Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis

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Summary

Background Although international guidelines support the administration of hormone therapies with or without targeted therapies in postmenopausal women with hormone-receptor-positive, HER2-negative metastatic breast cancer, upfront use of chemotherapy remains common even in the absence of visceral crisis. Because first-line or second-line treatments, or both, based on chemotherapy and on hormone therapy have been scarcely investigated in head-to-head randomised controlled trials, we aimed to compare these two different approaches.

Methods We did a systematic review and network meta-analysis with a systematic literature search on PubMed, Embase, Cochrane Central Register of Clinical Trials, Web of Science, and online archives of the most relevant international oncology conferences. We included all phase 2 and 3 randomised controlled trials investigating chemotherapy with or without targeted therapies and hormone therapies with or without targeted therapies as first-line or second-line treatments, or both, in postmenopausal women with hormone-receptor-positive, HER2-negative metastatic breast cancer, published between Jan 1, 2000, and Dec 31, 2017. Additional recently published randomised controlled trials relevant to the topic were also subsequently added. No language restrictions were adopted for our search. A Bayesian network meta-analysis was done to compare hazard ratios (HRs) for progression-free survival (the primary outcome), and to compare odds ratios (ORs) for the proportion of patients achieving an overall response (the secondary outcome). All treatments were compared to anastrozole and to palbociclib plus letrozole. This study is registered in the Open Science Framework online public database, registration DOI 10.17605/OSF.IO/496VR.

Findings We identified 2689 published results and 140 studies (comprising 50 029 patients) were included in the analysis. Palbociclib plus letrozole (HR 0·42; 95% credible interval [CrI] 0·25–0·70), ribociclib plus letrozole (0·43; 0·24–0·77), abemaciclib plus anastrozole or letrozole (0·42; 0·23–0·76), palbociclib plus fulvestrant (0·37; 0·23–0·59), ribociclib plus fulvestrant (0·48; 0·31–0·74), abemaciclib plus fulvestrant (0·44; 0·28–0·70), everolimus plus exemestane (0·42; 0·28–0·67), and, in patients with a *PIK3CA* mutation, alpelisib plus fulvestrant (0·39; 0·22–0·66), and several chemotherapy-based regimens, including anthracycline and taxane-containing regimens, were associated with better progression-free survival than was anastrozole alone. No chemotherapy or hormone therapy regimen was significantly better than palbociclib plus letrozole for progression-free survival. Paclitaxel plus bevacizumab was the only clinically relevant regimen that was significantly better than palbociclib plus letrozole in terms of the proportion of patients achieving an overall response (OR 8·95; 95% CrI 1·03–76·92).

Interpretation In the first-line or second-line setting, CDK4/6 inhibitors plus hormone therapies are better than standard hormone therapies in terms of progression-free survival. Moreover, no chemotherapy regimen with or without targeted therapy is significantly better than CDK4/6 inhibitors plus hormone therapies in terms of progression-free survival. Our data support treatment guideline recommendations involving the new combinations of hormone therapies plus targeted therapies as first-line or second-line treatments, or in both settings, in women with hormone-receptor-positive, HER2-negative metastatic breast cancer.

Funding None.

Introduction

The most common subtype of metastatic breast cancer is hormone-receptor-positive, HER2-negative breast cancer, accounting for approximately 65% of all metastatic breast tumours.[1,2] Despite a favourable prognosis relative to other subtypes of metastatic breast cancer, outcomes of hormone-receptor-positive, HER2-negative metastatic breast cancer remain poor, with a median overall survival

Research in context

Evidence before this study

We did a systematic literature search on Jan 2, 2018, to identify published phase 2 and 3 randomised controlled trials investigating the antitumour activity or clinical efficacy, or both, of chemotherapy with or without targeted therapies and of hormone therapies with or without targeted therapies in postmenopausal (physiological or induced by gonadotropin-releasing hormone analogues or surgery), hormone-receptor-positive, HER2-negative, metastatic breast cancer, as a first-line or second-line treatment, or both. The literature search was restricted to trials published from Jan 1, 2000, to Dec 31, 2017. Online electronic databases (PubMed, Embase, Cochrane Central Register of Clinical Trials, and Web of Science) and relevant international online congress proceedings were consulted. Reference lists from the most recent international guidelines were also consulted. Cross-references from published trials and most updated reviews or meta-analyses of therapeutic strategies in hormone-receptor-positive metastatic breast cancer were used to identify additional trials. There are few randomised controlled trials directly comparing hormone therapies with chemotherapies, in combination with or without targeted therapies, for first-line or second-line treatment, or both, of postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer. To date, network meta-analyses represent the only statistical approach to indirectly compare treatments, providing that these treatments have been compared to at least one common comparator.

Added value of this study

This study is, to our knowledge, the first to compare the efficacy and activity of all currently available chemotherapy and hormone therapy regimens, in combination with or without targeted therapies, including the recently approved CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib, the PI3K inhibitor alpelisib, and the mTOR inhibitor everolimus. To our knowledge, this study is also the first to directly compare all three CDK4/6 inhibitors combined with an aromatase inhibitor or fulvestrant and to incorporate results of the BOLERO-6 trial. Our results show that CDK4/6 inhibitors combined with endocrine agents are better than standard endocrine therapy. No chemotherapy regimen, with or without targeted agents, had significantly higher efficacy than CDK4/6 inhibitors plus hormone therapies. Moreover, the combination of CDK4/6 inhibitors plus hormone therapies showed a manageable toxicity profile, of intermediate severity between that of hormone therapies and that of chemotherapy with or without targeted therapies. There were no significant differences in progression-free survival among the three CDK4/6 inhibitors.

