Patritumab deruxtecan (HER3-DXd) in patients with active brain metastases of breast cancer (TUXEDO-3): a multicentre, single-arm, phase 2 trial

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Summary

Background Patritumab deruxtecan (HER3-DXd) is a novel antibody–drug conjugate targeting HER3, which is overexpressed in CNS metastases of metastatic breast cancer. We aimed to evaluate the activity and safety of HER3-DXd in patients with metastatic breast cancer and brain metastases that are newly diagnosed or progressing after local therapy.

Methods TUXEDO-3 trial is a multicohort, multicentre, open-label, single-arm phase 2 trial, done in six sites in Spain and Austria. In this cohort (1 of 3), we enrolled adults (≥18 years) with histologically documented breast cancer and radiologically documented metastatic disease, newly diagnosed brain metastases or brain metastases progressing after local treatment, at least one measurable brain lesion of ≥10 mm, and an Eastern Cooperative Oncology Group performance status of 0–2. Patients received HER3-DXd 5·6 mg/kg intravenously once every 3 weeks. The threshold for the primary endpoint was at least 15% of patients having intracranial response according to Response Assessment in Neuro-Oncology Brain Metastases criteria. Activity and safety analyses were done in the full analysis population (ie, all participants who received at least one dose of HER3-DXd). This trial (ClinicalTrials.gov NCT05865990 and European Union Clinical Trials Register 2023-503251-10-00) is ongoing and is no longer enrolling patients.

Findings Between Dec 12, 2023, and July 8, 2024, 21 evaluable female patients (five with luminal breast cancer, nine with HER2-positive breast cancer, and seven with triple-negative breast cancer) were recruited. 15 (71%) were White; race was not reported in the remaining six patients. The median number of previous treatment lines for advanced disease was 4 (IQR 2–4). Median treatment duration was 3·0 months (IQR 0·7–7·7), and median follow-up was 4·9 months (IQR 3·6–8·5). The primary endpoint was met with five (24%) of 21 patients having intracranial responses irrespective of the breast cancer subtype (overall response rate 23·8%, 95% CI 8·2–47·1). The most common grade 3 or worse treatment-emergent adverse events were neutropenia in three (14%) patients, diarrhoea in two (10%) patients, and asthenia and vomiting in one (5%) patient each. Serious adverse events occurred in six (29%) patients, with one (5%) patient having grade 2 pneumonitis related to the study treatment. No treatment-related deaths were reported.

Interpretation HER3-DXd showed promising clinical activity in patients with metastatic breast cancer and active brain metastases, and could offer a novel therapeutic option in this setting.

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Introduction

Brain metastases are a major concern across all breast cancer subtypes but are particularly common in triple-negative breast cancer and human epidermal growth factor receptor 2 (HER2/ERBB2)-positive disease.[1,2] Brain metastases increase morbidity and mortality,[3] cause neurological symptoms, and reduce quality of life.[4] Local treatment options, including neurosurgical resection, stereotactic radiosurgery, and whole brain radiotherapy (WBRT), have long been considered the standard of care[5] for brain metastases as the blood–brain barrier was assumed to prevent the activity of systemic drugs. Although stereotactic radiosurgery and neurosurgery followed by stereotactic radiosurgery provide excellent local disease control, WBRT has high rates of acute and chronic toxicity.[6] Providing treatment to patients with brain metastases progressing on previous local interventions, delaying WBRT, and simultaneously improving both local and systemic disease control has led to growing interest in systemic treatment options.

In HER2-positive breast cancer, the HER2CLIMB regimen, which consists of the third-generation

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Research in context

Evidence before this study

We searched in PubMed for studies published between Jan 1, 2020, and June 30, 2025, without language restrictions; key search terms were "antibody-drug conjugates", "breast cancer", "brain metastases", "HER3", and "patritumab deruxtecan". Existing evidence shows intracranial activity of trastuzumab deruxtecan in patients with HER2-positive and HER2-low breast cancer and brain metastases. HER3, a member of the *EGFR* family, is implicated in treatment resistance through the activation of downstream signalling pathways, and patritumab deruxtecan (HER3-DXd) has shown activity across all breast cancer subtypes, irrespective of HER3 expression. Metastases of brain cancer and non-small-cell lung cancer express higher levels of HER3 than primary tumours; however, gaps remain regarding the potential role of HER3-DXd in the treatment of brain metastases in patients with breast cancer.

Added value of this study

Despite clinical advances in the past 10 years, improved treatment strategies for brain metastases in patients with breast cancer remain urgently needed. A key therapeutic goal is to delay or avoid whole-brain radiotherapy while providing effective systemic treatment. Trastuzumab deruxtecan and the tyrosine-kinase inhibitor tucatinib are established systemic treatment options for HER2-positive breast cancer with brain metastasis. However, disease progression will eventually occur, and systemic approaches are needed for luminal and triple-negative breast cancer, for which local therapy remains the standard of care. In cohort 1 of the phase 2 TUXEDO-3 study, HER3-DXd was evaluated in patients with active breast cancer brain metastases across all subtypes, regardless of previous antibody–drug conjugate treatment or HER3 expression. We showed clinically meaningful activity in a heavily pretreated population, including patients previously treated with topoisomerase I inhibitor-based antibody–drug conjugates. Importantly, both quality of life and neurocognitive function were preserved, underscoring the potential clinical value of this approach.

Implications of all the available evidence

Evidence supports the efficacy of systemic therapies in treating brain metastases from HER2-positive breast cancer. The TUXEDO-3 trial establishes a proof of principle for the activity of antibody–drug conjugate-based therapy in patients with breast cancer and brain metastases beyond the HER2-positive setting, highlighting an important opportunity to address unmet needs in other subtypes. These findings could inform future clinical trial design and support the development of a broadly applicable, effective, and well tolerated systemic treatment strategy for patients with breast cancer and brain metastases.

