Immunol Genet J, Vol. 8, No. 1, 2025, pp.3-21 DOI: https://doi.org/10.18502/igj.v8i1.17990

Review Article

# Efficacy and Safety of Small-Molecule Human Epidermal Growth Factor Receptor 2 (HER2)-Targeting Tyrosine Kinase Inhibitor-Containing Regimens for Metastatic HER2-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials

**Amin Pastaki Khoshbin[1,2,3], Farzaneh Darbeheshti[4,5], Amin Doosti-Irani[6], Mahsa Keshavarz-Fathi[1,3], Mohammad Ali Mansournia[7*]**

[1] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[2] *School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[4] *Department of Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[5] *Medical Genetics Network (MeGeNe), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[6] *Department of Epidemiology, School of Public Health and Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran*
[7] *Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

Received: 12 August 2024; Accepted: 28 November 2024

## Abstract

To simultaneously compare the efficacy and safety of small-molecule Human Epidermal Growth Factor Receptor 2 (HER2)-targeting tyrosine kinase inhibitor (TKI)-containing regimens for metastatic HER2-positive breast neoplasm. MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of Science, and Scopus databases were systematically searched to identify randomized clinical trials (RCT) that investigated the difference in overall survival (OS), progression-free survival (PFS), overall response (OR), recurrence in central nervous system/brain metastasis (RCNS), total and grade 3 or 4 adverse events (AE), diarrheal AEs, and cardiac AEs of small-molecule HER2-targeting TKI-containing regimens in women with metastatic HER2-positive breast carcinoma. The revised Cochrane risk-of-bias tool for randomized trials (RoB2) was used to evaluate the risk of bias in the included studies. When applicable, pooled network estimates were synthesized by frequentist random-effect network meta-analysis using Stata MP Software (version 14). Twenty-three studies comprising 7497 eligible patients were included. In all, 17 small-molecule anti-HER2 TKI (Lapatinib, Neratinib, Afatinib, Pyrotinib, and Tucatinib)-containing and 10 other regimens were compared. In terms of increasing OS, the Pyrotinib/Capecitabine combination ranked first best among small-molecule HER2-targeting TKI-containing regimens. In terms of PFS, the Pyrotinib/Capecitabine combination prolonged PFS in comparison with all other small-molecule anti-HER2 TKI-containing regimens in the network. In the corresponding network, Pyrotinib/Capecitabine and Tucatinib/Trastuzumab/Capecitabine combinations ranked first best and second best among small-molecule anti-HER2 TKI-containing regimens. In terms of AE, the Tucatinib/Trastuzumab/Capecitabine combination ranked the highest for AE occurrence. Pyrotinib/Capecitabine and Tucatinib/Trastuzumab/Capecitabine combinations seemed to be the most efficacious small-molecule HER2-targeting TKI-containing regimens in metastatic HER2-positive breast cancer.

**Keywords:** Breast Neoplasms; HER2; Network Meta-Analysis; Protein Kinase Inhibitors

***Corresponding Author:** Mohammad Ali Mansournia
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
E-mail: mansournia_ma@sina.tums.ac.ir

**How to cite this article**
*Pastaki Khoshbin A, Darbeheshti F, Doosti-Irani A, Keshavarz-Fathi M, Mansournia MA. Efficacy and Safety of Small-Molecule Human Epidermal Growth Factor Receptor 2 (HER2)-Targeting Tyrosine Kinase Inhibitor-Containing Regimens for Metastatic HER2-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials. Immunol Genet J, 2025; 8(1): 3-21.* DOI: https://doi.org/10.18502/igj.v8i1.17990

## Introduction

Breast cancer is the most common incidence cancer and responsible for the largest number of cancer mortality among women globally. The number of new cases and deaths has been growing all over the world, with a more significant rise in the less-developed countries (1, 2). Metastatic disease comprises nearly 6% of all breast cancer cases at the initial diagnosis, and distant site recurrence occurs in about 12% of patients in previously treated non-metastatic breast cancer patients (3, 4). The higher stage is the most predictive of survival, with 5-year disease survival rates of 98% and 27% for stage I and Stage IV disease, respectively (3). Although survival has improved for all breast cancer stages, the improvement was less pronounced for metastatic disease (5), reflecting the need for more efficacious treatment options for metastatic breast cancer. Therefore, metastatic breast cancer is a burdensome health condition that deserves further research endeavor. Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer is a distinct subtype of breast neoplasms (6). HER2 is a transmembrane receptor tyrosine kinase belonging to the Epidermal Growth Factor Receptor (EGFR) family. It is encoded by erbb2 proto-oncogene, which is overexpressed in 15-20% of invasive adenocarcinomas of the breast. HER2 overexpression is associated with augmented proliferative and invasion potentials of neoplastic cells, more frequent axillary lymph node involvement, distant metastasis, and poorer prognosis (6, 7). However, HER2 overexpression enables its therapeutic targeting, which is one of the breakthroughs in the field of breast cancer therapy. Thus far, HER2 has been directly targeted in breast cancer by two main approved classes of medications. Antibody-based therapeutic targeting of HER2 encompasses conventional monoclonal antibodies against HER2, such as Trastuzumab (8) and Pertuzumab (9), and antibody-drug conjugates, including Ado-Trastuzumab Emtansine (T-DM1) (10) and Fam-Trastuzumab-Deruxtecan-Nxki (11). Another strategy of HER2 targeting is using small-molecule Tyrosine Kinase Inhibitors (TKI) that block the initiation of signaling cascades by HER2 molecule homodimers or heterodimers with other members of EGFR family (12). Approved drugs of this class for use in HER2-positive breast cancer constitute Lapatinib (13), Neratinib (14), Pyrotinib (15), and Tucatinib (16). Small-molecule HER2 targeting TKIs provide some potential advantages over antibody-based therapeutic targeting. Anti-HER2 monoclonal antibodies bind specifically to extracellular domains of HER2, whereas most small-molecule HER2 targeting TKIs block the cytoplasmic domain of other EGFR family receptors along with HER2, thus simultaneously inhibiting signal transduction from HER2 heterodimers with other EGFR family members (12, 17). In contrast to small-molecule HER2 targeting TKIs, monoclonal antibodies have limited penetrance into the central nervous system, and this may confer small-molecule HER2 targeting TKIs additional efficacy for preventing or controlling brain metastasis (18). Thus, small-molecule HER2 targeting TKIs are treatment options with promising roles in HER2-positive breast cancer. A large body of evidence addressing the efficacy and safety of small-molecule HER2-targeting TKIs in metastatic breast cancer has accumulated in the recent decade. Novel agents have been introduced, and the efficacy profiles of different regimens have been investigated. Nonetheless, there are still many unsettled issues regarding the relative efficacy of different agents and regimens due to the lack of direct head-to-head trials, the potential beneficial effects of small-molecule drugs over monoclonal antibodies in brain metastasis, and the cardiovascular safety of anti-HER2-containing regimens. A systematic review can methodically gather the available evidence on the efficacy and safety of this class of drug for metastatic HER2-positive breast cancer, and Network Meta-Analysis (NMA) can incorporate both direct and indirect information to synthesize evidence to answer the above questions. In this study, we performed a systematic review and NMA of Randomized Clinical Trials (RCT) to examine the clinical efficacy and safety of different small-molecule HER2-targeting TKI-containing regimens in women with metastatic HER2-positive breast cancer.

## Methods

### Protocol,Registration, and Report

The protocol for this systematic review was registered in the international Prospective Register of Systematic Reviews (PROSPERO) database at

the inception of the review project. The registration identification number is CRD42019131970. A table enlisting the amendments made, the stage of the review in which the amendment happened, and the rationale for that is available in **supplementary material 1 (Table S1)**. This report is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting systematic reviews with NMA (19).

**Eligibility Criteria**

The full description of trial eligibility criteria for inclusion in this systematic review is available in **supplementary material 1(Table S2)**. A brief review of eligibility criteria is below.

**Types of Studies**

RCTs were considered for inclusion in this systematic review. We did not limit potential studies according to the length of follow-up, the date of publication, publication status, and language.

**Types of Participants**

The population of interest was women with primary breast cancer who had distant metastasis and ErbB2/HER2-positive tumors. The age, race or ethnicity, menopausal status, hormone receptor status, and whether the current disease is a new diagnosis or a recurrence were not considered to affect studies in the systematic review. If a study entered both metastatic and locally advanced breast cancer patients, it was included in the review if, first, required data was available for metastatic patients separately and the total numbers of allocated metastatic patients to each intervention and comparison group were at least ten. If outcome data was not available separately for metastatic patients, but patients with metastatic disease constituted at least 80 percent of each intervention and comparison arms, the reported outcome for the entire population was used for the purpose of this review.

**Types of Interventions**

At least one arm of an RCT must have contained a small-molecule HER-2 targeting TKI, and at least another arm of the trial must have contained a systemic anti-cancer therapy or best supportive care or placebo with best supportive care in order to be deemed eligible for inclusion in the review.

