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REVIEW

CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials

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Abstract

Purpose Combining CDK4/6 inhibitors and endocrine therapy (ET) improved outcomes for the treatment of metastatic HR+/HER2− breast cancers. Here, we performed a meta-analysis of randomized clinical trials (RCTs) to better define the benefit and the risk of CDK4/6 inhibitors plus ET for endocrine-sensitive or endocrine-resistant population in metastatic HR+/HER2− breast cancer.

Method A systematic literature search of Pubmed, Embase, and the Cochrane Library was carried out up to 30 June 2018. Hazard ratios (HRs) and 95% confidence intervals (CIs) for progression-free survival (PFS), as well as odds ratios (ORs) for objective response rates, ≥ G3–G4 adverse events (AEs), and G3–G4 neutropenia were calculated for each trial. A meta-analysis was carried out using the random-effects model.

Results Eight RCTs were eligible including 4578 breast cancer patients. Adding CDK4/6 inhibitors to ET in endocrine-sensitive (HR 0.55, 95% CI 0.50–0.62) or endocrine-resistant setting (HR 0.51, 95% CI 0.43–0.61) significantly improved the PFS of metastatic HR+/HER2− breast cancers regardless of menopausal status and site of metastasis. Moreover, CDK4/6 inhibitors plus ET meaningfully improved objective response rate in endocrine-sensitive (ORs 0.62, 95% CI 0.52–0.73) or endocrine-resistant setting (ORs 0.33, 95% CI 0.24–0.47). The use of these drugs was characterized by a significant increase of G3–G4 AEs (OR 10.88, 95% CI 6.53–18.14).

Conclusion Emerging data provide a new standard treatment for advanced HR+/HER2− breast cancer, regardless of menopausal status, prior hormonal/chemotherapy treatments delivered, sites of metastasis. However, benefits should be balanced with longer treatment duration, toxicities, and costs.

Keywords Abemaciclib · Ribociclib · Palbociclib · Hormonal therapy · Breast cancer · Meta-analysis

Introduction

Breast cancer accounts for over one million cases per year resulting in the most frequently diagnosed neoplasm worldwide and the leading cause of cancer death in women [1]. Although metastatic breast cancer is still an incurable disease, the approval of novel effective chemotherapies and endocrine therapies (ET) led to an improvement of overall survival (OS) [2]. Hormonal receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2−) tumours represent the largest therapeutic subtype and are responsible for 65% of all breast cancers [3]. For many decades, targeting the oestrogen-receptor signalling pathway has represented the mainstay for the treatment of locally advanced and metastatic HR+/HER2− breast cancer [4]. However, all metastatic HR+/HER2− breast cancers progress despite the oestrogen-receptor pathway blockade and acquire resistance to ET [5]. The cyclin-dependent kinases (CDKs) are a large family of serine-threonine kinases involved in the regulation of cell cycle progression [6]. Cyclin D binds both CDK 4 and CDK 6 and induces the hyper-phosphorylation

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of the retinoblastoma (Rb) protein causing the progression of tumour cells from the G1 checkpoint to the S phase of cell cycle [6]. The de-regulation of Cyclin D/CDK4–6/Rb pathway is associated with the development of endocrine resistance in breast cancer [6]. This provides the rationale for the inhibition of Cyclin D/CDK4–6/Rb pathway in order to overcome the resistance to ET. In the last few years, several CDK inhibitors (CDKi) have been approved for the treatment of women with metastatic HR+/HER2− breast cancer [7–12]. Three prospective randomized clinical trials showed that upfront combination of palbociclib/ribociclib with letrozole significantly improved the progression-free survival (PFS) of postmenopausal women with advanced HR+/HER2− breast cancer [7–9]. Similarly, combining palbociclib/abemaciclib with fulvestrant meaningfully prolonged PFS compared with fulvestrant alone in women with any menopausal status who had previously progressed to ET [10, 11]. A randomized phase III trial (MONARCH 3) showed that abemaciclib plus a non-steroidal aromatase inhibitor (AI) significantly improved PFS compared with AI alone in postmenopausal women with advanced HR+/HER2− breast cancer who had no prior systemic treatment [12]. Recently, a randomized, double blind, phase III (MONALEESA 7) placebo-controlled trial revealed that adding ribociclib to tamoxifen or AI improved PFS in premenopausal woman with advanced HR+/HER2− breast cancer [13]. Furthermore, a randomized, double blind, phase III (MONALEESA 3) placebo-controlled trial showed that ribociclib plus fulvestrant meaningfully improved PFS in postmenopausal woman with advanced HR+/HER2− breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy [14].

In order to better define the benefit and the risk related to the combine use of CDKi 4/6 with ET in HR+/HER2− breast cancer, we performed a meta-analysis of published trials.

Method

The study design was a quantitative synthesis of RCTs aiming to evaluate the efficacy and safety of CDKi plus ET in HR+/HER2− breast cancers.

Study objectives

The co-primary objectives of the study were (I) to compare the impact on PFS duration and AEs incidence of CDKi plus ET versus ET alone in metastatic HR+ HER2− breast cancer patients in endocrine-sensitive and endocrine-resistant setting. Secondary objectives were (I) to compare the objective response rate (ORR) of CDKi plus ET versus ET alone in metastatic HR+/HER2− breast cancer patients in endocrine-sensitive and endocrine-resistant setting; (II) to compare the PFS in the subgroup of HR+/HER2− breast cancer patients with visceral metastasis and non-visceral metastasis treated with CDKi plus ET versus ET in endocrine-sensitive and endocrine-resistant setting; (III) to compare the incidence of grade 3 (G3) and G4 neutropenia in HR+/HER2− breast cancer patients treated with CDKi plus ET in endocrine-sensitive and endocrine-resistant setting, and in overall population.

