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INPLASY

Trastuzumab deruxtecan versus trastuzumab emtansine for HER2-positive breast cancer: a meta-analysis of phase 3 randomized trials with subgroup analysis by disease stage – a protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No funding received for this systematic review.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650093

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 May 2026 and was last updated on 16 May 2026.

INTRODUCTION

Review question / Objective Population: Adult patients (≥18 years) with pathologically confirmed HER2-positive breast cancer, any stage (metastatic or early-stage).
Intervention: Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg intravenously every 3 weeks.
Comparator: Trastuzumab emtansine (T-DM1) 3.6 mg/kg intravenously every 3 weeks.
Outcome: Primary – event-free survival (EFS), defined as progression-free survival (PFS) for metastatic setting and invasive disease-free survival (iDFS) for early-stage setting. Secondary – overall survival (OS), objective response rate, safety outcomes (interstitial lung disease, grade ≥3 adverse events, treatment discontinuation).

Rationale Trastuzumab emtansine (T-DM1) has been standard second-line therapy for HER2-positive metastatic breast cancer for over a decade. Trastuzumab deruxtecan (T-DXd) is a novel antibody-drug conjugate with a distinct mechanism. Recent phase 3 trials (DESTINY-Breast03 with 5-year follow-up, and DESTINY-Breast05) have shown superior efficacy of T-DXd over T-DM1. This meta-analysis integrates mature data to provide a contemporary synthesis across disease stages.

Condition being studied HER2-positive breast cancer (metastatic and early-stage/high-risk).

METHODS

Search strategy PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science. Search period: from database inception to April 15, 2026. No language restrictions. Example PubMed string: ("trastuzumab deruxtecan" OR "T-DXd" OR "DS-8201") AND ("trastuzumab emtansine" OR "T-DM1" OR "ado-trastuzumab emtansine") AND ("HER2-positive" OR "HER2+" OR "ERBB2") AND ("breast cancer" OR "breast neoplasm") AND ("randomized controlled trial" OR "phase 3").

Participant or population Adult patients (≥18 years) with histologically confirmed HER2-positive breast cancer, regardless of clinical stage (metastatic or early-stage/high-risk).

Intervention Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg intravenously every 3 weeks.

Comparator Trastuzumab emtansine (T-DM1) 3.6 mg/kg intravenously every 3 weeks.

Study designs to be included Phase 3 randomized controlled trials (open-label with blinded independent central review).

Eligibility criteria Inclusion: Phase 3 RCTs directly comparing T-DXd vs T-DM1 for HER2-positive breast cancer; reporting at least one of the outcomes of interest. Exclusion: Non-randomized studies, case reports, reviews, studies comparing with other drugs, duplicate publications, HER2-low breast cancer.

Information sources PubMed, Embase, Cochrane CENTRAL, Web of Science. Additionally, reference lists of included studies and relevant systematic reviews, and conference proceedings (San Antonio Breast Cancer Symposium 2025) were manually searched.

Main outcome(s) Primary outcome: Event-free survival (EFS), defined as progression-free survival (PFS) for metastatic breast cancer and invasive disease-free survival (iDFS) for early breast cancer. Hazard ratios (HR) with 95% confidence intervals (CI) will be used as the effect measure.

Additional outcome(s) Overall survival (OS) (HR with 95% CI); objective response rate (risk ratio with 95% CI); any-grade interstitial lung disease (ILD); grade ≥3 treatment-related adverse events; treatment discontinuation due to adverse events (proportions with 95% CI).

Data management Two independent reviewers extracted data using a standardized, pilot-tested extraction form. Discrepancies were resolved by consensus or a third reviewer. Data were managed using Microsoft Excel.

Quality assessment / Risk of bias analysis Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, evaluating five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Strategy of data synthesis Meta-analyses were performed using Review Manager (RevMan) version 5.4 and R version 4.2.0 (meta package). Hazard ratios for time-to-event outcomes were pooled using the generic inverse-variance method. A random-effects model (DerSimonian-Laird) was used for EFS; a fixed-effect model was used for OS. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test.

Subgroup analysis Subgroup analysis was performed by disease stage: metastatic breast cancer (DESTINY-Breast03 final analysis) vs high-risk early breast cancer (DESTINY-Breast05 interim analysis). Interaction was tested using the Altman-Bland method.

Sensitivity analysis Sensitivity analysis was conducted by excluding the 43-month interim dataset of DESTINY-Breast03, retaining only the 51-month final dataset and DESTINY-Breast05 dataset, using a random-effects model.

Language restriction No language restrictions.

Country(ies) involved China.

Other relevant information The systematic review and meta-analysis had been completed prior to submission of this registration. No amendments were made to primary or secondary outcomes after data analysis. The study was conducted in accordance with the PRISMA 2020 statement. This registration is submitted retrospectively but meets INPLASY requirements for completed reviews.

Keywords HER2-positive breast cancer; trastuzumab deruxtecan; trastuzumab emtansine; meta-analysis; randomized controlled trial; interstitial lung disease.

Dissemination plans The results will be submitted for publication in a peer-reviewed journal (e.g., Breast Cancer Research and Treatment, European Journal of Cancer, or similar).

Contributions of each author

Author 1 - Yongchang Chen - Designed the study, analyzed data, and wrote the manuscript.
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Author 4 - Hong Wang - Supervised the study, revised and approved the final manuscript.

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