RESEARCH PAPER

SAFETY AND EFFICACY OF TRASTUZUMAB EMTANSINE AND TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2 METASTATIC BREAST CANCER

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ABSTRACT

Background: Human Epidermal growth factor Receptor 2-positive Metastatic Breast Cancer is challenging to treat; therapies like trastuzumab emtansine and trastuzumab deruxtecan are used to target this subtype. Despite advancements in treatment, including anti-Human Epidermal growth factor Receptor 2 therapies like trastuzumab emtansine and trastuzumab deruxtecan, treatment resistance & disease progression remain significant challenges. This systematic review aims to compare safety and efficacy of trastuzumab emtansine and trastuzumab deruxtecan in patients with Human Epidermal growth factor Receptor 2-positive metastatic breast cancer. **Methods:** A systematic review of Randomized Controlled Trial from January 2019 to December 2024 and a literature search conducted in databases like Scopus, PUBMED, Embase, and Cochrane Library. **Results:** Seven Randomized Controlled Trial met the inclusion criteria. Trastuzumab deruxtecan showed a longer Progression-Free Survival sand higher objective response rate (78.9%) compared to Trastuzumab emtansine (36.9%). Trastuzumab deruxtecan exhibits more adverse events like pneumonitis and Interstitial Lung Disease. **Conclusions:** Trastuzumab deruxtecan demonstrated a reduced risk of disease progression, mortality rate and resulted in longer Progression-Free Survival compared to those on Trastuzumab emtansine among patients with Human Epidermal growth factor Receptor 2-positive Metastatic Breast Cancer previously treated with trastuzumab and taxane.

Keywords:

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The authors declare that there is no conflict of interest.

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Silviya Jenifer (S.J): Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing; **Sneha Raja (S.R):** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing; **Satish Srinivas Kondaveeti (S.S.K):** Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review and editing; **Sujatha Kuppusamy (S.K):** Writing – review and editing, Formal analysis**; Christian Gnanaraj Johnson (C.G.J):** Writing – review and editing, Formal analysis; **Jayasutha Jayram (J.J):** Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review and editing.

INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed malignancy among women globally, with over 2 million new cases reported in 2020. Over the last three decades, BC incidence and mortality rates have risen, largely due to the improvement in cancer detection, cancer registration, and risk factor patterns. Currently, those over 50 years of age account for nearly 80% of BC patients [1,2]. About 360,000 new instances of HER2 BC occur worldwide each year, making for 20–25% of all BC [3,4,5]. About 15–30% of breast tumors have HER2 gene amplification or overexpression [6]. Despite their improved clinical outcomes, HER2-targeted medications are not effective for metastatic tumors or localized cancer, and the majority of individuals will experience progression of the disease. The first-line treatment for newly diagnosed HER2-positive MBC involves a combination of Pertuzumab and Trastuzumab (anti-HER2 antibodies) with a taxane. Antibody drug conjugates (ADCs) are a class of targeted cancer therapies that combine monoclonal antibodies with cytotoxic payloads, designed to deliver targeted chemotherapy more selectively to cancer cells. Patients whose illness worsens after this course of treatment, second-line treatments include T-DXd and T-DM1 [7, 8, 9, 10].

T-DXd is comprised of a humanised anti-HER2 monoclonal antibody covalently linked to a potent topoisomerase I inhibitor payload (DXd) to form an antibody-drug conjugate (ADC). Its high drug-to-antibody ratio (8:1) enables efficient delivery of a substantial amount of DXd to HER2-expressing tumour cells. Following binding and internalization of T-DXd, the tetrapeptide-based linker is cleaved intracellularly, releasing the cytotoxic payload. Due to its membrane-permeable properties, DXd can diffuse into neighbouring neoplasm regardless of their HER2 expression, producing a bystander anti-tumour effect [13, 14, 15].

