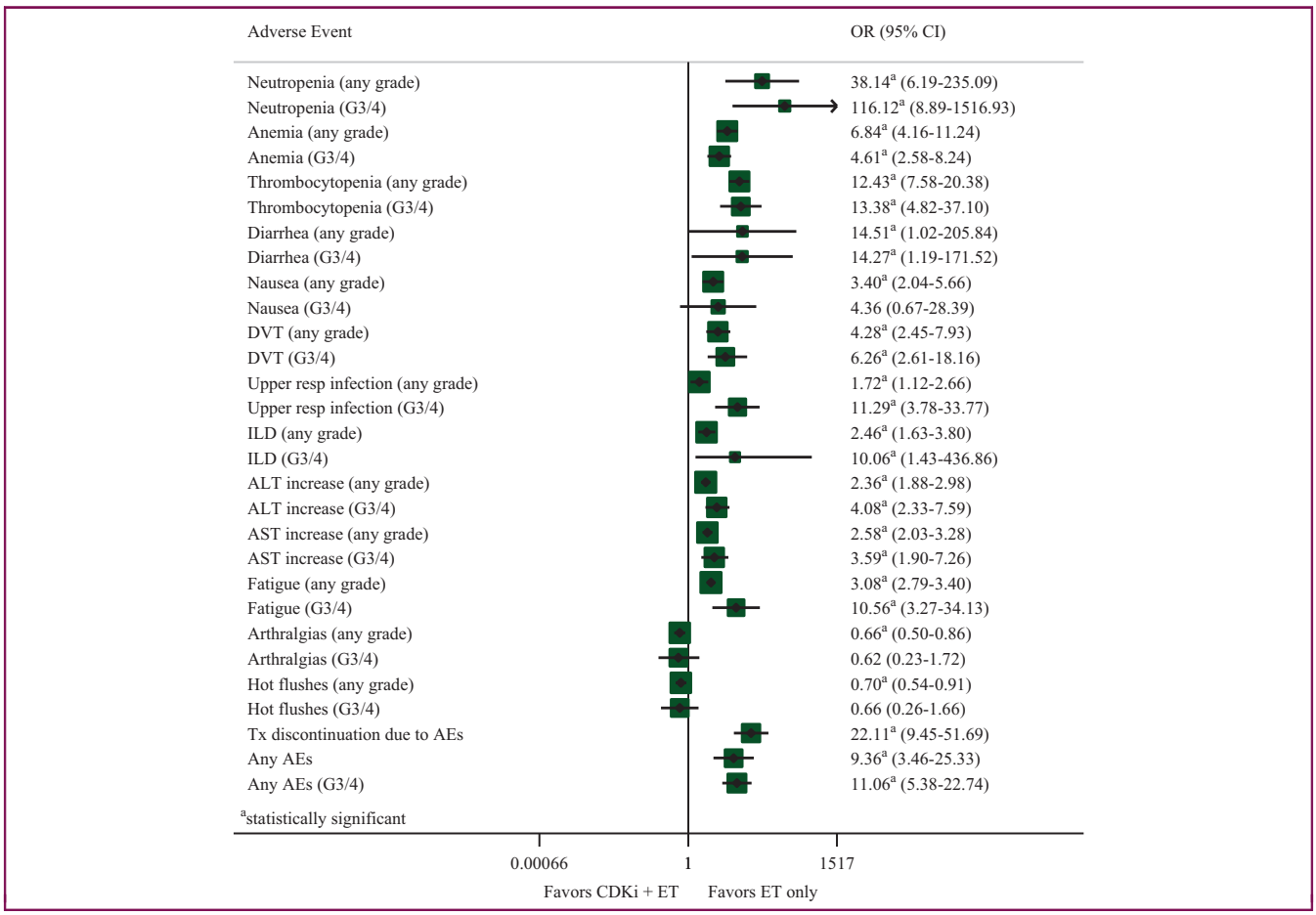

Figure 4. Forest plot for incidence of adverse events.
ORs for the following subgroups were reported based on the results of one study only: DVT (any grade/grade 3-4), ILD (any grade/grade 3-4), AST (any grade/grade 3-4), ALT (any grade/grade 3-4). AEs, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; CDKi, cyclin-dependent kinase inhibitor; CI, confidence interval; DVT, deep vein thrombosis; ET, endocrine therapy; G, grade; ILD, interstitial lung disease; OR, odds ratio; resp, respiratory; tx, treatment.

of 3.5% with abemaciclib reported after 15.5 months of follow-up decreased to 3.0% at 19.1 months. Furthermore, the divergence among the results of the three trials is not fully understood, and several explanations have been proposed, yet being speculative, at the moment.[6] First, the different risk profiles of the population enrolled in the three studies might have played a role in the discrepant findings: eligibility criteria relied only on anatomic stage in PALLAS (stage II and III), whereas in monarchE and PENELOPE-B biological characteristics were also considered. In PALLAS, ≈18% of patients with stage IIA disease were enrolled (versus 12% in monarchE), suggesting that the latter population had an overall higher risk of recurrence. Second, the different activity of palbociclib and abemaciclib is another hypothesis to explain these divergent findings: although belonging to the same class of CDK4/6is, palbociclib and abemaciclib have unique pharmacological characteristics.[13] Moreover, the higher discontinuation rate observed for palbociclib in PALLAS, its intermittent schedule of administration and also the different duration of treatment (1 year in PENELOPE-B and 2 years in PALLAS and monarchE) have been described as further possible explanations. In addition, in the monarchE trial, >30% of patients in each arm received tamoxifen as ET, and only 8% of these in combination with ovarian function suppression, which could be considered as a suboptimal treatment for high-risk patients. Whether optimal ET might dilute the treatment effect observed in the single positive trial is still an open question.

