Systematic Review and Meta-Analysis

Medicine®

OPEN

Endocrine therapies in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, pretreated, advanced breast cancer

A network meta-analysis

Cho-Hao Lee, MD[a], Yi-No Kang, MS[b], Ching-Liang Ho, MD, PhD[a], Chin Lin, PhD[c,d], Po-Huang Chen, MD[a], Yi-Ying Wu, MD[a], Tzu-Chuan Huang, MD[a,*]

Abstract

Background: Recently, many endocrine therapies have become available for hormone receptor-positive, human epidermal growth factor receptor 2-negative, pretreated, advanced breast cancer. Direct comparisons of these novel treatments to assess their added value, however, are lacking

Methods: Our aim was to synthesize available evidence to compare all current endocrine treatments for hormone receptor-positive / human epidermal growth factor receptor 2-negative advanced breast cancer. We performed a systematic review to identify available randomized controlled trial evidence. We searched Embase, MEDLINE, and the Cochrane Central Register of Controlled Clinical Trials. Two trials presented at international oncology congresses (American Society of Clinical Oncology [ASCO]) were added to include the most recent evidence. A frequent network meta-analysis was used, and the surface under cumulative ranking area (SUCRA) was calculated to determine the best treatment

Results: In total, 32 trials and 12,726 patients were identified, including 27 arms. Compared with fulvestrant 500 mg alone, novel target inhibitors combined with fulvestrant or exemestane had significantly prolonged progression-free survival with hazard ratios ranging from 0.62 to 0.82. Fulvestrant 500 mg plus palbociclib 125 mg and exemestane 25 mg plus entinostat 5 mg similarly extended progression-free survival (hazard ratio: 0.64 and 0.62 with SUCRA values of 91% and 92%, respectively). The exemestane 25 mg plus everolimus 10 mg combination had the best clinical benefit rate (risk ratio: 1.84, SUCRA: 91%) and overall response rate (risk ratio: 6.05, SUCRA: 97%)

Conclusions: On the basis of this analysis, the 2 combinations of exemestane plus everolimus and fulvestrant plus palbociclib were the best treatment options

Abbreviations: AE = adverse events, ASCO = American Society of Clinical Oncology, HR = hazard ratio, NMA = network meta-analysis, ORR = objective response rate, PFS = progression-free survival, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trials, SUCRA = surface under the cumulative ranking curves.

Keywords: breast cancer, endocrine therapy, hormone receptor, hormone therapy, network meta-analysis

Editor: Giandomenico Roviello.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Division of Hematology and Oncology Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, [b] Center for Evidence-Based Medicine, Department of Education, Taipei Medical University Hospital, [c] Graduate Institute of Life Sciences, National Defense Medical Center, [d] School of Public Health, National Defense Medical Center, Taipei, Taiwan.

[*] Correspondence: Tzu-Chuan Huang, Division of Hematology and Oncology Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Chenggong Rd., Neihu Dist., Taipei City 114, Taiwan (R.O.C.) (e-mail: tzuchuanhuang@mac.com).

How to cite this article: Lee CH, Kang YN, Ho CL, Lin C, Chen PH, Wu YY, Huang TC. Endocrine therapies in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, pretreated, advanced breast cancer: a network meta-analysis. Medicine 2020;99:13(e19618).

Received: 19 September 2019 / Received in final form: 4 December 2019 / Accepted: 21 February 2020

http://dx.doi.org/10.1097/MD.0000000000019618

1. Introduction

Breast cancer is the most commonly occurring type of cancer in women in the United States, and an estimated 231,840 new cases of invasive breast cancer were diagnosed during 2015.[1] Approximately 6% of patients with invasive breast cancer present distant metastases at the first diagnosis; also, some of the 31% presenting initially with regional spread have locally advanced disease that is not amenable to surgical resection with curative intent.[2] In addition, women presenting initially with early stage disease may later experience distant recurrence; for example, in a meta-analysis of women with early stage breast cancer, the 10-year recurrence rate among those treated with breast-conserving surgery and radiotherapy was 19.3%, with approximately three-fifths of recurrences occurring first as distant metastases.[3]

Breast cancer represents several diseases with unique biological subtypes defined by expression of hormone receptors (HRs) (estrogen receptor [ER] and/or progesterone receptor) and overexpression versus normal expression of human epidermal growth factor receptor 2 (HER2).[4] In surveillance, epidemiology, and end results program data from 2010, 83% of invasive breast cancers of known subtype were HR+, and nearly 90% of these were HER2−,[5] especially in postmenopausal women with advanced/metastatic breast cancer (ABC/MBC).[6,7] Despite the sometimes indolent course of the disease, HR+/HER2−, ABC/MBC remains incurable; patients with locally advanced unresectable breast cancer or distant metastases are candidates for systemic therapy to palliate symptoms and possibly prolong lifespan.

Guidelines suggest that endocrine therapy should be offered as the standard first-line treatment in patients who do not have visceral crises. After receiving the first-line endocrine therapy, many patients experience disease progression because of endocrine resistance and are offered chemotherapy or further endocrine therapy as the second-line therapy. Metastatic HR+ breast cancer may develop further resistance to standard endocrine therapies through genomic alterations in the ER and/or upregulation of other signaling pathways. Therefore, the development of new agents has aimed at reversing resistance to endocrine therapies. Various single-agent and combination regimens have been used as treatment options for patients with endocrine resistance, but the efficacy has not been acceptable.[8]

Until recently, the secondary line of endocrine therapies has included single agents or combinations of nonsteroidal aromatase inhibitors, steroidal aromatase inhibitors, selective ER degraders, epidermal growth factor receptor/HER1, cyclooxygenase-2, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway, cyclin D/cyclin-dependent kinases 4 and 6 (CDK4/6), histone deacetylation, multi-targeting tyrosine kinases/fibroblast growth factor receptor, androgen receptor, and mitogen-activated protein kinase are emerging as novel and promising combination options.

Based on recent 2-network meta-analyses (NMA) of relevant clinical trials,[9,10] endocrine therapies combined with novel agents, such as the mammalian target of rapamycin or CDK4/6 inhibitor, are thought to be preferable to combine with chemotherapy as the second-line treatment in postmenopausal women with HR+/HER2−ABC/MBC.

However, most of these novel trials only directly compared the new drugs with mono hormonal therapy, and an integrated comparison of progression-free survival (PFS) has not been made among the agents mentioned above. Therefore, we conducted a systematic literature review and NMA that included direct and indirect available evidence to evaluate and compare the efficacy and safety of available endocrine therapies in postmenopausal women with HR+/HER2− ABC/MBC whose disease had progressed after prior endocrine therapy (in a second-line setting).

