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ORIGINAL RESEARCH

Trastuzumab deruxtecan in human epidermal growth factor receptor 2-positive breast cancer brain metastases: a systematic review and meta-analysis☆

I. Michelon[1†], M. Vilbert[2*], A. D. Marinho[3†], C. E. R. Castro[4†], M. I. Dacoregio[5†], C. Stecca[6], L. R. Soares[7], M. V. Batista[8,9], S. Braga[8,9], A. Saeed[10] & L. Cavalcante[11*]

[1]Department of Medicine, Catholic University of Pelotas, Pelotas, Brazil; [2]Department of Medicine, Division of Hematology and Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, USA; [3]Department of Medicine, Federal University of the State of Rio de Janeiro, Rio de Janeiro; [4]Department of Medicine, University of Brasilia, Brasilia; [5]Department of Medicine, University of Centro Oeste, Guarapuava; [6]Department of Medicine, Parana Oncology Center, Curitiba; [7]Department of Medicine, Federal University of Goiás, Goiania, Brazil; [8]Medical Oncology Department, Hospital Prof. Doctor Fernando Fonseca, Amadora; [9]Haematology and Oncology Department, CUF Oncology, Sintra, Portugal; [10]Department of Medicine, Division of Hematology & Oncology, University of Pittsburgh Medical Center (UPMC), Pittsburgh; [11]Department of Medical Oncology, Novant Health Cancer Institute, Charlotte, USA

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Background: Trastuzumab deruxtecan (T-DXd) has shown promising results in patients with breast cancer brain metastases (BCBMs). We conducted a systematic review and meta-analysis to evaluate the effectiveness and safety of T-DXd in the human epidermal growth factor receptor 2 (HER2)-positive BCBM population.

Patients and methods: We searched PubMed, Embase, and Cochrane Library databases as well as American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) websites for clinical trials (CTs) and observational studies evaluating T-DXd in patients with HER2-positive BCBM. Heterogeneity was assessed with I^2 statistics. Random effects models were used for all statistical analyses, which were carried out using R software (version 4.2.2).

Results: Ten studies were included, six CTs ($n = 189$) and four observational studies ($n = 130$), with a total of 319 patients. The median progression-free survival was 15 months [95% confidence interval (CI) 13.9-16.1 months]. The objective response rate (ORR) was 61% (95% CI 52% to 70%), and the intracranial (IC)-ORR was 61% (95% CI 54% to 69%). No significant differences in ORR and IC-ORR were observed between CTs and observational studies ($P = 0.31$ and 0.58, respectively). The clinical benefit rate (CBR) was 80% (95% CI 52% to 94%), and the IC-CBR was 70% (95% CI 54% to 82%). The ORR was 68% (95% CI 57% to 77%) in the subgroup of patients with stable BMs and 60% (95% CI 48%-72%) in patients with active BM, with no significant difference between groups ($P = 0.35$).

Conclusions: Our systematic review and meta-analysis supports the IC activity of T-DXd in patients with stable BM and active BM.

Trial registration: International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42023422589.

Key words: trastuzumab deruxtecan, T-DXd, antibody-drug conjugate, brain metastases, human epidermal growth factor receptor 2, HER+, breast cancer

INTRODUCTION

Approximately 30%-50% of patients with breast cancer (BC) will develop brain metastases (BMs).[1] Among primary tumors, breast cancer has one of the highest incidences of BMs.[2] The incidence of central nervous system (CNS) progression in patients with BC is rising following the improvements in survival rates associated with systemic therapies.[1,2] Remarkably, the BC subtypes of human epidermal growth factor receptor 2-positive (HER2+) and triple-negative amplification tumors are more frequently associated with BMs.[2] Patients with the HER2+ subtype

*Correspondence to: Dr. Maysa Vilbert, Department of Medicine, Division of Hematology and Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, 5115 Centre Avenue, Pittsburgh, PA 15232, USA
E-mail: maysa.vilbert@gmail.com (M. Vilbert).
*Dr. Ludimila Cavalcante, Department of Medical Oncology and Hematology, University of Virginia Comprehensive Cancer Center, 1215 Lee Street, Charlottesville, VA 22903, USA
E-mail: ludi.cavalcante@gmail.com (L. Cavalcante).

†Medical Student.

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have a median time of 10.8 months to develop CNS metastases.[3] Unfortunately, this subgroup of patients suffers from poor quality of life and limited life expectancy, with overall survival ranging between 2 and 16 months.[3,4]

The recommended first-line therapy for metastatic HER2-positive BC includes dual HER2 blockade with trastuzumab and pertuzumab plus chemotherapy.[5] Initially, systemic therapies were thought to have limited efficacy in controlling brain lesions due to their inability to effectively cross the highly selective blood—brain barrier and achieve therapeutic levels to control brain disease.[6] Thus local therapies, namely, whole-brain radiotherapy, stereotactic radiotherapy, stereotactic and radiosurgery, have been the mainstay treatment for patients with BMs.[1] Despite these interventions, the prognosis of such patients remains dismal.[6]

Recent evidence suggests that the disruption of the blood—brain barrier by tumor cells could lead to changes in its permeability allowing large molecules to cross it.[6] The idea is supported in several clinical trials (CTs) evaluating antibody—drug conjugates (ADCs), specifically trastuzumab deruxtecan (T-DXd).[4,7] Composed of a humanized antibody covalently linked to the drug deruxtecan (a topoisomerase I blocking agent), T-DXd has shown high intracranial (IC) activity and improved survival in patients with breast cancer brain metastases (BCBMs) in recent studies.[4,7] Moreover, Destiny-Breast01 and Destiny-Breast03 showed the superiority of T-DXd compared with trastuzumab emtansine, another ADC, and other therapeutic modalities.[7,8]