**Types of Outcome Measures**

The list of outcomes of interest in this systematic review and their definitions can be found in the **supplementary material 1(Table S3)**. Primary outcomes were Overall Survival (OS) and Progression-Free Survival (PFS). The secondary outcomes were Overall Response (OR), Recurrence in Central Nervous System (RCNS), all grades and grades 3-4 Adverse Events (AE), all grades and grades 3-4 diarrheal AEs, all grades and grades 3-4 Left Ventricular Systolic Dysfunction (LVSD), and all grades and grades 3-4 Ejection Fraction Decrease (EFD).

**Information Sources and Search**

MEDLINE via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of Science Core Collection, and Scopus were systematically searched from the date of database inception to 27 May 2020. We scrutinized the reference list of included articles to identify other eligible studies. Duplicate records were reduced using EndNote X7 reference management software by title, year, and author filters, as well as manual de-duplicating. The search strategies were designed by APK and reviewed by NR and MM. We designed our search strategy in MEDLINE, CENTRAL, and Embase databases using a combination of free-texts and Medical Subject Headings. We used search filters in all databases except for CENTRAL to identify RCT. The full search strategies for all electronic databases are presented in the **supplementary material 1(Text S1)**.

**Study Selection**

Two reviewers (APK and FD) independently screened the titles and abstracts of the records. Then, the available full-texts of all the selected articles by both reviewers in the screening phase were evaluated by two reviewers (APK and FD) independently in order to find the studies that met the predetermined standardized criteria based on the characteristics of participants, interventions, comparisons, outcomes, and study design. If two reviewers had disagreed about the inclusion of a study, the final decision about inclusion would have been made by a third reviewer (MKF) after

discussing it with both reviewers.

**Data Collection Process and Data Items**

**Supplementary material 1 (Text S2)** provides full descriptions of the data collection process and data items.

**Geometry of the Network**

Both qualitative and quantitative approaches were utilized to describe network geometry properly. A network graph was drawn for each outcome of interest to visualize direct pairwise and indirect relations between available interventions. The nodes in the graph represent all systemic treatment regimens that were allocated to participants in each arm of eligible trials. The edges represent the availability of direct pairwise comparisons between the connected nodes in the included trials. The nodes were displayed as circles; the circle's diameter was weighted according to the number of available study arms that received the regimen as the allocated intervention. The edges were displayed as straight lines; the line thickness was weighted according to the number of direct comparisons between two nodes in the included studies. If the primary network of an outcome contained disconnected components, the networks with at least one common comparator were scrutinized from the primary network and illustrated with separate network graphs. Network graphs were prepared by Stata MP software (version 14) using the network graphs package (20). The following parameters were reported for a quantitative description of network geometry. These metrics have been shown to allow accurate reproduction of networks (21): the number of nodes, the number of edges, the number of studies per edge, density (the number of availableedges divided by the number of possible edges), the percentage of common comparators (the number of nodes that are common comparators divided by the number of nodes), the percentage of strong edges (the number of edges with more than one study per edge divided by the number of edges), and the median and interquartile ranges of edge thickness (the median and interquartile ranges of the number of studies per edge). Additionally, the total number of studies contributing to a network, the total number of participants in the entire network, and each node of the network were reported.

**Assessment of Risk of Bias within Individual Studies**

To evaluate the internal validity of each included study, two reviewers (APK and FD) evaluated the risk of bias using the "revised Cochrane risk-of-bias tool for randomized trials (RoB2)" (22). The risk of bias was assessed separately at the outcome level for OS, PFS, AE, and diarrheal AE outcomes. A full description of the risk of bias assessment process is available in **supplementary material 1 (Text S3)**.

**Summary Measures**

For pairwise comparisons, we computed HR with 95% CI for time-to-event outcomes and Relative Risk (RR) with 95% CI for binary outcomes as summary measures of the association between the regimen and the outcome. For the purpose of relative ranking of the available regimens in terms of the desired outcomes, the probability of being the first best treatment, the probability of being the second best treatment, the probability of being the third best treatment, and so on, mean rank and Surface under the Cumulative Ranking Curve (SUCRA) were estimated. SUCRA is the surface area under the curve of the cumulative distribution function of ranking probabilities (23).

**Assessment of Inconsistency**

The transitivity assumption was examined by perusing the distribution of possible effect modifiers in the studies contributing to a network. The effect modifiers evaluated were the age of the participants, the percentage of hormone receptor-positive patients, the percentage of patients who received trial treatment in the first-line setting, and the percentage of patients with CNS metastasis. If the transitivity assumption was met, consistency was tested. Consistency was statistically tested in each network using two approaches, including design-by-treatment interaction to test global inconsistency (24, 25) and node-splitting model to test the local inconsistency in the closed loops in the networks (26). A test of significance was performed for the difference between treatment effects obtained from direct and indirect evidence for every pairwise comparison in a

network. *P*-values < 0.1 were considered significant to reject the hypothesis of the consistency between treatment effects obtained from direct and indirect evidence. Due to the low power of the aforementioned methods to identify inconsistency, evidence of inconsistency in either method was considered sufficient to violate the transitivity assumption (27). If inconsistency was detected, network meta-regression incorporating effect modifiers as covariates to the NMA model was planned to be performed to assess the interaction between potential effect modifiers with treatment effect if a sufficient number of studies were available (28).

### Planned Method of Analysis

If transitivity and consistency assumptions were met, NMA in a frequentist statistical framework using a random-treatment effect multivariate meta-analysis model was performed for each connected network of interventions (29, 30). The probabilities that a treatment was the first best, the second best, and so on were estimated. The mean rank is the average ranking for each treatment. SUCRA is the area under the curve of cumulative probabilities over rank (31). Multi-arm trials were included in NMA and were considered independent pairwise comparisons for analysis. All statistical analyses were performed using Stata MP software (version 14) and the network meta package (30).

The intervention effects of all pairwise comparisons within a network were illustrated in a league table. In each network, the treatment effect of individual studies (point estimate and 95% CI), the pooled treatment effect grouped by design (point estimate and 95% CI), and the pooled overall treatment effect (point estimate and 95% CI) were showed for comparisons with available direct evidence in a network forest plot. The cumulative ranking plots of each treatment in networks were generated. A cumulative ranking plot is a line plot that displays rank on the horizontal axis and cumulative ranking probability on the vertical axis. Plots were drawn by Stata MP software (version 14) using the network graphs package (20).

### Additional Analyses

Pre-planned subgroup analyses of primary outcomes stratified by the line of treatment for metastatic disease (first-line vs. subsequent lines) were performed.

### Risk of Bias Across Studies

Non-reporting bias was evaluated by comparing the reported outcomes in the article with the pre-planned outcomes at the protocol stage, if available. If an outcome of interest had not been reported, the study's corresponding author would have been contacted and asked if the outcome had been measured in the trial. If selective non-reporting of outcomes was suspected, the readers of the review would be notified.

## Results

### Study Selection

Out of 14834 retrieved records, 23 studies (68 associated citations) finally met inclusion criteria and were considered eligible for qualitative synthesis **(Figure 1)**. The reasons for the exclusion of some notable studies can be found in **supplementary material 1(Table S4)** (Bischoff 2019 (15), Burstein 2014 (32), Gomez 2008 (33), Gomez 2016 (34), Lin 2011 (35), and Rixe 2009 (36)).

### Summary of Network Geometry

**Figure 2** is the network graph of the included studies. In all, 23 studies comprising 27 treatment regimens and 7497 eligible patients were included. All included studies had two parallel arms except for two (Cortes, 2015 (37) and Gradishar 2018 (38)) that were three-arm trials. The nodes in the order of abundance were tabulated in **supplementary material 1(Table S5)**. These studies contributed to five connected components.

### Study Characteristics

The detailed characteristics of included studies are tabulated in **supplementary material 1**(**Table S6** and **Table S7**). A summary of study characteristics is available in **Table 1**. With the exception of Haluska 2014 (39), all other trials were funded by a pharmaceutical company. The number of centers in which the trial was conducted was unclear for Haluska 2014 (39) Study. All other studies were multi-center clinical trials. We judged that information regarding the duration of follow-up was inadequately reported in six studies (Gradishar, 2018 (38), Haluska 2014 (39), Johnston 2013 (40), Lee 2017 (41), Saura 2019 (42), and Sim,

2019(43)). The range of reported median duration of follow-up was between 14 and 44.6 months.

The precise description of the participant characteristics is shown in **supplementary material 1 (Table S8)**, and a summary is provided in **Table 2**.

Overall, six different types of small-molecule HER2-targeting TKIs were used either as monotherapy or in combination with other systemic therapies (Lapatinib: 18 studies, 23 arms, and 3115 eligible patients; Neratinib: 3 studies, three arms, and 666 eligible patients; Afatinib: 2 studies, three arms, and 417 eligible patients; Pyrotinib: 2 studies, two arms, and 250 eligible patients; Tucatinib: 1 study, one arm, and 410 eligible patients; and Varlitinib: 1 study, one arm, and 24 eligible patients). In five studies (5 arms and 650 eligible patients), a placebo combined with other agents was used as a control treatment. The administered dose of Lapatinib was not reported in one study (Haluska, 2014 (39)). Three different doses of Lapatinib were used in other included studies (1000 mg once daily: 4 studies, 4 out of 23 arms, 398 eligible patients; 1250 mg once daily: 10 studies, 11 out of 23 arms, 1957 eligible patients; and 1500 mg once daily: 6 studies, 6 out of 23 arms, 696 patients). The planned doses of other small-molecule HER2-targeting TKIs were identical across studies (Neratinib: 240 mg once daily; Afatinib: 40 mg once daily; Pyrotinib: 400 mg once daily; Tucatinib: 300 mg twice daily; and Varlitinib: 400 mg twice daily). A table that presents the reported outcomes of interest in each study is available in **supplementary material 1(Table S9)**.

