Comparison of a histone deacetylase inhibitor plus exemestane with exemestane alone in hormone receptor-positive advanced breast cancer that progressed on prior endocrine therapy: A meta-analysis

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Abstract. Currently, endocrine therapy is the standard treatment for hormone receptor-positive advanced breast cancer (ABC). Despite the high sensitivity of anti-estrogen therapy, many breast cancer patients still experience disease progression, relapse, and reduced overall survival (OS) because of endocrine resistance. Several underlying mechanisms of this phenomenon include a change in hormone receptor expression, mutations in ESR1 and modification of important signaling pathways, but thus far none of these can be defined as the complete explanation. Additionally, it has been shown that in some breast cancers, expression of the estrogen receptor (ER) can be repressed by epigenetic modifications such as DNA methylation and histone deacetylation, and this could be a mechanism for endocrine resistance. Interestingly, although the efficacy of the combination of histone deacetylase (HADC) inhibitors and exemestane in hormone receptor-positive ABC that progressed on prior endocrine therapy has been investigated in several studies, whether pharmacologic blocking of HDAC activity acts as a therapeutic strategy remains highly controversial. Herein, we conducted a meta-analysis to evaluate the efficacy and safety of an HDAC inhibitor plus exemestane vs. exemestane alone in this setting. Our meta-analysis demonstrated that the combination group exhibited significantly prolonged progression-free survival (PFS) [hazard ratio (HR)=0.776, 95% confidence interval (CI)=0.675-0.892, P=0.000] and an improved objective response rate (ORR) (RR=1.612, 95% CI=1.085-2.396, P=0.018) compared to those treated with exemestane alone. Additionally, in terms of OS, the combination group failed to achieve a significant clinical OS benefit (HR=0.811, 95% CI=0.596-1.104, P=0.183). Although grade 3/4 toxicities were more common in the combination group, those toxicities were mostly asymptomatic and manageable. In conclusion, the addition of an HDAC inhibitor to exemestane significantly improves PFS over exemestane alone in hormone receptor-positive ABC patients who progressed on previous endocrine therapy. Identification of novel biomarkers to select patients who will benefit from this combination strategy is a high priority.

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Introduction

Breast cancer is the most common malignancy among women worldwide. In the US, approximately 284,200 new cases of breast cancer were diagnosed, accounting for 30% of female cancer cases in 2021 (1). Despite improvements in cancer treatment, the relapse and metastasis of breast cancer still present great difficulties for patients, most of whom are hormone receptor-positive.

Actually, for hormone receptor-positive advanced breast cancer (ABC) patients who do not have symptomatic visceral disease, endocrine therapy (ET) is the preferred first-line therapy (2,3). More importantly, ET is often continued in the second- and third-line setting, with chemotherapy deferred until the tumor becomes endocrine resistance and/or a visceral crisis is imminent. Although more than 70% of patients with ABC are hormone receptor-positive and candidates for ET, the clinical benefit will eventually diminish as endocrine resistance develops. Thus, a rapidly growing body of research has been undertaken to identify novel drugs or treatment strategies that could specifically reverse endocrine resistance.

For years, endocrine agents (such as exemestane or fulvestrant) that lack cross-resistance with existing treatments

are given to the patient after progression on prior endocrine therapy, thereby delaying the use of cytotoxic agents and maintaining quality of life (4). After several intracellular pathways were found to promote resistance to anti-estrogen therapy, novel endocrine drug combinations began to reform treatment schema and expand therapeutic options (5-7). Moreover, epigenetic modifications including DNA methylation and histone modifications, which both lead to chromatin remodeling, also contribute to endocrine resistance (8). It is widely known that histone deacetylases (HDACs) are proteins required for control of gene expression and exert an anti-proliferative effect and promote apoptosis (9). Entinostat, a class I selective oral HDAC inhibitor, has been shown to increase expression of both the estrogen receptor (ER) and the enzyme aromatase in a dose-dependent manner *in vitro*, which then sensitizes breast cancer cells to estrogen and subsequent inhibition by the aromatase inhibitor letrozole (10). Furthermore, entinostat was also able to epigenetically induce leukemia inhibitory factor receptor (LIFR) expression and activate a pro-dormancy program in breast cancer cells, thereby slowing breast cancer cell proliferation and reducing primary tumor growth *in vivo* (11). Thus, recently, several clinical trials have been initiated to assess the efficacy of HDAC inhibitors to restore sensitivity of breast cancer to hormone manipulation (12,13). In a randomized phase II trial (ENCORE 301, NCT00676663), entinostat in combination with exemestane was compared to exemestane plus placebo in hormone receptor-positive ABC patients who had received prior endocrine therapy. The ENCORE 301 trial demonstrated that entinostat significantly improved survival in hormone receptor-positive, HER2-negative ABC patients who exhibited progression on previous non-steroidal aromatase inhibitor (NSAI) therapy when combined with exemestane (14). Interestingly, E2112, a randomized phase III trial which closely mirrored the design of the ENCORE 301 trial, failed to replicate the promising results observed in the previous trial (15). In this regard, whether the combination of an HDAC inhibitor and exemestane provides survival benefit to the patients in this setting remains controversial. Hence, we performed a meta-analysis of phase II and phase III randomized controlled trials (RCTs) comparing the efficacy and toxicity of an HDAC inhibitor plus exemestane with exemestane alone in those hormone receptor-positive ABC patients who progressed on prior endocrine therapy.

