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REVIEW

Systematic review and meta-analysis of post-progression outcomes in ER+/HER2− metastatic breast cancer after CDK4/6 inhibitors within randomized clinical trials

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Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy (ET) deeply transformed the treatment landscape of hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer. Randomized clinical trials suggest that second progression-free survival (PFS2) was not compromised and time to subsequent chemotherapy (TTC) may be delayed. We carried out a meta-analysis to assess the benefit on PFS2 and on delaying the TTC.

Methods: We conducted a systematic literature search of randomized clinical trials with CDK4/6 inhibitors and ET reporting PFS2 or TTC of HR+/HER2− pre- or postmenopausal metastatic breast cancer. We also reviewed abstracts and presentations from all major conference proceedings. We calculated the pooled hazard ratios (HR) for PFS2 and TTC using random-effects models with 95% confidence intervals (CI). I^2 was used to quantify heterogeneity between results of the studies.

Results: Eight studies (MONALEESA-2/3/7, MONARCH-2/3, PALOMA-1/2/3) were included in this analysis ($N = 4580$ patients). PFS2 benefit was observed in patients who received CDK4/6 inhibitors plus ET (pooled HR = 0.68, 95% CI = 0.62-0.74, $I^2 = 0\%$) and also a delay in subsequent TTC (pooled HR = 0.65, 95% CI = 0.60-0.71, $I^2 = 0\%$). A benefit in terms of PFS (pooled HR = 0.55, 95% CI = 0.51-0.59, $I^2 = 0\%$) and overall survival (pooled HR = 0.76, 95% CI = 0.69-0.84, $I^2 = 0\%$) was also observed.

Conclusions: CDK4/6 inhibitors plus ET compared with ET alone improve PFS2 and TTC. The delay of chemotherapy may postpone the start of a more toxic treatment option, delaying related toxicities and potentially maintaining a better quality of life for patients, for a longer time. The benefit in PFS2 may postpone the onset of endocrine resistance and help further validate this treatment approach.

Key words: metastatic breast cancer, ER-positive/HER2-negative, endocrine therapy, CDK4/6 inhibitors, PFS2, TTC

INTRODUCTION

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy (ET) are standard of care (SOC) for patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC).[1] After progression with the combination, there are no established guidelines for an optimal sequencing of the different therapeutic options.

Post-progression therapies included chemotherapy alone, ET alone, chemotherapy plus ET or other biologics agents, including everolimus or ET plus other treatments.

An unmet clinical need is the identification of optimal standard ET associated with inhibitors of CDK4/6, mammalian target of rapamycin (mTOR), or phosphatidylinositol 3-kinase (PI3K), and new drugs directed toward potential mechanisms of resistance after progression to cyclin inhibitors.

Exploratory analyses available from single randomized clinical trials (RCTs) suggest that second progression-free survival (PFS2), the time from randomization to progression/death on second-line therapy, was not compromised by the use of CDK4/6 inhibitors plus ET and time to subsequent chemotherapy (TTC) may be delayed. As a result, in single trials, treatment with CDK4/6 inhibitors showed a positive effect on subsequent chemotherapy use, and the

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benefit obtained was maintained over subsequent lines of therapy.[2-13]

PFS2 is likely to become an important endpoint for regulatory and reimbursement evaluations in Europe and elsewhere, as a result of the recent European Medicines Agency (EMA) guidance (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf). Thus, there is a need to optimally understand the role that PFS2 is likely to play in clinical trial results and its application.

Therefore, we carried out a systematic literature search and a meta-analysis to evaluate the benefit of CDK4/6 inhibitors plus ET on PFS2 and on delaying the TTC.

METHODS

Trial selection

We conducted a systematic literature search using PubMed, The Cochrane Central Register of Controlled Trials and clinicaltrial.gov to select all available RCTs of CDK4/6 inhibitors and ET reporting PFS2 or TTC in first- or second-line setting for HR+/HER2− pre- or postmenopausal metastatic breast cancer (MBC). The research was conducted on 28 June 2021, using the following search string '(metastatic breast cancer) AND (palbociclib OR ribociclib OR abemaciclib) AND (PFS2 OR time to chemotherapy)'.

We also reviewed abstracts and presentations from all major conference proceedings [American Society of Clinical Oncology (ASCO) Annual Meeting, San Antonio Breast Cancer Annual Symposium, and the European Society of Medical Oncology Annual Meeting] presented between December 2014 and September 2021.

