Progression free survival and overall survival of CDK 4/6 inhibitors plus endocrine therapy in metastatic breast cancer: a systematic review and meta-analysis

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Abstract

PURPOSE: The introduction of CDK4/6 inhibitors plus endocrine therapy (ET) represents the most relevant advance in the management of HR-positive/HER2-negative metastatic breast cancer. We carried out a meta-analysis of randomized controlled trials (RCTs) with the aims of better characterising the efficacy of CDK4/6 inhibitors in some relevant subgroups and of testing heterogeneity between different compounds with particular focus on their ability to improve OS.

METHODS: We performed a systematic literature search to identify phase II/III RCTs of CDK4/6 inhibitors plus ET in AI-sensitive and AI-resistant patients. Pooled estimates of HRs were computed for PFS, OS and ORR analysis, by using both a fixed and random effect model. Predefined subgroup analyses were performed to better understand treatment effect concerning specific patients' characteristics. Pooled survival curves were generated by pooling the data of all trials.

RESULTS: 8 RCTs were included. Adding a CDK4/6 inhibitors to ET is beneficial in terms of PFS irrespective of the presence or not of visceral metastases, the number of metastatic sites, and the length of the TFI. The addition of CDK4/6 inhibitors significantly improves OS in AI-sensitive (HR 0.75, 95%CI [0.63-0.89]) and AI-resistant patients (HR 0.77, 95%CI [0.67-0.89]). Pooled data from each single drug show that Palbociclib remains the only class member not showing a statistically significant HR for OS (HR 0.83, 95% CI [0.68-1.02]).

CONCLUSION: Our meta-analysis confirms the efficacy of CDK4/6 inhibitors overall and in major patients subgroups, supporting the use of CDK4/6 inhibitors plus ET as standard treatment for most HR+ MBC patients.

1. Introduction

Breast cancer (BC) is the most common cancer and the most common cause of cancer-related death in women and it represents, with 266.000 new cases estimated in 2018 in USA, about 30% of all diagnosed tumours [1]. Despite the important advances in terms of prevention, diagnosis and availability of new treatments, metastatic breast cancer (MBC) remains an incurable disease and its evolution depends on several factors, such as site and extension of metastasis, histopathological characteristics and molecular profile of tumour.

In the last decade, preclinical and clinical research focused on identification of new treatment options able to prolong or restore the endocrine sensitivity, delaying the use of chemotherapy and improving the survival and the quality of life of these patients. In this scenario, deregulation of cell cycle represented one of the most interesting therapeutical targets, since dysregulation of cyclin D-CDK4/6-pRb pathway is frequent in hormone receptor positive (HR+) BC and represents a key mediator of endocrine resistance [2, 3]. Targeting CDK4/6 resulted in an efficient inhibition of this pathway in HR + BC [4, 5]. Currently, there are three orally highly selective inhibitors of CDK4/6, namely palbociclib (PD0332991), ribociclib (LEE011) and abemaciclib (LY2835219).

CDK4/6 inhibitors have been extensively studied in various clinical trials for patients with HR+/HER2-negative MBC. In general, the eligible population in these trials may be classified as: a) sensitive to aromatase inhibitors (AI-sensitive), which included patients that are either naïve to AI or late relapsers (> 12 months) since the stopping of the AI-based adjuvant treatment; or b) resistant to AI (AI-resistant), which included patients that are either pretreated with an AI in metastatic setting or relapsed during or early after ($\leq$ 12 months) the AI-based adjuvant treatment.

Palbociclib was the first inhibitor of CDK4/6 to receive an accelerated approval by Food and Drug Administration (FDA) in February 2015, in combination with letrozole as initial therapy for AI-sensitive advanced or metastatic BC, based on results from PALOMA-1 and PALOMA-2 trial [6–8]. More recently, based on data from PALOMA-3 trial, the indication was expanded to the combination with fulvestrant for both postmenopausal and pre-perimenopausal women with AI-resistant advanced or metastatic BC [9–11].

Ribociclib received FDA approval in March 2017, based on results from MONALEESA-2 trial, as initial endocrine-based therapy for AI-sensitive advanced or metastatic BC, in combination with an aromatase inhibitor and then, based on results from MONALEESA-7 trial, it was also approved for the treatment of peri/premenopausal women [12–16]. Furthermore, based on the results of the MONALEESA-3 trial [17], ribociclib was also approved in combination with fulvestrant for postmenopausal women with both AI-sensitive and AI-resistant advanced or metastatic BC.

