ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/330484105

Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials

Article *in* Breast Cancer Research and Treatment · January 2019

DOI: 10.1007/s10549-019-05133-y

CITATIONS
2

READS
106

10 authors, including:

Fausto Petrelli
ASST Bergamo Ovest
225 PUBLICATIONS **3,252** CITATIONS
SEE PROFILE

Antonio Ghidini
Casa di Cura Igea, Italy, Milan
29 PUBLICATIONS **121** CITATIONS
SEE PROFILE

Vito Amoroso
Spedali Civili di Brescia
79 PUBLICATIONS **523** CITATIONS
SEE PROFILE

Alfredo Berruti
Università degli Studi di Brescia
431 PUBLICATIONS **9,194** CITATIONS
SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Treatment of hepatic metastases by colorectal cancer View project

All content following this page was uploaded by Antonio Ghidini on 03 May 2019.

The user has requested enhancement of the downloaded file.

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-019-05133-y

REVIEW

Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials

Fausto Petrelli[1] · Antonio Ghidini[2] · Rebecca Pedersini[3] · Mary Cabiddu[1] · Karen Borgonovo[1] · Maria Chiara Parati[1] · Mara Ghilardi[1] · Vito Amoroso[3] · Alfredo Berruti[3] · Sandro Barni[1]

Received: 20 November 2018 / Accepted: 8 January 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Background Several trials have demonstrated the benefit of anti-CDK4/6 inhibitors plus endocrine therapy in estrogen receptor-positive (ER+) advanced breast cancer (BC), in first or subsequent lines of therapy. However, due to the lack of direct/indirect comparisons, there are no data demonstrating the superiority of one drug over the other. We compared the effectiveness of palbociclib, ribociclib, and abemaciclib in advanced ER + BC via an indirect adjusted analysis.

Methods We performed electronic searches in the PubMed, EMBASE, and Cochrane databases for prospective phase 3 randomized trials evaluating anti-CDK4/6 inhibitors plus endocrine agents. We compared the results with an adjusted indirect analysis of randomized-controlled trials. Outcomes of interest were progression-free survival (PFS), overall response rate (ORR) and G3–4 toxicities occurring in ≥ 5% of patients.

Results Six trials and six treatment arms including a total of 3743 participants, were included. For PFS and ORR analysis, the three agents were similar in both first- and second-line studies. All G3–4 toxicities were similar, with reduced risk of diarrhea for palbociclib versus abemaciclib (relative risk [RR] 0.13, 95% CI 0.02–0.92; $P = 0.04$) and of QTc prolongation for palbociclib versus ribociclib (RR 0.02, 95% CI 0–0.83; $P = 0.03$). Despite different inclusion criteria and length of follow-up, similar features were noticed among second-line studies with the exception of increased risk of anemia G3–4 and diarrhea G3–4 for abemaciclib.

Conclusions Based on PFS and ORR results of this indirect meta-analysis, palbociclib, ribociclib, and abemaciclib are equally effective in either first- or second-line therapy for advanced ER + BC. They, however, ported different toxicity profiles.

Keywords Breast cancer · CDK-4/6 inhibitors · Meta-analysis

Introduction

Women with estrogen receptor-positive (ER+) advanced breast cancer (BC) are usually treated with first-line endocrine therapy unless a visceral crisis or strongly symptomatic metastases exist. CDK4–6 inhibitors (palbociclib, ribociclib, or abemaciclib) extend progression-free survival when added to endocrine therapies in both first- and subsequent lines of therapy in this group of patients and now represent the standard of care [1–6]. Overall survival data are still immature, despite the update of a Paloma-3 study providing an increased median survival with the addition of palbociclib to fulvestrant alone in a pretreated setting [7]. These agents are a similar, but not identical, mechanism of action at the molecular level that consists of the inhibition of the phosphorylation of retinoblastoma proteins, preventing cell cycle progression and inducing arrest in the G1 phase [8]. These three agents increase the risk of leukopenia and/or neutropenia (mainly palbociclib and ribociclib) or diarrhea (abemaciclib), but the magnitude or their efficacy was apparently similar compared to the aromatase inhibitor

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05133-y) contains supplementary material, which is available to authorized users.

✉ Fausto Petrelli
faupe@libero.it

[1] Medical Oncology Unit, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, BG, Italy

[2] Medical Oncology Unit, Casa di Cura Igea, Milan, Italy

[3] Breast Unit, ASST Spedali Civili, Brescia, Italy

Published online: 18 January 2019

alone (about 50% less risk of progression) in all subgroups analyzed according to the site of metastases and previous exposure to hormonal agents. These results were formally replicated even in pretreated patients wherein they were combined with fulvestrant.