Materials and methods

Literature search and inclusion criteria. All the phase II or phase III randomized controlled trials (RCTs) which compared HDAC inhibitors plus exemestane with exemestane alone in hormone receptor-positive ABC which progressed on previous endocrine therapy from January 1, 1990 to December 31, 2021 from Pubmed, Cochrane library and Embase database were searched. We also searched for relevant ongoing studies in the ClinicalTrials.gov network (https://clinicaltrials.gov). In addition, posters and abstracts of the annual meeting of European Society of Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS) in the past 10 years were also scanned using the relevant keywords. The search algorithm was '[((breast OR mammary) AND (carcinoma OR neoplasm OR tumor OR cancer) AND (metastatic OR advanced OR relapse*) AND (pretreat*)) AND ((histone deacetylase inhibitors) OR (HDAC inhibitors))]'. All the reference lists of the included articles were scanned as well.

Our inclusion criteria were: i) prospective phase II or phase III RCTs; ii) RCTs comparing HDAC inhibitors plus exemestane with exemestane single agent in hormone receptor-positive ABC that progressed on previous endocrine therapy; iii) sufficient data for extraction, stratification, and calculation of the study was available. Comments, noncomparative studies, case reports, review articles were excluded.

Quality assessment. Two reviewers carefully evaluated the quality and the eligibility of the studies independently. Disagreements were resolved by discussion with a third reviewer. The quantitative Jadad scale was used to assess study quality: i) whether the trial reported an appropriate randomization method (0-2 scores); ii) whether the report included an appropriate blinding method (0-2 scores); iii) whether the report included an account of the number of withdrawals or dropouts.

Data extraction. The following useful information was extracted with a custom-made spreadsheet and were checked for accuracy: authors' names, date of publication, study design and allocated patient details in both the experimental and control group, main patient characteristics (patient no., median age, race, sex, menopausal status, hormone receptor and HER2 status, line of therapy, sensitivity to prior endocrine therapy), and data such as regimens, drug dose, progression-free survival (PFS), overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR) and corresponding pooled risk ratio (RR), pooled hazard ratio (HR), and 95% confidence interval (CI).

Statistically analysis. In order to appraise PFS and OS, HR and 95% CI were employed. Similarly, RR and 95% CI were used to evaluate the ORR, CBR and adverse effects (AEs). HRs, RRs and 95% CIs were collected from the original publications directly if they were reported. In addition, χ^2-based Q-test was used to estimate the heterogeneity between the groups (16). Heterogeneity was considered to exist at $P_{heterogeneity} < 0.1$ or $I^2 > 50\%$, and a random effect model was used. Otherwise, a fixed effect model was used (17). Moreover, publication bias was evaluated using funnel plot and regression test, according to the method reported by Begg and Egger. All the calculations were performed using the STATA version 12.0 software (Stata Corp.). Of note, HR >1 suggests more PFS or OS events in the combination group compared with exemestane single-agent group; RR >1 suggests more relevant AEs and better treatment response in the combination group, and vice versa.

Results

Study search and eligibility. As shown in Fig. 1, the search strategy yielded 165 records from Pubmed, Embase, Cochrane library and conference abstracts; 15 more results were added manually from other sources. Subsequently, 12 duplicates were removed. We scanned the titles and abstracts of the 168 records remaining, and then 21 references were accessed for eligibility. Finally, only 4 studies (14,15,18,19) that fulfilled the eligibility criteria were included in our qualitative synthesis.

Table I. Characteristics of the four trials eligible for the present meta-analysis.