2. Methods

We conducted a NMA with adherence to the guidelines provided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) report (see Table, Supplemental Digital Content 1, http://links.lww.com/MD/D981, which illustrates the PRISMA Extension Statement checklist) and the EQUATOR Network[11,12] and has been registered at PROSPERO (CRD42017058429). Ethical approval was not necessary because this study did not involve patient consent.

2.1. Search methods and selection criteria

We performed a systematic electronic search (see Table, Supplemental Digital Content 2, http://links.lww.com/MD/D982, which illustrates the Patient, Intervention, Comparison and Outcomes (PICOs) with relevant keywords, Supplemental Digital Content 3, http://links.lww.com/MD/D983, which illustrates the Search Strategy Database(s) in MEDLINE) of the Cochrane Central Register of Controlled Trials, Medline, and Embase for randomized controlled trials (RCTs). We also sought details of the zoning trials or protocols from clinicaltrial.gov to establish the eligibility of available evidence. Furthermore, specific online websites (FDA website; ASCO; American Association for Cancer Research, including the San Antonio Breast Cancer Symposium; and European Society for Medical Oncology) were searched. No language restrictions were applied. The latest searching date was on October 19, 2018.

The search was designed to identify all RCTs of endocrine therapies used to treat postmenopausal patients with HR+(or ER+)/HER2− and local ABC or MBC whose diseases had received prior endocrine treatment. Phase II and phase III trials and conference abstracts of definitely published protocols compared for efficacy or safety on the list were eligible. In the present study, we assumed that no relative effectiveness difference with or without placebo. Cross-over design RCTs were excluded due to hardly distinguish effects from different anti-cancer agents.

The trials included were those that evaluated the efficacy and safety of endocrine mono-therapies or combined with biological/target agents, including all available endocrine therapies.

RCTs that assessed the efficacy and safety of sub-sequential endocrine therapies according to the following outcomes were included:

(1) PFS/time to progression (TTP)
(2) Clinical benefit rate (CBR).
(3) Objective response rate (ORR)
(4) Grade 3/4 adverse events (AEs) (per the Common Terminology Criteria of Adverse Events v4.03).[13]
(5) Treatment discontinuation rate.

Efficacy was assessed according to the RECIST version 1.1. Analysis of overall survival was not performed in this study because the final overall survival data from most of the clinical trials were unavailable. We chose the longest follow-up time (end

of follow-up or death) as the measurement time point for all the outcomes

2.2. Data extraction

Two reviewers independently assessed the eligibility of all identified citations and extracted data from original trial reports by using a specifically designed form that captured information on the study characteristics, including patient characteristics, sample sizes, and details of interventions with comparisons and outcomes. To lower the chances of entry error, double data entry and cross-checks were performed.

For time to event outcomes (PFS), we extracted hazard ratios (HRs) and standard errors; for dichotomous outcomes (CBR, ORR, grade 3/4 AEs), we extracted the number of people with the event per arm. The outcomes from intention-to-treat design were collected. For the analysis, if the HR with standard error data was incomplete, we made attempts to contact the authors for further information.

Among the included studies, 4 trials evaluated PFS by local investigator assessment and by central assessment, but we only extracted the local investigator assessed data.[14–17] Salmon et al enrolled patients who received first-line or second-line endocrine therapy; we only extracted the data on those who received second-line endocrine therapies. Two conference abstracts[18,19] that had fully published trial protocols were included, and we extracted data from the conference abstract and assessed the quality from the published protocol.

2.3. Quality assessment

The selected studies' quality was assessed by 2 independent reviewers (CHL and CL) using the methodology and categories described in the Cochrane Collaboration Handbook.[20]

Seven domains (sequence generation, allocation concealment, blinding of participate and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias, other bias) were assigning a judgement of high, low, or unclear risk. During disagreements, a group discussion was conducted to arrive a consensus. Furthermore, we produced risk of bias graphs using the Review Manager 5.3 software.[21]

2.4. Data synthesis and statistical analysis

To simultaneously compare all endocrine therapies for each outcome, an NMA was conducted based on the assumptions of similarity, homogeneity, and transitivity. The similarity of studies makes NMA possible to generate exchangeable treatment effects and the transitivity assumption underlying NMA was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons. The frequentist NMA in the present study was performed by using the "netmeta" package (0.9–7) in R version 3.4.1.[22]

NMA synthesizes data from a network of trials that include multiple interventions and hence has the potential to rank the therapies according to the outcome. Under the framework of NMA, we ranked the evaluated regimens based on efficacy and safety in each trial. HR with 95% confidence intervals (CI) were calculated using the random-effect frequentist NMA based on the UK National Institute for Health and Care Excellence guidance[23] for PFS. Risk ratio with 95% CI were assessed for CBR, ORR, AE, and treatment discontinuous rates with random-effect model. A P-value of $<.05$ was considered as indicative of statistical significance.

A network graphs that represented the overall information of the trials included in the analysis was generated.[24] The contribution of each direct comparison to each network estimate was calculated according to the variance of the direct treatment effect and the network structure, later summarized in a contribution.[25]

The probability of a treatment being ranked was estimated at a specific place based on the results obtained using the surface under cumulative ranking curve (SUCRA) method. SUCRA is a simple transformation of mean rank, providing a hierarchy of treatments and accounts for location and variance of all relative treatment effects.[26,27] The larger the SUCRA value (ie, closer to 1) is, the better the rank of the intervention.[28] Forest plots summary relative mean effects, 95% CIs and predictions for all comparisons together.[29] To evaluate balance of benefit and harm of interventions, we performed scatter plot to compare the SUCRA value of progression free survival (PFS) and grade 3/4 AEs. Inconsistency referred to the differences between the various direct and indirect effects that were estimated for the same comparison. Inconsistency was evaluated by using the design-by-treatment interaction model. We further examined the direct and indirect effect size when the 2 test models reached statistical significance ($P<.05$). We also detected publication bias by funnel plot and Egger test. The scatter plots of SUCRA values, funnel plot, and Egger test were completed by using STATA software (Version 13.0; Stata Corporation, College Station, TX).

3. Results

3.1. Selection for eligible studies and study characteristics

The algorithm of this systematic literature review is shown in Figure 1. A total of 1119 citations were retrieved from the databases. After screening of the titles and abstracts, the full-text records of 61 eligible citations were screened. A total of 32 citations were included for qualitative analysis. These citations comprised 30 full publications and 2 conference abstracts.[18,19] There were 24 double-blind trials and 11 phase III trials. In total, 32 trials and 12,726 patients were identified, including 27 arms. (See Table, Supplemental Digital Content 4, http://links.lww.com/MD/D984, which illustrates the basic characterisitcs of RCTs) presents a summary of the characteristics of the included trials. The median age ranged from 55.4 to 68.0 years, and sample sizes ranged from 46 to 1147.