Unfortunately, despite the similar efficacy and overall response rate (ORR) and a slightly different but near-identical spectrum of adverse events, these three agents have not been compared with each other in a randomized manner.

We performed first a systematic literature review to identify the published randomized clinical trials (RCTs) in advanced ER + BC, including these three CDK4–6 inhibitors evaluating efficacy in first- or further line settings; we then carried out an indirect adjusted meta-analysis to synthesize the efficacy (PFS, ORR) and toxicity (grade [G]3–4 toxicities occurring in at least 5% of patients in experimental arms) of each regimen over the others.

Materials and methods

Study search and inclusion criteria

We searched Pubmed, EMBASE, and the Cochrane Library up to 14th October 2018 using terms *breast cancer* and *palbociclib, ribociclib, abemaciclib*, and *randomized trials*. We also reviewed reference lists for additional citations. We applied no language restriction. Two reviewers (FP and AG) independently assessed titles and abstracts and full-text articles of potentially relevant citations for inclusion. Disagreements were resolved by consensus. Trials published only in an abstract form (e.g., a conference proceeding) were not included. Studies were included if they were (1) randomized phase 3 trials comparing any CDK4/6 drug associated with endocrine therapy with endocrine therapy alone with or without placebo, (2) studies including ER + metastatic BC, and (3) first- or second-line trials reporting efficacy (OS and/or PFS and/or overall response rate [ORR] and safety outcomes (G3–4 toxicities of any treatment arms)). Ongoing studies with preliminary data only or observational studies were excluded.

Data extraction

Data extraction and assessment were made independently by two different authors (AG and FP), and disagreements were resolved by discussion with a senior author (VA). Quality judgement of selected trials was made following the Cochrane Handbook for Systematic Reviews of Interventions reported criteria, including sequence generation, selective outcome reporting, blinding of participants, personnel and outcome assessors; incomplete outcome data and allocation concealment. We defined as "+" a feature at low risk of bias, as "−" a feature at high risk of bias and as "?" if data were insufficient for a more precise judgement. Hazard ratios for PFS and ORR were extracted from each randomized trial. In addition, G3–4 events occurring in at least 5% of patients in experimental arms were analysed for relative risk (RR) compared to control arms. Author, year of publication, experimental arm, and number of patients were also reported for each trial. The quality appraisal of included studies was analyzed using the Jadad scale [9]. Two reviewers (AG and FP) independently assessed the quality of the studies, and publication bias and disagreement was resolved by discussion with a senior author (VA).

Data synthesis and statistical analysis

Our primary outcomes was PFS. Secondary endpoints were ORR, G3–4 toxicities described in at least 5% of patients in experimental arms and time to deterioration in quality of life. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the impact of CDK4/6 agents on PFS. A combined HR > 1 implied worse survival, and it was considered statistically significant if 95% CI for the combined HR did not overlap 1. We calculated the pooled HRs for PFS, estimating pooled RRs and 95% confidence intervals in a random or fixed-effect model. Statistical heterogeneity was assessed by calculating the percent of the total variance due to between-study variability (I^2 statistic). Higher I^2 values (> 50%) indicate greater between-study heterogeneity. Relative risks and confidence intervals were calculated using comprehensive meta-analysis software. We performed adjusted indirect comparisons using the method described by Bucher et al. [10]. In summary, the effect of intervention B relative to intervention A can be estimated indirectly as follows: using the direct estimators for the effects of intervention C relative to intervention A (effectAC) and intervention C relative to intervention B (effectBC): effectAB = effectAC–effectBC. The variance of the indirect estimator effect AB is the sum of the variances of the direct estimators: varianceAB = varianceAC + varianceBC. Transitivity and consistency are the important assumptions of indirect comparison meta-analysis related to the validity of indirect estimates. The plausibility of transitivity assumption was evaluated based on the individual study characteristics. Homogeneity was evaluated in the pooled analysis of the six studies and in subgroup analysis (bone-only and visceral subgroup). Similarly, consistency, the assumption that the direct effect estimates and the calculated indirect estimates for a given comparison are similar, was evaluated through heterogeneity, and was measured with the I^2 statistic.

We calculated indirect HR_{ind} and RR_{ind} for palbociclib, ribociclib, and abemaciclib for each outcome, adjusted by the results of their comparisons against the control arm (endocrine therapy alone with or without placebo).

Results

Six publications were included [1–6], corresponding to six phase-3 trials (Fig. 1; Supplementary Table 1a, b). Three trials included patients with not previously treated advanced ER + BC, and three included patients with pretreated advanced ER + BC and progressing while receiving adjuvant treatment or first-line therapy for metastatic disease. Overall, 3743 patients were included (1827 in first-line studies and 1916 in second-line studies). Overall, the included trials presented minimal risk of bias. Three comparisons were made in all settings: palbociclib versus ribociclib, palbociclib versus abemaciclib and ribociclib versus abemaciclib (Fig. 2).

