Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

TUXEDO-4: phase II study of trastuzumab-deruxtecan in HER2-low breast cancer with new or progressing brain metastases

Maximilian Marhold, Marta Vaz Batista, Isabel Blancas, Cristina Morales, Cristina Saura-Manich, Cristina Saavedra, Manuel Ruíz-Borrego, Patricia Cortez, Felipe Slebe, Marta Campolier, Juliana Carvalho Santos, José Antonio Guerrero-Martínez, Carlos Jiménez-Cortegana, Beate Rottenmanner, Heidrun Forstner, Rupert Bartsch & Matthias Preusser

To cite this article: Maximilian Marhold, Marta Vaz Batista, Isabel Blancas, Cristina Morales, Cristina Saura-Manich, Cristina Saavedra, Manuel Ruíz-Borrego, Patricia Cortez, Felipe Slebe, Marta Campolier, Juliana Carvalho Santos, José Antonio Guerrero-Martínez, Carlos Jiménez-Cortegana, Beate Rottenmanner, Heidrun Forstner, Rupert Bartsch & Matthias Preusser (2025) TUXEDO-4: phase II study of trastuzumab-deruxtecan in HER2-low breast cancer with new or progressing brain metastases, Future Oncology, 21:9, 1065-1073, DOI: 10.1080/14796694.2025.2470604

To link to this article: https://doi.org/10.1080/14796694.2025.2470604

FUTURE ONCOLOGY
2025, VOL. 21, NO. 9, 1065–1073
https://doi.org/10.1080/14796694.2025.2470604

Taylor & Francis
Taylor & Francis Group

CLINICAL TRIAL PROTOCOL

TUXEDO-4: phase II study of trastuzumab-deruxtecan in HER2-low breast cancer with new or progressing brain metastases

Maximilian Marhold[a], Marta Vaz Batista[b,c], Isabel Blancas[d,e,f], Cristina Morales[g], Cristina Saura-Manich[h], Cristina Saavedra[i,j], Manuel Ruíz-Borrego[k], Patricia Cortez[j], Felipe Slebe[c], Marta Campolier[c], Juliana Carvalho Santos[c], José Antonio Guerrero-Martínez[c], Carlos Jiménez-Cortegana[c], Beate Rottenmanner[a], Heidrun Forstner[a], Rupert Bartsch[a] and Matthias Preusser[a]

[a]Department of Medicine 1, Division of Oncology, Medical University of Vienna, Vienna, Austria; [b]Department of Oncology, Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal; [c]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain; [d]Department of Oncology, Hospital Universitario Clínico San Cecilio, Granada, Spain; [e]Medicine Department, University of Granada, Granada, Spain; [f]Área de Oncología Instituto de Investigación Biosanitaria de Granada, Granada, Spain; [g]Servicio de Oncología Médica, Hospital Universitario Reina Sofía, Córdoba, Spain; [h]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [i]Departamento de Oncología Médica, Hospital Universitario Ramón y Cajal, Madrid, Spain; [j]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain; [k]Servicio de Oncología Médica, Hospital Virgen del Rocío, Sevilla, Spain

ABSTRACT

Breast cancer (BC) is the most common cause of leptomeningeal disease (LMD) and the second most common cause of brain metastases (BMs) among all solid malignancies. Both BMs and LMD are associated with high morbidity and mortality and treatment options are limited. Trastuzumab deruxtecan (T-DXd), an antibody drug conjugate combining a HER2-targeting antibody with a topoisomerase I inhibitor, has shown activity in HER2-positive (HER2[+]) and HER2-low tumors in both preclinical and clinical settings. Similarly, T-DXd has shown efficacy in HER2[+] BC patients with central nervous system (CNS) involvement. However, data on activity in HER2-low BC patients with BMs and/or LMD using T-DXd are limited. TUXEDO-4 is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II trial (NCT06048718) that will recruit a total of 27 adult patients (13 in the first stage, and 14 in second stage depending on responses in the first stage) to evaluate T-DXd in the HER2-low metastatic BC population presenting with newly diagnosed or progressing BM with or without type II LMD.

Clinical trial registration: NCT06048718 (clinicaltrials.gov); 2023 -506,702-39–00 (EudraCT number).

PLAIN LANGUAGE SUMMARY

Breast cancer cells often spread to the brain (brain metastases) or the membranes surrounding the brain and spinal cord (leptomeningeal disease). Therapies to treat these serious conditions are limited. Trastuzumab deruxtecan (T-DXd), which targets a protein called HER2 (found on the surface of breast cells to control their growth) and includes a powerful anti-cancer component to kill the tumor cells, has shown clinically meaningful results in both HER2-positive (high concentration of HER2 proteins) and HER2-low (low concentration of HER2 proteins) breast cancers. Interestingly, T-DXd has successfully worked in HER2-positive breast cancer patients with brain metastases and/or leptomeningeal disease, but results in their HER2-low counterparts are limited. TUXEDO-4 is a medical study to evaluate the effectiveness of T-DXd in HER2-low breast cancer patients with recently diagnosed or worsening brain metastases, with or without aggressive leptomeningeal disease. The study is taking place in Austria and Spain, and will recruit 27 adult patients. TUXEDO-4 trial TUXEDO-4 is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II clinical trial evaluating the efficacy of trastuzumab-deruxtecan (T-DXd) in human epidermal growth factor receptor 2 (HER2)-low breast cancer (BC) patients presenting with newly diagnosed or progressing brain metastases (BMs), with or without type II leptomeningeal disease (LMD).

TUXEDO-4 TRIAL

TUXEDO-4 is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II clinical trial evaluating the efficacy of trastuzumab-deruxtecan (T-DXd) in human epidermal growth factor receptor 2 (HER2)-low breast cancer (BC) patients presenting with newly diagnosed or progressing brain metastases (BMs), with or without type II leptomeningeal disease (LMD).

ARTICLE HISTORY
Received 27 September 2024
Accepted 19 February 2025

KEYWORDS
Breast; brain/neurologic; metastasis; clinical trials; novel therapy

CONTACT Matthias Preusser matthias.preusser@meduniwien.ac.at Department of Medicine 1, Division of Oncology, Medical University of Vienna, Währinger Gürtel 18-20, Vienna 1090, Austria

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14796694.2025.2470604

Article highlights

Background
- Metastatic breast cancer (BC) is one of the main causes of brain metastases (BMs) and leptomeningeal disease (LMD) among all solid malignancies.
- Patients with BMs and/or LMD are usually excluded form clinical trials due to their poor outcomes, and treatment options are limited.
- Antibody-drug conjugates (ADCs) have emerged as a promising therapeutic option in tumors with central nervous system (CNS) involvement.