Implications of all the available evidence

Overall, our results support treatment algorithms recommended by the official oncology guidelines for first-line or second-line treatment, or both, of postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer without visceral crisis, with the new combinations of endocrine therapies and targeted agents.

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of 36 months.[2,3] The oestrogen receptor signalling pathway is the main driver of cancer cell growth and survival in these tumours, so endocrine-based therapies are considered the most effective treatments.[2] In the past decade, randomised controlled trials have led to the introduction of several innovative therapeutic strategies into clinical practice, consisting of new targeted therapies combined with hormone treatments, both in endocrine-sensitive and endocrine-resistant metastatic breast cancer. The most relevant examples of these new targeted therapies are the mTOR inhibitor everolimus and the CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib, which are used in combination with hormone therapies. Pivotal randomised controlled trials have proven the efficacy of these combinations as first and subsequent lines of treatment for postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer, with substantial improvements in patient outcomes.[4–10] As a result, according to all major international oncology guidelines, a sequence of endocrine-based treatments should be the preferred strategy in hormone-receptor-positive, HER2-negative metastatic breast cancer, except in instances of life-threatening visceral disease or visceral crisis.[11–14] Nevertheless, real-world data suggest that upfront use of chemotherapy is still common, even in the absence of visceral crisis.[15–18] This treatment approach might be partly due to the paucity of direct comparisons among hormone therapies and chemotherapy-based regimens for this subtype of metastatic breast cancer.

To provide additional evidence to guide treatment choices in postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer, we did a comprehensive systematic review and network meta-analysis to evaluate the efficacy and activity of several hormone therapy and chemotherapy regimens that have been investigated in randomised controlled trials as first-line or second-line treatments, or both.[19]

Methods

Search strategy and selection criteria

For this systematic review and network meta-analysis we searched the literature on Jan 2, 2018, to identify published phase 2 and 3 randomised controlled trials evaluating the anti-tumour activity or clinical efficacy, or both, of chemotherapy with or without targeted therapies and of hormone therapies with or without targeted therapies in postmenopausal (physiological or induced by gonadotropin-releasing hormone analogues or surgery) hormone-receptor-positive, HER2-negative

metastatic breast cancer, as first-line or second-line treatments, or both. The literature search was restricted to trials published from Jan 1, 2000, to Dec 31, 2017. Additional recently published randomised controlled trials relevant to the topic were added after their publication: MONALEESA 3 in August, 2018, when the main article was published; BOLERO-6 in June, 2018, when the main article was published; and SOLAR1 in October, 2018, when it was presented at the European Society of Medical Oncology (ESMO) meeting (appendix pp 3–18). Randomised controlled trials exclusively enrolling premenopausal patients and those with HER2-positive or triple-negative breast cancer were excluded from the analysis. The recommendations of the Cochrane Collaboration were followed to identify all relevant randomised controlled trials.[20] The full list of search terms is provided in the appendix (p 1); we used a combination of disease characteristics, study design, treatment setting, and strategies or drugs as search terms. We searched PubMed, Embase, Cochrane Central Register of Clinical Trials, and Web of Science, as well as American Society of Clinical Oncology (ASCO) and ESMO annual meetings and San Antonio Breast Cancer Symposiums (SABCS) online archives. Some records were also retrieved via cross-references from published trials, the main international oncology guidelines, and most updated reviews or meta-analyses of therapeutic strategies in hormone-receptor-positive, HER2-negative metastatic breast cancer.[11–14,21–24] Phase 2 or 3 randomised controlled trials published in the form of full papers, or as abstracts if full papers were not available, were included in the analysis. No language restrictions were adopted for our search. Two reviewers (FS and MG) independently assessed whether each selected randomised controlled trial met the predetermined criteria, and a third reviewer (DG) was consulted in case of disagreement. Additional details about the search strategy are provided in the appendix (p 1). The full reference list is reported in the appendix (pp 3–18).

See Online for appendix

Data analysis

Details about study design, patient characteristics, interventions, and previous treatments were extracted from each paper. When duplicate publications were identified, only the most recent and complete reports of randomised controlled trials were included. Hazard ratios (HR) and associated 95% CIs were extracted for progression-free survival and time to progression, when reported. Odds ratios (ORs) for the proportion of patients achieving an overall response, and associated 95% CIs, were also retrieved. These data had to be publicly available or computable from the included studies.

The primary outcomes were progression-free survival (defined as the time from randomisation to either death or disease progression, whichever occurred first) and time to progression (defined as the interval from randomisation to tumour progression). If both endpoints were reported in a randomised controlled trial, progression-free survival was selected for inclusion in the meta-analysis.[25,26] The proportion of patients achieving an overall response, defined according to Response Evaluation Criteria in Solid Tumors (RECIST), was selected as a secondary outcome.[27] We also did an exploratory analysis reporting the proportions of patients with grade 3–5 adverse events, according to Common Terminology Criteria for Adverse Events, version 4.[28]

Because of the heterogeneity of the studies included in the systematic review, a Bayesian random-effects network meta-analysis framework was used for each outcome, and results of the network meta-analysis are reported as HRs or ORs with 95% credible intervals (95% CrIs).[19] The parameters of the different models were estimated by use of a Markov Chain Monte Carlo method as implemented in the WinBUGS software package.[29] For further verification, all analyses were also done with a fixed-effects approach. As expected, the random-effects model provided a better fit to the data than the fixed-effects model. We assessed the risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[20] All analyses were done with WinBUGS (version 1.4.3).[29]

The internal validity of eligible studies was assessed according to the Cochrane Collaboration's Risk of Bias tool in Review Manager (version 5.3). Further details on the methods used are provided in the appendix (p 2).

