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REVIEW

Overcoming resistance to endocrine therapy in hormone receptor-positive human epidermal growth factor receptor 2-negative ($HR^+/HER2^-$) advanced breast cancer: a meta-analysis and systemic review of randomized clinical trials

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Abstract **New targeted therapies have been developed to overcome resistance to endocrine therapy (ET) and improve the outcome of $HR^+/HER2^-$ advanced breast cancer (ABC). We conducted a meta-analysis and systemic review on randomized controlled trials evaluating various targeted therapies in combination with ET in $HR^+/HER2^-$ ABC. PUBMED and EMBASE databases were searched for eligible trials. Hazard ratios (HRs) for progression-free survival (PFS), odds ratios (ORs) for objective response rate (ORR), clinical benefit rate (CBR), and toxicity were meta-analyzed. Twenty-six studies with data on 10 347 patients were included and pooled. The addition of cyclin-dependent kinase 4/6 inhibitors to ET significantly improved median PFS (pooled HR = 0.547, $P < 0.001$), overall survival (pooled HR = 0.755, $P < 0.001$), and tumor response rates (ORR, pooled OR = 1.478, $P < 0.001$; CBR, pooled OR = 1.201, $P < 0.001$) with manageable toxicities (pooled OR = 3.280, $P < 0.001$). The mammalian targets of rapamycin inhibitors and exemestane were not clinically beneficial for this pooled population including ET-naïve and ET-resistant patients. Moderate improvement in PFS (pooled HR = 0.686, $P < 0.001$) yet pronounced toxicities (pooled OR = 2.154, $P < 0.001$) were noted in the combination of phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors with fulvestrant. Future studies are warranted to optimize the population and the dosing sequence of these available options.**

Keywords endocrine-resistant; $HR^+/HER2^-$ advanced breast cancer; randomized clinical trials; meta-analysis; targeted therapy

Introduction

As the most prevalent cancer and the leading cause of cancer death among women, breast cancer represents a large burden to global health. A total of 2 088 849 breast cancer cases were diagnosed in 2018 [1]. The hormone receptor-positive human epidermal growth factor receptor 2-negative ($HR^+/HER2^-$) subtype, characterized by the expression of estrogen receptor (ER) and/or progesterone receptor (PR) without HER2 overexpression/amplification, accounts for approximately 70% of breast cancer patients [2]. Nearly 20% – 30% of patients with early stage disease become metastatic throughout the disease course [3].

For decades, hormonally directed therapies, including blockade of estrogen signaling, have been the mainstay treatments for local, advanced, or metastatic $HR^+/HER2^-$ breast cancer. However, some treatment-naïve patients display primary resistance to the treatment, and most of them eventually develop acquired resistance to endocrine therapy (ET). Given the limited options after resistance to previous ET, efforts have been made for the development of novel approaches for addressing endocrine resistance.

Previous studies have provided insights into the underlying mechanisms of endocrine resistance. Initial research identified the upregulation of tyrosine kinase signaling as a common mechanism of endocrine resistance [4]. Subsequent findings revealed crucial events contributing to resistance to ET, including mutations in the gene encoding ER (*ESR1*) [5,6], activation of mammalian target of rapamycin (mTOR) signaling pathway [7], dysregulation

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of cell cycle due to the overactivation of cyclin-dependent kinase 4 and 6 (CDK4/6) [8], epigenetic alterations [9], and somatic changes in genes, such as *PIK3CA*, *AKT1*, *HER2*, and *FGFR1* [10]. With the advancement in the understanding of the biology of $HR^+/HER2^-$ disease, new therapies targeting these resistance drivers have been developed to improve the efficacy of ET in advanced settings, namely, therapies using inhibitors for CDK4/6, mTOR, and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K); other receptor tyrosine kinase inhibitors (TKI); and histone deacetylase (HDAC) inhibitor. Additionally, other targeted therapies that enhance sensitivity to chemotherapy, including monoclonal antibodies and anti-angiogenesis agents, have been tested. However, the data are controversial. Evidence of the effectiveness of these drugs in treating endocrine-resistant breast cancer are needed for informed clinical decision making. In this study, a meta-analysis was performed to summarize available data from randomized clinical trials evaluating the efficacies of these targeted therapies in combination with ET in $HR^+/HER2^-$ advanced breast cancer. Given the apparent heterogeneity among different therapies, drug-specific analyses were carried out respectively.

Methods

Literature search and study selection

Systematic search for relevant studies published in English from 1966 to July 13, 2019 was conducted in the MEDLINE and EMBASE databases, and different combinations of keywords were used as follows: "breast OR mammary," "cancer OR carcinoma OR tumor OR neoplasm OR malignancy," "advanced OR metastatic OR metastasis OR recurrent OR stage IV OR relapse OR progression OR progressive OR resistant OR resistance," "hormone receptor-positive OR HR-positive OR HR^+ OR estrogen/progesterone receptor-positive OR ER/PR-positive OR ER/PR^+," "human epidermal growth factor receptor 2-negative OR HER2-negative OR $HER2^-$," "endocrine therapy OR tamoxifen OR fulvestrant OR aromatase inhibitor OR letrozole OR anastrozole OR exemestane OR selective estrogen receptor modulator OR AI OR nonsteroidal aromatase inhibitor OR steroidal aromatase inhibitor OR SERM OR antiestrogen OR estrogen antagonist OR estrogen blocker OR ET OR SERD OR selective estrogen receptor degrader," and "targeted therapy OR CDK4/6 inhibitor OR palbociclib OR abemaciclib OR ribociclib OR cyclin-dependent kinase inhibitor OR PI3K inhibitor OR phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitor OR mammalian target of rapamycin inhibitor OR mTOR inhibitor OR receptor tyrosine kinase inhibitor OR TKI OR histone deacetylase inhibitor OR HDAC OR monoclonal antibody OR anti-angiogenesis OR anti-angiogenetic OR bevacizumab OR avastin OR endostatin OR VEGFR inhibitor." The titles and abstracts of collected articles were reviewed, and impertinent studies were excluded. In addition, the reference lists of relevant studies were manually examined for the identification of eligible studies. Only the latest versions of duplicate publications were included.