In September 2017, results from MONARCH-2 trial [18] lead to quick approval of abemaciclib in combination with fulvestrant in women AI-resistant advanced or metastatic BC. In addition, MONARCH-3 study showed that the addition of abemaciclib to non-steroidal aromatase inhibitor (NSAI) significantly improves progression free survival (PFS) in patients with AI-sensitive advanced or metastatic BC [19, 20]. Abemaciclib has also been approved as a monotherapy for patients with HR-positive/HER2-negative MBC who have previously received endocrine therapy (ET) and chemotherapy, based on results from MONARCH-1 trial [21].

The inclusion of CDK4/6 inhibitors in combination with ET in international treatment guidelines, both for AI-sensitive and AI-resistant patients, represents the most relevant advance in the management of HR-positive/HER2-negative advanced or metastatic BC over the last years [22]. Some controversies, however, still hold, particularly as to whether: 1. CDK4/6 inhibitors are effective or necessary for indolent, very late relapsing disease (i.e. those relapsing > 38 months from stopping the adjuvant treatment); 2. these drugs are effective in the most aggressive diseases (i.e. early relapse and/or with visceral metastases and/or with high tumour burden) or rather chemotherapy is indicated in these cases; 3. there is different efficacy between different CDK4/6 inhibitors, particularly when the effect on overall survival (OS) is concerned. Indeed, only data from MONALEESA-3, MONALEESA-7 and MONARCH-2 trials show a significant OS improvement with adding CDK4/6 inhibitors to ET, while results from PALOMA-1, PALOMA-3 and MONALEESA-2 trials have not shown, so far, a statistically significant increase of OS for the combinations of palbociclib plus letrozole, palbociclib plus fulvestrant and ribociclib plus letrozole, respectively [11, 15, 16, 23–25].

We carried out a metanalysis of all randomized controlled trials (RCTs) with the aims of better characterising the efficacy of CDK4/6 inhibitors in some relevant subgroups of patients and of testing heterogeneity between different compounds with particular focus on their ability to improve OS.

2. Materials And Methods

This systematic review and meta-analysis was conducted using methods proposed by the Cochrane Collaboration, reported in accordance with the PRISMA statement (Supplemental Data) and was registered with PROSPERO [26, 27].

2.1 Search strategy

A comprehensive search of MEDLINE via PubMed and the Cochrane databases was performed using medical subject heading (MeSH) terms and text words related to CDK4/6 inhibitors and advanced or metastatic BC. Research was restricted from January 2010 until June 30, 2019 but two additional results, relevant to assess overall survival, were added: MONALEESA-3 and MONARCH-2, presented at European Society for Medical Oncology Meeting (ESMO) in September 2019. A computerized search was also run in order to identify abstracts and presentations of relevant unpublished studies, reported at the Annual Meetings of the American Society of Clinical Oncology (ASCO), at the San Antonio Breast Cancer Symposium (SABC) and at ESMO meetings over the last three years. Additional studies were hand-searched on Clinicaltrials.gov. Relevant review articles and references from retrieved articles were screened for additional eligible studies. Screening of citation obtained from literature search was performed by two independent reviewers (MP and PC), as well as the assessment of studies eligibility. Any disagreement was discussed and resolved by consensus between both reviewers or consulting a third reviewer (MDL). A PRISMA flow diagram was prepared to document the process of studies selection.

2.2 Eligibility criteria

We included phase II and phase III RTCs which fulfil the following eligibility criteria: i) patients with HR-positive/HER2-negative advanced or metastatic BC; ii) experimental arm including a selective inhibitor of CDK4/6 (palbociclib, ribociclib or abemaciclib); iii) control arm including standard of care (SOC) treatment +/- placebo; iv) availability of data regarding the primary outcome of interest (PFS/TTP reported in terms of hazard ratio and related CIs). SOC treatment includes ET only, such as aromatase inhibitors (i.e. anastrozole, letrozole, exemestane), oestrogen receptor modulators (i.e. tamoxifen) or selective oestrogen receptor downregulators (i.e. fulvestrant). Clinical trials that assessed the efficacy of CDK4/6 inhibitor as monotherapy were excluded, as well as clinical trials including chemotherapy based regimen and studies conducted in (neo)adjuvant setting. Cohort studies, case series, case reports and reviews were also excluded.