The project is registered in the Open Science Framework (OSF) online public database, registration DOI 10.17605/OSF.IO/496VR.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Overall, 2689 records were identified. 140 studies were selected as they met all the inclusion criteria and were included in network meta-analyses (figure 1). A study by Dixon and colleagues was included in the meta-analysis even though the study was published in 1992, because it is the only study comparing hormone therapies with chemotherapy, aside from the BOLERO-6 trial, which was published after the initial search was done (appendix pp 3, 18). Although randomised controlled trials specifically designed for triple-negative breast cancer were excluded from the analysis, as previously stated, several randomised controlled trials testing chemotherapy-containing regimens also included patients with triple-negative breast cancer. Moreover, older randomised controlled trials (published approximately before 2006) of hormone therapies enrolled patients with unknown hormone receptor status. Three (2%) of 140 trials were single-centre studies, 130 (93%) were multicentre trials,

and for the remaining seven (5%) trials the number of involved centres was not reported. A detailed description of all the studies included in the network meta-analysis, together with patient characteristics, is provided in the appendix (pp 19–40).

Among the 140 selected randomised controlled trials, 114 (81%) were included in a network created to analyse HRs for progression-free survival and time to progression (figure 2), and 135 (96%) were included in a network created to analyse ORs for the proportion of patients achieving an overall response (figure 3; full reference list in appendix, pp 3–18).

Overall, 50 029 patients were included in our network meta-analysis. Patient age ranged from 45·6 years to 72·6 years (median 58·0 years; IQR 55·0–63·0) and follow-up ranged from 4·2 months to 60·0 months (median 20·0 months; 14·9–29·1). For 47 (34%) of 140 trials, information about previous adjuvant or neoadjuvant systemic therapies was not reported. 91 (65%) randomised controlled trials were exclusively of first-line treatments, 33 (24%) included both first-line and second-line (or further-line) treatments, and 16 (11%) comprised at least second-line treatments. For patients enrolled in trials of hormone therapies, visceral involvement ranged between 9·0% and 87·0%, with a median of 53·0% (IQR 47·5–59·0). Visceral involvement for patients enrolled in trials of chemotherapies ranged between 9·0% and 91·3%, with a median of 72·6% (IQR 63·0–78·8).

All treatments were compared to anastrozole because it was the most common comparator present in the randomised controlled trials included in the network meta-analysis. All treatments were also compared to the combination of palbociclib plus letrozole, since this was the first combination of a CDK4/6 inhibitor plus hormone therapy approved for clinical practice, and remains the first-line standard of care, along with other CDK4/6 inhibitor plus hormone therapy combinations.

23 treatments were significantly better than anastrozole with regard to the primary endpoints of progression-free survival and time to progression, including the new first-line standard treatments palbociclib plus letrozole (HR 0·42; 95% CrI 0·25–0·70), ribociclib plus letrozole (0·43; 0·24–0·77), and abemaciclib plus anastrozole or letrozole (0·42; 0·23–0·76), and the second-line treatments palbociclib plus fulvestrant (0·37; 0·23–0·59), ribociclib plus fulvestrant (0·48; 0·31–0·74), abemaciclib plus fulvestrant (0·44; 0·28–0·70), everolimus plus exemestane (0·42; 0·28–0·67), and, in patients with a *PIK3CA* mutation, alpelisib plus fulvestrant (0·39; 0·22–0·66; appendix pp 57–58). Among regimens comprising chemotherapy with or without targeted therapies, several regimens were better than anastrozole, including fluorouracil plus epirubicin plus cyclophosphamide (HR 0·47; 95% CrI 0·26–0·93), paclitaxel plus bevacizumab (0·39; 0·18–0·88), capecitabine (0·41; 0·24–0·76), and eribulin (0·45; 0·23–0·89). No treatment was significantly better than palbociclib plus letrozole (appendix pp 59–60). However, palbociclib plus letrozole was significantly better than fulvestrant plus anastrozole (HR 0·47; 95% CrI 0·27–0·83), fulvestrant standard dose (0·52; 0·30–0·91), anastrozole (0·42; 0·25–0·70), letrozole (0·55; 0·40–0·74), exemestane (0·43; 0·25–0·75), and tamoxifen (0·38; 0·24–0·61).

Consistent findings were observed when all treatments were compared with regimens based on CDK4/6 inhibitors (data not shown). We found no significant differences in progression-free survival among the three CDK4/6 inhibitors in combination with an aromatase inhibitor: palbociclib plus letrozole versus ribociclib plus letrozole (HR 0·98; 95% CrI 0·58–1·66), palbociclib plus letrozole versus abemaciclib plus anastrozole or letrozole (1·01; 0·59–1·70), and abemaciclib plus anastrozole or letrozole versus ribociclib plus letrozole (0·97; 0·53–1·78). Moreover, we found no significant differences among the three CDK4/6 inhibitors in combination with fulvestrant: palbociclib plus fulvestrant versus abemaciclib plus fulvestrant (HR 0·83; 95% CrI 0·47–1·46), palbociclib plus fulvestrant versus ribociclib plus fulvestrant (0·77;

