Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): patient-reported outcomes from a randomised, open-label, multicentre, phase 3 trial

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Summary

Background In DESTINY-Breast02, patients with HER2-positive unresectable or metastatic breast cancer who received trastuzumab deruxtecan demonstrated superior progression-free and overall survival compared with those receiving treatment of physician's choice. We present the patient-reported outcomes (PROs) and hospitalisation data.

Methods In this randomised, open-label, phase 3 trial conducted at 227 clinical sites globally, enrolled patients had to be aged 18 years or older with HER2-positive unresectable or metastatic breast cancer that had progressed on trastuzumab emtansine and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (2:1) using block randomisation (block size of 3) to receive trastuzumab deruxtecan (5·4 mg/kg intravenously once every 21 days) or treatment of physician's choice by an independent biostatistician using an interactive web-based system. Patients and investigators remained unmasked to treatment. 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, which was progression-free survival based on blinded independent central review, has previously been reported. PROs were assessed in the full analysis set (all patients randomly assigned to the study) using the oncology-specific European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), breast cancer-specific EORTC Quality of Life Questionnaire Breast 45 (QLQ-BR45), and the generic HRQoL EQ-5D-5L questionnaire. Analyses included change from baseline and time to definitive deterioration for PRO variables of interest and hospitalisation-related endpoints. This study is registered with ClinicalTrials.gov, NCT03523585, and is closed to recruitment.

Findings Between Sept 6, 2018, and Dec 31, 2020, 608 patients were randomly assigned to receive either trastuzumab deruxtecan (n=406; two did not receive treatment) or treatment of physician's choice (n=202; seven did not receive treatment). Overall, 603 patients (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 (IQR 8·8–26·0) in the treatment of physician's choice group. Median treatment duration was 11·3 months (IQR 6·2–20·5) in the trastuzumab deruxtecan group and approximately 4·5 months in the treatment of physician's choice group (4·4 months [IQR 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). Baseline EORTC QLQ-C30 global health status (GHS) scores were similar with trastuzumab deruxtecan (n=393) and treatment of physician's choice (n=187), and remained stable with no clinically meaningful change (defined as ≥10-point change from baseline) over time. Median time to definitive deterioration was delayed with trastuzumab deruxtecan compared with treatment of physician's choice for the primary PRO variable EORTC QLQ-C30 GHS (14·1 months [95% CI 10·4–18·7] *vs* 5·9 months [4·3–7·9]; HR 0·5573 [0·4376–0·7099], p<0·0001) and all other prespecified PROs (EORTC QLQ-C30 subscales, EORTC QLQ-BR45 arm and breast symptoms, and EQ-5D-5L visual analogue scale). Patient hospitalisation rates were similar in the trastuzumab deruxtecan (92 [23%] of 406) and treatment of physician's choice (41 [20%] of 202) groups; however, median time to hospitalisation was 133 days (IQR 56–237) with trastuzumab deruxtecan versus 83 days (30–152) with treatment of physician's choice.

Interpretation Overall, GHS and quality of life were maintained for both treatment groups, with prespecified PRO variables favouring trastuzumab deruxtecan over treatment of physician's choice, suggesting that despite a longer treatment duration, there was no detrimental impact on patient health-related quality of life with trastuzumab deruxtecan. When considered with efficacy and safety data from DESTINY-Breast02, these results support the overall benefit of trastuzumab deruxtecan for patients with HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab emtansine.

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Introduction

About 15–20% of breast cancers are characterised by overexpression of HER2 and are categorised as HER2-positive (immunohistochemistry score of 3+, or an immunohistochemistry score of 2+ and in-situ hybridisation-positive).[1–5] HER2-positive breast cancer is an aggressive subtype associated with disease progression and poor prognosis in the advanced metastatic setting, with treatment options following trastuzumab emtansine having low efficacy;[5,6] as a result, a high unmet medical need exists in this patient population.

