ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Identifying the optimal therapeutics for patients with hormone receptor-positive, HER2-positive advanced breast cancer: a systematic review and network meta-analysis

Y. Wang[1†], H. Xu[1†], Y. Han[1], Y. Wu[1], Q. Sa[1] & J. Wang[1*]

[1] Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Available online xxx

Introduction: Hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-positive (HER2+) breast cancer is a distinct subtype with different prognosis and response to treatment. HER2-targeted therapy is currently recommended for patients with HR+/HER2+ advanced breast cancer. However, there is debate over which drugs to add on the basis of HER2 blockade yield the optimal efficacy. This systematic review and network meta-analysis was conducted to solve the problem.

Methods: Eligible randomized controlled trials (RCTs) comparing different interventions in HR+/HER2+ metastatic breast cancer were included. The outcomes of interest included progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (TRAEs). Pooled hazard ratios or odds ratios with credible intervals (CrIs) were calculated to estimate the predefined outcomes. The optimal therapeutics were identified by comparing the surface under the cumulative ranking curves (SUCRA).

Results: Totally, 23 literatures of 20 RCTs were included. Regarding PFS, significant differences were detected between single or dual HER2 blockade plus endocrine therapy (ET) versus ET alone and dual HER2 blockade plus ET versus physician's choice. Trastuzumab, pertuzumab plus chemotherapy significantly improved PFS than trastuzumab plus chemotherapy (hazard ratio 0.69, 95% CrI 0.50-0.92). The SUCRA values suggested the relatively better efficacy of dual HER2-targeted therapy plus ET (86%-91%) than chemotherapy (62%-81%) in prolonging PFS and OS. The HER2 blockade-containing regimens showed similar safety profiles in eight documented TRAEs.

Conclusions: Prominent status of dual-targeted therapy for patients with HR+/HER2+ metastatic breast cancer was revealed. Compared with chemotherapy-containing regimens, the ET-containing ones showed better efficacy and similar safety profiles, which could be recommended in clinical practice.

Key words: metastatic breast cancer, hormone receptor positive, human epidermal growth factor receptor 2 positive, efficacy, network meta-analysis

INTRODUCTION

The past two decades have witnessed the emergence of precision medicine in breast cancer, which is guided by the status of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2).[1] Tumors that simultaneously express HR and HER2 constitute approximately one-tenth of all subtypes of breast cancer.[2] It is believed that HR/HER2 co-positive breast cancer is an entity with relatively distinct biological behaviors and has different clinical outcome.[3] Within HER2-positive (HER2+) breast cancer, two large studies confirmed that HR-positive (HR+) disease had better disease-free survival (DFS) and overall survival (OS) compared with HR− disease.[4,5] And the relation was independent of some clinicopathological features and treatment patterns.[6]

Due to the unique characteristics of HR+/HER2+ breast cancer, the standard care and response to treatment is also different from other molecular subtypes. In the neoadjuvant setting, targeted therapy combined with chemotherapy is widely adopted in clinical practice. The NeoSphere study suggested that the pathological complete response rate of HR+ subgroup was significantly lower than

*Correspondence to: Dr Jiayu Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. Tel: +86-13641238489; Fax: +86-87788120

E-mail: drwangjy@126.com (J. Wang).

†These authors contributed equally to this work.

its counterparts in patients with HER2+ tumors.[7] As for the adjuvant management, other than targeted therapy and chemotherapy, the endocrine therapy (ET) is also emphasized in some patients. Plus, the ExteNET trial indicated that extended adjuvant neratinib for 1 year brought greater benefit in HR+ patients than in HR− patients.[8]

When it comes to the advanced stage, the optimal therapeutics is debated. But the certainty is that HER2-targeted therapy plus chemotherapy still occupies an essential position.[9,10] Apart from traditional anti-HER2 agents such as trastuzumab and pertuzumab, both the tyrosine kinase inhibitors (TKIs) and antibody−drug conjugates (ADCs) show promising prospects, which are also recommended by present guidelines.[11,12] Unlike HER2-enriched subtype, ET is of equal importance for patients with HR+ tumors. As the research moves along, the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have attracted extensive attention due to their satisfactory efficacy and acceptable security.[13]

In fact, based on anti-HER2 treatments, a lot of efforts have been put into exploring the de-escalation strategies regarding chemotherapy by emphasizing on ET.[14] Take the neoadjuvant setting as an example, both the TBCRC 006 and NA-PHER2 trials have demonstrated the feasibility of dual HER2 blockade and hormonal therapy in treating primary HR+/HER2+ breast cancer.[15,16] For patients with metastasis, many studies attempt to reveal the efficacy of different HER2-targeted agents and ET combinations without chemotherapy.[17-20] The recently published SYSUCC-002 trial was the first research to conduct a head-to-head comparison between trastuzumab plus ET or chemotherapy in the first-line setting. As expected, noninferior survival outcomes and well-tolerated toxicity were observed.[21]

Given that there are multiple treatment algorithms in treating HR+/HER2+ metastatic breast cancer, the optimal choice for this subtype remains unknown. Meanwhile, whether the chemotherapy-free strategy is practicable has garnered great attention. Thus, we conducted this study by synthesizing current evidence to shed light on the aforementioned issues.

METHODS

The protocol of this systematic review and network meta-analysis was registered on PROSPERO (ID: CRD42022379784) in advance. We reported this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement (PRISMA-NMA).[22]

Study identification and inclusion criteria

We searched comprehensively from major databases including PubMed, Embase, the Cochrane Library and ClinicalTrials.gov before 5 September 2022. A combination of keywords related to 'breast cancer', 'metastasis', 'HER2', 'HR', 'positive', 'anti-tumor drugs' and 'randomized controlled trial (RCT)' was used to identify eligible literatures. Thereinto, the antitumor drugs covered all the mainstay agents in treating breast cancer, including chemotherapy, ET, targeted therapy and immunotherapy. In addition, all the abstracts presented at international conferences during the last 3 years were manually browsed, comprising the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), San Antonio Breast Cancer Symposium (SABCS) and Chinese Society of Clinical Oncology (CSCO). The detailed searching strategy is elaborated in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101216.