Transitivity, homogeneity and consistency

Inclusion and exclusion criteria, as described above, did not vary systematically across studies. Baseline characteristics were varied but similar between individual trials,

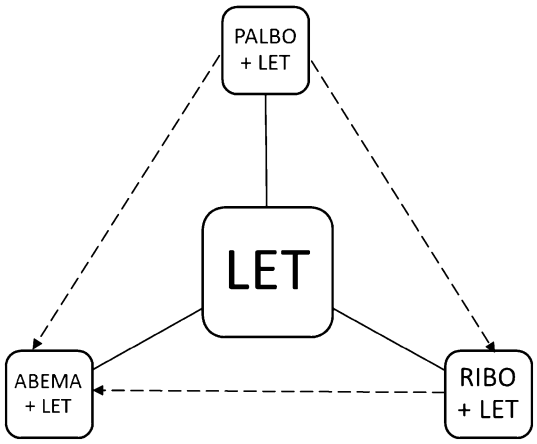

Fig. 2 Direct and indirect first line treatment comparison diagram. *LET* letrozole, *PALBO* palbociclib, *RIBO* ribociclib, *ABEMA* abemaciclib

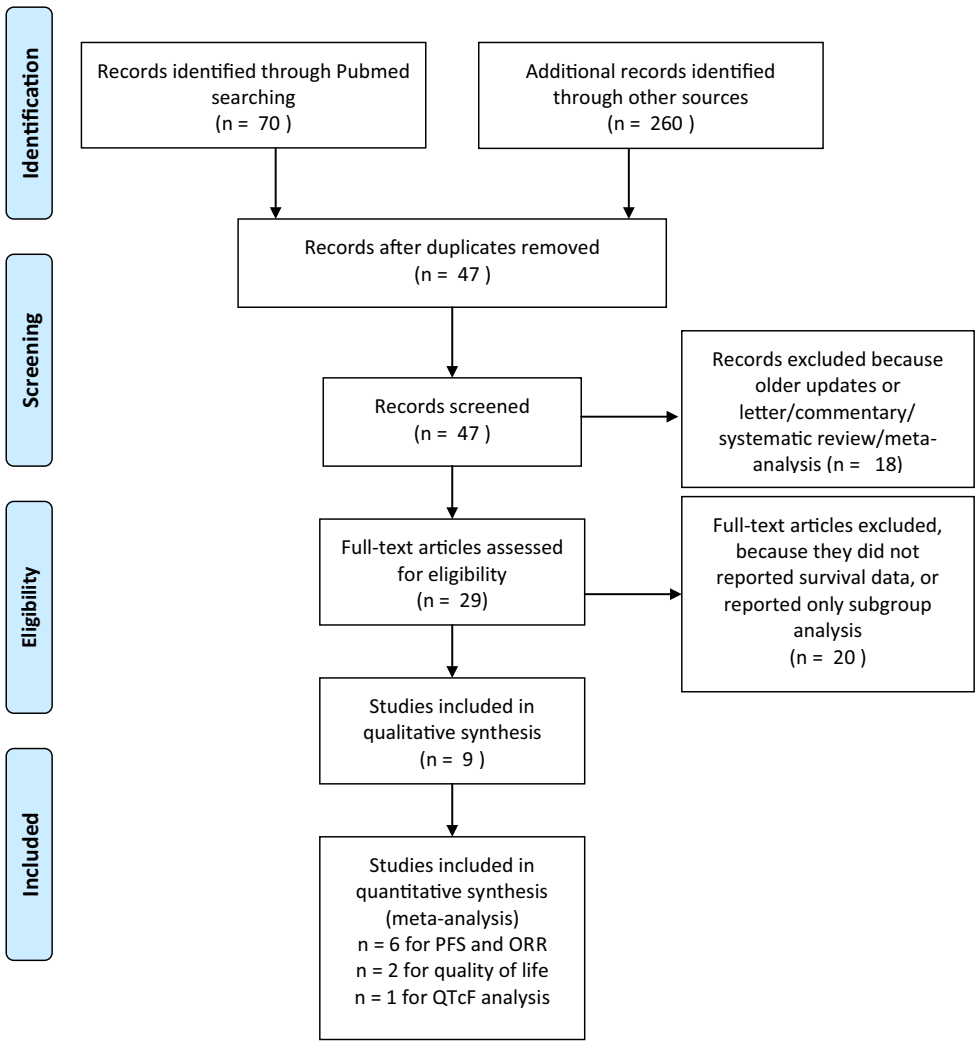

Fig. 1 Flow diagram of included studies

but summary baseline characteristics were comparable across direct comparisons in the six trials. De novo metastatic disease was similar in first-line studies (34, 37 and 39% for palbociclib, ribociclib, and abemaciclib studies). In second-line trials, only ribociclib + fulvestrant/placebo study included patients with de novo metastatic disease (20/17.4%, respectively). More patients in PALOMA-3 study received a previous first-line therapy than MONARCH-2 and MONALEESA-3 studies. All studies were placebo-controlled trials. First-line studies had a letrozole + placebo control arms except MONARCH-3 that permitted both letrozole or anastrozole + placebo control arms. All second-line studies had fulvestrant + placebo control arms. In all studies investigator-assessed PFS was the primary endpoint. Sample size was comparable across studies. Heterogeneity was evaluated in the whole population and in those patients with bone only and visceral disease. For three first-line trials, the pooled direct comparison showed a benefit of CDK4–6 inhibitors + aromatase inhibitors versus aromatase inhibitors alone (HR = 0.56, 95% CI 0.46–0.65; P for heterogeneity 0.93, $I^2 = 0\%$). For bone-only and visceral disease subgroups, the magnitude of effect was comparable and heterogeneity was low in the pooled analysis of trials ($P = 0.23$, $I^2 = 32\%$ and $P = 0.9$, $I^2 = 0\%$). Results were similar for 3 s line studies, even if studies had different length of follow-up, rate of pretreated patients, and PALOMA-3 study did not provide PFS in bone-only BCs.