Nevertheless, Destiny-Breast01 and Destiny-Breast03 included only patients with stable BMs.[7,8] Some recent trials partially address whether T-DXd is effective in patients with active or progressing BM after local treatment.[4,9] The DEBBRAH and TUXEDO-1 trials evaluated 21 and 15 patients, respectively, and reported elevated activity and impressive clinical benefit rates (CBRs).[4,9] Given the small population in CTs assessing active brain lesions and that stable BMs were only a subgroup analysis in several studies, the current evidence is limited. Therefore, we conducted a systematic review and meta-analysis to fully assess the efficacy and effectiveness of T-DXd in patients with HER2-positive BC with both stable and active BMs within CTs and in the real-world setting.

PATIENTS AND METHODS

This study was carried out following the guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[10] and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42023422589. The PRISMA checklist for the abstract and the manuscript can be found in Supplementary Table S1A and B, available at https://doi.org/10.1016/j.esmoop.2024.102233, respectively.

We systematically searched PubMed, Embase, and Cochrane databases, and the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) conference proceedings in May 2023. The search was last updated on 24 August 2023. The following combination of medical subject headings (MeSH) terms and Boolean connectors were used: 'breast cancer'; AND 'HER-positive' OR 'Human Epidermal Growth Factor Receptor'; AND 'T-DXd' OR 'Trastuzumab deruxtecan'. A full description of the search strategy used on each database can be found in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.102233. We have also searched the references of all included studies and relevant reviews about this topic.

We considered all CTs and cohort studies evaluating T-DXd in patients with HER2-positive BCBM eligible for our meta-analysis. Related or updated publications of the same study were considered for inclusion in different analyses. The exclusion criteria were (i) studies with overlapping populations; (ii) not original studies (reviews, letters to the editor, and commentaries); (iii) studies without the population of interest; (iv) studies assessing exclusively patients with leptomeningeal metastases (no measurable brain disease available); and (v) case report and case series.

Two authors (IM and ADM) independently screened the studies by title and abstract, selected the articles for full-text review, and extracted data from included studies. All inconsistencies between the authors were resolved by consensus or consulting a third author (MV). We collected data from individual studies on the study design, study location, number of patients, and patients' baseline characteristics (e.g. BM status, median age, hormone receptor status, and previous lines of therapy). We extracted data for pooled analysis on the following outcomes: (i) objective response rate (ORR); (ii) IC-ORR; (iii) CBR; (iv) IC-CBR; (v) progression-free survival (PFS); and (vi) adverse events.

The extracranial ORR was defined as the proportion of patients who achieved complete response (CR) or partial response (PR) per blinded independent central response (BICR) or investigator's assessment according to the RECIST, version 1.1.[4,7,9,11-20] The CBR was defined as the proportion of participants who achieved ORR (CR or PR) or stable disease according to the RECIST version 1.1 criteria lasting for a minimum of 6 months.[9,15,16]

Considering the seven studies assessing IC responses, the IC-ORR was described in six as the proportion of patients in whom the best CNS response was CR or PR per BICR or investigator's assessment.[4,7,9,11-14,17,18,20,21] Three used the RECIST criteria (version 1.1) and the other three used the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. In one retrospective study, we had access only to the abstract, and the definition of IC-ORR or criteria used were not provided.[21] In three out of four studies assessing IC-CBR, this consisted of the proportion of patients who achieved an IC objective response (CR or PR) or stable disease lasting for a minimum of 4 or 6 months.[4,9,17,18,20] Of the four studies, three used the RANO-BM criteria, and one used the RECIST (version 1.1) criteria.

Subgroup analyses were carried out according to (i) the studies' design (CTs versus observational studies), and (ii)

BM activity status (active versus stable BM). Patients with newly diagnosed untreated or progressive BMs were included in the active BM group. The stable BM group included patients with clinically or radiographically inactive or asymptomatic previously treated BMs. We also carried out an exploratory analysis to assess PFS of T-DXd compared with other therapies.

Two authors (IM and ADM) independently completed the risk of bias assessment, and conflicts were resolved by consensus or consulting a third author (MV). The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used to assess the risk of bias in nonrandomized CTs and retrospective cohort studies.[22] Following this protocol, each study is classified in low, moderate, serious, critical risk of bias, or no information based on seven domains: bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported result. Randomized controlled trials were assessed using the Risk-of-Bias 2 tool.[23] Accordingly, studies were classified as low, high, or unclear risk of bias across five domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data. The Egger test and funnel plots of individual study weights against point estimates were used to verify publication bias for the primary outcome (ORR).

R software (version 4.2.2; R Foundation, Vienna, Austria) was used to carry out all statistical analyses. The following packages were used: 'metafor'; 'meta'; and 'weight'. I^2 statistics were used to assess the heterogeneity. DerSimonian and Laird random-effects models were used in all analyses. Proportional meta-analyses were used for dichotomous outcomes and reported in percentages, with 95% confidence intervals (CIs). Logit-transformation of data was used when the individual study proportion was <0.2 or >0.8. In the case of a study with zero events, we used the doubled-arcsine transformation. Pooled analysis of individual studies' PFS was carried out using the mean of medians with the package 'metamedian'. Comparative meta-analyses were carried out using hazard ratio (HR) with 95% CIs.

