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ORIGINAL ARTICLE

Cyclin-dependent kinase 4/6 inhibitors as first-line treatment for post-menopausal metastatic hormone receptor-positive breast cancer patients: a systematic review and meta-analysis of phase III randomized clinical trials

Allan Ramos-Esquivel[1,2] · Hellen Hernández-Steller[1] · Marie-France Savard[3] · Denis Ulises Landaverde[2,4]

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Abstract

Background To compare the efficacy and toxicity of the combination of cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors and nonsteroidal aromatase inhibitors (AI) versus AI alone as first-line therapy for patients with advanced hormone receptor-positive breast cancer.

Materials and methods Phase III randomized clinical trials (RCT) were identified after a systematic review of electronic databases. A random-effect model was used to determine the pooled hazard ratio (HR) for progression-free survival (PFS) using the inverse-variance method. The Mantel–Haenszel method was used to calculate the pooled odds ratio (OR) for overall response, clinical benefit rate and treatment-related side effects. Heterogeneity was measured using the tau-squared and I^2 statistics.

Results After a systematic search, three phase III RCT ($n = 1827$) were included. The use of CDK 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) in combination with an AI was significantly associated with longer PFS compared to the use of letrozole or anastrozole alone (HR: 0.57; 95% CI 0.50–0.65; $p < 0.00001$), with no significant heterogeneity among trials. Similarly, overall response rate and clinical benefit rate were higher for patients who received the combination therapy than for patients allocated to AI alone. Grade 3 or higher treatment-related side effects were more frequently reported for patients who received CDK 4/6 inhibitors (OR: 7.51; 95% CI 6.01–9.38; $p < 0.00001$), these included mainly neutropenia, leukopenia and anemia.

Conclusion The addition of CDK 4/6 inhibitors (either abemaciclib, palbociclib, or ribociclib) to an AI (anastrozole or letrozole) significantly improved PFS, overall response rate, and clinical benefit rate in comparison with a nonsteroidal AI alone.

Keywords Abemaciclib · Breast cancer · Cyclin-dependent kinase · Palbociclib · Ribociclib

Introduction

Breast cancer is the most common malignancy in women and represents a leading cause of cancer-specific mortality worldwide [1]. Among post-menopausal women, Hormone Receptor (HR)-positive and Human Epidermal Growth Factor Receptor type 2 (HER2)-negative breast cancer is the most frequent subtype [2]. Similarly, almost two-thirds of patients with metastatic breast cancer have HR-positive tumors, and it is estimated that around 25% of patients with HR-positive breast cancer will eventually relapse [2–4].

Until recently, the backbone of treatment for post-menopausal women with a metastatic HR-positive and Her-2-negative breast cancer without visceral crisis has been

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✉ Allan Ramos-Esquivel
allan.ramos@ucr.ac.cr

[1] Departamento de Oncología Médica, Hospital San Juan de Dios, PO BOX: 1000-SJO, San Jose, Costa Rica

[2] Escuela de Medicina, Universidad de Costa Rica, San Jose, Costa Rica

[3] Department of Oncology, McGill University, Montreal, QC, Canada

[4] Departamento de Oncología Médica, Hospital México, San Jose, Costa Rica

based on endocrine therapy with steroidal (exemestane) or nonsteroidal (anastrozole or letrozole) aromatase inhibitors (AIs), estrogen receptor antagonists (fulvestrant), and selective estrogen receptor modulators (tamoxifen) [5]. However, intrinsic and acquired resistance to hormonal blockade is responsible for relapse and eventually death of patients. Therefore, multiple studies are exploring new strategies to overcome that resistance and to improve the outcomes of these patients. Everolimus administered in combination with exemestane is the first signal transduction inhibitor and non-cytotoxic agent approved in a second-line setting for estrogen receptor-positive, Her-2-negative post-menopausal metastatic patients that target outside the estrogen-receptor signaling pathway [6]. Lately, there has been a significant interest for therapies targeting the CDK4/6-D-type cyclin–RB pathway and clinical studies support the significant role for the cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors administered in combination with endocrine therapy in the treatment of metastatic HR-positive BC [7]. CDK4/6–Cyclin D complex allows the cell cycle progression from phase G1 to S through the phosphorylation of the retinoblastoma (Rb) gene product [8]. Hence, pre-clinical data on cancer cell lines panel demonstrated that the inhibition of CDK4/6–Cyclin D complex promotes G1 arrest which leads to senescence [9, 10]. Although these agents belong to the same drug class, previous studies have acknowledged some differences in their pleiotropic effects, pharmacodynamics, and pharmacokinetics [11]. To date, there is no formal head to head comparison among these inhibitors. Thus, the aim of this systematic review and meta-analysis is to evaluate and compare the efficacy and safety of the CDK 4/6 inhibitors used in combination with an AI as first-line treatment for metastatic HR-positive, HER2-negative breast cancer patients.