Phase II and III randomized controlled clinical trials (RCTs) were included. The trials included an intervention arm (therapy of interest + standard ET) and control arm (standard ET + placebo). ET included selective estrogen receptor modulators (tamoxifen), aromatase inhibitors (anastrozole, letrozole, and exemestane), selective estrogen receptor downregulators (fulvestrant), and ovarian function inhibition (OFI) for premenopausal women. The study treatment was administered until clinical disease progression, unacceptable toxicity, study withdrawal, completion, or termination. The study population included adult women aged $\geqslant$ 18 years with advanced or metastatic $HR^+/HER2^-$ breast cancer resistant to previous ET in either adjuvant or advanced setting. Non-English articles, reviews, letters to editors, cohort studies, case series, case reports, and laboratory studies were excluded.

Outcomes

For this meta-analysis, the primary outcome was progression-free survival (PFS) defined as the duration from randomization to the first identified disease progression or death from any cause. In studies about CDK4/6 inhibitors, primary outcomes included overall survival (OS), which was defined as the duration from randomization to the date of death. Secondary outcomes were tumor response rates and toxicity. Tumor response rates included (1) objective response rate (ORR) defined as the ratio of patients achieving a complete or partial response as their best response and (2) clinical benefit rate (CBR) defined as the ratio of patients with a complete or partial response or with a stable disease as their best response during treatment as evaluated by the Response Evaluation Criteria in Solid Tumors version 1.1 [11]. Toxicities were reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

Quality assessment

All included RCTs were systematically assessed using the Cochrane Collaboration Risk of Bias Tool. The major items examined were as follows: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity.

Data extraction

Two reviewers extracted data from eligible studies independently. In case of disagreement, a third reviewer was consulted to reach consensus. Data were collected with respect to the following aspects: (1) publication information including the last name of first author, year of publication, and registered name of the trial; (2) basic characteristics of studies, such as sample size, category of therapy, study design, and duration of follow-up; (3) study outcomes, including the median PFS of both arms, hazard ratio (HR), its 95% confidence interval (CI), *P* value, number of cases with objective response, clinical benefit, and ⩾ grade 3 adverse events in each arm. Specifically, for studies about CDK4/6 inhibitors, the median OS (or survival rate at given time point if median OS has not been reached) of both arms, HR, 95% CI, and *P* value were extracted. If data on HR and 95% CI was not available, the number of progression/death events and the size of each group were collected for the calculation of HR as previously described [12].

Statistical analysis

To evaluate the heterogeneity among included studies, Cochran's Q test and Higgins I-squared statistic were used. In case of substantial heterogeneity detected ($P < 0.05$), a random effect model was adopted to pool the estimated effect size (ES). If between-study heterogeneity was absent ($P > 0.05$), a fixed effect model was then applied to the calculation of the pooled ES. The funnel plot and the Egger's bias test were used in evaluating publication bias. All *P* values were two-sided, and $P < 0.05$ was considered statistically significant. All of the analyses were conducted using STATA version 15 (Stata, College Station, TX, USA).

Results

Literature search and study characteristics

The step-wise description of literature screening and study selection is shown in Fig. 1. A total of 26 randomized trials

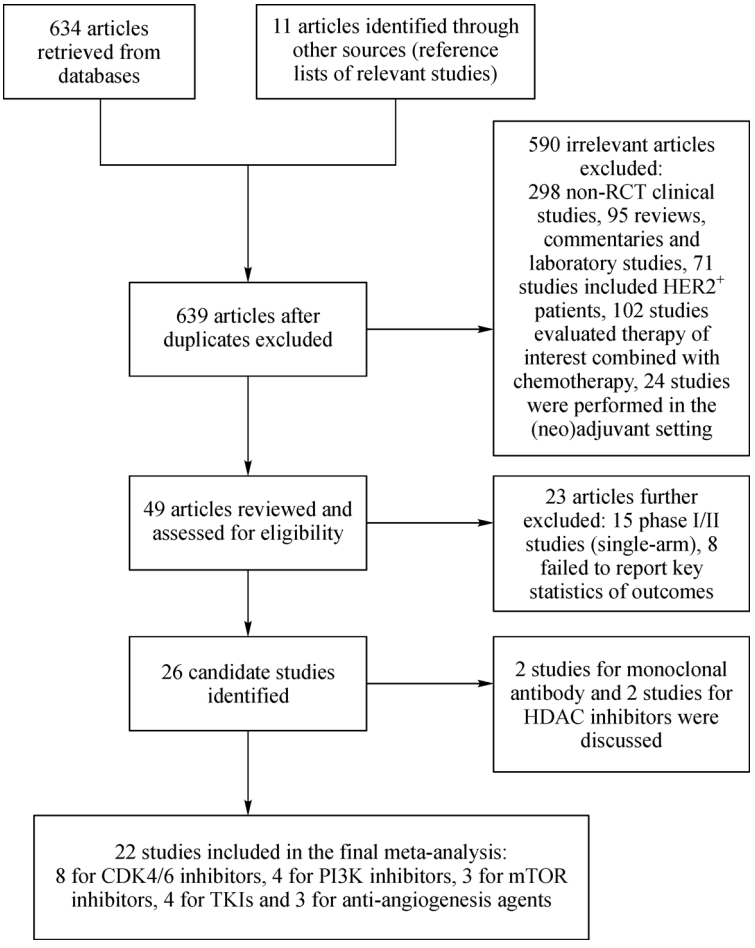

Fig. 1 Flow chart of literature review and study selection process.

were eligible and included, of which eight trials were about CDK4/6 inhibitors, four were about PI3K inhibitors, three were about mTOR inhibitors, four were about TKIs, and three were about anti-angiogenesis agents. Two studies on monoclonal antibody and two studies on HDAC inhibitors were discussed separately. Data on 10 347 patients with $HR^+/HER2^-$ advanced breast cancer were pooled in the meta-analysis. The characteristics of the studies are summarized in Table 1.