First author	Year	Phase	Randomized	Double-blind	Regimens	Jadad score	(Refs.)
Yardley *et al*	2013	II	Yes	Yes	Entinostat+Exemestane/ Placebo+Exemestane	3	(14)
Jiang *et al*	2019	III	Yes	Yes	Tucidinostat+Exemestane/ Placebo+Exemestane	3	(19)
Xu	2021	III	Yes	Yes	Entinostat+Exemestane/ Placebo+Exemestane	3	(18)
Connolly *et al*	2021	III	Yes	Yes	Entinostat+Exemestane/ Placebo+Exemestane	3	(15)

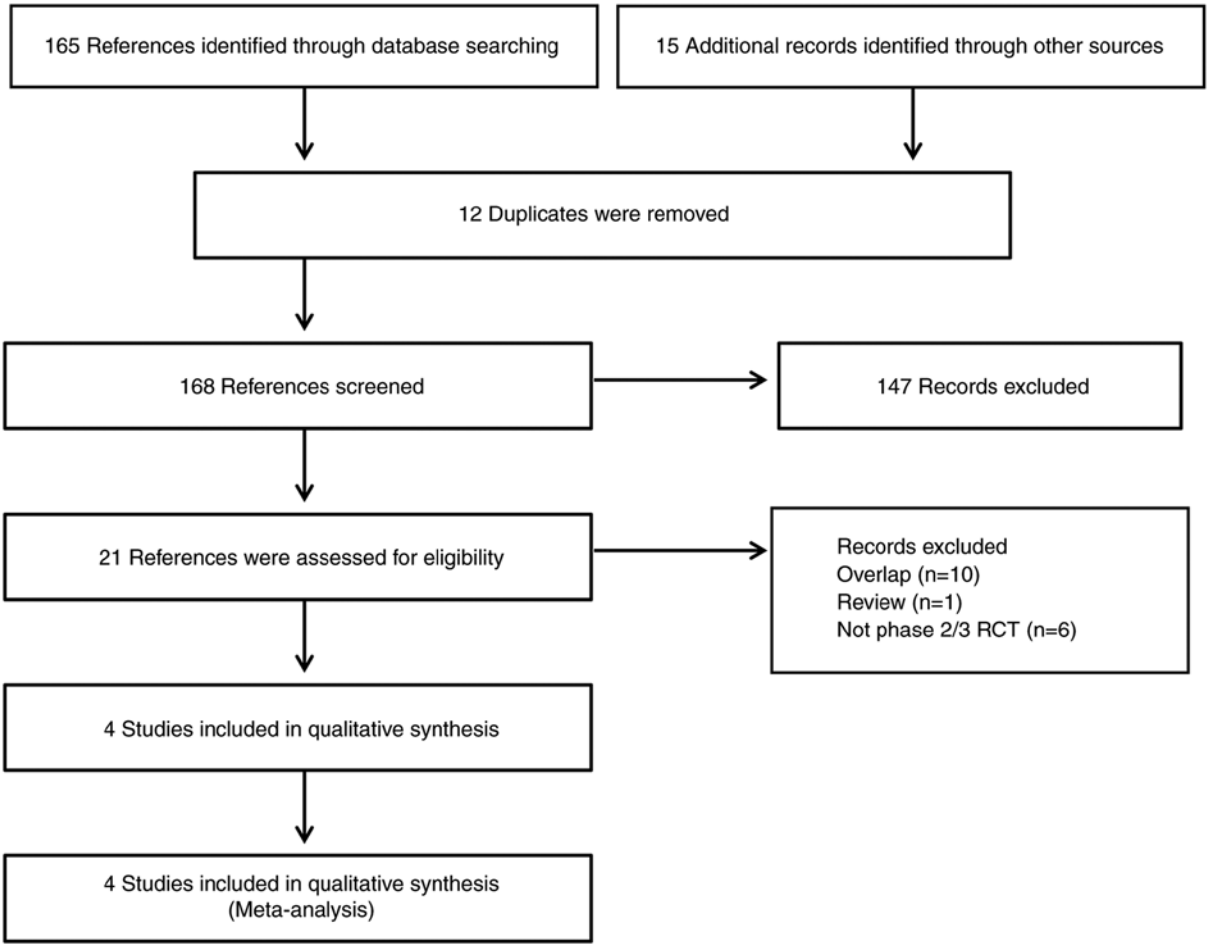

Figure 1. Flow diagram and results of our literature search.

Study characteristics and patients. A total of 1,457 hormone receptor-positive ABC patients who had progressed on prior endocrine therapy were eligible for this systematic review and meta-analysis. Of these, 848 patients received HDAC inhibitor and exemestane combination therapy, and 609 patients received placebo plus exemestane therapy (exemestane single-agent group). The characteristics of these studies are listed in Table I. In the four eligible studies, one was a phase II RCT and three were phase III RCTs. Concerning the HDAC inhibitors, entinostat was administered in 3 studies and tucidinostat was given in one study. As shown in Table II, the majority of the included patients were HER2-negative and postmenopausal. Of note, all the premenopausal or perimenopausal patients concurrently received ovarian function suppression (OFS) with a luteinizing-hormone-releasing-hormone agonist (LHRHa).