In this meta-analysis, we also evaluated the incidence of toxicities associated with adjuvant CDK4/6is. As expected, the addition of CDK4/6is to adjuvant ET was significantly associated with increased incidence of AEs, as well as with increased risk of early treatment discontinuation due to AEs.[14,15] Furthermore, the increase in the risk of clinically relevant AEs (grade ≥3) was even more pronounced than overall AEs (OR 11.06 versus 9.36), highlighting the important impact CDK4/6is may have on patients' well-being as well as on health care systems. The impact of CDK4/6is in terms of safety is particularly important in the early setting, in which patients are expected to be 'cured', and where arguments for and against each treatment should be carefully weighted, with survivorship and quality of life being questions of prime importance for these patients. The data on patient-reported outcomes assessed in these studies, which have not yet been presented and are eagerly awaited, may better characterize the risks and benefits associated with adjuvant CDK4/6is from patient's perspective, and inform future treatment guidelines.

The controversial role of CDK4/6is in the adjuvant setting underlines the need for better patient selection in phase III trials, as well as the use of study designs aimed at distinguishing between patients who require adjuvant therapy escalation, and those who can benefit from adjuvant ET alone and can be, therefore, spared useless additional toxicities. Thus far, no biomarkers have proven to predict the benefit of CDK4/6is in the locally advanced and metastatic setting, and several studies are trying to answer this question.[16-18] Moreover, in the era of molecular profiling, the identification of intrinsic subtypes could represent another tool to select patients who may benefit from CDK4/6is, with recent data supporting further investigation in this field.[19] Meanwhile, in the adjuvant setting, no criteria exist to select patients who might benefit from the addition of CDK4/6is to adjuvant ET.

Our meta-analysis has some limitations. First, only three trials were included, out of which two had unpublished data, and two of them with a short follow-up.[20-22] Ongoing studies are eagerly awaited to shed light on the role of CDK4/6is in EBC (NCT03701334, NCT03078751 and NCT03820830).[20,21] Second, different eligibility criteria and different definitions of 'high-risk' patients across the studies (i.e. anatomic stage in PALLAS, disease stage and biological characteristics in monarchE and CPS-EG score [a staging system considering clinical and pathological stage, estrogen receptor status and grade] in PENELOPE-B) limit the possibility of a direct comparison. Moreover, the heterogeneous subgroup classification across different studies further hindered data pooling: Ki-67 was categorized as low or high according to different cut-offs (20% in monarchE and 15% in PENELOPE-B), age was categorized using 65 years old as cut-off in monarchE, and 50 years old in PALLAS and PENELOPE-B, nodal status was categorized according to number of positive nodes in monarchE and according to TNM classification in PALLAS and PENELOPE-B. These heterogeneous definitions represent a challenge for oncologic clinical research, reinforcing the need to establish standard risk assessment and stratification factors across different clinical trials, in order to allow data pooling and facilitate comparisons among studies. In addition, data from studies evaluating two different drugs (palbociclib and abemaciclib) and distinct treatment durations (1 and 2 years) were pooled in this meta-analysis, which may limit the interpretation of pooled results. Furthermore, this is not an individual patient data meta-analysis, and high heterogeneity was observed in some analyses, mirroring the limited evidence published on this topic, thus far. Finally, not all studies provided complete safety data at the time of our analysis: due to the recent presentation in the form of conference proceedings, only partial data were available for PALLAS and PENELOPE-B. Recently, in February 2021, the full article of PALLAS trial has been published.[23]

By contrast, our study has some strengths. To our knowledge, this meta-analysis represents the most comprehensive and updated evaluation of the role of adjuvant CDK4/6is in EBC, describing not only the impact on patient outcomes but also their safety profile. Findings should be interpreted together with a comprehensive evaluation of the clinical relevance of adjuvant CDK4/6is in light of a longer follow-up and of their financial impact, which should be carefully evaluated before incorporating these agents into clinical practice.

CONCLUSIONS

The administration of adjuvant CDK4/6is to patients with HR+/HER2− EBC was associated with a trend toward an IDFS benefit and an increase in the risk of toxicities and treatment discontinuation. The role of CDK4/6is in the early disease setting remains controversial, particularly in low-risk patients, and a longer follow-up of these randomized controlled trials is needed before supporting a straightforward change in clinical practice.

FUNDING

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DISCLOSURE

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