Trastuzumab deruxtecan (T-DXd)
- T-DXd is an ADC consisting of an anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload through a chemical linker.
- This drug has shown clinical efficacy in human epidermal growth factor receptor 2-positive (HER2[+]) and HER2-low breast cancers. The Food and Drug Administration approved T-DXd for HER2[+] and HER2-low BC patients based upon the results of the DESTINY-Breast01, DESTINY-Breast03, and DESTINY-Breast04 trials, respectively.
- T-DXd has shown great efficacy in HER2[+] and some efficacy in HER2-low BC patients with CNS involvement. Of note, the DEBBRAH trial reported limited data of 3 IC responses in 6 patients (50% IC-ORR) in HER2-low advanced BC patients with untreated/asymptomatic BMs, and 2 IC responses in 6 patients (33.3% IC-ORR) in their progressing BMs counterparts.
- Results in HER2-low tumor involving BMs and/or LMD are limited.

TUXEDO-4
- TUXEDO-4 is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II clinical trial (NCT06048718).
- The primary endpoint is to assess the objective response rate (ORR) at any timepoint as by best CNS response according to RANO-BM criteria. Key secondary objectives are ORR as by best response determined locally by the investigator using the RECIST v.1.1 for extracranial (EC) and overall lesions, and bicompartmental clinical benefit and bicompartmental disease control rates determined locally by the investigator using the RANO-BM criteria for intracranial (IC) lesions and RECIST v.1.1 criteria for EC and overall lesions.
- Twenty-seven patients (13 in stage one, plus 14 in stage two if there are more than 2 responder patients in stage one) will be enrolled from 13 sites in Austria and Spain.

Conclusions
- If results are positive, this clinical trial could introduce T-DXd as a promising treatment option for HER2-low metastatic BC patients with newly diagnosed or progressing BMs with or without type II LMD.

1. Background and rationale

1.1. Treatment approaches in MBC, BMs, and LMD

BC was the most common-diagnosed type of cancer and the second-leading cause of cancer-related death among women during 2023 [1]. HER2-low BC accounts for more than 50% of all BC cases [2,3] and is defined by immunohistochemistry (IHC) score 1+ or IHC 2+/*in-situ* hybridization (ISH)– [2]. Metastatic BC (MBC) is one of the main causes of BMs and LMD among all solid malignancies [4,5]. BMs occur in approximately one-third of MBC patients [6]. Prognosis remains poor and survival rate after one year of diagnosis is approximately 20% [7]. Interestingly, prior studies have indicated that HER2-low BMs represent a high proportion among hormone receptor-positive and triple-negative BC BMs [8–10]. LMD is a debilitating condition that comprises 10–20% of all central nervous system (CNS) metastases and is developed in 5% of BC patients [11–13]. According to the EANO – ESMO Clinical Practice Guideline, type I LMD requires positive cerebrospinal fluid cytology or positive leptomeningeal biopsy, whereas type II LMD diagnosis only requires clinical findings and neuroimaging [14,15]. It has been demonstrated that patients with type I LMD have significantly poorer outcomes compared with their type II LMD counterparts [16,17]. Of note, patients with CNS involvement are usually excluded from clinical trials due to poor condition and short-term outcomes [18]. Therefore, data regarding potential CNS activity are usually not available from pivotal trials making CNS specific studies necessary.

Treatment strategies in the MBC setting substantially differ depending on the BC subtype. The development of anti-HER2 therapies (e.g., trastuzumab) remarkably improved survival in HER2-positive (HER2[+]) BC patients [19]. However, those treatments have not improved clinical outcomes in their HER2-low BC counterparts [20]. Combinations of endocrine therapy and targeted agents are effective for patients with hormone receptor – positive, HER2[–] MBC, but endocrine resistance may eventually occur, and alternative treatment approaches are needed [21,22]. In metastatic triple-negative BC, limited treatment options are currently available but recent years have seen the introduction of checkpoint-inhibitors, PARPi, and antibody-drug conjugates (ADCs) [23–25].

First-line therapies for metastases to the CNS include a variety of treatments such as local treatment with surgery, radiation therapy, stereotactic radiosurgery, chemotherapy, targeted therapy, or immunotherapy [26,27]. Stereotactic radiosurgery provides high local control rates [28] but may produce radionecrosis and dose spreading to a significant proportion of healthy brain tissues [29]. In addition, systemic therapy has demonstrated improved intracranial (IC) response rates and overall survival in HER2[+] BC patients with BMs [30] but has shown little improvement in other BC subtypes [31]. Also, the blood-brain barrier (BBB) plays a key role because it can limit the penetration of systemic drugs to treat metastatic lesions and treatments may not reach therapeutic levels in the CNS [32].

The development of ADCs, which are targeted therapies combining monoclonal antibodies with a cytotoxic payload through a chemical linker, has brought promising clinical activity in different solid tumor types [33] and holds promise for diseases with CNS involvement [34]. Different ADCs have shown favorable preclinical and clinical outcomes on BMs of HER2[+] BC, including trastuzumab-emtansine (T-DM1) or T-DXd [35]. Specifically, T-DXd has also shown clinically meaningful efficacy in previously treated HER2-low advanced BC patients [36].

1.2. T-DXd as a promising therapeutic option in HER2-low BC patients with BMs and/or LMD

T-DXd is an ADC consisting of a humanized anti-HER2 monoclonal antibody (trastuzumab) linked to a topoisomerase I inhibitor payload (deruxtecan) through a chemical tetrapeptide-based cleavable linker [37]. Once trastuzumab binds HER2 and T-DXd undergoes endocytosis, the linker is cleaved by lysosomal cathepsins, and deruxtecan is released inside

the cell to inhibit DNA replication and induce apoptosis by binding the topoisomerase I-DNA complex [38]. During BMs, T-DXd could not penetrate the BBB easily due to its large size, but tumor invasion may cause CNS damage and neovascularization, which would increase drug permeability [39].