Materials and methods

Search strategy and study selection

We followed the PRISMA statement for reporting systematic reviews and meta-analyses (checklist available as supplementary file) [12]. Two authors independently examined the abstracts retrieved by a search strategy in electronic databases (MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials) from October 2007 to October 2017 (Supplementary file). The research was conducted on October 3rd, 2017. Proceedings of the American Society of Clinical Oncology (ASCO) Annual Meeting, San Antonio Breast Cancer Annual Symposium, and the European Society of Medical Oncology Annual Meeting were also queried from 2012 to 2017 for relevant abstracts. In cases where a report of the same trial was obtained, the most recent results were included (corresponding to longer follow-up). Then, the authors examined full-text articles of potentially eligible studies according to the eligibility criteria. Disagreements on the inclusion of selected trials were resolved in discussions with another author.

Eligibility criteria

We decided to include only phase III randomized controlled trials (RCT) that reported the comparison of CDK 4/6 inhibitors plus hormonal treatment versus hormonal treatment alone as first-line therapy in metastatic HR-positive, HER2-negative breast cancer. We excluded trials with incomplete data.

Outcomes

The primary outcome was progression-free survival (PFS), calculated from the date of randomization to the date of progression (defined by the Response Evaluation Criteria in Solid Tumors "RECIST" 1.1 criteria [13] or death). The secondary outcomes were: (1) objective response rate (ORR): defined as the percentage of patients with complete or partial response as per RECIST 1.1 criteria (as assessed in all randomly assigned patients); and (2) clinical benefit (CBR): defined as a confirmed complete or partial response or stable disease lasting 24 weeks or more. We also evaluated the safety of each arm in all patients who received at least one dose of the study treatment. Adverse drug reactions (ADR) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Quality assessment

The risk of bias was evaluated by the authors using the Cochrane Collaboration Tool [11]. Publication bias was visually examined in a funnel plot. The risk of bias was categorized as 'low risk', 'high risk', or as 'unclear risk'.

Data collection and statistical analysis

For the primary efficacy outcome (PFS) we reported the hazard ratio (HR) with a corresponding 95% confidence interval (95% CI). For the association of the odds of overall response and clinical benefit rate we employed the Mantel–Haenszel odds ratio and its corresponding 95% CI. We used a random-effect model for the efficacy measures according to the DerSimonian–Laird method. The pooled hazard ratios and pooled odds ratios were calculated according to the inverse-variance method, as described by Parmar et al. [14]. Heterogeneity was determined by the Tau-squared and I^2 statistics. Data analysis was performed using RevMan 5.3 software.

Role of funding source

No funding source had any role in study design, data analysis, or writing of this manuscript.

Results

Study selection

Through the search strategy, we identified three trials [15–17] that compared 1106 patients treated with the combination of a CDK 4/6 inhibitor (abemaciclib, palbociclib or ribociclib) plus an aromatase inhibitor versus 721 patients treated with an aromatase inhibitor alone (letrozole 2.5 mg daily or anastrozole 1 mg per day on a continuous schedule). The PRISMA flow diagram for study inclusion is shown in Fig. 1.