Trastuzumab deruxtecan is a HER2-directed antibody–drug conjugate approved for patients with HER2-positive metastatic breast cancer who have received a previous anti-HER2 antibody-based regimen for metastatic disease or in the neoadjuvant or adjuvant setting, having replaced trastuzumab emtansine as the preferred second-line therapy in this patient population.[6,7] In the phase 3 DESTINY-Breast02 trial, trastuzumab deruxtecan demonstrated significant improvement compared with treatment of physician's choice (ie, capecitabine plus trastuzumab or capecitabine plus lapatinib) in median progression-free survival (17·8 months [95% CI 14·3–20·8] *vs* 6·9 months [5·5–8·4]; hazard ratio [HR] 0·36 [0·28–0·45]; p<0·0001) and median overall survival (39·2 months [32·7–not estimable] *vs* 26·5 months [21·0–not estimable]; HR 0·66 [0·50–0·86]; p=0·0021) in patients with trastuzumab emtansine-resistant HER2-positive metastatic breast cancer.[8] The overall safety profile of trastuzumab deruxtecan was consistent with that already established, with no new safety signals observed; adjudicated drug-related interstitial lung disease occurred in 42 (10%) of 404 patients (two patients with grade 5 events) in the trastuzumab deruxtecan group and one (<1%) of 195 patients (grade 3 event) in the treatment of physician's choice group.[8] After a median treatment duration of 11·3 months with trastuzumab deruxtecan (IQR 6·2–20·5) 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), 167 (41%) of 404 patients in the trastuzumab deruxtecan group and 60 (31%) of 195 patients in the treatment of physician's choice group had drug-related grade 3 or higher treatment-emergent adverse events; 46 (11%) patients in the trastuzumab deruxtecan group and 15 (8%) patients in the treatment of physician's choice group had serious drug-related treatment-emergent adverse events.[8]

Patient-reported outcomes (PROs) are important additional measures that enable comprehensive assessment of the impact of treatment on patients' health-related quality of life (HRQoL) and can be

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2003, and June 30, 2023, using the terms ("PROs" OR "patient-reported outcomes" OR "HRQoL") AND ("HER2-positive breast cancer" OR "metastatic breast cancer" OR "capecitabine" OR "trastuzumab" OR "lapatinib") to identify articles that describe patient-reported outcomes (PROs) for HER2-targeted therapies used in the metastatic breast cancer setting. The search revealed several articles describing health-related quality of life (HRQoL) in patients with breast cancer. Most of these studies assessed PROs through the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30) questionnaire and the breast cancer-specific (QLQ-BR23) questionnaire. Pain, physical functioning, gastric symptoms (eg, constipation or appetite loss), and insomnia were often reported as the most severe symptoms, although most studies showed no statistically significant differences in symptoms between comparator therapies. However, there were few studies published specifically about patients with HER2-positive breast cancer (a subgroup historically associated with poorer prognosis and less favourable outcomes than other breast cancer subgroups).

Added value of this study

DESTINY-Breast02 was a phase 3 trial that was conducted to investigate the antibody–drug conjugate trastuzumab deruxtecan versus treatment of physician's choice (capecitabine in combination with either trastuzumab or lapatinib) as third-line therapy in patients with HER2-positive metastatic breast cancer whose disease had progressed on trastuzumab emtansine. To our knowledge, DESTINY-Breast02 was the first phase 3 trial investigating a HER2-targeting therapy in patients who were resistant or refractory to trastuzumab emtansine. Our study reports PROs from DESTINY-Breast02 and provides insight into patient HRQoL on trastuzumab deruxtecan, which is currently approved for patients with HER2-positive metastatic breast cancer who have received a previous anti-HER2-based regimen. We show that patient HRQoL was maintained while on treatment and that deterioration of pain, breast, and arm symptoms, as well as physical functioning, was delayed with trastuzumab deruxtecan treatment versus treatment of physician's choice.

Implications of all the available evidence

When considered with previously published efficacy and safety data from DESTINY-Breast02, our findings provide comprehensive evidence of the benefits of trastuzumab deruxtecan in patients with trastuzumab emtansine-resistant HER2-positive metastatic breast cancer.

included as secondary endpoints to help support and contextualise the results of the primary endpoint.[9] Because PROs are self-reported without interpretation by health-care professionals, they provide crucial context for efficacy endpoints.[10] Furthermore, PRO assessments help us understand and improve patient perception and satisfaction with the quality of their care and generate better health outcomes than when they are not taken into account.[11] PRO measures are particularly important to consider in patients with HER2-positive metastatic breast cancer because both disease progression and disease treatment in this patient group have been shown to adversely affect patients' HRQoL and work productivity; therefore, mitigating declines in HRQoL might have wider economic and social benefits in addition to health outcomes.[12] Additionally, evaluating data regarding hospitalisation events can inform best practices for managing and reducing disease burden, potentially lowering costs for health-care services.[13] In this Article, we report the PROs and hospitalisation data from DESTINY-Breast02.