PFS and ORR with first-line agents

Hazard ratios for PFS were respectively 0.58 (95% CI 0.46–0.72), 0.56 (95% CI 0.43–0.72) and 0.54 (95% CI 0.41–0.72) for the three main direct comparisons of palbociclib, ribociclib, and abemaciclib. In indirect comparisons, all three first-line agents (CDK4–6 + aromatase inhibitors) were similar in term of PFS: HRs_{ind} 1.04 (95% CI 0.73–1.46), 1.07 (95% CI 0.75–1.54) and 1.04 (95% CI 0.71–1.52) respectively for palbociclib versus ribociclib, palbociclib versus abemaciclib and ribociclib versus abemaciclib comparisons. The treatment inconsistency was absent: P for heterogeneity 0.99, $I^2 = 0\%$. Similarly, ORR was not significantly different among the three comparisons: RR_{ind} 0.82 (95%CI 0.6–1.09), 0.87 (95%CI 0.63–1.19), and 1.06 (95%CI 0.77–1.47) (Supplementary Table 3a; Figs. 3, 4, 5) for palbociclib versus ribociclib, palbociclib versus abemaciclib and ribociclib versus abemaciclib comparisons. In direct comparisons, ORR was 42.1, 40.7, and 48.1% for the three experimental arms.

G3–4 toxicities with first-line agents

Rates of events reported in first-line trials with CDK4–6 inhibitors are reported in Supplementary Table 2. All G3–4 toxicities, G3–4 leukopenia, neutropenia, anemia, AST and ALT increase, diarrhea and QTcF increase beyond 480 ms (only for palbociclib versus ribociclib comparisons) were analyzed. No difference among agents were found except less G3–4 diarrhea with palbociclib compared with abemaciclib (RR_{ind} 0.13, 95% CI 0.02–0.92) and reduced risk of QTcF prolongation (RR_{ind} 0.02, 95% CI 0-0.15; $P = 0.002$) for palbociclib [11] compared to ribociclib (Supplementary Table 3a; Figs. 3, 4, 5). Two studies reported quality of life evaluation for first-line studies [12, 13]; through indirect comparison, palbociclib and ribociclib plus letrozole were associated with a similar time to deterioration in quality of life (HR = 0.94, 95% CI 0.72–1.24; $P = 0.73$). No published data were found for abemaciclib.