Risk-of-bias assessment

Table S1 shows the assessments of individual studies using the Cochrane Collaboration Risk of Bias Tool. Generally, the risk of bias was low, especially in terms of randomization and blinding. However, the BELLA-3 study did not report the procedures of sequence generation and allocation [13], and the study NCT00454805 by Hyams *et al*. failed to specify its blinding status [14]. Data on outcomes was incomplete in the studies by Robertson and Ibrahim [15,16], and the study by Ibrahim was not blinded.

Outcomes

CDK 4/6 inhibitor

For CDK 4/6 inhibitors, eight trials with 4634 patients were included in the present analysis. Data on outcomes were complete. Three trials were on palbociclib, three on ribociclib, and two on abemaciclib. No between-study heterogeneity was detected. The addition of CDK 4/6 inhibitor to ET was associated with a statistically significant reduction in the risk of progression (pooled HR 0.547, 95% CI 0.502–0.596, $P < 0.001$, $I^2 = 0.0\%$, Fig. 2A). We pooled the available data on overall survival (OS) from five trials (Table S2, $N = 2807$) and found treatment with CDK4/6 inhibitor and ET significantly reduced the risk of mortality (pooled HR 0.755, 95% CI 0.671–0.849, $P < 0.001$, $I^2 = 0.0\%$, Fig. S1). On response rate, a statistically significant improvement in ORR was observed after the addition of CDK 4/6 inhibitor compared with standard ET alone (pooled odds ratio (OR) 1.478, 95% CI 1.347–1.622, $P < 0.001$, $I^2 = 43.9\%$, Fig. 2B). Moreover, combining ET with CDK 4/6 inhibitor led to moderate improvement in CBR (pooled OR 1.201, 95% CI 1.115–1.294, $P < 0.001$, $I^2 = 69.2\%$, Fig. 2C). A significant increase in the risk of adverse events (AEs) with grade of $\geqslant 3$ was identified (pooled OR 3.280, 95% CI 2.575–4.180, $P < 0.001$, $I^2 = 85.7\%$, Fig. 2D).

PI3K inhibitor

Four trials with a population of 2379 patients were pooled. SOLAR-1 study enrolled two cohorts, cohort 1 ($N = 341$) comprising of patients with *PIK3CA* mutation while cohort 2 without ($N = 230$) [17]. In FERGI study, part I ($N = 168$) enrolled patients irrespective of their *PIK3CA* status, whereas part II ($N = 61$) only enrolled patients with positive *PIK3CA* mutation [18]. Given that *PIK3CA* mutation status might associate with a higher benefit of PI3K inhibitor, subgroup analysis was performed according to *PIK3CA* mutation status. In the *PIK3CA*-mutated group, the addition of PI3K inhibitor reduced risk in disease progression comparing to ET alone (pooled HR 0.686, 95% CI 0.586–0.803, $P < 0.001$, $I^2 = 42.6\%$, Fig. 3A). ORR was significantly improved (pooled OR 1.844, 95% CI 1.285–2.645, $P = 0.001$, $I^2 = 0.0\%$, Fig. 3B) but not for CBR (pooled OR 1.066, 95% CI 0.756–1.502, $P = 0.715$, $I^2 = 70.2\%$, Fig. 3C). In the group without *PIK3CA*-mutated cancer, PI3K inhibitor plus ET mildly decreased the risk of disease progression (pooled HR 0.819, 95% CI 0.701–0.956, $P = 0.011$, $I^2 = 0.0\%$, Fig. 3D). No benefit in response rate was derived by adding PI3K inhibitors (for ORR, pooled OR 0.942, 95% CI 0.552–1.610, $P = 0.828$, $I^2 = 46.9\%$, Fig. 3E, data were lacking for CBR in *PIK3CA* nonmutant patients in these trials). Furthermore, the addition of PI3K inhibitors to ET was associated with increased risk of toxicity (AE grade $\geqslant 3$, pooled OR 2.154, 95% CI 1.970–2.356, $P < 0.001$, $I^2 = 37.1\%$, Fig. 3F).

mTOR inhibitor

After screening and literature review, three RCTs were identified ($N = 1947$), two of which evaluated everolimus and one evaluated temsirolimus. A trend of risk reduction in disease progression was observed after the addition of mTOR inhibitors (pooled HR 0.606, 95% CI 0.365–1.008, $P = 0.054$, $I^2 = 93.6\%$, Fig. 4A). However, no benefit was shown in ORR (pooled OR 1.943, 95% CI 0.523–7.224, $P = 0.322$, $I^2 = 87.9\%$, Fig. 4B) or CBR (pooled OR 1.389, 95% CI 0.843–2.289, $P = 0.197$, $I^2 = 93.1\%$, Fig. 4C). Meanwhile, the risk of treatment-related toxicity was numerically increased after the addition of mTOR inhibitors (AE grade $\geqslant 3$, pooled OR 2.579, 95% CI 0.739–8.999, $P = 0.137$, $I^2 = 98.0\%$, Fig. 4D). Notably, great between-study heterogeneity was present throughout all outcome analyses.

