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

Fabrice André, Yeon Hee Park, Sung-Bae Kim, Toshimi Takano, Seock-Ah Im, Giuliano Borges, Joao Paulo Lima, Sercan Aksoy, Joaquin Gavila Gregori, Michelino De Laurentiis, Giampaolo Bianchini, Rebecca Roylance, Yasuo Miyoshi, Anne Armstrong, Rajni Sinha, Manuel Ruiz Borrego, Elgene Lim, Johannes Ettl, Rinat Yerushalmi, Flora Zagouri, Francois P Duhoux, Tanja Fehm, Dhiraj Gambhire, Jillian Cathcart, Cai Wu, Changan Chu, Anton Egorov, Ian Krop

Summary

Background In the single-arm, phase 2 DESTINY-Breast01 trial, trastuzumab deruxtecan showed robust activity in patients with HER2-positive metastatic breast cancer who were refractory or resistant to trastuzumab emtansine; a population with scarce effective treatments. In DESTINY-Breast02, we aimed to compare the efficacy and safety of trastuzumab deruxtecan with treatment of physician's choice in this patient population.

Methods This randomised, open-label, multicentre, phase 3 trial was conducted at 227 sites (hospitals, university hospitals, clinics, community centres, and private oncology centres) in North America, Europe, Asia, Australia, Brazil, Israel, and Türkiye. Eligible patients were aged 18 years or older, had unresectable or HER2-positive metastatic breast cancer, previously received trastuzumab emtansine, disease progression, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate renal and hepatic function. Patients were randomly assigned (2:1) to receive trastuzumab deruxtecan (intravenously at 5·4 mg/kg once every 3 weeks) or treatment of physician's choice using block randomisation. Treatment of physician's choice was either capecitabine (1250 mg/m²; orally twice per day on days 1–14) plus trastuzumab (8 mg/kg intravenously on day 1 then 6 mg/kg once per day) or capecitabine (1000 mg/m²) plus lapatinib (1250 mg orally once per day on days 1–21), with a 21-day schedule. The primary endpoint was progression-free survival based on blinded independent central review in the full analysis set. This study is registered with ClinicalTrials.gov, NCT03523585.

Findings Between Sept 6, 2018, and Dec 31, 2020, 608 patients were randomly assigned to receive trastuzumab deruxtecan (n=406; two did not receive treatment) or treatment of physician's choice (n=202; seven did not receive treatment). 608 (100%) patients were included in the full analysis set. The median age was 54·2 years (IQR 45·5–63·4) in the trastuzumab deruxtecan group and 54·7 years (48·0–63·0) in the treatment of physician's choice group. 384 (63%) patients were White, 603 (99%) were female, and five (<1%) were male. The median follow-up was 21·5 months (IQR 15·2–28·4) in the trastuzumab deruxtecan group and 18·6 months (8·8–26·0) in the treatment of physician's choice group. Median progression-free survival by blinded independent central review was 17·8 months (95% CI 14·3–20·8) in the trastuzumab deruxtecan group versus 6·9 months (5·5–8·4) in the treatment of physician's choice group (HR 0·36 [0·28–0·45]; p<0·0001). The most common treatment-emergent adverse events were nausea (293 [73%] of 404 with trastuzumab deruxtecan *vs* 73 [37%] of 195 with treatment of physician's choice), vomiting (152 [38%] *vs* 25 [13%]), alopecia (150 [37%] *vs* eight [4%]), fatigue (147 [36%] *vs* 52 [27%]), diarrhoea (109 [27%] *vs* 105 [54%]), and palmar–plantar erythrodysaesthesia (seven [2%] *vs* 100 [51%]). Grade 3 or higher treatment-emergent adverse events occurred in 213 (53%) patients receiving trastuzumab deruxtecan versus 86 (44%) receiving treatment of physician's choice; whereas drug-related interstitial lung disease occurred in 42 (10%; including two grade 5 death events) versus one (<1%).

Interpretation DESTINY-Breast02 shows the favourable benefit–risk profile of trastuzumab deruxtecan in patients with HER2 positive metastatic breast cancer, as previously reported in DESTINY-Breast01, and is the first randomised study to show that one antibody-drug conjugate can overcome resistance to a previous one.

Funding Daiichi Sankyo and AstraZeneca.

Introduction

Approximately 15–20% of patients with breast cancer are diagnosed with tumours characterised by overexpression of HER2 (also known as ERBB2).[1] Although HER2-targeted therapies have improved survival outcomes in this patient population, most patients have

Lancet 2023; 401: 1773–85

Published **Online** April 19, 2023 https://doi.org/10.1016/S0140-6736(23)00725-0

This online publication has been corrected. The corrected version first appeared at thelancet.com on December 7, 2023

See **Comment** page 1746

Institut Gustave Roussy, Université Paris Saclay, Villejuif, France (F André MD); **Samsung Medical Center, Seoul, South Korea** (Y Hee Park MD); **Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (S-B Kim MD); **The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan** (T Takano MD); **Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea** (S-A Im MD); **Clínica de Neoplasias Litoral, Itajaí, Brazil** (G Borges MD); **AC Camargo Cancer Center, São Paulo, Brazil** (J P Lima MD); **Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Türkiye** (S Aksoy MD); **Instituto Valenciano de Oncologia, Valencia, Spain** (J Gavila Gregori MD); **Istituto Nazionale Tumori IRCCS Fondazione G Pascale, Naples, Italy** (M De Laurentiis MD); **San Raffaele Hospital, Milan, Italy** (G Bianchini MD); **University College London Hospital, London, UK** (R Roylance MD); **Hyago College of Medicine University Hospital, Hyogo, Japan** (Y Miyoshi MD); **The Christie Hospital, Manchester, UK** (A Armstrong PhD); **Piedmont Cancer Institute, Atlanta, GA,**

USA (R Sinha MD)**; Hospital Universitario Virgen del Rocio, Seville, Spain** (M Ruiz Borrego MD)**; St Vincent's Hospital Sydney, Sydney, NSW, Australia** (E Lim PhD)**; Klinikum rechts der Isar der Technischen Universität München, Munich, Germany** (J Ettl MD)**; Rabin Medical Center-Beilinson Campus, Tel-Aviv University, Tel-Aviv, Israel** (R Yerushalmi MD)**; Alexandra General Hospital, Athens, Greece** (F Zagouri MD)**; Cliniques universitaires Saint-Luc, Brussels, Belgium** (F P Duhoux MD)**; Universitaetsklinikum Düsseldorf, Düsseldorf, Germany** (T Fehm MD)**; Daiichi Sankyo, Basking Ridge, NJ, USA** (D Gambhire MD, J Cathcart PhD, C Wu PhD, C Chu MD, A Egorov MD)**; Yale Cancer Center, New Haven, CT, USA** (I Krop MD)

Correspondence to: Dr Ian Krop, Yale Cancer Center, New Haven, CT 06520–8028, USA
ian.krop@yale.edu

Research in context

Evidence before this study

We searched PubMed for articles published from Nov 9, 2017, to Nov 9, 2022, using the search terms "HER2-targeted therapy", "HER2-positive", "breast cancer", "prior or previous trastuzumab emtansine", "second-line", and "third-line". This search was limited to English language publications. We wanted to identify articles discussing HER2-targeted therapies for patients with HER2 positive metastatic breast cancer whose disease has progressed after two or more HER2-targeted regimens, including trastuzumab emtansine. Results from the CLEOPATRA trial formed the basis for the current standard first-line recommendation for patients with advanced HER2-positive metastatic breast cancer—namely, a regimen of anti-HER2 monoclonal antibodies (trastuzumab plus pertuzumab) combined with a taxane. The anti-HER2 antibody-drug conjugate trastuzumab emtansine was recommended for second-line treatment based on the EMILIA study. The single-arm, phase 2, DESTINY-Breast01 trial reported robust antitumour activity with the anti-HER2 antibody-drug conjugate trastuzumab deruxtecan in patients who previously received trastuzumab emtansine, serving as the basis for accelerated approval in the third-line setting in 2019. The phase 3, DESTINY-Breast02 trial was designed to validate preliminary data reported in DESTINY-Breast01 and assess superiority of trastuzumab deruxtecan over treatment of physician's choice in patients with HER2-positive metastatic breast cancer who previously received trastuzumab emtansine. DESTINY-Breast02 is complementary to DESTINY-Breast03, which first reported superiority of trastuzumab deruxtecan over trastuzumab emtansine in 2021.