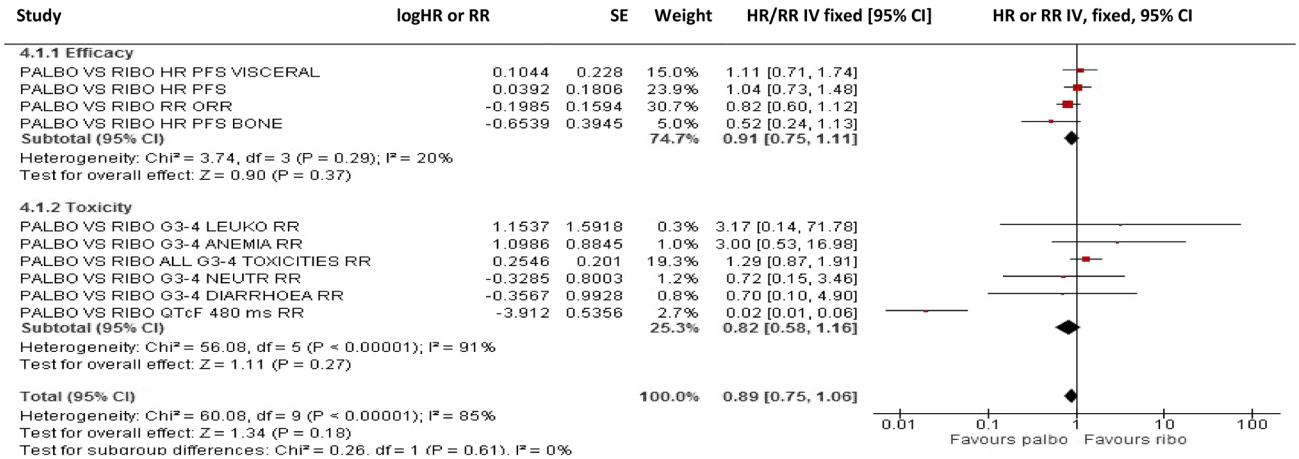

Fig. 3 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: palbociclib versus ribociclib

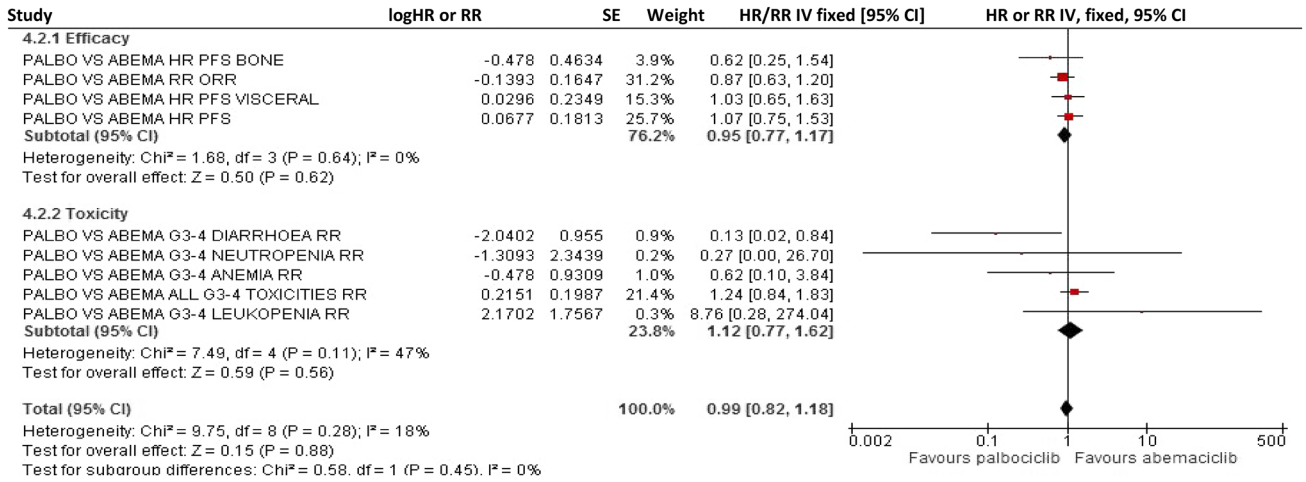

Fig. 4 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: palbociclib versus abemaciclib