Methods

Study design and participants

DESTINY-Breast02 was a randomised, open-label, phase 3 study conducted at 227 sites (hospitals, university hospitals, clinics, community centres, and private oncology centres) in North America, Europe, Asia, Australia, Brazil, Israel, and Türkiye to investigate the efficacy and safety of trastuzumab deruxtecan versus treatment of physician's choice in patients with trastuzumab emtansine-resistant HER2-positive unresectable or metastatic breast cancer. Details on the study design of DESTINY-Breast02 have been published previously.[8]

Patients aged 18 years and older with pathologically documented unresectable or metastatic breast cancer, or both, that was centrally confirmed as HER2-positive (immunohistochemistry score 3+, or immunohistochemistry score 2+ and in-situ hybridisation-positive on primary tumour or metastasis biopsy, per the American Society of Clinical Oncology College of American Pathologists guidelines) who had disease progression on or after trastuzumab emtansine and had an Eastern Cooperative Oncology Group performance status of 0 or 1 were eligible for enrolment in the study. Key exclusion criteria included previous treatment with capecitabine (previous treatment with lapatinib was permitted); a history of 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 the presence of clinically active brain metastases (defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms).[8] Patients with clinically inactive or treated brain metastases that were no longer symptomatic and did not require treatment were considered eligible for inclusion. Additional eligibility criteria are detailed in the study protocol.[8] The study protocol was approved by the institutional review board at each site, and the study was conducted in adherence with the International Conference on Harmonisation Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before study participation.

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 using 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 due to the various routes of drug administration, treatment schedules, and adverse event profiles between the treatment groups.

Procedures

Trastuzumab deruxtecan 5·4 mg/kg was administered intravenously once every 21 days (one treatment cycle). Treatment of physician's choice administration was capecitabine (1250 mg/m², orally twice a day on days 1–14 of each treatment cycle) with trastuzumab (8 mg/kg intravenously on day 1 then 6 mg/kg once a day) or capecitabine (1000 mg/m², frequency as above) with lapatinib (1250 mg orally once per day on days 1–21 of each treatment cycle). Two dose reductions were permitted for patients who were randomly assigned to the trastuzumab deruxtecan group. If toxic effects recurred after two dose reductions, the patient was withdrawn from the study. On the basis of available safety data, it was highly recommended that prophylactic antiemetic agents (eg, 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists, or steroids, or a combination of the three) be used before infusion of trastuzumab deruxtecan and on subsequent days.[8]

Tumour assessments were conducted every 6 weeks (±7 days) while patients remained on treatment. Patients were considered non-evaluable when no measurement was performed at a given timepoint. Study treatment continued until radiographic progressive disease (as per modified Response Evaluation Criteria in Solid Tumours [mRECIST] version 1.1), clinical progression (definitive clinical signs of progressive disease but a recent radiographic assessment did not meet criteria for progressive disease per mRECIST version 1.1), withdrawal of patient consent, death, or unacceptable toxicity. All clinical adverse events that occurred after patients signed the main informed consent form and up to

40 days (±7 days) after the last study treatment were recorded and reported as described in the study protocol.[8] Patient follow-up was performed 40 days (+7 days) after the last treatment administration and 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. Patient sex data were transferred from patient medical source documents to electronic medical records by the treating physician.

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. Results for the study's primary endpoint have been published previously.[8] Endpoints for health economics and outcomes research (PROs and hospitalisation data) were included as secondary endpoints in DESTINY-Breast02. PROs were assessed using the oncology-specific European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30), together with the breast cancer-specific EORTC Quality of Life Questionnaire Breast 45 (QLQ-BR45) (scored using the algorithm for EORTC QLQ-BR23 because the QLQ-BR45 algorithm was not validated at the time of the study[8]), as well as the generic HRQoL EQ-5D-5L questionnaire. PROs were assessed before infusion at the beginning of treatment cycles 1, 2, and 3, and then every two cycles thereafter, as well as at the 40-day (+7 day) and 3-month follow-up visits.

