INPLASY

Efficacy and Safety of Therapies for previously treated HER2-Positive Metastatic Breast Cancer: A Systematic Review and Network Meta-Analysis Protocol

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 March 2026 and was last updated on 15 March 2026.

INTRODUCTION

Review question / Objective Review question In patients with HER2-positive metastatic breast cancer, what are the relative efficacy and safety rankings of all available second-line and beyond anti-HER2-directed systemic therapies?
Review objectives
To compare the relative efficacy and safety of all available second-line and beyond treatment regimens for patients with HER2-positive metastatic breast cancer (mBC).

Rationale Breast cancer is the most commonly diagnosed malignancy among female patients worldwide. HER2-positive BC comprises approximately 15%-20% of all BC and is associated with an aggressive nature and poor prognosis. However, the therapeutic landscape for HER2-positive (HER2+) metastatic breast cancer has been revolutionized by the advent of HER2-targeted agents, starting with the FDA approval of trastuzumab in 1998. These targeted agents, including monoclonal antibodies (e.g., trastuzumab, pertuzumab), tyrosine kinase inhibitors (e.g., lapatinib, tucatinib, pyrotinib), and the latest generation of antibody-drug conjugates (ADCs) such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), now constitute the cornerstone of systemic management.
However, despite these advancements, the management of metastatic disease remains a formidable challenge, particularly in the second-line setting. While innovative therapies have prolonged the disease-controlled state, the inevitable emergence of treatment resistance means that late-stage HER2-positive breast cancer is still a life-threatening malignancy. Current clinical guidelines recommend various second-line regimens, yet these recommendations often stem from individual randomized controlled trials (RCTs) that compare a specific drug against a limited control arm. This has resulted in a fragmented therapeutic landscape where no head-to-head comparison was available for preferred second-line options.

Consequently, clinicians and policymakers face significant difficulty in determining the optimal treatment sequence to balance maximal efficacy against tolerability. In the absence of comprehensive direct evidence, decision-making often relies on cross-trial comparisons or subjective interpretations of relative benefits. A systematic review and network meta-analysis (NMA) is the most rigorous methodology to address this gap by integrating direct and indirect evidence. The results of this NMA will provide evidence-based recommendations to optimize clinical practice and refine treatment guidelines for this critical patient population facing limited subsequent therapeutic options.

Condition being studied Metastatic HER2-positive breast cancer.

METHODS

Search strategy We performed a systematic search in the database of PubMed, EMBASE, Cochrane Library and Web of Science, for literatures published from inception to September 2025. The keywords of the searching term are “breast cancer”, “HER2”, “metastatic” and “randomized controlled trial”. Detailed search strategy of each database will be provided with the manuscript.

