



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

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ABSTRACT

Background: Trastuzumab deruxtecan (T-DXd) has shown promising activity in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) and central nervous system (CNS) involvement. In this updated meta-analysis, we explore the effectiveness of T-DXd in a large subset of patients with HER2-positive BC and CNS disease.

Methods: A systematic search was made on September 16th, 2024, for studies investigating T-DXd in the scenario of HER2-positive BC and brain metastases (BMs) and/or leptomeningeal disease (LMD). We used random effects models for all statistical analyses.

Results: We included 18 studies with 786 HER2-positive BC patients with CNS involvement (16 studies with 750 BMs patients and three studies with 36 LMD patients). We observed high overall antitumor responses (objective response rate [ORR], 60.4 %; disease control rate [DCR], 94.4 %; and clinical benefit rate [CBR], 79.3 %) and a 12-month PFS of 64.7 % and OS of 82.7 %. Intracranial ORR, DCR, and CBR were seen in 62.2 %, 88.6 %, and 68.6 % of patients, respectively, and 67.4 % achieved intracranial PFS at 12 months. Both stable and active BMs subgroups derived similar benefit from T-DXd. Better intracranial responses were seen for 33 patients with untreated BMs compared to 56 patients with previously treated or progressing lesions (odds ratio 3.82, 95 % confidence interval 1.3–10.8, $p = 0.01$). For the LMD group, T-DXd elicited intracranial ORR and CBR in 59.4 % and 94.1 % of patients, respectively.

Conclusions: This updated meta-analysis continues to support the overall and intracranial activity of T-DXd in patients with HER2-positive BC and CNS involvement, including those with LMD.

Abbreviations: AEs, adverse events; ASCO, American Society of Clinical Oncology; ADCs, antibody-drug conjugates; BBB, blood–brain barrier; BC, breast cancer; BMs, brain metastases; CNS, central nervous system; CBR, clinical benefit rate; CT, clinical trial; CI, confidence interval; DCR, disease control rate; ESMO, European Society for Medical Oncology; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IC, intracranial; LMD, leptomeningeal disease; N, number of patients; ORR, objective response rate; OR, odds ratio; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PFS, progression-free survival; ROBINS I, Risk of Bias in Non-randomized Studies of Interventions; RoB2, Cochrane risk-of-bias tool for randomized trials; TKI, tyrosine kinase inhibitors; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; TTC, trastuzumab plus tucatinib plus capecitabine.

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Introduction

Breast cancer (BC) is the second leading cause of brain metastases (BMs), only after lung cancer [1]. Among BC subtypes, triple-negative and human epidermal growth factor receptor (HER2)-positive are at higher risk of central nervous system (CNS) progression [2,3]. For HER2-positive disease, current evidence estimates that up to 50 % of patients develop BMs [2,3]. Nonetheless, incidence rates are rising as systemic disease control rates and survival of BC patients are improving following the advances in diagnostic tools and targeted therapies [3].

The development of anti-HER2 agents, such as trastuzumab and pertuzumab, roughly three decades ago was a milestone in the treatment landscape of HER2-positive BC [4–6]. The phase III CLEOPATRA study randomized over 800 HER2-positive metastatic BC patients to receive the combination of trastuzumab (T) and docetaxel with or without pertuzumab (P) [6,7]. A significant survival benefit was associated with the pertuzumab-containing regimen [6,7]. In an exploratory analysis of this study, a longer brain metastases-free survival was also seen in favor of the pertuzumab cohort compared to placebo [8]. Yet, the overall incidence of CNS disease was similar between groups [8].

Despite the extracranial benefit, dual HER2 blockade with T plus P (TP) exhibited low intracranial activity in patients with CNS disease. A large retrospective study by Bergen *et al.* included 252 HER2-positive BC patients receiving different agents as first-line therapy following the diagnosis of BMs [9]. Although patients treated with TP achieved better survival rates compared to those on other regimens, the median progression-free survival (PFS) associated with TP was only eight months [9]. This was mainly attributed to the inability of large molecules to traverse through the blood–brain barrier (BBB) and achieve therapeutic levels [9]. Crossing the BBB has, therefore, imposed a historical challenge in delivering targeted therapies to the brain [10].

Several agents attempting to optimize drug uptake by brain tumor cells have been studied, however, most have failed to achieve satisfactory intracranial concentration and improve outcomes of BC and BMs patients [10–14]. In the last several years, an emerging class of compounds known as antibody-drug conjugates (ADCs) has transformed the treatment approach for several types of tumors [15,16]. In particular, trastuzumab deruxtecan (T-DXd) demonstrated impressive results in both early-stage and metastatic BC [17,18]. In patients with HER2-positive BC and BMs, T-DXd was shown to elicit high intracranial responses and survival rates and it is now recommended by international guidelines as the second-line option for patients with HER2-positive BC and stable BMs following one prior line in the metastatic setting [19,20]. Recently, the prospective DESTINY-Breast12 study has further validated the benefit of T-DXd in a larger subset of patients with HER2-positive BCBMs [21]. Retrospective evidence has also shown encouraging results of this ADC in patients with leptomeningeal disease (LMD), an even more challenging to treat group [22].

We previously studied the efficacy of T-DXd in a *meta-analysis* including ten studies with 319 HER2-positive BC patients with BMs [23]. In this updated *meta-analysis*, we included 18 studies with over 800 HER2-positive BC patients with CNS involvement, aiming to: (1) further confirm the overall and intracranial activity of T-DXd in a larger population; (2) perform analyses previously limited by the small number of patients; (3) explore new subgroup analyses; (4) include survival data; and (4) assess the intracranial benefit of T-DXd in a group of patients with LMD.

Methods

We performed this systematic review and *meta-analysis* following Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [24]. Table S1 displays the manuscript and abstract PRISMA checklist. This project was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration

number CRD42024591931.

Data Source and search Strategy

We performed our systematic search on PubMed, Embase, and Cochrane databases as well as the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) conference proceedings on September 16th, 2024. The terms and Boolean connectors used in each database are available in Table S2. We also manually checked relevant reviews about the topic and references of included studies.

Eligibility criteria

Our eligibility criteria consisted of published retrospective and prospective studies as well as clinical trials (CTs) – randomized and non-randomized – analyzing patients with HER2-positive metastatic BC and BMs or LMD receiving T-DXd and reporting at least one of the outcomes of interest described below. Abstracts from conference proceedings were considered for inclusion. No limitations were applied as the publication date or a comparator group. We restricted the inclusion to English-written reports only. Studies on patients with variable HER2-expressing tumors if at least the majority (>50 %) of patients had HER2-positive tumors or if reporting outcomes were stratified by HER2 status.

Main exclusion criteria were as follows: (1) lack of HER2-positive BC and BMs or LMD populations; (2) lack of outcomes for the population with CNS involvement; (3) T-DXd combined therapy; (4) ongoing studies with no preliminary results available; and (5) case reports, case series, reviews, and commentaries.

Data collection

Two authors (IM and CERC) independently performed the initial screening of reports by title and abstract, selected studies for a comprehensive review, collected data from included studies, and performed the quality assessment. Inconsistencies were resolved by consulting a third author (LC).

Outcomes and subgroup analyses

For the population with BMs, the outcomes of interest were: (1) overall objective response rate (ORR), (2) overall disease control rate (DCR), (3) overall clinical benefit rate (CBR); (4) overall PFS at 12 months; (5) overall survival (OS) at 12 months; (6) intracranial ORR (IC-ORR); (7) intracranial DCR (IC-DCR); (8) intracranial CBR (IC-CBR); and (9) intracranial PFS (IC-PFS) at 12 months. We also performed safety analyses, including the rate of dose adjustments, frequency of adverse events (AEs), and health-related quality of life.