HER2-directed tyrosine-kinase inhibitor tucatinib, the monoclonal antibody trastuzumab, and capecitabine, yielded prolonged intracranial disease control in pretreated patients with active (newly diagnosed or progressive) brain metastases.[7,8] In the past 10 years, it was established that, despite its large molecular size, the antibody–drug conjugate (ADC) trastuzumab deruxtecan showed intracranial activity in the same setting, presumably because the blood–brain barrier is replaced by a more permeable blood–tumour barrier at the metastatic site.[9–11] In the TUXEDO-1,[9] DEBBRAH,[12] and DESTINY-Breast12 trials,[11] the intracranial overall response rate by the Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria ranged from 46·2% to more than 70%, with a patient-level combined analysis of DEBBRAH, TUXEDO-1, and a retrospective cohort in the USA[13] supporting these outcomes.[14] Although systemic treatment of active brain metastases with tucatinib and trastuzumab deruxtecan is established in HER2-positive breast cancer, the disease will eventually progress. Additionally, systemic treatment of HER2-negative brain metastases is not well evidenced, necessitating novel treatment options.

Metastatic triple-negative breast cancer is characterised by high rates of CNS involvement[2] and short brain metastases-free survival.[14] Since brain metastases are commonly diagnosed in parallel with systemic disease progression, treatment strategies providing intracranial and extracranial disease control are required.[15] In hormone receptor (HR)-positive/HER2-negative metastatic disease, the incidence of brain metastases is lower, and they typically occur later in the disease course.[2,14] As a result, patients have often exhausted several standard treatment lines by the time brain metastases are diagnosed. In patients with HER2-low expressing tumours from the DEBBRAH trial, intracranial overall response rate was 41·7%, suggesting intracranial activity of ADCs beyond the HER2-positive subtype.[12]

Patritumab deruxtecan (HER3-DXd) is a HER3 (ERBB3)-directed next generation ADC that showed significant activity in pretreated metastatic breast cancer irrespective of subtype in a phase 1/2 trial,[16] and in the single-arm phase 2 ICARUS-Breast01 trial was reported to have high response rates and prolonged progression-free survival in patients with HR-positive/HER2-negative metastatic breast cancer.[17] Although a correlation of HER3-expression with HER3-DXd activity has not been proven to date, brain metastases of breast cancer and non-small-cell lung cancer (NSCLC) showed higher expression of HER3 compared with primary tumours,[18,19] and HER3 expression was linked to resistance to HER2-directed treatment,[20,21] supporting the use of HER3-DXd in patients with brain metastases who have been previously treated.

Based on this evidence, we conducted the prospective, international, multicentre, multicohort, single-arm phase 2 TUXEDO-3 trial to investigate the activity of HER3-DXd in patients with active brain metastases from metastatic breast cancer (cohort 1), active brain metastases from advanced NSCLC (cohort 2), and leptomeningeal disease of any solid tumour type (cohort 3). In this Article, we present activity and safety data from cohort 1 of the TUXEDO-3 trial, in patients with active brain metastases across all breast cancer subtypes.[22] The trial is ongoing and is no longer enrolling patients.

Methods

Study design and participants

TUXEDO-3 is an international, multicentre, single-arm, multicohort, phase 2 clinical trial evaluating the activity and safety of HER3-DXd in three independent cohorts of patients: patients with metastatic breast cancer and untreated or progressing brain metastases after local treatment (cohort 1), patients with advanced NSCLC and untreated or progressing brain metastases after local treatment (cohort 2), and patients with treatment-naive leptomeningeal disease or leptomeningeal disease progressing after radiotherapy from any advanced solid tumour. Participants were enrolled by sites' investigators at six sites: four hospitals in Spain and two in Austria (appendix pp 11–12). In this Article, we report the results of the first cohort.

Eligible participants were male or female, at least 18 years of age, and had histologically documented breast cancer; radiologically documented metastatic disease; newly diagnosed brain metastases or brain metastases progressing after local treatment; measurable disease according to RANO-BM criteria; one or more target lesions of at least 10 mm on T1-weighted gadolinium-enhanced MRI based on RANO-BM criteria; at least one previous line of systemic treatment for patients with triple-negative breast cancer, at least one previous line of endocrine therapy and at least one previous line of chemotherapy for patients with luminal breast cancer, or progression on at least two previous HER2-targeted therapies for patients with HER2-positive breast cancer; no indication for immediate local treatment; adequate bone marrow, liver, and renal function; locally established HER2 status; a life expectancy of 6 weeks or longer; left ventricular ejection fraction of 50% or better, as established by multigated acquisition scan or echocardiogram; a Karnofsky Performance Status of at least 70%; and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Key exclusion criteria were: previous systemic therapy with any anti-HER3 directed drug; allergy or hypersensitivity to HER3-DXd or its components; concurrent malignancy or malignancy within 5 years of study enrolment with the exception of carcinoma in situ of the cervix, non-melanoma skin carcinoma, or stage I uterine cancer; treatment with approved or investigational cancer therapy within 14 days before initiation of study drug; and active cardiac disease or a history of cardiac dysfunction or conduction abnormalities within 6 months before the trial. A detailed list of all inclusion and exclusion criteria is found in the appendix (pp 8–11). As these patients had brain metastases, visceral disease was defined as metastases in organs other than the CNS.

Laboratory tests performed during the screening period included haematological (white blood cell count, haemoglobin, platelets, and absolute neutrophil count) and biochemical parameters (serum albumin, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, international normalised ratio, and creatinine or creatinine clearance), urinalysis, and viral serology. A detailed list of laboratory tests for screening is in the appendix (p 9).

The TUXEDO-3 study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and applicable regulations and laws from the recruiting countries, which were Austria and Spain. The trial was approved by the corresponding local ethics committees of both countries (from the Fundación Instituto Valenciano de Oncología in Spain and the Medical University of Vienna in Austria, ethics approval ID is 4341). Written informed consent was obtained from each patient. None of the study participants received compensation for participation in this study. No cancer survivors or patient advocates were involved in the development of the research question, the study design, the selection of outcome measures, the conduct of the trial, the data analysis or interpretation, or writing of the manuscript. The trial is registered at ClinicalTrials.gov (NCT05865990) and the European Union Clinical Trials Register (EudraCT no. 2023-503251-10-00).

See Online for appendix

Procedures

In this trial, HER3-DXd was administered intravenously at the standard dose of 5·6 mg per kg bodyweight on day 1 of each 21-day cycle until disease progression (locally assessed), unacceptable toxicity, death, withdrawal, loss to follow-up, or investigator's decision. Dose interruption, reduction, and discontinuation were allowed as prespecified in the protocol. Patients discontinuing the study treatment period at any time before the study termination entered a post-treatment follow-up period, during which survival status and subsequent anticancer therapy information were collected every 3 months (plus or minus 7 days) from the last visit until death, loss to follow up, elective withdrawal from the trial, or end of trial, whichever occurred first.