Progression-free and overall survival. In this meta-analysis, the HRs and 95% CIs for PFS were extracted directly in all the four original studies included. A fixed-effect model was used to evaluate the pooled PFS because no obvious heterogeneity existed. Pooled HR for PFS was 0.776 (95% CI=0.675-0.892,

Table II. Patient characteristics and outcomes in the present meta-analysis.

First author	No. of patients	Menopausal status	HER2 status	ORR (doublet agents vs. single-agent)	Median PFS (doublet agents vs. single-agent, months)	Median OS (doublet agents vs. single-agent, months)	(Refs.)
Yardley *et al*	130	Post (100%)	Negative (90.8%)	6.3 vs. 4.6%	4.3 vs. 2.3	28.1 vs. 19.8	(14)
Jiang *et al*	365	Post (100%)	Negative	18 vs. 9%	7.4 vs. 3.8	NR	(19)
Xu	354	Pre, Peri, and Post	Negative	17.4 vs. 10.9%	6.32 vs. 3.72	NR	(18)
Connolly *et al*	608	Pre, Peri, and Post-	Negative	5.8 vs. 5.6%	3.3 vs. 3.1	23.4 vs. 21.7	(15)

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; doublet agents: histone plus exemestane; single-agent: placebo plus exemestane; Post, postmenopausal; Peri, postmenopausal; Pre, premenopausal; NR, not reported.

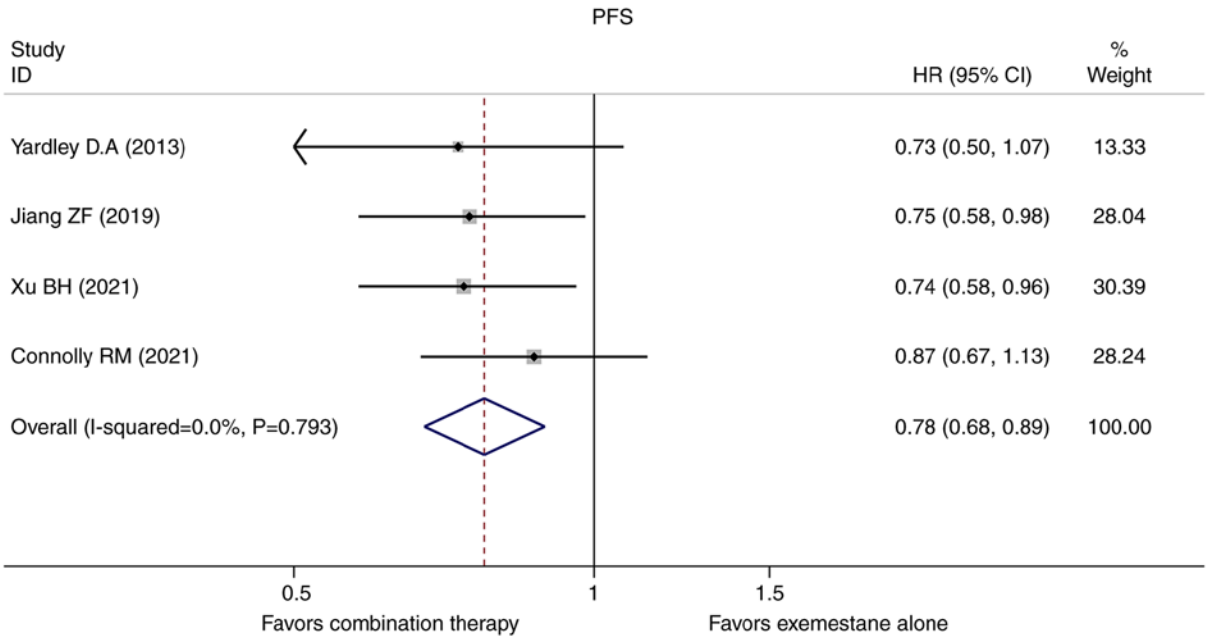

Figure 2. The pooled HR and 95% CI for PFS in the combination group and exemestane group. Combination therapy, a histone deacetylase inhibitor plus exemestane; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.

P=0.000, Fig. 2). Our results demonstrated that HDAC inhibitors plus exemestane combination therapy was associated with a 22.4% reduction in disease progression when compared with exemestane alone. In terms of OS, only three studies provided the HRs and the corresponding 95% CIs. A random-effect model was used to calculate the pooled HR and 95% for OS because a statistically significant heterogeneity existed ($P_{heterogeneity}$=0.110, I^2=54.6%). We found the combination of an HDAC inhibitor plus exemestane was insufficient to prolong OS of the hormone receptor-positive ABC patients who progressed after endocrine therapy when compared with exemestane alone (HR=0.811, 95% CI=0.596-1.104, P=0.183, Fig. 3).