Data sources and strategies

A literature search using Pubmed, Embase, and the Cochrane Library with no data restriction was carried out up to 30 June 2018. The search strategy included the keywords related to "breast cancer", "CDK inhibitors", "palbociclib", "ribociclib", "abemaciclib", "endocrine therapy", and "aromatase inhibitor". A computerized search of the abstracts reported at American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) library was performed from 2004 up to June 2018 in order to identify relevant unpublished studies. Specific keywords for each database and free text terms were combined with Boolean operators. Two reviewers (CM and CC) screened all full-text articles and abstracts independently. A third author (EZ) reviewed the search results to apply the eligibility criteria to both sets of search outcomes and acted as an arbiter in case of disagreement between the two reviewers (CM and CC). Finally, a crosscheck reference from review articles and relevant studies on the same topic was performed to confirm retrieval of all possible pertinent trials.

The work was done and reported according to PRISMA guidelines for reporting of systematic reviews [15].

Selection of the articles

Eligible studies had to fulfil the following inclusion criteria: (i) randomized phase II and III trials designed to evaluate the efficacy and safety of ET ± CDK4/6 inhibitors in the "endocrine-sensitive" and "endocrine-resistant" populations; (ii) the hazard ratio (HR) or odds ratio (OR) for PFS of the whole population and in the subgroup of metastatic women with HR+/HER2− breast cancer patients, ≥ G3–G4 adverse events (AEs), G3–G4 neutropenia, and ORR had to be reported or could be computed from data presented in the selected studies.

Studies excluded from the analysis were those with the following characteristics: (i) non-randomized prospective studies designed to evaluate the efficacy and safety of CDKi plus ET versus ET alone; (ii) retrospective studies; (iii) on-going studies which had not yet been presented or published at the time of the literature search. No language restriction was applied. For each eligible study, we collected study design, risks of bias, number of patients enrolled overall and into each treatment arm, main eligibility criteria of patients enrolled in each study number of PFS and ORR events, main ≥ G3–G4 AEs.

Statistical analysis

For data analysis, descriptive statistics were used to summarize baseline characteristics data. A quantitative synthesis (pooled analysis) was performed on eligible randomized clinical trials if methodologically appropriate. For time-to-event data, HR and 95% of confidence intervals (CIs) were used to compare results. A HR < 1 indicates that the use of CDKi plus ET yielded a lower probability of progression. A HR > 1 indicates that the use of CDKi increases the probability of progression. Odds ratios (ORs) based on events data were calculated to compare ≥ G3–G4 AEs, G3–G4 neutropenia, and ORs between CDKi plus ET versus ET alone. An OR < 1 indicates that the use of CDKi plus ET yielded a lower probability to develop lower ≥ G3–G4 AEs and G3–G4 neutropenia compared to ET alone. An OR > 1 indicates that the use of CDKi increases the probability of developing ≥ G3–G4 AEs and G3–G4 neutropenia.

The Mantel–Haenszel method was used to obtain random-effects model estimates of the pooled HR [16], because it is generally considered more appropriate than the fixed models in the presence of significant heterogeneity among studies [17]. Standard checks of the homogeneity assumption were carried out [18]. The Higgins' I^2 index was computed to obtain a quantitative measure of the degree of inconsistency in the results of the studies included [17]. All statistical analysis and the generation of forest plot were carried out using Cochrane RevMan version 5.2 software (Cochrane Tech, London, UK).

Results

The search strategy returned 268 records (Fig. 1): after the exclusion of 222 irrelevant publications, 46 were identified as records eligible for the present study. However, 33 full-text records were excluded because it did not fulfil all the prefixed eligibility criteria. Therefore, 13 records resulted eligible for our systematic review, but five were excluded because they were based on subgroup analysis or updated data after prior publication [19–23]. One phase II trial [7] and seven randomized phase III trials [8–14] reporting data on the efficacy and safety of CDKi plus ET vs ET alone were included and discussed. Five trials out of eight enrolled patients in endocrine-sensitive setting [7–9, 12, 13; 12, 13], two were carried in endocrine-resistant setting [10, 11], and only one trial included women ET naïve or who progressed to one prior line of ET [14]. A total of 4578 metastatic HR+/HER2− breast cancer patients (CDKi: 2792, ET: 1763) were enrolled in the eight trials. Main characteristics of these patients' cohorts are summarized in Table 1. Risks of bias assessment are summarized in Table 2.