Two HER3-DXd dose reductions were permitted from the starting dose (5·6 mg/kg bodyweight) in case of adverse events, first to 4·8 mg/kg, and subsequently to 3·2 mg/kg. HER3-DXd dose interruptions depended on the severity and resolution time of adverse events. For

grade 3 fatigue, asthenia, malaise, thrombocytopenia, nausea, and oral mucositis, dosing would be interrupted until resolution to grade 1 or lower, and resumed at the same dose if recovery occurred within 14 days; otherwise, the dose would be reduced by one level. Similarly, for grade 2 total bilirubin (in the absence of Gilbert's syndrome or liver metastases), grade 3 alanine aminotransferase or aspartate aminotransferase elevation, vomiting, diarrhoea, colitis, and other gastrointestinal adverse events, treatment would be interrupted and resumed at the same dose if resolved within 7 days, or reduced by one level if not. In cases of grade 3 neutropenia, anaemia, endocrine disorders, and elevated creatinine, as well as grade 4 lymphopenia, HER3-DXd would be interrupted until improvement to grade 2 or lower, with resumption at the same dose if resolved within 14 days, or reduced by one level if not. Grade 4 neutropenia and anaemia would require resolution to grade 2 or lower before resuming HER3-DXd at a lower dose. For grade 2 or higher heart failure, grade 3 or 4 febrile neutropenia, and grade 4 thrombocytopenia, treatment would be interrupted and resumed at a reduced dose following resolution to grade 1 or lower.

Cranial MRI, CT scan of the chest and abdomen, and (optionally) a bone scan were done before the first administration of HER3-DXd. Tumour staging investigations were conducted whenever disease progression was suspected by the investigator. Cranial MRI and CT of the chest and abdomen were done within 14 days of the next treatment cycle, every 6 weeks for the first three assessments, and every 9 weeks thereafter. Intracranial tumour response was assessed by local investigator using RANO-BM, and extracranial and overall response was evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1). At the investigator's discretion, these assessments were obtained at any time when clinically indicated or if progressive disease was suspected. Imaging continued to be performed until radiological evidence of disease progression based on RANO-BM criteria, the start of new anticancer treatment, withdrawal from the trial, death, or end of the trial, whichever occurred first. Laboratory tests were performed at the study site's local laboratory during the screening period, and on day 8 and day 15 of cycle 1, and on day 1 of each subsequent cycle.

Quality of life and neurocognitive and neurological function was assessed using paper forms during clinic visits and before any study or medical procedure on day 1 of cycles 1, 3, 5, and 8, and the end of treatment using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30), the brain cancer-specific questionnaire (QLQ-BN20), and the Neurologic Assessment in Neuro-Oncology (NANO) scale.

Adverse events were monitored during the screening period and on day 1 of each cycle, recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI–CTCAE) version 5.0. Data on patient sex were defined via electronic medical records, and ethnicity was self-reported and not collected on a mandatory basis.

Receptor expression was determined in baseline tissue samples during routine clinical diagnosis. HER3 immunohistochemical staining was performed using a proprietary assay developed by Ventana Medical Systems (Roche Tissue Diagnostics, Tucson, AZ, USA). HER3 immunohistochemistry was done using the primary antibody anti-HER3 clone SP438 (Roche Tissue Diagnostics). Slides with 4 µm thick, freshly cut tissue from formalin-fixed, paraffin-embedded tissue blocks of baseline tumour tissue samples were stained with haematoxylin II and rabbit monoclonal negative control. The presence of HER3 was scored using the OptiView DAB IHC Detection Kit (Roche Tissue Diagnostics). The samples were scored for membrane percent positivity and intensity of 0 (no intensity), 1+ (weak intensity), 2+ (moderate intensity), or 3+ (strong intensity). HER3 expression was quantified using H-scores assigned by experienced surgical pathologists at Roche Tissue Diagnostics (Tucson, AZ, USA). HER2, ER, and PgR expressions were established using VENTANA anti-HER2/neu (4B5), CONFIRM anti-ER (SP1), and CONFIRM anti-PgR (1E2) clones (all Roche Diagnostics), respectively. The ULTRAVIEW detection kit was used together with the Benchmark ULTRA system (Roche Diagnostics), and visualisation was done using diaminobenzidine. The samples included in this trial were managed and processed by the Biobank of the Ramón y Cajal Hospital-IRYCIS (Madrid, Spain; National Biobank Registry B.0000678), certified by ISO 9001:2015, following standardised procedures and using high-level databases of security.

Outcomes

The primary endpoint of cohort 1 from the TUXEDO-3 trial was the intracranial overall response rate, defined as the proportion of patients with intracranial complete response or partial response established locally by investigator, using RANO-BM criteria.[23] Secondary endpoints included investigator-assessed extracranial and bicompartmental overall response rates, clinical benefit rate (defined as the proportion of patients with a complete response, partial response, or stabilisation of disease for at least 24 weeks), disease control rate (defined as the proportion of patients with a complete response, partial response, or stabilisation of disease), time to response (defined as the period from treatment initiation to time of the first objective tumour response in patients with a complete response or partial response), duration of response (defined as the period from the first occurrence of a documented objective tumour response to disease progression or death from any cause in patients with a complete response or partial response),

progression-free survival (defined as the period from treatment initiation to first occurrence of disease progression or death from any cause, whichever occurred first, as per RANO-BM for intracranial lesions and as per RECIST version 1.1 for extracranial and bicompartmental lesions), and overall survival (defined as the period from treatment initiation to death from any cause or last available follow-up); best percentage of change in tumour burden; safety and toxicity according to NCI-CTCAE version 5.0; quality of life (using the results at cycle 1 of treatment as a reference to establish improvement or worsening; no thresholds were used); and neurological function using the NANO scale.[24] Additional secondary endpoints were centrally reviewed activity assessments; however, these analyses will be reported separately. The prespecified exploratory endpoints were activity endpoints according to HER3 and TROP2 expression levels, the association between HER3-DXd efficacy with breast cancer subtypes, activity endpoints for patients with and without previous ADC therapy, and predictive biomarkers, prognostic biomarkers, or both, in both blood and tumour samples. In this Article we report activity analyses based on tumoural HER3 expression and breast cancer subtypes.