TKI

Four studies with 608 patients were identified. Two of them assessed gefitinib, an epidermal growth factor receptor (EGFR) inhibitor [19,20]. One trial explored the efficacy of dovitinib and fibroblast growth factor receptor (FGFR) inhibitor, in combination with ET [21]. Another study involved vandetanib, an inhibitor of VEGF, EGFR,

Table 1 Characteristics of eligible studies

Study	Trial name	Size	Therapy	Menopausal status	Study design			
					Intervention group	*N*	Control group	*N*
Cristofanilli, 2016	PALOMA-3	521	CDK4/6 inhibitor	Any	Palbociclib + fulvestrant	345	Fulvestrant	172
Tripathy, 2018	MONALEESA-7	672	CDK4/6 inhibitor	Premenopausal	Ribociclib + TAM/AI + OFI	335	TAM/AI + OFI	337
Sledge, 2017	MONARCH 2	669	CDK4/6 inhibitor	Any	Abemaciclib + fulvestrant	446	Fulvestrant	223
Sonke, 2018	MONALEESA-2	668	CDK4/6 inhibitor	Postmenopausal	Ribociclib + letrozole	334	Letrozole	334
Goetz, 2017	MONARCH 3	493	CDK4/6 inhibitor	Postmenopausal	Abemaciclib + NSAI	328	NSAI	165
Finn, 2016	PALOMA-2	666	CDK4/6 inhibitor	Postmenopausal	Palbociclib + letrozole	444	Letrozole	222
Finn, 2015	PALOMA-1	165	CDK4/6 inhibitor	Postmenopausal	Palbociclib + letrozole	83	Letrozole	77
Slamon, 2018	MONALEESA-3	780	CDK4/6 inhibitor	Postmenopausal	Ribociclib + fulvestrant	484	Fulvestrant	242
Baselga, 2017	BELLA-2	1147	PI3K inhibitor	Postmenopausal	Buparlisib + fulvestrant	576	Fulvestrant	571
Di Leo, 2017	BELLA-3	432	PI3K inhibitor	Postmenopausal	Buparlisib + fulvestrant	289	Fulvestrant	143
Andre, 2019 (Cohort 1)	SOLAR-1 (PIK3CA mutation + cohort)	341	PI3K inhibitor	Postmenopausal	Alpelisib + fulvestrant	169	Fulvestrant	172
Andre, 2019 (Cohort 2)	SOLAR-1 (PIK3CA mutation-cohort)	230	PI3K inhibitor	Postmenopausal	Alpelisib + fulvestrant	115	Fulvestrant	115
Krop, 2016 (PART 1)	FERGI, PART1	168	PI3K inhibitor	Postmenopausal	Piclitisib + fulvestrant	89	Fulvestrant	79
Krop, 2016 (PART 2)	FERGI, PART2, PIK3CA mutation + cohort	61	PI3K inhibitor	Postmenopausal	Piclitisib + fulvestrant	41	Fulvestrant	20
Bachelot, 2012	GINECO	111	mTOR inhibitor	Postmenopausal	Everolimus + tamoxifen	54	Tamoxifen	57
Pritchard, 2013	BOLERO-2	724	mTOR inhibitor	Postmenopausal	Everolimus + exemestane	485	Exemestane	239
Wolff, 2013	HORIZON	1112	mTOR inhibitor	Postmenopausal	Temsirolimus + letrozole	550	Letrozole	553
Mosulino, 2017	NCT01528345	97	TKI	Postmenopausal	Dovitinib + fulvestrant	47	Fulvestrant	50
Cristofanilli, 2010	NCT00077025	93	TKI	Postmenopausal	Gefitinib + anastrozole	43	Anastrozole	50
Osborne, 2011	NCT00229697	289	TKI	Any	Gefitinib + tamoxifen	153	Tamoxifen	136
Clemons, 2014	OCOG ZAMBONEY	129	TKI	Postmenopausal	Vandetanib + fulvestrant	61	Fulvestrant	68
Dickler, 2016	Alliance	343	Anti-angiogenesis	Postmenopausal	Bevacizumab + letrozole	150	Letrozole	153
Hyams, 2013	NCT00454805	62	Anti-angiogenesis	Postmenopausal	Cediranib + fulvestrant	31	Fulvestrant	31
Martín, 2015	LEA	374	Anti-angiogenesis	Postmenopausal	Bevacizumab + letrozole/fulvestrant	190	Letrozole/fulvestrant	184
Jiang, 2019	NCT02482753	365	HDAC inhibitor	Postmenopausal	Tucidinostat + exemestane	244	Exemestane	121
Yardley, 2013	ENCORE 301	130	HDAC inhibitor	Postmenopausal	Entinostat + exemestane	64	Exemestane	66
Robertson, 2013	NCT00626106	156	Monoclonal antibody	Postmenopausal	Ganitumab + fulvestrant/exemestane	106	Fulvestrant/exemestane	50
Ibrahim, 2011	/	110	Monoclonal antibody	Postmenopausal	AS1402 + letrozole	56	Letrozole	53

(*Continued*)