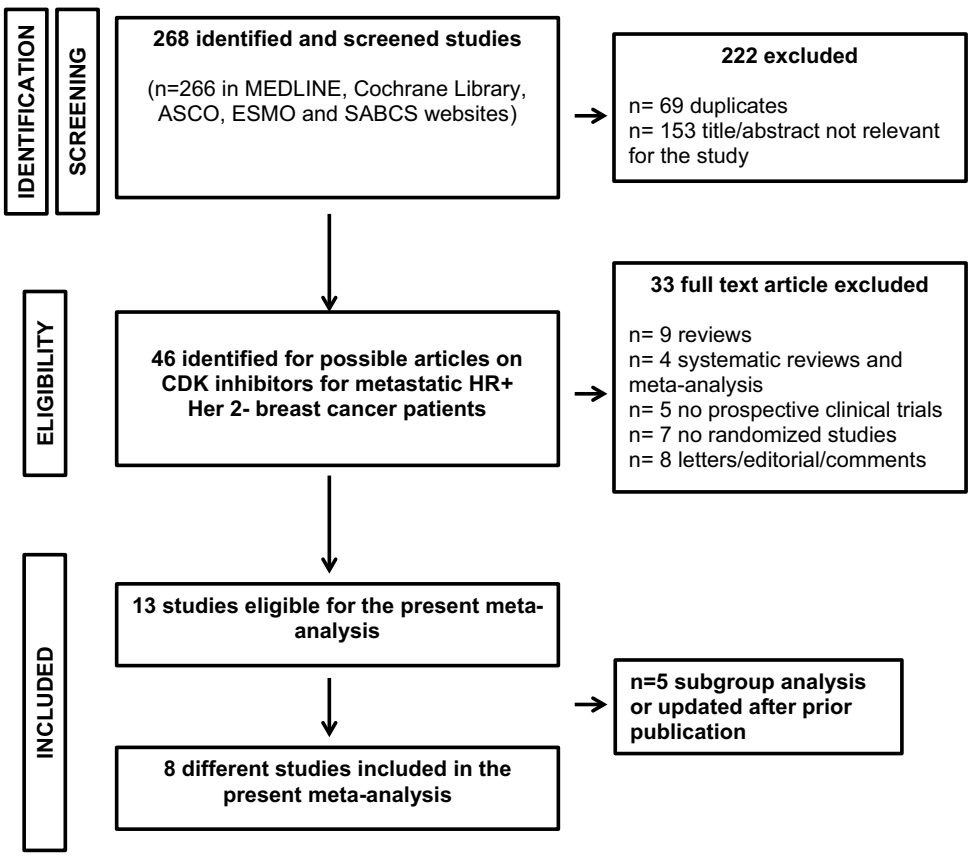

Fig. 1 The PRISMA flow chart summarizing the process for the identification of the eligible studies

Table 1 Main characteristics of the randomized studies included in the present meta-analysis

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥2%)
Paloma 1 [7]	Open label, randomized, phase II, palbociclib + letrozole versus letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.49 (95% CI 0.32–0.75)	HR 0.29 (95% CI 0.09–0.94)	HR 0.55 (95% CI 0.32–0.94)	43% (95% CI 32–54) in the palbociclib + letrozole arm vs 33% (95% CI 23–45) $P = 0{\cdot}13$ in the letrozole arm	54% neutropenia, 19% leukopenia, 6% anaemia, 5% fatigue, 4% diarrhoea, 2% nausea, 2% thrombocytopenia, 2% nausea, 2% dyspnoea, 2% back pain
Paloma 2 [8]	Double blind, randomized (2:1), phase III, palbociclib + letrozole versus placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.58 (95% CI 0.46–0.72)	HR 0.36 (95% CI 0.22–0.59)	HR 0.63 (95% CI 0.47–0.85)	42.1% (95% CI 37.5–46.9) in the palbociclib + letrozole arm versus 34.7% (95% CI 28.4–41.3) in the placebo + letrozole arm	66% neutropenia, 25% leukopenia, 5% anaemia, 2% febrile neutropenia, 2% fatigue, 2% asthenia, 2% thrombocytopenia
Monaleesa 2 [9]	Double blind, randomized (1:1), phase III trial, ribociclib + letrozole vs placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.56 (95% CI 0.43–0.72)	HR 0.69 (CI 95% 0.38–1.25)	NA	40.7% in the ribociclib + letrozole arm vs 27.5% in the placebo + letrozole arm	59% neutropenia, 21% leukopenia, 9% increased alanine aminotransferase (ALT), 6% increased aspartate aminotransferase (AST), 4% infections, 4% vomiting, 2% fatigue, 2% nausea
Monarch 3 [12]	Double blind, randomized (2:1), phase III, abemaciclib + AI (letrozole or anastrozole) versus abemaciclib + AI	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.54 (95% CI 0.41–0.72)	HR 0.58 (CI 95% 0.27–1.25)	HR 0.61 (95% CI 0.42–0.87)	48.2% in the abemaciclib + AI arm vs 24.5% in the placebo + AI arm	20% neutropenia, 9.5% diarrhoea, 8% leukopenia, 6% anaemia, 6% increased ALT, 5% infections, 2% fatigue, 2% increased blood creatinine

Table 1 (continued)

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥2%)
Paloma 3 [10]	Double blind, randomized (2:1), phase III, palbo + ful vs palbo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.42 (95% CI 0.32–0.56)	HR 0.36 (95% CI 0.22–0.60)	HR 0.45 (95% CI 0.32–0.63)	10.4% (95% CI 7.4–14.1) in the palbociclib + fulvestrant arm vs 6.3% (95% CI 3.2–11.0) in the placebo + fulvestrant arm (P = 0.16)	62% neutropenia, 25% leukopenia, 3% anaemia, 2% fatigue, 2% thrombocytopenia
Monarch 2 [11]	Double blind, randomized (2:1), phase III, abemaciclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.55 (95% CI 0.45–0.68)	HR 0.54 (95% CI 0.35–0.83)	HR 0.48 (95% CI 0.37–0.63)	35.2% (95% CI 30.8% − 39.6%) in the abemaciclib + fulvestrant arm vs 16.1% (95% CI 11.3% − 21.0%) in the placebo + fulvestrant arm (P = 0.001)	26.5% neutropenia, 13% diarrhoea, 9% leukopenia, 7% anaemia, 4% increased ALT, 3% fatigue, 3% nausea, 3% thrombocytopenia, 3% dyspnoea, 2.5% abdominal pain, 2% increased AST
Monaleesa 3 [14]	Double blind, randomized (2:1), phase III, ribociclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts, newly diagnosed or relapse > 12 months from (neo)-adjuvant ET, or progressed after one line of ET	1°and 2°line	PFS	HR 0.59 (95% CI 0.48–0.73)	HR 0.37 (95% CI 0.23–0.61)	HR 0.64 (95% CI 0.48–0.86)	32.4% (95% CI 28.3–36.6%) in the ribociclib + fulvestrant versus 21.5% (95% CI 16.3–26.7%) in placebo + fulvestrant (P = < 0.001)	46.6% neutropenia,13.5% leukopenia, 6.6% increased ALT, 45.3% nausea, 31.5% fatigue
Monaleesa 7 [13]	Double blind, randomized (1:1), phase III, ribociclib + tamoxifen or AI versus placebo + tamoxifen or AI	HR+ HER2−, premenopausal or perimenopausal pts, progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	1° line	PFS	HR 0.55 (95% CI 0.44–0.69)	HR 0.70 (95% CI 0.41–1.19)	HR 0.50 (95% CI 0.38–0.68)	35.1% (95% CI 30.1–40.6) in the ribociclib + tamoxifen or AI versus 24.6% (95% CI 20.2–29.6%)	61% neutropenia, 14% leukopenia, 5% increased ALT, 31% nausea, 22% fatigue