**Risk of Bias within Studies**

Traffic light graphs and bar plots representing inferred domain-specific and overall risk of bias for four study outcomes (OS, PFS, AE, diarrheal AE) and the reasons for rating down are provided as **supplementary material 2(Figure S1-6** and **Table S1)**. To summarize, the overall risk of bias was assessed to be low in 71.4%, 86.3%, 50%, and 82.3%, have some concerns in 19%, 9%, 25%, and 17.6%, be high in 9.5%, 4.5%, 25%, and 0% for OS, PFS, AE, and diarrheal AE respectively.

**Results of Individual Studies**

The reported results in terms of desired outcomes are tabulated in **supplementary material 1 (Table S10-20)**.

**Synthesis of Results, Exploration for Inconsistency, and Risk of Bias Across Studies**

**OS**

Twenty-one studies (7168 patients) contributed to five connected networks. The global network graph of all studies that reported OS outcomes, network graphs of each connected component, and a table that describes each connected component's geometric characteristics are available in **supplementary material 2(Figure S9-14** and **Table S2)**.

The main network of interventions (**supplementary material 2**, **Figure S10)** consisted of 11 studies (3918 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Capecitabine combination (9 studies, 1549 patients), Lapatinib and Vinorelbine combination (2 studies, 150 patients), Neratinib and Capecitabine combination (1 study, 307 patients), Pyrotinib and Capecitabine combination (1 study, 65 patients), Lapatinib, Capecitabine, and Cixutumumab combination (1 study, 45 patients), Tucatinib, Trastuzumab, and Capecitabine combination (1 study, 410 patients), and Neratinib monotherapy (1 study, 117 patients). All contributing trials enrolled patients who had received at least one line of treatment in a metastatic setting except for Janni 2015 (44) and Pivot 2015 (45), which recruited both previously treated and naïve to treatment patients. Nearly half of the participants in Murthy 2019 (16) study (48.2% in Tucatinib, Trastuzumab, and Capecitabine combination, 46% in Placebo, Trastuzumab, and Capecitabine combination) had CNS metastasis at baseline. The prevalence of baseline CNS metastasis in this trial was higher than in other trials. However, this may be related to active screening of brain metastasis by brain Magnetic Resonance Imaging (MRI) in patients without neurological symptoms at the start of the trial. There are no other substantial differences between distributions of possible effect modifiers across studies. No evidence of statistical inconsistency and publication bias was detected. Table 3 shows the pooled estimates of all pairwise comparisons. A forest plot is also provided in **supplementary material 1(Figure S1)**. According to the pooled network effect estimates, there were no significant differences between interventions in terms of OS. A table that presents the relative

ranking of treatment and cumulative rank plots is available in **supplementary material 1(Table S21** and **Figure S2)**. Pyrotinib and Capecitabine combination was the best small-molecule HER2-targeting TKI-containing regimen in terms of their effect on OS.

To the second connected network (**supplementary material 2**,**Figure S11)**, four studies (1642 patients) contributed. Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Taxane combination (3 studies, 591 patients) and Neratinib and Taxane combination (1 study, 242 patients). The distributions of effect modifiers were similar across studies. The design-by-treatment interaction model suggested the presence of global statistical inconsistency ($p$-value = 0.0005). Therefore, we withdrew to perform NMA, and due to a small number of studies, investigating inconsistency by meta-regression was not possible.

The third connected network (**supplementary material 2**,**Figure S12)** was made up of two studies (405 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib monotherapy (2 studies, 202 patients), Lapatinib and Trastuzumab combination (1 study, 148 patients), and Lapatinib and Pazopanib combination (1 study, 55 patients). Blackwell 2010 (44) enrolled previously treated patients while participants in Johnston 2013 (40) Had not received treatment in the metastatic setting. There are no other differences in reported effect modifiers. No evidence of statistical inconsistency was detected. The net league table, which presents network estimates of pairwise comparisons, forest plots, SUCRA table, and cumulative rank plots, is available in **supplementary material 1 (Table S22-23** and **Figure S3-4)**. According to the pooled network effect estimates, Lapatinib and Trastuzumab combination improved OS over Lapatinib monotherapy (HR: 0.74, 95% CI: 0.60-0.92). Also, the efficacy of the Lapatinib and Trastuzumab combination in prolonging OS ranked first among the above options based on SUCRA values.

The fourth connected network (**supplementary material 2**, **Figure S13)** was composed of two studies (629 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Afatinib and Vinorelbine combination (2 studies, 377 patients) and Afatinib monotherapy (1 study, 40 patients). All the patients in the Cortes 2015 (37) study had brain metastasis at the baseline, whereas 11.8% of the Harbeck 2016 (47) study participants had a metastatic brain disease. Only previously treated patients were enrolled in the Cortes 2015 (37) study, while more than 40% of participants in the Harbeck 2016 (47) study were treated in a first-line setting. No evidence of statistical inconsistency was detected. The net league table, forest plot, SUCRA table, and cumulative ranking plots are provided as **supplementary material 1(Table S24-25** and **Figure S5-6)**. According to the pooled network effect estimates, none of the interventions in this network had an OS advantage over the other treatment options.

The fifth connected network (**supplementary material 2**, **Figure S14)** was formed by two studies (574 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and AI combination (2 studies, 229 patients) and Lapatinib, Trastuzumab, and AI combination (1 study, 120 patients). All the participants of Johnston's 2009 (45) the study was naïve to treatment. On the contrary, the population enrolled in Gradishar 2018 (38) study was a mixture of naïve to treatment and previously treated patients. The distributions of other effect modifiers were similar in all arms of trials. No evidence of statistical inconsistency was detected. The net league table, forest plot, SUCRA table, and cumulative ranking plots are provided as **supplementary material 1(Table S26-27** and **Figure S7-8)**. According to the pooled network effect estimates, no significant differences between interventions were present. Lapatinib, Trastuzumab, and AI combination were the best small-molecule HER2-targeting TKI-containing regimens in terms of their effect on OS.

A pre-planned stratified analysis by the line of treatment for metastatic disease subgroups (first-line and subsequent lines) was performed. Network graphs, tables of network geometry (**supplementary material 2**,**Figure S15-19** and **Table S3-4)**, net league tables, network forest plots, SUCRA tables, and cumulative rank plots (**supplementary material 1**,**Figure S9-12** and **Table S28-31)** are available in **supplementary materials**. One connected network of interventions for

the first-line setting existed (**supplementary material 2**, **Figure S16)** and consisted of 4 studies (1642 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Taxane combination (3 studies, 591 patients) and Neratinib and Taxane combination (1 study, 242 patients). Globalstatistical inconsistency was noted ($p$-value = 0.0005), and NMA was not performed. Among naïve treatment patients in Harbeck 2016 (47) studies, the Afatinib and Vinorelbine combina- tion (136 patients) was inferior to the Trastuzum- ab and Vinorelbine combination (70 patients) (HR= 1.57, 95% CI: 1.03-2.38). Lapatinib and Capecitabine combination (117 patients) result- ed in shorter PFS (HR: 1.89, 95% CI: 1.07-3.35) than Trastuzumab and Capecitabine combina- tion (121 patients) among patients who had not received therapy in metastatic setting in Pivot 2015 (46) study. Collectively, 11 studies (3770 patients) formed two connected networks of in- terventions investigated for previously treated pa- tients. The first connected network (**supplementary material 2, Figure S18)** consisted of 9 studies (3355 patients). Small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Capecitabine combination (8 studies, 1358 patients), Neratinib and Capecitabine combination (1 study, 307 patients), Pyrotinib and Capecitabine combination (1 study, 65 patients), Lapatinib, Capecitabine, and Cixutumumab combination (1 study, 45 patients), Tucatinib, Trastuzumab, and Capecitabine combination (1 study, 410 patients), and Neratinib monotherapy (1 study, 117 patients). NMA revealed no significant differences between the efficacies of interventions in altering OS. Pyrotinib and Capecitabine combination was the best small-molecule HER2-targeting TKI-containing regimen in terms of their effect on OS in this network. The second connected network (**supplementary material 2, Figure S19)** contained two studies (415 patients). Small-molecule HER2-targeting TKI-containing regimens in this network were Afatinib and Vinorelbine combination (2 studies, 234 patients) and Afatinib monotherapy (1 study, 40 patients). The results of NMA were in concert with the original analysis. Overall, stratified analysis by the line of treatment showed consistent results with the primary analysis.

**PFS**

Twenty-two studies (7447 patients) contributed to five connected networks. The global network graph, network graphs of each connected network, and a table that describes each connected network's geometric characteristics are available in **supplementary material 2(Figure S20-25** and **Table S5)**.