Study	PFS (month)							Objective response (*N*)		Clinical benefit (*N*)		Adverse event (Grade 3/4, *N*)	
	Intervention group	Control group	HR	95% CI		*P* value	Follow-up	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group
				LL	UL								
Cristofanilli, 2016	9.5	4.6	0.46	0.36	0.59	0.0001	8.9	66	15	231	69	251	38
Tripathy, 2018	23.8	13	0.55	0.44	0.69	0.0001	19.2	137	100	265	235	257	100
Sledge, 2017	16.4	9.3	0.553	0.449	0.681	0.001	19.5	157	36	322	125	267	51
Sonke, 2018	25.3	16	0.56	0.43	0.72	0.0001	15.3	136	92	266	243	271	108
Goetz, 2017	NR	14.7	0.54	0.41	0.72	0.000021	17.8	158	57	256	118	180	35
Finn, 2016	27.6	14.5	0.58	0.46	0.72	0.001	23	187	77	377	156	336	54
Finn, 2015	20.2	10.2	0.488	0.319	0.748	0.0004	29.6	36	27	68	47	63	16
Slamon, 2018	20.5	12.8	0.593	0.48	0.732	0.001	20.4	157	52	340	152	392	16
Baselga, 2017	6.9	5	0.78	0.67	0.89	0.00021	37.6	68	44	252	240	447	192
Di Leo, 2017	3.9	1.8	0.67	0.53	0.84	0.0003	16.3	22	3	96	29	177	47
Andre, 2019 (Cohort 1)	11	5.7	0.65	0.5	0.85	0.001	20	45	22	104	78	216	102
Andre, 2019 (Cohort 2)	7.4	5.6	0.85	0.58	1.25	0.794	20	Unknown	Unknown	Unknown	Unknown		
Krop, 2016 (PART 1)	6.6	5.1	0.74	0.52	1.06	0.096	17.5	7	5	22	14	54	22
Krop, 2016 (PART 2)	5.4	10	1.07	0.53	2.18	0.84	12.9	3	1	8	7	15	7
Bachelot, 2012	8.6	4.5	0.54	0.36	0.81	0.0021	23.7	5	5	33	24	32	35
Pritchard, 2013	7.8	3.2	0.45	0.38	0.54	0.0001	18	61	4	249	63	330	13
Wolff, 2013	9	8.9	0.9	0.76	1.07	0.25	9.5	151	149	245	254	203	134
Mosulino, 2017	5.5	5.5	0.68	0.41	1.14	Unknown	20.5	13	5	31	21	32	19
Cristofanilli, 2010	14.7	8.4	0.55	0.32	0.94	Unknown	13.8	1	6	21	17	6	2
Osborne, 2011	10.9	8.8	0.84	0.59	1.18	0.314	Unknown	13	15	67	57	63	21
Clemons, 2014	5.8	4.8	0.94	0.64	1.36	0.73	Unknown	0	3	9	17	14	9
Dickler, 2016	20.2	15.6	0.75	0.59	0.96	0.016	42	68	49	78	80	79	23
Hyams, 2013	8	4	0.867	0.45	1.669	0.669	8	4	1	13	13	21	10
Martín, 2015	19.3	14.4	0.83	0.65	1.06	0.125	23.7	58	32	146	124	97	24
Jiang, 2019	7.4	3.8	0.75	0.58	0.98	0.033	13.9	45	11	114	43	184	20
Yardley, 2013	4.28	2.27	0.73	0.5	1.07	0.11	26.4	4	3	18	17	31	17
Robertson, 2013	3.9	5.7	1.17	0.91	1.5	0.44	Unknown	5	4	22	10	41	11
Ibrahim, 2011	Unknown	Unknown	0.947	0.496	1.805	Unknown	Unknown	7	14	39	41	34	35

CDK, cyclin-dependent kinase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; HDAC, histone deacetylase; TAM, tamoxifen; AI, aromatase inhibitor; NSAI, non-steroidal aromatase inhibitor; OFI, ovarian function inhibition.

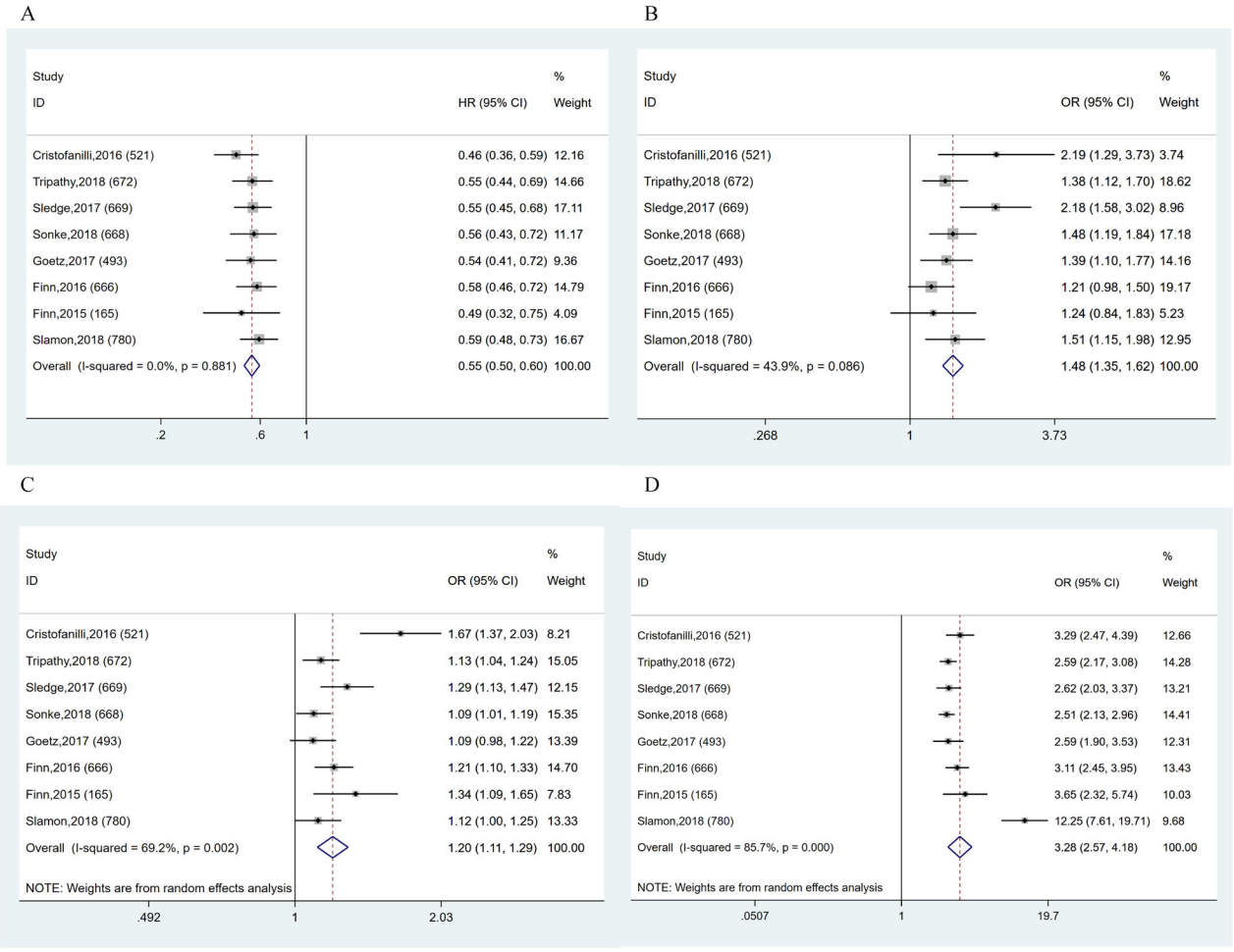

Fig. 2 Forest plots of the analyses about efficacy of cyclin-dependent kinase (CDK) 4/6 inhibitors plus endocrine therapy (ET) compared with ET alone in terms of progression-free survival (PFS, A), objective response rate (ORR, B), clinical benefit rate (CBR, C), and toxicity (D). Fixed (A, B) and random (C, D) effect models were used as the pooling method.