Added value of this study

To our knowledge, this study is the first phase 3 trial investigating a HER2-directed agent after patients have received trastuzumab emtansine. We show that trastuzumab deruxtecan is superior to conventional chemotherapy-based treatment options plus HER2-targeted agents in patients with HER2 positive metastatic breast cancer that is resistant or refractory to trastuzumab emtansine. Patients with HER2-positive metastatic breast cancer living in many countries where trastuzumab deruxtecan is not approved or wherein the indication varies have limited access to trastuzumab deruxtecan as a second-line therapy option. Additionally, based on the KATHERINE trial, most patients with residual breast cancer have previously received post-neoadjuvant trastuzumab emtansine because this drug is widely accepted as standard of care. Although access might still be limited with later lines of therapy, our study addresses the efficacy and safety of trastuzumab deruxtecan in patients with more advanced disease after trastuzumab emtansine treatment. We also showed the manageable safety of trastuzumab deruxtecan after two or more HER2-targeted regimens.

Implications of all the available evidence

The results of this trial support the clinical significance of using trastuzumab deruxtecan in patients with HER2-positive metastatic breast cancer and, to our knowledge, report for the first time in a randomised trial that an antibody-drug conjugate can overcome the resistance acquired to another antibody-drug conjugate. Considering that some patients might still receive trastuzumab emtansine in the second-line setting, this finding is clinically relevant. Trastuzumab deruxtecan has a superior benefit–risk ratio over conventional chemotherapy-based combinations with HER2-targeting agents. Further investigation on the real-world implication of using trastuzumab deruxtecan after trastuzumab emtansine, and the optimal treatment sequencing of antibody-drug conjugates are warranted.

disease progression due to acquired resistance.[2,3] As a result, HER2-positive metastatic breast cancer remains incurable and therefore new and effective treatment options are needed in this setting.[4] First-line treatment options include pertuzumab and trastuzumab in combination with a taxane.[5–7] The antibody-drug conjugate trastuzumab emtansine has been approved as second-line treatment for patients with HER2-positive metastatic breast cancer on the basis of results from the EMILIA trial.[8,9]

In later lines of therapy after trastuzumab emtansine, the standard of care for patients with HER2-positive metastatic breast cancer has not been well defined.[9] When this trial, DESTINY-Breast02, was initiated, available treatment options after trastuzumab emtansine included lapatinib with capecitabine, trastuzumab with capecitabine, or trastuzumab with other single-agent chemotherapy. Because these regimens have shown low objective response rates (approximately 9–27%) and short progression-free survival (median 3·3–6·1 months), more effective treatment options are needed for this patient population.[10–13]

Trastuzumab deruxtecan is an antibody-drug conjugate consisting of a humanised monoclonal anti-HER2 antibody bound to a cytotoxic topoisomerase I inhibitor by a cleavable linker.[14–16] Trastuzumab deruxtecan showed robust activity in the phase 2, single-arm, DESTINY-Breast01 trial[17] conducted in heavily pretreated patients with HER2-positive breast cancer who previously received trastuzumab emtansine, reaching objective response rates of 61% (95% CI 53–68; 112 of 184 patients) by independent central review and a median progression-free survival of 16·4 months (12·7–not estimable [NE]). These results led to accelerated approval of trastuzumab deruxtecan for patients with HER2-positive metastatic breast cancer who received at least two previous anti-HER2 antibody-based regimens.[17] Updated results from DESTINY-Breast01 have continued to show sustained

efficacy of trastuzumab deruxtecan after trastuzumab emtansine, with patients reaching a median progression-free survival of 19·4 months (14·1–25·0), median overall survival of 29·1 months (24·6–36·1), and objective response rates of 62% (55–69; 114 of 184 patients).[18]

DESTINY-Breast02 was designed as a confirmatory trial for DESTINY-Breast01. We aimed to compare the efficacy and safety of trastuzumab deruxtecan with treatment of physician's choice in patients with HER2 positive metastatic breast cancer which is resistant or refractory to trastuzumab emtansine.

Methods

Study design and participants

This randomised, open-label, multicentre, phase 3 trial was conducted at 227 sites (hospitals, university hospitals, clinics, community centres, and private oncology centres) in North America, Europe, Asia, Australia, Brazil, Israel, and Türkiye. Eligible patients were aged 18 years or older (as per local regulations), had pathologically documented unresectable or metastatic breast cancer that was centrally confirmed as HER2-positive (immunohistochemistry 3+ or 2+ or in situ hybridisation amplified on primary tumour or metastasis biopsy, as per guidelines from the American Society of Clinical Oncology College of American Pathologists),[19,20] previously received trastuzumab emtansine, documented radiological disease progression, an Eastern Cooperative Oncology Group performance status of 0 or 1, and protocol-defined adequate renal and hepatic function. Patients were excluded if they received previous treatment with capecitabine (previous lapatinib was permitted); had a history of any contraindication for capecitabine or trastuzumab and lapatinib; uncontrolled or clinically significant cardiovascular disease; current, suspected, or a history of non-infectious interstitial lung disease or pneumonitis that required corticosteroid therapy or that could not be ruled out by CT or MRI of the chest at screening; and spinal cord compression or clinically active brain metastases requiring corticosteroids or anticonvulsants. Those with clinically inactive brain metastases and treated asymptomatic brain metastases not requiring corticosteroids or anticonvulsants were allowed to enrol. The study initially allowed enrolment of patients with previously untreated and asymptomatic brain metastases; however, during enrolment the protocol was amended (study protocol version 3.0; March 8, 2019) to prohibit inclusion of patients with active brain metastases, as per the US Food and Drug Administration guidelines.[21] All patients provided written informed consent. Full eligibility criteria are shown in the protocol (appendix p 13). The protocol was approved by independent ethics committees or institutional review boards at each site. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomisation and masking

Patients were randomly assigned (2:1) to receive trastuzumab deruxtecan or treatment of physician's choice using block randomisation with a block size of 3. Randomisation was done by an independent biostatistician with an interactive web-based system and was stratified by hormone receptor status (positive or negative), previous pertuzumab treatment (yes or no), and history of visceral disease (yes or no). Patients and investigators remained unmasked to treatment because of the different routes of administration, treatment schedules, and adverse event profiles between treatment groups.

Procedures

Trastuzumab deruxtecan was administered intravenously at 5·4 mg/kg once every 3 weeks. Treatment of physician's choice was either capecitabine (1250 mg/m²; orally twice per day on days 1–14) plus trastuzumab (8 mg/kg intravenously on day 1 then 6 mg/kg once per day) or capecitabine (1000 mg/m²) plus lapatinib (1250 mg orally once per day on days 1–21), with a 21-day schedule for each treatment. Two dose reductions were permitted for patients receiving trastuzumab deruxtecan. When toxic effects recurred after two dose reductions, the patient was withdrawn from study treatment. Based on investigator's judgment, when clinically indicated, patients were allowed to discontinue one physician's choice treatment (either capecitabine or trastuzumab or lapatinib) and remain on the other. Study treatment was administered until radiographic progressive disease (as per modified Response Evaluation Criteria for Solid Tumours [mRECIST]; version 1.1),[22] clinical progression (with definitive clinical signs of progressive disease, but a recent radiographic assessment did not meet criteria for progressive disease as per mRECIST; version 1.1), an adverse event, patient withdrawal from treatment, loss to follow-up, protocol deviation, physician decision, or death. A follow-up visit was performed at 40 days (plus 7 days) after the last treatment administration or before starting a new anticancer therapy, whichever occurred first. Long-term follow-up occurred every 3 months from the 40-day follow-up visit until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurred first. Additional details on the assessments performed at each visit are provided in the study protocol (appendix p 13).

Outcomes

The primary endpoint was progression-free survival (defined as the time from randomisation to the first objective documentation of radiographic disease progression by blinded independent central review per mRECIST or death due to any cause) measured in the full analysis set.

The key secondary endpoint was overall survival (defined as the time from randomisation to death due to any cause). Other secondary efficacy endpoints were measured in the full analysis set and included confirmed

See Online for appendix

objective response rates (defined as the proportion of patients who reached a best overall response of complete response or partial response) by blinded independent central review and by investigator assessment, duration of response (defined as the time from the first documentation of objective response to the first documentation of disease progression) by blinded independent central review, and progression-free survival based on investigator assessment (defined as the time from randomisation to the first objective documentation of radiographic disease progression as assessed by the investigator per mRECIST or death due to any cause).