ET endocrine therapy, *HR+* hormone receptor positive, *ORR* overall response rates, *PFS* progression-free survival, *pts* patients

Table 2 Risks of bias assessment of the randomized studies included in the present meta-analysis

Trial	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting
MONALEESA-2 [9]	A computer-generated randomization schedule was used	Parallel assignment	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-2 [11]	A computer-generated randomization schedule was used	Web-based randomization scheme	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-3 [12]	A computer-generated randomization schedule was used	Centralized interactive Web response system	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-1 [7]	A computer-generated randomization schedule was used	Centralized interactive Web-based randomization system	Open label design	All randomized patients included in analyses	All outcome of interest reported
PALOMA-2 [8]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-3 [10]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-3	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-7	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature

PFS

One phase II trial [7] and five phase III trials [8, 9, 12–14] included in our systematic review assessed the efficacy of CDKi plus ET versus ET alone in endocrine sensitive setting; hence results were suitable for the meta-analysis (Fig. 2a). A total of 2009 patients were enrolled in the CDKi plus ET arm and 1381 in the ET arm. The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.55, 95% CI 0.50–0.62) for metastatic HR+/HER2− breast cancer patients in endocrine-sensitive setting. Moreover, combination treatment improved PFS both in women with visceral metastasis at presentation (HR 0.55, 95% CI 0.47–0.65) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.46–0.68) (Fig. 3a, c). Three phase III trials [10, 11] assessed the efficacy of CDKi plus ET versus ET alone and reported PFS HRs in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 2b). A total of 791 women were enrolled in the CDKi plus ET arm and 395 in the ET arm. All the women included in the two trials had been previously treated with ET. The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.51, 95% CI 0.43–0.61). The PFS advantage was significantly maintained both in patients with visceral metastasis (HR 0.47, 95% CI 0.38–0.58) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.43–0.73) (Fig. 3b, d).

Response

One phase II trial [7] and four phase III trials [8, 9, 12, 13] included in our systematic review reported on ORR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively (Fig. 4). A total of 871 ORR events occurred among 1525 patients treated with CDKi plus ET, and 786 in the 1139 women receiving ET alone. The combination of CDKi plus ET significantly improved the ORR compared to ET alone (ORs: 0.62, 95% CI 052–0.73) (Fig. 4a). Two phase III trials [10, 11] reported the OR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively, in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 4b). A total of 570 ORR events occurred among 793 patients treated with CDKi plus ET and 350 in the 397 women assigned to fulvestrant alone.

The addition of CDKi–ET was associated with a statistically significant ORR benefit (ORs 0.33, 95% CI 0.24–0.47).

Toxicities

All the trials included in our systematic review reported G3–G4 AEs occurring in the CDKi plus ET arm and in the ET alone arm (Fig. 5a). A total of 1107 out of 1541 patients (71.8%) treated with CDKi plus ET developed G3–G4 AEs

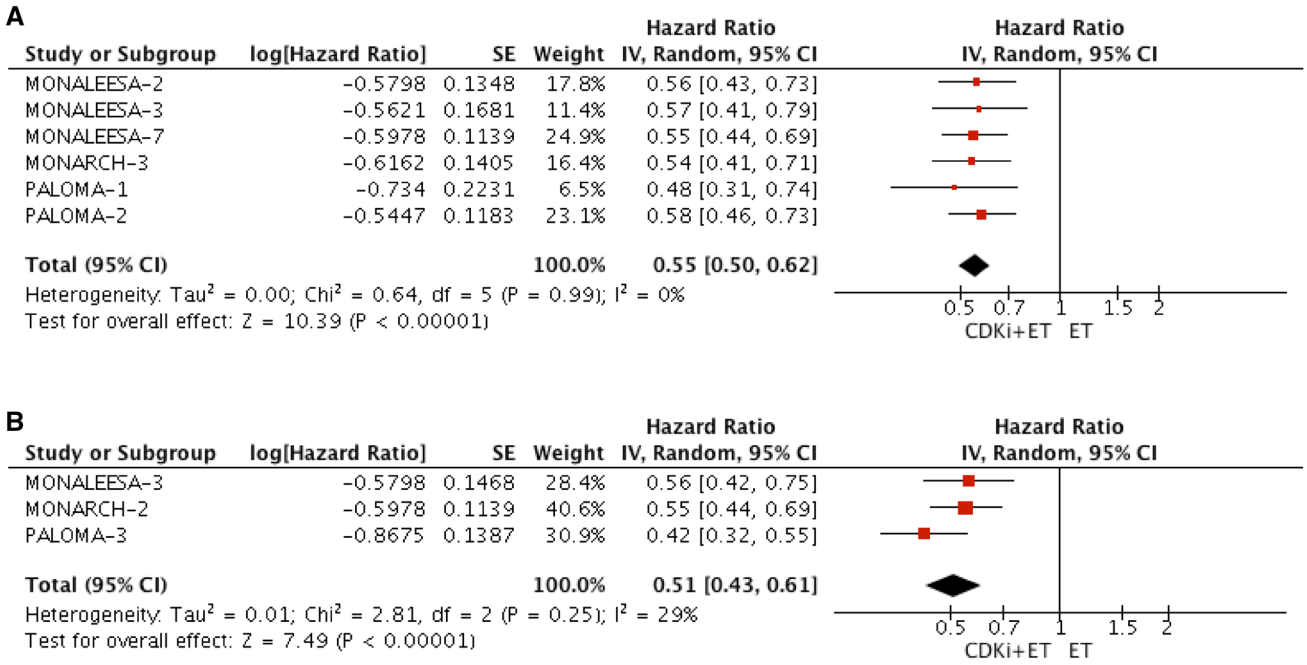

Fig. 2 Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in eight randomized trials of CDK inhibitors plus endocrine therapy compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**) advanced HR+ HER2− breast cancer women. Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy

compared to 313 out of 1127 women (27.8%) assigned to treatment with ET alone in endocrine-sensitive setting. The pooled ORs was 7.51 (95% CI 5.52–10.21), indicating a much higher probability of developing ≥ G3–G4 AEs for patients treated with CDKi and ET (Fig. 5a); however, significant heterogeneity between the four studies emerged (I^2 63%). Two phase III trials [10, 11] included in our systematic review assessed the activity of CDKi plus ET vs ET alone in endocrine-resistant setting: hence again results were suitable for our meta-analysis. A total of 506 out of 791 patients (64%) treated with CDKi plus ET, and 82 out of 395 women (20.7%) assigned to ET alone developed G3–G4 AEs. The pooled ORs was 7.09 (95% CI 3.53–14.25), again indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi plus ET (Fig. 5b); however, significant heterogeneity between the two studies emerged (I^2 83%). Again, we pooled together the eight randomized trials to assess the global impact in terms of G3–G4 AEs of combining CDKi with ET compared to ET alone [7–14]. A total of 2006 out of 2815 patients (71.2%) treated with CDKi plus ET and 411 out of 1763 women (23.3%) assigned to ET alone developed G3–G4 AEs. The pooled ORs was 9.64 (95% CI 6.00–15.49), indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi and ET (Fig. 5c); significant heterogeneity between the eight studies emerged (I^2 90%). However, the increased chance of developing G3–G4 toxicities for patients treated with CDKi plus ET may be influenced mostly by the odds to develop G3–G4 neutropenia (OR 10.88, 95% CI 6.53–18.14; Fig. 6).

Discussion

This meta-analysis shows that adding CDKi to ET significantly improves PFS compared to ET alone in HR+/HER2− metastatic breast cancer patients both in the endocrine-sensitive (HR 0.55) and endocrine-resistant population (HR 0.51) with similar odds of G3–G4 AEs (OR 7.51 vs. 7.09).

Patients with visceral metastases represent a challenging subgroup of HR+/HER2− breast cancer women as they have poorer prognosis than those without visceral involvement [24, 25].

According to the most recent international recommendations [26], ET should be preferred to chemotherapy as upfront treatment for metastatic HR+/HER2− breast cancer patients without organ dysfunction, for the lack of evidence of any benefit from using chemotherapy prior to ET [27, 28]. Despite this, many patients with visceral disease who are not in visceral crisis receive chemotherapy as early line treatment with increased toxicity and negative impact of quality of life [24, 25].

Our meta-analysis shows that the combination of CDKi plus ET provides an improvement in PFS compared to ET