Overall response rate. The ORR data was reported directly in all the four studies. The heterogeneity test indicated no significant heterogeneity found, thus the pooled RR was calculated using fixed-effect model subsequently. Consistent with the PFS, the combination group also exhibited improved ORR compared with the exemestane single-agent in the hormone receptor-positive advanced breast cancer patients who progressed on prior endocrine therapy (RR=1.612, 95% CI=1.085-2.396, P=0.018, Fig. 4).

Toxicities. With respect to the toxicities and safety, more side effects and drug-related treatment withdrawals were observed in the combination group in the majority of the included studies. All four studies included in this meta-analysis reported the grade 3/4 toxicities, and the pooled analysis showed that the combination group developed more grade 3/4 toxicities although most of them were asymptomatic (RR=6.663, 95% CI=5.166-8.595, P=0.000, Fig. 5). Importantly, few patients experienced a neutropenic fever even though the predominant treatment-related adverse effects in the combination group were hematological side effects such as neutropenia and anemia.

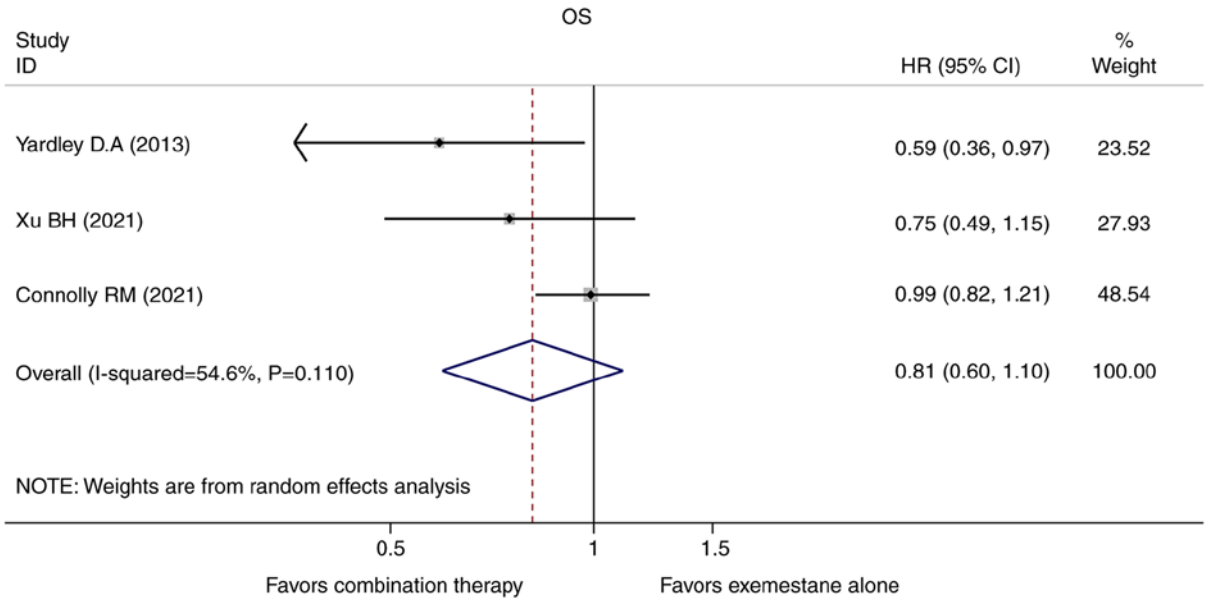

Figure 3. The pooled HR and 95% CI for OS. Combination therapy, a histone deacetylase inhibitor plus exemestane; HR, hazard ratio; CI, confidence interval; OS, overall survival.