Two independent reviewers (Y. Wang and H. Xu) carried out the searching process. Phase II or III RCTs that evaluated different interventions in patients with HR+/HER2+ advanced breast cancer were regarded as potentially eligible. The primary studies were excluded in the following circumstances: (i) participants included patients with unclear HR or HER2 status; (ii) comparison was conducted between the same kind of regimens; (iii) no data regarding survival outcomes or adverse effects were reported; (iv) studies that were non-RCTs or exploratory analysis of previously included RCTs. Titles and abstracts of the retrieved publications were firstly screened for eligibility, after which the full texts were further evaluated. Any discrepancies were discussed and resolved by consensus.

Data collection and quality assessment

The following basic data regarding the trial name, first author, publication year, sample size, current treatment lines for metastatic disease, interventions and controls were extracted and documented using Excel software. Of particular note, based on the original study protocols, the treatment lines of each trial were categorized into the first line only and more than the first line. The outcomes of interest were also recorded. The primary endpoint was progression-free survival (PFS), defined as the time interval between randomization and the first recurrence, progression, or death. The secondary endpoint was OS, defined as the time interval between randomization and death due to any cause. For the aforementioned survival data, the hazard ratios along with the corresponding 95% confidence intervals (CIs) were collected to conduct further analysis. The profile of treatment-related adverse events (TRAEs) was another outcome, and six included studies reported the related data.[17-21,23]

The assessment of risk of bias was carried out using the revised Cochrane risk-of-bias tool (RoB 2).[24] A total of five domains were evaluated: (i) the randomization process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome and (v) selection of the reported result. The overall bias of each study was the sum of the aforementioned five aspects. Then, each study was rated as 'high risk', 'low risk', or 'some concerns' by two co-authors separately.

Statistical analysis

This study was conducted basing on a Bayesian random-effects model by using the 'gemtc' and 'rjags' packages of R software version 4.1.1 (R Development Core Team,

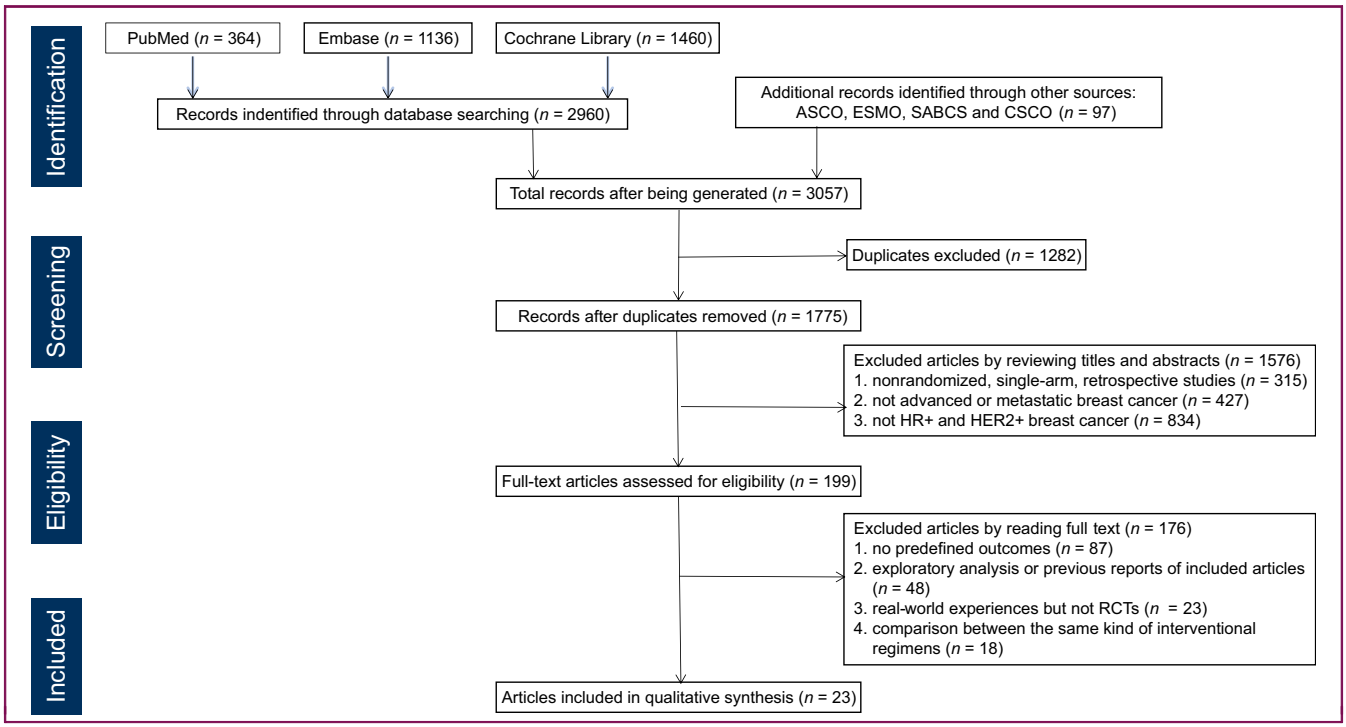

Figure 1. The flow chart of the detailed literature-screening process.
ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology; ESMO, European Society of Medical Oncology; HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor positive; RCTs, randomized controlled trials; SABCS, San Antonio Breast Cancer Symposium.

Boston, MA). The Markov chain Monte Carlo simulation method was used to implement the network meta-analysis. Three independent chains were set to fit the model with the amount of adaptation and simulation iterations as 10 000 and 50 000, respectively. Trace plots, density plots and the Brooks—Gelman—Rubin diagnosis plots were used to visualize the convergence of iterations. Hazard ratios and odds ratios with 95% credible intervals (CrIs) were generated to pool the estimates of survival outcomes and TRAEs, respectively. Network plots were drawn to illustrate the mutual relationships of direct and indirect comparisons. The synthesized outcomes were displayed using league tables and forest plots. The ranking probability of different interventions was assessed by calculating the surface under the cumulative ranking curve (SUCRA), which indicated the increasing efficacy of regimens from worst to best (0% to 100% correspondingly). A P value <0.05 was considered statistically significant. Lastly, the heterogeneity across the included studies was quantified by I^2 statistics and Cochrane's Q test. $I^2 > 50\%$ or $P < 0.10$ for Q test suggested the existence of conspicuous heterogeneity.