The EORTC QLQ-C30 global health status–quality of life (GHS-QoL) scale was the primary predefined PRO variable of interest. Secondary predefined PROs of interest were the EORTC QLQ-C30 pain and functioning (physical, emotional, and social functioning) subscales, the EORTC QLQ-BR45 breast cancer symptoms scale, and the EQ-5D-5L visual analogue scale (VAS). The QLQ-C30 GHS-QoL scale provides an overall measure of HRQoL, whereas the chosen subscales provide insight into the impact of disease on daily patient life; subscales of the QLQ-BR45 questionnaire were chosen as they provide an understanding of the impact of disease on daily life via a breast cancer-specific measure accounting for key aspects, such as pain and functioning. The time to definitive deterioration was assessed for the EORTC QLQ-C30 GHS-QoL, pain, and functioning (physical, emotional, and social functioning) subscales, the EORTC QLQ-BR45 breast and arm symptoms subscales, and the EQ-5D-5L VAS. Time to definitive deterioration was defined as the time between the date of randomisation and the date at which a definitive deterioration event was first seen. A definitive deterioration event was defined as an increase of 10 points or more from baseline on the symptom subscales or a decrease of 10 points or more on the functional, GHS-QoL, and EQ-5D-5L VAS scales (on at least two timepoints unless it was the last measurement).[14] If a patient did not have a definitive deterioration event before analysis cutoff, loss to follow-up, or withdrawal of consent, the time to definitive deterioration was censored at the date of the last evaluation. Death was considered deterioration if it occurred by the first survival follow-up (3 months from 40-day follow-up visit). Patients who died after the first survival follow-up were censored at the date of their last available questionnaire.[8]

Predefined hospitalisation-related secondary endpoints included date of admission and discharge from hospital, status upon discharge from hospital, and use of intensive care unit (ICU) services in hospital (length of ICU stay was defined as the aggregate duration of all ICU stays calculated as the difference between the date of discharge from ICU and date of admission to the ICU plus 1 day).

Statistical analysis

The study had a planned sample size of 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 on the basis of the TH3RESA trial.[15] The primary analysis was planned according to an assumed HR of 0·7, thus being scheduled to occur 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) 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, 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.[8]

PROs and hospitalisation-related data were summarised by timepoint for each treatment group for the full analysis set (defined as all patients randomly assigned to the study, including those who did not receive a dose of study treatment). A linear transformation was applied to the raw scores of the EORTC QLQ-C30 and QLQ-BR45 to obtain the final scale scores in a range of 0–100. A higher score represents a better QoL for the GHS-QoL scale and a better level of functioning for the functional scales; a higher score for a symptom scale represents a worse level of symptomatology. EQ-5D-5L VAS scores were presented as a measure of overall self-rated health status ranging from 0 (representing the worst health imaginable) to 100 (representing the best health imaginable). If data from the multi-item scales were missing, the raw scores were calculated using the completed items if at least 50% of the items had been answered; for single-item measures, the score was set as

	Trastuzumab deruxtecan group (n=406)*	Treatment of physician's choice group (n=202)
Age, years	54·2 (45·5–63·4)	54·7 (48·0–63·0)
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%)
Rest of the world	101 (25%)	49 (24%)
HER2 status (immunohistochemistry)†		
3+	326 (80%)	159 (79%)
2+ (ISH-positive)	79 (19%)	41 (20%)
2+ (ISH-negative or non-evaluable)	1 (<1%)	1 (<1%)
1+ (ISH-positive)	0	1 (<1%)
ECOG 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%)
Brain metastases at baseline§	74 (18%)	36 (18%)
Visceral disease	316 (78%)	160 (79%)
Number of previous lines of systemic therapy in the metastatic setting¶	2 (2–3)	2 (2–3)
0	1 (<1%)	0
1	16 (4%)	11 (5%)
2	158 (39%)	73 (36%)
3	131 (32%)	66 (33%)
4	52 (13%)	25 (12%)
≥5	48 (12%)	27 (13%)
(Continued from previous column)		
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%)
HER2 tyrosine kinase inhibitor	26 (6%)	17 (8%)
Other HER2 therapy	11 (3%)	6 (3%)
Hormone	164 (40%)	87 (43%)