Trastuzumab emtansine (T-DM1) combines the cytotoxic activity of the microtubule-antagonist compound DM1 with the HER2-targeted anticancer effects of trastuzumab. T- DM1 enhances the therapeutic index and reduces exposure of healthy tissue by enabling intracellular drug transport that targets HER2-overexpressing cells precisely [16, 17, 18]. Similar to trastuzumab, T-DM1 causes antibody-dependent cellular cytotoxicity, stops HER2 shedding, and suppresses HER2 signaling. For HER2 MBC that has previously received trastuzumab and a taxane treatment, T-DM1 is approved as a single agent therapy [19]. In view of its beneficial effect on HER2 metastatic breast cancer, In order to compare the safety & efficacy of trastuzumab deruxtecan with trastuzumab emtansine in HER2 breast cancer, we conducted a systematic review of randomized controlled trials (RCTs).

METHODOLOGY

The safety and efficacy of trastuzumab deruxtecan and trastuzumab emtansine as a treatment for patients with HER2 MBC were studied in this literature review by a quantitative analysis of the available RCTs.

SEARCH STRATEGY AND STUDY SELECTION:

We conducted a literature search in the database: Scopus, PUBMED, Cochrane Library & Embase from January 2019 - December 2024. In addition, we manually searched reference lists of all relevant review and original articles to find additional eligible studies. We searched using the following keywords “T-DXd”, “T-DM1”, “HER2 BC”. Boolean operators were used to combine specific keywords with free-text terms. We included full-text randomized controlled trials on T-DXd and T-DM1 for treating HER2-metastatic breast cancer, published in English-language. if they lacked full text, were duplicates, case reports, brief reports, conference proceedings, observational cohort studies, or non-randomized controlled trials were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed in conducting this systematic review [20].

DATA EXTRACTION AND ANALYSIS:

The data that was taken from all the included study comprised of publication year, Author name, study design, country of origin, inclusion criteria, exclusion criteria, interventions (including anti-HER2 therapy dose, duration, and type, number of patients in each group, chemotherapy type (trastuzumab with or without taxane), follow-up time, and treatment outcomes. Variations in the overview of the results have been assessed and solved. The initial screening, which involved reading the title and abstract, and the secondary screening, which involved reading the full text were done. PRISMA flowchart was used to describe the selection of studies.

The quality and reliability of the data were assessed for this study using the Cochrane Risk of Bias 2.0 Assessment for included RCTs. Deviations from intended interventions, randomization, measurement of outcomes, selective reporting and missing outcome data are the five core domains that this tool assesses. The overall judgement was based on each study's rating of low risk, some concerns or high risk of bias. Two independent reviewers performed the assessment, and any disagreements resolved by consensus [21,22]

RESULT:

Implementing the above search methodology, altogether 213 studies were selected of which, 8 studies were neglected because of duplication, 110 studies were excluded for not complying with the inclusion criteria (books, case reports, not breast cancer), 95 studies were retrieved and 36 studies were not retrieved (not relevant, conference abstracts, review article), 59 studies were selected out of which 29 were excluded due to unavailability of full text, 16 studies were excluded because of non RCT and 7 studies were excluded due to non-HER2 breast cancer. The remaining 7 Randomized Controlled Trials (RCTs) were included and reviewed summarized in Figure 1 [20]. Table 1 represents characteristics of selected studies of Trastuzumab deruxtecan and Trastuzumab emtansine for HER 2 metastatic breastcancer. Table 2 represents Cochrane Risk Of Bias 2.0 Assessment For Included Rcts. [21,22]

The patients, who had previously undergone a median of two lines of therapy, were randomly assigned to receive either T-DXd or T-DM1. The study found that T-DXd significantly outperformed T-DM1 in several critical metrics. Firstly, the objective response rate (ORR) was notably higher in the T-DXd group (78.9%) compared to the T-DM1 group (36.9%). Significant larger proportion of patients in the T-DXd group experienced a measurable reduction in tumor size compared with T-DM1. Additionally, the median progression-free survival (PFS), without disease progression, was higher for the T-DXd group compared to the T-DM1 group [12]. Stable brain metastases were reported in 23.8% of the T-DXd group and 19.8% of the T-DM1 group.