The largest network of interventions (**supplementary material 2**,**Figure S21)** was made up of 12 studies (4197 patients). The small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Capecitabine combination (9 studies, 1549 patients), Lapatinib and Vinorelbine combination (2 studies, 150 patients), Neratinib and Capecitabine combination (1 study, 307 patients), Pyrotinib and Capecitabine combination (2 study, 250 patients), Lapatinib, Capecitabine, and Cixutumumab combination (1 study, 45 patients), Tucatinib, Trastuzumab, and Capecitabine combination (1 study, 410 patients), and Neratinib monotherapy (1 study, 117 patients). Janni 2015 (47), Jiang 2019 (48), and Pivot (46) 2015 studies included both naïve to treatment and previously treated patients. Only patients who had received prior treatments in metastatic settings participated in other studies. Other transitivity assumption issues were similar to the corresponding ones in the OS network. There was no significant statistical inconsistency or publication bias. Table 4 represents the pooled estimates of all pairwise comparisons. A forest plot is provided in **supplementary material 1(Figure S13)**. According to the pooled network effect estimates, Pyrotinib and Capecitabine combination was more efficacious than all other interventions except for T-DM1. Tucatinib, Trastuzumab, and Capecitabine combination improved PFS over Lapatinib and Capecitabine combination (HR: 0.52, 95% CI: 0.35-0.78), Neratinib monotherapy (HR: 0.44, 95% CI: 0.24-0.79), Trastuzumab and Capecitabine combination (HR: 0.54, 95% CI: 0.41-0.72), and Capecitabine monotherapy (HR: 0.28, 95% CI: 0.17-0.44). The addition of Lapatinib or Neratinib to Capecitabine chemotherapy resulted in longer PFS than Capecitabine alone therapy (HR: 0.53, 95% CI: 0.41-0.67 and HR: 0.40, 95% CI: 0.27-0.58 respectively). T-DM1 was superior in improving PFS than Lapatinib and Capecitabine

combination (HR: 0.65, 95% CI: 0.50-0.85) and Neratinib monotherapy (HR: 0.55, 95% CI: 0.33-0.91). Pyrotinib and Capecitabine combination, Tucatinib, Trastuzumab, and Capecitabine combination, and Neratinib and Capecitabine combination achieved the first, the second, and the third highest SUCRA values among small-molecule HER2-targeting TKI-containing regimens respectively (**Table S32** and **Figure S14** in supplementary material 1). The structures of other connected networks of interventions that reported PFS were the same as their analogous OS networks. Due to the presence of global statistical inconsistency, NMA was not performed for the second ($p$-value = 0.0000) and the fifth ($p$-value = 0.0000) connected components. NMA was conducted to pool the evidence from the other two networks. Lapatinib and Trastuzumab combination improved PFS over Lapatinib monotherapy (HR: 0.74, 95% CI: 0.61-0.90). No other pairwise comparisons showed significant differences between the efficacies of interventions in altering PFS. Netleague tables, forest plots, SUCRA values tables, and cumulative rank plots are present in **supplementary material 1**(**Table S33-36** and **Figure S15-18)**. A pre-planned subgroup analysis by the line of treatment for metastatic disease (first-line and subsequent lines of treatment) was performed. Network graphs, tables of network geometry (**supplementary material 2**,**Figure S26-30** and **Table S6-7)**, net league tables, network forest plots, SUCRA tables, and cumulative rank plots (**supplementary material 1**,**Table S37-40** and **Figure S19-22)** are available as supplementary material. One connected network of interventions for the first-line (**supplementary material 2**, **Figure S27)** setting existed and consisted of four studies (1642 patients). This network was statistically inconsistent ($p$-value = 0.0000) and NMA was not performed. In the subgroups of patients who received their first line of treatment in the metastatic setting, the addition of Pyrotinib to Capecitabine chemotherapy (68 patients) significantly improved PFS compared to Capecitabine alone (27 patients) (HR: 0.15, 95% CI: 0.08-0.28) in Jiang 2019 (48) study. In the similar subgroup of patients in Pivot 2015 (46) study, Lapatinib combination with Capecitabine (117 patients) appeared less effective than Trastuzumab and Capecitabine combination (121 patients) (HR: 1.61, 95% CI: 1.13-2.29). Afatinib and Vinorelbine combination (136 patients) showed similar efficacy on PFS (HR: 1.1, 95% CI: 0.75-1.6) to Trastuzumab and Vinorelbine combination (70 patients) in patients who were naïve to treatment in Harbeck 2016 (49) study. For the subgroup of trials that reported PFS in patients who were previously treated, there were two connected components whose structures were identical to networks formerly described for subgroup analysis of OS outcome. According to the pooled network effect estimates, Pyrotinib and Capecitabine combination prolonged PFS more than all other interventions in its network except for T-DM1. The combination of Tucatinib, Trastuzumab, and Capecitabine had superior efficacy in terms of PFS than the Lapatinib and Capecitabine combination (HR: 0.57, 95% CI: 0.37-0.89) and Neratinib monotherapy (HR: 0.48, 95% CI: 0.26-0.90). The pooled estimates of other pairwise comparisons, as well as treatment ranking, were, to a great extent, in line with the primary analysis. In Jiang 2019 (48) study, participants who had received one line and two lines of treatment for metastatic disease prior to trial enrollment achieved longer PFS with Pyrotinib and Capecitabine combination compared to Capecitabine monotherapy (HR: 0.19, 95% CI: 0.12-0.33, and HR: 0.18, 95% CI: 0.09-0.36, respectively).

**AE**

Fourteen studies (4147 patients) contributed to four connected networks. The global network graph, network graphs of each connected component, and a table that describes each connected component's geometric properties are available in **supplementary material 2(Figure S31-35** and **Table S8).**

The first connected network (**supplementary material 2**, **Figure S32)** was comprised of eight studies (2506 patients). The small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and Capecitabine combination (7 studies, 935 patients), Lapatinib and Vinorelbine combination (1 study, 75 patients), Neratinib and Capecitabine combination (1 study, 303 patients), Pyrotinib and Capecitabine combination (1 study, 65 patients), Varlitinib and Capecitabine combination (1 study, 24 patients), Lapatinib, Capecitabine, and Cixu-

tumumab combination (1 study, 45 patients), and Tucatinib, Trastuzumab, and Capecitabine combination (1 study, 404 patients). According to the pooled network effect estimates, Tucatinib, Trastuzumab, and Capecitabine combination was associated with higher AE compared to Trastuzumab and Capecitabine combination (HR: 4.16, 95% CI: 1.04-16.66) and Capecitabine monotherapy (HR: 9.09, 95% CI: 1.4-50) (**supplementary material 1**,**Table S41** and **Figure S23)**. The order of small-molecule HER2-targeting TKI-containing regimens from lowest to highest AE occurrence

**Table 1.** Summary of Study Characteristics

| Study characteristics | Number of trials |
|---|---|
| **Phase of Trial** | |
| *II* | 11 (47.8%) |
| *III* | 12 (52.1%) |
| **Blinding** | |
| *Double-blind* | 5 (21.7%) |
| *Open-label* | 18 (78.2%) |
| **No. of centers** | |
| *Multi-center* | 22 (95.6%) |
| *Unclear* | 1 (4.3%) |
| **Country** | |
| *China* | 2 (8.6%) |
| *Japan* | 1 (4.3%) |
| *Multiple* | 18 (78.2%) |
| *South Korea* | 1 (4.3%) |
| *United States* | 1 (4.3%) |
| **Trial stopped early** | |
| *No* | 15 (65.2%) |
| *Yes, for benefit* | 3 (13%) |
| *Yes, for non-benefit* | 3 (13%) |
| *Yes, for slow-accrual* | 1 (4.3%) |
| *Unclear* | 1 (4.3%) |
| **Inclusion criteria-gender** | |
| *Only women* | 16 (69.5%) |
| *Both women and men* | 7 (30.4%) |
| **Inclusion criteria-stage** | |
| *Locally advanced or metastatic disease* | 8 (34.7%) |
| *Only metastatic disease* | 14 (60.8%) |
| *Unclear* | 1 (4.3%) |
| **Inclusion criteria-HER2 status** | |
| *Either status* | 2 (8.6%) |
| *Only HER2 positive* | 21 (91.3%) |
| **Inclusion criteria-HR status** | |
| *Either status* | 21 (91.3%) |
| *Only HR-positive* | 2 (8.6%) |
| **Inclusion criteria-line of treatment** | |
| *Both the first and subsequent lines* | 5 (21.7%) |
| *Only first line* | 6 (26%) |
| *Only subsequent lines* | 11 (47.8%) |
| *Unclear* | 1 (4.3%) |
| **Exclusion criteria-CNS metastasis** | |
| *Excluded* | 7 (30.4%) |
| *Not excluded* | 16 (69.5%) |
| **Exclusion criteria-lower than NL LVEF** | |
| *Excluded* | 20 (86.9%) |
| *Not excluded* | 1 (4.3%) |
| *NR* | 1 (4.3%) |
| *Unclear* | 1 (4.3%) |
| **Dose of Lapatinib** | |
| *1000 mg daily* | 4/23 (17.3%) |
| *1250 mg daily* | 11/23 (47.8%) |
| *1500 mg daily* | 6/23 (26%) |
| *NR* | 2/23 (8.6%) |