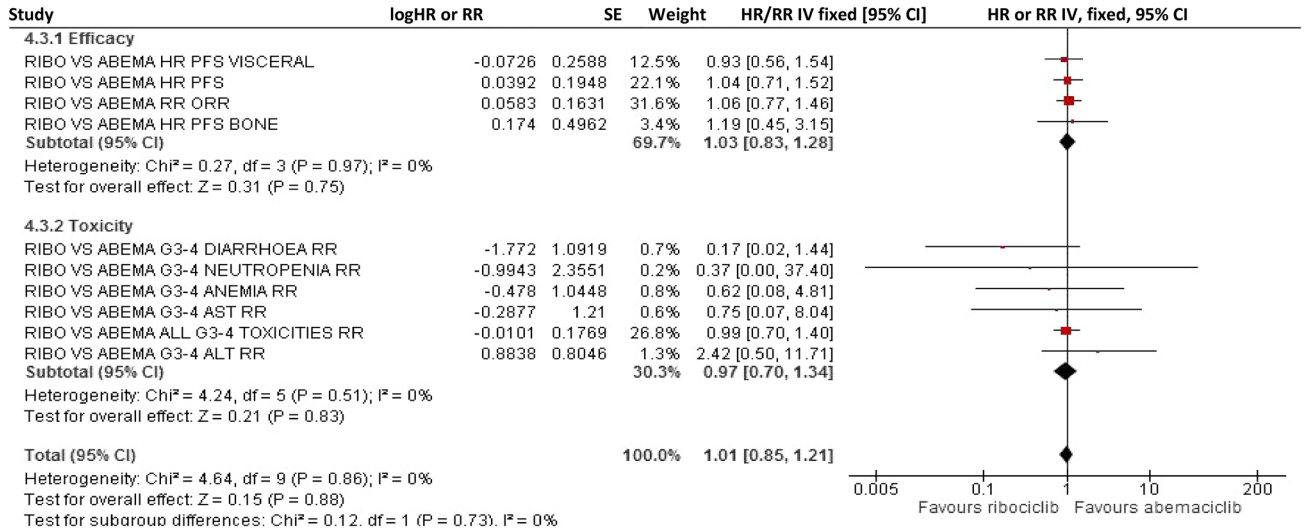

Fig. 5 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: ribociclib versus abemaciclib

PFS and ORR with second-line agents

Hazard ratios for PFS were respectively 0.46 (95% CI 0.36–0.59), 0.59 (95% CI 0.48–0.73) and 0.55 (95% CI 0.44–0.78) for the three main direct comparisons of palbociclib, ribociclib, and abemaciclib in second-line settings. In indirect comparisons, all three second-line agents (CDK4–6 + fulvestrant) were similar in term of PFS: HRs_{ind} 0.78 (95% CI 0.57–1.07), 0.84 (95% CI 0.61–1.14) and 1.07 (95% CI 0.81–1.43) for palbociclib versus ribociclib, palbociclib versus abemaciclib and ribociclib versus abemaciclib comparisons. (The treatment inconsistency was low: *P* for heterogeneity 0.29, $I^2 = 19\%$). Similarly, ORR was not significantly different among the three comparisons: RR_{ind} 1.21 (95% CI 0.66–2.22), 1.04 (95% CI 0.57–1.91), and 1.26 (95% CI 0.8–1.98) (Supplementary Table 3b).

G3–4 toxicities with second-line agents

Rate of events reported in second-line trials with CDK4–6 inhibitors are reported in Supplementary Table 2. All G3–4 toxicities (only for palbociclib and ribociclib comparison), G3–4 leukopenia, neutropenia, anemia, and diarrhea were analyzed. No differences among agents were found, except less G3–4 diarrhea with palbociclib and ribociclib compared with abemaciclib (RR_{ind} 0 [95% CI 0–0.15], $P = 0.002$ and

0.02 [95% CI 0–0.36], $P = 0.007$) and less G3–4 anemia with ribociclib compared to abemaciclib (RR_{ind} 0.18 [95% CI 0.03–1.04], $P = 0.05$) (Supplementary Table 3b).

Sensitivity analysis

A subgroup analysis was performed for PFS comparison in patients with bone-only or visceral metastases, respectively. All three agents were equally effective in both first-line and second-line setting in patients with advanced ER + BC and bone-only or visceral metastases (Supplementary Table 3a, b).

Discussion

First-line treatment of ER + advanced BC is now represented by the addition of one CDK4–6 inhibitor to an aromatase inhibitor or to fulvestrant, in the last case, after a previous treatment for advanced disease or relapse during adjuvant endocrine therapy. Three large phase 3 trials in first- and subsequent line settings have led to the approval of these combinations worldwide. Unfortunately, no direct comparison permits a comparison of the three agents with each other, and, in this case, the ideal approach is a meta-analysis with an indirect comparison evaluation [14]. Underlying all indirect comparisons are three basic assumptions. First, all the trials included must be comparable in terms of potential effect modifiers (e.g., trial or patient characteristics). Second, there must be no relevant heterogeneity between trial results in pairwise comparisons (assumption of homogeneity). Thirdly, there must be no relevant discrepancy or inconsistency between direct and indirect evidence (assumption of consistency). In particular, the first-line studies were similar according to prior adjuvant therapy, delivered in 46, 52 and 46% in the three trials. Similar rates of bone-only and visceral metastases were also reported (23, 20 and 21% and 48, 59 and 52%, respectively, in palbociclib, ribociclib and abemaciclib arms). De novo metastatic disease was recorded in 37, 34 and 39% in these trials. Finally, in all studies, an identical comparator arm (aromatase inhibitor or fulvestrant) and a similar magnitude of efficacy was recorded so these three assumptions are likely satisfied. A little concern was only raised by inclusion of more pretreated patients in second line PALOMA-3 study compared to MONARCH-2 and MONALEESA-3, with a shorter follow-up in the first study. All trials together provide a significant reduction in the risk of progression compared with endocrine therapy arm by about 50% while increasing significantly the risk of G3–4 toxicities.