RESULTS

Baseline characteristics

The initial search yielded 1422 results. After the removal of duplicates and exclusion by title and abstract, 74 studies were fully assessed. Most studies did not include patients with BMs or were published study protocols only, and therefore were excluded. A list of excluded studies after a comprehensive review can be found in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.102233. Finally, 10 studies with 15 related publications were included. Of these, four were observational studies ($n = 130$) and six CTs ($n = 189$; Figure 1).[4,7,9,11-21,24]

A total of 319 patients with HER2-positive BC and BM were assessed; 169 had stable, and 111 had active BM, and the remainder were not specified. Most of them were female

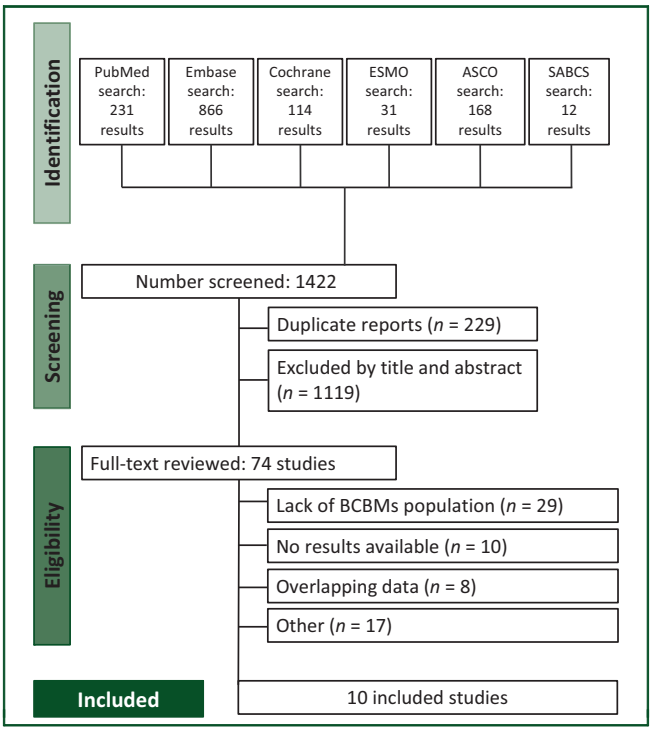

Figure 1. PRISMA flow diagram of study screening and selection. Green vertical boxes indicate each stage of the screening, and the horizontal boxes present more detailed information about the process, including the steps carried out in each stage.
ASCO, American Society of Clinical Oncology; BCBM, breast cancer brain metastasis; ESMO, European Society for Medical Oncology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SABCS, San Antonio Breast Cancer Symposium.

(171/173, 98.4%), had hormone receptor-positive tumors (126/210, 60%), and were classified as 0 or 1 (196/232, 84.5%) in the Eastern Cooperative Oncology Group (ECOG) performance status scale. Non-CNS-metastatic disease was reported in 81.8% of patients (108/132). The mean age was 54.3 years (95% CI 54.2-58). The median number of previous therapies ranged from two to six lines, and the median follow-up time was from 8.4 to 21.4 months.

In two retrospective studies, no information was available regarding patients with leptomeningeal disease.[17,19] In five studies, patients with leptomeningeal disease were excluded.[4,7,12,15,24] The DEBBRAH trial includes a cohort of patients with leptomeningeal carcinomatosis (LMC; cohort five).[9] However, we included only cohorts one, two, and three, which did not have patients with LMC. The other two studies included a few patients with leptomeningeal disease.[20,21] Murphy et al.[21] included only one patient with leptomeningeal disease. In the ROSET-BM trial, 2 patients had exclusively LMC, and 17 had both active BMs and LMC. Nevertheless, we used data regarding the population classified as analytically stable or active BMs without LMC for all efficacy analyses. The baseline characteristics of the population from each study are presented in Table 1.

Efficacy outcomes

In the pooled analysis of BCBM treated with T-DXd, the overall ORR was 61% (95% CI 52% to 70%). Retrospective