Statistical analyses

We planned to assign 20 patients to cohort 1. The protocol specified one interim analysis with ten evaluable patients, based on Simon's two-stage design. The study would continue with the second stage if at least one patient with intracranial overall response rate was observed. The clinically relevant threshold value for the final analysis in this cohort was three or more (≥15%) of 20 patients with an intracranial overall response rate. The null hypothesis was 5% or less of patients with an intracranial objective response and the alternative hypothesis was more than 25% of patients with an intracranial objective response, indicating clinically relevant activity. The null hypothesis would be rejected if at least 15% of patients had an intracranial objective response. This design yielded a type I error rate of 10% and a power of 88% to reject the null hypothesis. p values and 95% CIs were estimated.[25]

The primary endpoint and all efficacy endpoints were assessed in the full analysis set (all patients who met selection criteria and received at least one dose of study treatment). Safety endpoints were analysed on the safety analysis set (all patients who received at least one dose of study treatment) for all patients and for each study cohort. Investigator-assessed overall response rate, clinical benefit rate, and disease control rate were analysed in the full analysis set using 95% Clopper–Pearson CI. Duration of response and time to response were analysed in all patients who had an objective response (ie, a complete response or partial response), and were summarised with median (95% CIs). Progression-free survival and overall survival were estimated in the full analysis set using the Kaplan–Meier method, reporting the number of events and the median with 95% CIs. For progression-free survival and duration of response, data for patients who did not have documented progressive disease or who had not died within 9 weeks of the last tumour assessment were censored at the time of the last evaluable tumour assessment. Events such as study treatment discontinuation or the start of non-protocol anticancer therapies before progression-free survival events were censored at the time of the last evaluable tumour assessment. For overall survival, data for patients who were alive or lost to follow-up at the time of the analysis were censored at the last known alive date. No informative censoring was applied in the Kaplan–Meier analysis. Data for patients with no post-baseline information were censored at the time of treatment initiation plus 1 day for both overall survival and progression-free survival.

Results from quality of life questionnaires were summarised with median (95% CI). Only patients with at least one completed quality of life questionnaire at baseline were included in the quality-of-life analyses, and a final quality of life assessment was conducted at end of treatment. Changes along time from baseline assessments were analysed using a linear mixed-effect model and separately displayed for the overall patient population and for the respective responder and non-responder groups to identify differences in quality of life. Descriptive statistics were used to summarise safety data. For exploratory biomarker analyses, HER3 expression was analysed using the membrane/cytoplasmic H-score and as a continuous variable since there was not a validated cutoff to categorise HER3 expression into

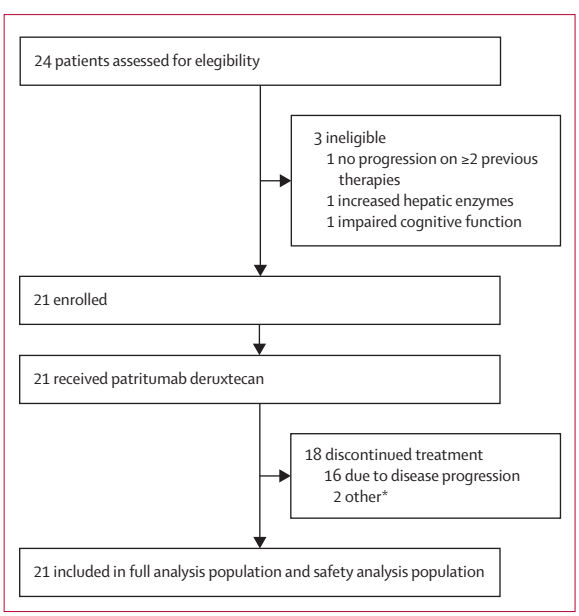

Figure 1: **Trial profile**
*Other: patient's decision (n=1) and adverse events (n=1).

groups (eg, expression *vs* no expression and low expression vs high expression). The association between biomarker expression and HER3-DXd activity was assessed using the Wilcoxon rank-sum test (Mann–Whitney *U* test) for binary variables and Cox-regression for time-to-event variables. The Wald test was used for hypothesis testing. Two-sided p values with an α of 0·05 or lower level of significance were used for all analyses, except for those involving HER3 expression due to the exploratory nature of this analysis. No adjustments for multiple testing were applied in the subgroup analyses due to their exploratory and hypothesis-generating nature. Data were expressed as the mean (SE). In this Article, we also report post-hoc activity analyses stratified by breast cancer subtype. Data analysis was performed using R software (version 4.3.2) within the RStudio environment (version 2023.12.1+402). No data monitoring committee was involved.

Role of the funding source

Medica Scientia Innovation Research, the sponsor of this trial, participated in the study design, collection, and analysis, interpretation of data, and writing of this report. Daiichi-Sankyo and MSD, the funders of this trial, reviewed and revised the final version of this report. Daiichi-Sankyo provided HER3-DXd for the trial.

	Patients (N=21)
Sex	
Female	21 (100%)
Male	0
Race	
White	15 (71%)
Not reported	6 (29%)
Median age at baseline, years (IQR; range)	
Age at baseline (years)	57·0 (44–61; 35·0–75·0)
ECOG performance status	
0	13 (62%)
1	7 (33%)
2	1 (5%)
Oestrogen receptor status	
Negative	10 (48%)
Positive	11 (52%)
Progesterone receptor status	
Negative	13 (62%)
Positive	8 (38%)
Hormone receptor status	
Negative	10 (48%)
Positive	11 (52%)
HER2 immunochemistry	
0	9 (43%)
1+	2 (10%)
2+	2 (10%)
In situ hybridisation and amplified	1 (5%)
In situ hybridisation and non-amplified	1 (5%)
3+	8 (38%)
HER2 status	
Negative	12 (57%)
Positive	9 (43%)
Breast cancer phenotype	
HER2-positive	9 (43%)
Luminal	5 (24%)
Triple-negative	7 (33%)
Advanced disease at diagnosis	
No	13 (62%)
Yes	8 (38%)
Status of brain metastasis	
Progressing after local therapy	15 (71%)
Untreated	6 (29%)
Visceral disease	
No	7 (33%)
Yes	14 (67%)
Brain-only disease	
No	17 (81%)
Yes	4 (19%)
Bone-only disease	
No	10 (48%)
Yes	11 (52%)
Liver metastases	
No	11 (52%)
Yes	10 (48%)
Neurological symptoms at baseline	
No	13 (62%)
Yes*	8 (38%)
Previous antibody–drug conjugates	
No	5 (24%)
Yes	16 (76%)
Trastuzumab deruxtecan	12 (57%)
Sacituzumab govitecan	4 (19%)
Datopotamab deruxtecan	1 (5%)
Previous tucatinib	
No	19 (91%)
Yes	2 (10%)
Previous treatment lines in advanced disease; median (IQR; range)	4 (2–4; 1–13)
HER2-positive	4 (4–4; 2–7)
Luminal	4 (3–4; 3–13)
Triple-negative	2 (1·5–3·5; 1–6)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. *Two patients received dexamethasone at baseline for the management of neurological symptoms (daily doses: 4 mg and 6 mg); in addition, 11 patients started prophylactic dexamethasone together with HER3-DXd at study initiation for the prevention of chemotherapy-induced nausea and vomiting (median dose 4 mg, range 2–8 mg); one patient received levetiracetam (1000 mg) for seizure prophylaxis at baseline.