2.3 Outcome for analysis

The main outcome of interest was the investigator-assessed progression free survival (PFS), defined as the time from randomisation to objective disease progression or death for any reason. Secondary outcomes were overall survival (OS), defined as the time from randomisation to date of death due to any cause, and objective response rate (ORR; proportion of patients achieving a complete or partial response). For PFS and OS analysis, the treatment effect was expressed as hazard ratio (HR) of CDK4/6-ET arm over the ET arm, so that an HR greater than one comes out in favour of standard arm, while an HR less than one comes out in favour of experimental arm. For ORR a meta-analysis of single proportions has been implemented, in order to calculate an overall proportion. All estimates of treatment effect were accompanied by 95% confidence intervals.

2.4 Data extraction and assessment of risk of bias

Data from eligible studies were extracted using a custom-made spreadsheet and were checked for accuracy. The following information were extracted from each study: first author, publication year, ClinicalTrials.gov Identifier, study design, regimen details in both experimental and control arm, allocated patients for each arm, main patient's characteristics (median age, line of therapy, sensitivity to ET), HRs and ORRs for the whole study population and for major subgroups of interest. 95% CIs related to HRs and ORRs were also extracted. Where available, the full protocol of each study was consulted to verify study objectives, population and other relevant information regarding study design and conduction. For publications reporting results from the same study, the most recent or complete publication reporting the information of interest was considered.

The risk of bias of included studies was assessed using the Cochrane Collaboration's tool; it is made up of six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential bias [28]. Data extraction and risk of bias for each study was independently assessed by MP and PC and disagreements were discussed and resolved by consensus between both reviewers or consulting a third reviewer (MDL).

2.5 Statistical methods

The pooled estimates of HRs and overall proportions of objective responses, with two-sided 95% CIs, were computed for PFS, OS and ORR analysis, by using both a fixed-effect model according the inverse-variance method [29] and a random-effect model of DerSimonian and Laird [30], in order to obtain more appropriate estimates of the average treatment effect in case of between-study heterogeneity. The assumption of homogeneity between studies was tested with Cochran's Q statistics [31] and the measure of the degree of inconsistency across studies was assessed with Higgins' I^2 index [32]. Where available, predefined subgroup analyses were performed, in order to better understand if the treatment effect changes because of specific patients' characteristics. Results obtained from the analyses were displayed by generating a forest plot. To estimate the absolute gain in terms of PFS, meta-analytic survival curves were calculated as suggest by Parmar et al [33]. A sensitivity analysis was carried out by using the leave-one-out cross validation method that recalculates the pooled estimates omitting one study at a time; this analysis is able to capture whether some features of included studies influence the pooled estimates. Publication bias was assessed using funnel plots and regression tests, according to the method reported by Egger [34]. A P-value < 0.05 was considered statistically significant. Data analysis was performed using R 3.4.1 software packages [35, 36]. To estimate the absolute benefit in terms of PFS, pooled survival curves were generated by pooling the data of all trials, among AI-sensitive and AI-resistant patients. The number at risk and the total number of events were extracted from

publications at specific time points based on available data, the survival probabilities were also extracted using the Digitizeit software (<https://www.digitizeit.de/>).

3. Results

3.1 Study selection and characteristics

The search strategy yielded 685 results from Pubmed, Cochrane database, conferences and clinicaltrials.gov. After the initial review of titles, 57 duplicates and further 593 results were discarded. We reviewed 35 abstract and 21 references were assessed for eligibility. Finally, we identified 8 randomized trials which fulfil the eligibility criteria. When possible, the latest publication of each trial was used for the meta-analysis. Two additional publications, presented at ESMO conference in September 2019, were included after database searching for OS analysis. The PRISMA flow diagram and the complete search strategy are available as Supplemental Data.