3.2. Single agents

Anastrozole 1 mg; anastrozole 10 mg; letrozole 0.5 mg; letrozole 2.5 mg; exemestane 25 mg; fulvestrant 250 mg; fulvestrant 500 mg; fulvestrant 500 mg followed by 250 mg; aminoglutethimide 250 mg; megestrol acetate 160 mg.

3.3. Aromatase inhibitor-based therapies

Anastrozole 1 mg + gefitinib 500 mg; anastrozole 1 mg + fulvestrant 250 mg; anastrozole 1 mg + fulvestrant 500 mg/250 mg; exemestane 25 mg + entinostat 5 mg; exemestane 25 mg + abiraterone acetate + prednisone; exemestane 25 mg + celecoxib 800 mg; exemestane 25 mg + everolimus 10 mg; exemestane 50 mg + enzalutamide 160 mg.

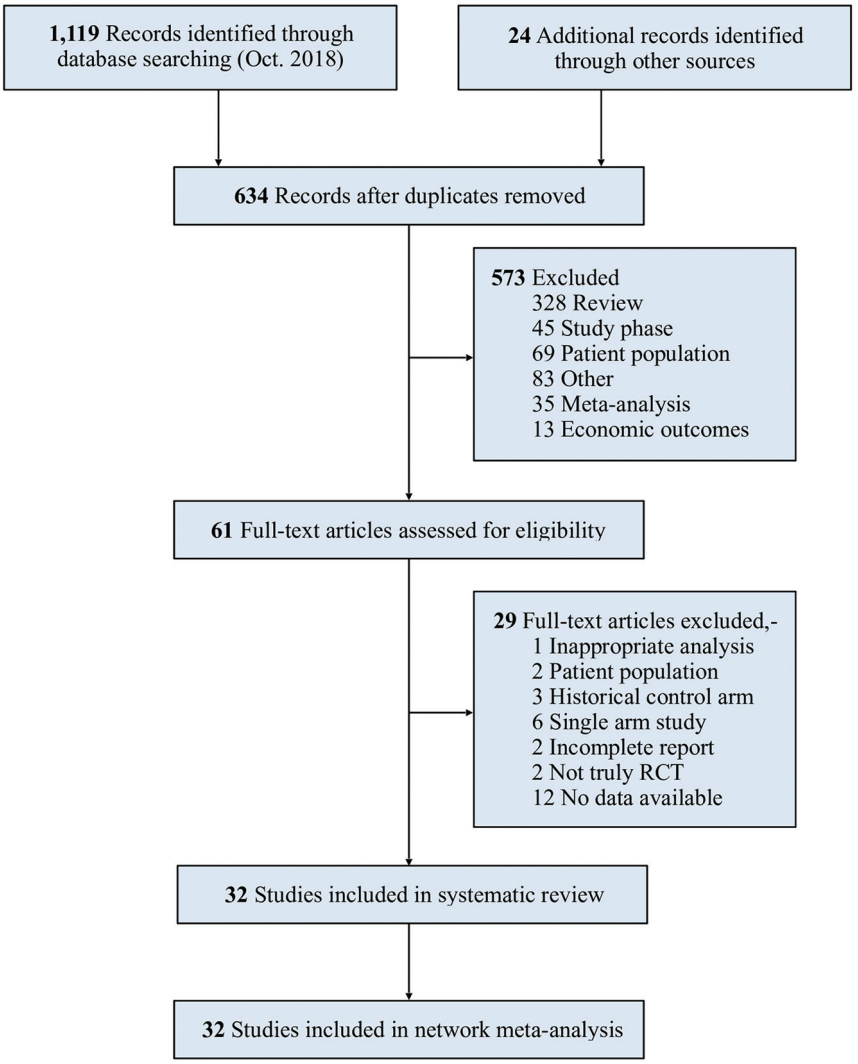


Figure 1. PRISMA flowchart. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

3.4. Selective ER degraders-based therapies

Fulvestrant 500 mg + palbociclib 125 mg; fulvestrant 500 mg + abemaciclib 300 mg; fulvestrant 500 mg + ribociclib 600 mg; fulvestrant 500 mg + selumetinib 75 mg; fulvestrant 500 mg + pictilisib 340 mg; fulvestrant 500 mg + taselisib 4 mg; fulvestrant 500 mg + dovitinib 500 mg; fulvestrant 500 mg + buparlisib 100 mg.

3.5. Others

Abiraterone acetate + prednisone.

3.6. NMA

Figure 2 describes the integral network for alternative options in ER-positive postmenopausal with previously treated advanced breast cancer patients.

3.7. PFS

Figure 3A presents the NMA results of PFS from a total of 32 studies (27 arms, 12,726 cases), in which fulvestrant 500 mg was the reference. All treatments were sorted on the basis of their ranking along with their HR and 95% CI in comparison with that of fulvestrant 500 mg. The probability scores for being the most effective treatment were also listed. A total of 7 combination therapies had significantly prolonged PFS with HRs ranging from 0.62 to 0.82 compared with intramuscular fulvestrant 500 mg alone (Fig. 3A). Among the significant findings, 2 therapies were based on exemestane 25 mg. For 1, exemestane 25 mg combined with entinostat 5 mg had a lower HR than fulvestrant 500 mg (HR: 0.62, 95% CI: 0.42–0.90, SUCRA: 91%). For another, exemestane 25 mg combined with everolimus 10 mg also resulted in a better PFS than fulvestrant 500 mg (HR: 0.69, 95% CI: 0.56–0.86, SUCRA: 85%). The other 5 significant findings were 5 fulvestrant-based therapies. The first one was fulvestrant 500 mg combined with palbociclib 125 mg (HR: 0.64, 95% CI: 0.53–0.77, SUCRA: 92%), the second was fulvestrant 500 mg combined with abemaciclib 300 mg (HR: 0.71, 95% CI: 0.60–0.83, SUCRA: 83%), the third was fulvestrant 500 mg combined with taselisib 4 mg (HR: 0.70, 95% CI: 0.55–0.89, SUCRA: 83%), the fourth was fulvestrant 500 mg combined with ribociclib 600 mg (HR: 0.72, 95% CI: 0.60–0.86, SUCRA:

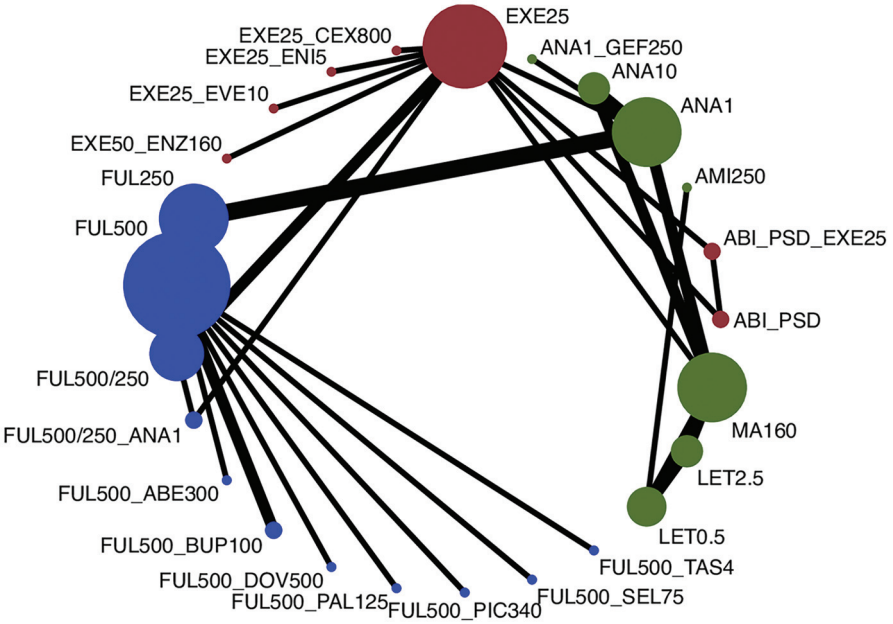


Figure 2. A Network Graph of evidence used in network meta-analysis. (Directly comparable treatments are linked with a line. Green squares means conventional endocrine therapies; Khaki squares means comparisons of Exemestane; Orange squares means comparisons of Fulvestrant). FUL500_PAL125 = Fulvestrant (500 mg) + Palbociclib (125 mg); EXE25_ENI5 = Exemestane (25 mg) + Entinostat (5 mg); EXE25_EVE10 = Exemestane (25 mg) + Everolimus (10 mg); FUL500_ABE300 = Fulvestrant (500 mg) + Abemaciclib (300 mg); FUL500_TAS4 = Fulvestrant (500 mg) + Taselisib (4 mg); FUL500_RIB600 = Fulvestrant (500 mg) + Ribociclib (600 mg); FUL500_SEL75 = Fulvestrant (500 mg) + Selumetinib (75 mg); FUL500_BUP100 = Fulvestrant (500 mg) + Buparlisib (100 mg); EXE25_CEX800 = Exemestane (25 mg) + Celecoxib (800 mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25 mg); LET0.5 = Letrozole (0.5 mg); FUL500/250 = = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25 mg); FUL500_PIC340 = Fulvestrant (500 mg) + Pictilisib (340 mg); FUL500_DOV500=Fulvestrant (500 mg) + Dovitinib (500 mg); FUL500/250_ANA1 = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg) + Anastrozole (1 mg); FUL500 = Fulvestrant (500 mg); ANA10 = Anastrozole (10 mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250 mg); EXE50_ENZ160 = Exemestane (50 mg) + Enzalutamide (160 mg); ANA1_GEF250 = Anastrozole (1 mg) + Gefitinib (250 mg); MA160 = Megestrol acetate (160 mg); ANA1 = Anastrozole (1 mg); AMI250 = Aminoglutethimide (250 mg).

81%), and the fifth was fulvestrant 500 mg combined with buparlisib 100 mg (HR: 0.82, 95% CI: 0.75–0.90, SUCRA: 65%). Briefly, the top 3 therapies for PFS among ABC/MBC were fulvestrant 500 mg plus palbociclib 125 mg, exemestane 25 mg plus entinostat 5 mg, and exemestane 25 mg plus everolimus 10 mg.

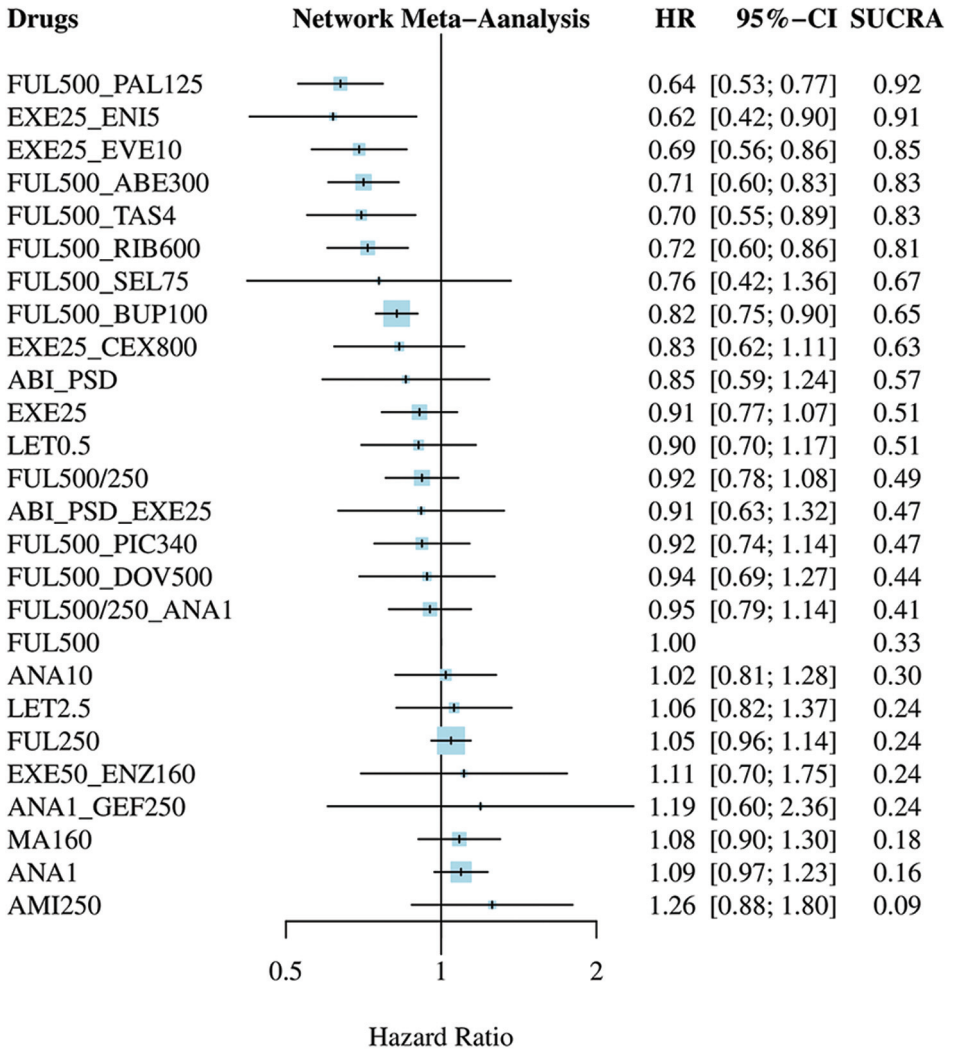
The inconsistency was not serious in the NMA of PFS although the design-by-treatment interaction model reached statistical significance. The design-by-treatment interaction model reflected inconsistency between designs (Q: 11.15, p: 0.025) though there was no significance in within designs (Q: 9.85, p: 0.454) (see Table, Supplemental Digital Content 5, http://links.lww.com/MD/D985, which illustrates the Inconsistency results of PFS & Adjust funnel plot of primary analysis). We followed significant findings to check the inconsistency contributors. Then, we found similar trends between network estimates and direct estimates (see Table, Supplemental Digital Content 6, http://links.lww.com/MD/D986, which illustrates the summary of finding for endocrine therapies of primary outcomes).