Prespecified exploratory efficacy endpoints were time to response (defined as the time from randomisation to the first documentation of objective response based on blinded independent central review), best percentage change in the sum of the diameter of measurable tumours (defined as the change in percentage from baseline to the best [minimum] post-baseline sum of the diameters of target lesions), and clinical benefit rate (defined as the sum of complete response rate, partial response rate, and stable disease for more than 6 months) by blinded independent central review; and progression-free survival on the next line of therapy (progression-free survival 2; defined as time from randomisation to first progression on the next line of therapy or death due to any cause, whichever occurred first) based on investigator assessment. Prespecified subgroup analyses for progression-free survival were performed for age (<65 or ≥65 years), hormone receptor status (positive or negative), previous pertuzumab treatment (yes or no), history of visceral disease (yes or no), baseline brain metastases (yes or no), previous lines of therapy (less than three or three or more), and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1).

Safety endpoints included serious adverse events, treatment-emergent adverse events and those associated with treatment discontinuation, dose reduction and dose interruption, adverse events of special interest (interstitial lung disease or pneumonitis and left ventricular dysfunction), physical examination findings, vital sign measurements, standard clinical laboratory parameters, electrocardiogram parameters, echocardiogram or multi-gated acquisition scan findings, and antidrug antibodies. All adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

The planned sample size was 600 patients. Median progression-free survival was hypothesised as 4·7 months in the trastuzumab deruxtecan group and 3·3 months in the treatment of physician's choice group based on the TH3RESA trial,[10] in which the median progression-free survival for the treatment of physician's choice was 3·3 months (hazard ratio [HR] 0·5; a clinically relevant improvement with trastuzumab emtansine [progression-free survival 6·2 months]). Assuming a true HR of 0·7, the primary analysis was planned when approximately 372 progression-free survival events were observed by blinded independent central review, to achieve 90% power at a two-sided 5% significance level to reject the null hypothesis. Because the accrual rate of these events was lower than projected, the protocol was amended for the primary analysis to occur when approximately 372 progression-free survival events were observed or 18 months from when the last patient was randomly assigned, whichever occurred first. Median overall survival was hypothesised to be 20 months in the trastuzumab deruxtecan group and 15 months in the treatment of physician's choice group. Assuming a true HR of 0·75, a total of 434 overall survival events would be needed to achieve 80% power at a two-sided 5% significance level to reject the null hypothesis. The final sample size was established based on overall survival analysis.

The primary endpoint and key secondary endpoint were tested hierarchically, such that overall survival was only tested when progression-free survival was statistically significant (two-sided α 0·05). A stratified log-rank test was used to compare progression-free survival and overall survival between treatment groups. Group sequential testing with two overall survival interim analyses was planned, with the first at the time of progression-free survival primary analysis and the second when approximately 304 (information fraction of 70%) overall survival events have been observed. The final analysis will occur at approximately 434 overall survival events if neither interim analysis is significant. The two-sided α is set at 0·05 for all overall survival analyses using the Lan-DeMets implementation of O'Brien-Fleming α spending function with 3 looks and the boundary for statistical significance was p=0·0040 with 229 overall survival events. HRs and corresponding 95% CIs were estimated using a stratified Cox proportional hazards regression model. Log-rank analyses and Cox proportional hazards were stratified using the randomisation strata.

Efficacy analyses and other exploratory analyses were performed in the full analysis set (defined as all patients randomly assigned to the study, including those who did not receive a dose of study treatment). Safety analyses were performed in the safety analysis set (defined as patients who received at least one dose of study treatment). The per protocol set was defined as all patients in the full analysis set who complied with the protocol in terms of exposure to study treatment, availability of tumour assessments, and absence of major protocol deviations likely to affect efficacy outcomes. Sensitivity analyses of the primary endpoint were performed on the per protocol analysis set.

Exposure-adjusted incidence rates were calculated as the ratio of patients with at least one incidence of the adverse event divided by total patient-years of exposure and were recorded for any-grade treatment-emergent

adverse events and grade 3 or higher treatment-emergent adverse events. Patient-years of exposure was the total treatment duration of all patients within each treatment group, with year used as the denominator for the exposure-adjusted incidence rate. For the treatment of physician's choice group, the longest treatment duration among the two combination drugs was used to calculate patient-years of exposure. All potential cases of interstitial lung disease or pneumonitis were assessed by an independent adjudication committee and suspected cases were managed according to protocol-specified management guidelines. East (version 6.4) software was used to determine the sample size calculation. All statistical analyses were performed using SAS (version 9.3 or higher). Median duration of follow-up was defined as the study duration equal to the date last known alive minus the date of randomisation plus 1. This study is registered with ClinicalTrials.gov, NCT03523585.

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 6, 2018, and Dec 31, 2020, 816 patients with HER2-positive metastatic breast cancer were screened and 608 were randomly assigned to receive either trastuzumab deruxtecan (n=406) or treatment of physician's choice (n=202; figure 1). Two (<1%) patients did not receive trastuzumab deruxtecan and seven (3%) did not receive treatment of physician's choice. 608 (100%) patients were included in the full analysis set.

Baseline patient characteristics are shown in the table. The median age was 54·2 years (IQR 45·5–63·4) in the trastuzumab deruxtecan group and 54·7 years (48·0–63·0) in the treatment of physician's choice group. Most patients were White (384 [63%] of 608). 603 (99%) patients were female and five (<1%) were male. A similar proportion of patients had positive hormone receptor status (238 [59%] of 406 in the trastuzumab deruxtecan group *vs* 118 [58%] of 202 in the treatment of physician's choice group). Most patients received previous pertuzumab treatment (318 [78%] *vs* 156 [77%]). Visceral disease was reported in 316 (78%) patients in the trastuzumab deruxtecan group versus 160 (79%) in the treatment of physician's choice group and brain metastases at baseline occurred in 74 (18%) versus 36 (18%) patients. De novo metastatic breast cancer (stage IV at initial diagnosis) occurred in 139 (34%) patients in the trastuzumab deruxtecan group and 49 (24%) in the treatment of physician's choice group and the median time from initial diagnosis to study treatment was 53·7 months (IQR 29·4–88·6) versus 54·9 months (30·6–87·5). Patients in both treatment groups had a median of two (IQR two to three) lines of previous systemic therapy (excluding hormone therapy) in the metastatic or locally advanced setting.

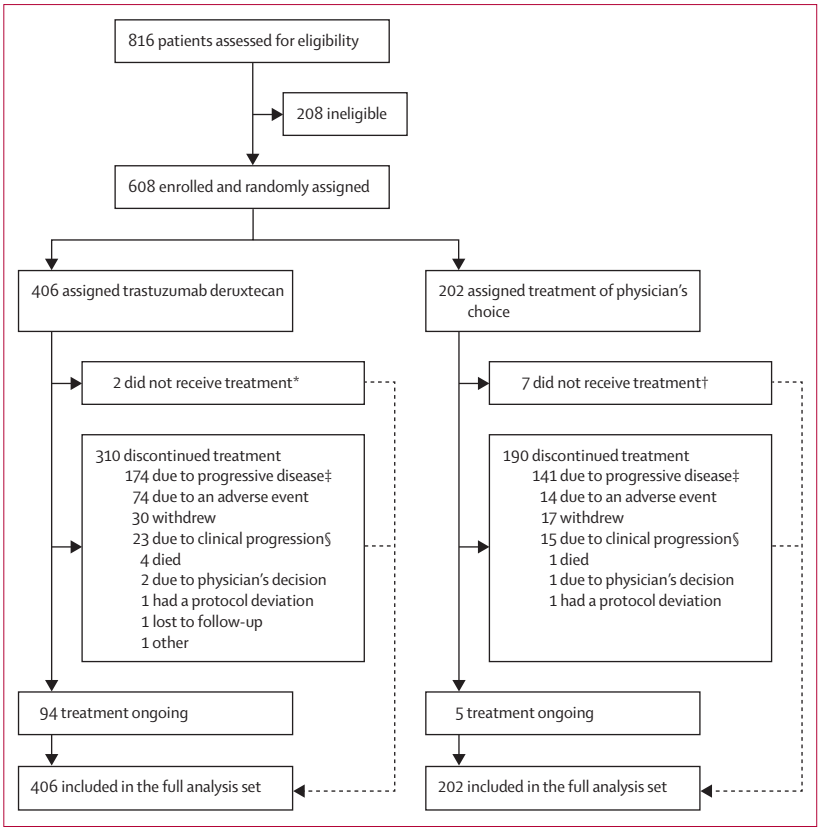

Figure 1: **Trial profile**
mRECIST=modified Response Evaluation Criteria in Solid Tumours. *One patient with grade 2 lung disease and one with grade 3 lung infection, which precluded initiation of study treatment. †Seven patients withdrew consent after random assignment. ‡As per mRECIST. §Clinical signs of progressive disease, but a recent radiographic assessment did not meet criteria for progressive disease as per mRECIST.