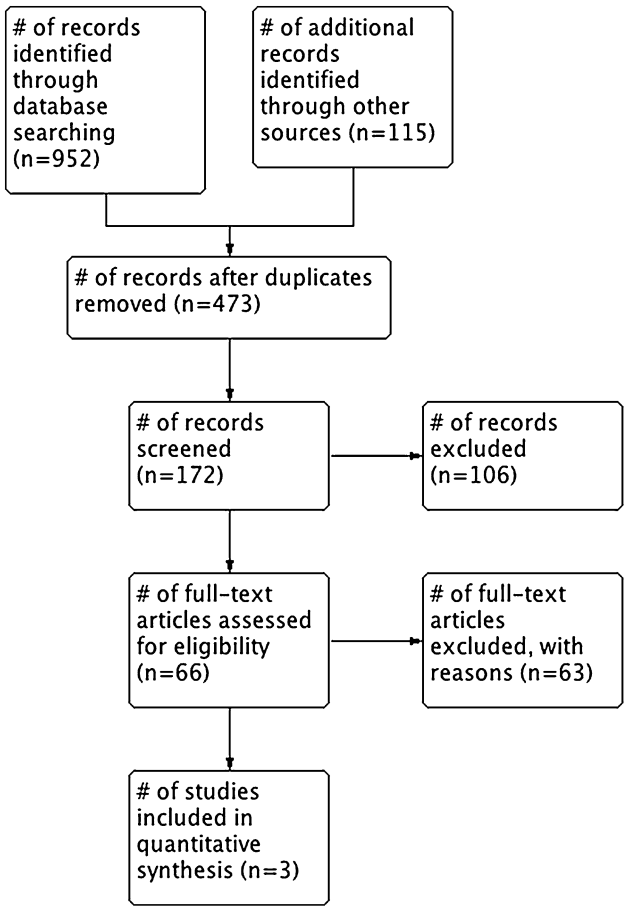

Fig. 1 PRISMA flow diagram for systematic review

Description of studies and patients

Table 1 summarizes the main characteristics of each trial. Palbociclib and ribociclib were tested in combination with letrozole 2.5 mg/day in the PALOMA-2 and MONALEESA-2 trials, respectively [15, 16]. Abemaciclib was used in combination with anastrozole 1 mg/day (19.9%) or letrozole 2.5 mg/day (79.1%) (as per physician's choice) in the MONARCH-3 trial [16]. The primary outcome was PFS in all trials (Table 2). Table 1 also resumes the main characteristics of patients for each trial.

Outcomes

Progression-free survival

As shown in Table 2 and Fig. 2, the combination of a CDK 4/6 inhibitor plus an AI resulted in an improvement in PFS (pooled HR = 0.57; 95% CI 0.50–0.65). We did not detect a significant source of heterogeneity regarding this specific outcome ($Tau^2 < 0.01$; I^2: 0%; $p = 0.93$).

Objective response

The odds of objective response were significantly higher with the combination of any CDK 4/6 inhibitor plus AI versus AI alone (Mantel–Haenszel OR: 1.75; 95% CI 1.41–2.18). We did not detect significant heterogeneity regarding this outcome (Tau^2: 0.01; I^2: 0%; $p = 0.72$)(Fig. 3).

Clinical benefit

The addition of a CDK 4/6 inhibitor plus an AI significantly increased the odds of clinical benefit (Mantel–Haenszel OR: 1.81; 95% CI 1.40–2.34). We did not detect heterogeneity regarding this specific outcome ($Tau^2 < 0.01$; I^2: 0%; $p = 0.52$) (Fig. 4).

Treatment-related side effects

As shown in Table 2, the number of serious adverse side effects was higher in patients allocated to the combination treatment in comparison with patients who received any AI alone. The odds of having any grade 3 or 4 treatment-related side effect were significantly higher in patients receiving the experimental combination (Mantel–Haenszel OR: 7.51; 95% CI 6.01–9.38) (Fig. 5). The most common all-grade toxicity was neutropenia ranging from 66.5% (palbociclib)