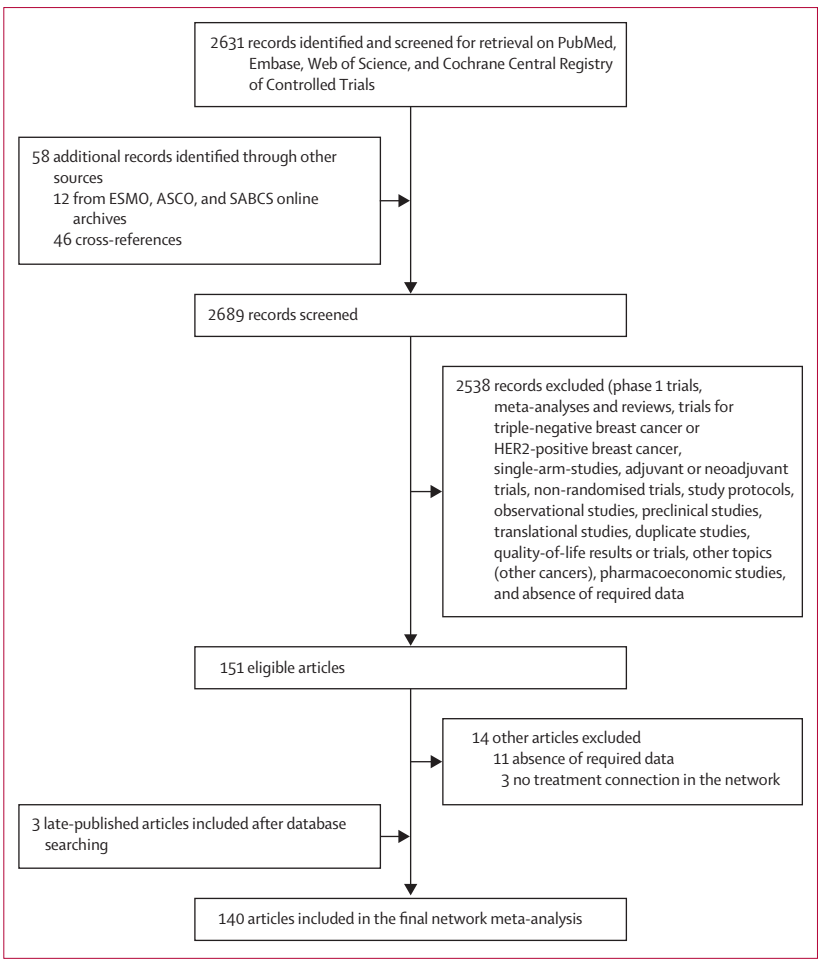

Figure 1: **Study selection**
ASCO=American Society of Clinical Oncology. ESMO=European Society of Medical Oncology. HR=hazard ratio. OR=odds ratio. SABCS=San Antonio Breast Cancer Symposiums.

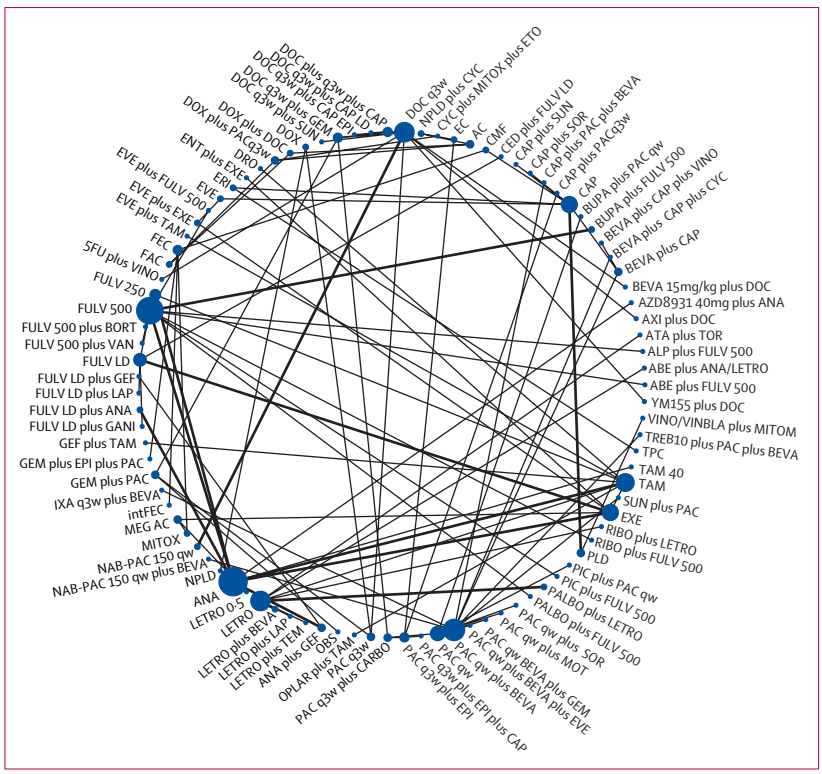

Figure 2: **Network meta-analysis of progression-free survival and time to progression**
Direct comparisons are represented by the black lines connecting the treatments. Line width is proportional to the number of trials including every pair of treatments, whereas circle size is proportional to the total number of patients for each treatment in the network. 5FU=fluorouracil. ABE=abemaciclib. AC=doxorubicin plus cyclophosphamide. ALP=alpelisib. ANA=anastrozole. ATA=atamestane. AXI=axitinib. BEVA=bevacizumab. BMF=bendamustine plus methotrexate plus fluorouracil. BORT=bortezomib. BUPA=buparlisib. CAP=capecitabine. CARBO=carboplatin. CED=cediranib. CIS=cisplatin. CMF=cyclophosphamide plus methotrexate plus fluorouracil. CYC=cyclophosphamide. DASA=dasatinib. DOC=docetaxel. DOX=doxorubicin. DRO=droloxifene. EC=epirubicin plus cyclophosphamide. ENT=entinostat. EPI=epirubicin. ERI=eribulin. ETO=etoposide. EVE=everolimus. EXE=exemestane. FAC=fluorouracil plus doxorubicin plus cyclophosphamide. FEC/CEF=fluorouracil plus epirubicin plus cyclophosphamide. FULV 250=fulvestrant 250 mg without loading dose. FULV 500=fulvestrant, standard dose. FULV LD=fulvestrant 250 mg with loading dose. GANI=ganitumab. GEF=gefitinib. GEM=gemcitabine. IDO=idoxifene. Int=intensive. IXA=ixabepilone. LAP=lapatinib. LD=low dose. LETRO=letrozole, standard dose 2·5 mg. LETRO 0·5=letrozole 0·5 mg. MA=megestrol acetate. MITOM=mitomycin C. MITOX=mitoxantrone. MMM=mitoxantrone plus mitomycin C plus methotrexate. MOT=motesanib. NAB-PAC=nab paclitaxel. NPLD=non-pegylated liposomal doxorubicin. OBS=observation. OPLAR=octreotide pamoate long acting release. PAC=paclitaxel. PALBO=palbociclib. PIC=pictilisib. PLD=pegylated liposomal doxorubicin. q3w=every 3 weeks. qw=weekly. RIBO=ribociclib. SELU=selumetinib. SOR=sorafenib. SUN=sunitinib. TAM=tamoxifen, standard dose 20 mg. TAM 40=tamoxifen 40 mg. TEM=temsirolimus. TI=time intensive. TOR=toremifene. TPC=treatment of physician's choice. TREB=trebananib. VAN=vandetanib. VINBLA=vinblastine. VINO=vinorelbine.