As of June 30, 2022 (data cutoff; 18 months from the time the last patient was randomly assigned), 94 (23%) of 404 patients in the trastuzumab deruxtecan group and five (3%) of 195 in the physician's choice group remained on treatment. 310 (77%) patients discontinued trastuzumab deruxtecan, with four (1%) due to death, and 190 (97%) discontinued treatment of physician's choice, with one (<1%) due to death (figure 1). In the trastuzumab deruxtecan group, the causes of death were trastuzumab deruxtecan-related interstitial lung disease (n=1), disease progression (n=1), cerebral oedema (not related to treatment; n=1), and haemorrhage (not related to treatment; n=1). In the treatment of physician's choice group, the cause of death was disease progression (n=1). The main reasons for discontinuation included progressive disease (174 [43%] in the trastuzumab deruxtecan group *vs* 141 [72%] patients in the treatment of physician's choice group), adverse events (74 [18%] *vs* 14 [7%]; drug-related or non-drug related), patient withdrawal (30 [7%] *vs* 17 [9%]), and clinical progression (23 [6%] *vs* 15 [8%]). The median follow-up was 21·5 months (IQR 15·2–28·4) in the trastuzumab deruxtecan group and 18·6 months

	Trastuzumab deruxtecan (n=406)*	Treatment of physician's choice (n=202)
Median age, years	54·2 (45·5–63·4)	54·7 (48·0–63·0)
<65	321 (79%)	164 (81%)
≥65	85 (21%)	38 (19%)
Sex		
Female	403 (99%)	200 (99%)
Male	3 (<1%)	2 (<1%)
Race		
White	257 (63%)	127 (63%)
Black or African American	10 (2%)	7 (3%)
Asian	122 (30%)	56 (28%)
American Indian or Alaskan Native	2 (<1%)	0
Native Hawaiian or Pacific Islander	0	1 (<1%)
Other	15 (4%)	11 (5%)
Region		
Asia	112 (28%)	52 (26%)
Europe	152 (37%)	78 (39%)
North America	41 (10%)	23 (11%)
Australia, Brazil, Israel, and Türkiye	101 (25%)	49 (24%)
HER2 status (immunohistochemistry)†		
3+	326 (80%)	159 (79%)
2+ (in situ hybridisation positive)	79 (20%)	41 (20%)
2+ (in situ hybridisation negative or non-evaluable)	1 (<1%)	1 (<1%)
1+ (in situ hybridisation positive)	0	1 (<1%)
Eastern Cooperative Oncology Group performance status		
0	228 (56%)	121 (60%)
1	177 (44%)	81 (40%)
2	1 (<1%)	0
Hormone receptor status‡		
Positive	238 (59%)	118 (58%)
Negative	165 (41%)	83 (41%)
Visceral disease	316 (78%)	160 (79%)
Brain metastases§	74 (18%)	36 (18%)
Any previous systemic cancer therapy		
Trastuzumab	404 (>99%)	202 (100%)
Trastuzumab emtansine	404 (>99%)	202 (100%)
Taxane	386 (95%)	197 (98%)
Pertuzumab	318 (78%)	156 (77%)
Other systemic therapy	289 (71%)	157 (78%)
Anti-HER2 tyrosine kinase inhibitor	26 (6%)	17 (8%)
Other anti-HER2 therapy (except HER2 tyrosine kinase inhibitor)	11 (3%)	6 (3%)
Hormone therapy	164 (40%)	87 (43%)
Lines of previous systemic therapy in the metastatic setting¶		
0	2 (<1%)	0
1	18 (4%)	12 (6%)
2	192 (47%)	92 (46%)
3	123 (30%)	63 (31%)
4	42 (10%)	13 (6%)
≥5	29 (7%)	22 (11%)
Median number of lines	2 (2–3)	2 (2–3)

Data are median (IQR) or n (%). *Two patients were randomly assigned to receive trastuzumab deruxtecan, but were not treated. †Only samples with HER2 immunohistochemistry 2+ were tested by HER2 gene amplification (in situ hybridisation), except for one with immunohistochemistry 1+. ‡For three (<1%) patients in the trastuzumab deruxtecan group and one (<1%) in the treatment of physician's choice group we could not determine the hormone receptor status based on factors reported from electronic data capture. §Patients with clinically inactive or treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants might also be included. ¶Excluding hormone therapy but including regimens indicated for advanced or metastatic disease or rapid progression within 6 months of (neo) adjuvant therapy (12 months for pertuzumab).

Table: **Baseline patient characteristics**

(8·8–26·0) in the treatment of physician's choice group.

Median progression-free survival by blinded independent central review was 17·8 months (95% CI 14·3–20·8) in the trastuzumab deruxtecan group versus 6·9 months (5·5–8·4) in the treatment of physician's choice group (HR 0·36 [0·28–0·45]; p<0·0001; figure 2A). At 12 months, the proportion of patients who were alive without disease progression was 62·3% (57·0–67·1) with trastuzumab deruxtecan versus 27·2% (20·1–34·8) with treatment of physician's choice; whereas at 24 months, 42·2% (36·5–47·8) versus 13·9% (7·9–21·6) were alive without disease progression. Prespecified subgroup analyses showed consistent benefit in progression-free survival as assessed by blinded independent central review with trastuzumab deruxtecan over treatment of physician's choice in all subgroups, regardless of hormone receptor status, previous treatment with pertuzumab, history of visceral disease, and brain metastases at baseline (figure 2B).

The median overall survival was 39·2 months (95% CI 32·7–NE) in the trastuzumab deruxtecan group versus 26·5 months (21·0–NE) in the treatment of physician's choice group (HR 0·66 [0·50–0·86]; p=0·0021; figure 3). The difference in overall survival between the treatment groups crossed the boundary for statistical significance, which was 0·0040 at this analysis. The proportion of patients alive at 12 months was 89·4% (85·9–92·1) with trastuzumab deruxtecan versus 74·7% (67·6–80·4) with treatment of physician's choice; whereas at 24 months, the corresponding percentages were 65·9% (60·7–70·7) versus 54·3% (46·3–61·6).