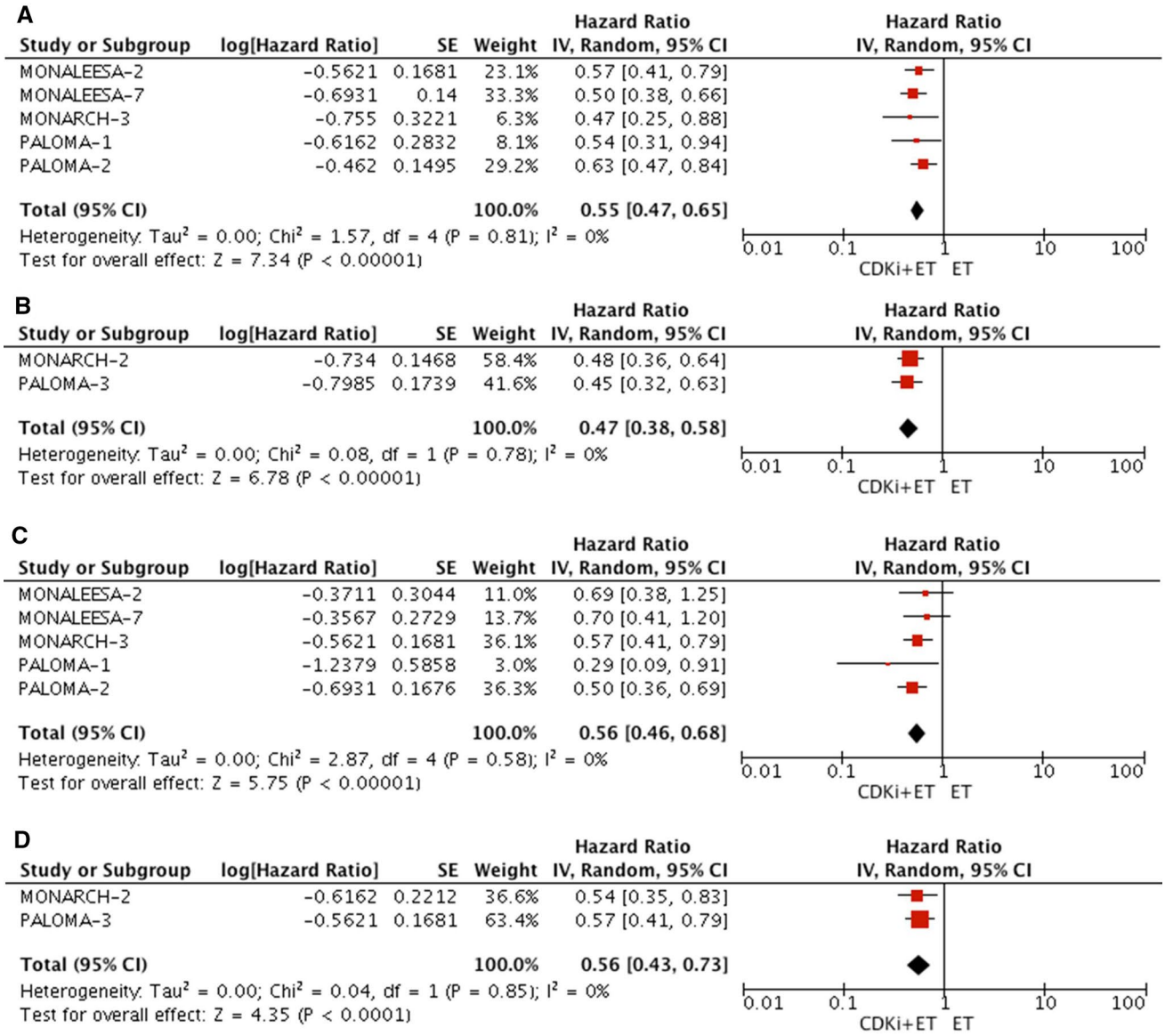

Fig. 3 Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in randomized trials of CDK inhibitors plus endocrine therapy compared ET alone for endocrine sensitive, endocrine resistant in advanced HR+ HER2− breast cancer women with visceral metastasis (**a, b**) and non-visceral metastasis (**c, d**). Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrinal therapy

both in the presence and in the absence of visceral metastasis (Fig. 3). The PFS benefit of CDKi in the subgroup with visceral involvement is maintained both in endocrine-sensitive (HR 0.55) and endocrine-resistant setting (HR 0.47). The remarkable results in the endocrine-resistant subgroup, that is known to present a more aggressive disease, as well as the evidence of enhanced activity over endocrine monotherapy in terms of response rate identify the CDKi plus ET combination as a new and even more effective option for patients with visceral metastases.

Given the lack of trials directly comparing the efficacy of CDKi plus ET vs chemotherapy, a recent Network meta-analysis assessed the efficacy of palbociclib plus letrozole and palbociclib plus fulvestrant vs chemotherapy in postmenopausal women with HR+ HER2− advanced or metastatic breast cancer in first- and second-line setting. Both palbociclib combination treatments provided meaningfully improvements in PFS compared to capecitabine and mitoxantrone, and trended toward improvements compared to paclitaxel, docetaxel, and other monotherapy

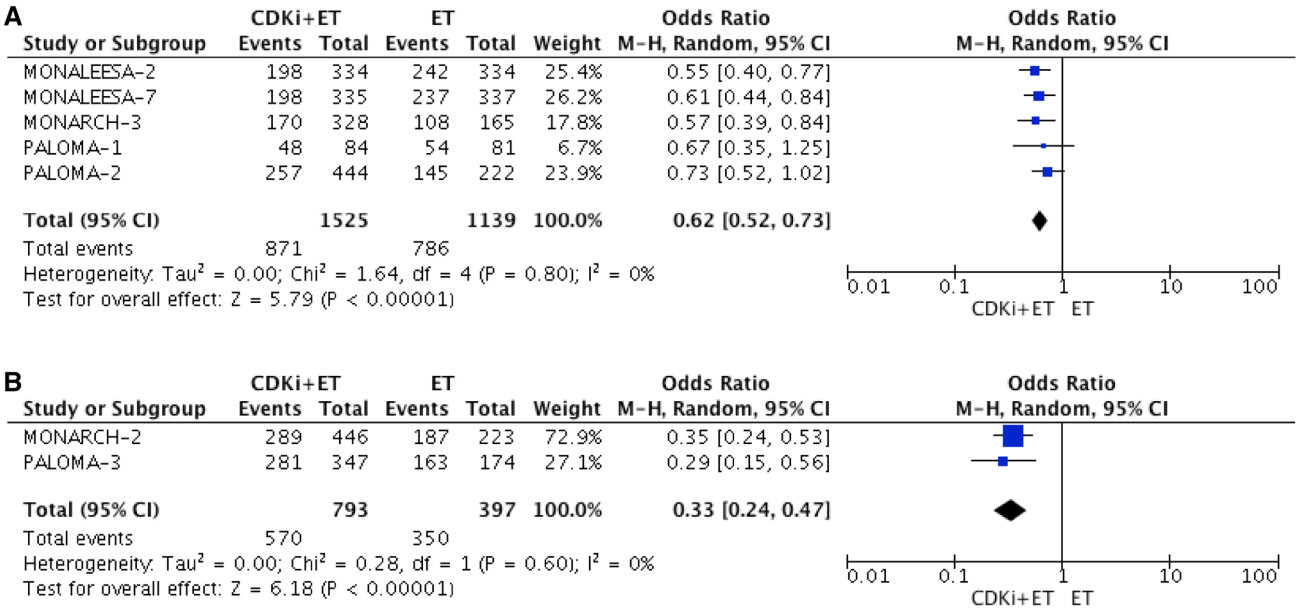

Fig. 4 Forest plot of Odds ratios (ORs) objective response rate (ORR) in seven randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive disease (**a**), endocrine-resistant disease (**b**) in advanced or metastatic HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* Odds ratios

or combination chemotherapy regimens [29]. Therefore, CDKi plus ET represent a new effective option for HR+/HER2− breast cancer patients and should be preferred to upfront chemotherapy.

Our systematic review and meta-analysis indicate that the use of CDKi in combination with ET significantly increases the incidence of G3–G4 AEs (OR 9.64). These data are remarkable and should be carefully considered on the light of the longer duration of the treatment.