We followed the PRISMA statement for reporting systematic reviews and meta-analysis.[14]

Two authors independently examined the abstracts retrieved by the search strategy. We included only the most recent and complete report of controlled trials (corresponding to longer follow-up) when duplicate publications were identified. 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 included phase II and III RCTs fulfilling the following eligibility criteria: (i) patients with HR+/HER2− advanced or metastatic breast cancer; (ii) experimental arm including a selective inhibitor of CDK4/6 (palbociclib, ribociclib or abemaciclib); (iii) control arm including SOC treatment and/or placebo; (iv) availability of data regarding the primary outcome of interest [PFS2/TTC reported in terms of hazard ratio (HR) and related confidence intervals (CIs)].

SOC treatment included ET only, such as aromatase inhibitors (i.e. anastrozole, letrozole, exemestane), estrogen receptor modulators (i.e. tamoxifen) or selective estrogen receptor down-regulators (i.e. fulvestrant).

Clinical trials that assessed the efficacy of CDK4/6 inhibitor as monotherapy were excluded, as well as clinical trials including a chemotherapy-based regimen and studies conducted in a (neo)adjuvant setting. Cohort studies, case series, case reports and reviews were also excluded.

Data extraction

From each study, we extracted the name of the study, first author and year of publication, line of therapy, study drugs under investigation, number of patients, median survival (months) and HR for PFS2, TTC, PFS and overall survival (OS). We also retrieved the type of the first antineoplastic treatment received after the discontinuation of the trial regimen.

Statistical methods

The primary outcomes of interest were PFS2 and TTC. The definition of these outcomes, as described in the publications of the included studies, has been reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100332. A certain degree of heterogeneity was present: in particular, how patients not moving to a subsequent line of therapy (due to death or other reasons) were considered in the statistical estimation of PFS2 and TTC was not specified in some studies, or was inconsistent in others (e.g. death before chemotherapy initiation was considered both as a TTC censoring event in the MONARCH-3 trial and a TTC event of interest in the PALOMA-2 trial).

HRs and CIs for PFS2, TTC, PFS and OS were translated into log-HRs and the corresponding variances. We calculated the pooled HR for PFS2, TTC, PFS and OS with 95% CIs using random-effects models. Weights were taken equal to the inverse of the reported within-study variance plus the between-study variance, estimated with the moment estimator.

Heterogeneity between studies' results was quantified using the I^2 statistic which expresses the percentage of the total observed variability due to study heterogeneity.

Analysis was carried out with R software (version 4.0.2).

RESULTS

The search strategy yielded 63 results from Pubmed, the Cochrane database, conferences and clinicaltrials.gov. After the initial review of titles and abstracts, we identified eight RCTs (MONALEESA-2/3/7, MONARCH-2/3, PALOMA-1/2/3)[2-13] which fulfilled the eligibility criteria. When possible, the latest publication of each trial was used. Publications ranged from 2015 to 2021.

Overall, 4580 patients were randomized. In five trials (MONALEESA-2/7, MONARCH-3, PALOMA-1/2) the combination of CDK4/6 inhibitors plus ET was administered as first-line therapy, two trials (MONARCH-2 and PALOMA-3) were in second- or subsequent-line of therapy whereas MONALEESA-3 treated patients with fulvestrant and cyclin/placebo inhibitor were in first and second line. Main

characteristics and results of the studies included in the meta-analysis are summarized in Table 1.

All studies had available results for TTC, whereas only five studies reported PFS2 (MONALEESA-3/7, MONARCH-2/3 and PALOMA-3). A forest plot showing results of the meta-analysis is reported in Figure 1. A clear PFS2 benefit was observed in patients who received CDK4/6 inhibitors plus ET (pooled HR = 0.68, 95% CI = 0.62-0.74, I^2 = 0%; Figure 1 left panel) and also a delay in subsequent TTC (pooled HR = 0.65, 95% CI = 0.60-0.71, I^2 = 0%; Figure 1 right panel). A benefit in terms of PFS (pooled HR = 0.55, 95% CI = 0.51-0.59, I^2 = 0%) and OS (pooled HR = 0.76, 95% CI = 0.69-0.84, I^2 = 0%) was also observed (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100332).