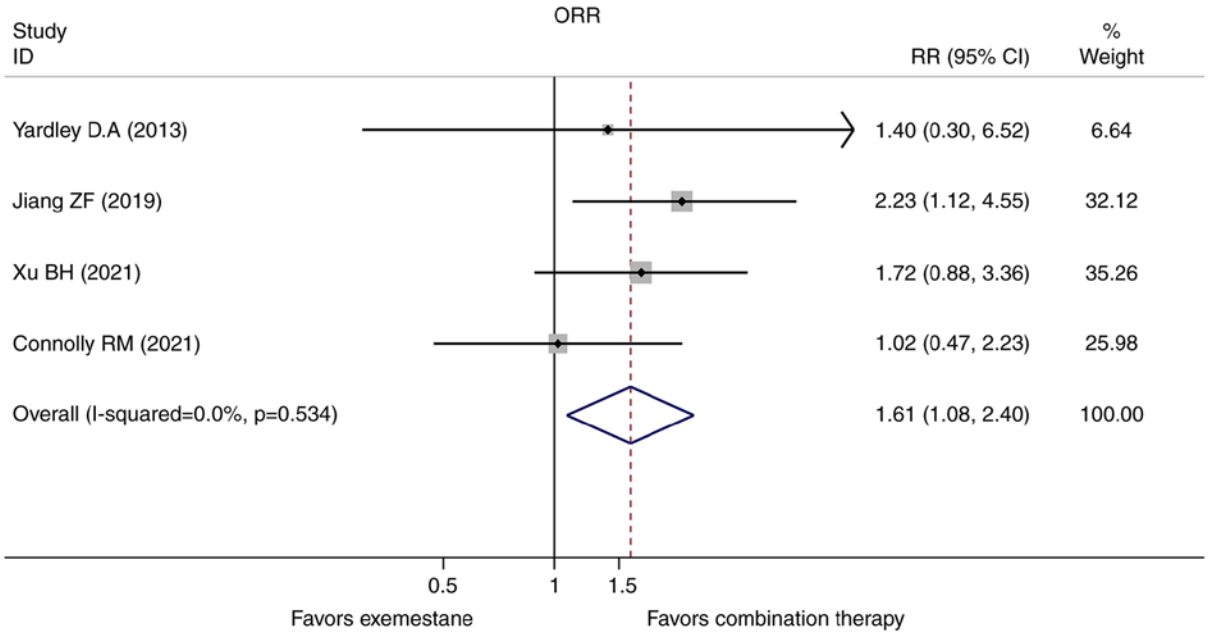

Figure 4. The pooled RR and 95% CI for ORR. Combination therapy, a histone deacetylase inhibitor plus exemestane; RR, risk ratio; CI, confidence interval; ORR, overall response rate.

Publication bias. We also evaluated the publication bias using several methods. The results of the Begg's test and the Egger's test showed that no obvious publication bias existed (PFS: Begg's test: P=1.000, Egger's test: P=0.719; ORR: Begg's test: P=0.734, Egger's test: P=0.718). As shown in Fig. 6A and B, symmetric funnel plots of the trials included in this meta-analysis suggested no evidence of publication bias.

Discussion

Despite the great advances that have been made in diagnostics and treatments for breast carcinoma, a substantial proportion of patients are still diagnosed with advanced or metastatic disease at initial presentation or develop disease relapse. In fact, approximately 70-75% patients with advanced breast cancer (ABC) are hormone receptor-positive, and endocrine therapy is the recommend treatment because of the excellent clinical efficacy and manageable safety profile (20). Unfortunately, a significant number of patients inevitably develop endocrine resistance, which remains a major clinical challenge.

In the past few decades, the treatment landscape for hormone receptor-positive/HER2-negative ABC has evolved rapidly. Accumulating preclinical evidence has demonstrated that resistance to endocrine therapy is a multi-step procedure in which