3.8. CBR and overall response rate (ORR)

We further explored the results of CRB and ORR (see Table, Supplemental Digital Content 7, http://links.lww.com/MD/D987, which illustrates the Summary of clinical benefit rate and ORR, Supplemental Digital Content 8, http://links.lww.com/MD/D988, which illustrates the NMA of secondary outcomes). Exemestane 25 mg plus everolimus 10 mg was found to be the best meaningful therapy both in CBR (risk ratio: 1.84, 95% CI: 1.21–2.80, SUCRA: 91%) and ORR (risk ratio: 6.05, 95% CI: 1.75–20.87, SUCRA: 97%). Fulvestrant 500 mg combined with palbociclib 125 mg, or abemaciclib 300 mg, or taselisib 4 mg, or dovitinib 500 mg all revealed both better efficacies in CBR and ORR than fulvestrant 500 mg alone. However, the difference in CBR or ORR between the combination of exemestane 25 mg plus entinostat 5 mg with fulvestrant 500 mg alone were not significantly different (see Table, Supplemental Digital Content 7, http://links.lww.com/MD/D987, which illustrates the Summary of clinical benefit rate and overall response rate, Supplemental Digital Content 8, http://links.lww.com/MD/D988, which illustrates the NMA of secondary outcomes).

3.9. Grade 3/4 and treatment discontinuation

In the safety evaluation, 6 fulvestrant 500-mg-based therapies combined with either CDK 4/6 or PIK3 inhibitors all showed statistically significant increases in the risk of grade 3/4 AEs. Fulvestrant 500-mg-based therapies combined with palbociclib 125 mg, abemaciclib 300 mg, taselisib 4 mg, ribociclib 600 mg, pictilisib 340 mg, or buparlisib 100 mg increased the risk of grade 3/4 AEs more than 3 times as they were compared with fulvestrant 500 mg alone, the risk ratios ranged from 3.00 to 12.22 (Fig. 3B, see Table, Supplemental Digital Content 9, http://links.lww.com/MD/D989, which illustrates the summary of grade 3/4 AEs and treatment discontinuation rate).



A

Figure 3. The network meta-meta-analyses results (presented as hazard ratio). (A) Forest plot of progression free survival (Cumulative ranking). (B) Forest plot of adverse events (Cumulative ranking). FUL500_PAL125 = Fulvestrant (500 mg) + Palbociclib (125 mg); EXE25_ENI5 = Exemestane (25 mg) + Entinostat (5 mg); EXE25_EVE10 = Exemestane (25 mg) + Everolimus (10 mg); FUL500_ABE300 = Fulvestrant (500 mg) + Abemaciclib (300 mg); FUL500_TAS4 = Fulvestrant (500 mg) + Taselisib (4 mg); FUL500_RIB600 = Fulvestrant (500 mg) + Ribociclib (600 mg); FUL500_SEL75 = Fulvestrant (500 mg) + Selumetinib (75 mg); FUL500_BUP100 = Fulvestrant (500 mg) + Buparlisib (100 mg); EXE25_CEX800 = Exemestane (25 mg) + Celecoxib (800 mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25 mg); LET0.5 = Letrozole (0.5 mg); FUL500/250 = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25 mg); FUL500_PIC340 = Fulvestrant (500 mg) + Pictilisib (340 mg); FUL500_DOV500 = Fulvestrant (500 mg) + Dovitinib (500 mg); FUL500/250_ANA1 = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg) + Anastrozole (1 mg); FUL500 = Fulvestrant (500 mg); ANA10 = Anastrozole (10 mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250 mg); EXE50_ENZ160 = Exemestane (50 mg) + Enzalutamide (160 mg); ANA1_GEF250 = Anastrozole (1 mg) + Gefitinib (250 mg); MA160 = Megestrol acetate (160 mg); ANA1 = Anastrozole (1 mg); AMI250 = Aminoglutethimide (250 mg). CI = confidence interval, HR = hazard ratio, RR = risk ratio, SUCRA = surface under the cumulative ranking curve.

In terms of treatment discontinuation, fulvestrant 500 mg plus buparlisib 100 mg, exemestane 25 mg plus everolimus 10 mg, and fulvestrant 500 mg plus pictilisib 340 mg had statistically significantly higher discontinuation rates than that of fulvestrant 500 mg alone, and the risk ratio ranged from 5.96 to 7.34. The results of fulvestrant 500 mg plus buparlisib 100 mg and fulvestrant 500 mg plus pictilisib 340 mg were consistent with the increased incidence of grade 3/4 AEs (see Table, Supplemental Digital Content 8, which illustrates the NMA of secondary outcomes, Supplemental Digital Content 9, which illustrates the summary of grade 3/4 AEs and treatment discontinuation rate).