RESULTS

Study selection and baseline characteristics

In total, 3057 search results were identified. Carrying out the screening process shown in Figure 1, 23 publications of 20 RCTs were included into the final analysis. The quality assessment of each study is displayed in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101216. Table 1 presents the basic information and survival data of included studies. Among them, the triple-arm studies were divided into two cohorts.[17,23] No exact sample size of HR+/HER2+ breast cancer patients was reported in the BOLERO-3 study.[25] Thus, apart from the BOLERO-3 study, there were 2163 and 1985 patients in the interventional and control groups for PFS analysis, respectively. For OS analysis, the sample size was 908 and 862 for the interventional and control groups, respectively.

To facilitate the further analysis, we integrated and classified the interventions into 14 categories (Figure 2A). The included agents of TKIs were lapatinib, afatinib, neratinib and pyrotinib, while ADC only represented trastuzumab emtansine (T-DM1). For different endpoints, the enrolled RCTs were different. As for PFS, Figure 2A and B displayed 14 and 8 kinds of regimens involving 20 and 10 direct comparisons in all treatment lines and the first line only, respectively. The network plot of OS in all treatment lines is shown in Figure 2C, which consisted of eight interventions involving seven direct comparisons.

Efficacy

PFS and OS were two predefined endpoints of efficacy in this analysis. Regarding PFS, the pairwise comparisons between every two regimens are displayed in the upper right part of Table 2. The significant differences appeared in the comparisons of TKI or trastuzumab plus ET versus ET alone (hazard ratio 0.68, 95% CrI 0.51-0.91; hazard ratio 0.69, 95% CrI 0.51-0.93). As for the regimens containing dual-targeted agents, trastuzumab and pertuzumab plus ET or chemotherapy showed remarkable advantages than the

Table 1. The baseline characteristics and outcomes of the included RCTs

Study	Author, published year	Regimen (no. of TPBC patients)		Median PFS for TPBC (HR, 95% CI)	Median OS for TPBC (HR, 95% CI)	Current treatment line for advanced TPBC
		Interventional group	Control group			
EMILIA[39,40]	Verma et al., 2012. Diéras et al., 2017	T-DM1 (282)	Lapatinib + capecitabine (263)	NA versus NA (0.72, 0.58-0.91)	NA versus NA (0.62, 0.46-0.85)	First or more lines
TH3RESA[41,42]	Krop et al., 2014, 2016	T-DM1 (208)	Physician's choice (103/105)[a]	NA versus NA (0.56, 0.41-0.76)	NA versus NA (0.71, 0.52-0.97)	Second or more lines
Johnston et al.[43]	Johnston et al., 2009	Lapatinib + letrozole (111)	Letrozole (108)	8.2 versus 3.0 months (0.71, 0.53-0.96)	33.3 versus 32.3 months (0.74, 0.5-1.1)	First line
CALGB 40302[44]	Burstein et al., 2014	Lapatinib + fulvestrant (24)	Fulvestrant (30)	5.9 versus 3.3 months (1.23, 0.69-2.18)[b]	NA	First or more lines
ALTERNATIVE[17,c]	Johnston et al., 2021	Lapatinib + trastuzumab + AI (120)	Trastuzumab + AI (117)	11 versus 5.6 months (0.62, 0.45-0.88)	46.0 versus 40.0 months (0.60, 0.35-1.04)	First to second lines
ALTERNATIVE[17,c]	Johnston et al., 2021	Lapatinib + AI (118)	Trastuzumab + AI (117)	8.3 versus 5.6 months (0.85, 0.62-1.17)	45.1 versus 40.0 months (0.91, 0.55-1.51)	First to second lines
WJOG6110B/ ELTOP[45]	Takano et al., 2017	Lapatinib + capecitabine (27)	Trastuzumab + capecitabine (27)	NA versus NA (0.80, 0.46-1.37)	NA	First to third lines
NCT02422199[46]	Ma et al., 2019	Pyrotinib + capecitabine (37)	Lapatinib + capecitabine (43)	NA versus NA (0.36, 0.19-0.66)	NA	First to third lines
PHOEBE[47]	Xu et al., 2021	Pyrotinib + capecitabine (62)	Lapatinib + capecitabine (58)	NA versus NA (0.63, 0.38-1.06)	NA	First to third lines
NEfERT-T[48]	Awada et al., 2016	Neratinib + paclitaxel (128)	Trastuzumab + paclitaxel (123)	12.7 versus 12.9 months (1.05, 0.78-1.42)	NA	First line
LUX-Breast 1[49]	Harbeck et al., 2016	Afatinib + vinorelbine (101/ 99)[a]	Trastuzumab + vinorelbine (44)	NA versus NA (1.22, 0.77-1.95)	NA versus NA (0.96, 0.58-1.60)	First or more lines
monarcHER[23,c]	Tolaney et al., 2020	Abemaciclib + trastuzumab + fulvestrant (79)	Chemotherapy + trastuzumab (79)	8.3 versus 5.7 months (0.67, 0.45-1.00)	NA	Third or more lines
monarcHER[23,c]	Tolaney et al., 2020	Abemaciclib + trastuzumab (79)	Chemotherapy + trastuzumab (79)	5.7 versus 5.7 months (0.94, 0.64-1.38)	NA	Third or more lines
TAnDEM[20]	Kaufman et al., 2009	Trastuzumab + anastrozole (103)	Anastrozole (104)	4.8 versus 2.4 months (0.63, 0.47-0.84)	28.5 versus 23.9 months (NA, NA-NA)	First line
eLEcTRA[19]	Huober et al., 2012	Trastuzumab + letrozole (26)	Letrozole (31)	14.1 versus 3.3 months (0.67, 0.35-1.29)	NA	First line
PERTAIN[18]	Rimawi et al., 2018	Trastuzumab + pertuzumab + AI (129)	Trastuzumab + AI (129)	18.9 versus 15.8 months (0.65, 0.48-0.89)	NA	First line
SYSUCC-002[21]	Hua et al., 2022	Trastuzumab + endocrine therapy (196)	Trastuzumab + chemotherapy (196)	19.2 versus 14.8 months (0.88, 0.71-1.09)	33.9 versus 32.5 months (0.82, 0.65-1.04)	First line
AVEREL[50]	Gianni et al., 2013	Trastuzumab + docetaxel + bevacizumab (115)	Trastuzumab + docetaxel (107)	NA versus NA (0.81, 0.59-1.11)	NA	First line
BOLERO-3[25]	André et al., 2013	Trastuzumab+ vinorelbine + everolimus (NA)	Trastuzumab + vinorelbine (NA)	NA versus NA (0.93, 0.72-1.20)	NA	First to third lines
NCT00294996[51]	Baselga et al., 2014	Trastuzumab + paclitaxel + NPLD (75)	Trastuzumab + paclitaxel (81)	NA versus NA (1.01, 0.68-1.51)	NA versus NA (0.96, 0.65-1.42)	First line
CLEOPATRA[11,52]	Swain et al., 2015, 2020	Trastuzumab + pertuzumab + docetaxel (189)	Trastuzumab + docetaxel (199)	NA versus NA (0.73, 0.58-0.91)	NA versus NA (0.74, 0.58-0.96)	First line
PUFFIN[53]	Xu et al., 2020	Trastuzumab + pertuzumab + docetaxel (53)	Trastuzumab + docetaxel (48)	NA versus NA (0.59, 0.35-0.99)	NA	First line