Table 1: **Baseline characteristics**

Results

Between Dec 12, 2023, and July 8, 2024, a total of 24 female patients were assessed for eligibility, and three did not meet inclusion criteria. Therefore, 21 female patients with metastatic breast cancer and untreated or progressing brain metastases after local treatment were enrolled (figure 1). Five (24%) of 21 participants had luminal breast cancer, nine (43%) had HER2-positive breast cancer, and seven (33%) had triple-negative breast cancer (table 1). Eight (38%) of the 21 participants had advanced disease at diagnosis, and the median number of previous treatment lines in the advance setting was 4 (IQR 2–4). 15 (71%) of 21 patients had progressive brain metastases and the remaining six (29%) had newly diagnosed untreated brain metastases. Of 15 patients who had progressive brain metastases, three (20%) had undergone stereotactic radiosurgery, ten (67%) had received whole brain radiotherapy, and two (13%) had not received local therapy for brain metastases. Previous systemic treatments included ADCs (16 [76%] of 21 patients) and tucatinib (two patients [10%]). The median age at inclusion was 57·0 years (IQR 44–61) years, ECOG-PS was 0 in 13 (62%) of 21 patients and eight (38%) had neurological symptoms at baseline. 14 patients (67%) had visceral disease and four (19%) had brain-only disease.

At data cutoff (Feb 28, 2025), three (14%) of 21 patients were still on treatment. Reasons for treatment discontinuation included progressive disease (16 patients [76%]), patient's decision (one patient [5%]), and adverse events (one patient [5%]). Reasons for study discontinuation were death due to progressive disease (six patients [29%]), death due to adverse events (one patient [5%]), and loss to follow-up (one patient [5%]).

In the first stage of this trial (enrolment between Dec 12, 2023 and April 24, 2024), two of the ten planned patients had a confirmed intracranial response, meeting the predefined threshold for the interim analysis. Therefore, 11 additional participants were enrolled in the second stage, which concluded on July 8, 2024.

At data cutoff, median treatment duration was 3·0 months (IQR 0·7–7·7), and median follow-up was 4·9 months (IQR 3·6–8·5). Five (24%) of the 21 evaluable patients had confirmed intracranial responses (locally assessed), meaning the primary endpoint of this trial was met, including two (40%) of five with luminal breast cancer, two (40%) with triple-negative breast cancer, and one (20%) with HER2-positive breast cancer (figure 2). One (20%) of five patients with triple-negative breast cancer and the one patient (20%) with HER2-positive breast cancer had received previous ADCs. Three (60%) of the five patients with confirmed response had untreated brain metastases and two (40%) had brain metastases progressing after previous local therapy (one patient was treated with whole brain radiotherapy and one underwent radiosurgery). The number of previous systemic treatment lines in advanced disease

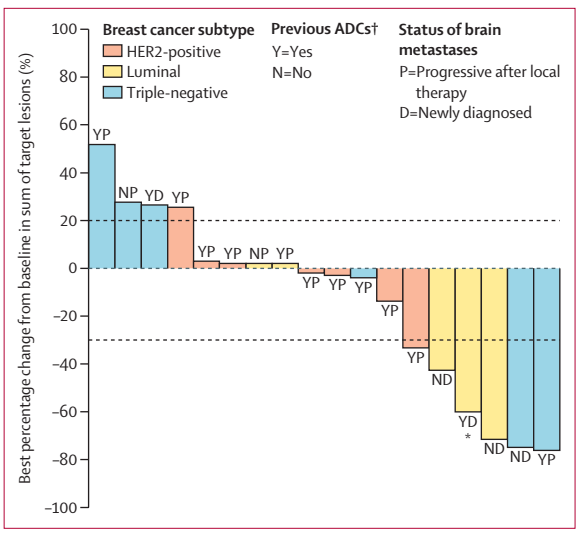

Figure 2: **Best percentage of change in tumour burden for intracranial lesions according to RANO-BM criteria**

Of the 21 patients enrolled, three discontinued treatment before the first post-baseline evaluation, so the percentage of change for 18 patients is shown. Dashed horizontal lines at 20% and –30% represent thresholds to consider progressive disease and partial response, respectively, in the diameter of target lesions according to RANO-BM criteria. ADC=antibody–drug conjugate. RANO-BM=Response Assessment in Neuro-Oncology Brain Metastases. *Unconfirmed response (locally assessed). †All previous ADCs had a topoisomerase I inhibitor as payload.

was one for two (40%) responding patients and four (60%) for three responding patients.

Among all 21 patients, six (29%) had partial response (ie, reduction of more than 30% in the best percentage change of target lesions), seven (33%) had stabilisation of disease, and five (24%) had progressive disease of intracranial lesions according to RANO-BM criteria (although 20% increase in the sum of extracranial target lesions was not reached for one patient). Response could not be evaluated in the remaining three patients (14%) as they discontinued treatment before the first post-baseline evaluation. According to RECIST version 1.1, 17 patients had extracranial lesions at baseline, and two (12%) of these had partial response, nine (53%) had stabilisation of disease, and three (18%) had progressive disease (although 20% increase in the sum of target lesions was not reached for two patients). Among the 21 patients included in the analysis of bicompartmental response, three (14%) had partial response, 11 (52%) had stabilisation of disease, four (19%) had progressive disease (although 20% increase in the sum of bicompartmental target lesions was not reached for two patients), and three (14%) did not have evaluable response due to discontinuing treatment before the first post-baseline evaluation. The response outcomes are shown in figure 2 and the appendix (p 4).