We performed subgroup analyses according to study's design (CTs/prospective vs real-world/retrospective studies), BMs status (stable vs active), and treatment status within the active group (untreated vs previously treated/progressing). Moreover, we explored the efficacy of T-DXd in patients with vs without baseline BMs.

For patients with LMD, we pooled the IC-ORR and IC-CBR for analysis. Studies reporting outcomes for only one patient were not considered for analysis. Median OS and PFS were reported in table format.

Intracranial OS in the BMs population and other outcomes in the LMD group were not pooled for analysis due to unavailability of data. We used the most recent data whenever it was available for all the included studies [25,26].

Details about the study's population and the definition of stable and active BMs are shown in Table S4. Additionally, the outcomes contributing to the *meta-analysis*, definition of endpoints criteria used in each study are provided in Table S5.

Quality assessment

Non-randomized studies (CTs and real-world) were analyzed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS I) tool [27]. For randomized studies, we used the Cochrane risk-of-bias tool for randomized trials (RoB 2) [28]. We checked for publication bias in the ORR (*i.e.*, the outcome with the higher number of studies included) analysis through the funnel plot of individual study weights against point estimates and the Egger test.

Exploring heterogeneity and sensitivity analyses

The Baujat plot was used to assess the contribution of each study to the overall effect and heterogeneity of the ORR analysis [29].

Two small-size cohorts enrolling patients with HER2-positive and HER2-low/negative BC and BMs were considered for inclusion [30,31]. In Kabbraji *et al.* and Dannehl *et al.*, 15 out of 18 patients and eleven out of 16 patients were HER2-positive, respectively. Nonetheless, a sensitivity leave-one-out analysis was performed for all outcomes including these studies.

The studies DESTINY-Breast02/03 initially enrolled patients with untreated and asymptomatic BMs [19,32]. In further protocol amendments, only patients with previously treated and asymptomatic BMs were allowed. In this *meta-analysis*, the study DESTINY-Breast02 did not contribute to analyses stratified by BM status (stable vs active). On the other hand, and since we did not have access to individual patient data, we opted to include DESTINY-Breast03 in the stable group. We performed leave-one-out sensitivity analyses of all outcomes for the stable BMs group.

Statistical analysis

Proportional *meta-analyses* were performed using the number of events per total population and were reported in percentages with 95 % confidence intervals (CI). In analyses with studies reporting extreme (< 0.2 or > 0.8) proportions or zero events, we applied logit and double arcsine transformations, respectively. For binary outcomes, we pooled the odds ratio (OR) with 95 % CIs. We used inverse variance (IV) for proportional analyses and Mantel-Haenszel (MH) methods for comparative endpoints. In all of them, random-effects models were used. We explored between-study heterogeneity using Cochran's Q test and I^2 statistics ($p < 0.10$ and $I^2 \geq 25$ % were associated with considerable heterogeneity). P values inferior to 0.05 were considered statistically significant for binary endpoints and subgroup differences. All analyses were carried out using R software (version 4.2.2; R Foundation, Vienna, Austria).

Results

Systematic review

Our systematic search yielded 1,943 results, 49 of which were selected for a comprehensive review. Most studies were excluded for lacking patients with HER2-positive BC and CNS involvement or due to unavailability of data for this subgroup. Finally, 18 studies with 21 related publications were included (Fig. 1) [19,21,22,25,26,30–45]. Of them, eight were CTs at different phases, nine were real-world retrospective studies whereas one was an ambispective phase IV study.

Baseline characteristics

Sixteen studies with 750 patients with BMs were included [19,21,22,25,26,30–42]. Most patients had stable BMs (45.7 %, $n = 343$), whereas 38.4 % had active BMs ($n = 288$). T-DXd was consistently administered at a dose of 5.4 mg/kg. Most patients had Eastern Cooperative Oncology Group (ECOG) performance status of zero to one (67.5

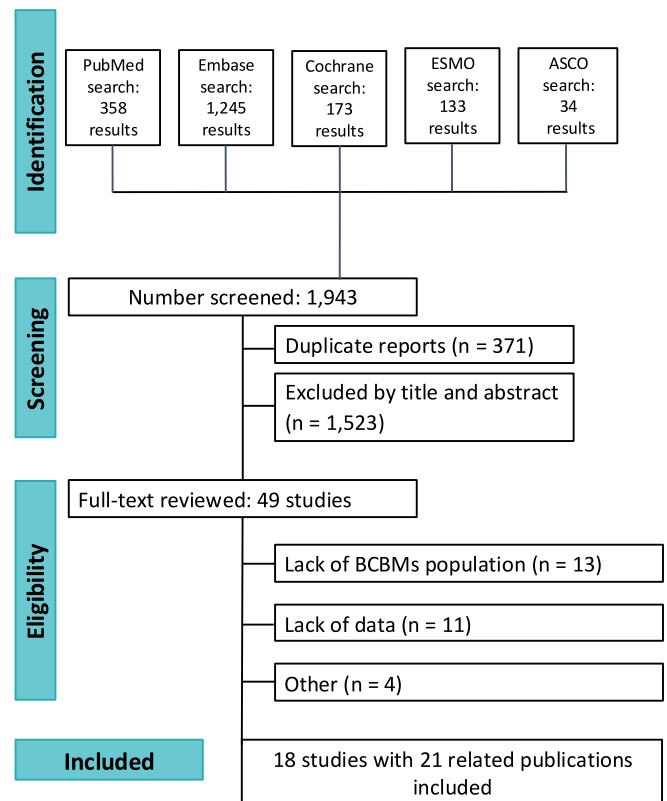


Fig. 1. PRISMA flow diagram of study screening and selection. Blue vertical boxes indicate each stage of the screening, and the horizontal boxes present more detailed information about the process, including the steps performed in each stage. ASCO: American Society of Clinical Oncology; BCBMs: breast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

%, $n = 506$) and hormone receptor-positive tumors (47.3 %, $n = 355$). Median age and follow-up time ranged from 46 to 69 years and from seven to 26.5 months, respectively. Other baseline characteristics of studies on BMs, such as previous CNS therapies and a median number of prior therapies, are shown in Table 1A. In most of these studies, LMD patients were excluded. In just two studies, which included both BMs and LMD patients ($n = 18$), data was not presented separately for each group [38,41].

We included four studies encompassing 36 patients with LMD (Table 1B) [22,25,43–45]. In two studies, information as to cerebrospinal fluid cytology (CSF) was not provided. In the two others, five out of eleven patients had a positive CSF. Median age and follow-up time ranged from 42.5 to 57 years and from 12 to 20.4 months, respectively (Table 1B).

Overall efficacy in the BMs cohort

Overall, 60.4 % (95 % CI, 53.6–67 %) out of 573 patients achieved an ORR, and 94.4 % (95 % CI, 92.1–96.5 %) out of 553 achieved DCR on T-DXd (Fig. 1A and B). No significant differences were detected between CTs/prospective and real-world/retrospective studies ($p > 0.05$, Fig. 2A and B). The pooled CBR of three studies with 42 patients was 79.3 % (95 % CI, 63.6–89.4 %, Fig. 2C). Among six studies with 449 patients, the 12-month PFS was 64.7 % (95 % CI, 59.4–69.7 %, Fig. 2D). The pooled analysis of four studies with 393 patients revealed a 12-month OS of 82.7 % (95 % CI, 69–91.1 %, Fig. 2E).