Data are median (IQR) or n (%), unless otherwise stated. This table has been reproduced from André and colleagues (*Lancet* 2023)[8] with modification. ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2. ISH=in-situ hybridisation. TPC=treatment of physician's choice. *Two patients were randomly assigned to receive trastuzumab deruxtecan but were not treated. †Only samples with HER2 immunohistochemistry score ≥2 were tested by HER2 gene amplification (in-situ hybridisation), except for one with immunohistochemistry score ≥1. ‡Three patients (1%) in the trastuzumab deruxtecan group and one patient (0·5%) in the TPC group had indeterminate hormone receptor status (neither oestrogen receptors nor progesterone receptors positive and oestrogen receptors indeterminate or progesterone receptors indeterminate) based on factors reported from electronic data capture. §Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included. ¶Includes regimens indicated for advanced or metastatic disease or rapid progression within 6 months of (neo)adjuvant therapy (12 months for pertuzumab); line of therapy does not include hormone therapy.

Table: **Baseline patient demographics**

missing. Changes from baseline over time were assessed for all EORTC QLQ-C30 and EORTC QLQ-BR45 subscales and were summarised descriptively; results were no longer considered informative for a group once patient numbers dropped below 10%. The nausea or vomiting, diarrhoea, and fatigue symptom subscales of EORTC QLQ-C30 were analysed post hoc.

Time to definitive deterioration was compared between the two treatment groups using the stratified log-rank test (stratified using the randomisation strata). Because PROs were not included in the hierarchical testing plan for DESTINY-Breast02, reported p values are nominal and not adjusted for multiplicity. The significance threshold was set as p=0·05. The survival distributions for time to definitive deterioration were presented descriptively as Kaplan-Meier curves. Patients were censored if they had no baseline or post-baseline assessments. A stratified Cox regression model (stratified using the randomisation strata) was used to estimate the time to definitive deterioration along with 95% CIs. Discharge status, length of hospital stay (days), length of ICU stay (days), and time to first hospitalisation (defined as the time from the date of randomisation to the date of the first hospitalisation during the study treatment) were summarised using descriptive statistics. All statistical analyses were performed using SAS, version 9.3 or higher. This study was registered with ClinicalTrials.gov, NCT03523585, and is closed to recruitment.

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, writing of the report, reviewing of the manuscript, and the decision to submit the manuscript for publication.

Results

Between Sept 6, 2018, and Dec 31, 2020, 816 patients with HER2-positive breast cancer were screened, and 608 patients were randomly assigned to receive either trastuzumab deruxtecan (n=406) or treatment of physician's choice (n=202); two patients from the trastuzumab deruxtecan group did not receive treatment and seven patients from the treatment of physician's choice group withdrew consent after randomisation (appendix p 14).[8] A list of the clinical centres at which patients were enrolled can be found in the appendix (pp 1–9). 603 (99%) of 608 patients were female and five (<1%) were male. 74 (18%) of 406 participants in the trastuzumab deruxtecan group had brain metastases at baseline (per investigator) and 316 (78%) had visceral disease, whereas 36 (18%) of 202 participants in the treatment of physician's choice group had brain metastases at baseline (per investigator) and 160 (79%) had visceral disease (table).[8] Patients in DESTINY-Breast02 received study treatment in the advanced disease setting and had shown progression after two or more HER2-targeting therapies, with a median of two (IQR 2–3) previous lines of systemic therapy in the metastatic setting for both groups (table).[8]

As of data cutoff on June 30, 2022, 94 (23%) of 404 patients in the trastuzumab deruxtecan group and five (3%) of 195 patients in the treatment of physician's choice group were still receiving treatment. A description of post-trial anti-cancer therapies received by the patients can be found in the appendix (p 10). The median treatment duration 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).[8] The median duration of follow-up was 21·5 months (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.[8]

The compliance rate for all the health-related patient questionnaires was 92% or higher at baseline (before treatment initiation) for both treatment groups (393 [97%] of 406 for QLQ-C30 and QLQ-BR45 and 391 [96%] for EQ-5D-5L in the trastuzumab deruxtecan group; 187 [93%] of 202 for QLQ-C30 and QLQ-BR45 and 186 [92%] for EQ-5D-5L for the treatment of physician's choice group), 79% or higher at cycles 3–39 for the trastuzumab deruxtecan group (42 [79%] of 53 for QLQ-C30, QLQ-BR45, and EQ-5D-5L at cycle 39), and more than 84% at cycles 3–21 in the treatment of physician's choice group (22 [88%] of 25 for QLQ-C30, QLQ-BR45, and EQ-5D-5L at cycle 21), after which the number of patients remaining in each group dropped to 10% or less (39 [10%] of 406 for QLQ-C30, QLQ-BR45, and EQ-5D-5L in the trastuzumab deruxtecan group at cycle 41; 17 [8%] of 202 for QLQ-C30 and QLQ-BR45 and 16 [8%] for EQ-5D-5L in the treatment of physician's choice group at cycle 23) and the results were no longer considered informative.