0·44–1·35), and abemaciclib plus fulvestrant versus ribociclib plus fulvestrant (0·93; 0·54–1·61).

For the secondary endpoint of the proportion of patients achieving an overall response, 27 therapies were shown to be significantly better than anastrozole (appendix pp 61–62). Among regimens comprising hormone therapies with or without targeted therapies, the most clinically relevant were everolimus plus exemestane (OR 4·50; 95% CrI 1·35–15·55) and abemaciclib plus fulvestrant (3·60; 1·22–10.77); palbociclib plus letrozole (1·85; 0·59–5·69), ribociclib plus letrozole (2·34; 0·65–8·48), abemaciclib plus anastrozole or letrozole (2·28; 0·62–8·29), palbociclib plus fulvestrant (2·61; 0·80–8·66), and ribociclib plus fulvestrant (1·81; 0·61–5·38) were not significantly better than anastrozole. Several chemotherapy regimens with or without targeted therapies were better than anastrozole, including paclitaxel plus bevacizumab (OR 16·48; 95% CrI 2·30–119·82), paclitaxel once weekly (15·0; 1·93–116·16), and docetaxel every 3 weeks plus epirubicin (7·64; 1·12–48·89). When compared with palbociclib plus letrozole, no treatment resulted in a significantly higher proportion of patients achieving an overall response, except for paclitaxel once weekly plus bevacizumab (OR 8·95; 95% CrI 1·03–76·92; appendix pp 63–64). However, none of the other CDK4/6 inhibitor plus hormone therapy combinations was significantly different to any of the clinically approved chemotherapy-based regimens in terms of overall response (data not shown). We found no significant difference in the proportion of patients achieving an overall response with palbociclib plus letrozole versus ribociclib plus letrozole (OR 0·79; 95% CrI 0·25–2·53), with palbociclib plus letrozole versus abemaciclib plus anastrozole or letrozole (0·81; 0·25–2·65), or with ribociclib plus letrozole versus abemaciclib plus anastrozole or letrozole (1·03; 0·27–3·91). Moreover, we observed no significant difference with palbociclib plus fulvestrant versus abemaciclib plus fulvestrant (OR 0·72; 95% CrI 0·18–2·98), with palbociclib plus fulvestrant versus ribociclib plus fulvestrant (1·44; 0·36–5·90), or with abemaciclib plus fulvestrant versus ribociclib plus fulvestrant (2·00; 0·53–7·52).

The extent of heterogeneity between studies as measured by the random-effects model was assessed by inspecting the estimate of the corresponding SD. For the analysis of the log-HR, the average SD was 0·15 (95% CrI 0·06–0·26); for the analysis of the log-OR, the average SD was 0·43 (0·30–0·60).

Adverse events were reported differently in the included studies, so a systematic assessment of safety was not possible. However, we did an exploratory analysis of the proportions of patients with grade 3–5 adverse events.[28] We only considered grade 3–5 adverse events that were reported in 2% or more patients for each study.

The main adverse events, subdivided according to treatment categories, are reported in the appendix (pp 41–56). The proportions of adverse events are reported as ranges according to the values reported in different randomised controlled trials. Single-agent chemotherapy was associated with fewer adverse events than combination chemotherapy (appendix pp 41–52). The most frequent drug-specific adverse events were alopecia, most frequently observed with doxorubicin, docetaxel, vinorelbine, paclitaxel, and gemcitabine; stomatitis, most frequently associated with doxorubicin; febrile neutropenia, most frequently associated with docetaxel; hand-foot syndrome, mostly associated with capecitabine; and motor and sensory neurological disorders, mostly associated with taxanes. Combination

chemotherapy was associated with higher frequencies of haematological and biochemical adverse events than single-agent chemotherapy (appendix pp 41–52). However, grade 3–5 neutropenia and leucopenia were also frequent with single-agent chemotherapy.