Table 1
 Characteristics of included studies in this systematic review and meta-analysis according to the population assessed:

Study	Design	Location	BMs status, n			T-DXd regimen	Age (years), median (range)	ECOG PS 0–1, n (%)	HR+, n (%)	Number of previous therapies ^b	Prior CNS treatment, n (%)	Follow-up in months ^a
			Active	Stable	Total							
DESTINY-Breast01 [33]	Phase II CT	Multicenter	0	24	24	5.4 mg/kg	58 (33–85)	24 (100)	9 (37.5)	median (range): 6 (3–16)	RT: 14 (58.3); CX: 1 (4.2); CX + RT: 3 (12.5); CX + RT + cap: 1 (4.2)	11.1 (0.7–19.9)
DESTINY-Breast02 [32]	Randomized phase III CT	Multicenter	0 ^c	74	74	5.4 mg/kg	NA	NA	NA	median (range): 2 (2–3) ^d	NA	21.5 (15.2–28.4) ^d
DESTINY-Breast03 [19]	Randomized phase III CT	Multicenter	0 ^c	43	43	5.4 mg/kg	52.8 (29.2–76.2)	43 (100)	23 (53.5)	0–1 lines: 15 pts (34.9 %); 2 lines: 28 pts (65.1 %)	RT alone: 16 (37.2); CX alone: 1 (2.3); CX + RT: 6 (14)	16.2 (0–32.7) ^d
DESTINY-Breast07 [34] ^e	Phase Ib/II	Multicenter	35	0	35	5.4 mg/kg	49 (33–70)	35 (100)	19 (54.3)	NA	NA	16.2 (NA)
DESTINY-Breast12 [21]	Prospective phase IIIb/IV	Multicenter	106	157	263	5.4 mg/kg	52 (28–86)	263 (100)	165 (62.7)	median (range):1 (0–4)	RT: 158 (60.1); WBRT: 40 (15.2); SRS: 15 (5.7)	15.4 (0.1–30)
DAISY [35] ^e	Phase II CT	France	0	12	12	5.4 mg/kg	60.5 (32–70)	12 (100)	6 (50)	<5 lines: 6 pts (50 %); ≥ 5 lines: 6 pts (50 %)	NA	NA
Dannehl 2024 [30] ^f	Real-world (retrospective)	Germany	5	11	16	5.4 mg/kg	58 (IQR, 52.5–62)	NA	10 (62.5)	median (range): 2.5 (2–15)	CX alone: 4 (25); WBRT: 6 (37.5); SRS: 4 (25); WBRT + SRS: 4 (25)	12.7 (NA)
DEBBRAH [36]	Phase II CT	Spain and Portugal	13	8	21	5.4 mg/kg	53 (36–77)	21 (100)	16 (76.2)	1 line: 3 pts (14.3 %); 2 lines: 5 pts (23.8 %); 3 lines: 1pt (4.8 %); 4 lines: 2 pts (9.5 %); 5 lines: 10 pts (47.6 %)	WBRT: 10 (47.6); CX: 6 (28.6); SRS/SRT: 7 (33.3)	8.4 (1.4–12.6)
DE-REAL [37] ^e	Real-world (retrospective)	Italy	NA	NA	39	5.4 mg/kg	NA	NA	NA	NA	NA	NA
Kabraji 2023 [31] ^g	Real-world (retrospective)	United States	10	7	18 ^h	NA	46 (35–69)	NA	10 (55.6)	median (range): 4 (0–10)	CX: 4 (22); WBRT: 9 (50); SRS: 11 (61)	7 (NA)
Murphy 2023 [38] ^e	Real-world (retrospective)	Ireland	NA	NA	30	NA	53.8 (38–77)	NA	18 (60)	mean: 3.7 (NA)	WBRT (NA); SRS (NA)	NA
Nakajima 2022 [39]	Real-world (retrospective)	Japan	NA	NA	9	NA	59.5 (42–78) ^d	NA	NA	NA	NA	10.1 (95 % CI, 8.4–12)
Pearson 2023 [40]	Real-world (retrospective)	United Kingdom	10	1	12	NA	50 (IQR: 43–53)	12 (100)	8 (67)	median (range): 2 (2–6)	CX: 1 (8); SRS: 4 (33); WBR: 8 (67)	13.8 (95 % CI, 11.1–17)
REALITY-01 [41] ^e	Ambispective phase IV	France	21	NA	60	5.4 mg/kg	NA	NA	NA	NA	NA	17.7 (NA) ^d
ROSET-BM [22,25]	Real-world (retrospective)	Japan	73	6	79 ⁱ	NA	NA	81 (77.9) ^d	59 (56.7) ^j	median (range): 4 (3–7) ^d	WBRT: 56 (53.8); CX: 27 (26); SRS: 64 (61.5) ^d	20.4 (95 % CI, 16.4–22.5) ^k
TUXEDO-1 [26,42]	Phase II CT	Austria	15	0	15	5.4 mg/kg	69 (30–76)	15 (100)	12 (80)	median (range): 2 (1–5)	WBRT: 3 (20); SRT/SRS: 3 (20); WBRT + SRT/SRS and/or CX: 3 (20)	26.5 (95 % CI, 23.5–NA) ^k

BMs: brain metastases; cap: capecitabine; CNS: central nervous system; CT: clinical trial; CI: confidence interval; CX: surgery; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hormone receptor; IQR: interquartile range; NA: not available; n: number of patients; pts: patients; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; T-DXd: trastuzumab deruxtecan; WBRT: whole-brain radiotherapy. a: follow-up time was given in months (range) unless indicated otherwise; b: number of previous therapies was reported as median (range) in most studies, except in three studies (DESTINY-Breast03, DAISY, and DEBBRAH), where the information was categorized by treatment groups (e.g., 0–1 lines); c: these studies initially allowed active brain metastases but in further protocol amendments only stable brain metastases were allowed. Therefore, they were included in the stable BM category for all analyses; d: data referring to the general population of the study; e: indicates abstracts from conference proceedings; f: In this study, 11 out of 16 patients (69 %) were human epidermal growth factor (HER2)-positive while 5 patients (31 %) exhibited HER2-low tumors; g: In this study, eight patients were classified with HER2-positive and seven as HER2-negative tumors; h: this study includes 18 patients, however, only 15 had evaluable CNS disease and among them, three patients had unknown brain metastases statuses; i: 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. j: values correspond to estrogen receptor-positive and it considers the total population of the study (n = 104); k: indicates the longer follow-up.

(B) Studies including patients with breast cancer and LMD.

(continued on next page)

Table 1 (continued)

Study	Design	Location	Total, n	Baseline CSF Cytology, n (%)		Age (years), median (range)	ECOG PS 0–1, n (%)	HR+, n (%)	Number of previous therapies	Prior CNS treatment, n (%)	Follow-up in months ^a
				Positive	Negative						
Alder 2023 [43]	Real-world (retrospective) Phase II CT	United States	8	2 (25)	3 (37.5)	42.5 (37–56)	NA	6 (75)	4.5 (3–6)	WBRT: 3 (37.5); SRS+WBRT: 4 (50)	NA
DEBBRAH [44]		Spain and Portugal	3	3 (100)	0	57 (42–69) ^b	NA	NA	4 (1–8) ^b	NA	12 (2.5–18.6)
Rogawski 2024 [45]	Real-world (retrospective)	United States	6	NA	NA	2 (20–75) ^b	NA	NA	2 (0–5) ^b	NA	NA
ROSET-BM [22,25]	Real-world (retrospective)	Japan	19	NA	NA	NA	NA	NA	4 (3–7)	WBRT: 56 (53.8) CX: 27 (26) SRS: 64 (61.5) ^b	20.4 (95% CI, 16.4, 22.5)

CFS: cerebrospinal fluid cytology; CNS: central nervous system; CT: clinical trial; CI: confidence interval; CX: surgery; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hormone receptor; LMD: leptomeningeal disease; NA: not available; n: number of patients; SRS: stereotactic radiosurgery; WBRT: whole-brain radiotherapy. a: follow-up time was given in months (range) unless indicated otherwise; b: data referring to the general population of the study.