Table 1. Design and characteristics of included studies in the meta-analysis

Study	Design	Location	Status of brain metastases			T-DXd dose	Age (years), median (range)	HR+, *n* (%)	Prior CNS treatment, *n* (%)	Previous therapies[a]	ECOG PS (*n*)		Follow-up in months[a]	Previous therapies
			Active (*n*)	Stable (*n*)	Total (*n*)						0-1	≥2		
DESTINY Breast01[7,11]	Phase II CT	Multicenter[b]	0	24	24	5.4 mg/kg	58.0 (33.0-85.0)	9 (37.5%)	RT: 14 (58.3) CX: 1 (4.2) RT + CX: 3 (12.5)[c]	6 (3-16)	24	0	11.1 (0.7-19.9)	Trastuzumab, T-DM1, pertuzumab, other anti-HER2 therapies, HER2 TKI, hormone therapy, other systemic therapies
DESTINY Breast02[24]	Phase III CT	Multicenter[d]	0	74	74	5.4 mg/kg	54.2 (45.5-63.4)[e]	NA	NA	2 (2-3)[e]	NA	NA	21.5 (15.2-28.4)	Trastuzumab, T-DM1, pertuzumab, other anti-HER2 therapies, HER2 TKI, hormone therapy, other systemic therapies[e]
DESTINY Breast03[12-14]	Phase III CT	Multicenter[f]	0	43	43	5.4 mg/kg	54.3 (47.0-62.8)[e]	NA	NA	2 (1-3)[e]	43	0	28.4 (22.1-32.9)	Trastuzumab, T-DM1, pertuzumab, other anti-HER2 therapies, HER2 TKI, hormone therapy, other systemic therapies[e]
DAISY[m,15,16]	Phase II CT	France	0	12	12	5.4 mg/kg	60.5 (32.0-70.0)	6 (50)	NA	≥5 lines: 6 <5 lines: 6[g]	12	0	NA	NA
DEBBRAH[9]	Phase II CT	Spain and Portugal	13	8	21[h]	5.4 mg/kg	53.0 (36.0-77.0)	16 (76.2)[i]	WBRT: 10 (47.6) CX: 6 (28.6) SRS/SRT: 7 (33.3)	NA	21	0	8.4 (1.4-12.6)	Trastuzumab, T-DM1, pertuzumab, other anti-HER2 therapies, HER2 TKI, hormone therapy, other systemic therapies
Kabraji et al. (2023)[17,18]	Retrospective cohort	United States	10[j]	2[j]	15[j]	NA	46 (35.0-69.0)	8 (53)	WBRT: 9 (50) CX: 4 (22) SRS: 11 (61)[k]	4 (0-10)	NA	NA	7 (NA)[l]	Trastuzumab, pertuzumab, T-DM1, TKI
Murphy et al. (2023)[m,21]	Retrospective cohort	Ireland	NA	NA	27[n]	NA	54.5 (NA)	16 (59)	NA	3.7[o]	NA	NA	NA	Trastuzumab, pertuzumab, docetaxel, capecitabine neratinib, gemcitabine and lapatinib
Nakajima et al. (2022)[19]	Retrospective cohort	Japan	NA	NA	9	NA	59.5 (42.0-78.0)[e]	NA	NA	NA	NA	NA	10.1 (95% CI 8.4-12.0)	T-DM1
ROSET-BM[20]	Retrospective cohort	Japan	73[p]	6	79[p]	NA	NA	59 (56.7)[q]	WBRT: 59 (56.7) CX: 27 (26) SRS: 64 (61.5)[e]	4 (3-7)	81[e]	16[e]	11.2 (0.9-17.0)	Trastuzumab, pertuzumab, TDM-1, lapatinib
TUXEDO-1[4]	Phase II CT	Austria	15	0	15	5.4 mg/kg	69 (30.0-76.0)	12 (80)	WBRT: 3 (20) SRT/SRS: 3 (20) WBRT + SRT/SRS and/or CX: 3 (20)	2 (1-5)	15	0	12 (95% CI 8-NR)	Trastuzumab, pertuzumab, TDM-1, lapatinib

CI, confidence interval; CNS, central nervous system; CT, chemotherapy; CX, surgery; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; NA, data not available; NR, not reached; RT, radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; STS, stereotactic radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

[a]The number of previous therapies and follow-up time are presented in median (range), unless indicated otherwise. *N* of previous therapies were presented as median, unless stated otherwise (Murphy 2023 presented the number of previous therapies in mean and Daisy presented as greater than/equal or less than 5 lines of therapies).

[b]Breast 01: the United States, Belgium, Canada, France, Italy, Japan, Korea, Spain, and the United Kingdom.

[c]In this study, one patient was also treated with capecitabine.

[d]Breast 02: the United States, Australia, Belgium, Brazil, Czechia, France, Germany, Greece, Israel, Italy, Japan, Korea, Spain, Turkey, and the United Kingdom.

[e]Data available only for the general population of the study.

[f]Breast 03: the United States, Australia, Belgium, Brazil, Canada, China, France, Germany, Hong Kong, Italy, Japan, Korea, Spain, Taiwan, and the United Kingdom.

[g]Data are presented as greater than/equal or less than five lines of therapies.

cohort studies and CTs yielded similar results ($P = 0.31$; Figure 2A). The IC-ORR was 61% (95% CI 54% to 69%), and no significant difference was observed between observational and interventional studies ($P = 0.58$; Figure 2B). Overall clinical benefit was achieved in 80% (95% CI 52% to 94%) of patients, whereas IC-CBR was seen in 70% (95% CI 54% to 82%; Figure 3A and B, respectively).

The median PFS was 15 months (95% CI 13.9-16.1). We carried out an exploratory analysis including two RCTs that assessed the PFS of individuals treated with T-DXd compared with those who received other interventions, namely, trastuzumab emtansine or treatment of physician's choice. We found a reduction of 70% in rates of disease progression compared with other interventions (HR 0.30, 95% CI 0.20-0.45; $I^2 = 0\%$; $P < 0.001$; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102233).

Stable versus active BM

Among 95 patients with stable BM, the ORR was 68% (95% CI 57% to 77%). In 109 patients with active IC lesions, the ORR was 60% (95% CI 48% to 72%). The subgroup comparison showed no differences between them ($P = 0.35$; Figure 4A).

In 65 patients with stable IC disease, 68% (95% CI 41% to 90%) achieved an IC-objective response. Similar results were observed in 80 patients with active brain lesions, with an IC-ORR of 61% (95% CI 48% to 73%). The subgroup comparison was nonsignificant ($P = 0.65$; Figure 4B).

Adverse events

Adverse events of any grade were reported in four studies.[4,9,11] In the analysis of 60 patients, 98% (95% CI 90% to 100%) had adverse events of any grade (Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2024.102233). Adverse event leading to dose reduction was seen in 29% (95% CI 10% to 60%) of patients and to dose interruption or delay in 25% (95% CI 18% to 33%) among 164 patients (Supplementary Figure S2B and C, available at https://doi.org/10.1016/j.esmoop.2024.102233, respectively). The most common adverse events were fatigue (29%, 95% CI 14% to 52%) and nausea (18%, 95% CI 0% to 49%), followed by neutropenia (17%, 95% CI 7% to 30%; Supplementary Figure S3A-C, available at https://doi.org/10.1016/j.esmoop.2024.102233, respectively). Grade 1-2 events were significantly more frequent than grade 3 for both fatigue and nausea.