The most frequent grade 3–5 adverse events observed with hormone therapies were increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, mostly with tamoxifen and exemestane; hyperglycaemia, mostly with anastrozole; pain (general), mostly with tamoxifen and exemestane; bone pain, mostly with tamoxifen and anastrozole; arthralgia, mostly with letrozole and exemestane; asthenia, mostly with exemestane and anastrozole; dyspnoea and constipation, mostly with anastrozole; anaemia, mostly with tamoxifen and exemestane; and hypoalbuminaemia, only with anastrozole (appendix pp 53–54). Hormone therapy plus targeted therapy combinations were associated with diarrhoea, mostly observed with abemaciclib plus anastrozole, abemaciclib plus letrozole, abemaciclib plus fulvestrant, and alpelisib plus fulvestrant; rash and fatigue, mostly observed with alpelisib plus fulvestrant; stomatitis and pneumonia, mostly observed with everolimus plus exemestane; and high frequencies of neutropenia and leucopenia were observed with the combinations of ribociclib and palbociclib plus letrozole or fulvestrant (appendix pp 55–56). Grade 3–5 increases in AST and ALT concentrations were observed with ribociclib plus letrozole, abemaciclib plus fulvestrant, palbociclib plus fulvestrant, and everolimus plus exemestane. Additionally, hyperglycaemia was reported with alpelisib plus fulvestrant.

A detailed risk of bias evaluation is reported in the appendix (pp 64, 65).

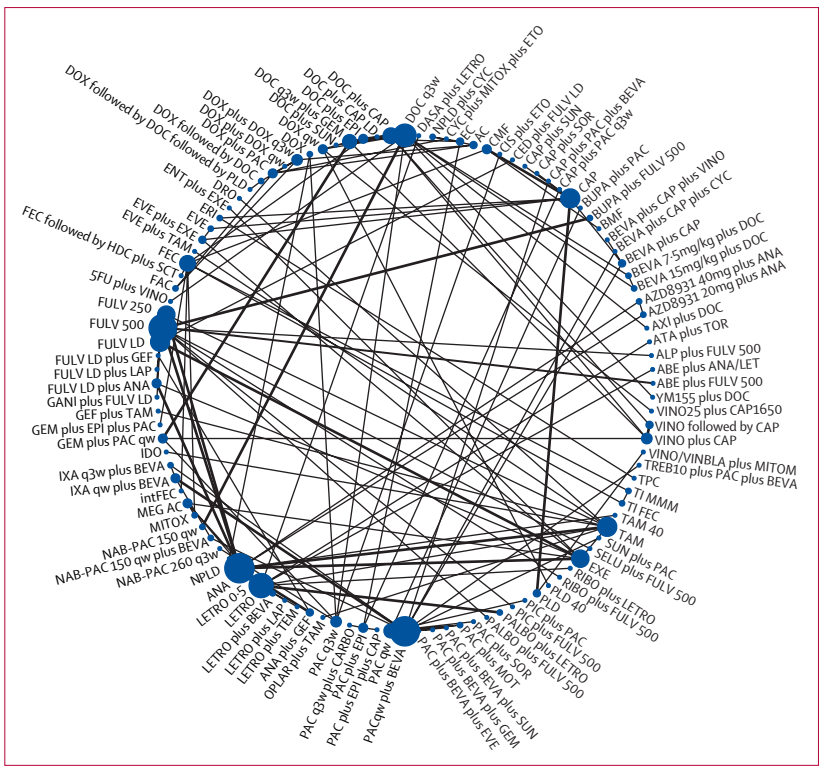

Figure 3: **Network meta-analysis of the proportion of patients achieving an overall response**
Direct comparisons are represented by the black lines connecting the treatments. Line width is proportional to the number of trials including every pair of treatments, while circle size is proportional to the total number of patients for each treatment in the network. 5FU=fluorouracil. ABE=abemaciclib. AC=doxorubicin plus cyclophosphamide. ALP=alpelisib. ANA=anastrozole. ATA=atamestane. AXI=axitinib. BEVA=bevacizumab. BMF=bendamustine plus methotrexate plus fluorouracil. BORT=bortezomib. BUPA=buparlisib. CAP=capecitabine. CARBO=carboplatin. CED=cediranib. CIS=cisplatin. CMF=cyclophosphamide plus methotrexate plus fluorouracil. CYC=cyclophosphamide. DASA=dasatinib. DOC=docetaxel. DOX=doxorubicin. DRO=droloxifene. EC=epirubicin plus cyclophosphamide. ENT=entinostat. EPI=epirubicin. ERI=eribulin. ETO=etoposide. EVE=everolimus. EXE=exemestane. FAC=fluorouracil plus doxorubicin plus cyclophosphamide. FEC/CEF=fluorouracil plus epirubicin plus cyclophosphamide. FULV 250=fulvestrant 250 mg without loading dose. FULV 500=fulvestrant, standard dose. FULV LD=fulvestrant 250 mg with loading dose. GANI=ganitumab. GEF=gefitinib. GEM=gemcitabine. HDC=high dose chemotherapy. IDO=idoxifene. Int=intensive. IXA=ixabepilone. LAP=lapatinib. LD=low dose. LETRO=letrozole, standard dose 2·5 mg. LETRO 0·5=letrozole 0·5 mg. MA=megestrol acetate. MITOM=mitomycin C. MITOX=mitoxantrone. MMM=mitoxantrone plus mitomycin C plus methotrexate. MOT=motesanib. NAB-PAC=nab paclitaxel. NPLD=non-pegylated liposomal doxorubicin. OBS=observation. OPLAR=octreotide pamoate long acting release. PAC=paclitaxel. PALBO=palbociclib. PIC=pictilisib. PLD=pegylated liposomal doxorubicin. q3w=every 3 weeks. qw=weekly. RIBO=ribociclib. SCT=stem-cell transplant. SELU=selumetinib. SOR=sorafenib. SUN=sunitinib. TAM=tamoxifen, standard dose 20 mg. TAM 40=tamoxifen 40 mg. TEM=temsirolimus. TI=time intensive. TOR=toremifene. TPC=treatment of physician's choice. TREB=trebananib. VAN=vandetanib. VINBLA=vinblastine. VINO=vinorelbine.