Drug-related TEAE resulted in treatment discontinuation in 20% of patients in the T-DXd group and 7% of patients in the T-DM1. Common adverse events included nausea, neutropenia, fatigue, and vomiting, with a higher incidence of drug-related ILD or pneumonitis observed in the T-DXd group compared to T-DM1. Dose reduction due to drug-related TEAEs was reported in 25% of patients treated in T-DXd and 15% of those treated with T-DM1 [23]. Despite these adverse events, the efficacy results demonstrated significant benefits of T-DXd over T-DM1, making T-DXd a promising management for HER2-positive MBC. The time to first documented progression on next- line therapy was also significantly longer for T-DXd compared to T-DM1, reinforcing the overall superior efficacy of T-DXd in patients [24].

The risk of bias assessment indicated that most included trials were of high methodological quality. Five studies consistently demonstrated low risk across all domains, reflecting strong randomization methods, complete outcome reporting, and reliable assessments. Importantly, none of the trials was rated at high risk of bias. This highlights the overall robustness of the included evidence. The consistency of findings across well-conducted RCTs strengthens confidence in the study conclusions [21, 22]

DISCUSSION

Patients with HER2-positive MBC on T-DXd demonstrated lower risk of disease progression or death compared to those patients treated with T-DM1. The duration of PFS was significantly longer with T-DXd than with T-DM1 [8]. In the real-world second-line setting, the median PFS is 12.1 months for T-DXd [27] and 8 to 12 months for those receiving T-DM1 [23]. Patients on T-DXd showed a higher rate of tumor size reduction or complete tumor disappearance, compared with T-DM1.

Intracranial PD (progressive disease) was observed in fewer patients randomised to T-DXd than those assigned to T-DM1 [24]. Although the overall incidence of grade ≥3 TEAEs was comparable between treatment groups, neutropenia occurred more frequently with T-DXd, whereas thrombocytopenia was more common with T-DM1. Fatigue, gastrointestinal disorders, and hematologic toxicities were the most common adverse events observed with both treatments. However, ILD and pneumonitis occurred more frequently in patients receiving T-DXd than in those receiving T-DM1, highlighting the need for careful monitoring [23]. The incidence of drug-related adverse events leading to treatment

discontinuation, dose reduction, or treatment interruption was higher in patients treated with trastuzumab deruxtecan than in those receiving T-DM1. Although T-DXd was associated with a greater frequency of TEAEs than T-DM1, a larger number of patients continued treatment with T-DXd. The overall safety profile of T-DXd was considered to be manageable. Both T-DXd and T-DM1 demonstrated a clinically meaningful benefit in overall survival. The longest reported median PFS of T-DXd observed in the study by Sara A Hurvitz et al., supports the utilization of T-DXd as the standard of care for second- line treatment of patients with HER2-positive MBC [28,29].

CONCLUSION

T-DXd demonstrated a reduced risk of disease progression, mortality rate and resulted in longer PFS compared to those on T-DM1 among patients with HER2-positive MBC previously treated with trastuzumab, and taxane. Even though T-DXd was associated with a greater frequency of TEAEs than T-DM1, a larger number of patients continued treatment with T-DXd due to superior efficacy and manageable safety profile. Clinicians should consider T-DXd as the preferred second-line therapy with vigilant pulmonary monitoring.

ABBREVATION

Breast cancer (BC), Metastatic breast cancer (MBC), Human epidermal growth factor receptor 2 (HER2), Estrogen receptor (ER), Brain metastases (BM), Trastuzumab deruxtecan (T-DXd), Trastuzumab emtansine (T-DM1), Antibody-drug conjugate (ADC), Objective response rate (ORR), Progression-free survival (PFS), Interstitial lung disease (ILD), Treatment emergent adverse effect (TEAE), Response Rate (RR).