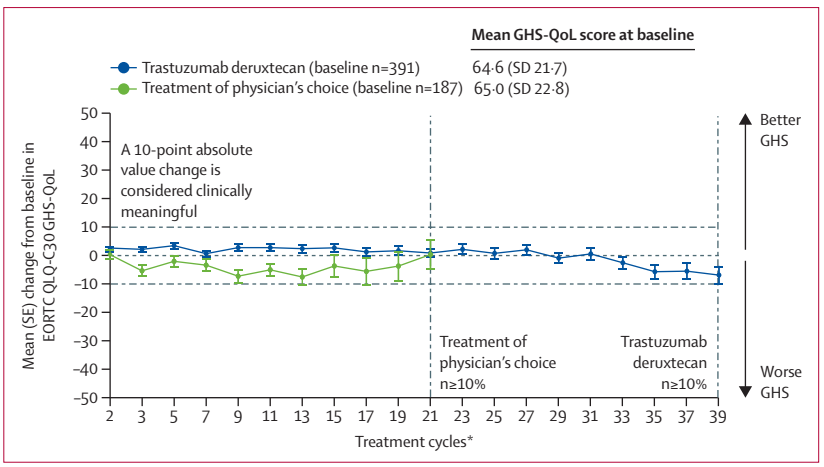

Figure 1: **Change from baseline of EORTC QLQ-C30 GHS-QoL**
EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. QLQ-C30=Quality of Life Core 30 questionnaire. QoL=quality of life. *On day 1 of a cycle, scores range from 0 to 100; a higher score represents a higher GHS or overall QoL.

See Online for appendix

Mean EORTC QLQ-C30 GHS-QoL scores at baseline were similar between the trastuzumab deruxtecan (64·6 [SD 21·7]) and treatment of physician's choice groups (65·0 [SD 22·8]; figure 1; appendix p 11). The GHS-QoL scores were maintained (±10 points) over time, until cycle 39 in the trastuzumab deruxtecan group and until cycle 21 in the treatment of physician's choice group, after which results were no longer considered informative because less than 10% of patients remained in each group (figure 1). Patients in the trastuzumab deruxtecan group had longer median time to definitive deterioration of GHS-QoL than those in the treatment of physician's choice group (14·1 months [95% CI 10·4–18·7] *vs* 5·9 months [4·3–7·9]; HR 0·5573 [95% CI 0·4376–0·7099], p<0·0001; figure 2).

Patients had delayed time to definitive deterioration with trastuzumab deruxtecan compared with treatment of physician's choice for secondary PRO measures of interest, including the QLQ-C30 physical functioning (median time to definitive deterioration 18·7 months [95% CI 15·5–22·9] *vs* 6·8 months [5·7–8·8]; HR 0·4637 [95% CI 0·3575–0·6014], p<0·0001) and pain symptom scales (18·7 months [14·1–23·8] *vs* 5·8 months [5·0–7·0]; HR 0·3779 [0·2941–0·4857], p<0·0001; figure 3). In the trastuzumab deruxtecan group, 170 (42%) of 406 patients had a definitive deterioration event in pain symptoms compared with 110 (54%) of 202 patients in the treatment of physician's choice group. Furthermore, patients had prolonged median time to definitive deterioration with trastuzumab deruxtecan compared with treatment of physician's choice for the QLQ-BR45 breast (HR 0·4164 [95% CI 0·2928–0·5921], p<0·0001) and arm symptoms scales (HR 0·5737 [0·4415–0·7456], p<0·0001; appendix p 15), as well as in the VAS score of the EQ-5D-5L questionnaire (HR 0·5906 [0·4583–0·7610], p<0·0001;