**CNS, Central Nervous System; HER, Human Epidermal Growth Factor Receptor; HR, Hormone Receptor; LVEF, Left Ventricular Ejection Fraction; NL, Normal; NR, Not Reported**

**Table 2.** Summary of Eligible Participant Characteristics

| Eligible participant characteristics | Summary measure |
|---|---|
| **Number of eligible participants** | |
| *Min* | 50 |
| *1st quartile* | 116.5 |
| *Median* | 279 |
| *3rd quartile* | 493.5 |
| *Max* | 991 |
| *Mean* | 325.9 |
| **Mean of age (year)** | 53.6 |
| **HR+ (percent)** | 58.6% |
| **CNS metastasis+ (percent)** | 11.7% |
| **First-line (percent)** | 37.2% |

**CNS, Central Nervous System; HR, Hormone Receptor; Max, Maximum; Min, Minimum**

ranks were Lapatinib and Capecitabine combination, Varlitinib and Capecitabine combination, Pyrotinib and Capecitabine combination, Neratinib and Capecitabine combination, Lapatinib, Capecitabine, and Cixutumumab combination, Lapatinib and Vinorelbine combination, and Tucatinib, Trastuzumab, and Capecitabine combination (**supplementary material 1**,**Table S42** and **Figure S24**).

Two studies (444 patients) contributed to the second connected component. The small-molecule HER2-targeting TKI-containing regimens in this connected network were Lapatinib monotherapy (2 studies, 219 patients), Lapatinib and Trastuzumab combination (1 study, 149 patients), and Lapatinib and Pazopanib combination (1 study, 76 patients). Two other studies (625 patients) constituted the third connected component. The small-molecule HER2-targeting TKI-containing regimens in this connected component were Af-

**Table 3.** Netleague Table-Overall Survival (OS)-component 1

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **PC** | - | - | - | - | 0.69 (0.4, 1.19) | - | - | - | - | - |
| 0.92 (0.20,4.28) | **TDM1** | - | - | - | **0.74 (0.63, 0.87)** | - | - | - | - | - |
| 0.93 (0.16,5.34) | 1.01 (0.18,5.56) | **TTC** | - | - | - | - | - | **0.66 (0.5, 0.88)** | - | - |
| 0.84 (0.12,6.08) | 0.91 (0.13,6.37) | 0.91 (0.11,7.50) | **LCCX** | - | 0.96 (0.52,1.72) | - | - | - | - | - |
| 0.60 (0.13,2.81) | 0.65 (0.15,2.91) | 0.65 (0.12,3.59) | 0.71 (0.10,4.99) | **C** | 1.14 (0.92,1.4) | - | - | - | - | - |
| 0.69 (0.23,2.11) | 0.75 (0.26,2.15) | 0.74 (0.19,2.85) | 0.82 (0.16,4.19) | 1.15 (0.40,3.33) | **LC** | - | 1.13 (0.93,1.38) | 1.34 (0.95, 1.9) 0.58 (0.26, 1.31) | 1.01 (0.59,1.69) | 0.8 (0.53,1.2) |
| 0.75 (0.10,5.40) | 0.81 (0.12,5.66) | 0.80 (0.10,6.66) | 0.89 (0.09,8.91) | 1.24 (0.18,8.72) | 1.08 (0.21,5.54) | **V** | - | - | 0.93 (0.63,1.38) | - |
| 0.78 (0.17,3.66) | 0.85 (0.19,3.79) | 0.84 (0.15,4.67) | 0.93 (0.13,6.51) | 1.30 (0.29,5.86) | 1.14 (0.39,3.28) | 1.05 (0.15,7.37) | **NC** | - | - | - |
| 0.61 (0.15,2.46) | 0.67 (0.18,2.53) | 0.66 (0.23,1.91) | 0.73 (0.12,4.52) | 1.02 (0.27,3.91) | 0.89 (0.39,2.02) | 0.82 (0.13,5.12) | 0.78 (0.20,2.99) | **TC** | - | - |
| 0.70 (0.14,3.54) | 0.76 (0.16,3.68) | 0.75 (0.13,4.48) | 0.83 (0.11,6.19) | 1.16 (0.24,5.68) | 1.01 (0.31,3.28) | 0.93 (0.30,2.90) | 0.89 (0.18,4.35) | 1.14 (0.27,4.78) | **LV** | - |
| 0.55 (0.11,2.78) | 0.60 (0.12,2.89) | 0.59 (0.10,3.52) | 0.66 (0.09,4.87) | 0.92 (0.19,4.46) | 0.80 (0.25,2.57) | 0.74 (0.10,5.51) | 0.70 (0.15,3.41) | 0.90 (0.22,3.75) | 0.79 (0.15,4.16) | **N** |

**Hazard ratios (HR) and their corresponding 95% Confidence Intervals (CI) of pooled network estimates of Overall Survival (OS) are presented in the lower triangle's cells. The values are related to the comparison of the intervention inside the uppermost cell in the column versus the rightmost cell in the row. Hazard ratios (HR) and their corresponding 95% Confidence Intervals (CI) of OS reported in individual studies are presented in the upper triangle's cells. The values are related to the comparison of the intervention inside the leftmost cell in the row versus the lowermost cell in the column. Effect estimates are marked in bold when the *P*-value is less than 0.05.**

**C, Capecitabine; LC, Lapatinib+Capecitabine; LCCX, Lapatinib+Capecitabine+Cixutumumab; LV, Lapatinib+Vinorelbine; N, Neratinib; NC, Neratinib+Capecitabine; PC, Pyrotinib+Capecitabine; TC, Trastuzumab+Capecitabine; TTC, Tucatinib+Trastuzumab+Capecitabine; V, Vinorelbine**

**Table 4.** Netleague Table-Progression-Free Survival (PFS)-component 1

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **PC** | - | - | - | **0.18 (0.13, 0.26)** | **0.36 (0.23, 0.58)** | - | - | - | - | - |
| **0.53 (0.37,0.77)** | **TDM1** | - | - | - | **0.65 (0.54, 0.77)** | - | - | - | - | - |
| 0.67 (0.42,1.07) | 1.25 (0.77,2.04) | **TTC** | - | - | - | - | - | **0.54 (0.42, 0.71)** | - | - |
| **0.36 (0.17,0.76)** | 0.68 (0.32,1.43) | 0.54 (0.24,1.21) | **LCCX** | - | 0.96 (0.52,1.72) | - | - | - | - | - |
| **0.18 (0.15,0.23)** | **0.35 (0.24,0.50)** | **0.28 (0.17,0.44)** | 0.51 (0.24,1.07) | **C** | **1.81 (1.35,2.5)** | - | - | - | - | - |
| **0.35 (0.27,0.44)** | **0.65 (0.50,0.85)** | **0.52 (0.35,0.78)** | 0.96 (0.48,1.94) | **1.88 (1.48,2.39)** | **LC** | - | **1.31 (1.08,1.61)** | **1.3 (1.04, 1.64)** 0.81 (0.55,1.21) | 1.19 (0.74,1.88) | 0.84 (0.62,1.12) |
| **0.36 (0.18,0.69)** | 0.67 (0.34,1.31) | 0.53 (0.25,1.11) | 0.98 (0.39,2.51) | 1.93 (0.99,3.75) | 1.02 (0.55,1.90) | **V** | - | - | 1.16 (0.81,1.63) | - |
| **0.46 (0.31,0.66)** | 0.85 (0.57,1.27) | 0.68 (0.41,1.12) | 1.26 (0.59,2.69) | **2.47 (1.70,3.60)** | 1.31 (0.98,1.75) | 1.28 (0.65,2.54) | **NC** | - | - | - |
| **0.36 (0.25,0.52)** | 0.68 (0.46,1.00) | **0.54 (0.41,0.72)** | 1.00 (0.47,2.13) | **1.96 (1.35,2.85)** | 1.04 (0.78,1.38) | 1.02 (0.51,2.01) | 0.79 (0.53,1.19) | **TC** | - | - |
| **0.41 (0.24,0.71)** | 0.77 (0.45,1.34) | 0.62 (0.33,1.16) | 1.14 (0.49,2.67) | **2.24 (1.31,3.83)** | 1.19 (0.74,1.92) | 1.16 (0.78,1.72) | 0.91 (0.52,1.59) | 1.14 (0.66,2.00) | **LV** | - |
| **0.29 (0.18,0.48)** | **0.55 (0.33,0.91)** | **0.44 (0.24,0.79)** | 0.81 (0.35,1.84) | 1.58 (0.96,2.60) | 0.84 (0.55,1.30) | 0.82 (0.39,1.75) | 0.64 (0.38,1.08) | 0.81 (0.48,1.36) | 0.71 (0.37,1.35) | **N** |

**Hazard ratios (HR) and their corresponding 95% Confidence Intervals (CI) of pooled network estimates of Progression-Free Survival (PFS) are presented in the lower triangle's cells. The values are related to the comparison of the intervention inside the uppermost cell in the column versus the rightmost cell in the row. Hazard ratios (HR) and their corresponding 95% Confidence Intervals (CI) of PFS reported in individual studies are presented in the upper triangle's cells. The values are related to the comparison of the intervention inside the leftmost cell in the row versus the lowermost cell in the column. Effect estimates are marked in bold when the *P*-value is less than 0.05.**