REFERENCE

1. Lukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers, 13*(17), 4287.
2. Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., & Bray, F. (2020). Global Cancer Observatory: Cancer Today; International Agency for Research on Cancer: Lyon, France. Retrieved from https://gco.iarc.fr/today
3. Schlam, I., & Swain, S. M. (2021). HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. *npj Breast Cancer, 7*(56). https://doi.org/10.1038/s41523-021-00265-1
4. Spector, N. L., & Blackwell, K. L. (2009). Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer. *Journal of Clinical Oncology, 27*(35), 5838–5847
5. Yarden, Y., & Sliwkowski, M. X. (2001). Untangling the ErbB signalling network. *Nature Reviews Molecular Cell Biology, 2*(2), 127-137.
6. Iqbal, N., & Iqbal, N. (2014). Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Molecular Biology International, 2014*, 852748. https://doi.org/10.1155/2014/852748
7. Cortés, J., Kim, S. B., Chung, W. P., et al. (2022). Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *New*
8. *England Journal of Medicine, 386*(12), 1143-1154.
https://doi.org/10.1056/NEJMoa2115022
9. Harbeck, N., Penault-Llorca, F., Cortes, J., et al. (2019). Breast cancer. *Nature Reviews Disease Primers, 5*, 66. https://doi.org/10.1038/nrdp.2019.66
10. Zelizer, S., Gallagher, G.B., Gonen, M. *et al.* Evaluating post-T-DXd treatment strategies in HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* **215**, 19 (2026). https://doi.org/10.1007/s10549-025-07853-w
11. Cardoso, F., Paluch-Shimon, S., Senkus, E., et al. (2020). 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology, 31*, 1623-1649.
12. Cortés, J., Hurvitz, S. A., Im, S. A., et al. (2024). Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY- Breast03 trial. *Nature Medicine, 30*, 2208–2215. https://doi.org/10.1038/s41591-024-03021-7
13. Martín, M., Pandiella, A., Vargas-Castrillón, E., Díaz-Rodríguez, E., Iglesias-Hernangómez, T., Martínez Cano, C., et al. (2024). Trastuzumab deruxtecan in breast cancer. *Critical Reviews in Oncology/Hematology, 198*, 104355. https://doi.org/10.1016/j.critrevonc.2024.104355
14. Lewis Phillips, G. D., Li, G., Dugger, D. L., Crocker, L. M., Parsons, K. L., Mai, E., Blättler, W. A.,
Lambert, J. M., Chari, R. V., Lutz, R. J., Wong, W. L., Jacobson, F. S., Koeppen, H., Schwall, R. H., Kenkare-Mitra, S. R., Spencer, S. D., & Sliwkowski, M. X. (2008). Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. *Cancer Research, 68*, 9280- 9290.
15. Nakada, T., Masuda, T., Naito, H., Yoshida, M., Ashida, S., Morita, K., Miyazaki, H., Kasuya, Y.,

Ogitani, Y., Yamaguchi, J., Abe, Y., & Honda, T. (2016). Novel antibody drug conjugates containing exatecan derivative-based cytotoxic payloads. *Bioorganic & Medicinal Chemistry Letters, 26*(4), 1542- 1545.

16. Verma, S., Miles, D., Gianni, L., et al. (2012). Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in New England Journal of Medicine, 2013 Jun 20;368(25):2442]. *New England Journal of Medicine, 367*(19), 1783-1791. https://doi.org/10.1056/NEJMoa1209124

17. Krop, I. E., LoRusso, P., Miller, K. D., et al. (2012). A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *Journal of Clinical Oncology, 30*(32), 3234-3241.

18. Burris, H. A. III, Rugo, H. S., Vukelja, S. J., et al. (2011). Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *Journal of Clinical Oncology, 29*(4), 398-405.