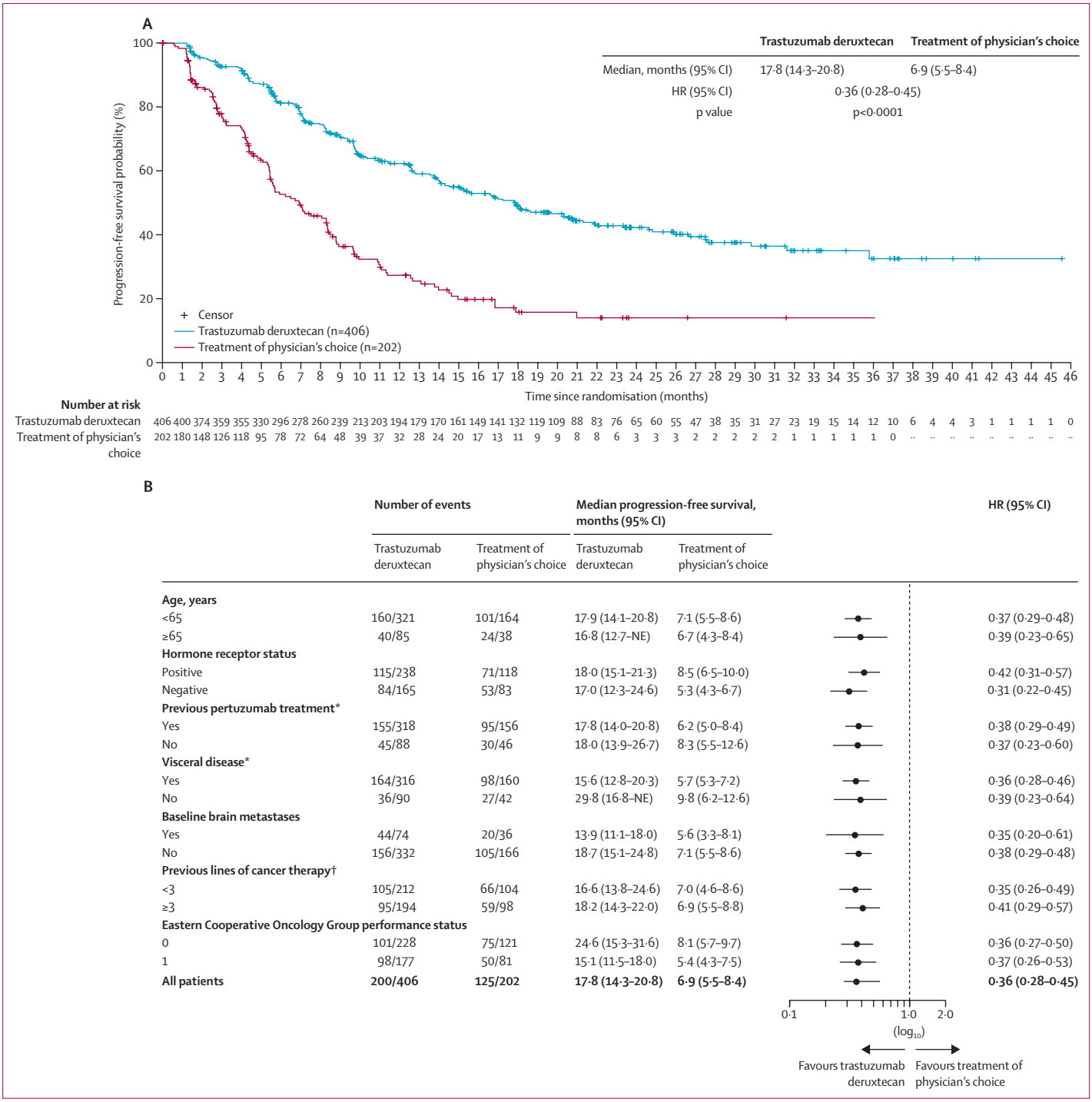

Figure 2: **Kaplan-Meier curves of progression-free survival**
Progression-free survival (A) and subgroup analysis of progression-free survival (B) by blinded independent central review. HR=hazard ratio. NE=not estimable. *Subgroup values derived from baseline. †Excluding hormone therapy.

Confirmed objective responses by blinded independent central review were observed in 283 (70%) of 406 patients in the trastuzumab deruxtecan group versus 59 (29%) of 202 patients in the treatment of physician's choice group (figure 4; appendix p 2). 57 (14%) patients in the trastuzumab deruxtecan group versus ten (5%) in the treatment of physician's choice group reached a complete response and 226 (56%) versus 49 (24%) reached a partial

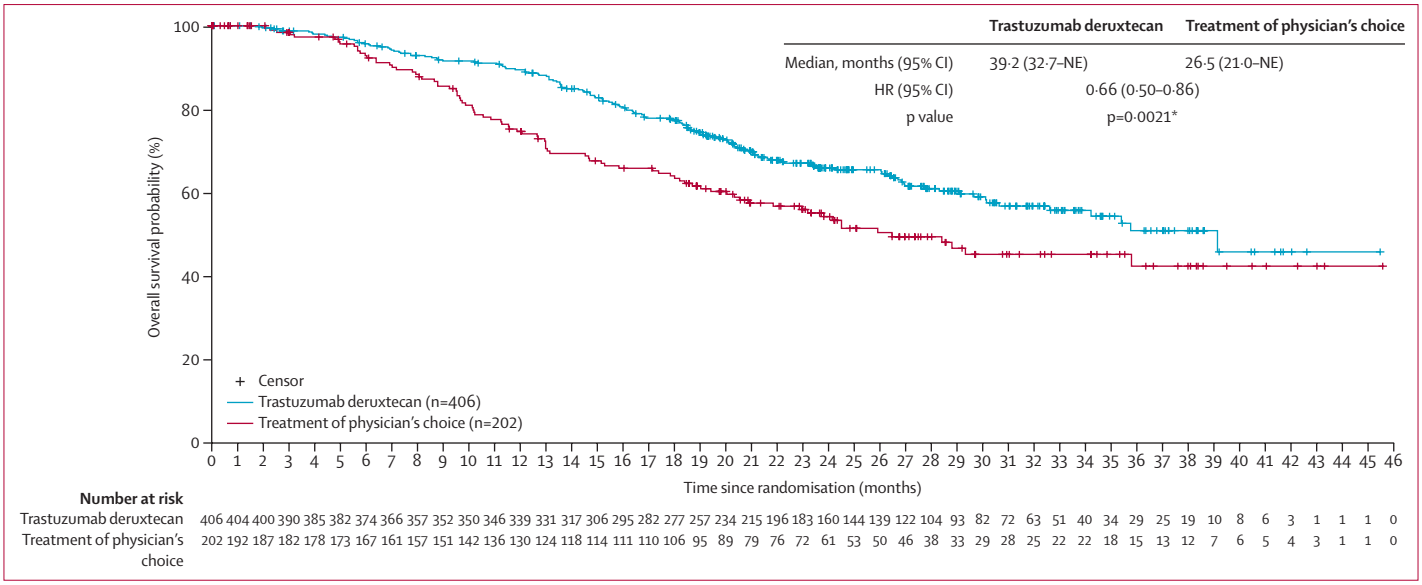

Figure 3: **Kaplan-Meier curves of overall survival**
NE=not estimable. *Boundary for statistical significance is p=0·0040.

response. Progressive disease as best response was observed in 19 (5%) patients in the trastuzumab deruxtecan group and 26 (13%) in the treatment of physician's choice group. Investigator-assessed objective responses in both treatment groups were similar to the responses assessed by blinded independent central review (appendix p 2). The median duration of response was 19·6 months (95% CI 15·9–NE) with trastuzumab deruxtecan and 8·3 months (5·8–9·5) with treatment of physician's choice. Median progression-free survival by investigator assessment was 16·7 months (14·3–19·6) with trastuzumab deruxtecan versus 5·5 months (4·4–7·0) with treatment of physician's choice (HR 0·28 [0·23–0·35]; p<0·0001; appendix pp 2, 11). Progression-free survival data in the per protocol analysis set was consistent with the full analysis set (appendix p 4).

For the exploratory efficacy endpoints, the 6-month clinical benefit rate was 82% (95% CI 78–86; 334 of 406 patients) with trastuzumab deruxtecan and 46% (39–53; 93 of 202) with treatment of physician's choice (appendix p 2) and median progression-free survival 2 was 35·8 months (28·4–NE) versus 15·8 months (13·5–21·0; HR 0·45 [0·34–0·59]). Of patients who discontinued study treatment, 220 (71%) of 310 in the trastuzumab deruxtecan group and 140 (74%) of 190 in the treatment of physician's choice group received subsequent systemic cancer treatment after the trial (appendix p 5). The systemic cancer treatment in the trastuzumab deruxtecan group included trastuzumab (126 [41%] of 310), trastuzumab deruxtecan (18 [6%]), trastuzumab emtansine (three [<1%]), anti-HER2 tyrosine kinase inhibitors (124 [40%]), and other systemic therapies (188 [61%]). In the treatment of physician's choice group, 94 (49%) of 190 patients received trastuzumab, 52 (27%) received trastuzumab deruxtecan, five (3%) received trastuzumab emtansine, 42 (22%) received anti-HER2 tyrosine kinase inhibitors, and 107 (56%) received other systemic therapies after discontinuing study treatment (appendix p 5).

Median duration of treatment was 11·3 months (IQR 6·2–20·5) with trastuzumab deruxtecan and approximately 4·5 months with treatment of physician's choice (4·4 months [2·5–8·7] with trastuzumab, 4·6 months [2·1–8·9] with capecitabine, and 4·5 months [2·1–10·6] with lapatinib). Any-grade treatment-emergent adverse events occurred in 403 (>99%) of 404 patients receiving trastuzumab deruxtecan versus 185 (95%) of 195 receiving treatment of physician's choice, with grade 3 or higher treatment-emergent adverse events reported in 213 (53%) versus 86 (44%) patients (appendix p 6). Drug-related treatment-emergent adverse events were reported in 394 (98%) patients who received trastuzumab deruxtecan, with 167 (41%) having grade 3 or higher drug-related events. Exposure-adjusted incidence rates were lower in patients who received trastuzumab deruxtecan than in those who received treatment of physician's choice in terms of treatment-emergent adverse events of any-grade (0·85 *vs* 1·66) and grade 3 or higher (0·45 *vs* 0·77).