**C, Capecitabine; LC, Lapatinib+Capecitabine; LCCX, Lapatinib+Capecitabine+Cixutumumab; LV, Lapatinib+Vinorelbine; N, Neratinib; NC, Neratinib+Capecitabine; PC, Pyrotinib+Capecitabine; TC, Trastuzumab+Capecitabine; TTC, Tucatinib+Trastuzumab+Capecitabine; V, Vinorelbine**

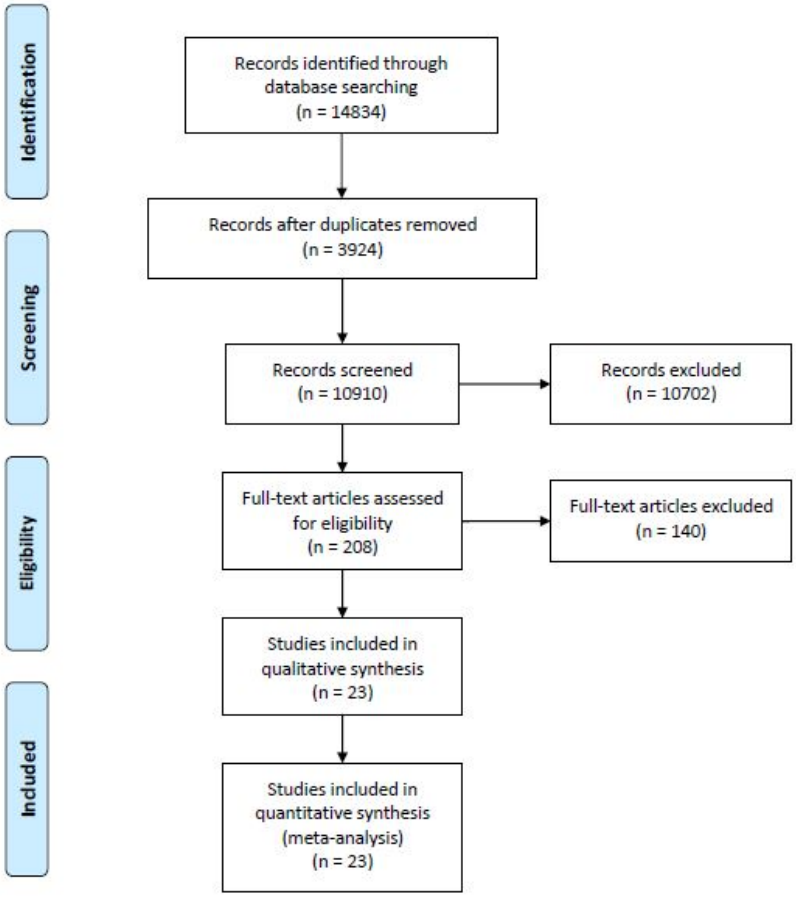


**Figure 1.** Flow diagram of study selection process

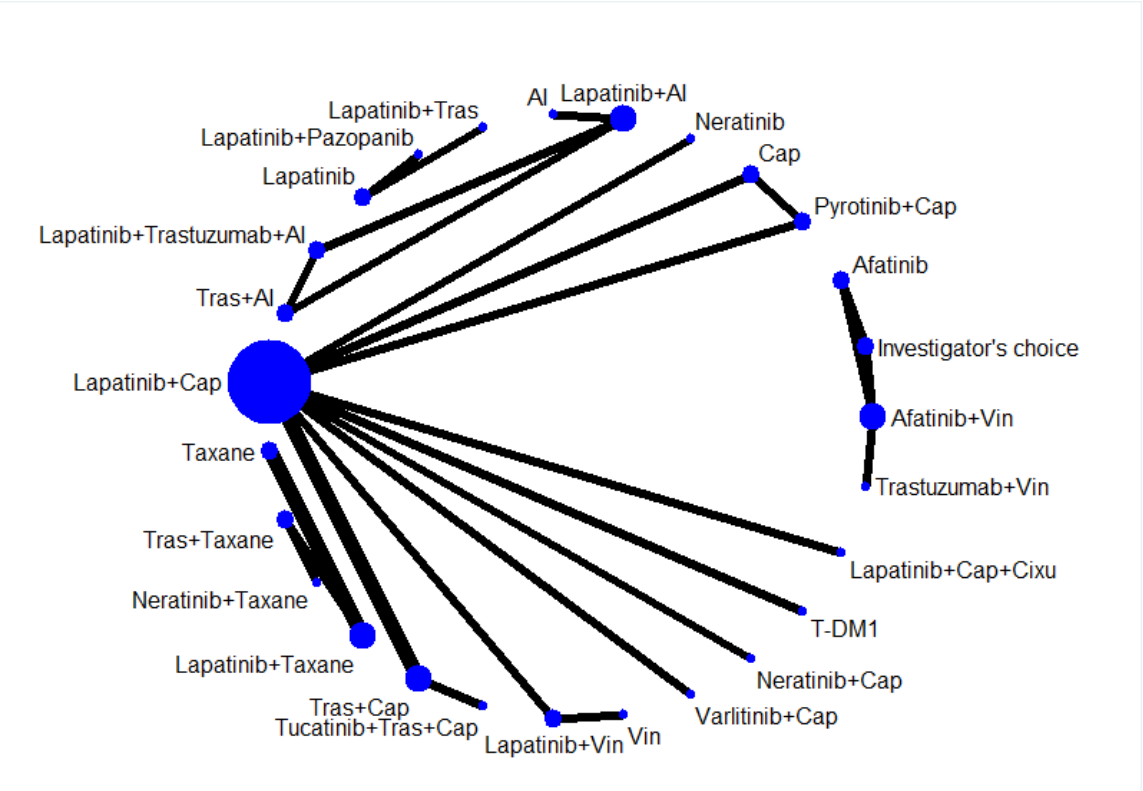


**Figure 2.** Global network graph of included studies. The nodes are displayed as circles; the diameter of circle is weighted according to the number of available study arms which received the regimen as the allocated intervention. The edges are displayed as straight lines; the line thickness is weighted according to the number of direct comparisons between two nodes in the included studies. AI, Aromatase Inhibitor; Cap, Capecitabine; Cixu, Cixutumumab; Tras, Trastuzumab; Vin, Vinorelbine.

atinib and Vinorelbine combination (2 studies, 374 patients) and Afatinib monotherapy (1 study, 40 patients). According to the pooled network effect estimates, the interventions in each connected component were not significantly different in terms of AE. The netleague tables, forest plots, SUCRA-based ranking tables, and cumulative rank plots are available in **supplementary material 1 (Table S43-46** and **Figure S25-28)**.

The remaining connected component was made up of 2 studies (572 patients). The small-molecule HER2-targeting TKI-containing regimens in this connected component were Lapatinib and AI combination (2 studies, 232 patients) and Lapatinib, Trastuzumab, and AI combination (1 study, 118 patients). Local statistical inconsistency was present ($p$-value = 0.004) and we did not perform NMA.

## Other Outcomes

Synthesis, exploration for inconsistency and risk of bias across studies for OR **(Text S4)**, RCNS **(Text S5)**, G34AE **(Text S6)**, AED **(Text S7)**, G34AED **(Text S8)**, LVSD/G34LVSD **(Text S9)**, and EFD/G34EFD **(Text S10)** outcomes are reported in **supplementary material 1**.

To the best of our knowledge, this is the first systematic review and NMA that simultaneously compares the efficacy and safety of small-molecule HER2-targeting TKI-containing regimens for metastatic HER2-positive breast cancer patients. We synthesized evidence for a range of clinically relevant outcomes and ranked treatment options to provide guidance for clinical decision-making. Results of NMA revealed that the Pyrotinib and Capecitabine combination improved PFS in all pairwise comparisons with other treatment options in its network except T-DM1 and ranked first in improving PFS based on SUCRA-based values.

Pooled network evidence was in line with the direct evidence from Jiang 2019 (48) and Ma 2019 (15). Studies showed the ability of Pyrotinib and Capecitabine combination to prolong PFS over Placebo and Capecitabine combination and Lapatinib and Capecitabine combination, re-

spectively. In the same network of interventions, the combination of Tucatinib, Trastuzumab, and Capecitabine ranked second best in regard to increasing PFS. The above findings were further re-confirmed by subgroup analysis stratified by the line of treatment for metastatic disease. Both of these regimens have been recently added to the therapeutic armamentarium of metastatic HER2-positive breast cancer and the results of our review substantiated their role in the treatment of metastatic HER2-positive breast cancer patients. Despite improvement in PFS, none of the interventions in the network was shown to be superior over other treatment options in terms of OS. Similarly, among all individual direct studies, OS advantage has been only reported for T-DM1 over Lapatinib and Capecitabine combination (50) and the addition of Tucatinib to Trastuzumab and Capecitabine combination (16).