19. Krop, I. E., Lin, N. U., Blackwell, K., Guardino, E., Huober, J., Lu, M., ... & Miles, D. (2015). Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Annals of Oncology, 26*(1), 113-119. https://doi.org/10.1093/annonc/mdu486

20. Haddaway NR, Page MJ, Pritchard CC, et al. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022; 18(2): e1230, doi: 10.1002/cl2.1230, indexed in Pubmed: 36911350

21. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. (2019). *RoB 2: A revised tool for assessing risk of bias in randomized trials*. BMJ, 366, l4898. https://doi.org/10.1136/bmj.l4898

22. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). (2022). *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3*. Cochrane. Available from: https://training.cochrane.org/handbook

23. Iwata, H., Xu, B., Kim, S.-B., et al. (2024). Trastuzumab deruxtecan versus trastuzumab emtansine in Asian patients with HER2-positive metastatic breast cancer. *Cancer Science, 115*, 3079-3088. https://doi.org/10.1111/cas.16234

24. Hurvitz, S. A., Kim, S.-B., Chung, W.-P., Im, S.-A., Park, Y. H., Hegg, R., et al. (2024). Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open, 9*(5).

25. **André F, Hee Park Y, Kim SB, et al.** Trastuzumab Deruxtecan versus Treatment of Physician's Choice in Patients with HER2-Positive Unresectable and/or Metastatic Breast Cancer (DESTINY-Breast02): A Randomised, Open-Label, Multicentre, Phase 3 Trial. *Lancet.* 2023;401(10390):1773–1785. doi:**10.1016/S0140-6736(23)00724-0**.

26. **Cortés J, Corigliano G, Kim SB, et al.** Health-Related Quality of Life with Trastuzumab Deruxtecan versus Trastuzumab Emtansine in Patients with HER2-Positive Metastatic Breast Cancer: Results from the DESTINY-Breast03 Trial. *ESMO Open.* 2023;8(6):102045. doi:**10.1016/j.esmoop.2023.102045**.

27. Tarantino, P., et al. (2024). Outcomes with trastuzumab deruxtecan (T-DXd) by HER2 status and line of treatment in a large real-world database of patients with metastatic breast cancer. *Journal of Clinical Oncology, 42*, 1077-1077.

28. Hurvitz, S. A., Hegg, R., Chung, W. P., Im, S. A., Jacot, W., et al. (2023). Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomized, open-label, phase 3 trial. *Lancet (London, England), 401*(10371), 105–117.

29. Hamilton, E. P., Petry, V., Bragaia, H., et al. (2022). Trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with HER2-positive (HER2+) unresectable and/or metastatic breast cancer (mBC): safety follow-up of the randomized, phase 3 study DESTINY- Breast03. *Proceedings of the American Society of Clinical Oncology, 40*, 1000.

Figures:

Figure 1

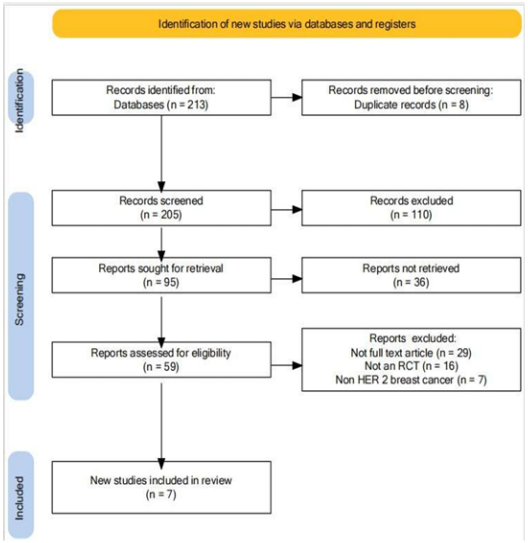

Figure 1: Prisma Chart

Tables:

TABLE 1: CHARACTERISTICS OF SELECTED STUDIES ON TRASTUZUMAB DERUXTECAN AND TRASTUZUMAB EMTANSINE FOR HER2 METASTATIC BREASTCANCER

SI. NO	AUTHOR	STUDY DESIGN	INCLUDED CRITERIA	EXCLUDED CRITERIA	INTERVENTION/ COMPARTOR	FOLLOW-UP	TREATMENT OUTCOME	ADVERSE EFFECT
1	Javier cortes *et al*., (2024)[12]	randomized, multicenter, open-label Phase III clinical trial.	Adults aged 18 years or older. Pathologically documented HER2-positive BC that is unresectable or metastatic. Patients must have received prior treatment with	Patients with Prior treatment with an anti-HER2 antibody-drug conjugate (ADC). Spinal cord compression or clinically active central nervous	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	28 months.	Trastuzumab deruxtecan (T-DXd) demonstrated significantly improved efficacy over trastuzumab emtansine (T-DM1).	Left ventricular dysfunction or left ventricular ejection fraction decrease and

			trastuzumab and a taxane in the metastatic setting.	system (CNS) metastases. Clinically significant cardiac disease. History of interstitial lung disease (ILD) or pneumonitis requiring				pneumonitis.
				steroids or ILD/pneumonitis at screening.				
2.	S. A. Hurvitz *et al.,* (2024)[24]	Randomized, multicenter, open-label, phase III study.	Patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast	Patients with history of non-infectious interstitial lung disease (ILD)/pneumoniti	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	28 months for trastuzumab deruxtecan	Patients with HER2-positive m BC whose disease progressed after trastuzumab and a	Interstitial lung disease and Pneumonitis.

			cancer previously treated with trastuzumab and a taxane. Patients with clinically inactive/asymptomatic brain metastasis.	s that required glucocorticoids or had suspected ILD/pneumonitis that could not be ruled out by imaging at screening.		26 months for trastuzumab emtansine (T-DM1)	taxane achieved a substantial benefit from treatment with T-DXd compared with T-DM1, including those with baseline BMs.	

3.	Hiroji Iwata *et al.,*(2024)[23]	Open-label, multicenter, randomized, active-controlled, phase 3 study	Patients whose age is ≥18 years with centrally confirmed / pathologically documented HER2-positive unresectable or m BC that was previously treated with trastuzumab and taxane.	Patients who had previous treatment with an anti-HER2 ADC, including T-DM1, uncontrolled or clinically significant cardiovascular disease; ongoing ILD or	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	29.0 months for Trastuzumab Deruxtecan 26.0 months with trastuzumab emtansine	In Asian DESTINY-Breast03 patients with HER2-positive m BC previously treated with trastuzumab (with or without pertuzumab) and a	Nausea, neutropenia, fatigue, vomiting and Pneumonitis.

				pneumonitis, history of ILD or pneumonitis that required steroids, or suspected ILD or pneumonitis that could not be ruled out by imaging and spinal cord compressi			taxane, T-DXd had a substantially larger clinical benefit (longer PFS and OS) compared with T-DM1.	
				on or brain metastases that were symptomatic or required treatment with steroids or anticonvulsants.				

4.	Fabrice Andre *et al.,* (2023) [25]	Randomized, open-label, multicenter, phase 3 trial	Patients aged 18 years or older had pathologically documented unresectable or metastatic breast cancer that was centrally confirmed as HER2-positive breast cancer. Patients	Patients who received previous treatment with capecitabine, patients with history of any contraindication for capecitabine or trastuzumab and	Trastuzumab Deruxtecan Vs Physician choice	21·5 months for trastuzumab deruxtecan group 18·6 months in the treatment of	DESTINY-Breast02 show the favourable benefit–risk profile of trastuzumab deruxtecan in	Nausea, vomiting, fatigue, diarrhea and interstitial lung disease.			previously received trastuzumab emtansine, documented radiological disease progression, protocol defined adequate renal and hepatic function.	lapatinib, cardiovascular disease, history of non-infectious interstitial lung disease or pneumonitis, spinal cord compression or clinically active brain metastases.		physician choice	patients with HER2 positive metastatic breast cancer resistant or refractory to	

							trastuzumab emtansine, as previously reported in DESTINY-Breast01, and support this drug as the preferred therapy for patients who received trastuzumab emtansine.	