Quality assessment

Overall, the three nonrandomized trials and five retrospective studies included in this analysis were considered to have a moderate risk of bias (Supplementary Table S4A and B, available at https://doi.org/10.1016/j.esmoop.2024.102233, respectively).[4,9,11,15,17,19-21] They predominantly lacked adjustment for confounding factors (i.e. the number of previous therapies before T-DXd), failing to meet the specified criteria for the first domain. The two RCTs met

[h]In the Debbrah trial, the cohort with untreated BM was included in the group with active BM.
[i]In the DEBBRAH trial, 16 patients were progesterone receptor positive and estrogen receptor negative.
[j]In this study, 18 patients met the eligibility criteria; however, only 15 had CNS evaluable and the BCBM status was available for only 12 patients.
[k]In this study, clinical activity was available for 15 patients with evaluable CNS disease; however, data on prior CNS treatment were available for 18 patients.
[l]In this study, the data cut-off was at 7 months of follow-up.
[m]Conference presentations or abstracts.
[n]In Murphy 2023 one out of the 27 patients had leptomeningeal disease.
[o]Mean value of the number of previous therapies.
[p]In the ROSET-BM study, 104 patients were included. Among these, 73 had active BM without leptomeningeal carcinomatosis, 17 patients had both active BM and leptomeningeal carcinomatosis, two had only leptomeningeal carcinomatosis, and 6 were not classified.
[q]In ROSET-BM, the values for HR+ correspond to estrogen receptor positive and it considers the total population of the study ($N = 104$).

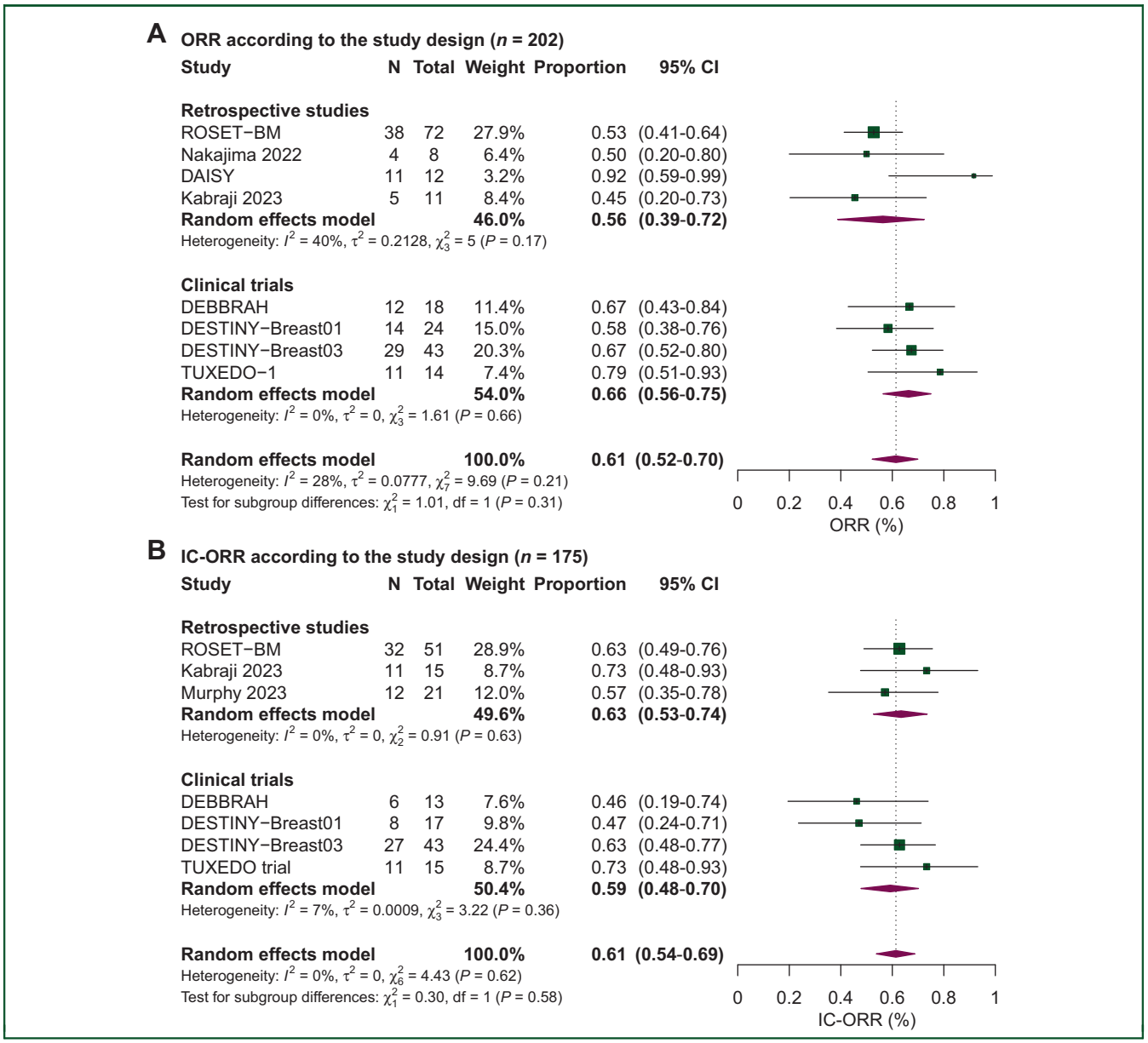

Figure 2. (A) ORR and (B) IC-ORR in patients with breast cancer and brain metastases.[4,7,9,11-21] Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. Kabraji 2023 includes one HER-negative patient. For the ORR analysis, we incorporated data on the extracranial response from the Kabraji 2023. In Murphy 2023 and DESTINY-Breast01, data were available for only 21 and 17 patients, respectively. For the ORR of the DEBBRAH trial we used data from patients with IC or extracranial lesions. The analysis by Murphy 2023 includes one patient with leptomeningeal disease.
HER, human epidermal growth factor receptor; IC, intracranial; ORR, objective response rate.

most criteria for all domains and were determined to be at a low risk of bias.[12,24] The funnel plot analysis for the ORR revealed no indication of a publication bias (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2024.102233), further supported by a nonsignificant Egger's test ($z = 1.31$, $P = 0.19$).