Locally assessed intracranial overall response rate was 23·8% (95% CI 8·2–47·1; five of 21). The bicompartmental (intracranial and extracranial lesions) overall response rate was 14·3% (95% CI 3·1–36·3; three of 21 patients)

and the overall response rate for extracranial lesions was 11·8% (1·5–36·4; two of 17). Clinical benefit rate was 33·3% (95% CI 14·6–57·0; seven of 21) for intracranial lesions, 28·6% (95% CI 11·3–52·2; six of 21 patients) for bicompartmental lesions, and 29·4% (95% CI 10·3–56·0; five of 17) for extracranial lesions. Disease control rate was 61·9% (95% CI 38·4–81·9; 13 of 21) for intracranial lesions, 66·7% (95% CI 43·0–85·4; 14 of 21) for bicompartmental lesions, and 64·7% (95% CI 38·3–85·8; 11 of 17) for extracranial lesions. The median time to response was 1·5 months (95% CI 1·4–6·0) for intracranial lesions, 2·8 months (95% CI 1·5–6·0) for bicompartmental lesions, and 2·7 months (95% CI 2·6–2·8) for extracranial lesions. Median duration of response for intracranial lesions was 6·7 months (95% CI 6·0–not reached [NR]) and was 5·5 months (95% CI 5·5–NR) for extracranial lesions. Median duration of response could not be calculated for bicompartmental lesions due to the short follow-up period at data cutoff. Median progression-free survival for intracranial lesions was 4·0 months (1·4–8·5; 14 events), extracranial lesions was 4·7 months (1·8–NR; nine events), and bicompartmental lesions was 4·3 months (1·6–8·5; 12 events; appendix p 5). The number of patients censored to assess progression-free survival for intracranial, extracranial, and bicompartmental lesions is reported in the appendix (pp 2–3) Median overall survival was not reached, as more than 50% of patients were still alive at data cutoff (three [14%] of 21 patients were still on treatment, and ten [48%] were in follow-up at the end of treatment; appendix p 5).

Eight (38%) of 21 patients had neurological symptoms at baseline, including symptoms related to gait (six patients [29%]), strength (four patients [19%]), language (one patient [5%]), ataxia in upper extremity (one patient [5%]), and visual fields (one patient [5%]). At data cutoff, neurological function evaluation as per the NANO scale reported that 17 (81%) of 21 participants had neurological stability, and no patients had neurological response or neurological deterioration during study treatment. Neurological assessments in the remaining four participants (19%) could not be performed due to the absence of post-baseline evaluations. The parameters assessed using the QLQ-C30 questionnaire remained stable between the first cycle and the end of treatment, and there was a slight improvement, especially for global health status, at cycle 8 (appendix p 6). The parameters of future uncertainty and visual disorder, assessed using the QLQ-BN20 questionnaire, remained stable between the first cycle and the end of treatment, whereas motor dysfunction and communication deficit decreased (appendix p 6).

Treatment-emergent adverse events of any grade were reported in 18 (86%) of 21 patients (nine [43%] grade ≥3; table 2). Treatment-emergent adverse events of grade 1 or 2 occurring in at least 10% of patients and all of grade 3–5 were: asthenia (seven patients [33%], one [5%] grade ≥3), nausea (seven patients [33%], none grade ≥3), diarrhoea (five patients [24%], two [10%] grade ≥3), alopecia (five patients [24%], none grade ≥3), neutropenia (four patients [19%], three [14%] grade ≥3), vomiting (four patients [19%], one [4%] grade ≥3), and thrombocytopenia, dysgeusia, and aspartate aminotransferase increased (four [19%] patients for each treatment-emergent adverse event, none grade ≥3), and anaemia, alanine transferase increased, and dizziness (three [14%] patients for each adverse event, none grade ≥3; table 3, appendix p 12).

Treatment-related treatment-emergent adverse events were reported in 17 (81%) of 21 patients. Serious treatment-emergent adverse events (grade ≥3) were reported in six (29%) of 21 patients (including peripheral oedema, pain, dyspnoea, pleural effusion, pulmonary embolism, bacterial arthritis, vomiting, back pain, and deep vein thrombosis; one patient each with some having more than one event simultaneously; appendix pp 15–16). Grade 2 interstitial lung disease was the only serious treatment-related treatment-emergent adverse event. One patient died due to treatment-emergent adverse events (pulmonary thromboembolism; not related to the treatment).

Interruption of HER3-DXd due to treatment-emergent adverse events occurred in two (10%; one due to grade 2 fatigue and one due to grade 3 nervous system disorder) of 21 patients and permanent discontinuation in one patient (5%; due to grade 5 pulmonary thromboembolism). Dose reductions of HER3-DXd due to treatment-emergent adverse events occurred in four patients (19%; grade 3 fatigue in three patients [14%], grade 3 diarrhoea in two patients [10%], and grade 4 platelet count decrease in one patient [5%]).

	Patients (N=21)
All adverse events	18 (86%)
Treatment-emergent adverse events	18 (86%)
Treatment-related	17 (81%)
Serious treatment-emergent adverse events	6 (29%)
Treatment-related	1 (5%)
Grade 3 or 4 treatment-emergent adverse events	9 (43%)
Treatment-related	5 (24%)
Adverse events of special interest	1 (5%)
Treatment-related	0
Death due to treatment-emergent adverse events	1 (5%)
Treatment-related	0
Treatment-emergent adverse events leading to dose reduction	4 (19%)
Treatment-emergent adverse events leading to interruption	2 (10%)
Treatment-emergent adverse events leading to permanent discontinuation	1 (5%)

Data are n (%).

Table 2: **Adverse events in patients with metastatic breast cancer with untreated or progressing brain metastases**

Preplanned exploratory analyses based on tumoural HER3 expression are reported in the appendix (pp 2 and 7) as are post-hoc analyses of activity endpoints among breast cancer subtypes (pp 2, 7, and 17–18).