Although we believe that more research is needed to fully elucidate this finding, it may be explained by insufficient power to detect effect differences by small-sized studies or shared resistance mechanisms between HER2-targeting medications that preclude the effectiveness of other HER2-targeting drugs after the failure of another drug with a similar mechanism of action. In the face of improved efficacy, the use of small-molecule HER2-targeting TKI-containing regimens was associated with more incident adverse events, especially diarrheal adverse events. Tucatinib, Trastuzumab, and Capecitabine combination ranked as the intervention with the highest probability of ranking first and further for causing AE, and Pyrotinib and Capecitabine combination ranked first in regard to diarrheal adverse events. This may signify the necessity for pharmacological diarrhea preventive measures when using Pyrotinib and Capecitabine combination in the clinics. The evidence on the relation of small-molecule HER2-targeting TKI-containing regimens and cardiac adverse events was weak due to a small number of studies that reported the outcomes of interest and poor connectedness of the network of interventions.

This review is subjected to some limitations. Most of the studies were judged to be of low risk of bias in regard to assessing OS, PFS, and diarrheal AE outcomes but 50% of studies that reported AE outcome were judged to be of high risk of bias or at least having some concerns for bias. The most common reason for appraising these studies to be in higher risks of bias was the lack of blinding in these studies which could introduce measurement bias. Thus, the results of synthesis for AE outcome should be interpreted with more cautions. The main objective of our study was to compare the efficacy and safety of small-molecule HER2-targeting TKI-containing regimens with each other in the population of patients with metastatic HER2-positive breast cancer. A more comprehensive systematic review and NMA is required to incorporate all the possible competing interventions for this population and aid confident decision-making regarding the best intervention for metastatic HER2-positive breast cancer.

We thoroughly evaluated the similarity of possible effect modifiers' distributions across studies to ensure that transitivity assumptions are met. We performed subgroup analysis of primary outcomes stratified by the line of treatment. However, not all competing interventions in studies are perfectly jointly randomizable as the participants in trials had received different prior treatments before they were enrolled. For instance, in Murthy 2019 (16) study, Tucatinib, Trastuzumab, and Capecitabine combination outperformed the combination of Trastuzumab and Capecitabine in patients who had been already progressed on Trastuzumab, Pertuzumab, and T-DM1. The trials which investigated the efficacy of Pyrotinib and Capecitabine combination (Jiang 2019 (48) and Ma 2019 (15)) had more heterogeneous included populations; most of them were previously treated with Trastuzumab, Taxane, and an Anthracycline. Another weak point of our work was the disconnectedness of the available network of interventions which made comparing all available treatment options impossible. A particular issue in this regard was the inability to compare Capecitabine-based chemotherapy backbone with Taxane-based chemotherapy backbone used in combination with small-molecule HER2-targeting TKI.

Again, a future more comprehensive systematic review and NMA and new direct trials may obviate this problem. The networks of interventions for RCNS and cardiac AEs were composed of small numbers of studies. Inconsistent defini-

tion of these outcomes in different studies was one of the reasons for scarcity of evidence about them but still we could not rule out the possibility of non-reporting bias. The results of our synthesis are in the main consistent with previously available systematic reviews and real-world data. Paracha et al. performed a systematic review and NMA of HER2-targeting agent-containing regimens for metastatic HER2-positive breast cancer patients that had received Trastuzumab and Taxane. The nodes in their network of interventions included T-DM1, Trastuzumab and Capecitabine combination, Pertuzumab, Trastuzumab, and Capecitabine combination, Lapatinib and Capecitabine combination, Neratinib monotherapy, and Capecitabine monotherapy. Of note, RCTs of Pyrotinib-based and Tucatinib-based therapies had not been published to the data of their review's search of literature. T-DM1 achieved the highest SUCRA-based ranking for both OS and PFS outcomes. However, the OS differences between T-DM1 and other treatments were not statistically significant and T-DM1 was found to significantly prolong PFS only in comparison with Capecitabine monotherapy (51). In other systematic reviews and meta-analyses, the combination of Lapatinib and chemotherapy or Lapatinib and endocrine therapy improved OS and PFS compared with chemotherapy or endocrine therapy alone (52, 53).

Cohort studies of metastatic HER2-positive breast cancer patients in real clinical settings haveshown acceptable efficacy of Lapatinib (54-56), Neratinib (57), Pyrotinib (58, 59)-based treat- ments for this population. Also, these agents have shown clinical activity in controlling brain met- astatic disease (58-62). Observational evidence has suggested the superior efficacy of the com- bined small-molecule HER2-targeting TKIs and chemotherapy over the single-agent small-molecule HER2-targeting TKI (54, 57). This finding is in line with the results of our NMA. The results of this review may have implications on thefield's future research prioritization. T-DM1 is a well-evidenced treatment option for metastatic HER2-positive breast cancer after the failure ofTrastuzumab and Taxane (63).

Considering the promising effects of Pyrotinib/Capecitabine and Tucatinib/Trastuzumab/ Capecitabine combinations, future RCTs directly comparing these treatments with T-DM1 in the second-line setting are warranted. Tucatinib, Trastuzumab, and Capecitabine showed encouraging results in RCT setting. Additionally, observational studies have shown clinical activity of Lapatinib, Trastuzumab, and Chemotherapy combination in metastatic HER2-positive breast cancer, even in the first line setting (56). Triplet-therapy with Trastuzumab, a small-moleculeHER2-targeting TKI, and chemotherapy may be a favorable combination for being evaluated in the first-line setting in comparison with the recom- mended regimen of Trastuzumab/Pertuzumab/ Taxane combination.

## Conclusion

considering general limitations of NMA and particular issues related to this systematic review, Pyrotinib/Capecitabine and Tucatinib/Trastuzumab/Capecitabine combinations showed promising superior efficacy in comparisons with other small-molecule HER2-targeting TKI-containing regimens in metastatic HER2-positive breast cancer patients.

## Funding

This study was supported by a grant from Tehran University of Medical Sciences (TUMS). The funder had no involvement in study design, data collection, statistical analysis and the publication of study results. The study is not supported by any industrial company and none of the authors has any potential conflicts of interest in this regard.

## Conflict of Interest

The authors declare no competing interests.

## Acknowledgment

We are deeply thankful to Dr. Ahmad Awada, Dr. Henry Gomez, Dr. Cristina Saura, Dr. Toshimi Takano, and Dr. Binghe Xu for providing us with the data and information of their studies. We should show our sincere gratitude to Dr. Anna Chaimani and Dr. Ian White for providing insightful advice regarding using Stata MP Software for performing NMA.

## References

1. Ji P, Gong Y, Jin ML, Hu X, Di GHShao ZM. The

Burden and Trends of Breast Cancer From 1990 to 2017 at the Global, Regional, and National Levels: Results From the Global Burden of Disease Study 2017. Front Oncol. 2020;10:650.
2. Li N, Deng Y, Zhou L, Tian T, Yang S, Wu Y, et al. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Hematol Oncol. 2019;12(1):140.
3. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438-51.
4. Wu X, Baig A, Kasymjanova G, Kafi K, Holcroft C, Mekouar H, et al. Pattern of Local Recurrence and Distant Metastasis in Breast Cancer By Molecular Subtype. Cureus. 2016;8(12):e924-e24.
5. Narod SA, Iqbal JMiller AB. Why have breast cancer mortality rates declined? Journal of Cancer Policy. 2015;5:8-17.
6. Wang JXu B. Targeted therapeutic options and future perspectives for HER2-positive breast cancer. Signal Transduct Target Ther. 2019;4(1):34.
7. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene. 2007;26(45):6469-87.
8. Balduzzi S, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, et al. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2014;2014(6):CD006242.
9. Zagouri F, Sergentanis TN, Chrysikos D, Zografos CG, Filipits M, Bartsch R, et al. Pertuzumab in breast cancer: a systematic review. Clin Breast Cancer. 2013;13(5):315-24.
10. Peddi PFHurvitz SA. Ado-trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer: latest evidence and clinical potential. Ther Adv Med Oncol. 2014;6(5):202-9.
11. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020;382(7):610-21.
12. Schroeder RL, Stevens CLSridhar J. Small molecule tyrosine kinase inhibitors of ErbB2/HER2/Neu in the treatment of aggressive breast cancer. Molecules (Basel, Switzerland). 2014;19(9):15196-212.
13. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733-43.
14. Saura C, Oliveira M, Feng YH, Dai MS, Chen SW, Hurvitz SA, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With >/= 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020;38(27):3138-49.
15. Bischoff J, Barinoff J, Mundhenke C, Bauerschlag DO, Costa S-D, Herr D, et al. A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in trastuzumab-pretreated patients with HER-2-positive metastatic breast cancer (E-VITA). Anti-Cancer Drugs. 2019;30(4):394-401.
16. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020;382(7):597-609.
17. Xuhong JC, Qi XW, Zhang YJiang J. Mechanism, safety and efficacy of three tyrosine kinase inhibitors lapatinib, neratinib and pyrotinib in HER2-positive breast cancer. Am J Cancer Res. 2019;9(10):2103-19.
18. Venur VALeone JP. Targeted Therapies for Brain Metastases from Breast Cancer. Int J Mol Sci. 2016;17(9):1543.
19. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, 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):777-84.
20. Chaimani ASalanti G. Visualizing Assumptions and Results in Network Meta-analysis: The Network Graphs Package. The Stata Journal. 2015;15(4):905-50.
21. Tonin FS, Borba HH, Mendes AM, Wiens A, Fernandez-Llimos FPontarolo R. Description of network meta-analysis geometry: A metrics design study. PLOS ONE. 2019;14(2):e0212650.
22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
23. Daly CH, Neupane B, Beyene J, Thabane L, Straus SEHamid JS. Empirical evaluation of SUCRA-based treatment ranks in network meta-analysis: quantifying robustness using Cohen's kappa. BMJ Open. 2019;9(9):e024625.
24. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AEWhite IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3(2):98-110.