Drug-related treatment-emergent adverse events associated with drug discontinuation occurred in 58 (14%) of 404 patients receiving trastuzumab deruxtecan and ten (5%) of 195 receiving treatment of physician's choice. The most common treatment-emergent adverse events associated with drug discontinuation were pneumonitis (25 [6%]) and interstitial lung disease (15 [4%]) with trastuzumab deruxtecan and palmar–plantar erythrodysaesthesia (three [2%]) with treatment of physician's choice. Drug-related treatment-emergent

adverse events associated with drug interruption occurred in 132 (33%) patients who received trastuzumab deruxtecan versus 76 (39%) who received treatment of physician's choice; whereas those associated with dose reduction occurred in 95 (24%) versus 89 (46%). Drug-related treatment-emergent adverse events associated with death were reported in four (<1%) patients in the trastuzumab deruxtecan group (two had pneumonitis, one had acute myeloid leukaemia, and one had pneumonia) and none in the treatment of physician's choice group (appendix p 6).

The most common any-grade treatment-emergent adverse events (≥15% of patients in either treatment group) were nausea (293 [73%] of 404 with trastuzumab deruxtecan *vs* 73 [37%] of 195 with treatment of physician's choice), vomiting (152 [38%] *vs* 25 [13%]), alopecia (150 [37%] *vs* eight [4%]), fatigue (147 [36%] *vs* 52 [27%]), diarrhoea (109 [27%] *vs* 105 [54%]), and palmar–plantar erythrodysaesthesia (seven [2%] *vs* 100 [51%]; appendix p 7). The most common grade 3 or higher treatment-emergent adverse events were neutrophil count decreased (43 [11%] with trastuzumab deruxtecan *vs* four [2%] with treatment of physician's choice), anaemia (32 [8%] *vs* six [3%]), neutropenia (31 [8%] *vs* four [2%]), nausea (27 [7%] *vs* five [3%]), palmar–plantar erythrodysaesthesia (one [<1%] *vs* 20 [10%]), and diarrhoea (11 [3%] *vs* 14 [7%]). The most common treatment-emergent adverse events by worst toxicity grade are shown in the appendix (p 8). At the time of study initiation, antiemetic agents were not recommended; however, the protocol was later amended (version 5; April 23, 2020) to include recommendations for prophylactic antiemetic treatment before patients received trastuzumab deruxtecan. 292 (72%) patients in the trastuzumab deruxtecan group and 60 (31%) in the treatment of physician's choice group received antiemetics during study treatment. In the trastuzumab deruxtecan group, 79 (20%) had more than two episodes of nausea versus two (<1%) in the treatment of physician's choice group, and 30 (7%) had more than two episodes of vomiting versus one (<1%).

Drug-related interstitial lung disease, as adjudicated by an independent committee, occurred in 42 (10%) patients receiving trastuzumab deruxtecan (11 with grade 1 events, 26 with grade 2 events, three with grade 3 events, and two with grade 5 death events) and in one (<1%; grade 3) receiving treatment of physician's choice (appendix p 10). Median time to onset of adjudicated drug-related interstitial lung disease was 29·9 weeks (IQR 12·3–48·0) with trastuzumab deruxtecan and 2·9 weeks with treatment of physician's choice.

Left ventricular dysfunction was reported in 18 (4%) patients who received trastuzumab deruxtecan (17 ejection fraction decreased [two with grade 3] and one had left ventricular dysfunction [grade 1]) and in three (2%) who received treatment of physician's choice (one ejection fraction decreased [grade 1] and two had cardiac failure [one with grade 3]). Treatment was discontinued due to left ventricular dysfunction in two (<1%) patients in the trastuzumab deruxtecan group and one (<1%) in the treatment of physician's choice group.

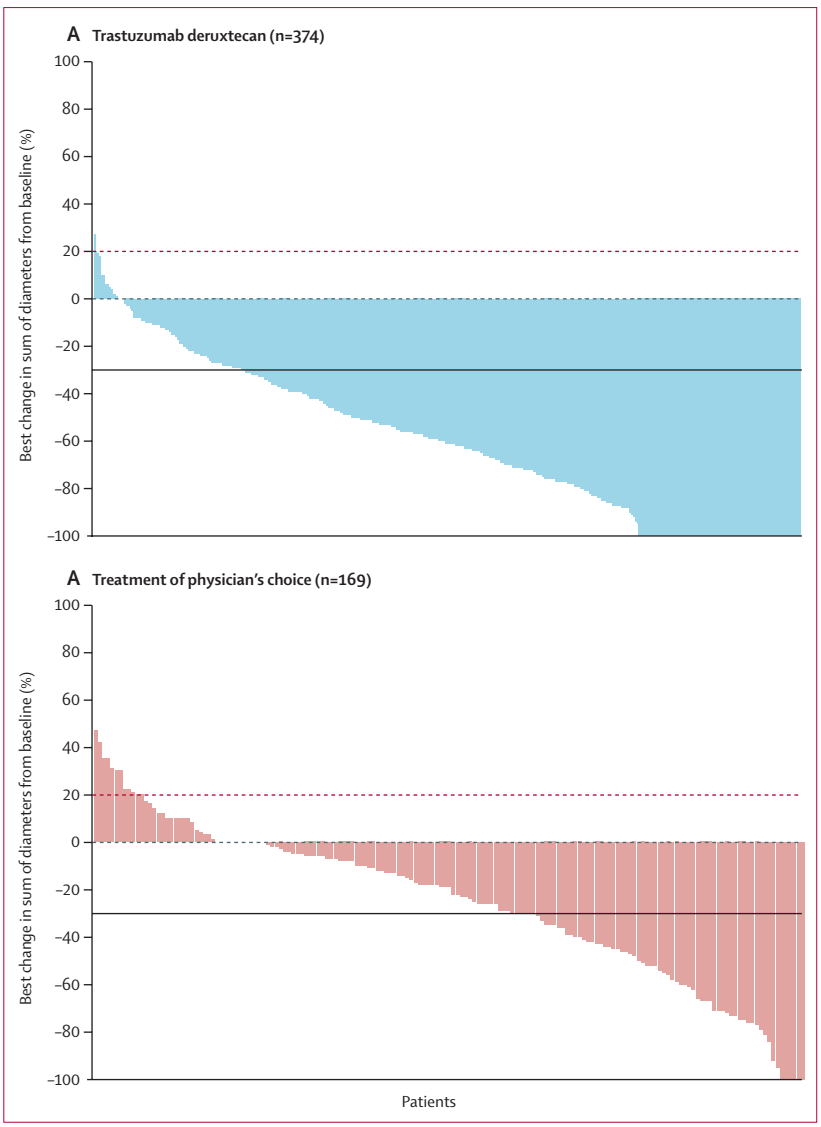

Figure 4: **Antitumour activity of trastuzumab deruxtecan (A) and treatment of physician's choice (B)**
Baseline was defined as the last measurement taken before the randomisation date. For each patient, the best (minimum) percentage change from baseline in the sum of diameters for all target lesions was represented by a vertical line, plotted in order of greatest percentage increase to greatest percentage decrease. Only patients with measurable disease at baseline and at least one post-baseline assessment were included in the waterfall plots. The red line at 20% indicates progressive disease, and the black line at –30% indicates a partial response.

Discussion

Patients with HER2-positive metastatic breast cancer refractory or resistant to trastuzumab emtansine have scarce treatment options. At 18 months from random assignment of the last patient, we observed a 10·9-month improvement in median progression-free survival (by blinded independent central review) with trastuzumab deruxtecan compared with treatment of physician's choice. Overall efficacy results in the treatment of physician's choice group were consistent with or better than those

observed in previous studies that used similar chemotherapy regimens,[10–12,23,24] whereas the longer progression-free survival with trastuzumab deruxtecan was a statistically significant and clinically meaningful improvement versus treatment of physician's choice. Consistent progression-free survival benefit with trastuzumab deruxtecan versus treatment of physician's choice was shown across all prespecified subgroups, including by randomisation stratification factors (hormone receptor status, previous treatment with pertuzumab, and history of visceral disease) and presence of baseline brain metastases. Progression-free survival assessed by blinded independent central review and by investigators for trastuzumab deruxtecan versus treatment of physician's choice were consistent in our study, confirming the adequate assessment of tumour response by investigators.