CNS efficacy in the BMs cohort

The intracranial ORR, DCR, and CBR were as follows: 62.2 % (n = 268/424, 95 % CI, 56.7–67.9 %); 88.6 % (n = 270/302, 95 % CI, 81.6–93.2 %); and 68.6 % (n = 87/124, 95 % CI, 59.6–76.4 %), respectively (Fig. 3. A–C). Responses were fairly similar between CTs and real-world studies (p > 0.05). The 12-month intracranial PFS of 383 patients (four studies) was 67.4 % (95 % CI, 58.1–76.7 %, Fig. 3D).

Stable versus active BMs

In all analyses exploring overall antitumor responses (ORR, DCR, CBR) and survival of T-DXd according to BMs status, similar rates were seen between patients with stable and active brain lesions (test for subgroup differences, p > 0.05; Fig. 4). Intracranial ORR was numerically higher but nonsignificant in stable BMs (n = 134) compared to the active group (n = 181) (72.7 % vs 60.5 %, respectively, Fig. 5A). The DCR analysis revealed a slightly better rate for patients with active BMs (Fig. 4B). However, only three studies with 57 patients were included in the stable BMs subgroup, compared to six studies with 120 patients in the active cohort. Therefore, this finding may only reflect a limited sample size in the stable subset. Both stable (n = 168) and active (n = 198) groups achieved a 12-month intracranial PFS superior to 65 % (test for subgroup difference, p = 0.64, Fig. 5C).

Untreated versus previously treated/progressive BMs

Three studies assessed the intracranial ORR of patients with untreated BMs (n = 33) compared to those with previously treated or progressing lesions (n = 56) within the active BMs cohort. Although only a few patients were included, intracranial responses were consistently higher in the first group (OR 3.82, 95 % CI 1.34–10.84, p = 0.012, I² = 0 %; Fig. S1).

Efficacy in BMs versus non-BMs cohorts

Compared to patients without BMs at baseline, those with CNS involvement had lower ORR (OR 0.63, 95 % CI 0.47–0.84, p = 0.002, I² = 0 %, Fig. S2A). Yet, the DCR was not statistically different between groups (n = 977; OR 0.67, 95 % CI 0.33–1.35, p = 0.26, I² = 23 %; Fig. S2B). Comparable rates were also observed for PFS and OS at 12 months (Fig. S3C and D), although only two studies with different designs and sample sizes could be included.

LMD subgroup

The intracranial ORR was 59.4 % (95 % CI, 38.5–77.4 %) across four studies with 26 patients with LMD (Fig. S3A). In all but one study, the IC-ORR was greater than or equal to 50 %. In the phase II DEBBRAH trial, no patient among the three HER2-positive patients included achieved a complete or partial response. Nevertheless, most achieved prolonged disease stability of over 24 weeks. Our pooled analysis of three studies with 20 patients revealed an IC-CBR of 94.1 % (95 % CI, 74.1–100 %, Fig. S3B). The median OS and PFS are shown in Table S6.

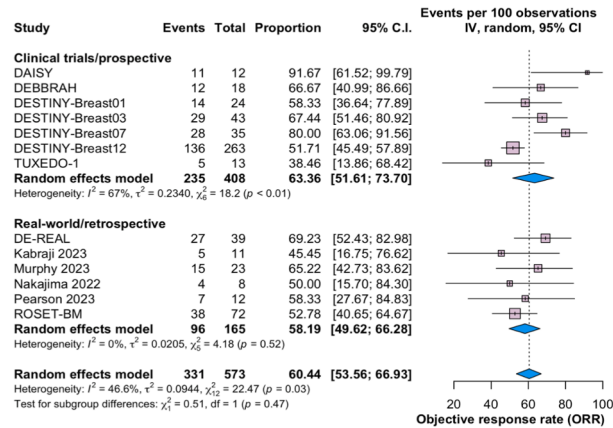
Safety in the BMs cohort

AEs of any grade were observed in almost all patients (Fig. S5A). Dose reductions and treatment discontinuation were required in 28.2 % and 16.7 % of cases, respectively (Fig. S5B and C). All grade and severe AEs commonly reported include nausea, fatigue, constipation, and neutropenia (Figs. S5 and S6).

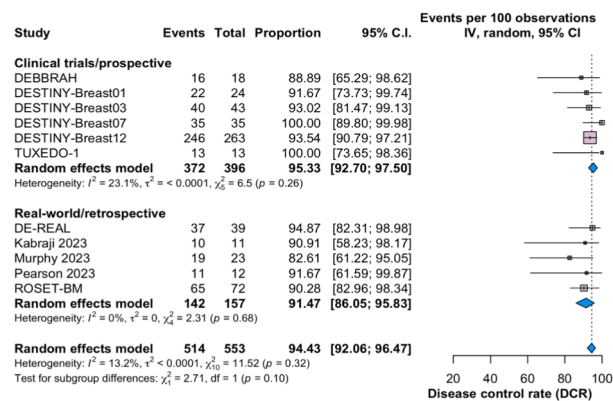
Health-related quality of life

Four studies were found to report health-related quality of life

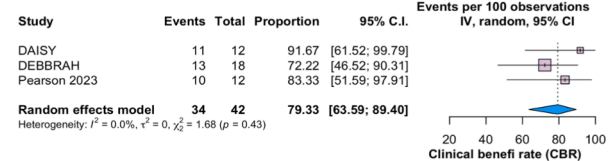
(A) Objective response rate (ORR) according to study design



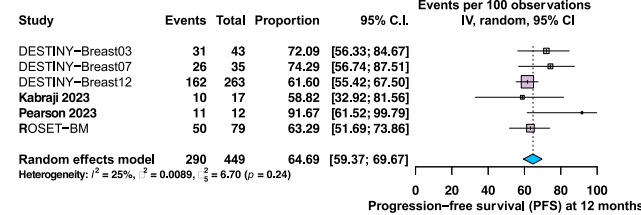
(B) Disease control rate (DCR) according to study design



(C) Clinical benefit rate (CBR)