T-DXd 5.4 mg/kg administered by intravenous (IV) infusion every 3 weeks was suggested as an effective dose for HER2 [+] BC patients [40]. T-DXd has shown pharmacological efficacy in this BC population [41–43], including objective response rates (ORR) of more than 60% in the DESTINY-Breast01 trial [42] and 79.7% in the DESTINY-Breast03 trial [41]. In HER2-low BC patients, T-DXd provided a significantly improved median progression-free survival (PFS) versus physician's treatment choice in both the DESTINY-Breast04 (10.1 vs. 5.4 months, respectively) and DESTINY-Breast06 (13.2 vs. 8.1 months, respectively) [36,44]. Due to the beneficial results with T-DXd, the Food and Drug Administration (FDA) approved the use of this therapy to treat HER2[+] and HER2-low BC patients.

Importantly, T-DXd has also shown encouraging IC efficacy in HER2[+] BC patients with BMs [45–49] and/or LMD [50,51]. The TUXEDO-1 trial reported IC responses of 73.3% and 78.6% in the intention-to-treat and per protocol populations, respectively, as well as a clinical benefit rate of 92.9% in patients with newly diagnosed untreated or progressing BMs [45]. The DEBBRAH study achieved a 16-week PFS rate of 87.5% in patients with non-progressing BMs after local therapy, and IC-ORR of 50.0% and 44.4% in those with asymptomatic untreated BMs and progressing BMs after local therapy, respectively [52]. In the DESTINY-Breast03 trial, the first interim analysis provided an investigator-assessed median PFS of 25.1 months with T-DXd versus 7.2 months with T-DM1 in patients with clinically stable, previously treated BMs [41]. In the second interim analysis, T-DXd demonstrated a significant, clinically meaningful median PFS by blinded independent central review of 28.8 months compared to 6.8 months with T-DM1 [53]. Long-term survival analyses from this trial showed median PFS by investigator assessment of 29.0 versus 7.2 months, 36-month PFS rate of 45.7% versus 12.4%, and median OS of 52.6 versus 42.7 months using T-DXd versus T-DM1, respectively [53]. The pooled analysis of the DESTINY-Breast01, 02, and 03 showed robust IC responses compared to the comparator drug, reporting similar ORR and PFS between those patients with treated/stable BMs (45.2% and 12.3 months) and those with untreated/active BMs (45.5% and 18.5 months) [48]. The DESTINY-Breast12 trial exhibited overall PFS at 12 months of 61.6%, being 62.9% in those with stable BMs and 59.6% in those with active BMs, as well as an ORR of 49.7% and 54.7%, respectively [49].

Some analyses have further suggested that T-DXd may have activity in HER2-low BC patients with CNS involvement [47,54–56]. Updated results from the DEBBRAH trial reported that HER2-low advanced BC patients with untreated BMs achieved an IC-ORR of 50% and IC clinical benefit rate (CBR) of 66.7%, whereas those with progressing BMs obtained IC-ORR of 33.3% and IC-CBR of 50.0% [57]. The small size ($n = 6$) of patients with progressing HER2-low BMs in DEBBRAH, however, hinders reliable estimation of response rates. Of note, studies have reported that the outcome of HER2-low BC patients with BMs may be dismal compared to their HER2 [+] BC counterparts [58,59]. Based on the current scenario, the TUXEDO-4 trial was designed to assess the efficacy and safety of T-DXd in patients with HER2-low BC who have either newly diagnosed or progressing BM, with or without the presence of type II LMD. This study will address a critical need by aiming to enhance clinical outcomes and quality in this patient cohort.

2. Study design

TUXEDO-4 is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II clinical trial (NCT06048718) to evaluate the efficacy of T-DXd in HER2-low BC patients presenting with newly diagnosed or progressing BMs (Figure 1). Twenty-seven patients (13 in stage one plus 14 in stage two if there are more than 2 responder patients in stage one) will be enrolled from 13 sites in Austria and Spain (Figure 2). Enrollment began in June 2024, and the study is estimated to be completed in July 2026. Key inclusion and exclusion criteria are shown in Table 1.

3. Intervention

Eligible patients will receive T-DXd at 5.4 mg/kg administered as IV infusion every 3 weeks, on day 1 of each 21-day cycle. Patients will receive T-DXd until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason or as per physician's choice.

T-DXd dose will be reduced to 4.4 mg/kg (first reduction) and 3.2 mg/kg (second reduction) in case of toxicity. More than two dose reductions or dose re-escalation are not allowed. The doses of T-DXd to be administered must be recalculated if the patient's body weight has changed by 10% from baseline.

4. Patient population

Patients will be women or men ≥18 years of age, with HER2-low expression presenting with newly diagnosed or progressing BMs, with or without type II LMD, one or more brain lesions (≥10 mm per local radiological assessment), KPS ≥ 70%, and ECOG PS 0–2 (further eligibility criteria are shown in Table 1). A total of 27 patients will be recruited.

5. Objectives and endpoints

The primary objective of the TUXEDO-4 study is to assess the efficacy of T-DXd, defined as objective response rate (ORR) at any timepoint as judged by best CNS response according to RANO-BM criteria. Key secondary objectives are (i) to assess ORR as judged by best response determined locally by the investigator using the RECIST v.1.1 criteria for extracranial (EC) and overall lesions, (ii) to assess the bicompartmental CBR (Bi-CBR), defined as the sum of complete response (CR) rate, partial response (PR) rate and stable disease (SD) rate

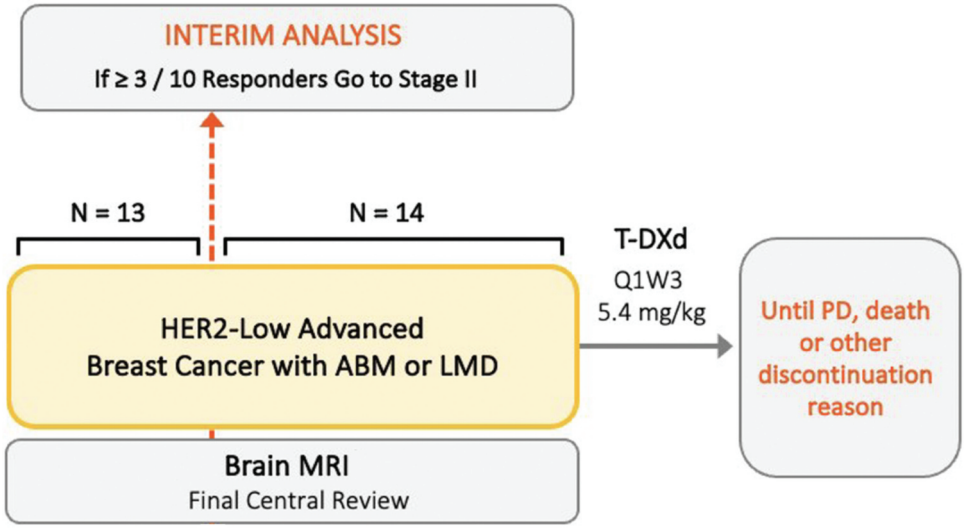

Figure 1. TUXEDO-4 study design. ABM: active (newly diagnosed or progressing after prior local therapy) brain Metastases; HER2: human epidermal growth factor receptor 2; LMD: leptomeningeal Disease; MRI: magnetic resonance imaging; PD: progression of disease; T-DXd: Trastuzumab Deruxtecan.