The improvement in overall survival was also statistically significant and clinically meaningful with trastuzumab deruxtecan and showed a HR of 0·66 in the risk of death compared with treatment of physician's choice. Overall survival curves diverged early around 6 months, with a 14·7% absolute improvement at 12 months. An improvement of 12·7 months was seen in median overall survival with trastuzumab deruxtecan compared with treatment of physician's choice. Approximately 27% of patients in the treatment of physician's choice group who discontinued study treatment went on to receive trastuzumab deruxtecan after the trial, which probably contributed to the median overall survival showed by treatment of physician's choice. Future analyses with longer follow-up should explore overall survival benefit across patient subgroups.

Confirmed objective response rates were substantially higher with trastuzumab deruxtecan than with treatment of physician's choice and the median duration of response was considerably longer. 14% of patients who received trastuzumab deruxtecan had a complete response as best response compared with 5% who received treatment of physician's choice. Fewer patients discontinued treatment in the trastuzumab deruxtecan group than in the treatment of physician's choice group (77% *vs* 97%), with 23% versus 3% of patients remaining on treatment at the primary analysis; most discontinuations were related to progressive disease. In total, more patients discontinued treatment with trastuzumab deruxtecan due to adverse events (18% *vs* 7% with treatment of physician's choice) and patient withdrawal (7% *vs* 9%). Further analyses of treatment outcomes in this population might be warranted. Overall, patients who received trastuzumab deruxtecan remained on treatment longer, had higher objective response rates, and longer duration of response, progression-free survival, and overall survival compared with those who received treatment of physician's choice. Disease progression or death on the next line of therapy after study treatment (progression-free survival 2) strongly favoured the trastuzumab deruxtecan group, and future analyses will provide more clarity due to low progression-free survival 2 data maturity in this analysis.

Acknowledging that cross-trial comparisons should be interpreted with caution, the clinical efficacy outcomes seen with trastuzumab deruxtecan in DESTINY-Breast02 were numerically greater than those observed with current treatment options for patients with HER2-positive metastatic breast cancer who have progressed after two or more anti-HER2 therapies. Median progression-free survival with other HER2-targeted therapies (such as trastuzumab emtansine [TH3RESA trial], margetuximab [SOPHIA trial], tucatinib [HER2CLIMB trial], and neratinib [NALA trial])[10–12,23,24] previously ranged from 5·6 to 7·8 months in this setting; whereas median overall survival ranged from 21·0 to 22·7 months and objective response rates ranged from 22·0% to 40·6%.

The overall safety profile of trastuzumab deruxtecan in this study was consistent with the established safety of this drug, with no new safety signals observed.[17,25,26] Although the rate of drug-related and non-drug-related treatment-emergent adverse events were similar between treatment groups, treatment-emergent adverse events associated with drug discontinuation were higher with trastuzumab deruxtecan than with treatment of physician's choice (14% *vs* 5%). Exposure-adjusted incidence rates, which account for differences in median treatment duration between treatment groups, in terms of any-grade and grade 3 or higher treatment-emergent adverse events were lower with trastuzumab deruxtecan than treatment of physician's choice. Patient-reported outcomes are being evaluated for DESTINY-Breast02 to measure the effect of treatment with trastuzumab deruxtecan versus treatment of physician's choice on the quality of life.

The most common any-grade treatment-emergent adverse events reported among patients in the trastuzumab deruxtecan group were gastrointestinal in nature. In both treatment groups a substantial number of patients received antiemetics, which might have reduced the frequency of recurrent nausea and vomiting events. However, given that 20% of patients in the trastuzumab deruxtecan group still had two or more episodes of nausea and 7% had two or more episodes of vomiting, earlier antiemetic prophylaxis with trastuzumab deruxtecan treatment might further reduce the occurrence of these treatment-emergent adverse events.

Interstitial lung disease is an important risk associated with trastuzumab deruxtecan treatment.[25,26] In our study, the median time to onset of adjudicated drug-related interstitial lung disease was 29·9 weeks. The incidence of adjudicated drug-related grade 5 interstitial lung disease was lower in DESTINY-Breast02 compared with DESTINY-Breast01 (two [<1%] *vs* five [3%] patients), and there were no grade 4 events in either study.[17,18] Management guidelines for interstitial lung disease or pneumonitis were incorporated during the DESTINY-Breast01 trial[27] and followed up throughout our study. Current management guidelines advise closely

monitoring patients for signs and symptoms of interstitial lung disease or pneumonitis, immediately and actively managing all suspected events with corticosteroids, and delaying or stopping trastuzumab deruxtecan. These revised guidelines might explain the numerically lower rates of grade 5 interstitial lung disease or pneumonitis events observed in DESTINY-Breast02 compared with DESTINY-Breast01. Further research should be supported to explore the mechanisms of interstitial lung disease and better identify and describe the most at-risk patient groups. In our opinion, broad implementation of trastuzumab deruxtecan into routine clinical practice for the treatment of breast cancer should provide additional data of efficacy and safety, including interstitial lung disease or pneumonitis, which can be assessed in large observational studies and real-world data. The retrospective, observational DESTINY-Respond study will investigate real-world data on the efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive and HER2-low metastatic breast cancer, including those with interstitial lung disease or pneumonitis.

Our study included patients with clinically stable, asymptomatic brain metastases (18% in both treatment groups had brain metastases at baseline). This subgroup showed clinically meaningful improvement in progression-free survival with trastuzumab deruxtecan compared with treatment of physician's choice. Future exploratory studies of detailed treatment and survival outcomes in this subgroup of patients with baseline brain metastases are planned.

One limitation of our study was the exclusion of patients with symptomatic or clinically active brain metastases. Another limitation is that the treatment of physician's choice group was restricted to capecitabine plus either trastuzumab or lapatinib, although many combination strategies with other chemotherapy agents and HER2-directed drugs approved within the past few years are now used as later lines of therapy for patients HER2-positive metastatic breast cancer. Capecitabine was chosen because capecitabine-containing regimens are the most prescribed in this setting;[9] however, our results with trastuzumab deruxtecan cannot be directly compared with regimens containing chemotherapy agents other than capecitabine or with other HER2-directed agents.

Before trastuzumab deruxtecan was approved as a second-line treatment option for patients with HER2-positive metastatic breast cancer, trastuzumab emtansine was the guideline-recommended treatment in this setting.[28] Currently, trastuzumab deruxtecan is the recommended second-line treatment for these patients based on efficacy and safety results from DESTINY-Breast03.[25,26]

Results from DESTINY-Breast02 show the favourable benefit–risk profile of trastuzumab deruxtecan in patients with HER2 positive metastatic breast cancer resistant or refractory to trastuzumab emtansine, as previously reported in DESTINY-Breast01, and support this drug as the preferred therapy for patients who received trastuzumab emtansine. To our knowledge, this study is the first randomised trial to show a significant benefit of one antibody-drug conjugate treatment in patients who have progressed on another antibody-drug conjugate, providing an optimistic outlook for sequential antibody-drug conjugate treatments to improve disease outcomes in patients with HER2-positive metastatic breast cancer and other patient populations.

Contributors

FA and IK conceptualised and designed the study, acquired data, and performed quality control. YHP, S-BK, TT, S-AI, GBo, JPL, SA, JGG, MDL, GBi, RR, YM, EK, AA, RS, MRB, EL, JE, RY, FZ, FPD, and TF acquired the data and performed quality control. DG, JC, CW, CC, and AE designed the study, were responsible for oversight, and analysed the data. IK and S-AI have accessed and verified all the data in the study. All authors drafted, revised, and approved the final manuscript and had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