(D) Progression-free survival (PFS) at 12 months



(E) Overall survival (OS) at 12 months

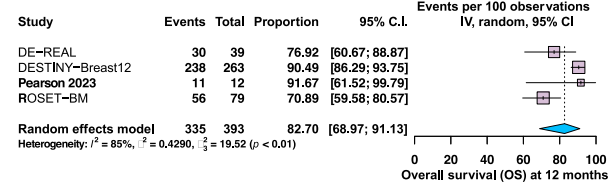
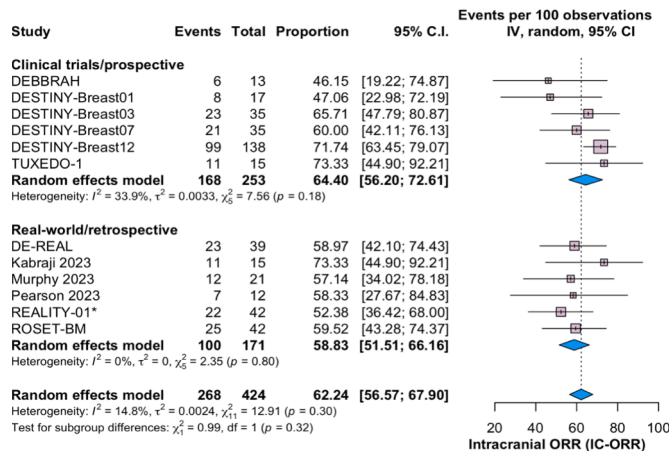
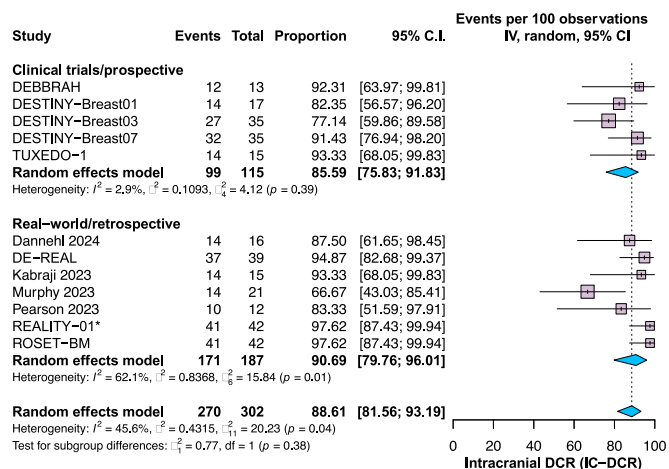


Fig. 2. Overall ORR (A); DCR (B); CBR (C); 12-month PFS (D); and 12-month OS (E) in patients with HER2-positive BMs on T-DXd. Proportions for each study are represented by a square, and the horizontal line crossing the squares indicates the 95 % confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effect. BMs: brain metastases; CBR: clinical benefit rate; CI: confidence intervals; DCR: disease control rate; HER2: human epidermal growth factor 2; IV: inverse variance; ORR: objective response rate; OS: overall survival; PFS: progression-free survival. For the ORR and DCR in the DEBBRAH trial, we considered patients with measurable intracranial or extracranial lesions as per RECIST v.1.1. In the study by Pearson et al., we used the confirmed ORR, which was taken as the best response from extracranial and intracranial disease combined. In the study by Murphy et al., overall response data was unavailable for seven out of 30 patients; therefore, only 23 patients were included in the analyses. In the ROSET-BM study, we used data for analytical active (n = 61) and stable (n = 11) patients for antitumor analyses. For this same study, we used updated data for survival analyses.

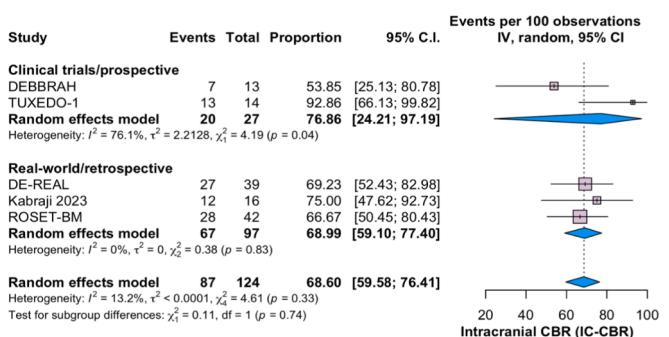
(A) Intracranial ORR (IC-ORR) according to study design



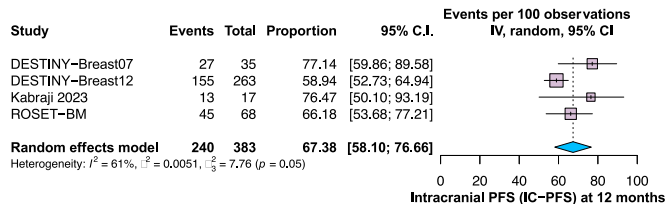
(B) Intracranial DCR (IC-DCR) according to study design



(C) Intracranial CBR (IC-CBR) according to study design



(D) Overall intracranial PFS (IC-PFS) at 12 months



(caption on next page)

Fig. 3. Intracranial ORR (A); DCR (B); CBR (C); 12-month PFS (D); and 12-month OS (E) in patients with HER2-positive BMs on T-DXd. Proportions for each study 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. BMs: brain metastases; CBR: clinical benefit rate; CI: confidence intervals; DCR: disease control rate; HER2: human epidermal growth factor 2; IV: inverse variance; ORR: objective response rate; OS: overall survival; PFS: progression-free survival. *We included this ambispective study in the 'real-world/retrospective' category due to its heterogeneous design compared to prospective studies. In DESTINY-Breast01, 17 patients had reported tumor measurements for brain lesions, however only 15 of 17 patients had data available to evaluate responses in the brain. In the study by Murphy et al., intracranial response data was unavailable for nine out of 30 patients; therefore, only 21 patients were included in the analyses. In the ROSET-BM study, we used data for analytical active (n = 61) and stable (n = 11) patients for antitumor analyses.

(Table S7) [26,36,44,46,47]. For DESTINY-Breast02/03, data was not available separately for patients with BMs. All studies evaluated quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and breast cancer-specific tools, whereas only the TUXEDO-1 trial included a brain-specific tool. Both DESTINY-Breast02/03 also applied the Euro-QoL EQ-5D-5L questionnaire. Global health status was maintained for patients under T-DXd therapy across all studies. Moreover, in the two randomized studies, time to deterioration and other patient-reported outcomes favored T-DXd over the control groups.

Sensitivity analyses

All leave-one-out analyses revealed fairly consistent results with the observed overall effect for each analysis (Fig. S7, Fig. S8 and Fig.S9).

Exploring heterogeneity

The Baujat plot for the overall ORR revealed two outliers: DESTINY-Breast12 and DESTINY-Breast07 (Fig. S10). The first consists of the study with the largest population included in this *meta*-analysis. Therefore, it is expected to have an important influence on the effect size. On the other hand, DESTINY-Breast07 has been shown to greatly contribute to the overall heterogeneity. As the only study investigating T-DXd in earlier treatment lines, the high heterogeneity may be due to its somewhat different design.

Quality assessment

All 16 non-randomized (real-world and CTs of different phases) studies were judged at moderate risk of bias, mainly due to the non-randomized design and limited sample size, failing to meet the criteria for the first two domains (Table S8) [21,22,25,26,30,31,33–45]. The two randomized CTs met criteria for most domains and were judged to be at low risk of bias (Table S8) [19,32]. The funnel plot analysis showed a symmetrical distribution of studies (Fig. S11), further confirmed by the Egger test ($t = 1.86$; $p = 0.091$).

Discussion

This systematic review and updated *meta*-analysis comprises 18 studies with 786 HER2-positive BC patients with CNS involvement treated with T-DXd. Although in most studies patients received multiple prior lines of therapies, we observed high overall antitumor responses (ORR, 60.4 %; DCR, 94.4 %; and CBR, 79.3 %) and a 12-month PFS of 64.7 % and OS of 82.7 %, including both CTs/prospective and real-world/retrospective studies. Intracranial ORR, DCR, and CBR were seen in 62.2 %, 88.6 %, and 68.6 % of cases, respectively, and 67.4 % achieved intracranial PFS at 12 months. Moreover, both stable and active BMs subgroups derived benefit from T-DXd. Consistently better intracranial responses were seen for 33 patients with untreated BMs compared to 56 patients with previously treated or progressing lesions. For the LMD group, T-DXd elicited intracranial ORR and CBR in 59.4 % and 94.1 % of cases, respectively. Toxicity was consistent with previously published data.