The results of this adjusted indirect comparison show that, in both first- and second-line settings, palbociclib, ribociclib, and abemaciclib plus endocrine agents (aromatase inhibitors or fulvestrant) are equally effective in terms of PFS delay, ORR and time to quality of life deterioration. No difference was found in terms of benefit in particular subgroups (bone-only and visceral metastases BC patients). Some differences are instead observed in terms of expected toxicities. We chose main G3–4 toxicities with at least a 5% rate in each experimental arm. We also computed, in the analysis QTcF prolongation, a peculiar adverse event reported with ribociclib, which should be taken into account when balancing the burden of toxicity associated with these drugs. Palbociclib was associated with a significantly reduced risk of G3–4 diarrhea compared to abemaciclib (1.4 vs. 9.5%) and with less QTcF prolongation beyond 480 ms compared to ribociclib (0 vs. 3.3%) in first-line trials. In second-line studies, palbociclib and ribociclib were associated with less G3–4 diarrhea (0 and 0.6 vs. 13.4%) and G3–4 anemia (3 and 3.1 vs. 7.2%) respect to abemaciclib.

Compliance with treatment is important for providing and maintaining the benefit of cure in real life other that in clinical trials. Bone marrow toxicities and gastrointestinal toxicities are of concern for maintaining an adequate dose intensity and adherence to treatment, in particular aged patients as that of advanced luminal BC. Patients treated during a post-marketing period seem more heterogenous than those randomized in registrative trials; however, adverse events similarly appeared in US experiences [15, 16]. Analysis of PALOMA trials according to age showed that, despite myelosuppression being numerically higher in older patients (> 75 years), neutropenia G3–4 was similar and febrile neutropenia was rare in this subgroup [17]. Diarrhea is also of concern during chronic treatments. In this case, in the abemaciclib arms, most patients (76.3 and 70.1%) who experienced diarrhea did not undergo any treatment modifications, and discontinuation of the study drug as the result of diarrhea was 2.3 and 2.9% only in MONARCH-3 and 2 studies. Palbociclib and abemaciclib, despite similar mechanisms of action, retain slightly different biological and molecular effects on tissue, and this can be the reason for the spectrum of toxicities observed (in particular anemia and diarrhea) [18]. Cardiac toxicity is also of concern in elderly patients with BC. In the Hortobagiy et al. study, among patients suffering from QTcF prolongation, most were able to continue treatment at the 600 mg dose of ribociclib without interruption. In these cases, QTcF monitoring with a proactive strategy and avoiding concomitant medications at risk of QTcF prolongation is the cornerstone of prevention of these events. In a subgroup analysis of elderly (> 65 years) versus non-elderly patients in first-line study, the incidence of QTcF prolongation was similar across subgroups. The similar incidence of QTcF prolongation across age groups is due to the lack of an age-related effect on ribociclib exposure in pharmacokinetic analysis [19]. Even early data deriving from

phase I–II studies in patients with cancer reassure clinicians about cardiac safety of palbociclib-approved dose [20].

Our study has several potential limitations. First, although we found little statistical heterogeneity and used a fixed-effect model, only data of PFS were analyzed because OS outcomes were not mature. Second, this analysis applies only to postmenopausal patients because a formal analysis of premenopausal women made post-menopausal with the addition of LHRH analogues was not available for all agents. Third, data on QTcF prolongation for palbociclib phase 3 study derive only from a sub-study group, including 77 patients and not from the whole population of the PALOMA 2 trial. However, there are some strengths. This indirect comparison is based on the assumption of a similar activity of control arm in both first- and subsequent lines of therapy. This was true in particular for the former (about 30% of ORR and 14 months of median PFS at the cutoff analyzed) trials with consistent activity of aromatase inhibitors in first-line treatment for advanced disease. In addition, this is the first indirect comparison of efficacy and toxicity of the three labeled CDK4–6 inhibitors, and it confirms a similar potency even with a different toxicity profile.

Choice of treatment in advanced BC depends on several factors, including patients' preference, comorbidities, and disease burden. Despite the assumptions and limitations of this meta-analysis, our results do not define a clear superiority of one CDK4–6 inhibitor through an indirect comparison. Still, there is uncertainty regarding which is the best drug algorithm (chemotherapy vs. upfront combination of endocrine therapy with a CDK-4/6 inhibitor), the best companion (aromatase inhibitor or fulvestrant) as first-line therapy or whether the patients can benefit from endocrine therapy alone. Sequence strategy (first-line anti-CDK4–6 plus aromatase inhibitors followed by fulvestrant versus endocrine therapy alone followed by fulvestrant plus anti-CDK4–6 agents at progression) is still a dilemma and the aim of an ongoing study (SONIA trial, ClinicalTrials.gov Identifier: NCT03425838).