DISCUSSION

This meta-analysis evaluated patients with HER2-positive breast cancer and BMs treated with T-DXd, in both CTs and real-world settings. Our findings showed remarkable outcomes: an overall ORR of 61%, an IC-ORR of 61%, an overall CBR of 80%, and an IC-CBR of 70%. The use of T-DXd resulted in benefits for all patients with HER2-positive breast cancer and BMs regardless of subgroup: (i) patients with stable and active BM and (ii) in the CT and real-world setting. Moreover, patients on T-DXd achieved a median PFS of 15 months and had a 70% reduction in the risk of disease progression compared with other therapeutic approaches.

The introduction of monoclonal antibodies dramatically changed the treatment approaches of patients with HER2-positive BC.[11,25] Promising results of anti-HER2 therapies prompted further investigation of their efficacy in patients with BM.[11,25] The HER2CLIMB was the first randomized CT to include heavily pretreated patients with active BMs.[26]

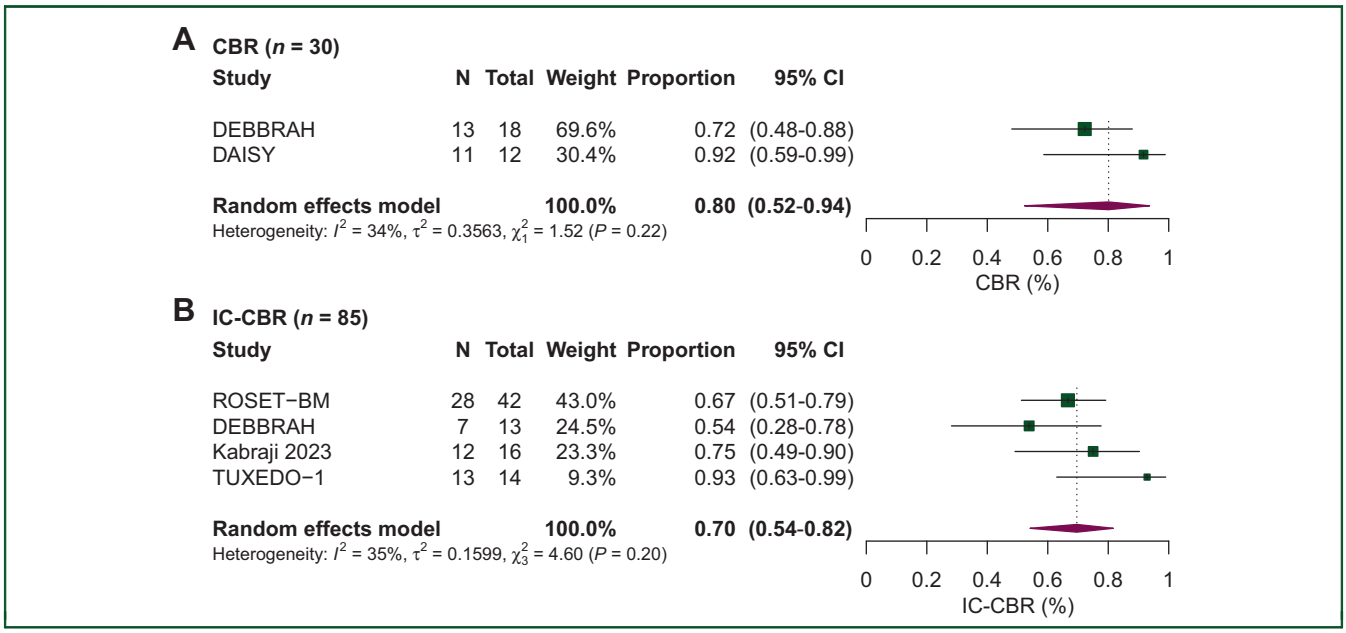

Figure 3. **(A) Clinical benefit rate (CBR) and (B) intracranial (IC)-CBR in patients with breast cancer with brain metastases.**[4,9,15-18,20] Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval (CI). The diamonds represent the estimated overall effect of the meta-analysis based on random effects.