Although the BBB is deemed the main obstacle in hindering penetration of systemic therapies to the brain, its disruption during disease

progression may favor intracranial drug delivery [10]. This was previously seen in a study in which an increase in trastuzumab CSF levels was associated with an impaired BBB following radiotherapy and LMD [48]. Yet, trastuzumab still failed to trigger considerable intracranial activity, and its relatively large molecular size was considered one of the key rate-limiting factors in this process [10,15]. This prompted the rationale for the development of low-weight molecules that could better penetrate the BBB and enhance drug uptake in the brain [11]. In this scenario, tyrosine kinase inhibitors (TKIs) emerged as a potential approach due to their small molecular size and potent targeting abilities [11]. The combination of a small TKI, lapatinib, and capecitabine as first-line therapy for brain disease yielded CNS responses in 66 % out of 44 HER2-positive BC patients with untreated BMs in the phase II LANDSCAPE trial [12]. Subsequently, the groundbreaking randomized HER2-CLIMB trial established the role of triple therapy with tucatinib (an oral TKI), trastuzumab, and capecitabine (TTC) [13]. In 291 patients with HER2-positive BC and BMs at baseline, a 52 % reduction in the risk of disease progression or death was seen in favor of the tucatinib group (HR 0.48; 95 % CI, 0.34–0.69; $p < 0.001$). This placed the TTC regimen as the preferred systemic treatment for HER2-positive BC patients with active BMs after one prior anti-HER2 therapy in the metastatic setting [49].

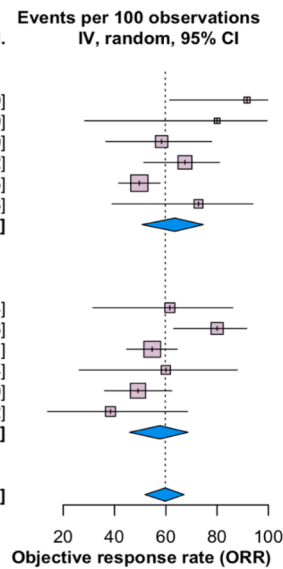
Despite their complex design and large molecular size, ADCs yielded unprecedented efficacy in the subset of patients with brain tumors from BC [16,50]. Designed to synergistically combine high selectivity and potent cytotoxic effects, these agents are acknowledged as 'biological missiles' by some authors [51]. The antibody component acts by binding to specific antigens expressed in tumor cells and, once internalized, ADCs release a cytotoxic payload within the tumor microenvironment [51]. In the case of T-DXd, the antibody trastuzumab is linked through a cleavable linker to a topoisomerase I inhibitor (deruxtecan) [15,51]. Neighboring tumor cells that do not express the target antigen may also be affected by the payload's anticancer effects, a phenomenon known as the bystander effect [15,51]. The precise mechanism behind ADCs activity in brain lesions remains unclear [10]. However, it may be partially explained by the BBB disruptions that allow larger molecules to cross it [10,16].

Among the ADCs studied so far in HER2-positive BC, T-DXd has been the frontrunner [32]. The phase III DESTINY-Breast03 trial reported a 72 % reduction in the risk of disease progression or death associated with T-DXd over a second-generation ADC, T-DM1 (n = 524, HR 0.28, 95 % CI, 0.22–0.37, $p < 0.001$) [32]. Following this, T-DXd was granted accelerated approval as the second-line treatment in HER2-positive BC patients progressing on prior anti-HER2 therapy [52,53]. The activity of ADCs in patients with HER2-positive BC/BMs was previously shown in an exploratory analysis of the phase IIIB KAMILLA trial, in which 21.4 % and 42.9 % of 126 patients achieved an overall ORR and CBR, respectively, under treatment with T-DM1 [54]. Although the DESTINY-Breast03 trial included only 43 patients with BMs on the T-DXd arm, it showed a high intracranial response of 65.7 % [19]. In this same subset, T-DXd was associated with a remarkable improvement in survival compared to 39 patients on T-DM1 (HR for disease progression or death 0.25, 95 % CI, 0.13–0.45) [19].

More recently, DESTINY-Breast12, a phase IIIB/IV CT, has reinforced the benefit of T-DXd in a larger cohort of 263 patients with HER2-positive BC and BMs [21]. In the overall BM cohort – including both stable and active BMs – 51.7 % of patients achieved an ORR and the 12-month PFS was 61.6 %, whereas the IC-ORR and 12-month IC-PFS were

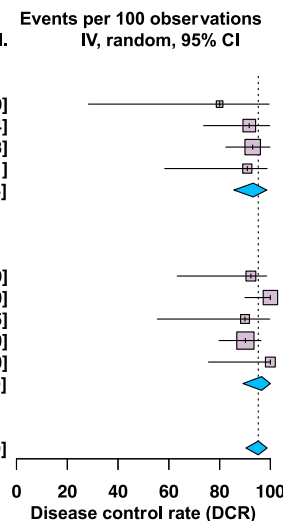
(A) Objective response rate (ORR)

Study	Events	Total	Proportion	95% C.I.
Stable				
DAISY	11	12	91.67	[61.52; 99.79]
DEBBRAH	4	5	80.00	[28.36; 99.49]
DESTINY-Breast01	14	24	58.33	[36.64; 77.89]
DESTINY-Breast03	29	43	67.44	[51.46; 80.92]
DESTINY-Breast12	78	157	49.68	[41.61; 57.76]
ROSET-BM	8	11	72.73	[39.03; 93.98]
Random effects model	144	252	63.51	[50.73; 74.63]
Heterogeneity: $I^2 = 55.9\%$, $\tau^2 = 0.1868$, $\chi^2_3 = 11.33$ ($p = 0.05$)				
Active				
DEBBRAH	8	13	61.54	[31.58; 86.14]
DESTINY-Breast07	28	35	80.00	[63.06; 91.56]
DESTINY-Breast12	58	106	54.72	[44.75; 64.41]
Pearson 2023	6	10	60.00	[26.24; 87.84]
ROSET-BM	30	61	49.18	[36.14; 62.30]
TUXEDO-1	5	13	38.46	[13.86; 68.42]
Random effects model	135	238	57.66	[45.89; 68.62]
Heterogeneity: $I^2 = 51.6\%$, $\tau^2 = 0.1792$, $\chi^2_5 = 10.34$ ($p = 0.07$)				
Random effects model	279	490	59.75	[51.93; 67.11]
Heterogeneity: $I^2 = 49.2\%$, $\tau^2 = 0.1287$, $\chi^2_{11} = 21.67$ ($p = 0.03$)				
Test for subgroup differences: $\chi^2_1 = 0.46$, $df = 1$ ($p = 0.50$)				



(B) Disease control rate (DCR)

Study	Events	Total	Proportion	95% C.I.
Stable				
DEBBRAH	4	5	80.00	[28.36; 99.49]
DESTINY-Breast01	22	24	91.67	[73.73; 99.74]
DESTINY-Breast03	40	43	93.02	[82.44; 99.83]
ROSET-BM	10	11	90.91	[58.35; 98.71]
Random effects model	76	83	93.26	[85.61; 98.58]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi^2_3 = 1.13$ ($p = 0.77$)				
Active				
DEBBRAH	12	13	92.31	[63.31; 98.49]
DESTINY-Breast07	35	35	100.00	[90.00; 100.00]
Pearson 2023	9	10	90.00	[55.50; 99.75]
ROSET-BM	55	61	90.16	[79.81; 96.30]
TUXEDO-1	13	13	100.00	[75.59; 100.00]
Random effects model	124	132	96.53	[89.17; 100.00]
Heterogeneity: $I^2 = 44\%$, $\tau^2 = 0.0087$, $\chi^2_4 = 7.17$ ($p = 0.13$)				
Random effects model	200	215	95.23	[90.40; 98.70]
Heterogeneity: $I^2 = 15\%$, $\tau^2 = 0.0031$, $\chi^2_8 = 9.37$ ($p = 0.31$)				
Test for subgroup differences: $\chi^2_1 = 0.86$, $df = 1$ ($p = 0.35$)				