Discussion

The findings of this large network meta-analysis confirm that the combination of CDK4/6 inhibitors plus hormone therapies is better than standard hormone therapies as first-line or second-line treatments for postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer. In terms of progression-free survival or time to progression, no standard treatment schedule of chemotherapy with or without targeted therapy was significantly better than CDK4/6 inhibitors plus hormone therapies, which, in turn, showed a favourable and manageable toxicity profile. No significant differences in efficacy and overall activity were observed among the three CDK4/6 inhibitors.

In the past decade, several practice-changing randomised controlled trials have shown the efficacy of innovative therapeutic strategies as first-line or second-line treatments, or both, for patients with hormone-receptor-positive, HER2-negative metastatic breast cancer, leading to substantial improvements in patient outcomes. The efficacy of hormone therapies in particular has been potentiated by combining them with new targeted therapies, such as the CDK4/6 inhibitors or mTOR and PI3K inhibitors. Median progression-free survival has almost doubled and the proportion of patients achieving an overall response significantly improved in all pivotal trials of hormone therapies combined with CDK4/6 inhibitors, mTOR inhibitors, and PI3K inhibitors, compared with standard hormone therapies alone.[4–10,30] Results of these trials have substantially changed treatment algorithms, further supporting the recommendation of oncology guidelines to adopt a sequence of all the available endocrine-based treatments and delay chemotherapy until occurrence of certain forms of endocrine resistance or clinical evidence of visceral crisis.[11–14]

Nevertheless, chemotherapy-based regimens are still widely used as upfront therapy, sometimes without strict clinical justification.[15–18] To date, few data are available from randomised controlled trials directly comparing hormone therapies to chemotherapy-based treatment regimens in this disease subset. Indeed, in the past three decades, only two randomised controlled trials addressing this issue have been published (appendix pp 3, 18).[31,32] Besides those two trials, only one large retrospective analysis was done of patients with hormone-receptor-positive, HER2-negative metastatic breast cancer who were sensitive to aromatase inhibitors, which compared front-line hormone therapies to induction chemotherapy.[33] Moreover, the new combinations of hormone therapies plus targeted therapies have not been directly compared head to head in randomised controlled trials (ie, palbociclib *vs* ribociclib *vs* abemaciclib) and new trials are unlikely to be designed to address this question. This research gap leaves some degree of uncertainty about the optimal treatment algorithm in patients with hormone-receptor-positive, HER2-negative metastatic breast cancer. In this context, an inclusive and methodologically solid network meta-analysis could provide indirect evidence supporting physicians' treatment choice.

In terms of progression-free survival or time to progression, our results show that hormone therapies plus targeted therapies as first-line or second-line treatments, or in both settings, remain the best treatment choice, because chemotherapy was not shown to be better than endocrine therapy with targeted agents even when highly active chemotherapy regimens (ie, taxane-based or anthracycline-based regimens, or regimens containing both drugs) were used as a comparator. Treatment strategies involving hormone therapies plus targeted therapies, including inhibitors of tumour metabolism such as alpelisib or everolimus plus hormone therapies and the three CDK4/6 inhibitors plus hormone therapies, were all significantly better than single-agent hormone therapies with anastrozole. Several chemotherapy regimens, including some based on taxanes or anthracyclines, or both, did not show significantly better efficacy in comparison with hormone therapies alone (eg, anastrozole). This observation is valuable, especially for countries where CDK4/6 inhibitors, and targeted therapies in general, are not available yet.

With regard to the proportion of patients achieving an overall response, by comparison with contemporary single-agent chemotherapy and combination chemotherapy regimens with or without targeted therapies, palbociclib plus letrozole was significantly less active than bevacizumab-containing treatments only, including paclitaxel plus bevacizumab, although paclitaxel plus bevacizumab failed to show greater activity than the other combinations of CDK4/6 inhibitors plus hormone therapies. However, to correctly interpret these data, it is important to consider that studies of chemotherapy plus bevacizumab also enrolled patients with triple-negative disease, higher proportions of whom might achieve overall responses with these regimens than would be typically observed in patients with hormone-receptor-positive, HER2-negative breast cancer. Among the hormone-receptor-positive, HER2-negative subgroups in the TURANDOT and the CALGB 40502 trials, 35% to 46% of patients achieved an overall response with paclitaxel plus bevacizumab.[34,35] Notably, despite all the limitations of indirect comparisons, the proportion of patients achieving an overall response was not higher than that observed in trials of CDK4/6 inhibitors as first-line treatments.

None of the three CDK4/6 inhibitors, either combined with an aromatase inhibitor or fulvestrant, appeared to be better than the others in terms of both progression-free survival and the proportion of patients achieving an overall response; this observation provides new evidence for another crucial point of uncertainty regarding treatment choices in the first-line and second-line setting for hormone-receptor-positive, HER2-negative metastatic breast cancer.

The exploratory analysis of safety showed that the toxicity of combinations comprising CDK4/6 inhibitors plus hormone therapies was of intermediate severity between that of standard hormone therapies and that of chemotherapy with or without targeted therapies. Moreover, although haematological adverse events were frequent with regimens containing CDK4/6 inhibitors, they were not accompanied by consistent rates of febrile neutropenia.[4–10] Some distinctive grade 3–5 adverse events differentiate the combination of abemaciclib (mostly diarrhoea) from palbociclib-containing and ribociclib-containing therapies (mostly haematological and hepatic toxicity), and from everolimus plus exemestane (mostly stomatitis and pneumonia) or alpelisib plus fulvestrant (mostly hyperglycaemia and rash). Side-effects are reported differently in large international trials. Over-reporting or under-reporting can occur, depending on the location and setting of the study or as a result of different race-dependent safety profiles. Head-to-head comparisons are the best way to understand differences in safety profiles. The effect of different treatments on quality of life is even more complex. Fortunately, quality-of-life assessments are now systematically included as an important secondary endpoint in trials investigating different treatments in metastatic breast cancer. Despite these challenges, safety profiles, together with efficacy data and evidence of the effect of treatments on quality of life,[36,37] support the use of hormone therapies plus targeted therapies and support delaying administration of chemotherapy. However, financial costs remain a major issue. Access to new drugs, as well as the direct and indirect costs of treatment, vary substantially from one country to another. High-quality pharmacoeconomic studies are therefore needed to integrate costs into treatment algorithms.