The safety profile of CDKi is mainly influenced by hematologic toxicity, with a significant risk of developing G3–G4 neutropenia over ET alone (OR 10.88). Our results are in line with a recently published meta-analysis comparing the safety profile of different targeted agents in combination to ET, where the addition of CDKi was associated to a greater risk to develop G3–4 toxicities respect to mTOR, PI3K, and HER2 inhibitors [30]. Despite the hematologic toxicity as a class-specific AE and the increased risk of G3–4 neutropenia, the incidence of febrile neutropenia (FN) with CDKi is 1.2 over 0.1% with ET.

CDKi effects bone marrow through cell cycle arrest and not through cell apoptosis and this is rapidly reversible when the targeted agent is stopped [31]. This mechanism could explain the low rate of FN as well as the low rate of treatment discontinuation due to AEs observed with CDKi in these trials.

When evaluating risk and benefits of a specific treatment, AEs should be considered for their influence on quality of life (QoL). Neutropenia has been shown to have a minimal impact on QoL and this was confirmed in two recent publications, where CDKi plus ET maintained QoL and improved pain scores over ET [23, 32].

Our results highlight that adding CDKi to ET improves clinical outcomes compared to ET alone, regardless the number of prior treatments received and sites of metastasis with manageable toxicity and represent an alternative option to current standard treatment, including chemotherapy. Data from three randomized trials enrolling pre- and perimenopausal patients reported a significant PFS advantage for CDKi and ET over ET [13, 21, 33], demonstrating that this combination is effective irrespective of the menopausal status.

Unfortunately, clinical trials included in this meta-analysis were not powered to detect an OS advantage and indeed the majority of survival results are still pending. Survival results from the PALOMA-1 phase II trial were presented at ASCO annual meeting 2017 [34], demonstrating a non-significant trend toward better OS for the combination of palbociclib and letrozole vs letrozole as frontline treatment for HR+/HER2− advanced breast cancer [37.5 vs. 34.5 months, HR 0.897 (95% CI: 0.623–1.294); $P = 0.281$]. Preliminary survival data after 26.4 months follow-up from the MONALEESA-2 were recently published but are still immature for any conclusion [35]. Longer follow-up is strongly awaited to obtain final OS from the other trials in order to check the effectiveness of these drugs. However, the observed PFS benefit is consistent across the eight trials and is clinically relevant; even in the absence of mature data, the

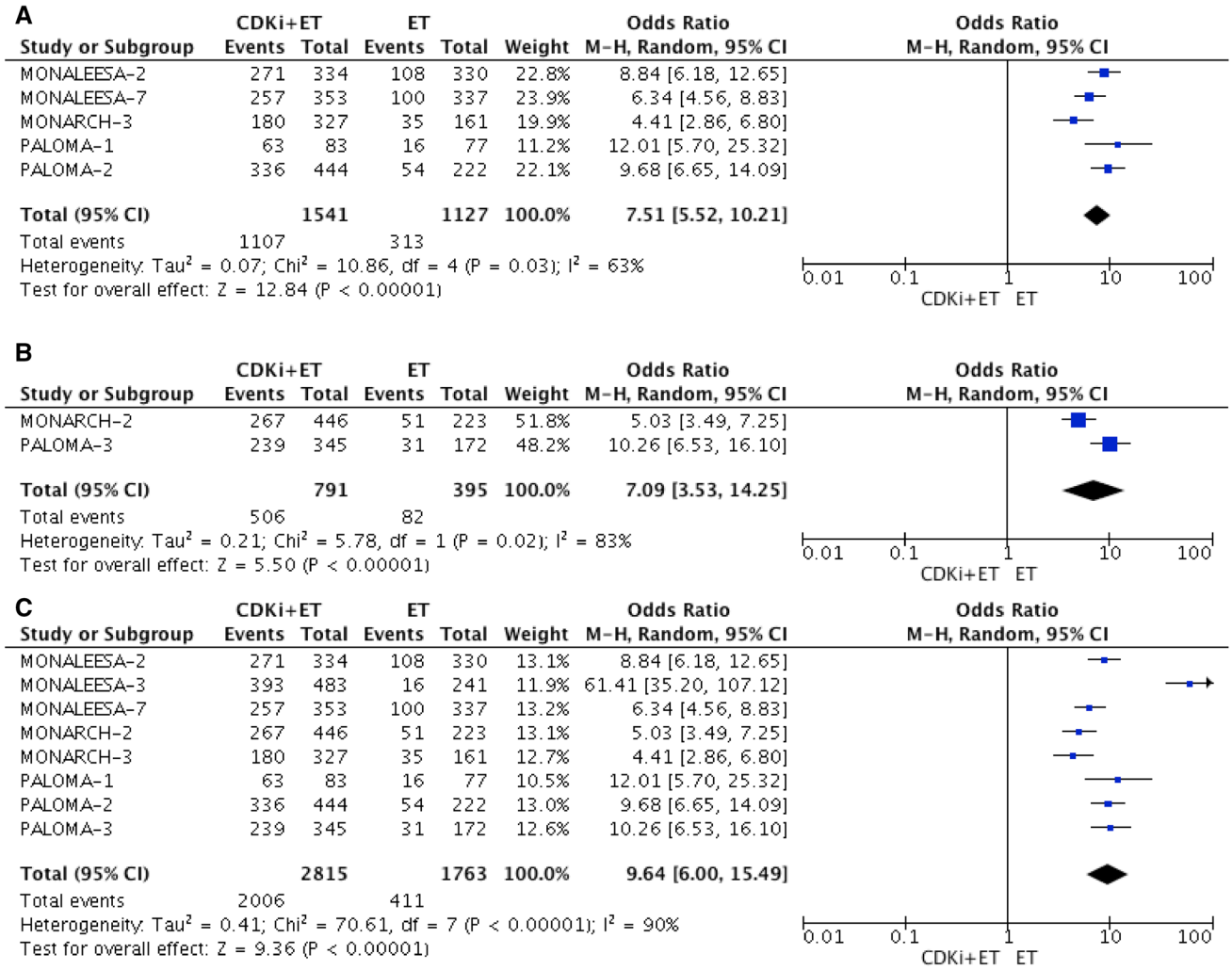

Fig. 5 Forest plot of odds ratios (ORs) for ≥G3–G4 AE in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

magnitude of PFS benefit is likely to translate in a significant improvement in OS [36, 37].