Table 1 General characteristics of patients and trials

Trial	MONARCH-3 trial		PALOMA-2 trial		MONALEESA-2 trial	
Drug	Abemaciclib $N = 328$	Control $N = 165$	Palbociclib $N = 444$	Control $N = 222$	Ribociclib $N = 334$	Control $N = 334$
Dose	150 mg BID on continuous schedule	Anastrozole 1 mg/day or letrozole 2.5 mg/d (continuous schedule)	125 mg/day (3 weeks of treatment followed by one week off)	Letrozole 2.5 mg/day (continuous schedule)	600 mg/day (3 weeks of treatment followed by one week off)	Letrozole 2.5 mg/day (continuous schedule)
Median age (years) (range)	63 (38–87)	63 (32–88)	62 (30–89)	61 (28–88)	62 (23–91)	63 (29–88)
Ethnicity, no. (%)						
White	186 (56.7)	102 (61.8)	344 (77.5)	172 (77.5)	269 (80.5)	280 (83.8)
Asian	103 (31.4)	45 (27.3)	65 (14.6)	30 (13.5)	28 (8.4)	23 (6.9)
Black			8 (1.8)	3 (1.4)	10 (3)	7 (2.1)
Other	11 (3.4)	7 (4.2)	27 (6.1)	17 (7.7)	27 (8.1)	24 (7.2)
ECOG performance status, no. (%)	Not reported	Not reported				
0			257 (57.9)	102 (45.9)	205 (61.4)	202 (60.5)
1			78 (40.1)	117 (52.7)	129 (38.6)	132 (39.5)
2			9 (2)	3 (1.4)	0	0
Disease stage at diagnosis, no. (%)	Not reported	Not reported				
≤ III			260 (58.6)	137 (61.7)	1 (0.3)	3 (0.9)
IV			138 (31.1)	72 (32.4)	333 (99.7)	331 (99.1)
Unknown			46 (10.3)	13 (5.9)		
Hormone receptor status, no. (%)	Not reported	Not reported	Not reported	Not reported		
Estrogen receptor positive					332 (99.4)	333 (99.7)
Progesterone receptor positive					271 (81.1)	278 (83.2)
Disease-free interval, no. (%)	Not reported	Not reported				
Newly diagnosed			167 (37.6)	81 (36.5)	114 (34.1)	113 (33.8)
Existing disease						
≤ 12 months			99 (22.3)	48 (21.6)	4 (1.2)	10 (3)
> 12 months			178 (40.1)	93 (41.9)	216 (64.7)	211 (63.2)
Previous treatment, no. (%)						
Neoadjuvant or adjuvant chemotherapy	125 (38.1)	66 (40)	213 (48)	109 (49.1)	146 (43.7)	145 (43.4)

Table 1 (continued)

Trial	MONARCH-3 trial		PALOMA-2 trial		MONALEESA-2 trial	
Neoadjuvant or adjuvant endocrine therapy	150 (45.7)	80 (48.5)	229 (56.1)	126 (56.8)	175 (52.4)	171 (51.2)
Anastrozole			56 (12.6)	29 (13.1)	47 (14.1)	42 (12.6)
Exemestane			30 (6.8)	13 (5.9)	19 (5.7)	25 (7.5)
Goserelin			5 (1.1)	6 (2.7)	6 (1.8)	3 (0.9)
Letrozole			36 (8.1)	16 (7.2)	34 (10.2)	25 (7.5)
Tamoxifen			209 (47.1)	98 (44.1)	140 (41.9)	145 (43.4)
Other			10 (2.3)	5 (2.3)	2 (0.6)	4 (1.2)
No. of metastatic sites, no. (%)	Not reported	Not reported				
0			0	0	2 (0.6)	1 (0.3)
1			138 (31.1)	66 (29.7)	100 (21.9)	117 (35)
2			117 (26.4)	52 (23.4)	118 (35.3)	103 (30.8)
≥ 3			189 (42.5)	104 (46.9)	114 (34.1)	113 (33.8)
Site of metastases, no. (%)						
Visceral	172 (52.4)	89(53.9)	214 (48.2)	110 (49.5)	197 (59)	196 (58.7)
Non-visceral	86 (26.2)	37 (22.4)	230 (51.8)	112 (50.5)	135 (41)	137 (41.3)
Bone only	70 (21.3)	39 (23.6)	103 (23.2)	48 (21.6)		
Inclusion criteria	Have a diagnosis of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer Have locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease Post-menopausal women Have either measurable disease or non measurable bone-only disease Eastern Cooperative Oncology Group [ECOG] 0–2 Have adequate organ function Have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture prior to randomization and recovered from the acute effects of therapy Are able to swallow capsules		Adult women with locoregionally recurrent or metastatic disease not amenable to curative therapy Confirmed diagnosis of ER positive breast cancer No prior systemic anti-cancer therapy for advanced ER+ disease Post-menopausal women Measurable disease as per Response Evaluation Criterion in Solid Tumors [RECIST] or bone-only disease Eastern Cooperative Oncology Group [ECOG] 0–2 Adequate organ and marrow function Patient must agree to provide tumor tissue		Women with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy Post-menopausal women No prior systemic anti-cancer therapy for advanced disease Patient with a histologically and/or cytologically confirmed diagnosis of estrogen receptor-positive and/or progesterone receptor-positive breast cancer by local laboratory and HER2-negative breast cancer Patients with either: Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented) If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation) Eastern Cooperative Oncology Group [ECOG] 0–1	