25. White IR, Barrett JK, Jackson DHiggins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012;3(2):111-25.
26. Dias S, Welton NJ, Caldwell DMAdes AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine. 2010;29(7-8):932-44.
27. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020) 2020 [Available from: www.training.cochrane.org/handbook.
28. Jansen JPNaci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Medicine. 2013;11(1):159.
29. Chaimani A, Higgins JPT, Mavridis D, Spyridonos PSalanti G. Graphical Tools for Network Meta-Analysis in STATA. PLOS ONE. 2013;8(10):e76654.
30. White IR. Network meta-analysis. The Stata Journal. 2015;15(4):951-85.
31. Riley RD, Jackson D, Salanti G, Burke DL, Price M, Kirkham J, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. BMJ. 2017;358:j3932.
32. Burstein HJ, Cirrincione CT, Barry WT, Chew HK, Tolaney SM, Lake DE, 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):3959-66.
33. Gomez HL, Doval DC, Chavez MA, Ang PC, Aziz Z, Nag S, et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. J Clin Oncol. 2008;26(18):2999-3005.
34. Gomez HL, Neciosup S, Tosello C, Mano M, Bines J, Ismael G, et al. A Phase II Randomized Study of Lapatinib Combined With Capecitabine, Vinorelbine, or Gemcitabine in Patients With HER2-Positive Metastatic Breast Cancer With Progression After a Taxane (Latin American Cooperative Oncology Group 0801 Study). Clin Breast Cancer. 2016;16(1):38-44.
35. Lin NU, Eierman W, Greil R, Campone M, Kaufman B, Steplewski K, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. J Neurooncol. 2011;105(3):613-20.
36. Rixe O, Franco SX, Yardley DA, Johnston SR, Martin M, Arun BK, et al. A randomized, phase II, dose-finding study of the pan-ErbB receptor tyrosine-kinase inhibitor CI-1033 in patients with pretreated metastatic breast cancer. Cancer Chemother Pharmacol. 2009;64(6):1139-48.
37. Cortes J, Dieras V, Ro J, Barriere J, Bachelot T, Hurvitz S, et al. Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. Lancet Oncol. 2015;16(16):1700-10.
38. Johnston SRD, Hegg R, Im SA, Park IH, Burdaeva O, Kurteva G, 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: ALTERNATIVE. J Clin Oncol. 2018;36(8):741-48.
39. Haluska P, Bernath AM, Ballman KV, Dueck AC, Linden HM, Goetz MP, et al. Randomized phase II trial of capecitabine and lapatinib with or without cixutumumab in patients with HER2+ breast cancer previously treated with trastuzumab and an anthracycline and/or a taxane: NCCTG N0733 (Alliance). Journal of Clinical Oncology. 2014;32(15_suppl):632-32.
40. Johnston SR, Gomez H, Stemmer SM, Richie M, Durante M, Pandite L, et al. A randomized and open-label trial evaluating the addition of pazopanib to lapatinib as first-line therapy in patients with HER2-positive advanced breast cancer. Breast Cancer Res Treat. 2013;137(3):755-66.
41. Lee SC, Chen SC, Dai MS, Lee GE, Liu CL, Chan A, et al. Multicenter phase 2 trial of varlitinib versus lapatinib in combination with capecitabine in patients with HER2+ metastatic breast cancer (MBC) who failed prior trastuzumab therapy. Annals of Oncology. 2017;28:x30-.
42. Saura C, Oliveira M, Feng Y-H, Dai M-S, Hurvitz SA, Kim S-B, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. Journal of Clinical Oncology. 2019;37(15_suppl):1002-02.

43. Sim SH, Park IH, Jung KH, Kim SB, Ahn JH, Lee KH, et al. Abstract P6-17-23: Randomized phase II study of lapatinib plus vinorelbine versus vinorelbine in patients with HER2 positive metastatic breast cancer progressed after lapatinib and trastuzumab treatment. Cancer Research. 2019;79(4_Supplement):P6-17-23-P6-17-23.
44. Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30(21):2585-92.
45. Johnston S, Pippen J, Jr., Pivot X, Lichinitser M, Sadeghi S, Dieras V, 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):5538-46.
46. Pivot X, Manikhas A, Zurawski B, Chmielowska E, Karaszewska B, Allerton R, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015;33(14):1564-73.
47. Janni W, Sarosiek T, Karaszewska B, Pikiel J, Staroslawska E, Potemski P, et al. Final overall survival analysis of a phase II trial evaluating vinorelbine and lapatinib in women with ErbB2 overexpressing metastatic breast cancer. Breast. 2015;24(6):769-73.
48. Jiang Z, Yan M, Hu X, Zhang Q, Ouyang Q, Feng J, et al. Pyrotinib combined with capecitabine in women with HER2+ metastatic breast cancer previously treated with trastuzumab and taxanes: A randomized phase III study. Journal of Clinical Oncology. 2019;37(15_suppl):1001-01.
49. Harbeck N, Huang CS, Hurvitz S, Yeh DC, Shao ZM, Im SA, 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 Oncology. 2016;17(3):357-66.
50. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
51. Paracha N, Reyes A, Dieras V, Krop I, Pivot XUrruticoechea A. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. Breast Cancer Res Treat. 2020;180(3):597-609.
52. Botrel TEA, Paladini LClark OAC. Lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of HER-2-overexpressing locally advanced or metastatic breast cancer: systematic review and meta-analysis. Core evidence. 2013;8:69-78.
53. Kawalec P, Lopuch SMikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. Clin Breast Cancer. 2015;15(2):90-100 e1.
54. Zhao W, Bian L, Wang T, Zhang S, Li J, Xu F, et al. Effectiveness of second-line anti-HER2 treatment in HER2-positive metastatic breast cancer patients previously treated with trastuzumab: A real-world study. Chin J Cancer Res. 2020;32(3):361-69.
55. Xie Y, Ge R, Sang D, Luo T, Li W, Ji X, et al. Real-world data of lapatinib and treatment after lapatinib in patients with previously treated HER2-positive metastatic breast cancer: A multicenter, retrospective study. Cancer Med. 2020;9(9):2981-88.
56. Li Y, Gong C, Lu Q, Zhou Z, Luo T, Li W, et al. Real-World Data of Triplet Combination of Trastuzumab, Lapatinib, and Chemotherapy in HER2-Positive Metastatic Breast Cancer: A Multicenter Retrospective Study. Front Oncol. 2020;10:271.
57. Shepherd STC, Lee K, Mohammed K, Patel K, Allen M, Johnston SRD, et al. Efficacy and tolerability of neratinib in advanced HER-2 positive breast cancer: A single institution experience. Annals of Oncology. 2019;30:iii59.
58. Chen Q, Ouyang D, Anwar M, Xie N, Wang S, Fan P, et al. Effectiveness and Safety of Pyrotinib, and Association of Biomarker With Progression-Free Survival in Patients With HER2-Positive Metastatic Breast Cancer: A Real-World, Multicentre Analysis. Front Oncol. 2020;10(811):811.
59. Lin Y, Lin M, Zhang J, Wang B, Tao Z, Du Y, et al. Real-World Data of Pyrotinib-Based Therapy in Metastatic HER2-Positive Breast Cancer: Promising Efficacy in Lapatinib-Treated Patients and in Brain Metastasis. Cancer Res Treat. 2020;52(4):1059-66.
60. Abraham J, Montero AJ, Jankowitz RC, Salkeni MA, Beumer JH, Kiesel BF, et al. Safety and Efficacy of T-DM1 Plus Neratinib in Patients

With Metastatic HER2-Positive Breast Cancer: NSABP Foundation Trial FB-10. J Clin Oncol. 2019;37(29):2601-09.
61. Freedman RA, Gelman RS, Anders CK, Melisko ME, Parsons HA, Cropp AM, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol. 2019;37(13):1081-89.
62. Metzger Filho O, Leone JP, Li T, Tan-Wasielewski Z, Trippa L, Barry WT, et al. Phase I dose-escalation trial of tucatinib in combination with trastuzumab in patients with HER2-positive breast cancer brain metastases. Ann Oncol. 2020;31(9):1231-39.
63. Mok TSK, Paz-Ares L, Wu YL, Novello S, Juhasz E, Aren O, et al. Association Between Tumor Egfr and Kras Mutation Status and Clinical Outcomes in Nsclc Patients Randomized to Sorafenib Plus Best Supportive Care (BSC) or Bsc Alone: Subanalysis of the Phase III Mission Trial. Annals of Oncology. 2012;23:ix5.