Table 2 shows the type of the first antineoplastic treatment received after the discontinuation of the trial regimen. Considering the five RCTs in first line (MONALEESA-2/7, MONARCH-3, PALOMA-1/2), patients received as first subsequent antineoplastic therapy after the discontinuation of the study, on average, ET in 65% of cases (min-max 48%-83%), chemotherapy in 44% (min-max 32%-73%) of cases, CDK4/6 inhibitors up to 38% of cases (on average in 18% of cases) and mTOR inhibitors in 17% of cases (min-max 14%-24%). Also in MONARCH-2 and PALOMA-3 ET was administered on average in 55% of cases (min-max 37%-71%), chemotherapy in 66% of cases (min-max 56%-76%), CDK4/6 inhibitors in 9% of cases (min-max 2%-21%) and mTOR inhibitors in 24% of cases (min-max 15%-33%). Patients enrolled in MONALEESA-3 treated with fulvestrant and CDK4/6/placebo inhibitor in first and second line subsequently received ET, chemotherapy, CDK4/6 inhibitor and mTOR inhibitor in 55%, 43%, 20% and 30% of cases, respectively.

DISCUSSION

This systematic review and meta-analysis clearly confirm that the combination of CDK4/6 inhibitors plus ET compared with ET alone is able to improve PFS2 (pooled HR = 0.68, 95% CI = 0.62-0.74, I^2 = 0%) and TTC (pooled HR = 0.65, 95% CI = 0.60-0.71, I^2 = 0%). This improvement was seen in both endocrine-resistant and endocrine-sensitive patient populations.

This finding is important because it validates the selection algorithm for first- and second-line treatment of ER+/HER2− ABC and underlines that delaying chemotherapy is not detrimental to patients, but can be beneficial because it can avoid unnecessary toxicity, potentially improving quality of life.

Despite the recommendations of the major international guidelines supporting the first-line use of combination ET and cyclin inhibitors for patients with MBC, even in the presence of visceral involvement, some oncologists in common clinical practice are still doubtful, favoring the use of chemotherapy in the first line. To further support the results of RCTs confirming the survival benefit in addition to PFS, the recent update of the outcome results of PALOMA-3

Table 1. Main characteristics and results of the studies included

	1st line										≥2nd line				1st and 2nd line	
	MONALEESA-2		MONALEESA-7		MONARCH-3		PALOMA-1		PALOMA-2		MONARCH-2		PALOMA-3		MONALEESA-3	
	Rib + L	Pbo + L	Rib + T/NSAI	Pbo + T/NSAI	Abe + NSAI	Pbo + NSAI	Pal + L	L	Pal + L	Pbo + L	Abe + F	Pbo + F	Pal + F	Pbo + F	Rib + F	Pbo + F
N	334	334	335	337	328	165	84	81	444	222	446	223	347	174	484	242
PFS2 median, months	NR	NR	NE	32.3	NR	NR	NR	NR	NR	NR	23.1	20.6	18.8	14.1	37.4	28.1
PFS2 HR (95% CI)	NR		0.69 (0.55-0.87)		0.64 (0.50-0.82)		NR		NR		0.68 (0.56-0.82)		0.68 (0.56-0.84)		0.69 (0.57-0.84)	
TTC median, months	50.6	38.9	NE	36.9	NR	NR	26.7	17.7	40.4	29.9	50.2	22.1	17.6	8.8	48.1	28.8
TTC HR (95% CI)	0.74 (0.61-0.91)		0.60 (0.46-0.77)		0.51 (0.38-0.69)		0.66 (0.45-0.99)		0.74 (0.59-0.92)		0.63 (0.50-0.78)		0.58 (0.47-0.73)		0.70 (0.57-0.88)	
PFS median, months	25.3	16.0	23.8	13.0	28.2	14.8	20.2	10.2	27.6	14.5	16.9	9.3	11.2	4.6	20.6	12.8
PFS HR (95% CI)	0.57 (0.46-0.70)		0.55 (0.44-0.69)		0.53 (0.42-0.67)		0.49 (0.32-0.75)		0.56 (0.46-0.69)		0.54 (0.45-0.65)		0.50 (0.40-0.62)		0.59 (0.49-0.71)	
OS median, months	63.9	51.4	NE	40.9	NR	NR	37.5	34.5	NR	NR	46.7	37.3	34.9	28.0	53.7	41.5
OS HR (95% CI)	0.76 (0.63-0.93)		0.71 (0.54-0.95)		NR		0.90 (0.62-1.29)		NR		0.76 (0.61-0.95)		0.81 (0.64-1.03)		0.73 (0.59-0.90)	

Abe, abemaciclib; CI, confidence interval; F, fulvestrant; HR, hazard ratio; L, letrozole; NE, not estimable; NR, not reported; NSAI, nonsteroidal aromatase inhibitor (letrozole or anastrozole); OS, overall survival; Pal, palbociclib; Pbo, placebo; PFS, progression-free survival; PFS2, second progression-free survival; Rib, ribociclib; T, tamoxifen; TTC, time to chemotherapy.

