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Efficacy and Safety of Trastuzumab Deruxtecan in HER2-High and HER2-Low Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - Chi Mei Medical Center, Liouying (CLFHR11432).

Review Stage at time of this submission - Completed but not published.

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 24 July 2025 and was last updated on 24 July 2025.

INTRODUCTION

Review question / Objective To investigate the efficacy and safety of trastuzumab deruxtecan in HER2-high and HER2-low breast cancer.

Rationale Trastuzumab deruxtecan (T-DXd), a HER2-targeted antibody–drug conjugate, has recently received approval for treating HER2-high and HER2-low breast cancer, highlighting the need to evaluate its efficacy across varying levels of HER2 expression. This meta-analysis addresses a gap in current evidence by evaluating the efficacy and safety of T-DXd in both HER2-high and HER2-low breast cancer subgroups.

Condition being studied The PICO framework (population, intervention, comparison, and outcome) guiding this meta-analysis was defined as follows: population (P): human participants; Intervention (I): T-DXd; Comparison (C): choice of physician or control treatment; and outcome (O): efficacy and safety.

METHODS

Search strategy Two investigators (T.-S.W. and S.-Y.H.) independently conducted comprehensive electronic searches of PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov using the keywords “Trastuzumab deruxtecan” and “breast cancer.” The search encompassed all records from the inception of each database to May 17, 2025.

Participant or population Human participants.

Intervention Trastuzumab Deruxtecan.

Comparator Choice of physician or control treatment.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies were included based on the following criteria: (1) randomized controlled trials (RCTs) involving human participants; (2) RCTs evaluating T-DXd as the intervention; (3) reporting

of efficacy outcomes such as progression-free survival (PFS) and overall survival (OS); and (4) availability of safety data on adverse events including anemia, neutropenia, nausea, vomiting, diarrhea, decreased appetite, interstitial lung disease or pneumonia, reduced left ventricular ejection fraction, and alopecia.

Information sources Two authors (T.-S.W. and S.-Y.H.) made independent electronic searches in the PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov using the keywords "Trastuzumab deruxtecan" and "breast cancer." The search encompassed all records from the inception of each database to May 17, 2025.

Main outcome(s) The primary outcome of this study was to evaluate the efficacy of T-DXd in enhancing PFS and OS.

Additional outcome(s) Secondary outcomes included the incidence of interstitial lung disease or pneumonitis and reductions in left ventricular ejection fraction. Additionally, commonly reported adverse events—including anemia, neutropenia, nausea, vomiting, diarrhea, and decreased appetite—were evaluated.

Data management Two independent reviewers (T.-S.W. and S.-Y.H.) extracted relevant data from the included studies, including the name of the first author, year of publication, participant characteristics (e.g., sex and HER2 IHC status), sample size, and reported values for primary and secondary outcomes. When essential data were not available in the published manuscripts, the corresponding authors were contacted to obtain the original data.

Quality assessment / Risk of bias analysis The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias 2 tool for randomized trials (RoB 2, version 2; London, United Kingdom). This tool evaluates five key domains: the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of reported results, culminating in an overall risk of bias judgment.

Strategy of data synthesis Given the variability in the types of TDX formulations across the included studies, a random-effects model was employed to account for this meta-analysis [15]. All analyses were conducted using Comprehensive Meta-Analysis software, version 4 (Biostat, Inc.). A p-value < 0.05 was considered statistically significant.

The primary outcome was evaluated by calculating hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). For secondary outcomes, risk ratios (RRs) and their 95% CIs were computed. In cases of zero-event outcomes in one or both arms, a continuity correction of 0.5 was applied. Between-study heterogeneity was assessed using the I^2 statistic, with I^2 values of 25%, 50%, and 75% interpreted as representing low, moderate, and high heterogeneity, respectively.

Subgroup analysis Subgroup analyses were conducted based on HER2 expression subtypes. Meta-regression analyses were conducted to examine the relationship between treatment effect and duration of response, with respect to PFS as previously defined.

Sensitivity analysis To evaluate the robustness of the meta-analysis findings, sensitivity analyses were conducted using a one-study removal approach, in which each study was sequentially excluded to assess its influence on the overall effect estimate.

Language restriction No language limit.

Country(ies) involved Taiwan.

Keywords Trastuzumab deruxtecan, HER2, breast cancer, meta-analysis, systematic review.

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