The eight RCTs included in this systematic review and meta-analysis were published between 2015 and 2019 and randomised a total of 4580 patients, of which 2802 received a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) in association with ET (NSAI, tamoxifene or fulvestrant) and 1778 received standard ET alone or in combination with placebo. Overall survival results from MONALEESA-3 and MONARCH-2 studies presented after database searching were also included for secondary outcome analysis [23, 24]. The main characteristics of each trial included are summarised in Table 1. Palbociclib was tested in combination with letrozole 2.5 mg/day in the PALOMA-1 and PALOMA-2 trial, for AI-sensitive patients, [6–8, 37] and in combination with fulvestrant 500 mg every 28 days in the PALOMA-3 trial, for AI-resistant [11, 38–40]. Ribociclib was investigated in combination with letrozole 2.5 mg/day in the MONALEESA-2 trial for AI-sensitive postmenopausal women [12, 15, 16, 41–44], in combination with tamoxifene or NSAI (with goserelin to suppress ovarian function) in premenopausal AI-sensitive women in the MONALEESA-7 trial [16, 45], and in combination with fulvestrant both for AI-sensitive and AI-resistant patients in the MONALEESA-3 trial [17]. Finally, abemaciclib was used in combination with anastrozole 1 mg/day or letrozole 2.5 mg/day, as per physician choice, for AI-sensitive patients in the MONARCH-3 trial, [19, 20] and in combination with fulvestrant 500 mg every 28 days for AI-resistant patients in the MONARCH-2 trial [18, 24]. The main outcome was the PFS for all trials and OS and ORR were secondary outcomes for all trials. OS estimates were available only for PALOMA-1, PALOMA-3, MONALEESA-2, MONALEESA-3, MONALEESA-7 and MONARCH-2 trials, while OS data were still pending for the PALOMA-2 and MONARCH-3 trials.

Table 1

First author, year (study name)	Phase	Population	Experimental arm (n)	Control arm (n)	Endocrine status	Median PFS Exp arm	Median PFS Ctrl arm	HR (95% CI)
Hortobagyi GN, 2018 (MONALEESA-2)	III	Post-menopausal AI-sensitive	Ribociclib + Letrozole (334)	Letrozole + Placebo (334)	Sensitive	25.3 (23.0–30.3)	16 (13.4–18.2)	0.568 (0.457–0.704)
Slamon DJ, 2018 (MONALEESA-3)	III	Post-menopausal AI-sensitive & AI-resistant	Ribociclib + Fulvestrant (484)	Fulvestrant + Placebo (242)	Mixed	20.5 (18.5–23.5)	12.8 (10.9–16.3)	0.593 (0.480–0.732)
Tripathy D, 2018 (MONALEESA-7)	III	Pre-menopausal AI-sensitive	Ribociclib + Tamoxifene or NSAI+ Goserelin (335)	Placebo + Tamoxifene or NSAI (337)	Mixed	23.8 (19.2–NR*)	13.3 (11.0–16.4)	0.553 (0.441–0.694)
Sledge GW, 2019 (MONARCH-2)	III	Pre/Post-menopausal AI-resistant	Abemaciclib + Fulvestrant (446)	Fulvestrant + Placebo (223)	Resistant	16.4 (not reported)	9.3 (not reported)	0.553 (0.449–0.681)
Johnston S, 2019 (MONARCH-3)	III	Pre/Post-menopausal AI-sensitive	Abemaciclib + NSAI (328)	Placebo + NSAI (165)	Sensitive	28.1 (not reported)	14.7 (not reported)	0.540 (0.418–0.698)
Finn RS, 2015 (PALOMA-1)	II	Pre/Post-menopausal AI-sensitive	Palbociclib + Letrozole (84)	Letrozole (81)	Sensitive	20.2 (13.8–27.5)	10.2 (5.7–12.6)	0.488 (0.319–0.748)
Rugo HS, 2019 (PALOMA-2)	III	Pre/Post-menopausal AI-sensitive	Palbociclib + Letrozole (444)	Letrozole (222)	Sensitive	27.6 (22.4–30.3)	14.5 (12.3–17.1)	0.563 (0.461–0.687)
Cristofanilli M, 2016 (PALOMA-3)	III	Pre/Post-menopausal AI-resistant	Palbociclib + Fulvestrant (521)	Fulvestrant + Placebo (347)	Resistant	9.5 (9.2–11.0)	4.6 (3.5–5.6)	0.46 (0.36–0.59)

3.2 Risk of bias

Overall the risk of selection, performance, attrition, detection and reporting bias was very low, because all trials were double blind, with exception of PALOMA-1 study that was a phase II, open-label study. The risk-of-bias in each study is reported as Supplemental Data.