An example of the search conducted in PubMed is as follows: ((("Breast Neoplasms"[MeSH Terms] OR "breast neoplasm"[Title/Abstract] OR "neoplasm breast"[Title/Abstract] OR "breast tumors"[Title/Abstract] OR "breast tumor"[Title/Abstract] OR "tumor breast"[Title/Abstract] OR "tumors breast"[Title/Abstract] OR "neoplasms breast"[Title/Abstract] OR "breast cancer"[Title/Abstract] OR "cancer breast"[Title/Abstract] OR "mammary cancer"[Title/Abstract] OR "cancer mammary"[Title/Abstract] OR "cancers mammary"[Title/Abstract] OR "mammary cancers"[Title/Abstract] OR "malignant neoplasm of breast"[Title/Abstract] OR "breast malignant neoplasm"[Title/Abstract] OR "breast malignant neoplasms"[Title/Abstract] OR "malignant tumor of breast"[Title/Abstract] OR "breast malignant tumor"[Title/Abstract] OR "breast malignant tumors"[Title/Abstract] OR "cancer of breast"[Title/Abstract] OR "cancer of the breast"[Title/Abstract] OR "mammary carcinoma human"[Title/Abstract] OR (("Carcinoma"[MeSH Terms] OR "Carcinoma"[All Fields] OR "Carcinomas"[All Fields] OR "carcinoma s"[All Fields]) AND "human mammary"[Title/Abstract]) OR (("Carcinoma"[MeSH Terms] OR "Carcinoma"[All Fields] OR "Carcinomas"[All Fields] OR "carcinoma s"[All Fields]) AND "human mammary"[Title/Abstract]) OR "human mammary carcinomas"[Title/Abstract] OR (("mammaries"[All Fields] OR "mammary glands, human"[MeSH Terms] OR ("Mammary"[All Fields] AND "glands"[All Fields] AND "Human"[All Fields]) OR "human mammary glands"[All Fields] OR "Mammary"[All Fields] OR "Breast"[MeSH Terms] OR "Breast"[All Fields]) AND "carcinomas human"[Title/Abstract]) OR "human mammary carcinoma"[Title/Abstract] OR (("mammaries"[All Fields] OR "mammary glands, human"[MeSH Terms] OR ("Mammary"[All Fields] AND "glands"[All Fields] AND "Human"[All Fields]) OR "human mammary glands"[All Fields] OR "Mammary"[All Fields] OR "Breast"[MeSH Terms] OR "Breast"[All Fields]) AND "neoplasms human"[Title/Abstract]) OR (("human s"[All Fields] OR "humans"[MeSH Terms] OR "humans"[All Fields] OR "Human"[All Fields]) AND "mammary neoplasm"[Title/Abstract]) OR "human mammary neoplasms"[Title/Abstract] OR (("neoplasm s"[All Fields] OR "Neoplasms"[MeSH Terms] OR "Neoplasms"[All Fields] OR "Neoplasm"[All Fields]) AND "human mammary"[Title/Abstract]) OR (("Neoplasms"[All Fields] OR "Neoplasms"[MeSH Terms] OR "Neoplasms"[All Fields] OR "Neoplasm"[All Fields]) AND "human mammary"[Title/Abstract]) OR (("mammaries"[All Fields] OR "mammary glands, human"[MeSH Terms] OR ("Mammary"[All Fields] AND "glands"[All Fields] AND "Human"[All Fields]) OR "human mammary glands"[All Fields] OR "Mammary"[All Fields] OR "Breast"[MeSH Terms] OR "Breast"[All Fields]) AND "neoplasm human"[Title/Abstract]) OR "breast carcinoma"[Title/Abstract] OR "breast carcinomas"[Title/Abstract] OR "carcinoma breast"[Title/Abstract] OR "carcinomas breast"[Title/Abstract]) AND ("neoplasm metastasis"[MeSH Terms] OR "neoplasm recurrence, local"[MeSH Terms] OR "Metastase"[Title/Abstract] OR "Metastases"[Title/Abstract] OR "Metastasis"[Title/Abstract] OR (("metastasation"[All Fields] OR "metastasic"[All Fields] OR "metastasing"[All Fields] OR "metastasise"[All Fields] OR "metastasised"[All Fields] OR "metastasises"[All Fields] OR "metastasising"[All Fields] OR "metastasization"[All Fields] OR "metastasizes"[All Fields] OR "metastasizing"[All Fields] OR "neoplasm metastasis"[MeSH Terms] OR ("Neoplasm"[All Fields] AND "Metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "Metastase"[All Fields] OR "Metastases"[All Fields] OR "metastasize"[All Fields] OR "metastasized"[All Fields]) AND "Neoplasm"[Title/Abstract]) OR "metastasis neoplasm"[Title/Abstract] OR "neoplasm metastases"[Title/Abstract] OR "metastatic"[Title/Abstract] OR "advanced"[Title/Abstract] OR