and RET signaling [22]. The addition of TKI to ET resulted in a statistically significant reduction in the risk of progression (pooled HR 0.787, 95% CI 0.638–0.971, $P = 0.026$, $I^2 = 0.1\%$, Fig. S2A). The addition of TKI was not associated with benefit in ORR (pooled OR 0.770, 95% CI 0.243–2.441, $P = 0.658$, $I^2 = 66.3\%$, Fig. S2B) or CBR (pooled OR 1.130, 95% CI 0.931–1.371, $P = 0.217$, $I^2 = 57.7\%$, Fig. S2C), but was related to the elevated risk of AEs (AE grade ⩾ 3, pooled OR 2.225, 95% CI 1.682–2.943, $P < 0.001$, $I^2 = 0.0\%$, Fig. S2D).

Anti-angiogenesis agents

Three RCTs were included in the analysis ($N = 779$), two of which were trials (Alliance and LEA study) on bevacizumab [23,24] and one on cediranib [14]. A statistically significant decrease in the risk of progression was observed after the addition of anti-angiogenesis agents (pooled HR 0.794, 95% CI 0.672–0.938, $P = 0.007$, $I^2 = 0.0\%$, Fig. S3A). A mild improvement in ORR (pooled OR 1.582, 95% CI 1.255–1.993, $P < 0.001$, $I^2 = 0.0\%$, Fig. S3B) was observed, but not in CBR (pooled OR 1.079, 95% CI 0.965–1.207, $P = 0.182$, $I^2 = 0.0\%$, Fig. S3C). The addition of anti-angiogenetic targeted therapy was associated with statistically higher risk of toxicity (AE grade ⩾ 3, pooled OR 3.433, 95% CI 2.657–4.435, $P < 0.001$, $I^2 = 40.0\%$, Fig. S3D).

Other targeted therapies combining with ET

Two RCTs with consistent findings on monoclonal antibodies were reviewed. In a trial of 156 patients with HR$^+$/HER$^-$ ABC, Robertson *et al.* evaluated addition of ganitumab, a blocker of insulin-like growth factor-1 receptor (IGF-1R), to ET [16]. PFS, tumor response rates and incidence of toxicities did not differ significantly