AI, aromatase inhibitors; CI, confidence interval; HR, hazard ratio; NA, not available; NPLD, non-pegylated liposomal doxorubicin; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trials; T-DM1, trastuzumab emtansine; TPBC, triple-positive breast cancer.

[a]The sample size was documented separately since the number of patients included in the analyses of PFS and OS in TH3RESA and LUX-Breast 1 studies was different.

[b]The hazard ratio reported in the CALGB 40302 study was for fulvestrant over fulvestrant + lapatinib.

[c]The ALTERNATIVE study and monarcHER study were divided into two cohorts, respectively, because the comparisons were among three kinds of regimens.

mono-endocrine agents (hazard ratio 0.45, 95% CrI 0.27-0.76; hazard ratio 0.55, 95% CrI 0.31-0.93); TKI, trastuzumab plus ET also displayed better efficacy than ET (hazard ratio 0.44, 95% CrI 0.26-0.74). Compared with physician's choice, both dual HER2 blockade (trastuzumab + TKI or pertuzumab) plus ET and ADC significantly improved PFS (hazard ratio 0.41, 95% CrI 0.18-0.95; hazard ratio 0.43, 95% CrI 0.19-0.96; hazard ratio 0.56, 95% CrI 0.37-0.84). The combination consisting of trastuzumab, pertuzumab and chemotherapy obviously yielded better efficacy than the regimens without pertuzumab (hazard ratio 0.69, 95% CrI 0.50-0.92). To sum up, HR+/HER2+ breast cancer patients treated with anti-HER2 agents displayed obviously better PFS compared with ET only. In addition, dual HER2 blockade showed a clear trend in improving PFS compared with single-targeted therapy.

Then, the SUCRA values were calculated to identify the optimal therapeutics for patients. Table 3 shows the ranking sequence of 14 regimens, among which dual HER2 blockade (including trastuzumab plus TKI or pertuzumab) combined with ET was the most effective (89% and 87%) for PFS of all lines. Trastuzumab, CDK4/6 inhibitors plus ET as well as trastuzumab, pertuzumab plus chemotherapy were slightly inferior to the abovementioned regimens (76% and 75%).

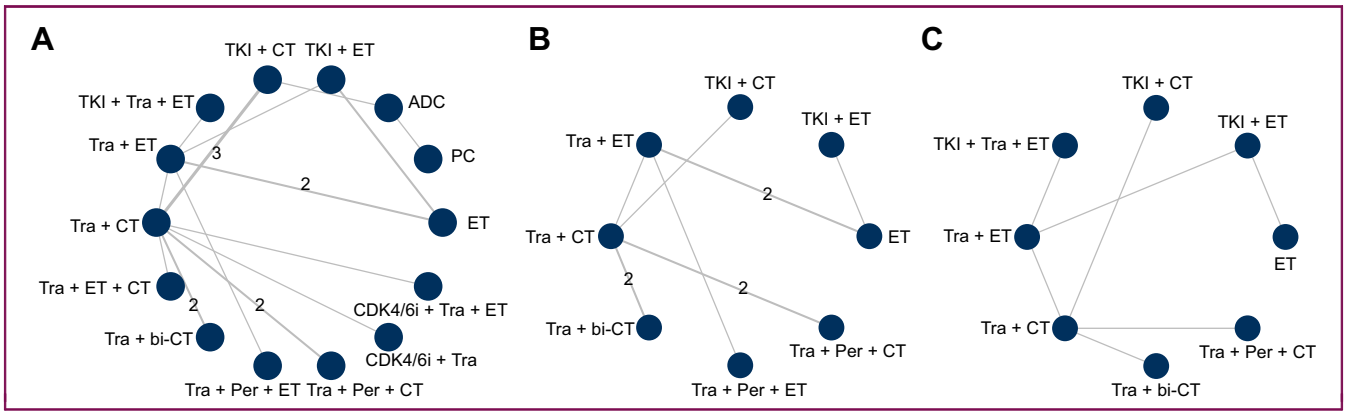

Figure 2. The network plots of all predefined survival outcomes. Network plots of PFS of all lines (A), PFS of first line (B) and OS (C). Every node represents one kind of intervention while the lines denote direct comparisons, on which the numbers mean the quantities of RCTs. Most of the head-to-head comparisons occurred only once with no explicitly marked number. ADC, antibody—drug conjugate; bi-CT, dual-drug chemotherapy; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, chemotherapy; ET, endocrine therapy; PC, physician's choice; Per, pertuzumab; TKI, tyrosine kinase inhibitor; Tra, trastuzumab.