"secondary"[Title/Abstract] OR "recurrent"[Title/Abstract] OR "inoperable"[Title/Abstract] OR "unresect*"[Title/Abstract] OR "disseminated"[Title/Abstract] OR "incurable"[Title/Abstract] OR "metastat*"[Title/Abstract] OR "late stage"[Title/Abstract] OR "stage iii*"[Title/Abstract] OR "stage 3*"[Title/Abstract] OR "stage iv*"[Title/Abstract] OR "stage 4*"[Title/Abstract]) AND (("genes, erbb 2"[MeSH Terms] OR "receptor, erbb 2"[MeSH Terms] OR "human epidermal growth factor receptor 2"[Title/Abstract] OR "human epidermal growth factor receptor type 2"[Title/Abstract] OR "HER2"[Title/Abstract] OR "HER-2"[Title/Abstract] OR "ErbB2"[Title/Abstract] OR "Erb-B2"[Title/Abstract] OR "ERBB-2"[Title/Abstract] OR "c-erbb-2"[Title/Abstract] OR "cerbb2"[Title/Abstract] OR "Her2neu"[Title/Abstract] OR "her 2 neu"[Title/Abstract]) AND ("Positive"[Title/Abstract] OR "enriched"[Title/Abstract] OR "overexpressing"[Title/Abstract] OR "overexpressed"[Title/Abstract] OR "positivity"[Title/Abstract] OR "overexpression"[Title/Abstract] OR "amplif*"[Title/Abstract] OR "her2 positive"[Title/Abstract])) AND ("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH Terms] OR "Controlled Clinical Trials as Topic"[MeSH Terms] OR "Random Allocation"[MeSH Terms] OR "Double-Blind Method"[MeSH Terms] OR "Single-Blind Method"[MeSH Terms] OR "Cross-Over Studies"[MeSH Terms] OR "Placebos"[MeSH Terms] OR "Randomized"[Text Word] OR "Randomised"[Text Word] OR "RCT"[Text Word] OR "RCTs"[Text Word] OR "control groups"[MeSH Terms] OR "control group"[Text Word] OR "control groups"[Text Word] OR "Controlled Clinical Trial"[Publication Type] OR "cross over study"[Text Word] OR "Cross-Over Studies"[Text Word] OR "double blind"[Text Word] OR "placebo*"[Text Word] OR "placebos*"[Text Word] OR "RaCT"[Text Word] OR "RaCTs"[Text Word] OR "research design"[MeSH Terms:noexp] OR "research design"[Text Word] OR "Research designs"[Text Word] OR "single blind"[Text Word] OR (("single*"[Text Word] OR "double*"[Text Word] OR "triple*"[Text Word]) AND ("blind*"[Text Word] OR "mask*"[Text Word])) OR "volunteer*"[Text Word] OR "trial"[Title])) NOT (("congress"[Publication Type] AND 1980/01/01:2022/09/30[Date – Publication]) OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "Review"[Publication Type] OR "systematic review"[Publication Type] OR "comment"[Publication Type] OR "lecture"[Publication Type])) AND 1980/01/01:2025/09/30[Date – Publication].

Participant or population Patients with metastatic or advanced HER2-positive BC who are treated in second-line metastatic settings are included. HER2-positive BC is defined as histologically or cytologically confirmed with immunohistochemistry (IHC) score of 3+ or 2+ and /or HER2 gene amplification by in situ hybridization. There is no limitation on age, sex, co-morbidity, or hormone receptor status.

Intervention The group of interventions includes all relevant HER2-directed systemic treatment regimens currently used in the second-line settings. This includes, but is not limited to: monoclonal antibodies (e.g., trastuzumab, pertuzumab), antibody-drug conjugates (e.g., T-DM1, T-DXd), tyrosine kinase inhibitors (e.g., lapatinib, tucatinib, pyrotinib), combinations of the above with chemotherapy or endocrine therapy.

Comparator The comparator interventions included chemotherapy, lapatinib plus chemotherapy, and other relevant HER2-directed systemic therapies used as control groups in clinical trials of second-line mBC.

Study designs to be included Randomized controlled trials.

Eligibility criteria Inclusion criteria
1) Interventional clinical trials that included patients with previously treated metastatic or advanced HER2-positive BC. HER2-positive BC is defined as histologically or cytologically confirmed with immunohistochemistry (IHC) score of 3+ or 2+ and /or HER2 gene amplification by in situ hybridization.
2) Randomized controlled trials (RCTs) investigating HER2-directed systemic treatment regimens in the second-line and beyond setting.
Exclusion criteria
1) Non-randomized studies (e.g., single-arm trials, observational studies, cohort studies, case reports, reviews, editorials, letters).
2) Studies including participants with early-stage BC, HER2-negative BC, or a mixed HER2 status without randomized subgroup data in the HER2+ population, a mixed population with all lines of treatment, and studies investigating adjuvant/neoadjuvant therapies.
3) Studies where all participants had a history of more than two prior lines of anti-HER2 treatment for metastatic disease.

4) Studies involving treatment-naive patients receiving first-line (1L) therapy for metastatic disease.
5) Studies whose primary objective is to explore or compare different chemotherapy backbones when combined with the same anti-HER2 agent (e.g., comparing one taxane vs. another or vs. taxane-containing combination, or comparing taxane vs. anthracycline)
6) Studies without reporting outcome of progression free survival (PFS), defined as the time from randomization to disease progression (as defined by relevant criteria, typically RECIST) or death from any cause, whichever occurs first.
7) For the purpose of the Network Meta-Analysis, PFS must be reported as a Hazard Ratio (HR) with a 95% Confidence Interval (CI) comparing the intervention to the control arm. If the HR and CI are not explicitly stated, the study may still be included only if they can be accurately estimated from the published Kaplan-Meier curve using established methods.
8) Exclude studies including participants received maintenance therapy for metastatic BC.