Several limitations of the present pooled analysis should be acknowledged; these include the lack of individual patient data (all data extracted are not based on individual patient data, but were retrieved from published articles), absence of mature OS data from most of the trials included in the present meta-analysis.

Nonetheless, these limitations probably do not significantly influence the overall interpretation of our findings, which strongly suggest that adding CDKi to ET significantly improved clinical outcome of ER+/HER2− breast cancers despite an increased ≥G3–G4 AEs.

Conclusion

Emerging data provide a new standard treatment for advanced HR+/Her2− breast cancer, regardless of menopausal status, prior hormonal/chemotherapy treatments delivered, sites of metastasis. However, benefits should be balanced with longer treatment duration, toxicities, and costs. Mature OS data are awaited. Head-to-head trials are warranted to compare the efficacy of CDKi plus ET or chemotherapy especially for women with high tumour burden and visceral metastases in order to improve patient's selection and maximize the benefit from the combined approach.

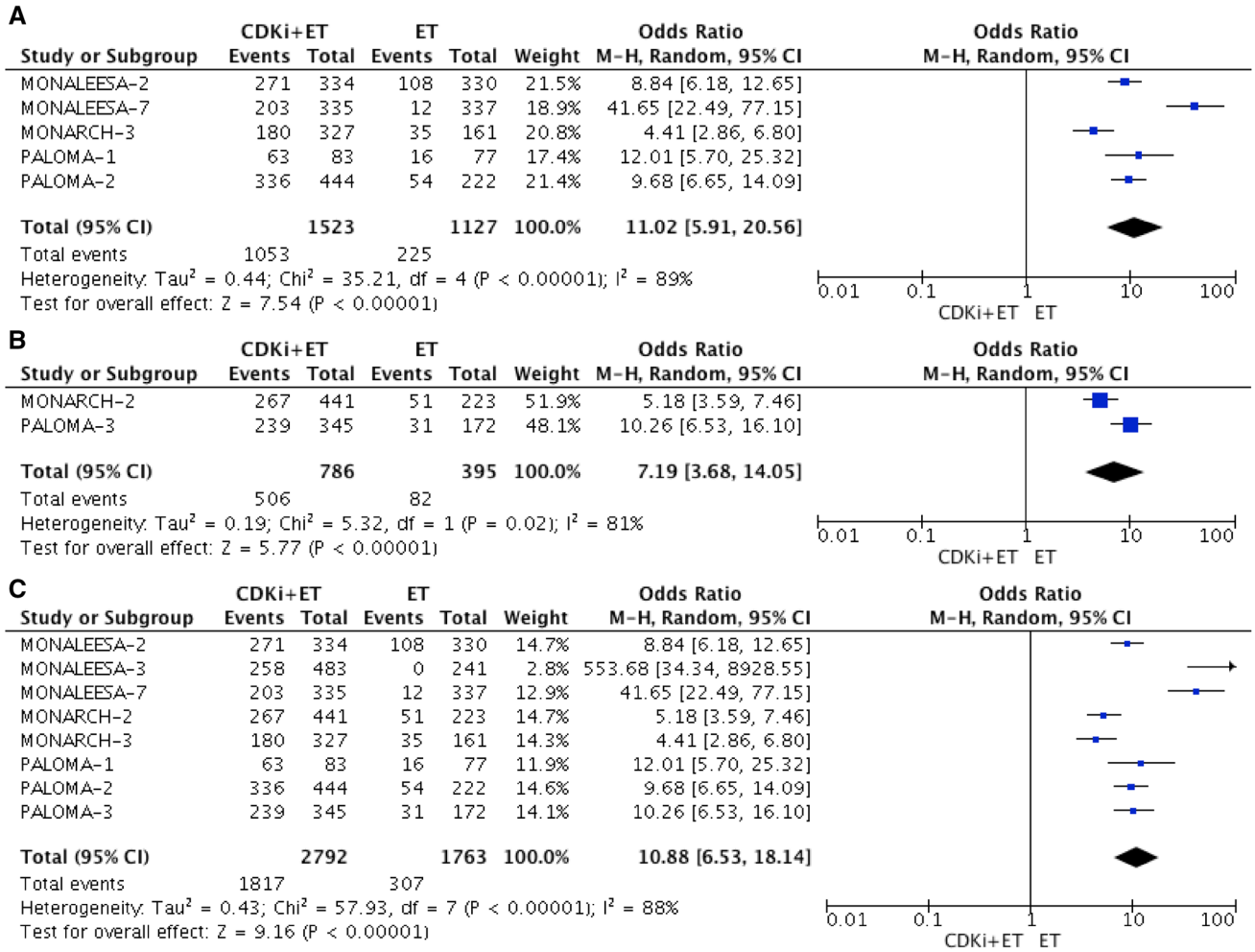

Fig. 6 Forest plot of odds ratios (ORs) for ≥G3–G4 neutropenia in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population (**c**) in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

Ethical approval This study does not contain any studies with human participants or animals performed by any of the authors.

Informed consent It was unnecessary given this study does not contain any studies with human participants or animals performed by any of the authors.

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