The study evaluated the combination of tucatinib, an oral tyrosine kinase inhibitor, with trastuzumab and capecitabine in 198 patients with metastatic BC compared with placebo plus trastuzumab and capecitabine in 93 patients.[26] Patients with BMs treated with tucatinib had a median PFS of 7.6 months (95% CI 6.2-9.5 months) versus 5.4 months (95% CI 4.1-5.7 months) in the control group ($P < 0.001$).[26] Moreover, patients in the tucatinib group presented with a 52% reduction in the risk of disease progression.[26]

The PATRICIA phase II trial evaluated the combination of high-dose trastuzumab and pertuzumab in patients with CNS metastases who had progressed on prior radiotherapy.[27-29] The study reported a limited IC-ORR of 11% and a CBR of 51% at 6 months.[28,29] Another study, KAMILA, investigated the first ADC in metastatic BC, ado-trastuzumab emtansine (T-DM1).[30] An exploratory analysis of this single-arm phase IIIb trial in a subgroup of patients with active or stable BMs revealed a median PFS of 5.5 months, ORR of 21.4%, and CBR of 42.9%.[30] Regarding IC disease, 42.9% of patients achieved objective responses; among those without prior radiation therapy, the IC-ORR was 49.3%.[30]

In the DESTINY-Breast 03 trial, T-DXd demonstrated superior antitumor responses compared with T-DM1.[12,13] Specifically in patients with BM and prior radiation therapy, T-DXd led to a 75% reduction in the progression of disease or death.[13] Based on these outstanding results, T-DXd was approved for second-line therapy in metastatic HER2-positive BC following progression or failure on anti-HER2-based regimens.[31] The remarkable tumor activity of T-DXd expanded to patients with BMs.[11] DESTINY-Breast01 investigated T-DXd in patients previously treated with T-DM1 therapy.[7] In a subgroup analysis of patients with stable BM, the ORR was 58% and the IC-ORR was 41.2%.[11] The study included heavily pretreated patients with BC. Conversely, DESTINY-Breast03 mainly enrolled patients with two or three previous lines of therapy.[12] Hence the responses to treatment were even better: ORR of 67% and IC-ORR of 61%.

Notably, DESTINY-Breast01 and 03 included only patients with stable BM. The question of whether T-DXd works in patients with active BM was investigated by the phase II trials, DEBBRAH and TUXEDO-1, and the retrospective cohort studies, ROSET-BM and Kabraji et al. 2023.[4,9,17,20] In these studies, the IC responses ranged from 44% to 73.3%.[4,9,17,20] Our pooled analysis demonstrated a promising IC-ORR of >60%. It revealed that patients with either stable or active brain disease can significantly benefit from the antitumor activity of T-DXd. Moreover, the TUXEDO-1 trial showed an impressive CBR of 92.9%, similar to our findings.[4] Remarkably, in the TUXEDO-1 trial, all six patients with untreated, newly diagnosed brain lesions achieved response rates of 100%.

T-DXd is recommended by the ESMO guideline as a second-line choice for patients with treated stable BM.[31] However, for patients with active BM (new untreated or progressive BM), the preferred systemic therapy is tucatinib—capecitabine—trastuzumab, based on the HER2CLIMB study.[26,32] This trial included 174 patients with active BM and demonstrated a median OS of 21.4 months.[26,32] In addition, HER2CLIMB reported a CNS-PFS of 9.9 months (95% CI 8.4-11.7) and an IC-ORR of 47.1% (95% CI 23% to 72.2%).[32] In this meta-analysis, which included heavily pretreated patients with stable and active CNS disease, T-DXd had an overall PFS of 15 months (95% CI 13.9-16.1) and a risk of reduction of 70% compared with other treatments. In addition to great extracranial disease control, the IC-ORR was 61% in 80 patients with active brain lesions,