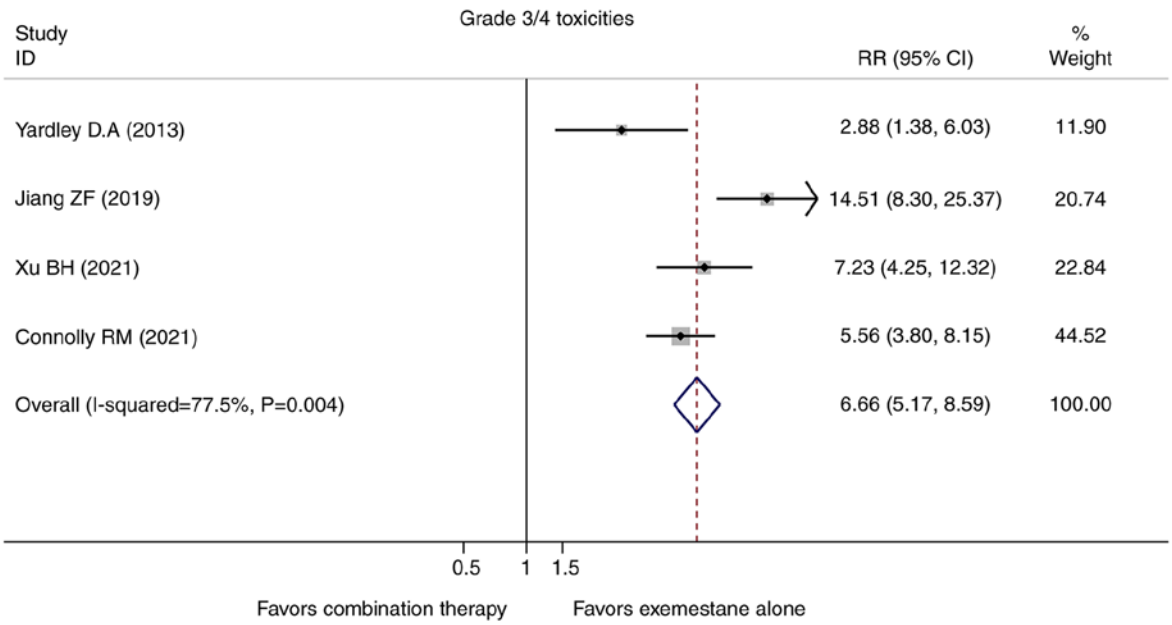

Figure 5. Forest plot of relative risk of treatment-induced grade 3-4 toxicities. Combination therapy, a histone deacetylase inhibitor plus exemestane; RR, risk ratio; CI, confidence interval.

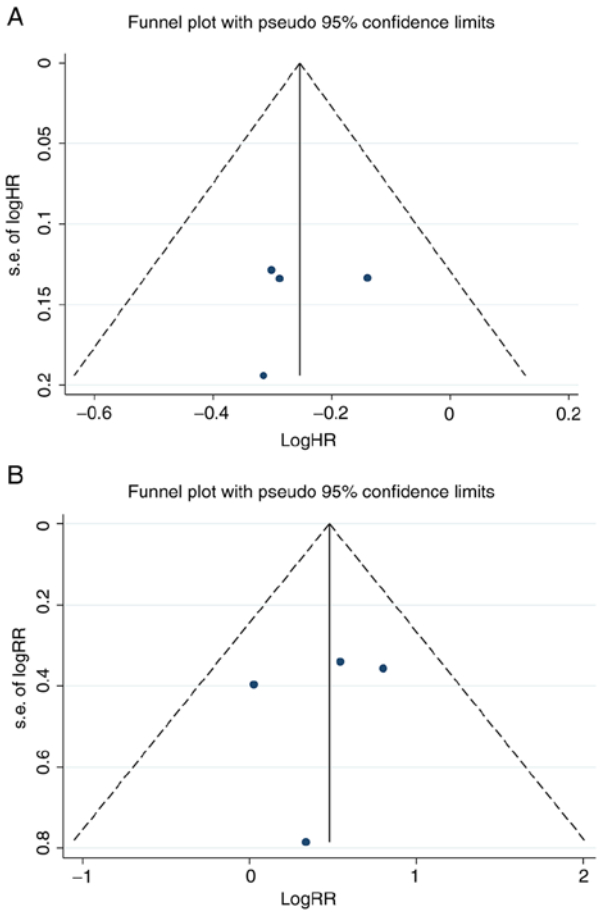

Figure 6. Funnel plot of publication bias in the meta-analysis. (A) PFS. (B) ORR. HR, hazard ratio; PFS, progression-free survival; ORR, overall response rate.

many cellular and molecular parameters are involved (21). Increasing clinical trials aimed to evaluate the feasibility of rational combinations of endocrine and non-endocrine agents targeting the endocrine resistance-related signaling pathway have been initiated; even those have only modest activity when used alone, to abrogate endocrine resistance (22-24). Additionally, several studies have also suggested the critical role of epigenetic modifications in the development of hormone resistance (25,26). Additionally, various inhibitors targeting DNA methylation and histone deacetylation enzyme are now attracting particular attention as well (8). It is reported that quisinostat, a class I and II HDAC, potentiated doxorubicin-induced cytotoxicity in both breast cancer stem cells (CSCs) and non-CSCs derived from various breast cancer cell lines *in vitro* (27). Moreover, researchers have also demonstrated that low-dose entinostat adjuvant therapy was able to inhibit metastases by disturbing the metastatic niche in a xenograft model of breast cancer (28). Although HDAC inhibitors act as promising cancer-treatment candidates in preclinical studies, their therapeutic value in hormone receptor-positive ABC patients resistant to traditionally endocrine agents remain unclear. The results of randomized controlled trials evaluating the potential role of HDAC inhibitors in hormone receptor-positive ABC are inconsistent.