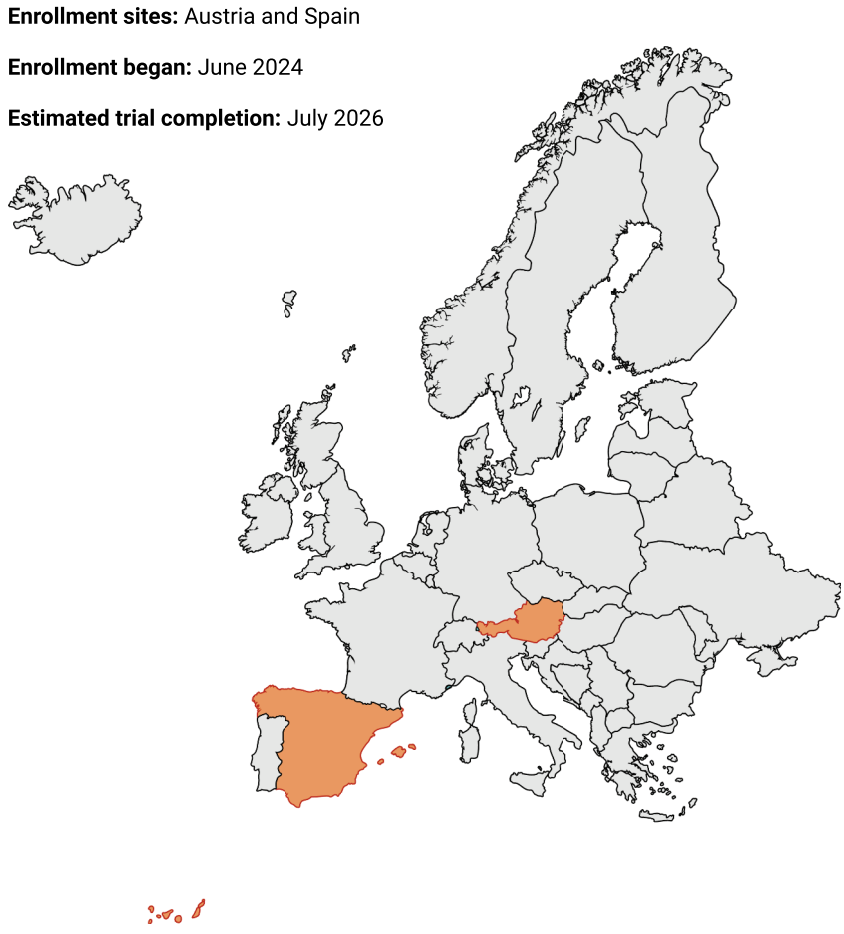

Figure 2. Map of the participating countries in the TUXEDO-4 trial. *created in BioRender. Jiménez-Cortegana, C. (2025)* https://biorender.com/i68m714.

≥24 weeks, and determined locally by the investigator using the RANO-BM criteria for IC lesions and RECIST v.1.1 criteria for EC and overall lesions, and (iii) to assess the bicompartmental disease control rate (Bi-DCR), defined as the sum of CR rate, PR rate, and SD rate, and determined locally by the investigator using the RANO-BM criteria for IC lesions and RECIST v.1.1 criteria for EC and overall lesions. Of note, bicompartmental assessments were carried out to provide

Table 1. Key eligibility criteria in the TUXEDO-4 study.

Inclusion criteria*
• Female or male patients ≥18 years.
• Radiologically documented metastatic breast cancer with locally documented HER2-low status according to the 2018 ASCO/CAP guidelines.
• Life expectancy ≥12 weeks.
• KPS ≥70% and ECOG PS 0–2.
• Newly diagnosed or progressive BM without indication for immediate local therapy.
• ≥1 brain lesion (≥10 mm per local radiological assessment), measurable by RANO-BM criteria.
• Must have undergone ≥1 line of systemic treatment in the advanced setting.
• LVEF ≥50% by either ECHO or MUGA scan within 28 days before enrollment.
• Adequate bone marrow, liver, renal, and coagulation function.
Exclusion criteria**
• Treatment with approved or investigational cancer therapy within 4 weeks or targeted agents within 3 weeks prior to initiation of study drug.
• Prior treatment with T-DXd and allergy or hypersensitivity to T-DXd or any of its components.
• Myocardial infarction within 6 months before enrollment.
• LVEF <50% by either ECHO or MUGA scan within 28 days before treatment.
• Lung-specific intercurrent clinically significant illnesses; autoimmune, connective tissue or inflammatory disorders; or prior pneumonectomy.
• Pregnant or lactating women.
• Abnormal clinical laboratory tests; infection with hepatitis B virus or hepatitis C virus; or non-controlled human immunodeficiency virus infection.
• Major surgical procedure (requiring general anesthesia) or significant traumatic injury within 21 days prior to enrollment, or patients who have not recovered from the side effects.
• Uncontrolled seizures, central nervous system disorders, or serious and/or unstable preexisting psychiatric disability.

ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; BM: Brain metastases; ECHO: Echocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; KPS: Karnofsky Performance Status; LVEF: Left ventricular ejection fraction; MUGA: Multigated acquisition; RANO: Response Assessment in Neuro-Oncology; T-DXd: Trastuzumab-deruxtecan.
*Patients must meet all inclusion criteria.
**Patients meeting any exclusion criteria must be excluded.

Table 2. TUXEDO-4 endpoints.