Chemotherapy plus single HER2 blockade (30% and 27%), physician's choice (11%) and endocrine monotherapy (10%) were the most likely to rank the bottom.

To eliminate the impact of treatment lines for metastatic disease on PFS, we further filtered the RCTs exclusively implemented in the first-line setting. The pairwise analyses are shown in the lower left part of Table 2. Pooled results suggested the better tendency of ET, trastuzumab with or without pertuzumab over ET (hazard ratio 0.64, 95% CrI 0.42-0.98; hazard ratio 0.42, 95% CrI 0.21-0.81). Similar to the results with mixed treatment lines, the SUCRA values in the first-line setting shown in Table 3 also indicated the superiority of dual HER2 blockade and ET over other interventions in prolonging PFS (91%). Chemotherapy-based dual anti-HER2 regimens tended to perform poorer (81%) compared with the ET-based ones.

As for OS, the pairwise comparisons showed no salient difference in all interventions (Table 4). The SUCRA values revealed that patients treated with trastuzumab, TKI plus ET were the most likely to obtain the best OS (86%), followed by trastuzumab, pertuzumab plus chemotherapy (62%). Then came the combinations of TKI or trastuzumab and ET (61% and 52%). Chemotherapy with single HER2 blockade (30%-38%) and ET (34%) ranked the worst (Table 3).

Safety

Totally, eight kinds of TRAEs of all grades could be analyzed in this study, including diarrhea, fatigue, nausea, vomiting, arthralgia, headache, cough and anorexia. The included interventions were further classified for the convenience of analyzing. There was no significant difference in all collected TRAEs (Supplementary Figures S2-S9, available at https://doi.org/10.1016/j.esmoop.2023.101216). Particularly, on the basis of HER2-targeted therapy, the addition of ET showed similar safety profile to the chemotherapy-containing regimens.

DISCUSSION

For patients with HER2+ breast cancer, the anti-HER2 therapy plays an indispensable role in treatment. The introduction of trastuzumab, the first monoclonal antibody of HER2, brings great benefit in both early[26] and metastatic[27] HER2+ breast cancer. Subsequent studies suggested that dual HER2 blockade further improved the clinical efficacy. Trastuzumab, pertuzumab combined with chemotherapy is regarded as a standard regimen in all settings for HER2+ breast cancer.[7,11,28] In addition, monoclonal antibody plus TKIs such as trastuzumab-lapatinib in early stage[29] and trastuzumab-pyrotinib in advanced stage[30] were also proved to be effective. A recent meta-analysis by Chen et al.[31] focused on the HER2 inhibitors as neoadjuvant therapy for triple-positive breast cancer by synthesizing 13 RCTs, which consolidated the status of double-targeted therapy. Here we came to a similar conclusion that dual-targeted therapy was better than single HER2 blockade in prolonging PFS and OS from the pairwise comparisons and SUCRA values. Trastuzumab plus pertuzumab or small molecular TKIs all displayed satisfactory efficacy when combined with chemotherapy or ET. And, this tendency was visible regarding different study endpoints.

Different from the HR− population, HR+ patients could derive benefits from ET. Considering the conspicuous adverse events of chemotherapy, replacing the chemotherapy with ET to obtain similar efficacy and avoid great toxicity is under study. The present meta-analysis attempted to explore whether and when the chemotherapy-free strategies could be applied to HR+/HER2+ breast cancer patients. Considering that there were few head-to-head studies, both direct and indirect comparisons were conducted in this study. The pooled results indicated that HER2-targeted therapy displayed better efficacy when combined with ET than with chemotherapy in improving PFS and OS. And the superiority of chemotherapy-free regimens remained regardless of prior treatment lines. The regimens composed by single or dual anti-HER2 agents all showed the same tendency. On the basis of trastuzumab, both pertuzumab and TKIs were allowed to form the regimen. Regarding safety, existing data did not detect differences among the included interventions by comparing eight kinds of TRAEs. To summarize, our study revealed good efficacy