The aim of this meta-analysis was to determine the clinical activity and safety of HDAC inhibitors in combination with endocrine agents such as exemestane in treating breast cancer patients who suffered relapse after previous endocrine therapy. Our results demonstrated that the combination of an HDAC inhibitor plus exemestane appears to be more efficacious compared with exemestane alone. A longer PFS was shown in the combination group with a 22.4% relative reduction in the risk of disease progression (HR=0.776, 95% CI=0.675-0.892, P=0.000, Fig. 2). Consistent with the PFS, ORR was also relatively higher in the combination group (RR=1.612, 95% CI=1.085-2.396, P=0.018, Fig. 4). However, the pooled analysis revealed that the OS was similar in both groups (HR=0.811, 95% CI=0.596-1.104, P=0.183, Fig. 3). Indeed, OS can be challenging to assess in metastatic breast cancer (MBC),

given that patients may receive multiple subsequent therapies after progression that can affect OS, thereby confounding its reliability as the most robust end point. And PFS is currently regarded as the most appropriate primary endpoint in clinical trials that focus on treatment algorithms for hormone receptor-positive/HER2-negative MBC population. Therefore, it is no surprise that the significantly improved PFS did not translate into clinical benefit of OS in the present meta-analysis (29). Taken together, our results clearly indicate that the combinatorial therapy of an HDAC inhibitor and exemestane is a promising strategy to overcome endocrine resistance.

Actually, marginal survival gains of cytotoxic drugs or targeted agents are often offset by persistent treatment-related adverse effects in cancer (30). In this meta-analysis, as compared with single-agent exemestane, the incidence of treatment-related grade 3/4 adverse events was more common in the combination group (Fig. 4). The predominant treatment-related adverse events in the combination group were hematological toxicities including neutropenia, thrombopenia and anemia. Although the improved efficacy came at a cost of a modest increase in toxicities, the combination of an HADC inhibitor administered together with exemestane was associated with a manageable safety profile.

Honestly, our work has several important limitations and these results should be interpreted cautiously. First, this meta-analysis has several sources of heterogeneity: different treatment regimens, various prior endocrine agents and different patient selections that inevitably introduced possible elements of bias to the pooled analyses. For example, some patients included in our meta-analysis had HER2 overexpression and were premenopausal (14). It is well-known that HER2 activation has been identified as one of the most important underlying mechanisms of endocrine resistance across a range of experimental model systems and clinical trials (31). HER2 is found to crosstalk with many well-defined oncogenic pathways closely related to endocrine resistance. Therefore, HER2-positive patients and those anti-HER2 therapies themselves will definitely confound the pooled results in turn (32,33). Moreover, the menopausal status also contributed to the heterogeneity. For the perimenopausal and premenopausal patients included, although LHRHa was given simultaneously with the endocrine agents, the possibility that the administered LHRHa had impact on the final estimation could not be ruled out. After all, LHRHa, which was able to achieve OFS by sustained suppression of the release of follicle-stimulating hormone and luteinizing hormone from the pituitary (34), was reported as an effective endocrine approach in breast cancer (35,36). Second, the surgery, radiotherapy, line of therapy in the advanced setting, metastatic sites, tumor burden, prior chemotherapy regimens, as well as anti-estrogen treatment drugs and sequence in these eligible studies were also heterogeneous. In addition, the sensitivities to the most recent endocrine therapy were also not homogeneous. Not even to mention that some patients received prior CDK4/6 inhibitors or fulvestrant, and whether the subsequent treatments including HDAC inhibitors could provide therapeutic possibility for this population remain unknown. Third, not all of the included studies administered the same HDAC inhibitor to the patients. Among the four studies included, entinostat was administrated in three studies, and tucidinostat was administrated in one study. With regret, we were not able to perform subgroup analysis based on endocrine resistance status, different HDAC inhibitors, prior anti-estrogen agents and metastatic sites, because only four studies were available in this meta-analysis with fewer studies reporting these results in the subgroups. Finally, the present meta-analysis was not conducted based on the individual patient data but on the HRs or RRs and their corresponding 95% CIs of each study. Despite all these limitations, our study is a meaningful meta-analysis to evaluate the role of the combination of an HDAC inhibitor plus exemestane in hormone receptor-positive ABC that progressed on previous endocrine therapy.

In conclusion, our meta-analysis revealed that HDAC inhibitors in combined with exemestane were associated with a superior clinical benefit with more frequent adverse effects when compared to exemestane alone in the hormone receptor-positive ABC patients refractory to previous endocrine agents. Further studies which focus on the discovery of new potentially predictive biomarkers capable of identifying the most appropriate population who will definitely benefit from HDAC inhibitor-based combination strategy are urgently needed.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LX, WJ and YC made substantial contributions to the conception and design of the current meta-analysis. WJ and YG wrote the manuscript. Literature search, quality assessment, data extraction, analysis and interpretation were performed by CG, WL, LL and YG. LL and WJ confirmed the authenticity of all the raw data. YG and LL revised the manuscript and polished the language. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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