Table 1 (continued)

Trial	MONARCH-3 trial	PALOMA-2 trial	MONALEESA-2 trial
Exclusion criteria	Patients with visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis Inflammatory breast cancer Clinical evidence or history of central nervous system (CNS) metastasis Concurrent use of endocrine therapy for locoregionally recurrent or metastatic breast cancer Prior (neo)adjuvant endocrine therapy with a disease-free interval ≤ 12 months from completion of treatment Prior use of chemotherapy for locoregionally recurrent or metastatic breast cancer Prior treatment with everolimus or any cyclin-dependent kinase (CDK) 4/6 inhibitor	Confirmed diagnosis of HER2 positive disease Patients with advanced, symptomatic, visceral spread that are at risk of life-threatening complication in the short term Known uncontrolled or symptomatic CNS metastases Prior (neo)adjuvant treatment with letrozole or anastrozole with disease-free interval ≤ 12 months from completion of treatment Prior treatment with any CDK 4/6 inhibitor	Patient who received any CDK4/6 inhibitor or any prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy) for advanced breast cancer Prior (neo)adjuvant treatment with letrozole or anastrozole with disease-free interval ≤ 12 months from completion of treatment Concurrent use of any anti-cancer therapy Concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer Patient with active cardiac disease or a history of cardiac dysfunction Concurrent use of inducers or inhibitors of CYP3A4
Enrollment time	From November 2014 to November 2015	From February 2013 to July 2014	From January 24th 2014 to March 24th 2015
Primary end point	Progression-free-survival	Progression-free survival	Progression-free survival
Secondary end points	Overall survival Duration of response Disease control rate Clinical benefit rate Quality of life	Overall survival Overall response rate Safety	Overall survival Objective response Clinical benefit response Patient reported outcomes Pharmacokinetic effects Safety

to 21.1% (abemaciclib), followed by leukopenia and anemia. Nonetheless, rates of febrile neutropenia were low, ranging from 1.8% (palbociclib) to 0.3% (abemaciclib). Some toxicities were only reported for specific CDK 4/6 inhibitors. For example, abemaciclib was associated with grade 3 increased blood creatinine in 7 patients (2.1%), and ribociclib use was linked to QT prolongation of more than 60 ms in 9 patients (2.7%).

Subgroup analyses

The PFS analyses according to age, ethnicity, performance status, and disease setting (de novo metastatic versus recurrent metastatic) are presented as supplementary files. The combination treatment resulted in significant benefit for all abovementioned subgroups in comparison with the use of an AI alone. We found no heterogeneity in all the pre-specified subgroups, with the exception of race. Specifically, patients from Asia exhibited a higher benefit of the experimental treatment (HR: 0.38; 95% CI 0.26–0.54) versus patients from other part of the world (HR: 0.55; 95% CI 0.45–0.67).

Risk of bias

The risk of bias assessment is presented in a supplementary file.

All included trials were double blind with low risk of selection, performance, attrition, detection, and reporting bias. We did not detect evidence of substantial publication bias in the funnel plot analysis (Supplementary file).

Discussion

This systematic review and meta-analysis summarizes available data from published phase III randomized clinical trials regarding the PFS benefit of first-line therapy when adding CDK 4/6 inhibitors to an AI in patients with HR-positive, HER2-negative breast cancer [15–17].