3.10. Scatter plots

We generated 2 scatter plots: one combined PFS with CBR to distinguish the true clinical efficacy, and the other put PFS and grade 3/4 AEs together to consider efficacy and safety together. When assessing the effect of CRB and PFS together, fulvestrant 500 mg plus palbociclib 125 mg and exemestane 25 mg plus

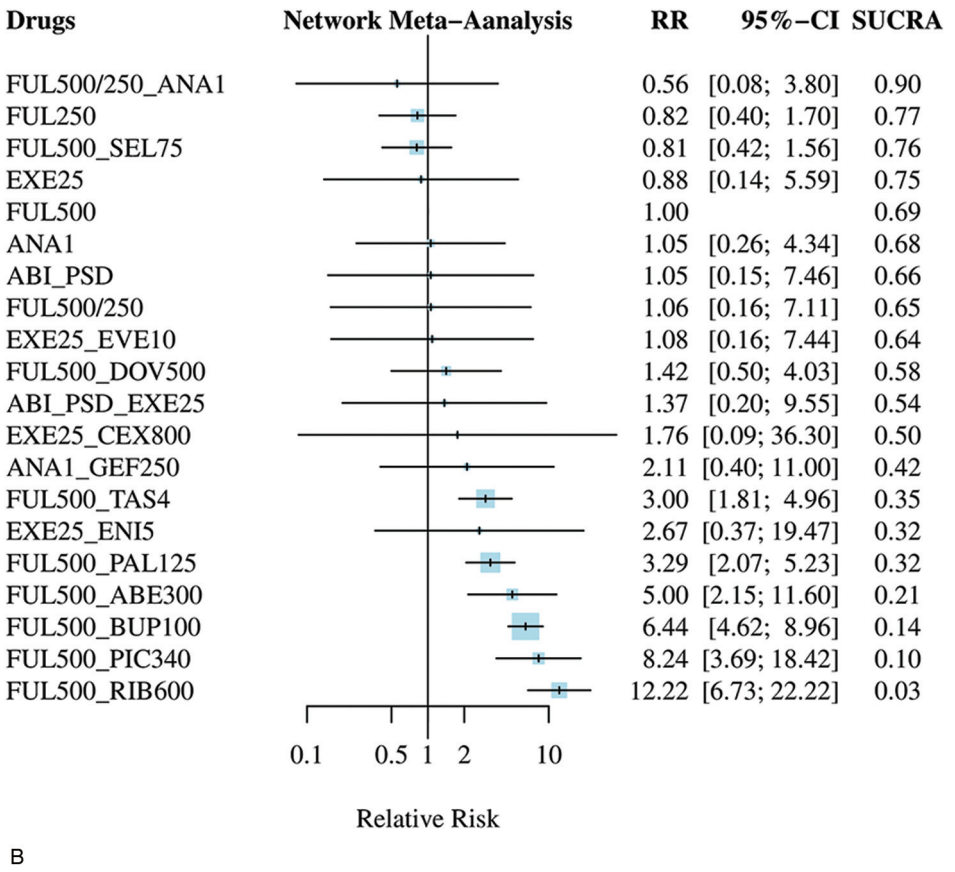


Figure 3. (Continued).

everolimus 10 mg were the top 2 choices for postmenopausal pretreated ABC/MBC patients (Fig. 4A). If safety was the top priority, exemestane 25 mg plus everolimus 10 mg was the optimal therapy (Fig. 4B).

4. Discussion

The lack of direct post-first line endocrine therapeutic comparisons in studies with ABC/MBC patients necessitates the use of indirect treatment comparisons as optional approaches to obtain estimates of relative effects and safety, to guide treatment decisions, and to inform future clinical trials and methodologies. Our present systematic literature review and NMA were conducted to compare PFS rates for all available endocrine single or combined therapies as treatment following prior endocrine therapy.

We found evidence that either fulvestrant 500-mg-based or exemestane 25-mg-based combination therapies showed improved efficacy in terms of PFS/TTP relative to that for fulvestrant 500 mg alone. Both fulvestrant 500 mg plus palbociclib 125 mg and exemestane 25 mg plus entinostat 5 mg were similarly superior to any other options in the prolongation of PFS/TTP. Exemestane 25 mg plus everolimus 10 mg had the most favorable efficacy regarding CBR and ORR. However, fulvestrant 500 mg plus palbociclib 125 mg and exemestane 25 mg plus entinostat 5 mg showed a statistically significant increased incidence of grade 3/4 AEs relative to that of fulvestrant 500 mg alone; exemestane 25 mg plus everolimus 10 mg had a neutral effect on the incidence rate of AEs but a high treatment discontinuation rate.

Novel inhibitors in combination with endocrine therapy have brought endocrine-based therapy to the forefront of HR+ breast cancer treatment. However, balancing the risk-to-benefit ratio is the biggest issue for clinicians. High treatment discontinuation due to AEs of exemestane plus everolimus were noted in the BALLET trial[30] and BOLERO-2 trial[31] (17.1% and 26.3%, respectively). The BALLET trial further showed that the rate of study discontinuation due to everolimus toxicity was $\leq$33.4%.[30] The combinations of CDK 4/6 inhibitors showed significant increases in grade 3/4 AEs; the main toxicity associated with palbociclib, ribociclib, and abemaciclib treatment was bone marrow suppression resulting in neutropenia and leukopenia.[14,32–35] In most cases, CDK 4/6 inhibitor-related AEs were not severe, and patients were able to promptly recover after dosage adjustments.[36,37] However, delays in the start of therapy because of the need for dose reductions were also cited as a significant and costly problem.

Even though the combination of exemestane 25 mg plus entinostat 5 mg (androgen receptor inhibitor) showed a promising effect on HR+ ABC patients, clinicians should remain cautious because of the limited data (lack of safety data) that were extracted from the 2017 ASCO conference abstract.

Our analysis not only focused on traditional second-line endocrine therapies but also included several up-to-date treatment options not included in a previous NMA.[38] The