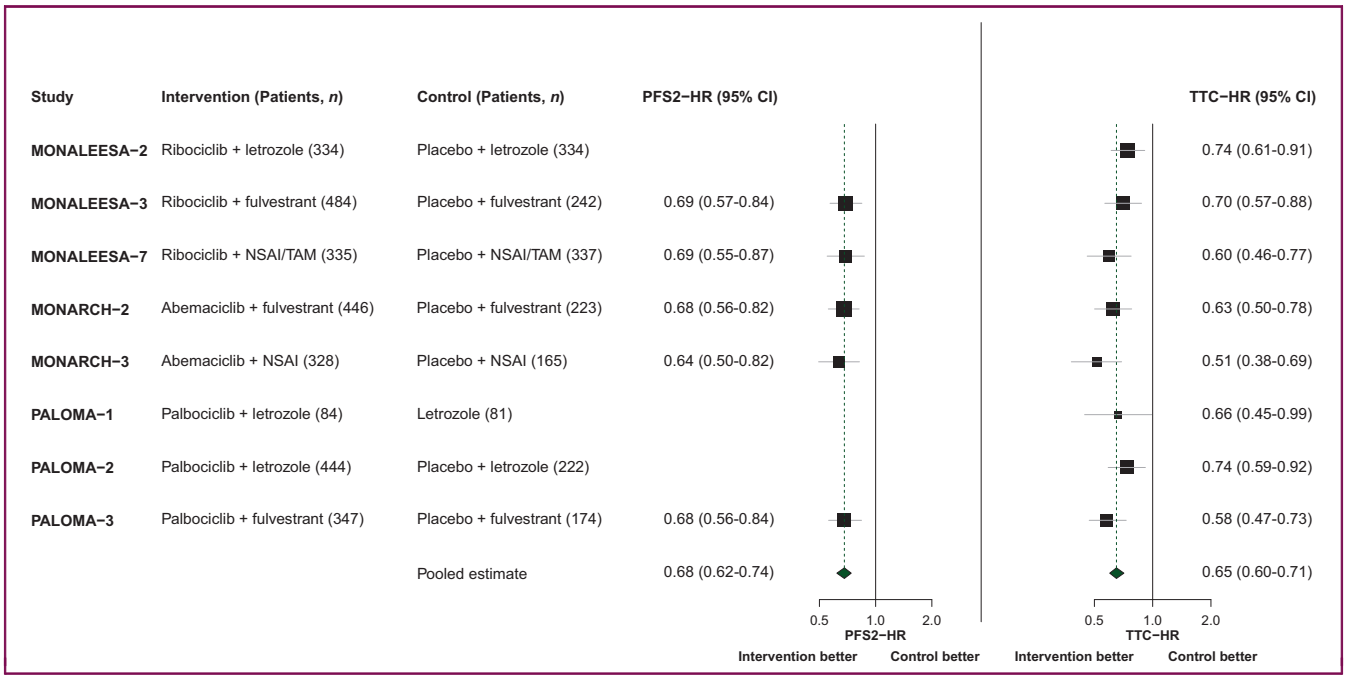

Figure 1. Forest plot for second progression-free survival (PFS2) and time to chemotherapy (TTC).
CI, confidence interval; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; TAM, tamoxifen.

and MONALEESA-3 and in the various subgroups confirms the advantage of using cyclin inhibitors, even in patients with more extensive or aggressive disease.[2,15]

Recent systematic reviews and meta-analyses confirmed the efficacy of CDK4/6 inhibitors overall and in major patient subgroups, highlighting the differences and similarities between different compounds.[16] Authors provided more precise estimates of the effect size for PFS, OS and objective response rate. Likewise, a benefit in terms of PFS (pooled HR = 0.55, 95% CI = 0.51-0.59, I^2 = 0%) and OS (pooled HR = 0.76, 95% CI = 0.69-0.84, I^2 = 0%) was also observed in the present meta-analysis. These results, taken together, provide additional strength to the individual RCTs, supporting the use of CDK4/6 inhibitors in combination with ET as standard treatment of most HR+ MBC patients.[17,18]

The results of the present meta-analysis point in the same direction, supporting the role of this treatment strategy in both endocrine-sensitive and endocrine-resistant disease in delaying PFS2 and time to chemotherapy initiation.

Patients will benefit more and for a longer period of time from a treatment, mostly oral, that is more manageable and substantially less toxic than chemotherapy.

Thus, the observed benefit in PFS2 may postpone the onset of endocrine resistance and may help further validate this treatment approach.