(C) Progression-free survival (PFS) at 12 months

Study	Events	Total	Proportion	95% C.I.
Stable				
DESTINY-Breast03	31	43	72.09	[56.33; 84.67]
DESTINY-Breast12	99	157	63.06	[55.00; 70.61]
ROSET-BM	9	12	75.00	[42.81; 94.51]
Random effects model	139	212	66.65	[58.94; 74.37]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0010$, $\chi^2_2 = 1.89$ ($p = 0.39$)				
Active				
DESTINY-Breast07	26	35	74.29	[56.74; 87.51]
DESTINY-Breast12	63	106	59.43	[49.46; 68.87]
Pearson 2023	8	10	80.00	[44.39; 97.48]
ROSET-BM	41	67	61.19	[48.50; 72.86]
Random effects model	138	218	65.30	[57.03; 73.57]
Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0024$, $\chi^2_3 = 4.68$ ($p = 0.20$)				
Random effects model	277	430	65.08	[60.49; 69.68]
Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0001$, $\chi^2_6 = 6.73$ ($p = 0.35$)				
Test for subgroup differences: $\chi^2_1 = 0.05$, $df = 1$ ($p = 0.82$)				

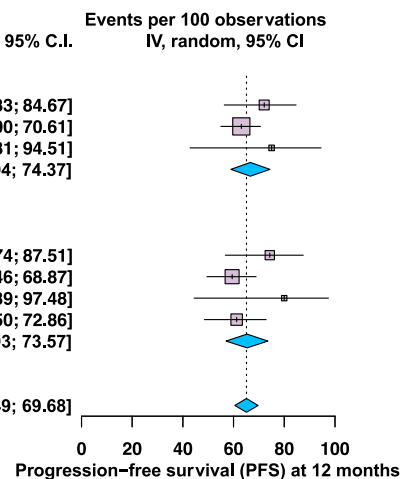


Fig. 4. Overall ORR (A); DCR (B); and 12-month PFS (C) in patients with HER2-positive stable vs active BMs on T-DXd. Proportions for each study are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. BMs: brain metastases; CI: confidence intervals; DCR: disease control rate; HER2: human epidermal growth factor 2; IV: inverse variance; ORR: objective response rate; PFS: progression-free survival. For the ROSET-BM study, we used updated data for survival analyses.

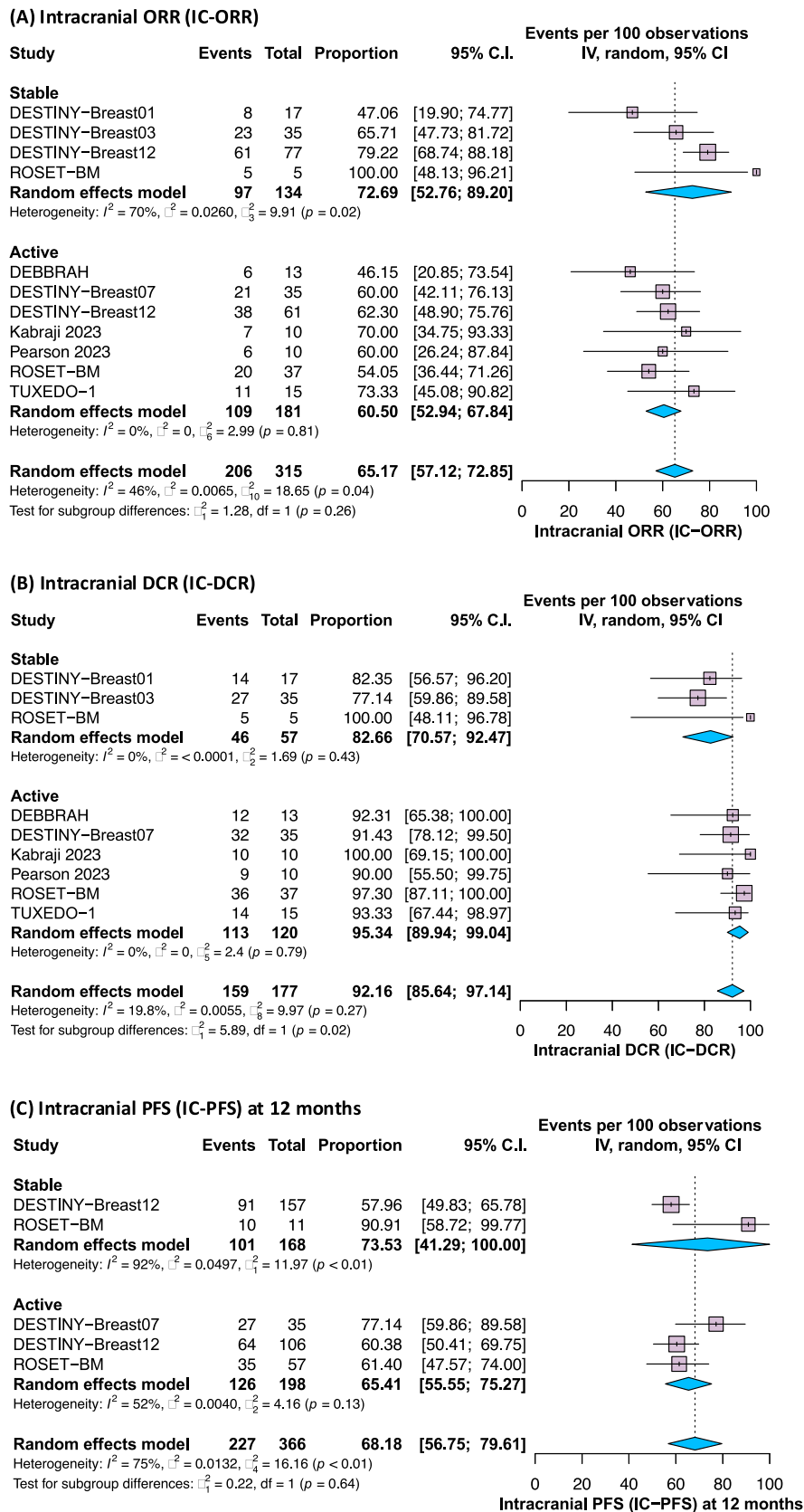


Fig. 5. Intracranial ORR (A); DCR (B); and 12-month PFS (C) in patients with HER2-positive stable vs active BMs on T-DXd. Proportions for each study are represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects. BMs: brain metastases; CI: confidence intervals; DCR: disease control rate; HER2: human epidermal growth factor 2; IV: inverse variance; ORR: objective response rate; PFS: progression-free survival. In DESTINY–Breast01, 17 patients had reported tumor measurements for brain lesions, however only 15 of 17 patients had data available to evaluate responses in the brain. For the ROSET–BM study, we used updated data for survival analyses.