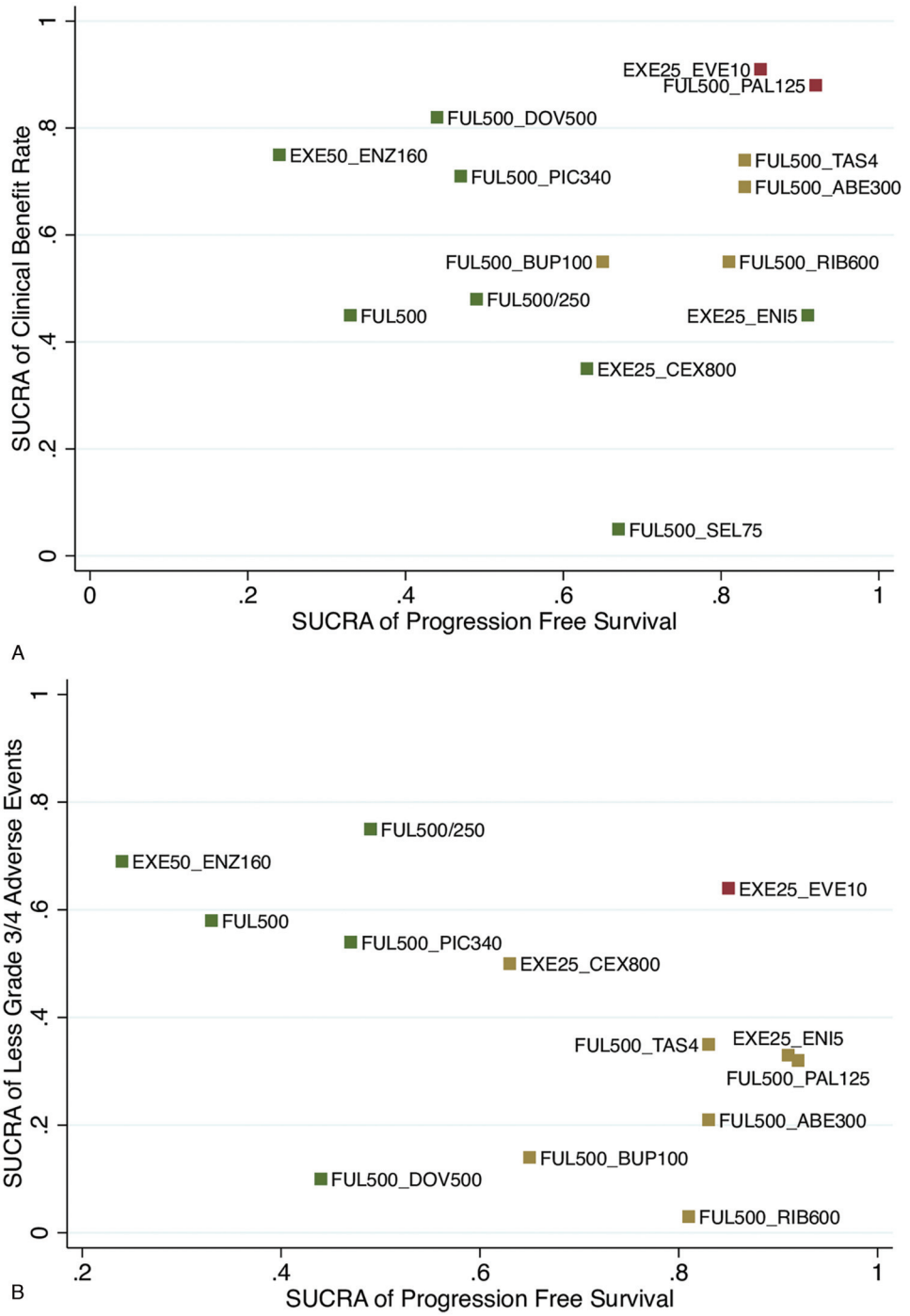


Figure 4. Scatter plots of network meta-analyses, presenting with cumulative SCRUA values (the closer to 1.0, the better). (A) Association of progression free survival (*X*-axis) and clinical benefit rate (*Y*-axis). (B) Association of progression free survival (*X*-axis) and grade 3/4 adverse events (*Y*-axis). FUL500_PAL125 = Fulvestrant (500 mg) + Palbociclib (125 mg); EXE25_ENI5 = Exemestane (25 mg) + Entinostat (5 mg); EXE25_EVE10 = Exemestane (25 mg) + Everolimus (10 mg); FUL500_ABE300 = Fulvestrant (500 mg) + Abemaciclib (300 mg); FUL500_TAS4 = Fulvestrant (500 mg) + Taselisib (4 mg); FUL500_RIB600 = Fulvestrant (500 mg) + Ribociclib (600 mg); FUL500_SEL75 = Fulvestrant (500 mg) + Selumetinib (75 mg); FUL500_BUP100 = Fulvestrant (500 mg) + Buparlisib (100 mg); EXE25_CEX800 = Exemestane (25 mg) + Celecoxib (800 mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25 mg); LET0.5 = Letrozole (0.5 mg); FUL500/250 = = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25 mg); FUL500_PIC340 = Fulvestrant (500 mg) + Pictilisib (340 mg); FUL500_DOV500 = Fulvestrant (500 mg) + Dovitinib (500 mg); FUL500/250_ANA1 = Loading Fulvestrant (500 mg) and follow by Fulvestrant (250 mg) + Anastrozole (1 mg); FUL500 = Fulvestrant (500 mg); ANA10 = Anastrozole (10 mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250 mg); EXE50_ENZ160 = Exemestane (50 mg) + Enzalutamide (160 mg); ANA1_GEF250 = Anastrozole (1 mg) + Gefitinib (250 mg); MA160 = Megestrol acetate (160 mg); ANA1 = Anastrozole (1 mg); AMI250 = Aminoglutethimide (250 mg).

newly developed target therapies of fulvestrant 500 mg plus palbociclib 125 mg, exemestane 25 mg plus entinostat 5 mg and exemestane 25 mg plus everolimus 10 mg similarly extended PFS, but there were significant safety concerns. More large head-to-head clinical trials are needed.

This study adhered to the PRISMA reporting guidelines.[12] However, there were a some limitations associated with the analyses that should be considered. The key limitation is heterogeneity in the selection biases, introduced primarily by the fact that the included trials span 2 decades. The publication years of the included studies ranged from 1997 and 2018, so some changes in clinical practices occurred over time. However, the structure of the eligible evidence networks restricted our ability to adjust for these systematical bias. The other limitation that influenced the robustness of our analysis was the indirect nature of the evidence governed by the degrees of separation in the evidence network, such that the comparative estimates of the fulvestrant 500-mg-based combination treatments were connected through the fulvestrant 500 mg comparator alone. Additionally, the present study was not designed to analyze outcomes by patient subgroups. Despite these issues, considerable effort was made to account for heterogeneity and inconsistency by using best practices.[12,26] Various sensitivity analyses were performed, all of which yielded similar findings to those of the main analyses.

5. Conclusion

In summary, the findings of our NMA based on RCTs data suggest that some fulvestrant 500-mg or exemestane 25-mg-based combination therapies may have better PFS rates than those of traditional endocrine treatments for the treatment of postmenopausal ER-positive ABC/MBC following prior endocrine therapy. While taking the benefit/harm balance into consideration, fulvestrant 500 mg plus palbociclib 125 mg and exemestane 25 mg plus everolimus 10 mg showed similar favorable prolongation of PFS, yet exemestane 25 mg plus everolimus 10 mg seems to be a tolerable treatment because of lower AE rate. In a field that is evolving as rapidly as treatment of HR+ breast cancer, it is inevitable that any single analysis represents only a snapshot of the current state of knowledge. However, our analyses add to the evidence base that can guide treatment decisions in this patient population.