Overall, our statistical approach showed an increase of the PFS for patients treated with the combination of abemaciclib, palbociclib or ribociclib and an aromatase inhibitor in comparison to those treated with an AI alone. This benefit was shown for all the aforementioned agents with no evidence of substantial heterogeneity among trials. Furthermore, the rates of clinical benefit and objective response were very similar among the included CDK 4/6 inhibitors. Notably, the median progression-free survival was almost 25 months, which is approximately 10 months longer than that seen with other therapies in the first-line setting, such as anastrozole [18], letrozole, [19], tamoxifen [18, 19], exemestane [20], and fulvestrant [21].

Although the overall efficacy of abemaciclib, palbociclib and ribociclib was very similar, the pattern of side effects was different among these agents. As shown in Fig. 5, rates of grade 3 or 4 adverse events were more frequently reported in patients treated with ribociclib (83.2%), followed by palbociclib (75.7%), and abemaciclib (27.5%). However, the rate of treatment modification due to adverse events, serious adverse events and deaths due to adverse events was more frequently reported in patients treated with abemaciclib compared to those treated with ribociclib and palbociclib. Interestingly, the most common grade 3 and 4 adverse events observed in patients treated with palbociclib and ribociclib were neutropenia and leukopenia, and this was not associated with a clinically meaningful risk of infections or febrile neutropenia. Indeed, previous pre-clinical models have suggested that CDK inhibitors induce bone marrow suppression through a reversible cell cycle arrest. In contrast, chemotherapeutic cytotoxic agents induce DNA damage and apoptosis [22]. This might explain why the grade 3 and 4 neutropenia mediated by CDK inhibitors were not associated with a proportional increase in the risk of febrile neutropenia. Although it is not possible to draw definite conclusions from this indirect comparison, we can make the hypothesis that this different pattern of toxicity observed for each experimental drug might be explained by a different potency to the selective inhibition of CDK 4/6 and different mechanisms of toxicity [23]. For instance, increased blood creatinine was only reported for abemaciclib due to its inhibitory effect on renal tubular secretion of creatinine [17]. This agent was also associated with higher rates of grade 3 and 4 diarrhea. Analogously, QT prolongation was only described for ribociclib.

A striking feature of the addition of CDK 4/6 inhibitors to endocrine therapy is that it provided a consistent PFS benefit across all pre-specified subgroups including age, ethnicity, prior endocrine therapy or chemotherapy, ECOG performance status, site of metastatic disease, number of metastatic site, and disease-free interval. However, there was a trend of higher PFS in Asian patients than in other ethnicities. Although this subgroup comprised only 26.6% of all patients, it has been previously documented that patients from this ethnicity have better outcomes than White patients, probably as a result of different pharmacokinetics, efficacy or tolerance to CDK inhibitors [24].

Despite the PFS benefit shown in this analysis, overall survival data are not yet available, but given the important benefits observed point towards the possibility of a promising survival advantage. Further studies should determine if comparable benefits are observed when CDK4/6 inhibitors are used in combination with anti-Her-2 agents in HER-2