3.3 Progression free survival

PFS hazard ratios were directly available for all included studies. Single study HRs ranged from 0.46 to 0.59 and were all statistically significant. Pooled analysis showed a statistically significant improvement in PFS for patients treated with CDK4/6 inhibitor in combination with ET versus patients treated with ET alone (HR 0.547 [95% CI 0.504, 0.594], p-value < 0.0001). Both a fixed-effect model and a random-effect model were implemented, as initially planned, also if no heterogeneity between studies was detected (I^2 0%; χ^2 2.95, p 0.89), as well as publication bias (Egger test, p 0.09). Forest plot, test for publication bias detection and sensitivity analysis are available as Supplemental data.

3.4 Subgroups analysis

A subgroup analysis was implemented according the following criteria: endocrine sensitivity, site of metastasis, number of organs involved and treatment free interval.

AI-sensitivity and Treatment Free Interval (TFI)

Based on the aforementioned definitions, we pooled PFS estimates for AI-sensitive patients and AI-resistant patients among all trials included in this analysis. Patients with 'de novo' disease were considered as a separate group. A total of 5329 patients were included in this group, of which 2852 were AI-sensitive, 1536 AI-resistant and 941 patients had de novo disease. MONALEESA-2, MONALEESA-7, MONARCH-3, PALOMA-1 and PALOMA-2 studies enrolled exclusively AI-sensitive patients while MONARCH-2 and PALOMA-3 enrolled AI-resistant patients only; MONALEESA-3 enrolled both sensitive and resistant patients. It also enrolled 'de novo' patients (19% of the total), but separate estimates for these patients are not available. 'De novo' patients of the MONALEESA-3 trial were, therefore, included in the AI-sensitive for the purpose of this meta-analysis. No between-group difference was observed (I^2 0%; χ^2 4.92, p-value 0.960). The pooled HRs were very similar in AI-sensitive, 'de novo' AI-resistant patients.

Treatment free interval (TFI) was defined as the time from the end of the adjuvant therapy to randomization. TFI was analysed at four time points: ≤ 24 months, > 24 months, ≤ 36 months and > 36 months. Overall 1391 patients were included in this analysis, of which 199 had a TFI ≤ 24 months, 686 had a TFI > 24 months, 244 had a TFI ≤ 36 months and 262 had a TFI > 36 months. No significant heterogeneity was observed (I^2 0%; χ^2 6.22, p-value 0.622). The pooled analysis confirm the beneficial effect of adding CDK 4/6 inhibitor to standard ET regardless the treatment free interval. The estimated pooled HRs according the AI-sensitivity and TFI is shown in Fig. 1.

Site of Metastases and number of metastatic sites

A total of 5862 patients were grouped by site of metastasis, of which 2429 had visceral disease (including patients belonging to liver-or-lung subgroup from MONALEESA-2, MONALEESA-3 and MONALEESA-7 trials), 929 had bone only disease and 2504 had no bone only disease (including patients with both visceral and bone disease). The a total of 2845 patients was grouped by number of metastatic sites, of which 782 had only one metastatic site at study entry, 635 had two metastatic sites and 1428 had three or more metastatic sites. No heterogeneity was detected, so the fixed effect model was considered. The pooled results of meta-analysis, showed a statistically significant improvement in PFS with a similar HR for all these subgroups (Fig. 2).

3.5 Objective Response

ORR data were available for all studies. Pooled estimates of ORR were summarized as bar-plot, forest plots are available as Supplemental Data. Figure 3 shows the bar-plot of pooled ORR in all randomly assigned patients and in patients with measurable disease according AI-sensitivity. Overall 2318 patients treated with CDK 4/6 inhibitor plus ET and 1536 patients treated with ET alone were included in this analysis, while 1781 patients had measurable disease (1195 treated with CDK 4/6 inhibitor + ET and 586 treated with ET alone). The meta-analysis shows an increased ORR in patients treated with CDK 4/6 inhibitors, both in AI-sensitive (pooled ORR = 43.3% for CDK4/6 inhibitors treated patients) and AI-resistant group (pooled ORR = 26.5% for CDK4/6 inhibitor treated patients). Patients treated with CDK 4/6 inhibitor reached a pooled ORR of 55% in AI-sensitive group and 35.6% AI-resistant group. Results of analysis according the CDK 4/6 inhibitor are available as Supplemental Data.