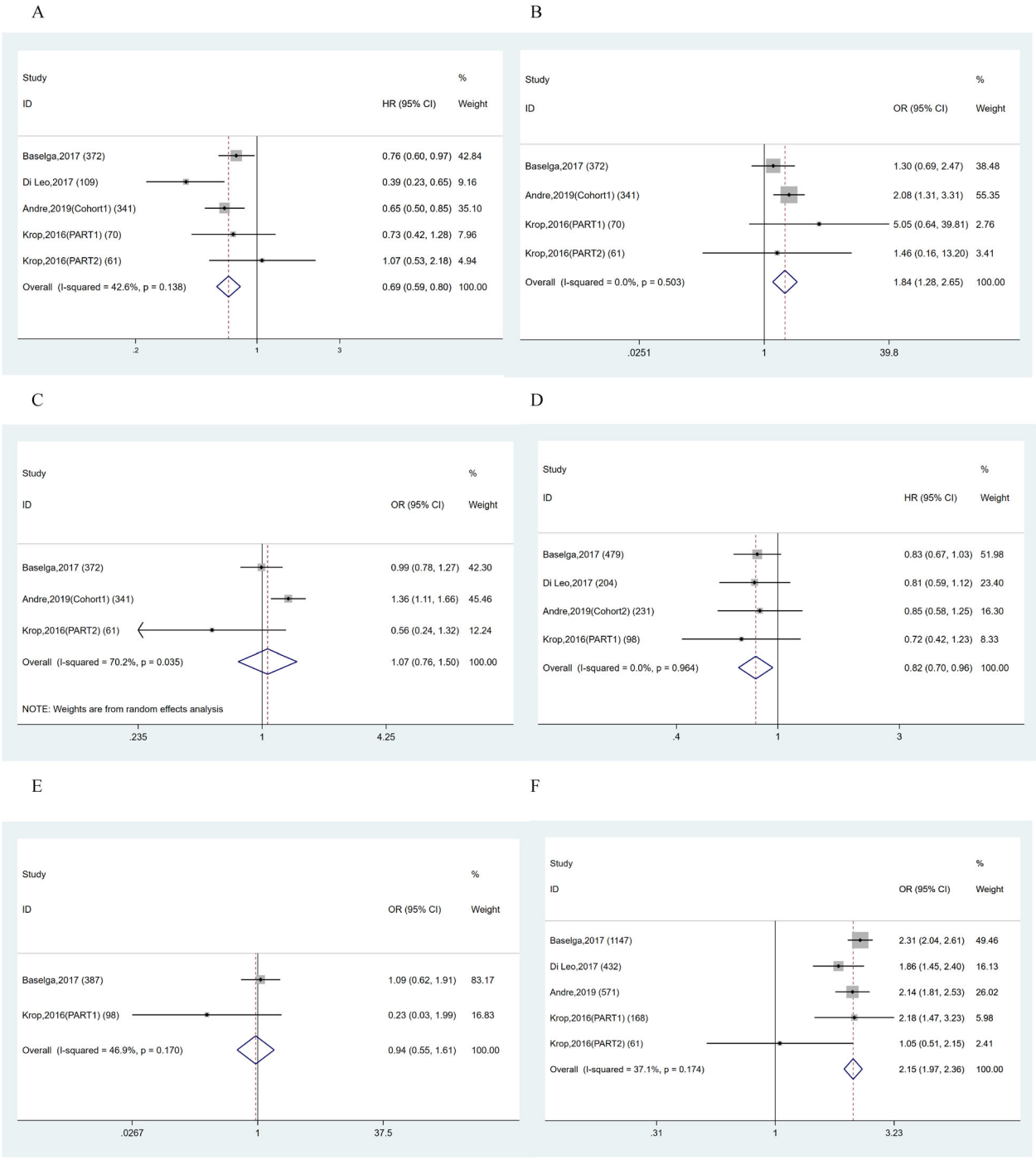

Fig. 3 Forest plots of the analyses about efficacy of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitors plus endocrine therapy (ET) compared with ET alone in terms of progression-free survival (PFS, A), objective response rate (ORR, B), and clinical benefit rate (CBR, C) in *PIK3CA* mutant patients. For *PIK3CA* nonmutant patients, pooled effect sizes regarding PFS (D) and ORR (E) were shown. Toxicity (F) of PI3K inhibitors was analyzed in the total nonselected population. Fixed (A, B, D, E, F) and random (C) effect models were used as the pooling methods.

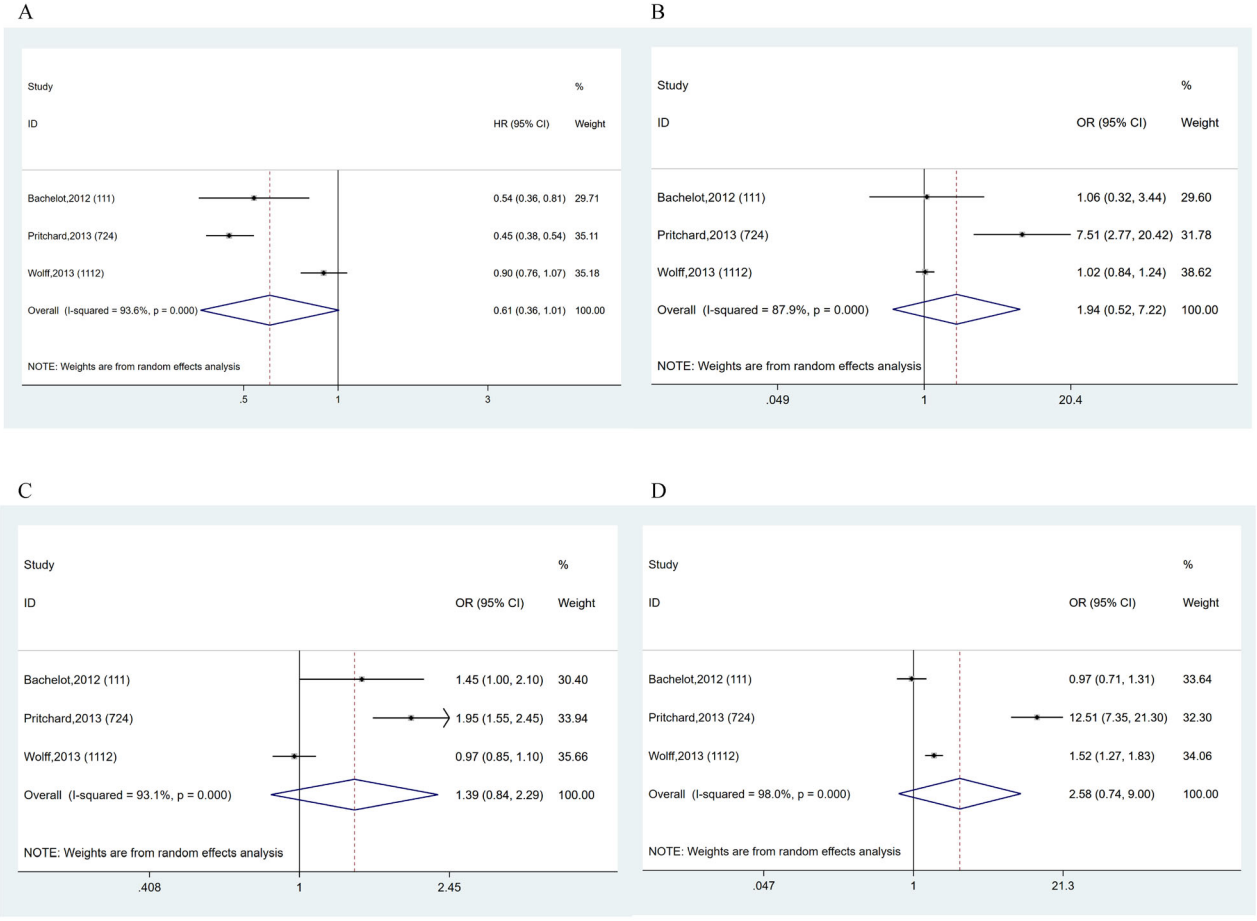

Fig. 4 Forest plots of the analyses about efficacy of mammalian target of rapamycin (mTOR) inhibitors plus endocrine therapy (ET) compared with ET alone in terms of progression-free survival (PFS, A), objective response rate (ORR, B), clinical benefit rate (CBR, C), and toxicity (D). Random effect model was used as the pooling method.

between two arms, but overall survival was poor in the ganitumab group. No further development was performed thereafter. Another trial by Ibrahim *et al.* (N = 110) assessing AS1402 targeting the aberrantly glycosylated antigen MUC1 was terminated in advance due to the trend toward early disease progression in the experimental arm, confirmed later in their final analysis [15].