Table 2 Main outcomes for each included trial

Trial		MONARCH-3 trial		PALOMA-2 trial		MONALEESA-2 trial	
Drug		Abemaciclib		Palbociclib		Ribociclib	
Follow-up		17.8 months		23 months		15.3 months	
Median progression-free survival: experimental vs. control group, months		Not reached vs. 14.7 HR = 0.54 (95% CI 0.41–0.72) $p = 0.000021$		24.8 vs. 14.5 HR = 0.58 (95% CI 0.46–0.72) $p < 0.001$		25.3 vs. 16 HR = 0.57 (95% CI 0.46–0.70) $p < 0.0001$	
	Experimental	Control	Experimental	Control	Experimental	Control	
Objective response rate % (95% CI)	48.2 (42.8–53.6)	34.5 (27.3–41.8)	42.1 (37.5–46.9)	34.7 (28.4–41.3)	40.7 (35.4–46.0)	25.5 (22.8–32.3)	
Complete response, no. (%)	5 (0.5)	0	Not reported	Not reported	Not reported	Not reported	
Clinical benefit rate, % (95% CI)	78.0 (73.6–82.5)	71.5 (64.6–78.4)	84.9 (81.2–88.1)	70.3 (63.8–76.2)	79.6 (75.3–84.0)	72.8 (68–67.5)	
Treatment modification due to adverse events, no. (%)	64 (19.6)	4 (2.5)	43 (9.7)	13 (5.9)	25 (7.5)	7 (2.1)	
Discontinuation	142 (43.4)	10 (6.2)	160 (36)	3 (1.4)	169 (50.6)	14 (4.2)	
Reduction							
Serious adverse events, no. (%)	90 (27.5)	24 (14.9)	87 (19.6)	28 (12.6)	71 (21.3)	39 (11.8)	
Deaths due to adverse events, no. (%)	8 (2.4)	2 (1.2)	3 (0.9)	1 (0.3)	4 (0.9)	1 (0.3)	
Treatment-related adverse events (grade III–IV), no. (%)							
Any	180 (55)	35 (21.8)	336 (75.7)	54 (24.4)	271 (83.2)	108 (32.7)	
Neutropenia	69 (21.1)	2 (1.2)	295 (66.5)	3 (1.4)	198 (59.3)	3 (0.9)	
Leukopenia	25 (7.6)	1 (0.6)	110 (24.8)	0	70 (21)	2 (0.6)	
Anemia	19 (5.8)	2 (1.2)	24 (5.4)	4 (1.8)	4 (1.2)	4 (1.2)	
Fatigue/asthenia	6 (1.8)	0	18 (4.1)	1 (0.5)	8 (2.4)	3 (0.9)	
Vomiting	4 (1.2)	3 (1.9)	2 (0.5)	3 (1.4)	12 (3.6)	3 (0.9)	
Diarrhea	31 (9.4)	2 (1.2)	6 (1.4)	3 (1.4)	4 (1.2)	3 (0.9)	
Increased alanine aminotransferase	22 (7)	3 (1.9)	NR	NR	31 (9.3)	4 (1.2)	
Increased aspartate aminotransferase	12 (3.8)	1 (0.6)	NR	NR	19 (5.7)	4 (1.2)	
Median duration of exposure	16 cycles	15 cycles	Not reported		13.0 mo	12.4 mo	
Median relative dose intensity (%)	86	98	93	100	88	100	

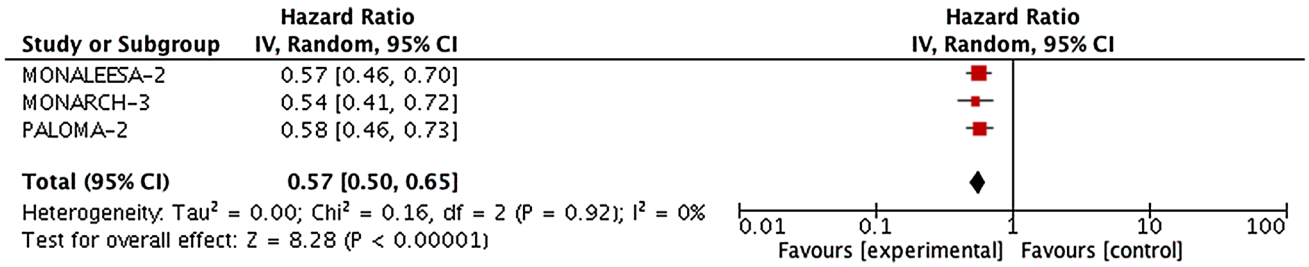

Fig. 2 Forest plot for progression-free survival

positive metastatic breast cancer, and in association with chemotherapy for triple-negative tumors. In searching for a rationale at the molecular level, pre-clinical data based on cell lines suggested that the ones sensitive to CDK 4/6 inhibitors had luminal features whereas the resistant ones had basal-like features. Furthermore, sensitivity to palbociclib