3.6 Overall survival

Overall survival (OS) data were available only for MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-2, PALOMA-1 and PALOMA-3 trial [11, 15, 16, 23–25]. This analysis included a total of 3421 patients, of which 2030 treated with CDK 4/6 inhibitors and 1391 treated with ET alone. The pooled HR indicates a statistically significant reduction in the risk of dying for patients receiving the CDK4/6 inhibitor (HR 0.763 [95% CI 0.683; 0.852], p-value < 0.0001); this effect is independent of whether patients were AI-sensitive or not. When grouped by CDK4/6 inhibitor, a statically significant reduction in the hazard of dying was apparent for Ribociclib and Abemaciclib only, but not for Palbociclib (Fig. 4). However, the test for heterogeneity

(I^2 0%; χ^2 1.44, p-value 0.919) suggests that discrepant OS results among different CDK4/6 inhibitors may be explained by chance. Meta-analysis of OS in overall population is available as Supplemental Data.

3.7 Pooled survival curves

Since no heterogeneity emerged from the overall PFS analysis (A), it is possible to pool the PFS data to better estimate the absolute benefit gained by adding a CDK4/6 inhibitor to ET. Pooled PFS curves show a median PFS of 26.5 months in AI-sensitive patients treated with CDK 4/6 inhibitors (10.9 months improvement over ET alone). In the AI-resistant population, median PFS was 14.1 months for patients treated with CDK 4/6 inhibitors (7 months improvement over ET alone) (Fig. 5).

4. Discussion

The development of CDK 4/6 inhibitors has changed the therapeutic management of HR + MBC. Palbociclib, ribociclib, and abemaciclib are all orally active, highly selective reversible inhibitors of CDK4 and CDK6 approved by the Food and Drug Administration, the European Medicine Agency (EMA) and other regulatory agencies worldwide for HR + MBC in combination with AIs and fulvestrant. While there is general agreement on the efficacy and the manageable toxicity of these drugs, some controversies still hold in the interpretation of clinical trials data, particularly when subgroups data are concerned. This meta-analysis was carried out to contribute to resolve controversial issues by: 1. providing more reliable estimates of efficacy in some controversial subgroups; 2. increasing the statistical power to evaluate the impact on OS; 3. testing for significant heterogeneity between different compounds; 4. refining the overall estimates of efficacy, in case of no heterogeneity detection.

Despite uniform recommendation from guidelines, chemotherapy is still overused in HR + MBC, particularly in situations in which an intense tumour debulking is desirable. This behaviour relies on the diffused perception, among both oncologists and patients, that chemotherapy is a more potent treatment, yielding on average a higher ORR than ET-based treatments. In contrast, our meta-analysis confirms that the combination of a CDK4/6 inhibitors and ET yields a very high rate of tumour regression, which is on average as high as 55% for patients with measurable disease, with no heterogeneity among different compounds. To the best of our knowledge, this ORR is higher than we would expect with mono-chemotherapy and comparable (but still lower) to what we would expect with an aggressive polychemotherapy in HR + pts populations. Therefore, the use of chemotherapy as the best mean to obtain tumour debulking in HR + MBC should be definitely considered obsolete.

It has been argued that the addition of CDK4/6 inhibitors to ET may not produce relevant benefits for less aggressive tumours, namely tumours with bone-only metastases or long TFI or limited number of metastases. This debate was based on subgroup analyses from single trials. In contrast, our meta-analysis demonstrates that adding a CDK4/6 inhibitors to ET is beneficial in terms of PFS irrespective of the presence or not of visceral metastases, the number of metastatic sites, and the length of the TFI. The test for heterogeneity in these subgroup analysis indicates that minor differences, if present, are due to chance; we should, therefore, assume that the pooled estimate in the overall population is the best estimate of the treatment effect size in each subgroup of patients.