Primary endpoint	ORR at any timepoint determined by best central nervous system response per RANO-BM criteria.
Secondary endpoints	• ORR for EC and overall lesions, defined by rate of CR or PR, locally determined by the investigator per RECIST v.1.1 criteria. • Bi-CBR*, defined as CR+PR+SD ≥24 weeks, locally determined by the investigator. • Bi-DCR*, defined as CR+PR+SD, locally determined by the investigator. • Time to response*, defined from treatment initiation to first objective tumor response (tumor shrinkage ≥30%) in patients with CR or PR. • Duration of response*, defined from the first occurrence of a documented objective response to disease progression or death from any cause, in patients with CR or PR. • Best percentage of change in tumor burden*. • Progression-free survival, defined from treatment initiation to the first occurrence of disease progression or death from any cause. • Overall survival, defined from treatment initiation to death from any cause, determined locally by the investigator. • Safety and tolerability as per NCI-CTCAE v.5.0. • Assessment of quality of life with EORTC QLQ-c30, the brain- specific tool (BN20), and the breast-specific tool BR45. • Neurologic function as per NANO scale.
Exploratory endpoints	• Evaluation of biomarkers associated with brain damage. • Evaluation of response to T-DXd. • Assessment of HER2 gene copy number changes throughout the treatment

Bi-CBR: Bicompartmental clinical benefit rate; Bi-DCR: Bicompartmental disease control rate; CR: Complete response; EC: Extracranial; EORTC QLQ: European Organisation For Research And Treatment Of Cancer Core – Quality of Life questionnaire; HER2: Human epidermal growth factor receptor 2; IC: Intracranial; NANO: Neurologic Assessment in Neuro-Oncology; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events; ORR: Overall response rate; PR: Partial response; RANO-BM: Response Assessment in Neuro-Oncology for Brain Metastasis; RECIST: Response evaluation criteria in solid tumors; SD: Stabilization of disease; T-DXd: Trastuzumab-deruxtecan
*These secondary endpoints were assessed as per RANO-BM criteria for IC and RECIST v.1.1 for EC and overall lesions.

more comprehensive insights on how T-DXd affects both IC and EC diseases. All endpoints, including additional secondary endpoints and exploratory endpoints, are summarized in Table 2.

6. Study procedures

Participants will be enrolled into the study after signing the ICF. Different evaluations will be performed and reviewed during the screening phase to confirm that patients meet all eligibility criteria before enrollment. Those evaluations will include (but will not be limited to) cranial MRI and computed tomography (CT) scan of chest, abdomen, and pelvis, bone scan, and blood tests. A tumor tissue sample will be collected for determination of HER2 status. Demographic data, such as age, sex, or self-reported ethnicity, and clinical information such as significant diseases, history of cancer, or surgical interventions will be recorded.

The initial T-DXd dose will be administered as a 90-minute IV infusion, and subsequent doses as 30-minute infusions if there is no infusion-related reaction. IC tumor response will be assessed by local investigator using RANO-BM criteria, extracranial and overall responses by local investigator using RECIST v.1.1 criteria. Response to T-DXd will be assessed within ten days before the third administration, within ten days before the fifth administration, and every nine weeks thereafter.

Key safety assessments will include evaluations of vital signs, peripheral oxygen saturation, laboratory tests, physical examinations, ECOG PS, LVEF, quality of life and neurocognitive function using the EORTC QLQ-c30, the QLQ-BN20, the QLQ-BR45, and the NANO scale.

Post-treatment follow-ups will be carried out in patients to collect survival and subsequent anti-cancer therapy information every 3 months until death, lost to follow-up, elective withdrawal from the study, or the end of study.

7. Statistical analysis

7.1. Sample size determination

The sample size was calculated based on Simon's two-stage design, which was used to minimize patient exposure to ineffective treatments and reduce costs by allowing for early termination if initial results are unpromising. This method was previously used in the TUXEDO-1 trial [45] and is being used in the TUXEDO-2 and TUXEDO-3 trials [60,61] because it balances ethical considerations and statistical rigor, providing a clear framework for deciding whether to proceed with further development based on predefined success thresholds.

A total of 27 patients will be enrolled. Of them, thirteen patients will be recruited in the first stage. The study will be stopped for futility if there are ≤2 (15.4%) IC responses in this stage. If not, 14 additional patients will be recruited in the second stage.

7.2. Primary endpoint analysis

The hypothesis is that T-DXd may exhibit clinical activity among HER2-low BC patients with BM, and with or without type II LMD. Based on the EC response rate reported in the DESTINY-Breast04 and preliminary data from cohort 3 of the DEBBRAH trial [36,52], a CNS ORR of ≥42% will be considered as indicating clinically relevant activity (alternative hypothesis). Similarly, since we expected a poor drug response based on the Destiny-Breast04 physician's choice arm [42], a CNS ORR of ≤16% will be considered clinically unmeaningful (null hypothesis). This design yields a one-sided type I error rate of 5% and a power of 90% to reject the null hypothesis.

Primary endpoint will be analyzed on the full analysis and per protocol sets, which will involve all patients who meet selection criteria and receive at least one dose of T-DXd. Koyama T and Chen H methods for Simon's two-stage design, and 95% Pearson-Clopper and Wilson confidence intervals (CI) will be also used. The primary endpoint will be met with ≥8 out of 27 (29.6%) patients exhibiting IC response.

7.3. Secondary endpoint analysis

Secondary endpoint analyses will be carried out in the full population. The proportion of responders will be calculated with the uniformly minimum variance unbiased estimator (UMVUE), to ensure precise estimates, and p-value and 95% CI with Koyama and Chen method, to better analyze censoring and survival data [62]. These methods will provide more confident and accurate conclusions about treatment efficacy. ORR, CBR, and DCR will be given by the number and the rate of patients with response, clinical benefit, and disease control, respectively. 95% Clopper-Pearson CI will be calculated.

The following key secondary endpoint analyses will be performed: TTR and DoR (median in months, range, interquartile range and Kaplan–Meier estimations), PFS and OS (Kaplan–Meier plots, number and percentage of events, median survival, and CI based on "log-log" method), adverse events (AEs), treatment emergent adverse events (TEAEs), serious AEs, grade ≥3 TEAEs, TEAEs leading to dose interruption, reduction, or permanent discontinuation based on MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs). Descriptive analyses will involve physical examination, ECOG status, vital signs, physical examination, ophthalmologic assessment, ECG, ECHO, MUGA scan, pregnancy test, and laboratory parameters (at each cycle), as well as duration of treatment (months), duration of follow-up (months), number of cycles, number of patients with dose interruptions, reductions, and permanent discontinuations, and relative dose intensity for study drugs. Demographic data and other baseline characteristics will be presented for all patients who receive at least one dose of study treatment.