Table 2. The Pairwise comparisons among different regimens of PFS

Traditional ET	1.06 (0.49-2.28)	0.59 (0.31-1.14)	**0.68 (0.51-0.91)**	0.82 (0.48-1.38)	**0.44 (0.26-0.74)**	**0.69 (0.51-0.93)**	0.79 (0.50-1.25)	0.73 (0.40-1.33)	0.70 (0.41-1.22)	**0.45 (0.27-0.76)**	**0.55 (0.31-0.93)**	0.74 (0.38-1.45)	0.53 (0.27-1.03)
—	**PC**	**0.56 (0.37-0.84)**	0.64 (0.29-1.41)	0.77 (0.44-1.32)	**0.41 (0.18-0.95)**	0.65 (0.32-1.34)	0.74 (0.40-1.38)	0.69 (0.33-1.43)	0.66 (0.33-1.34)	**0.43 (0.19-0.96)**	0.51 (0.25-1.01)	0.70 (0.32-1.55)	0.50 (0.22-1.09)
—	—	**ADC**	1.14 (0.60-2.21)	1.37 (0.95-1.98)	0.74 (0.36-1.52)	1.17 (0.66-2.10)	1.33 (0.84-2.11)	1.23 (0.68-2.24)	1.18 (0.68-2.05)	0.76 (0.38-1.55)	0.92 (0.52-1.57)	1.25 (0.64-2.45)	0.89 (0.46-1.74)
0.71 (0.42-1.22)	—	—	**TKI + ET**	1.20 (0.69-2.05)	0.64 (0.37-1.12)	1.02 (0.74-1.40)	1.16 (0.71-1.85)	1.08 (0.58-1.97)	1.03 (0.58-1.81)	0.67 (0.39-1.11)	0.81 (0.45-1.39)	1.10 (0.55-2.14)	0.78 (0.39-1.52)
0.76 (0.33-1.78)	—	—	1.07 (0.40-2.85)	**TKI + CT**	0.53 (0.29-1.01)	0.85 (0.55-1.35)	0.97 (0.73-1.29)	0.90 (0.56-1.46)	0.86 (0.56-1.31)	0.56 (0.30-1.02)	0.67 (0.43-1.00)	0.91 (0.52-1.59)	0.65 (0.37-1.14)
—	—	—	—	—	**TKI + Tra + ET**	1.59 (1.02-2.45)	1.81 (1.03-3.18)	1.67 (0.85-3.34)	1.60 (0.85-3.06)	1.03 (0.57-1.91)	1.25 (0.65-2.33)	1.70 (0.82-3.56)	1.21 (0.57-2.52)
0.64 (0.42-0.98)	—	—	0.89 (0.45-1.76)	0.84 (0.40-1.71)	—	**Tra + ET**	1.14 (0.79-1.62)	1.05 (0.63-1.77)	1.01 (0.63-1.63)	0.65 (0.43-1.00)	0.79 (0.48-1.24)	1.07 (0.59-1.92)	0.76 (0.42-1.40)
0.73 (0.38-1.40)	—	—	1.02 (0.45-2.39)	0.95 (0.56-1.60)	—	1.14 (0.70-1.90)	**Tra + CT**	0.93 (0.64-1.36)	0.89 (0.65-1.21)	0.57 (0.33-1.00)	**0.69 (0.50-0.92)**	0.94 (0.59-1.51)	0.67 (0.41-1.09)
—	—	—	—	—	—	—	—	**Tra + ET + CT**	0.96 (0.58-1.56)	0.62 (0.32-1.21)	0.75 (0.45-1.19)	1.02 (0.55-1.87)	0.72 (0.39-1.34)
0.65 (0.31-1.39)	—	—	0.90 (0.37-2.33)	0.85 (0.45-1.66)	—	1.01 (0.55-1.94)	0.89 (0.61-1.33)	—	**Tra + bi-CT**	0.65 (0.35-1.21)	0.78 (0.49-1.18)	1.06 (0.60-1.86)	0.75 (0.42-1.35)
0.42 (0.21-0.81)	—	—	0.58 (0.25-1.39)	0.55 (0.22-1.34)	—	0.65 (0.39-1.11)	0.57 (0.28-1.17)	—	0.65 (0.27-1.44)	**Tra + Per + ET**	1.21 (0.63-2.19)	1.64 (0.78-3.37)	1.16 (0.57-2.41)
0.50 (0.23-1.07)	—	—	0.70 (0.27-1.73)	0.66 (0.33-1.23)	—	0.79 (0.40-1.45)	0.69 (0.46-1.00)	—	0.77 (0.43-1.31)	1.20 (0.51-2.69)	**Tra + Per + CT**	1.36 (0.78-2.43)	0.96 (0.56-1.75)
—	—	—	—	—	—	—	—	—	—	—	—	**CDK4/6i + Tra**	0.71 (0.35-1.40)
—	—	—	—	—	—	—	—	—	—	—	—	—	**CDK4/6i + Tra + ET**

Data are represented as hazard ratios and corresponding 95% credible intervals (CrIs). The upper right part displays the PFS of all lines, while the lower left part displays the PFS of first line. For PFS of all lines and OS, hazard ratios <1 favored the column-defining treatment. For PFS of first line, hazard ratios <1 favored the row-defining treatment. Significant results are in bold.

ADC, antibody—drug conjugate; bi-CT, dual-drug chemotherapy; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, chemotherapy; ET, endocrine therapy; OS, overall survival; PC, physician's choice; Per, pertuzumab; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; Tra, trastuzumab.

Table 3. The SUCRA values for PFS of all lines, PFS of the first line and OS

Interventions	SUCRA values of different outcomes		
	PFS of all lines	PFS of the first line	OS
TKI + Tra + ET	0.89	—	0.86
Tra + Per + ET	0.87	0.91	—
CDK4/6i + Tra + ET	0.76	—	—
Tra + Per + CT	0.75	0.81	0.62
ADC	0.66	—	—
TKI + ET	0.51	0.43	0.61
Tra + ET	0.48	0.55	0.52
Tra + bi-CT	0.47	0.53	0.38
Tra + ET + CT	0.42	—	—
CDK4/6i + Tra	0.40	—	—
Tra + CT	0.30	0.36	0.30
TKI + CT	0.27	0.33	0.38
PC	0.11	—	—
Traditional ET	0.10	0.08	0.34

ADC, antibody—drug conjugate; bi-CT, dual-drug chemotherapy; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, chemotherapy; ET, endocrine therapy; PC, physician's choice; Per, pertuzumab; TKI, tyrosine kinase inhibitor; Tra, trastuzumab.

and acceptable toxicity of dual HER2 blockade combined with hormonal therapy.

The SYSUCC-002 trial was the only included RCT which was conducted in a head-to-head manner comparing the efficacy and safety between anti-HER2 therapy plus ET or chemotherapy in patients with HR+/HER2+ metastatic breast cancer.[21] The final results reported that the ET group acquired a median PFS of 19.2 months, which was non-inferior to the chemotherapy group (hazard ratio 0.88, 95% CI 0.71-1.09, $P < 0.0001$). A remarkable higher tendency of TRAEs was also observed in the chemotherapy group. One outstanding problem in this study was that its design did not contain pertuzumab due to the lack of accessibility at that time. Hence, the noninferiority of ET versus chemotherapy basing on dual anti-HER2 agents could not be verified by the SYSUCC-002 trial. Obviously, our present analysis fills the gap since it further supports the efficacy of dual HER2 blockade with ET. Besides, the pooled outcomes indicated that this regimen could be implemented from the first line to the posterior line. In conclusion, for HR+/HER2+ breast cancer patients, the chemotherapy-free HER2-targeted therapy is viable when metastasis occurs for the first time. It is better to defer the chemotherapy-based regimen until the disease has progressed. By this way, the efficacy and toxicity could be better balanced especially for the elderly patients.