Our network meta-analysis has some limitations. First, we acknowledge the heterogeneity among the included

studies, treatments, and patient populations, as a result of the long publication period considered (18 years), as also shown by the estimation of the random effects. Diagnostic advances could have produced a stage migration (ie, improvements in diagnosis of metastatic disease over time) that might have influenced disease features and patient prognosis. Advances in histopathology, including changes to techniques for assessing hormone receptor status, might also have provided better selection of patients deriving benefit from hormone therapies.

Large phase 3 trials investigating CDK4/6 inhibitors have shown consistent benefit of these agents combined with hormone therapies when compared with hormone therapies alone, independently of clinical subgroups. However, the benefits of chemotherapy are possibly more pronounced in more aggressive and less endocrine-sensitive tumours than in slowly growing, highly endocrine-sensitive tumours. Our network meta-analysis did not allow analysis of specific subgroups to detect a differential effect according to subpopulations. It would be interesting to do this subgroup analysis in the large phase 3 PEARL trial (NCT02028507), which directly compares palbociclib plus exemestane or plus fulvestrant versus capecitabine. No information is available about the efficacy of CDK4/6 inhibitors in patients presenting with a visceral crisis, as these patients were excluded from these trials.

Additionally, we were unable to do separate analyses for first-line, second-line, and subsequent lines of therapy, since only a few studies included in the network meta-analysis (mostly recent trials) focused on one specific line of therapy (ie, randomised controlled trials of purely first-line or second-line treatments). Additionally, although randomised controlled trials specifically designed for patients with triple-negative breast cancer had been excluded, several studies investigating chemotherapy regimens enrolled also patients with triple-negative breast cancer, as previously mentioned. Other important endpoints cannot be analysed accurately by our network meta-analysis. In particular, whether a specific sequence affects overall survival remains a major debate. Unfortunately, to our knowledge, few trials have been designed to answer this clinically relevant question. The SONIA trial (NCT03425838) will investigate the optimal position of CDK4/6 inhibitors in the first-line or second-line setting for patients receiving a non-steroidal aromatase inhibitor in the first-line setting, and fulvestrant in the second-line setting for hormone-receptor-positive, HER2-negative metastatic breast cancer.

We did not report publication bias because the approaches developed to assess this type of bias in network meta-analyses have limitations and their effectiveness is often debated. Moreover, verifying the presence of publication bias in network meta-analyses is notoriously challenging, as funnel plots within this context need a special adjustment because the studies compare different pairs of interventions.[38] However, our analysis includes most of the available literature on the topic, which might mitigate the effect of publication bias. Finally, all network meta-analyses share the same limitations of standard pairwise meta-analyses.[39,40] Moreover, these meta-analyses are based on an additional set of assumptions, the foremost being consistency between direct and indirect evidence, on which a lot of research is still ongoing.[41]

Despite these limitations, we believe the results of this large network meta-analysis are timely, clinically meaningful, and methodologically reliable. The internal validity of the eligible studies was successfully assessed with the most appropriate risk of bias analysis.[20] Our data are consistent with previously published network meta-analyses, although, to our knowledge, this analysis comprises the largest number of randomised controlled trials ever reported in hormone-receptor-positive, HER2-negative metastatic breast cancer and is the first comprehensive network meta-analysis to provide an indirect comparison of all CDK4/6 inhibitors plus aromatase inhibitors or fulvestrant and chemotherapy-based regimens.[21–24] Moreover, this network meta-analysis is the first to include the BOLERO-6 trial, which, despite its small sample size, represents the only contemporary study directly comparing a hormone therapy plus targeted therapy (everolimus plus exemestane) versus chemotherapy (capecitabine), a regimen that is currently used in clinical practice (appendix p 18).[32] Results from the ongoing phase 3 PEARL trial are likely to provide additional evidence on this topic. According to the results of our network meta-analysis, if patients with hormone-receptor-positive, HER2-negative metastatic breast cancer are treated with CDK4/6 inhibitors in the first-line setting, they might still benefit from hormone therapies such as the combination of everolimus plus exemestane, or alpelisib plus fulvestrant in patients with a *PIK3CA* mutations, and thus delay chemotherapy.

In conclusion, our results corroborate the treatment algorithms recommended by the official oncology guidelines, supporting the use of new combinations of hormone therapies plus targeted therapies in the first-line or second-line setting in patients with hormone-receptor-positive, HER2-negative metastatic breast cancer without visceral crisis.

Contributors

FS, MG, and DG conceived the study. FS, MG, and DG did the literature search. FS, CR, and SV extracted the required data. CR did the analysis of bias. SV did the statistical analyses. All authors contributed to data interpretation and wrote, revised, and approved the final version of the manuscript.

Declaration of interests

FS declares travel and accommodation expenses paid by Pfizer and Celgene. GA, MG, and SDP declare honoraria from Roche, Pfizer, AstraZeneca, Novartis, Celgene, Eli Lilly, Amgen, and Eisai. GJ reports grants, personal fees, and non-financial support from Novartis, grants,

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