FA reports grants or speaker compensation or advisory board participation for Sanofi, Novartis, Pfizer, Lilly, AstraZeneca, Daiichi Sankyo, and Roche. YHP reports grants from MSD, Pfizer, AstraZeneca, and Roche; consulting fees from AstraZeneca, MSD, Pfizer, Eisai, Lilly, Roche, Bixink, Daiichi Sankyo, Menarini, Everest, and Novartis; honoraria from AstraZeneca, Pfizer, Lilly, MSD, Roche, Daiichi-Sankyo, and Novartis; and advisory board participation for AstraZeneca, Pfizer, Roche, Novartis, and Menarini. S-BK reports grants from Novartis, Sanofi-Aventis, Dongkook Pharmaceutical; payment for expert testimony from Novartis, AstraZeneca, Lilly, Dae Hwa Pharmaceuticals, ISU Abxis, and Daiichi Sankyo; meeting or travel support (or both) from Novartis, AstraZeneca, and Lilly; advisory board participation for Novartis, AstraZeneca, Lilly, and Daiichi Sankyo; and stock in Genopeaks and Neogene Therapeutics. TT reports honoraria for lectures from Daiichi Sankyo, Chugai, Eisai, Eli Lilly, and Celltrion Healthcare. S-AI reports grants from AstraZeneca, Eisai, Daewoong Pharmaceutical, Daiichi Sankyo, Pfizer, Roche, and Boryung Pharmaceutical; and consulting fees from AstraZeneca, Hanmi, Eisai, Lilly, MSD, Idience, Novartis, Pfizer, Roche, GSK, Daiichi Sankyo, and Bertis. JPL reports grants from MSD, Bristol Myers Squibb, Taiho, Janssen, Mink, Agenus, Daiichi Sankyo, AstraZeneca, Roche, and Seagen; payment or honoraria from Bristol Myers Squibb, AstraZeneca, and Daiichi Sankyo; meeting or travel support (or both) from MSD, Bristol Myers Squibb, and AstraZeneca; and stock in Janssen. SA reports honoraria and consulting compensation from AstraZeneca, Bristol Myers Squibb, Lilly, Merck, Novartis, and Pfizer. JGG reports payment or honoraria, meeting or travel support (or both), and advisory board participation for AstraZeneca, Daiichi Sankyo, Novartis, Roche, Lilly, Seagen, and Pfizer. MDL reports payment or honoraria, meeting or travel support (or both), and advisory board participation for AstraZeneca, Eli Lilly, Novartis, Roche, Pfizer, Seagen, Daiichi Sankyo, MSD, GSK, and Sanofi; and payment or honoraria from Celltrion and Organon. FPD reports grants from Fondation Belge Contre le Cancer; consulting fees from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Gilead Sciences, and Seagen; and meeting or travel support (or both) from Amgen, Roche, Teva, Pfizer, Daiichi Sankyo, and AstraZeneca. GBi reports consulting fees from Roche, AstraZeneca, MSD, Daiichi Sankyo, Gilead, Sanofi, and Seagen; payment or honoraria from Roche, AstraZeneca, Daiichi Sankyo, Lilly, MSD, Chugai, Eisai, Gilead, and Seagen; meeting or travel support (or both) from Roche, Pfizer, MSD, Chugai, Novartis, and AstraZeneca; and advisory board participation for Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, MSD, Chugai, Daiichi Sankyo, Eisai, Gilead, Seagen, Exact Science, and Agendia. RR reports grants from National Institute for Health and Care Research; consulting fees from IQVIA, Eli Lilly, G1 Therapeutics, Daiichi Sankyo, and AstraZeneca; payment or honoraria from Daiichi Sankyo and AstraZeneca; meeting or travel support (or both) from G1 Therapeutics, Roche, Daiichi Sankyo, and Bristol Myers Squibb;

and advisory board participation for Pfizer. YM reports grants from Daiichi Sankyo, Eisai, Chugai, MSD, Kyowa-Kirin, Eli Lilly, and Taiho; consulting fees from Daiichi Sankyo; and payment or honoraria from Daiichi Sankyo, Chugai, Eisai, Eli Lilly, AstraZeneca, Pfizer, Taiho, and Kyowa-Kirin. AA reports grants or contracts from AstraZeneca; meeting or travel support (or both) from MSD and Novartis; advisory board participation for MSD; a leadership role for the Royal College of Obstetricians and Gynaecologists Pregnancy and Breast Cancer Guidelines; and stock or stock options with AstraZeneca. EL reports consulting fees from Ellipses; speaker compensation from AstraZeneca, Lilly, Pfizer, Roche, Novartis, and Gilead; meeting or travel support (or both) from AstraZeneca, Novartis, and Gilead; advisory board participation for AstraZeneca, Lilly, Pfizer, Roche, Novartis, Gilead, and Eisai; leadership or fiduciary roles in the Breast Cancer Trials Scientific Advisory Board and University of New South Wales Medicine Faculty Advisory Board; and research support from Novartis and Pfizer. JE reports consulting fees, honoraria, meeting or travel support (or both), and advisory board participation for Daiichi Sankyo, Lilly, Roche, Pfizer, Novartis, Gilead, Seagen, and AstraZeneca. RY reports a research grant from Roche; and consulting fees and honoraria from Roche, Pfizer, Eli Lilly, Novartis, Gilead, Medison, MSD, and AstraZeneca. FZ reports grants, consulting fees, payment or honoraria, advisory board participation for, research support, leadership or fiduciary roles, and stock or stock options in AstraZeneca, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, Genesis Pharmaceuticals, and Roche. TF reports advisory board participation for Daiichi Sankyo, Novartis, Roche, Pfizer, MSD, and Teva Pharmaceuticals. CW was an employee of Daiichi Sankyo during the study. DG, JC, CC, and AE report employment by Daiichi Sankyo. AE reports stock in Daiichi Sankyo. IK reports grants from Pfizer, MacroGenics, Genentech (Roche); consulting fees from AstraZeneca, Daiichi Sankyo, Genentech (Roche), Bristol Myers Squibb, MacroGenics, Taiho Oncology, and Seagen; payment or honoraria from AstraZeneca; advisory board participation for Novartis and Merck; and leadership, fiduciary roles, and stock in Puretech. GBo, RS, and MRB declare no competing interests.

Data sharing

For more on **data requests** see https://vivli.org/

Anonymised individual participant data and supporting clinical study documents are available upon request. In cases where data are provided in accordance with company policies and procedures, Daiichi Sankyo will continue to protect the privacy of the company and clinical study participants. Data sharing criteria and the procedure for requesting access can be found on https://vivli.org/ourmember/daiichi-sankyo/.

Acknowledgments

This study was funded by Daiichi Sankyo and AstraZeneca. We thank the patients and their families for participation and the study site staff for contributions. We also thank Fernando Bergantinos for contribution to the study. Medical writing support was funded by Daiichi Sankyo and provided by Caylin Bosch (ApotheCom, Cape Town, South Africa).

References

1 American Cancer Society. Understanding a breast cancer diagnosis. 2022. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html#written_by (accessed Sept 23, 2022).

2 Grinda T, Antoine A, Jacot W, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open* 2021; **6:** 100114.

3 Wu X, Yang H, Yu X, Qin JJ. Drug-resistant HER2-positive breast cancer: molecular mechanisms and overcoming strategies. *Front Pharmacol* 2022; **13:** 1012552.

4 Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primers* 2019; **5:** 66.

5 Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol* 2019; **30:** 766–73.

6 Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21:** 519–30.

7 Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; **366:** 109–19.

8 Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367:** 1783–91.

9 Tarantino P, Prat A, Cortes J, Cardoso F, Curigliano G. Third-line treatment of HER2-positive advanced breast cancer: from no standard to a Pandora's box. *Biochim Biophys Acta Rev Cancer* 2021; **1875:** 188487.

10 Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15:** 689–99.

11 Rugo HS, Im SA, Cardoso F, et al. Efficacy of margetuximab *vs* trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2021; **7:** 573–84.

12 Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol* 2020; **38:** 3138–49.

13 Yokoe T, Kurozumi S, Nozawa K, et al. Clinical benefit of treatment after trastuzumab emtansine for HER2-positive metastatic breast cancer: a real-world multi-centre cohort study in Japan (WJOG12519B). *Breast Cancer* 2021; **28:** 581–91.

14 Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)* 2019; **67:** 173–85.

15 Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res* 2016; **22:** 5097–108.

16 Doi T, Shitara K, Naito Y, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol* 2017; **18:** 1512–22.

17 Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020; **382:** 610–21.

18 Saura Manich C, Modi S, Krop I, et al. 279P trastuzumab deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer (MBC): updated survival results from a phase II trial (DESTINY-Breast01). *Ann Oncol* 2021; **32** (suppl 5)**:** s485–86 (abstr).

19 Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol* 2018; **36:** 2105–22.

20 Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 2013; **31:** 3997–4013.

21 US Food and Drug Administration. Cancer clinical trial eligibility criteria: brain metastases. 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-brain-metastases (accessed Dec 22, 2022).

22 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

23 Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol* 2017; **18:** 743–54.

24 Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 2020; **382** (suppl)**:** 597–609.

25 Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med* 2022; **386:** 1143–54.

26 Hurvitz SA, Hegg R, Chung WP, 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* 2023; **401:** 105–17.

27 Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. *ESMO Open* 2022; **7:** 100554.

28 Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021; **32:** 1475–95.