Author contributions

Conceptualization: Cho-Hao Lee and Ching-Liang Ho
Data curation: Ching-Liang Ho and Chin Lin.
Methodology: Chin Lin and Yi-No Kang.
Software: Cho-Hao Lee and Chin Lin.
Validation: Yi-Ying Wu and Ching-Liang Ho.
Formal analysis: Cho-Hao Lee and Po-Huang Chen.
Investigation: Cho-Hao Lee and Po-Huang Chen.
Writing – original draft preparation: Cho-Hao Lee.
Writing – review & editing: Yi-No Kang, Ching-Liang Ho and T. C.H

Cho-Hao Lee orcid: 0000-0002-6061-5168.

References

[1] Society AC. Cancer facts & Figures 2015. 2015; Available at: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed date October 2018.

[2] Howlader N NA, Krapcho M, Miller D et al. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD: National Cancer Institute. 2016; Available at: http://seer.cancer.gov/csr/1975_2013/ Accessed date September 2018.

[3] Darby S, McGale P, Correa C, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG)Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet (London, England) 2011;378:1707–16.

[4] Onitilo AA, Engel JM, Greenlee RT, et al. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009;7:4–13.

[5] Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014; 32:3307–29.

[6] Joy AA, Ghosh M, Fernandes R, et al. Systemic treatment approaches in her2-negative advanced breast cancer-guidance on the guidelines. Curr Oncol 2015;22(Suppl 1):S29–42.

[7] Migliaccio I, Malorni L, Hart CD, et al. Endocrine therapy considerations in postmenopausal patients with hormone receptor positive, human epidermal growth factor receptor type 2 negative advanced breast cancers. BMC Med 2015;13:1–6.

[8] Wolters R, Regierer AC, Schwentner L, et al. A comparison of international breast cancer guidelines - do the national guidelines differ in treatment recommendations? Eur J Cancer 2012;48:1–1.

[9] Chirila C, Mitra D, Colosia A, et al. Comparison of palbociclib in combination with letrozole or fulvestrant with endocrine therapies for advanced/metastatic breast cancer: network meta-analysis. Curr Med Res Opin 2017;33:1457–66.

[10] Wilson FR, Varu A, Mitra D, et al. Systematic review and network meta-analysis comparing palbociclib with chemotherapy agents for the treatment of postmenopausal women with HR-positive and HER2-negative advanced/metastatic breast cancer. Breast Cancer Res Treat 2017;166:167–77.

[11] Systematic reviews/Meta-analyses/HTA | Study Designs | The EQUATOR Network. UK EQUATOR Centre CfSiM, NDORMS, University of Oxford. Available at: https://www.equator-network.org/?post_type=eq_guidelineseq_guidelines_study_design=systematic-reviews-and-meta-analyseseq_guidelines_clinical_specialty=0eq_guidelines_report_section=0s=. [Accessed February 23, 2018]

[12] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.

[13] Zhang S, Liang F, Tannock I. Use and misuse of common terminology criteria for adverse events in cancer clinical trials. BMC Cancer 2016;16:1–6.

[14] Cristofanilli M, Turner NC, Bondarenko I, et al. 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, phase 3 randomised controlled trial. Lancet Oncol 2016;17:425–39.

[15] Musolino A, Campone M, Neven P, et al. Phase II, randomized, placebo-controlled study of dovitinib in combination with fulvestrant in postmenopausal patients with HR(+), HER2(-) breast cancer that had progressed during or after prior endocrine therapy. Breast Cancer Res 2017;19:1–4.

[16] Sledge GWJr, Toi M, Neven P, et al. 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 2017;35:2875–84.

[17] Di Leo A, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:87–100.

[18] J Baselga JCC, De Laurentiis M, Dieras V, et al. SANDPIPER: phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enriched for pts with PIK3CA-mutant tumours. Ann Oncol 2016;27(Supplement 6): vi68–99.

[19] I Krop VA, Colleoni M, Traina T, et al. Results from a randomized placebo-controlled phase 2 trial evaluating exemestane ± enzalutamide in patients with hormone receptor–positive breast cancer. Am Assoc Cancer Res 2017;77:1–3.
[20] Higgins JP GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0.: The Cochrane Collaboration; 2013; Available at: http://handbook.cochrane.org/. Accessed date October 2018.
[21] Review Manager (RevMan) [Computer program]. Version 5.3.: Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
[22] Gerta Rücker GS, Ulrike Krahn and Jochem König. Package "Netmeta": Network Meta-Analysis Using Frequentist Methods (R Package Version 0.9-7.). 2017 [cited 2017 08.04]; Available at: https://CRAN.R-project.org/package=netmeta. Accessed date November 2018.
[23] Leyva F, Plummer CJ. National Institute for Health and Care Excellence 2014 guidance on cardiac implantable electronic devices: health economics reloaded. Europace 2015;17:339–42.
[24] Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80–97.
[25] Krahn U, Binder H, Konig J. A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol 2013;13:1–8.
[26] Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC good practice task force report. Value Health 2014;17:157–73.
[27] Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9:1–4.
[28] Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:1–9.
[29] Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805–20.
[30] Jerusalem G, Mariani G, Ciruelos EM, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol 2016;27:1719–25.
[31] Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870–84.
[32] DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. Clin Cancer Res 2015;21:995–1001.
[33] Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. New Engl J Med 2016;375:1925–36.
[34] Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738–48.
[35] Geoerger B, Bourdeaut F, DuBois SG, et al. A phase I study of the CDK4/6 inhibitor ribociclib (LEE011) in pediatric patients with malignant rhabdoid tumors, neuroblastoma, and other solid tumors. Clin Cancer Res 2017;23:2433–41.
[36] Murphy CG, Dickler MN. The role of CDK4/6 inhibition in breast cancer. Oncologist 2015;20:483–90.
[37] Vidula N, Rugo HS. Cyclin-dependent kinase 4/6 Inhibitors for the treatment of breast cancer: a review of preclinical and clinical data. Clin Breast Cancer 2016;16:8–17.
[38] Generali D, Venturini S, Rognoni C, et al. A network meta-analysis of everolimus plus exemestane versus chemotherapy in the first- and second-line treatment of estrogen receptor-positive metastatic breast cancer. Breast Cancer Res Treat 2015;152:95–117.