Similar to the significance of adding anti-HER2 agents for HER2+ breast cancer patients, the addition of CDK4/6 inhibitors to traditional ET has dramatically improved survival for patients with HR+ breast cancer.[32] The monarcHER study firstly explored the efficacy of using CDK4/6 inhibitors in heavily pretreated HR+/HER2+ advanced breast cancer patients.[23] The results showed a median PFS of 8.3 months for the trastuzumab plus fulvestrant and CDK4/6 inhibitors arm compared to 5.7 months for the control group (hazard ratio 0.67, 95% CI 0.45-1.00) with tolerable toxicity. Our study conducted indirect comparisons between the regimens with or without CDK4/6 inhibitors. We found that the therapeutic strategy in the monarcHER study ranked high among all the interventions, second only to regimens containing dual HER2 blockade. The substantial advantages of CDK4/6 inhibitors on the basis of traditional ET were demonstrated. Apart from abemaciclib, the efficacy of other CDK4/6 inhibitors such as palbociclib[33] and ribociclib[34] was also investigated in the similar setting, all of which showed promising clinical activity. In light of the satisfactory outcomes of dual inhibiting CDK4/6 and HER2 confirmed by previous RCTs and our meta-analysis, we speculate that the combination of CDK4/6 inhibitor, ET and dual HER2 blockade will bring greater benefit than current regimens. Actually, the PATINA trial is ongoing to compare the efficacy and safety of adding palbociclib to dual HER2 blockade and ET maintenance after induction treatment for HR+/HER2+ metastatic breast cancer.[35]

Extensive crosstalk exists between the HER2 and HR signaling pathways, as previous studies demonstrated.[36] The bi-directional interaction contributes to the resistance to either HER2-targeted therapy or ET, thus further promoting disease progression. The simultaneous inhibition of HER2 and HR may reverse the drug resistance, exerting synergistic antitumor activity and prolonging the survival for HR+/HER2+ breast cancer patients.[37] The sophisticated mechanisms of the HER2/HR crosstalk precipitate the regimens involving dual blockade. Moreover, CDK4 and CDK6 act as the downstream of estrogen receptor and HER2 pathway, whose inhibitors can improve the sensitivity to anti-HER2 therapy.[38] This shows that the combination of anti-HER2 agents, traditional hormonal therapies and CDK4/6 inhibitors could generate promising efficacy on the level of mechanism.

Table 4. The Pairwise comparisons among different regimens of OS

Traditional ET							
1.35 (0.66-2.76)	**TKI + ET**						
1.04 (0.24-4.42)	0.77 (0.22-2.70)	**TKI + CT**					
2.02 (0.54-7.79)	1.50 (0.49-4.65)	1.94 (0.53-7.17)	**TKI + Tra + ET**				
1.22 (0.43-3.52)	0.91 (0.42-1.98)	1.18 (0.43-3.25)	0.60 (0.27-1.35)	**Tra + ET**			
1.01 (0.29-3.50)	0.75 (0.27-2.02)	0.96 (0.44-2.11)	0.50 (0.18-1.39)	0.82 (0.43-1.58)	**Tra + CT**		
1.05 (0.25-4.40)	0.78 (0.23-2.67)	1.00 (0.35-2.86)	0.52 (0.14-1.82)	0.86 (0.32-2.27)	1.05 (0.51-2.14)	**Tra + bi-CT**	
1.35 (0.33-5.40)	1.00 (0.30-3.34)	1.29 (0.46-3.57)	0.67 (0.19-2.26)	1.10 (0.43-2.81)	1.34 (0.68-2.57)	1.28 (0.49-3.43)	**Tra + Per + CT**

Data are represented as hazard ratios and corresponding 95% credible intervals (CrIs). For PFS of all lines and OS, hazard ratios <1 favored the column-defining treatment. For PFS of first line, hazard ratios <1 favored the row-defining treatment. Significant results are in bold.

ADC, antibody—drug conjugate; bi-CT, dual-drug chemotherapy; CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor; CT, chemotherapy; ET, endocrine therapy; OS, overall survival; PC, physician's choice; Per, pertuzumab; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; Tra, trastuzumab.

Inevitably, limitations also existed in this study. Firstly, there were differences between the included studies, such as the demographics of patients and prior treatment lines. Heterogeneity was unavoidable though we did a subgroup analysis. Secondly, to facilitate the comparison, we further classified each agent investigated in the RCTs into different kinds of interventions. In this way, the specific drug in the combinations with optimal efficacy could not be identified. Lastly, the SUCRA value should be interpreted with caution since it could merely reflect the intervention rankings instead of the degree of absolute discrepancy. When applying the findings to clinical practice, the resistance to ET, drug accessibility and safety profiles should be taken into account. In light of lacking sufficient direct evidence, more head-to-head studies comparing the efficacy of chemotherapy and ET for metastatic HR+/HER2+ breast cancer are warranted in the future.

CONCLUSION

Our finding shows that for advanced HR+/HER2+ breast cancer, the regimens containing dual HER2 blockade displayed better efficacy, either combining with chemotherapy or ET. On the basis of dual HER2 blockade, the addition of ET ranked higher than adding chemotherapy regarding efficacy. In conclusion, our study indicated that chemotherapy-free regimens were feasible in clinical practice.

ACKNOWLEDGEMENTS

We would like to thank Bin Lu from Peking Union Medical College (PUMC) for his kind support in the statistical work.

FUNDING

This work was supported by CAMS Innovation Fund for Medical Sciences (CIFMS) [grant number 2021-I2M-1-014].

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The data presented in this study are available on request from the corresponding author.