Two RCTs on HDAC inhibitors were identified. Yardley *et al.* (N = 130) demonstrated a trend toward improved PFS (HR 0.73, 95% CI 0.5–1.07, P = 0.11) by adding entinostat to exemestane in ER + ABC, with moderately higher rates of grade 3/4 toxicities [25]. One phase III trial (N = 365) evaluating tucidinostat plus exemestane in advanced hormone receptor-positive breast cancer was recently published [26]. The addition of tucidinostat improved the median PFS from 3.8 months to 7.4 months (HR 0.75, 95% CI 0.58–0.98, P = 0.033) with increased risk of toxicities (OR 4.562, 95% CI 3.038–6.852).

Discussion

For decades the paradigm in management of HR$^+$/HER2$^-$ advanced breast cancer has been endocrine therapy with various mechanisms [27]. Inevitably, at some point during the disease course, patients develop endocrine resistance regardless of initial response. Despite the limited efficacy and apparent toxicities of chemotherapy, it remains the only option after the failure of ET regimens. Numerous molecular signaling pathways underpinning endocrine resistance were discovered, and new compounds targeting these pathways have been developed to overcome resistance to ET. In recent years, these targeted therapies have been evaluated in clinical studies, but inconsistent findings have been obtained. In this meta-analysis and systematic review, we collected and pooled data from randomized trials assessing the efficacy of targeted therapies and ET in comparison with therapies using ET

alone in $HR^+/HER2^-$ ABC. Analyses were performed based on the separate categories of therapy in order that therapy-specific evidence for clinical practice could be obtained.

CDK 4/6 inhibitor

Cell cycle modulation using CDK 4/6 inhibitors to block the transition from G_1 into S phase are potent in $HR^+/HER2^-$ ABC [28]. Our analysis validated that adding CDK4/6 inhibitors to ET significantly improved survival and tumor response, but this effect was accompanied with moderately elevated risk of toxicities. Given the high quality of trials, data set with a large sample size, and absence of inter-study heterogeneity, the results were considered to be robust, providing further evidence to support clinical application. Based on the notable benefit in PFS [29–32], CDK 4/6 inhibition has been approved in the first/second line treatment of $ER^+/HER2^-$ ABC in combination with AI or fulvestrant. Despite their efficacy, toxicities, most commonly hematologic toxicity, should be considered (neutropenia 40%–80%, leukopenia 28%–50%) [19,32–35]. Abemaciclib displayed a distinct safety profile, and neutropenia, diarrhea, nausea, and fatigue were the most common AEs [32,36]. The high incidence of neutropenia was not complicated by infections and was manageable generally.

mTOR inhibitor

mTOR signaling is important to the mediation of resistance to endocrine treatment. mTOR inhibitors include rapalogues (everolimus and temsirolimus) and ATP-competitive inhibitors, and the versatility of the former has been demonstrated in phase III clinical trials. However, in our analysis, no significant benefit in PFS and tumor response was observed after the addition of mTOR inhibitors to ET. The results should be interpreted with caution, given the marked heterogeneity among the three trials. The majority of the participants in the HORIZON study [37] were endocrine therapy-naïve (about 60%), whereas GINECO [38] and BOLERO-2 [39] studies enrolled patients who progressed or recurred on previous nonsteroidal aromatase inhibitors (NSAIs). In the GINECO and BOLERO-2 studies, everolimus was administered daily continuously. In the HORIZON study, temsirolimus was dosed intermittently, and this procedure possibly led to the suboptimal inhibition of mTOR signaling. Although everolimus has been approved for patients who are resistant to NSAIs, further research is needed to identify predictive markers for the selection of the right population.

PI3K inhibitor

Preclinical studies have indicated regulatory feedback loops involving PI3K/Akt/mTOR pathway and found that these loops eventually lead to the failure of potent mTOR inhibitors. Approaches targeting mTOR pathway upstream are theoretically attractive. PI3K inhibitors under clinical evaluation include pan-PI3K [7,13,18] and isoform-specific [17] inhibitors. Given that *PIK3CA* mutation, as shown in SOLAR-1 and BELLE-3 study, can be a strong indicator of sensitivity to PI3K inhibitor [17], we performed subgroup analysis based on *PIK3CA* mutation status, which indicated that adding PI3K inhibitors to fulvestrant significantly improves PFS in *PIK3CA* mutant patients rather than the nonmutant patients. Moderate heterogeneity was present among involved studies. The possible reasons are the differences in efficacy and safety profiles among the classes of PI3K inhibitors. Given the limited benefit and increased toxicity, further research is needed to identify the optimal population and dosing sequence.

TKI and anti-angiogenesis agents and monoclonal antibody

For compounds targeting oncogenic cellular receptors, such as EGFR, FGFR, VEGFR, and IGF-1R, regardless of small-molecule kinase inhibitor or monoclonal antibody, we derived similar results from pooled data. Mild reduction in risk of disease progression and increased risk of AEs were observed with TKI plus ET. Findings were similar to those of anti-angiogenesis agents. Studies on various monoclonal antibodies suggested disappointing results, and little improvement in clinical outcome was observed. Thus, future studies on biomarkers discriminating potential responders are warranted.

HDAC inhibitor

Another promising approach to overcome endocrine resistance in HR^+/HER^- ABC is to re-sensitize cancer cells to estrogen depletion by using HDAC inhibitors. Previous work showed epigenetic modifications, such as histone deacetylation, can induce the loss or suppressed expression of hormone receptors in breast cancer cells [40]. *In vitro* and *in vivo*, HDAC inhibitors can increase the expression of ER and aromatase restoring the sensitivity of breast cancer cells to hormonal blockade [40]. Adding entinostat or tucidinostat to exemestane improved the median PFS, and significant improvements were observed in patients who were resistant to NSAI [25,26]. Increased protein acetylation in peripheral blood mononuclear cells might indicate sensitivity to entinostat [25].

Conclusions

The addition of CDK 4/6 inhibitors to ET significantly improved clinical outcomes with manageable toxicities in $HR^+/HER2^-$ ABC.

For other targeted therapies, predictive biomarkers need to be explored for the identification of responders. Future studies are warranted to optimize the dosing sequence of these available options.

Compliance with ethics guidelines

Wenjie Zhu and Binghe Xu declare no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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