Overall survival data are relatively immature. Despite this, pooling current estimates from relevant trials demonstrates that the addition of CDK4/6 inhibitors to ET does produce an OS improvement. This improvement is evident both in AI-sensitive pts and AI-resistant pts, strongly supporting the use of CDK4/6 inhibitors as gold standard treatment in both patient populations. A controversial issue is whether these drugs are equally effective in prolonging OS, because, so far, only Ribociclib and Abemaciclib have demonstrated a statistically significant improvement of OS in at least one trial [24]. In our meta-analysis, when pooling data from different trials for each single drug, Palbociclib still remains the only class member to not show a statistically significant HR for OS. However, this result should be interpreted with caution because the test for interaction indicates that the differences between the pooled HRs for the three CDK4/6 inhibitors may well be ascribed to chance (Fig. 4). Therefore, as above, one should assume that the best HR estimate for each drug is that of the overall pooled estimate (HR =

0.76; $p < 0.001$) (Fig. 4). Yet, because such results pertain to indirect comparisons, we cannot exclude that there could still be moderate, but clinically relevant, differences in efficacy between different compounds, which could only be identified in a direct randomized comparison.

Some limitation of our study need discussion. First, like for all meta-analysis of published data a publication bias may in theory have overemphasized a positive result. However, we used data from trials published in extenso and from trials reported at meetings to minimize publication bias and the results of the egger test indicates the absence of a relevant publication bias in our analysis. Second, akin all studies based on aggregated data, our meta-analysis, does not reach the level of evidence obtainable with a meta-analysis based on individual patient data (IPD) because: (1) it is impossible to determine the appropriateness of random assignment procedures; (2) trial heterogeneity can only be statistically tested, but never verified; and (3) it is not possible to do an intention-to-treat analysis because data from excluded patients cannot be retrieved. However, in our case, all authors declared their data were based on the intention-to-treat principle and the analysis of potential biases indicates that major biases in the included trials are unlikely. Furthermore, provided a rigorous methodology is used, pooling aggregated data, as in our case, yields information that is far superior to the simple descriptive across trial comparison.

5. Conclusions

Our meta-analysis confirms the efficacy of CDK4/6 inhibitors overall and in major patients subgroups, helps highlighting differences and similarities between different compounds and provides pooled (more precise) estimates of the effect size for PFS, OS and ORR. These results lend further strength to the evidence from single RCTs, supporting the use of CDK4/6 inhibitors in combination with ET as standard treatment for most HR + MBC pts.

Declarations

Ethical Approval and Consent to participate: Not Applicable

Consent for publication: Not Applicable

Availability of supporting data: The datasets generated during the current meta-analysis is available from the corresponding author on reasonable request. All data analysed during this meta-analysis are included in the corresponding published articles, as reported in table 1.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: Study concepts and study design were developed by MP, MDL and PC. MP, PC and GDG were responsible for data acquisition and quality control of data and algorithms. Data analysis and its interpretation were performed by MP, PC, MR and SC. MP and PC performed all statistical analysis. MP, MDL and DC were responsible for manuscript preparation and editing. MDL, MP, PC, FN, GI, RC, VDL, FDR contributed in manuscript review. All authors read and approved the final manuscript.

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Additional File

Additional file contains supplemental data such as full search strategy, the risk of bias graph, the funnel plot for publication bias detection, the sensitivity analysis performed and the forest plot of overall progression free survival.

List Of Abbreviations

Abbreviation	Definition
Als	Aromatase Inhibitors
BC	Breast Cancer
CDK 4/6	Cyclin Dependent Kinase 4/6
CIs	Confidence Intervals
EMA	European Medicine Agency
ET	Endocrine Therapy
FDA	Food and Drug Administration
HR+	Hormone Receptor Positive
IPD	Individual Patients data
MBC	Metastatic Breast Cancer
NSAI	Non Steroidal Aromatase Inhibitors
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
SOC	Standard Of Care
TFI	Treatment Free Interval
TTP	Time To Progression

Figures

Figure 1

Pooled comparison of PFS according endocrine sensitivity and treatment free interval.

Figure 2

Pooled comparison of PFS according site of metastasis (visceral disease, bone only disease and no bone only disease) and number of organs involved (1, 2, 3+).

Figure 3

Bar-plot of pooled ORR in all randomly assigned patients and in patients with measurable disease according ET sensitivity status.

Figure 4

Meta-analysis of overall survival (OS) grouped by AI sensitivity and CDK 4/6 inhibitor.

Figure 5

Meta-curves of PFS for AI-sensitive and AI-resistant patients.

Supplementary Files

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