71.7 % and 58.9 %, respectively. Patients had received a median of one prior anti-HER2 therapy in the metastatic setting but were tucatinib naive [21]. Therefore, the intracranial benefit may be mainly attributed to T-DXd. Accordingly, in our analyses including more heavily pre-treated patients, the overall and intracranial efficacy of T-DXd were notably high.

Prior to DESTINY-Breast12, few clinical studies had explored T-DXd activity in active BMs. DEBBRAH and TUXEDO-1, both phase II studies, included 13 and 15 patients with active lesions, respectively [26,36,42]. TUXEDO-1 registered an IC-ORR superior to 70 % and a median PFS of 21 months on longer follow-up [26]. In DEBBRAH trial, a great number of patients received more than five prior lines of therapy [36]. In spite of this, the IC-ORR ranged between 50 % and 44.4 % in patients with untreated and progressing BMS, respectively [36]. Furthermore, the ROSET-BM study further indicated the effectiveness of T-DXd in active lesions in a real-world setting [22,25]. In our pooled analyses, patients with active BMs had comparable responses to those with stable disease, suggesting that both groups benefit from T-DXd treatment.

It is known that brain tumor development leads to a breakdown of tight junctions, leading to increased BBB permeability [10]. Therefore, the stage of BMs development could also guide the choice of HER-2 targeted therapies in breast cancer [55]. For instance, *in vivo* imaging methods have been developed to evaluate the integrity of the BBB, such as radiolabeled tracers combined with imaging modalities that can visualize BMs in HER2-positive patients [56]. Ultimately, the integration of these modalities aimed at determining the state of the barrier may help optimize therapeutic approaches in patients with breast cancer BMs [56]. Smaller lipophilic TKIs such as tucatinib may be able to target metastases at earlier stages than ADCs, and the cytotoxicity of different ADC payloads may guide the choice of ADC therapy [57].

Interestingly, there is also a suggestion that treatment status may affect responses. In our small subgroup analysis comparing patients with untreated to previously treated or progressing BMs, an enhanced CNS activity was consistently seen in the untreated group across all studies [21,36,42]. This may indicate a greater efficacy in treating BMs patients with T-DXd in earlier lines. At the time this *meta*-analysis was conducted, only the primary results from module seven (which included only active BMs) of the DESTINY-Breast07 trial were available. This phase Ib/II trial was specifically designed to investigate T-DXd in the first or second-line treatment of BMs from HER2-positive BC [34]. Out of 35 patients in this study, 21 (60 %) achieved IC-ORR and median IC-PFS was 15.4 months [34]. Despite encouraging results, more mature data are awaited to fill some of the gaps on the early use of T-DXd in the scenario of HER2-positive CNS involvement.

The benefit of T-DXd also appears to extend to patients with LMD. Due to its widespread and aggressive behavior, LMD represents a critical subgroup within the metastatic BC population, and most therapies fail to trigger durable responses and improve their prognosis [58,59]. Nevertheless, in the cohort by Alder *et al.* including eight patients with HER2-positive BC and LMD, 50 % achieved CNS ORR, and all patients had clinical benefit on T-DXd [43]. In two other real-world studies, even higher intracranial responses were seen in the LMD group [22,45]. Although in the DEBBRAH trial no patient achieved objective responses in cohort 5 (untreated LMD patients), most had prolonged stabilization [44]. In this study, median OS and PFS were 13.3 and 8.9 months, respectively [44]. To date, DEBBRAH is the only prospective study investigating T-DXd in BC patients with LMD, and more data on this subset is urgently needed.

Our findings highlight the efficacy and effectiveness of T-DXd in patients with CNS disease from HER2-positive BC. However, a number of challenges are yet to be addressed. Firstly, many patients progress while on ADC treatment, and little is known about pathways leading to ADC resistance, and ways to prevent or overcome it [60,61]. Other ADCs are currently being tested for metastatic BC and brain disease and may expand systemic alternative options for this population [62,63]. The preferred sequence of ADCs for patients who progressed on a prior ADC

or those who may be fit for multiple agents warrants investigation [64]. Additionally, there are currently no head-to-head comparisons between T-DXd and triple regimen with TTC, which may render difficulties in treatment selection of HER2-positive BC and BMs patients [11]. Moreover, the combination of T-DM1 with tucatinib has recently demonstrated encouraging activity in the primary results of the randomized HER2-CLIMB02 study, including the active BMs subgroup [65]. Thus, upcoming combined regimens may further broaden the treatment landscape of patients with HER2-positive BC with CNS involvement.

This systematic review and *meta*-analysis has limitations. Considerable heterogeneity was observed in some analyses, which may have been influenced by the inclusion of studies with different designs. Moreover, some studies had slightly different eligibility criteria, endpoint definitions and criteria for assessing intracranial lesions (RECIST vs RANO-BM). A few of the included reports were conference proceedings of which more mature data is awaited. Frequently, patients with CNS involvement were a small cohort within the overall metastatic BC population. Thus, in some subgroup analyses, a limited number of patients was included. Lastly, we could not perform adjusted analyses based on factors such as prior systemic therapies, radiotherapy, and time from last CNS treatment. To mitigate some of these limitations, we carried out all analyses using random-effects models and explored heterogeneity through the Baujat plot. We also performed several subgroup and sensitivity analyses.

Conclusions

This systematic review and updated *meta*-analyses continues to support the robust activity of T-DXd in patients with stable and active BMs from HER2-positive BC in both clinical and real-world studies. Overall and intracranial responses were superior to 60 %, with an overall 12-month PFS of 64.7 % and OS of 82.7 %. Approximately 67 % of patients did not experience intracranial disease progression at 12 months of treatment. Patients with LMD also had notable intracranial ORR and CBR. Nevertheless, prospective studies on LMD patients are highly needed. Upcoming research on T-DXd in earlier lines, ADC resistance, and sequence, as well as combined therapies, may fill some of the current gaps regarding the management of patients with HER2-positive BC and CNS involvement.

CRedit authorship contribution statement

Isabella Michelon: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Resources, Visualization, Writing – original draft. **Caio E.R. Castro:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Resources, Visualization, Writing – original draft. **Thiago Madeira:** Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. **Maria Inez Dacoregio:** Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. **Carlos Stecca:** Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft. **Leonardo R. Soares:** Conceptualization, Investigation, Resources, Visualization, Writing – original draft. **Anwaar Saeed:** Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft, Supervision. **Maysa Vilbert:** Conceptualization, Formal analysis, Investigation, Resources, Visualization, Writing – original draft, Supervision. **Ludimila Cavalcante:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Resources, Visualization, Writing – original draft, Supervision.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The authors I.M., C.E.R.C., T.M., M.I.D., C.S., M.V. declare no conflicts of interest. L.R.S. has served as a speaker for MSD, AstraZeneca and Roche, and as a medical writer for BD and Daiichi Sankyo. A.S. reports consulting or advisory board role with AstraZeneca, Bristol-Myers Squibb, Merck, Exelixis, Pfizer, Xilio therapeutics, Taiho, Amgen, Autem therapeutics, Arcus therapeutics, KAHR medical, and Daiichi Sankyo; institutional research funding from AstraZeneca, Bristol-Myers Squibb, Merck, Clovis, Exelixis, Actuate therapeutics, Incyte Corporation, Daiichi Sankyo, Five prime therapeutics, Amgen, Innovent biologics, Dragonfly therapeutics, Oxford Biotherapeutics, Arcus therapeutics, and KAHR medical. L.C. reports consulting or advisory role for Actuate Therapeutics, Pliant Therapeutics, Janssen, and CDR-Life. Stock, and other ownership interests in Actuate Therapeutics].

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2025.102882>.

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