REFERENCES

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747-752.
2. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055.
3. Vici P, Pizzuti L, Natoli C, et al. Triple positive breast cancer: a distinct subtype? *Cancer Treat Rev*. 2015;41(2):69-76.
4. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Impact of hormone receptor status on patterns of recurrence and clinical outcomes among patients with human epidermal growth factor-2-positive breast cancer in the National Comprehensive Cancer Network: a prospective cohort study. *Breast Cancer Res*. 2012;14(5):R129.
5. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29(25):3366-3373.
6. Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast*. 2015;24(suppl 2):S26-S35.
7. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.
8. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700.
9. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
10. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36(26):2736-2740.
11. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530.
12. Chien AJ, Rugo HS. Tyrosine kinase inhibitors for human epidermal growth factor receptor 2-positive metastatic breast cancer: is personalizing therapy within reach? *J Clin Oncol*. 2017;35(27):3089-3091.
13. The Lancet. Breast cancer targeted therapy: successes and challenges. *Lancet*. 2017;389(10087):2350.
14. Prat A, Baselga J. Dual human epidermal growth factor receptor 2 (HER2) blockade and hormonal therapy for the treatment of primary HER2-positive breast cancer: one more step toward chemotherapy-free therapy. *J Clin Oncol*. 2013;31(14):1703-1706.
15. Rimawi MF, Mayer IA, Forero A, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. *J Clin Oncol*. 2013;31(14):1726-1731.
16. Gianni L, Bisagni G, Colleoni M, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. *Lancet Oncol*. 2018;19(2):249-256.
17. Johnston SRD, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer: updated results of ALTERNATIVE. *J Clin Oncol*. 2021;39(1):79-89.
18. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. *J Clin Oncol*. 2018;36(28):2826-2835.
19. Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. *Breast*. 2012;21(1):27-33.
20. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. 2009;27(33):5529-5537.
21. Hua X, Bi XW, Zhao JL, et al. Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for patients with hormone receptor-positive and HER2-positive metastatic breast cancer (SYSUCC-002). *Clin Cancer Res*. 2022;28(4):637-645.

22. 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(11):777-784.
23. Tolaney SM, Wardley AM, Zambelli S, et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2020;21(6):763-775.
24. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
25. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2014;15(6):580-591.
26. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-3752.
27. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-792.
28. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
29. Guarneri V, Dieci MV, Griguolo G, et al. Trastuzumab-lapatinib as neoadjuvant therapy for HER2-positive early breast cancer: survival analyses of the CHER-Lob trial. *Eur J Cancer*. 2021;153:133-141.
30. Xu B, Yan M, Ma F, et al. LBA19 Pyrotinib or placebo in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer (PHILA): a randomized phase III trial. *Ann Oncol*. 2022;33:S1387.
31. Chen D, Jin L, Xu Y, Bhandari A, Wang O. ErbB inhibitors as neoadjuvant therapy for triple-positive breast cancer: a network meta-analysis. *Am J Transl Res*. 2021;13(11):12129-12140.
32. Schettini F, Giudici F, Giuliano M, et al. Overall survival of CDK4/6-inhibitor-based treatments in clinically relevant subgroups of metastatic breast cancer: systematic review and meta-analysis. *J Natl Cancer Inst*. 2020;112(11):1089-1097.
33. Ciruelos E, Villagrasa P, Pascual T, et al. Palbociclib and trastuzumab in HER2-positive advanced breast cancer: results from the phase II SOLTI-1303 PATRICIA trial. *Clin Cancer Res*. 2020;26(22):5820-5829.
34. Spring LM, Clark SL, Li T, et al. Phase 1b clinical trial of ado-trastuzumab emtansine and ribociclib for HER2-positive metastatic breast cancer. *NPJ Breast Cancer*. 2021;7(1):103.
35. Loibl S, Metzger O, Mandrekar SJ, et al. PATINA: a randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (MBC). *Ann Oncol*. 2018;29:viii121.
36. Wu VS, Kanaya N, Lo C, Mortimer J, Chen S. From bench to bedside: what do we know about hormone receptor-positive and human epidermal growth factor receptor 2-positive breast cancer? *J Steroid Biochem Mol Biol*. 2015;153:45-53.
37. Montagna E, Colleoni M. Hormonal treatment combined with targeted therapies in endocrine-responsive and HER2-positive metastatic breast cancer. *Ther Adv Med Oncol*. 2019;11:1758835919894105.
38. Agostinetto E, Debien V, Marta GN, Lambertini M, Piccart-Gebhart M, de Azambuja E. CDK4/6 and PI3K inhibitors: a new promise for patients with HER2-positive breast cancer. *Eur J Clin Invest*. 2021;51(7):e13535.
39. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791.
40. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732-742.
41. Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(7):689-699.
42. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017;18(6):743-754.
43. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27(33):5538-5546.
44. Burstein HJ, Cirrincione CT, Barry WT, et al. Endocrine therapy with or without inhibition of epidermal growth factor receptor and human epidermal growth factor receptor 2: a randomized, double-blind, placebo-controlled phase III trial of fulvestrant with or without lapatinib for postmenopausal women with hormone receptor-positive advanced breast cancer-CALGB 40302 (Alliance). *J Clin Oncol*. 2014;32(35):3959-3966.
45. Takano T, Tsurutani J, Takahashi M, et al. A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP. *Breast*. 2018;40:67-75.
46. Ma F, Ouyang Q, Li W, et al. Pyrotinib or lapatinib combined with capecitabine in HER2-Positive metastatic breast cancer with prior taxanes, anthracyclines, and/or trastuzumab: a randomized, phase II study. *J Clin Oncol*. 2019;37(29):2610-2619.
47. Xu B, Yan M, Ma F, et al. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(3):351-360.
48. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol*. 2016;2(12):1557-1564.
49. Harbeck N, Huang CS, Hurvitz S, et al. Afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one previous trastuzumab treatment (LUX-Breast 1): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2016;17(3):357-366.
50. Gianni L, Romieu GH, Lichinitser M, et al. AVEREL: a randomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. *J Clin Oncol*. 2013;31(14):1719-1725.
51. Baselga J, Manikhas A, Cortés J, et al. Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel in HER2-positive metastatic breast cancer. *Ann Oncol*. 2014;25(3):592-598.
52. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.
53. Xu B, Li W, Zhang Q, et al. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (PUFFIN): a phase III, randomized, double-blind, placebo-controlled study. *Breast Cancer Res Treat*. 2020;182(3):689-697.