According to these data, based on similar effect on PFS and ORR and despite a different toxicity profile, there is still no clinical tool aiding decision-making for first-line and subsequent therapies for the treatment of advanced ER + BC. Ongoing biomarker studies will elucidate the best strategy in the whole ER + BC population and subgroups (luminal A vs. B disease) [21].

The choice should be dictated by physician judgment and based on current health authorities' approval of the drugs, previous treatment, and toxicity profile that, in some circumstances (i.e., cardiovascular comorbidities/use of drug interfering with QTcF interval, gastrointestinal disorder or pre-existing anemia), may dictate the choice of one agent over the other.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

Informed consent Not applicable (no informed consent required).

References

1. Slamon DJ, Neven P, Chia S et al (2018) Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 36(24):2465–2472. https://doi.org/10.1200/JCO.2018.78.9909
2. Sledge GW, Toi M, Neven P et al (2017) MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 35(25):2875–2884. https://doi.org/10.1200/JCO.2017.73.7585
3. Cristofanilli M, Turner NC, Bondarenko I et al (2016) Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phas. Lancet Oncol 17(4):425–439. https://doi.org/10.1016/S1470-2045(15)00613-0
4. Goetz MP, Toi M, Campone M et al (2017) MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 35(32):3638–3646. https://doi.org/10.1200/JCO.2017.75.6155
5. Finn RS, Martin M, Rugo HS et al (2016) Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 375(20):1925–1936. https://doi.org/10.1056/NEJMoa1607303
6. Hortobagyi GN, Stemmer SM, Burris HA et al (2016) Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 375(18):1738–1748. https://doi.org/10.1056/NEJMoa1609709
7. Turner NC, Slamon DJ, Ro J et al (2018) Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med.NEJMoa1810527. https://doi.org/10.1056/NEJMoa1810527
8. Chen P, Lee NV, Hu W et al (2016) Spectrum and degree of CDK drug interactions predicts clinical performance. Mol Cancer Ther 15(10):2273–2281. https://doi.org/10.1158/1535-7163.MCT-16-0300
9. Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17(1):1–12. https://doi.org/10.1016/0197-2456(95)00134-4
10. Bucher HC, Guyatt GH, Griffith LE, Walter SD (1997) The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 50(6):683–691. https://doi.org/10.1016/S0895-4356(97)00049-8
11. Durairaj C, Ruiz-Garcia A, Gauthier ER et al (2018) Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. Anticancer Drugs 29(3):271–280. https://doi.org/10.1097/CAD.0000000000000589
12. Rugo HS, Diéras V, Gelmon KA et al (2018) Impact of palbociclib plus letrozole on patient-reported health-related quality of life: Results from the PALOMA-2 trial. Ann Oncol 29(4):888–894. https://doi.org/10.1093/annonc/mdy012
13. Verma S, O'Shaughnessy J, Burris HA et al (2018) Health-related quality of life of postmenopausal women with hormone

receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer treated with ribociclib + letrozole: results from MONALEESA-2. Breast Cancer Res Treat 170(3):535–545. https://doi.org/10.1007/s10549-018-4769-z
14. Kiefer C, Sturtz S, Bender R (2015) Indirect comparisons and network meta-analyses: estimation of effects in the absence of head-to-head trials—part 22 of a series on evaluation of scientific publications. Dtsch Ärzteblatt Int 112(47):803–808. https://doi.org/10.3238/arztebl.2015.0803
15. Kish JK, Ward MA, Garofalo D et al (2018) Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval. Breast Cancer Res 20(1):1–8. https://doi.org/10.1186/s13058-018-0958-2
16. Stearns V, Brufsky AM, Verma S et al (2018) Expanded-access study of palbociclib in combination with letrozole for treatment of postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer. Clin Breast Cancer. https://doi.org/10.1016/j.clbc.2018.07.007
17. Rugo HS, Turner NC, Finn RS et al (2018) Palbociclib plus endocrine therapy in older women with HR+/HER2: advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer 101:123–133. https://doi.org/10.1016/j.ejca.2018.05.017
18. Knudsen ES, Hutcheson J, Vail P, Witkiewicz AK (2017) Biological specificity of CDK4/6 inhibitors:dose response relationship, in vivo signaling, and composite response signature. Oncotarget 8(27):43678–43691. https://doi.org/10.18632/oncotarget.18435
19. Sonke GS, Hart LL, Campone M et al (2018) Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat 167(3):659–669. https://doi.org/10.1007/s10549-017-4523-y
20. Zheng J, Amantea M, Wang D (2015) Effect of palbociclib concentration on heart rate-corrected QT interval in patients with cancer. Can Res 75:9 SUPPL. 1
21. Ribnikar D, Volovat SR, Cardoso F (2018) Targeting CDK4/6 pathways and beyond in breast cancer. Breast 8(43):8–17

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

View publication stats