8. Conclusions

If the results of the TUXEDO-4 trial are positive, T-DXd could be introduced as a promising treatment option for HER2-low metastatic BC patients with newly diagnosed or progressing BMs with or without type II LMD. The results of this trial may influence future clinical guidelines. Larger, randomized trials comparing T-DXd with other treatments of active BMs – especially whole-brain radiotherapy – are worth considering.

Acknowledgments

The TUXEDO-4 team is grateful to all patients and their families. We acknowledge the trial teams of the participating sites and Daiichi Sankyo, which is the funder of the TUXEDO-4 study. The design of this clinical trial was communicated as a poster presentation at the San Antonio Breast Cancer Symposium (SABCS) 2024, held on December 10–13, 2024.

Author contributions

Study idea: Maximilian Marhold.
Study concept: Maximilian Marhold, Matthias Preusser, and Rupert Bartsch.
Protocol writing: Maximilian Marhold, Marta Vaz-Batista, Felipe Slebe, Marta Campolier, Juliana Carvalho-Santos, José Antonio Guerrero-Martínez, Carlos Jiménez-Cortegana, Matthias Preusser, and Rupert Bartsch.
Study participation, patient accrual, data entry: Maximilian Marhold, Marta Vaz-Batista, Isabel Blancas, Cristina Morales, Cristina Saura-Manich, Cristina Saavedra, Manuel Ruíz-Borrego, Patricia Cortez, Rupert Bartsch, and Matthias Preusser.
Writing and approval of manuscript: All authors.

Disclosure statement

Maximilian Marhold has received honoraria for lectures, advisory board participation and consultation from Roche, Eli Lilly, Novartis, AstraZeneca, Daiichi Sankyo, Pfizer, MSD, Gilead, and Medmedia; and travel support from Amgen, Gilead, Roche, Novartis, Pierre Fabre, Daiichi Sankyo, and Eisai.

Marta Vaz-Batista has received honoraria from Daichii Sankyo, GSK, and AstraZeneca; consulting or advisory role from Daichii Sankyo and AstraZeneca; speakers' bureau from Novartis; and travel, accomodation, and expenses from AstraZeneca.

Isabel Blancas has received grants and research support to the Institution from AstraZeneca, Lilly, Pfizer and Roche; honoraria and advisor collaboration from AstraZeneca, Roche, Novartis, Eisai, Celgene, Pfizer, Lilly, Pierre–Fabre, Bristol–Myers Squibb, Daiichi Sankyo, Grünenthal, Seagen, and Veracyte; and support for attending meetings and/or travel from AstraZeneca, Roche, Novartis, Pfizer, Lilly, Pierre-Fabre, Bristol-Myers Squibb, and Daiichi Sankyo.

Cristina Saura-Manich has received research support and consulting or advisory role from Genentech, AstraZeneca, Aragon Pharmaceuticals, Bayer Pharma, Byondis, Boehringer Ingelheim, Bristol-Myers Squibb, Cytomx Therapeutics, Daiichi Sankyo, F. Hoffmann-La Roche, Eisai, Genomic Health, GlaxoSmithKline, Innoup Farma, Eli Lilly, Macrogenics, Menarini Ricerche, Merck Sharp & Dohme, Merus, Millennium Pharmaceuticals, Novartis, Pfizer, Pierre Fabre, PintPharma, Puma Biotechnology, Sanofi, Seattle Genetics, and Zymeworks.

Manuel Ruíz-Borrego has received consulting fees from Roche and Puma, and honoraria expenses from Roche/Genentech, Pfizer, and Novartis.

Felipe Slebe, Marta Campolier, Juliana Carvalho-Santos, José Antonio Guerrero-Martínez, and Carlos Jiménez-Cortegana declare to be full-time employees at MEDSIR.

Rupert Bartsch has received honoraria from AstraZeneca, BMS, Daiichi-Sankyo, Eisai, and Eli-Lilly; consulting or advisory role from AstraZeneca, Daichi, Eisai, and Eli-Lilly; research funding from Daiichi-Sankyo; and travel, accommodations, and expenses from MSD, Daiichi-Sankyo, Novartis, and Pfizer.

Matthias Preusser has received honoraria for lectures, consultation and advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape, OncLive.

Cristina Morales, Cristina Saavedra, Patricia Cortez, Beate Rottenmanner, and Heidrun Forstner have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding

The TUXEDO-4 trial has been funded by Daiichi Sankyo, who has been involved in the decision to publish, and the preparation of the manuscript.

Ethical conduct of research

The investigators have obtained appropriate institutional review board approval (Comité de Ética de la Investigación con Medicamentos. Hospital Arnau de Vilanova-Llíria, Valencia, Spain; and the Federal Office for Safety in Healthcare, Austria) to carry out the TUXEDO-4 trial (approval number 2023 -506,702-39-00_9622). The investigators have also followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. Written informed consent is required and has been obtained from the participants involved.