In fact, after the EMA guidance proposal of using PFS2 as a surrogate for OS in oncologic clinical trials, this measure is likely to become an important endpoint for regulatory and reimbursement evaluations in Europe and elsewhere (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf). Therefore, there is a need to optimally understand the role that PFS2 is likely to play in clinical trial results and their application.

In a recent systematic review and meta-analysis, PFS2 strongly correlates with OS, supporting the use of PFS2 to measure long-term clinical benefit when OS cannot be assessed.[19]

This meta-analysis, however, may have some limitations. Firstly, like all meta-analyses of published data, publication bias could theoretically overemphasize a positive result.

Though, the data used come from studies published in full and from trials reported at meetings (e.g. data from abstracts not peer-reviewed) from controlled trials and audited for the purpose of obtaining approval of the experimental drugs by the regulatory authorities in each country.

Furthermore, it is an analysis based on aggregated data and therefore cannot reach the level of evidence obtainable with a meta-analysis based on individual patient data, because it is impossible to determine the adequacy of the randomization procedures of individual trials; the heterogeneity of the trials can only be statistically tested, but never verified; and finally, it is not possible to perform an intention-to-treat analysis because the data of excluded patients cannot be retrieved. Finally, another limitation depends on the fact that the definitions of PFS2 and TTC are not homogeneous across all studies analyzed here.

In any case, all authors of the RCTs had stated that the published data were based on the intention-to-treat principle, so potential bias would be unlikely. In the present meta-analysis, analysis of aggregated data with rigorous methodology may provide more impactful information than that emerging from individual studies or from simple comparison between them.

Table 2. First subsequent antineoplastic therapy among patients who discontinued the trial regimen[a]

	1st line								2nd line				1st and 2nd line	
	MONALEESA-2		MONALEESA-7		MONARCH-3		PALOMA-1	PALOMA-2	MONARCH-2		PALOMA-3		MONALEESA-3	
	Rib + L (*N* = 334)	Pbo + L (*N* = 334)	Rib + T/NSAI (*N* = 35)	Pbo + T/NSAI (*N* = 337)	Abe + NSAI (*N* = 328)	Pbo + NSAI (*N* = 165)	Pal + L (*N* = 84)	Pal + L (*N* = 444)	Abe + F (*N* = 446)	Pbo + F (*N* = 223)	Pal + F (*N* = 347)	Pbo + F (*N* = 174)	Rib + F (*N* = 484)	Pbo + F (*N* = 242)
No. of patients with subsequent systemic therapy	267	286	151	205	178	123	66	227	281	180	248	140	295	177
ET (%)	65.2	65.0	53.0	47.8	81.5	82.1	75.8	60.8	66.2	70.6	40.3	37.1	54.2	55.9
CT (%)	31.8	32.9	44.4	49.8	52.2	66.7	71.2	36.6	71.2	75.6	55.6	62.1	44.1	42.4
mTOR (%)	NR	NR	17.2	14.6	20.8	23.6	18.2	13.7	30.2	33.3	16.1	15.0	27.5	34.5
CDK4/6i (%)	24.7	38.1	14.6	25.4	7.9	22.0	1.5	0	9.3	21.1	2.4	6.4	13.6	29.9
Eribulin (%)	NR	NR	NR	NR	6.7	8.1	NR	NR	22.4	13.3	2.8	2.1	NR	NR

Abe, abemaciclib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ET, endocrine therapy; F, fulvestrant; L, letrozole; mTOR, mammalian target of rapamycin; NR, not reported; NSAI, nonsteroidal aromatase inhibitor (letrozole or anastrozole); Pal, palbociclib; Pbo, placebo; Rib, ribociclib; T, tamoxifen.

[a] All percentages were calculated on the basis of the number of patients who received any systemic treatment after the discontinuation of the trial intervention.

The heterogeneity of the definitions of the outcomes analyzed in this meta-analysis may in fact be a limitation. However—as the results show—no heterogeneity was observed in the effect estimates associated with treatment.

Conclusion

This systematic review and meta-analysis of PFS2 and TTC outcomes from major RCTs with CDK4/6 inhibitors plus ET confirms that, compared with ET alone, the combination with CDK4/6 inhibitors improves PFS2 and TTC. This finding is important because the delay in initiating chemotherapy may postpone the start of a more toxic treatment option, delaying related toxicities and potentially maintaining a better quality of life for patients, for a longer period of time. In addition, the observed benefit in PFS2 may postpone the onset of endocrine resistance and help further validate this treatment approach for patients with ER+/HER2− MBC.

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DISCLOSURE

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