Discussion

To our knowledge, TUXEDO-3 is the first study investigating HER3-DXd in the context of active breast cancer brain metastases. The results of this phase 2 trial provide evidence of clinically meaningful activity of HER3-DXd in this cohort of patients. In the breast cancer cohort, the primary endpoint was met with responses observed in five of 21 patients, an overall response rate of 23·8% (95% CI 8·2–47·1), irrespective of breast cancer subtype and previous ADC treatment.

The HER2CLIMB trial established the triple combination of tucatinib, trastuzumab, and capecitabine as a potential standard of care for patients with active HER2-positive breast cancer brain metastases.[7,8] The regimen had an intracranial response rate of 47·3%, according to the RECIST version 1.1 criteria, in the subset of patients with measurable disease at baseline;[8] however, compared with TUXEDO-3, HER2CLIMB enrolled patients who were less heavily pretreated and only a small proportion of them had measurable intracranial disease.[7,8] During the past 5 years, patients given trastuzumab deruxtecan have been shown to have unprecedented intracranial response rates and prolonged disease control, even in the presence of brain metastases.[11,26] In contrast, the role of systemic therapy in patients with brain metastases of HER2-negative brain cancer remains poorly defined, which is of particular concern as parallel intracranial and extracranial progression is common in triple-negative breast cancer and CNS involvement occurs late during the course of HR-positive/HER2-negative metastatic disease in patients progressing on standard treatment. In pretreated metastatic triple-negative breast cancer, the TROP2-directed ADC sacituzumab govitecan prolonged progression-free survival and overall survival compared with conventional chemotherapy.[27] However, in the smaller subgroup of patients with stable brain metastases at baseline who were enrolled in the ASCENT trial (61 patients), median progression-free survival was only 2·8 months in the sacituzumab govitecan group, with an overall response rate equally low at 3%.[28] By contrast, in the subgroup of patients with active brain metastases and HER2-low expressing tumours enrolled in the DEBBRAH trial (12 patients), overall response rate by RANO-BM criteria was 41·7%.[12] The existing evidence supports the intracranial activity of deruxtecan-based ADCs beyond the HER2-positive subtype in principle. For TUXEDO-3, HER3-DXd was selected as the drug harbours activity across all breast cancer subtypes;[16] HER3-DXd has not been evaluated in earlier metastatic treatment lines to date and it could provide clinical activity in patients pretreated with other topoisomerase I-based ADCs due to a switch in target.

	Grade 1–2	Grade 3	Grade 4	Grade 5 (deaths)	Any grade*
All treatment-emergent adverse events	17 (81%)	9 (43%)	2 (10%)	1 (5%)	18 (86%)
General disorders and administration site conditions	8 (38%)	4 (19%)	0	0	11 (52%)
Asthenia	6 (29%)	1 (5%)	0	0	7 (33%)
Fatigue	1 (5%)	2 (10%)	0	0	3 (14%)
Mucosal inflammation	1 (5%)	1 (5%)	0	0	2 (10%)
Pain	1 (5%)	1 (5%)	0	0	2 (10%)
Peripheral oedema	0	1 (5%)	0	0	1 (5%)
Gastrointestinal disorders	11 (52%)	3 (14%)	0	0	11 (52%)
Nausea	7 (33%)	0	0	0	7 (33%)
Diarrhoea	3 (14%)	2 (10%)	0	0	5 (24%)
Vomiting	3 (14%)	1 (5%)	0	0	4 (19%)
Blood and lymphatic system disorders	5 (24%)	2 (10%)	1 (5%)	0	8 (38%)
Neutropenia	1 (5%)	2 (10%)	1 (5%)	0	4 (19%)
Thrombocytopenia	4 (19%)	0	0	0	4 (19%)
Anaemia	3 (14%)	0	0	0	3 (14%)
Nervous system disorders	9 (43%)	2 (10%)	0	0	10 (48%)
Dysgeusia	4 (19%)	0	0	0	4 (19%)
Dizziness	3 (14%)	0	0	0	3 (14%)
Nervous system disorder	1 (5%)	1 (5%)	0	0	2 (10%)
Epilepsy	0	1 (5%)	0	0	1 (5%)
Investigations	6 (29%)	0	1 (5%)	0	7 (33%)
Aspartate aminotransferase increased	4 (19%)	0	0	0	4 (19%)
Alanine aminotransferase increased	3 (14%)	0	0	0	3 (14%)
Platelet count decreased	0	0	1 (5%)	0	1 (5%)
Infections and infestations	7 (33%)	1 (5%)	0	0	8 (38%)
Bacterial arthritis	0	1 (5%)	0	0	1 (5%)
Skin and subcutaneous tissue disorders	5 (24%)	0	0	0	5 (24%)
Alopecia	5 (24%)	0	0	0	5 (24%)
Musculoskeletal and connective tissue disorders	3 (14%)	1 (5%)	0	0	4 (19%)
Back pain	0	1 (5%)	0	0	1 (5%)
Respiratory, thoracic, and mediastinal disorders	2 (10%)	2 (10%)	0	1 (5%)	3 (14%)
Pulmonary embolism	0	0	0	1 (5%)	1 (5%)
Dyspnoea	0	1 (5%)	0	0	1 (5%)
Pleural effusion	0	1 (5%)	0	0	1 (5%)
Vascular disorders	1 (5%)	1 (5%)	0	0	2 (10%)
Deep vein thrombosis	0	1 (5%)	0	0	1 (5%)

Data are n (%). Adverse events of grade 1 or 2 occurring in at least 10% of patients and all grade 3–5 adverse events are presented (all adverse events are listed in the appendix pp 12–15). *Number of patients who had an adverse event of any grade.

Table 3: **Treatment-emergent adverse events stratified by grade**

In post-hoc analyses, responses to HER3-DXd were found across all breast cancer subtypes. Although intracranial overall response rate in the patient with HER2-positive breast cancer was considerably lower than in previous reports,[11,13,29] it needs to be acknowledged that we enrolled a heavily pretreated population. The results obtained in those patients with HER2-negative breast cancer were similar to those in the HER2-low cohort of DEBBRAH.[12] In this context, comparison with more substantiated data from larger trials evaluating trastuzumab deruxtecan activity in active brain

metastases of HER2-low expressing metastatic breast cancer, such as TUXEDO-4, will be of interest.[29] In addition, in the DESTINY-Breast12 trial, intracranial overall response rate was 50·0% (19 of 38 patients) in patients with progressing brain metastasis, and 82·6% (19 of 23 patients) in patients with untreated brain metastases.[11] Although our trial had a smaller sample size, we observed a similar trend in obtaining higher intracranial overall response rate in patients with untreated brain metastases compared with those with progressing brain metastases.