Data sharing statement

Data collected within this study will be made available to researchers after contacting the corresponding author and upon revision and approval based on scientific merit by the TUXEDO-4 trial management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes and the trial protocol will be provided after the completion of a data sharing agreement that will be set up by the study sponsor (MEDSIR). All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The estimated timeframe for response will be within 30 days. Please address requests for data to the corresponding author.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. doi: 10.3322/caac.21763
2. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(17):1951–1962. doi: 10.1200/JCO.19.02488
3. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer. 2021;7(1):1. doi: 10.1038/s41523-020-00208-2
4. Bailleux C, Eberst L, Bachelot T. Treatment strategies for breast cancer brain metastases. Br J Cancer. 2021;124(1):142–155. doi: 10.1038/s41416-020-01175-y
5. Hofer S, Le Rhun E. Leptomeningeal metastases from solid tumours. Memo-Mag Eur Med Oncol. 2021;14(2):192–197. doi:10.1007/s12254-021-00693-6
6. Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro-Oncol. 2021;23(6):894–904. doi: 10.1093/neuonc/noaa285
7. Slimane K, Andre F, Delaloge S, et al. Risk factors for brain relapse in patients with metastatic breast cancer. Ann Oncol Off J Eur Soc Med Oncol. 2004;15(11):1640–1644. doi: 10.1093/annonc/mdh432
8. Chehade R, Freeman M, Jerzak K. 53P 'HER2-LOW' breast cancer brain metastases: an opportunity for targeted systemic therapies in a high-need patient population. Ann Oncol. 2022;33:S145. doi: 10.1016/j.annonc.2022.03.068
9. Chehade R, Nofech-Mozes S, Plotkin A, et al. HER2-LOW BREAST CANCER BRAIN METASTASES: INCIDENCE and TREATMENT IMPLICATIONS. Neuro-Oncol Adv. 2023;5(Supplement_2):i8–i8. doi: 10.1093/noajnl/vdad071.032
10. Chehade R, Nofech-Mozes S, Plotkin A, et al. Human epidermal growth factor receptor 2–low breast cancer brain metastases: an opportunity for targeted systemic therapies in a high-need patient population. JCO Precis Oncol. 2024;8(8):e2300487. doi: 10.1200/PO.23.00487
11. Altundag K, Bondy ML, Mirza NQ, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. Cancer. 2007;110(12):2640–2647. doi: 10.1002/cncr.23088
12. Kim H-J, Im S-A, Keam B, et al. Clinical outcome of central nervous system metastases from breast cancer: differences in survival depending on systemic treatment. J Neurooncol. 2012;106(2):303–313. doi: 10.1007/s11060-011-0664-8
13. Franzoi MA, Hortobagyi GN. Leptomeningeal carcinomatosis in patients with breast cancer. Crit Rev Oncol Hematol. 2019;135:85–94. doi: 10.1016/j.critrevonc.2019.01.020
14. Bartsch R, Jerzak KJ, Larrouquere L, et al. Pharmacotherapy for leptomeningeal disease in breast cancer. Cancer Treat Rev. 2024;122:102653. doi: 10.1016/j.ctrv.2023.102653
15. Le Rhun E, Weller M, Van Den Bent M, et al. Leptomeningeal metastasis from solid tumours: EANO–ESMO clinical practice guideline for diagnosis, treatment and follow-up. ESMO Open. 2023;8(5):101624. doi: 10.1016/j.esmoop.2023.101624
16. Le Rhun E, Devos P, Weller J, et al. Prognostic role of the EANO ESMO classification of leptomeningeal metastases. Ann Oncol. 2019;30(v144):v144. doi: 10.1093/annonc/mdz243.001

17. Le Rhun E, Devos P, Weller J, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. Neuro-Oncol. 2021;23(7):1100–1112. doi: 10.1093/neuonc/noaa298
18. Sharma AE, Corbett K, Soliman H, et al. Assessment of phase 3 randomized clinical trials including patients with leptomeningeal disease: a systematic review. JAMA Oncol. 2023;9(4):566. doi: 10.1001/jamaoncol.2022.7364
19. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2002;20(3):719–726. doi: 10.1200/JCO.2002.20.3.719
20. Fehrenbacher L, Cecchini RS, Geyer CE, et al. NSABP B-47/NRG oncology phase III randomized trial comparing adjuvant chemotherapy with or without trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and With IHC 1+ or 2. J Clin Oncol Off J Am Soc Clin Oncol. 2020;38(5):444–453. doi: 10.1200/JCO.19.01455
21. Sammons SL, Topping DL, Blackwell KL. HR+, HER2– advanced breast cancer and CDK4/6 inhibitors: mode of action, clinical activity, and safety profiles. CCDT. 2017;17(7):637–649. doi: 10.2174/1568009617666170330120452
22. Wang X, Zhao S, Xin Q, et al. Recent progress of CDK4/6 inhibitors' current practice in breast cancer. Cancer Gene Ther. 2024;31(9):1283–1291. doi: 10.1038/s41417-024-00747-x
23. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;384(16):1529–1541. doi: 10.1056/NEJMoa2028485
24. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet Lond Engl. 2011;377(9769):914–923. doi: 10.1016/S0140-6736(11)60070-6
25. Ou Y, Wang M, Xu Q, et al. Small molecule agents for triple negative breast cancer: current status and future prospects. Transl Oncol. 2024;41:101893. doi: 10.1016/j.tranon.2024.101893
26. Boire A. Metastasis to the central nervous system. Contin Lifelong Learn Neurol. 2020;26(6):1584–1601. doi: 10.1212/CON.0000000000000939
27. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J Clin Oncol. 2022;40(5):492–516. doi: 10.1200/JCO.21.02314
28. Kowalchuk RO, Niranjan A, Hess J, et al. Stereotactic radiosurgery and local control of brain metastases from triple-negative breast cancer. J Neurosurg. 2023;138(6):1608–1614. doi: 10.3171/2022.10.JNS221900
29. Reynolds TA, Jensen AR, Bellairs EE, et al. Dose gradient index for stereotactic radiosurgery/radiation therapy. Int J Radiat Oncol. 2020;106(3):604–611. doi: 10.1016/j.ijrobp.2019.11.408
30. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs placebo, both in combination with Trastuzumab and capecitabine, for Previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB randomized clinical trial. JAMA Oncol. 2023;9(2):197. doi: 10.1001/jamaoncol.2022.5610
31. Mills MN, Figura NB, Arrington JA, et al. Management of brain metastases in breast cancer: a review of current practices and emerging treatments. Breast Cancer Res Treat. 2020;180(2):279–300. doi: 10.1007/s10549-020-05552-2
32. Terceiro LEL, Ikeogu NM, Lima MF, et al. Navigating the blood–brain barrier: challenges and therapeutic strategies in breast cancer brain metastases. Int J Mol Sci. 2023;24(15):12034. doi: 10.3390/ijms241512034
33. Kondrashov A, Sapkota S, Sharma A, et al. Antibody-drug conjugates in solid tumor oncology: an effectiveness payday with a targeted payload. Pharmaceutics. 2023;15(8):2160. doi:10.3390/pharmaceutics15082160
34. Mair MJ, Bartsch R, Le Rhun E, et al. Understanding the activity of antibody–drug conjugates in primary and secondary brain tumours. Nat Rev Clin Oncol. 2023;20(6):372–389. doi: 10.1038/s41571-023-00756-z
35. Epaillard N, Bassil J, Pistilli B. Current indications and future perspectives for antibody-drug conjugates in brain metastases of breast cancer. Cancer Treat Rev. 2023;119:102597. doi: 10.1016/j.ctrv.2023.102597
36. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in Previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9–20. doi: 10.1056/NEJMoa2203690
37. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nat Rev Drug Discov. 2023;22(2):101–126. doi: 10.1038/s41573-022-00579-0
38. Azar I, Alkassis S, Fukui J, et al. Spotlight on Trastuzumab Deruxtecan (DS-8201,T-DXd) for HER2 mutation positive non-small cell lung cancer. Lung Cancer Targets Ther. 2021;12:103–114. doi: 10.2147/LCTT.S307324
39. Niwinska A, Pogoda K, Jagiello-Gruszfeld A, et al. Intracranial response rate in patients with breast cancer brain metastases after systemic therapy. Cancers (Basel). 2022;14(4):965. doi:10.3390/cancers14040965
40. Tamura K, Tsurutani J, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Lancet Oncol. 2019;20(6):816–826. doi: 10.1016/S1470-2045(19)30097-X
41. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022;386(12):1143–1154. doi: 10.1056/NEJMoa2115022
42. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in Previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610–621. doi: 10.1056/NEJMoa1914510
43. André F, Park YH, Kim S-B, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. The Lancet. 2023;401(10390):1773–1785. doi: 10.1016/S0140-6736(23)00725-0
44. Curigliano G, Hu X, Dent RA, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): primary results from DESTINY-Breast06 (DB-06). J Clin Oncol. 2024;42(17_suppl):LBA1000–LBA1000.
45. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat Med. 2022;28(9):1840–1847. doi: 10.1038/s41591-022-01935-8
•• **The TUXEDO-1 study showed high clinical benefit rate in HER2-positive breast cancer patients with newly diagnosed untreated or progressing BMs.**
46. Jerusalem G, Park YH, Yamashita T, et al. Trastuzumab deruxtecan in HER2-positive metastatic breast cancer patients with brain metastases: a DESTINY-Breast01 subgroup analysis. Cancer Discov. 2022;12(12):2754–2762. doi: 10.1158/2159-8290.CD-22-0837
47. Vaz Batista M, Pérez-García JM, Garrigós L, et al. The DEBBRAH trial: trastuzumab deruxtecan in HER2-positive and HER2-low breast cancer patients with leptomeningeal carcinomatosis. Med N Y N. 2024;6(1):00312–X. doi: 10.1016/j.medj.2024.08.001
48. Hurvitz SA, Modi S, Li W, et al. A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. Ann Oncol. 2023;34:S335–S336. doi: 10.1016/j.annonc.2023.09.554
•• **The pooled analysis of the DESTINY-Breast01, 02 and 03 showed robust IC responses using T-DXd compared to the comparator drug in HER2-positive breast cancer patients with brain metastases.**
49. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med. 2024;30(12):3717–3727.