5.	Sara A Hurvitz *et al.,* (2023) [27]	Open-label, randomized, multicenter, phase 3 trial	Patients who aged 18 or older, had HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane, had an Eastern Cooperative Oncology Group performance status 0–1, and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1	Patients with the history of interstitial lung disease or pneumonitis, patients who had been previously treated with an anti-HER2 antibody–drug conjugate in the metastatic setting or if they had uncontrollable or clinically significant cardiovascular disease.	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	28·4 months for trastuzumab deruxtecan 26·5 months for trastuzumab emtansine	Trastuzumab deruxtecan showed a statistically significant improvement in overall survival	Interstitial lung disease and Pneumonitis.												

							with HER2-positive metastatic breast cancer previously treated with trastuzumab.	
6	Jcortes *et al.,*(2023)[26]	Open-label, multicenter, phase III study.	Patients who	Patients with presence of clinically active central nervous system metastases, previous	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	14.3 months for Trastuzumab Deruxtecan 6.9 Months for trastu	Health related quality of life was maintained longer by those receiving T- DXd versus T-DM1.	Nausea, vomiting, and fatigue, neutropenia, thrombocyte-

			had expericenced as	treatment with an HER2 antibody drug conjugate, or a history of noninfectious ILD for which they had received glucocorticoids or suspected ILD that		zumab emtansine		penia, leukopenia and pneumonitis.
				e progression on or after trastuzumab and a taxane in the advanced/metastatic setting.	could not be ruled out by imaging at screening.				
7.	Javier cortes *et al.,* (2022) [8]	A phase 3, multicenter, open-label, rando	Patients with HER2-positive unresectable or metastatic breast cancer that had	Patients with brain metastases that were symptomatic or required treatmen	Trastuzumab Deruxtecan Vs Trastuzumab emtansine	28 months for trastuzumab deruxtecan (T-DXd	Treatment with trastuzumab deruxtecan showed a benefit over	Interstitial lung disease and pneumonitis

		mized, active-control led trial.	progressed during or after treatment with trastuzumab and a taxane. Patients with brain metastases were eligible for enrollment if they had clinically stable, previously treated brain	t; if they had previously been treated with a HER2 antibody – drug conjugate, including trastuzumab emtansine, in the context of		) 26 months for trastuzumab emtansine (T-DM1)	trastuzumab emtansine with respect to progression-free survival.	

			metastases.	metastatic disease; if they had a history of noninfectious interstitial lung disease for which they had received glucocorticoids; or if they had				

				suspected interstitial lung disease that could not be ruled out by imaging.				

TABLE 2: COCHRANE RISK OF BIAS 2.0 ASSESSMENT FOR INCLUDED RCTs [21-22]

Study (Author, Year)	**Randomization process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of outcomes**	**Selection of reported results**	**Overall risk of bias**
Javier cortes *et al*., (2024) [12]	Low	Low	Low	Low	Low	Low
S. A. Hurvitz *et al.,* (2024) [24]	Low	Low	Low	Low	Low	Low
Hiroji Iwata *et al.,*(2024) [23]	Low	Low	Low	Low	Low	Low
Fabrice Andre	Some concerns	Low	Low	Low	Some concerns	Some concerns

et al., (2023) [25]						
SaraA Hurvitz *et al.,* (2023) [27]	Low	Low	Low	Low	Low	Low
J cortes *et al.,*(2023) [26]	Low	Some concerns	Low	Some concerns	Low	Some concerns
Javier cortes *et al.,* (2022) [8]	Low	Low	Low	Low	Low	Low