Information sources PubMed, EMBASE, Cochrane Library and Web of Science.

Main outcome(s) Primary Outcome: The primary outcome is progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression or death from any cause. The treatment effect for PFS will be expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

Additional outcome(s) Secondary Outcomes: Secondary outcomes include overall survival (OS), objective response rate (ORR), and safety. Safety endpoints will focus on the incidence of grade 3 or higher adverse events (AEs) and AEs of special interest. All AEs will be evaluated and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For dichotomous safety data (e.g., AE rates), odds ratios (ORs) with 95% CIs will be utilized as the effect size for comparison.

Data management Data extraction will be completed using a data extraction form. The retrieved information will be cross-checked. Any disagreement will be discussed and a third reviewer will be involved if necessary. If important variables/ information are missing, attempts will be made to contact the authors of the included studies. The extracted data will include information on participants, study methods, concept, context, and key findings related to the outcome measurement relevant to the review question. The study outcomes of PFS and ≥10% grade 3 and higher AEs with corresponding effect size of HR and OR will be collected and compared. When long-term follow-up and updated data of a same clinical trial are reported, only the most recent and comprehensive data are included.

Quality assessment / Risk of bias analysis Quality assessment is performed according to Cochrane risk-of-bias tool (2.0). The assessment will be made based on five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of the reported result. Results from these five domains will be synthesized and recognized as low risk, high risk, or some concerns.

Strategy of data synthesis The network meta-analysis (NMA) will be conducted within a Bayesian framework using Markov Chain Monte Carlo (MCMC) simulation, implemented via the gemtc package in R software. This approach enables the simultaneous comparison of multiple treatment regimens by synthesizing direct and indirect evidence.
For time-to-event outcomes (e.g., PFS and OS), the treatment effect will be expressed as hazard ratios (HRs) with corresponding 95% credible intervals (CrIs). For dichotomous outcomes, objective response rate (ORR) will be compared using odds ratios (ORs) with 95% CrIs, while adverse events (AEs) will be analyzed using risk ratios (RRs) with 95% CrIs.
Model selection between fixed-effect and random-effect models will be based on the deviance information criterion (DIC) and the assessment of heterogeneity. Convergence of the MCMC chains will be assessed using the Gelman-Rubin statistic (potential scale reduction factor, PSRF), with values below 1.05 indicating satisfactory convergence.
To evaluate the relative ranking of interventions, the surface under the cumulative ranking curve (SUCRA) will be calculated. SUCRA values range from 0% to 100%; higher values indicate a greater probability of being among the most effective or safe treatments. All effect estimates will be presented with their 95% CrIs, and inferences will be based on the posterior probabilities.

Subgroup analysis To further assess the comparative efficacy of therapeutic regimens within specific clinical contexts, subgroup network meta-analyses will be performed exclusively for the primary outcome (PFS) in patients with hormone receptor-positive status, those with documented

brain metastases at baseline, and those presenting with visceral involvement. These analyses will be conducted contingent upon the availability of sufficient subgroup-level data from the included randomized controlled trials to ensure robust treatment comparisons within each predefined cohort.

Sensitivity analysis To assess the robustness of the findings from this network meta-analysis, we will conduct sensitivity analyses. To examine the presence of global inconsistency within the entire evidence network, we will compare the goodness-of-fit between the consistency model and the inconsistency model. Model fit will be evaluated using the deviance information criterion (DIC) within a Bayesian framework. The judgment criteria are as follows: If the DIC value of the inconsistency model is more than 5 points lower than that of the consistency model, it indicates significant global inconsistency. In this scenario, the estimates from the consistency model may be unreliable, and priority should be given to the results of the inconsistency model, or the findings should be interpreted with caution. Conversely, if the difference in DIC values is less than 5, it suggests no substantial global inconsistency, supporting the assumption of the consistency model; thus, the results from the consistency model can be used as the primary basis for analysis.

Language restriction English.

Country(ies) involved China.

Keywords HER2-positive, metastatic breast cancer, network meta-analysis.

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