At a median follow-up of 4·9 months, median intracranial progression-free survival was 4·0 months. These results indicate the ability of HER3-DXd to generate disease control. Although absolute progression-free survival was lower than with trastuzumab deruxtecan in HER2-positive metastatic breast cancer brain metastases, results do compare well with the HER2-low cohort of DEBBRAH, in which median progression-free survival was 5·4 months.[12]

Global health status, as measured by EORTC QLQ-C30, improved over the treatment period and worsened only on disease progression. A similar pattern was observed for physical and emotional functioning, as well as future uncertainty. Neurological function, assessed by NANO scale, remained stable over the entire treatment period in all 15 patients with available data, suggesting a potential advantage over local therapy. Regarding safety, the most common adverse events were asthenia, nausea, alopecia, and diarrhoea. The most common grade 3 or worse adverse event was neutropenia, but no cases of febrile neutropenia were reported. Although previous reports might indicate a lower overall interstitial lung disease risk for HER3-DXd compared with trastuzumab deruxtecan,[11] a single patient died due to grade 5 pulmonary thromboembolism (not related to HER3-DXd). In summary, results regarding quality of life, neurocognitive function, and safety suggest that HER3-DXd has an acceptable tolerability profile in patients with active brain metastases, for whom maintaining quality of life is paramount.

Our trial is limited by the single-arm phase 2 design, the overall low number of patients, and the inclusion of participants with different breast cancer subtypes and heterogeneous pretreatments. In addition, activity endpoints were assessed by local investigators and central radiology review, but in this Article we only include assessment per investigators (central review evaluations are planned for the end of the trial), which might introduce variability and potential bias in the evaluation of radiological findings. In clinical practice, treatment decisions for patients with brain metastases will also be influenced by factors such as the number and locations of metastatic lesions, neurological symptoms, performance status, breast cancer subtype, and the status of extracranial disease (stable *vs* progressive). Prognostic tools, such as the diagnosis-specific graded prognostic assessment, can help guide local treatment decisions.[30]

Despite these limitations and the lower response rates observed in this cohort compared with those reported for trastuzumab deruxtecan in HER2-positive breast cancer brain metastases—likely due to HER3 not being a primary oncogenic driver—findings from TUXEDO-3 remain clinically relevant. The findings indicate antitumour activity of HER3-targeted therapy in heavily pretreated patients with active brain metastases of HER2-negative brain cancer, for whom local therapy remains the current standard of care. In addition, HER3-DXd showed activity after previous ADCs and irrespective of the breast cancer subtype. Future studies of HER3-DXd with a larger sample size in the context of patients with brain metastases that focus on predictive biomarkers, ADC sequencing strategies, and multimodal approaches are warranted.

Contributors

Conception and design: RB and MP. Patient recruitment and data acquisition: RB, MM, JG-N, MG, MR-B, RG, MV, and AL-C. Collection and assembly of data: all authors. Data analysis: JAG. Data interpretation: all authors. Manuscript writing and review: all authors. Final approval of the manuscript: all authors. All authors accessed and verified the underlying data reported in the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

RB declares honoraria from AstraZeneca, BMS, Daiichi-Sankyo, Eisai, and Eli Lilly; a consulting or advisory role for AstraZeneca, Daichi, Eisai, and Eli Lilly; research funding from Daiichi-Sankyo; and travel, accommodation, and expenses from MSD, Daiichi-Sankyo, Novartis, and Pfizer. MM declares a consulting or advisory role for Eli Lilly, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Gilead; funding for attendance at speakers bureaus from Eli Lilly, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Gilead; research funding from Daiichi-Sankyo; and travel, accommodation, and expenses from MSD, Gilead, Novartis, Eli Lilly, and Daiichi-Sankyo. MG declares honoraria from Novartis, Gilead, AstraZeneca, and Pfizer; personal support for attending meetings or travel from Roche, Pfizer, AstraZeneca, and Gilead; and honoraria for advisory board participation from Gilead, Novartis, AstraZeneca, and Pfizer. RG declares stock or other ownership in Novo Nordisk and Eli Lilly; honoraria from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, AbbVie, Gilead, Daiichi-Sankyo, and Sanofi; consulting or advisory roles for Celgene, Novartis, Roche, BMS, Takeda, AbbVie, AstraZeneca, Janssen, MSD, Amgen, Merck, Gilead, Daiichi-Sankyo, and Sanofi; research funding from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, AbbVie, Gilead, and Daiichi-Sankyo; and travel, accommodation, and expenses from Roche, Amgen, Janssen, AstraZeneca, Novartis, MSD, Celgene, BMS, AbbVie, Gilead, and Daiichi-Sankyo. MV declares speaker fees from Pfizer, Novartis, Roche, MSD, Gilead, Seagen, Pierre Fabre, Eisai, and Sanofi-Aventis; and investigation funding from Fundación Quirónsalud. AL-C declares research support from Roche, Agendia, Eli Lilly, Pfizer, Novartis, MSD, Gilead, and Daiichi-Sankyo; consulting or advisory roles for Eli Lilly, Roche, Pfizer, and Novartis; funding for attendance at speakers bureaus from Eli Lilly, AstraZeneca, MSD, Pfizer, and Novartis; travel support from Roche, Pfizer, AstraZeneca, Steamline Therapeutics, and MSD; a patent for HER2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy (US 2019/ 0338368 A1; licensed); and stock or other ownership in MAJ3 Capital and Initia-Research. JC declares a consulting or advisory role for Roche, AstraZeneca, Seattle Genetics, Daiichi-Sankyo, Eli Lilly, MSD, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals,

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Data sharing

Data collected within the TUXEDO-3 trial will be made available to researchers after contacting the corresponding author and on review and approval on the basis of scientific merit by the TUXEDO-3 management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes, and statistical analysis plan will be provided after the completion of a data-sharing agreement that will be set up by the study sponsor, Medica Scientia Innovation Research, and Daiichi-Sankyo. All data provided will be anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Estimated timeframe for response will be within 30 days. Please address requests for data to the corresponding author via email.

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