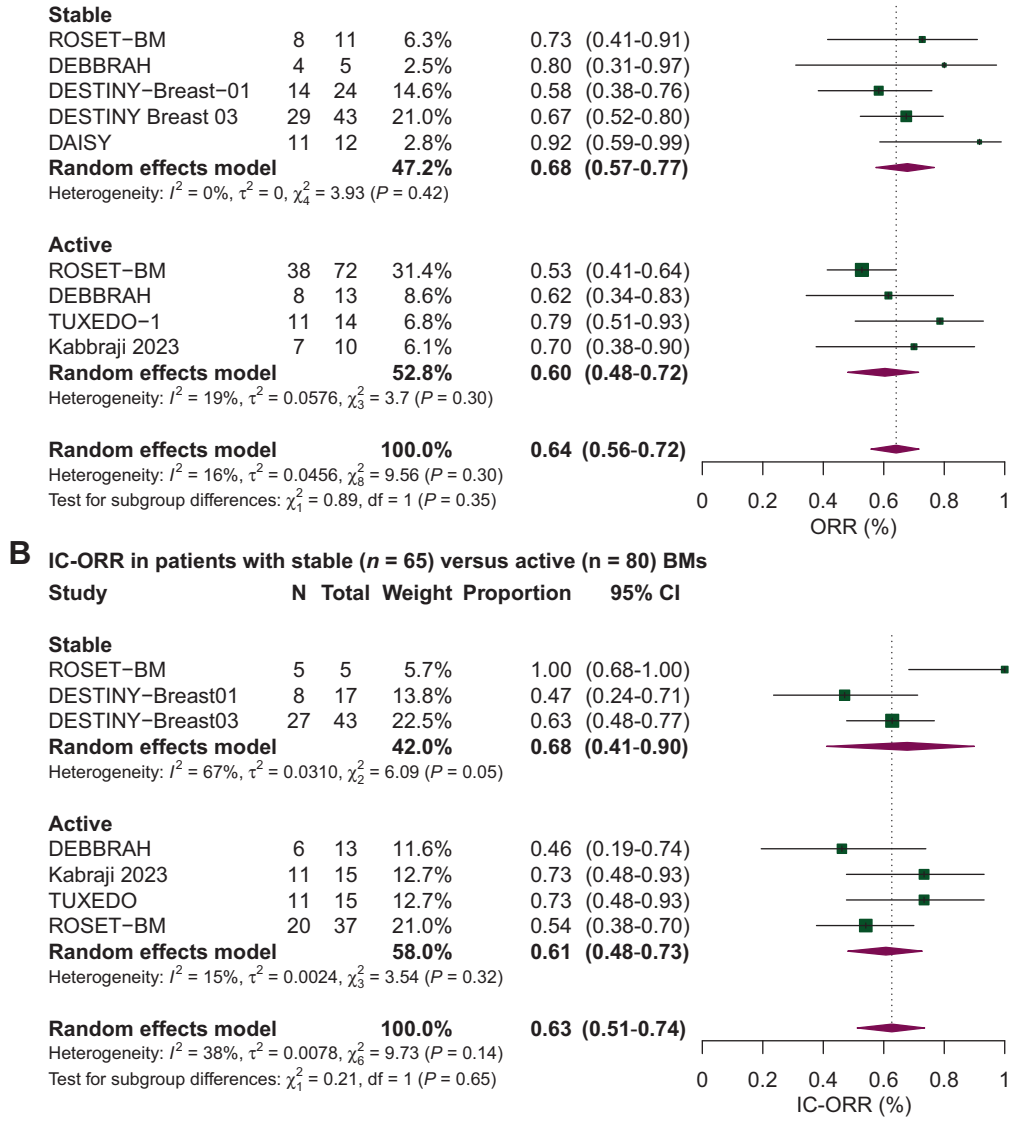

Figure 4. (A) Objective response rate (ORR) and (B) intracranial (IC)-ORR according to brain metastases status.[4,7,9,11-18,20] Proportions for each trial are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval (CI). The diamonds represent the estimated overall effect of the meta-analysis based on random effects.
BM, brain metastasis.

higher than the IC-ORR achieved by the tucatinib combination. This meta-analysis demonstrated the benefit of T-DXd in the largest sample of patients with active brain lesion treated with T-DXd in the literature.

The studies included in our meta-analysis still needed to mature to pool OS probabilities. The DESTINY-Breast03 trial showed a trend toward improved OS in favor of T-DXd for patients with BM (HR 0.54, 95% CI 0.29-1.03).[12] At 28.4 months of follow-up, the median OS was not reached (95% CI 23.8-not evaluable) for patients with BMs on T-DXd.[12] In addition, the ROSET-BM study recently reported a 12-month OS rate of 74.9% (95% CI 64.5% to 82.6%). More mature data and results from ongoing studies with potential combinations of T-DXd with other drugs are awaited (NCT04739761, NCT04539938, NCT04487236, and NCT04538742). The combination of T-DXd and tucatinib may boost their effectiveness, and it is under investigation in the phase II trial HER2CLIMB-04. The phase IIIb/IV DESTINY-12 study is ongoing and will prospectively assess T-DXd in real-world patients with stable and active BM.[33,34]

Some critical unanswered questions in BC BM are the role and sequence of radiation therapy, the optimal sequencing of systemic therapies, and the best option in patients progressing on T-DXd.[35,36] With these new agents, we will hopefully be able to spare patients from whole-brain radiotherapy and its significant side-effects, such as the neurocognitive decline.[36] Further investigations about combinations of T-DXd with more

modern radiation therapy techniques and if and when radiation therapy is needed in this new landscape are warranted.[35] New ADCs have been developed, such as DP303c in a phase I trial and trastuzumab duocarmazine (T-duo) in the phase III Tulip trial.[37,38] The latter showed benefits in PFS but not in OS.[37] Unfortunately, we still lack predictive biomarkers of response that could aid in tailoring patients to the best therapeutic strategy. Patients progressing on T-DXd can receive a third line of tucatinib—trastuzumab—capecitabine or T-DM1.[31,39] Another promising option is the combination of tucatinib and T-DM1, assessed in the HER2CLIMB-02 trial.[40] According to a press release, HER2CLIMB-02 met its primary endpoint of PFS and will be presented soon.[41]

Concerning safety, we found a high rate of adverse events among patients treated with T-DXd. Fortunately, most were grades 1-2, aligning with previous trial findings.[4,9,11,12] The occurrence of interstitial lung disease (ILD) was not assessed due to the unavailability of data from individual studies. However, a recent meta-analysis from Soares et al.[42] assessing T-DXd-related ILD and cardiotoxicity in 1970 metastatic BC found an ILD incidence of 11.7%. Most cases reported were mild and well-managed according to standard guidelines.

This study has some limitations. This meta-analysis had a small number of patients, especially for some analyses, such as the CBR. The included studies used different criteria to assess IC and extracranial responses, which may explain some of the high heterogeneity. The slightly different definitions of active and stable BMs across studies and including studies with different designs (e.g. retrospective studies and CTs) may have also contributed to heterogeneity. Because of the unavailability of data from individual studies, we could not carry out analyses based on previous local treatment for BMs or assess their influence on our results. Besides, we only had access to an abstract from the DAISY trial, and more mature data are awaited.[15] Some studies, such as TUXEDO-1, were small sample-size trials conducted in a single-center institution, which brings the potential for bias.[4] To reduce some of these limitations, we used random-effects models in all analyses and conducted sensitivity analyses based on the studies' design.

Conclusions

Our systematic review and meta-analysis support the antitumor activity of T-DXd in treating stable and active BM in patients with HER2-positive breast cancer. T-DXd demonstrated great benefit in overall objective and IC responses, >50%, highlighting its clinical efficacy and real-world effectiveness in this population. Thus, our findings suggest that T-DXd should be considered for the second-line treatment of patients with HER2-positive BC and stable and active BMs. Further studies are ongoing investigating the IC activity of T-DXd and its combination with other therapies. They will aid in guiding treatment decisions for patients with BCBMs.

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DATA SHARING

All research data presented in this study are accessible upon request to the corresponding author.

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