•• **The DESTINY-Breast12 trial exhibited promising overall PFS at 12 months and ORR in HER2-positive breast cancer patients with brain metastases.**

50. Alder L, Trapani D, Bradbury C, et al. Durable responses in patients with HER2+ breast cancer and leptomeningeal metastases treated with trastuzumab deruxtecan. NPJ Breast Cancer. 2023;9(1):19. doi: 10.1038/s41523-023-00519-0
51. Niikura N, Yamanaka T, Nomura H, et al. Treatment with trastuzumab deruxtecan in patients with HER2-positive breast cancer and brain metastases and/or leptomeningeal disease (ROSET-BM). NPJ Breast Cancer. 2023;9(1):82. doi: 10.1038/s41523-023-00584-5
52. Pérez-García JM, Vaz Batista M, Cortez P, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: the DEBBRAH trial. Neuro-Oncol. 2023;25(1):157–166. doi: 10.1093/neuonc/noac144
53. Hurvitz SA, Hegg R, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet Lond Engl. 2023;401 (10371):105–117. doi: 10.1016/S0140-6736(22)02420-5

• **The DESTINY-Breast03 trial demonstrated clinically meaningful median PFS using T-DXd compared toT-DM1 in HER2-positive breast cancer patients.**

54. Wolf B, Dunet V, Dubruc E, et al. Response of brain and meningeal metastases to trastuzumab-deruxtecan in a patient with HER2-Low breast cancer: a case report. Case Rep Oncol. 2023;16(1):1425–1435. doi: 10.1159/000534572
55. Kabraji S, Ni J, Sammons S, et al. Preclinical and clinical efficacy of trastuzumab deruxtecan in breast cancer brain metastases. Clin Cancer Res Off J Am Assoc Cancer Res. 2023;29(1):174–182. doi: 10.1158/1078-0432.CCR-22-1138
56. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. Nat Med. 2023;29(8):2110–2120. doi: 10.1038/s41591-023-02478-2
57. Vaz Batista M, Perez-Garcia JM, Cortez P, et al. Trastuzumab deruxtecan in patients with previously treated HER2-low advanced breast cancer and active brain metastases: the DEBBRAH trial. ESMO Open. 2024;9(9):103699. doi: 10.1016/j.esmoop.2024.103699
58. Podder V, Ranjan T, Bardhan M, et al. Comparative survival analysis of patients with HER2-low and HER2-positive metastatic breast cancer with or without brain metastases treated with trastuzumab deruxtecan. J Clin Oncol. 2024;42(16_suppl):1036–1036. doi: 10.1200/JCO.2024.42.16_suppl.1036
59. Epaillard N, Lusque A, Jacot W, et al. Incidence and outcome of brain and/or leptomeningeal metastases in HER2-low metastatic breast cancer in the French ESME cohort. ESMO Open. 2024;9 (5):103447. doi: 10.1016/j.esmoop.2024.103447
60. Bartsch R, Berghoff AS, Furtner J, et al. 187P stage I results of a phase II study of datopotamab deruxtecan (DATO-DXd) in triple-negative breast cancer (TNBC) patients (pts) with active brain metastases (TUXEDO-2). ESMO Open. 2024;9:103209. doi: 10.1016/j.esmoop.2024.103209
61. Bartsch R, Vaz Batista M, Berghoff AS, et al. Patritumab deruxtecan (HER3-DXd) in active brain metastases from metastatic breast and non-small cell lung cancers, and leptomeningeal disease from advanced solid tumors: the TUXEDO-3 phase II trial. J Clin Oncol. 2024;42(16_suppl):TPS2091–TPS2091. doi: 10.1200/JCO.2024.42.16_suppl.TPS2091
62. Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008;27(16):3145–3154. doi:10.1002/sim.3123