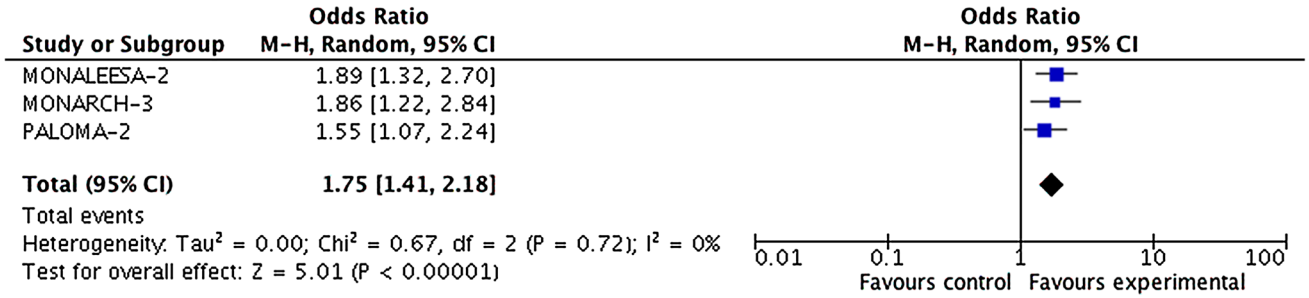

Fig. 3 Forest plot for objective response

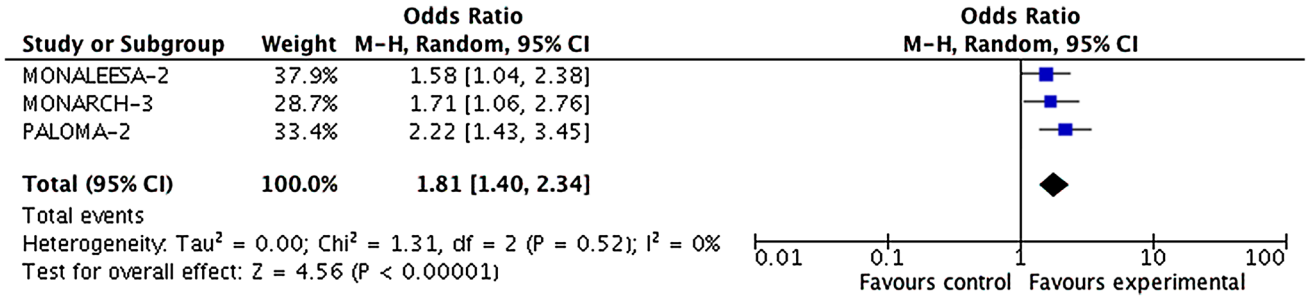

Fig. 4 Forest plot for clinical benefit

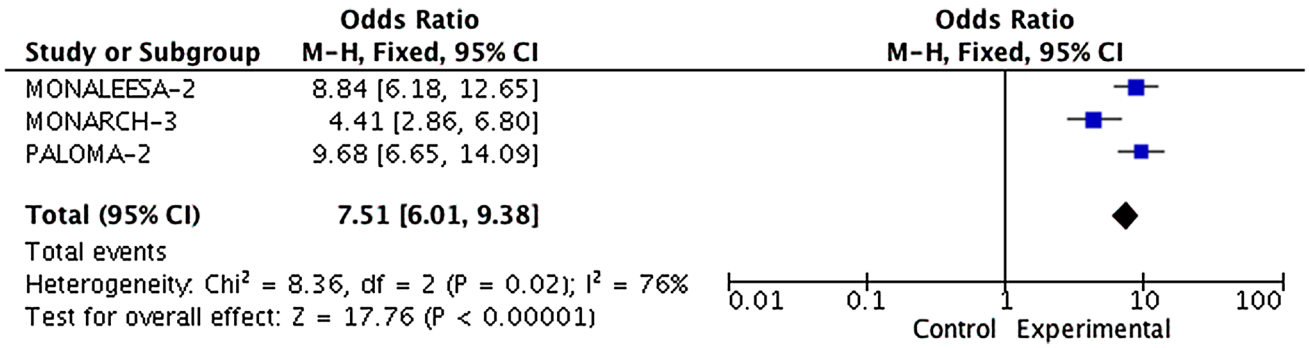

Fig. 5 Forest plot for treatment-related side effects

was associated specifically with high levels of Rb and Cyclin D [25].

Conclusions

In conclusion, the addition of CDK 4/6 inhibitors (abemaciclib, palbociclib, or ribociclib) to an AI (anastrozole or letrozole) significantly improved PFS, ORR and CBR when compared with a nonsteroidal AI used alone, with an acceptable safety profile, similarly in three major randomized phase III clinical trials. Therefore, CDK 4/6 inhibitors represent an important therapeutic advance that changes the paradigm of first-line treatment for metastatic HR-positive and HER2-negative breast cancer.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to disclose.

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