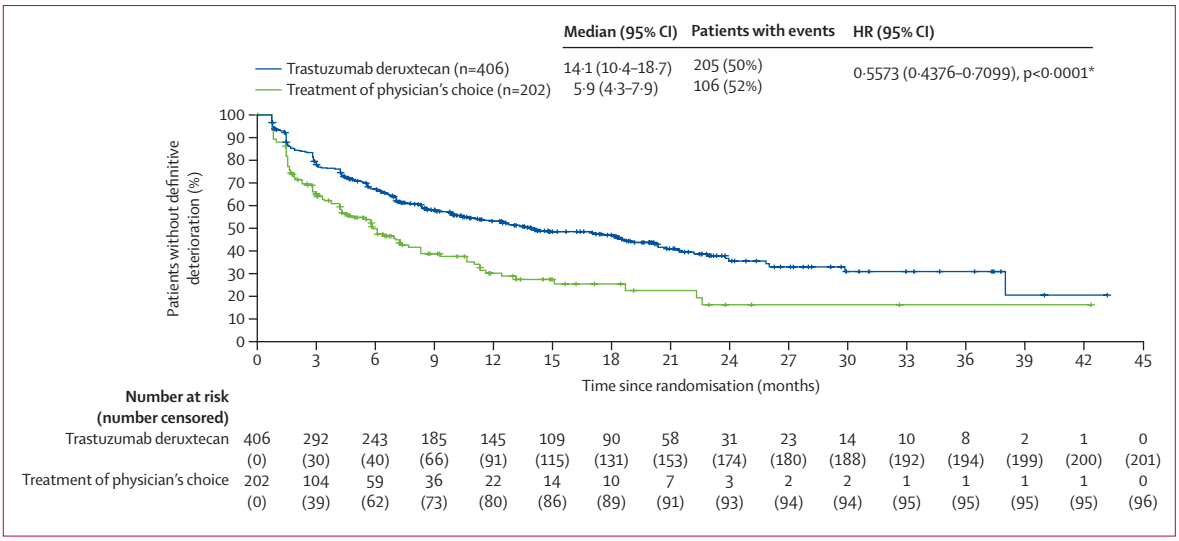

Figure 2: **Kaplan–Meier analysis for time to definitive deterioration of EORTC QLQ-C30 GHS-QoL**
EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. HR=hazard ratio. QLQ-C30=Quality of Life Core 30 questionnaire. QoL=quality of life. *Nominal p values are two-sided and based on a stratified log-rank test and not adjusted for multiple testing.

appendix p 16). Time to definitive deterioration was delayed with trastuzumab deruxtecan compared with treatment of physician's choice across all prespecified PRO variables of interest (figure 4). Regression analysis showed that HRs for time to definitive deterioration favoured trastuzumab deruxtecan over treatment of physician's choice for the prespecified PRO variables (appendix p 13).

Although not prespecified, we also evaluated the nausea or vomiting, diarrhoea, and fatigue symptom subscales of EORTC QLQ-C30 in post-hoc analyses, because these were common drug-related treatment-emergent adverse events in DESTINY-Breast02.[8] The time to definitive deterioration for QLQ-C30 nausea or vomiting was 5·7 months (95% CI 4·3–7·6) with trastuzumab deruxtecan and 6·1 months (5·6–8·8) with treatment of physician's choice. A clinically relevant increase in QLQ-C30 nausea or vomiting changes from baseline scores (>10-point change) was observed with trastuzumab deruxtecan during early treatment cycles (up to cycle 3), after which scores decreased to levels similar to treatment of physician's choice and remained stable over time (appendix p 17). Mean changes from baseline scores in QLQ-C30 diarrhoea symptoms remained stable over time among patients in the trastuzumab deruxtecan group, whereas patients in the treatment of physician's choice group had a clinically relevant increase in diarrhoea symptoms throughout the assessment period. Furthermore, patients in the trastuzumab deruxtecan group had delayed time to definitive deterioration for QLQ-C30 diarrhoea symptoms compared with treatment of physician's choice (23·5 months [95% CI 20·2–not estimable] *vs* 5·4 months [2·1–6·4]; HR 0·3406 [0·2606–0·4452], p<0·0001; appendix p 18). The mean changes from baseline scores for QLQ-C30 fatigue symptoms also remained stable over time in both treatment groups (data not shown); however, changes from baseline scores were higher for patients in the treatment of physician's choice group than for those in the trastuzumab deruxtecan group. Time to definitive deterioration for QLQ-C30 fatigue symptoms was also delayed with trastuzumab deruxtecan compared with treatment of physician's choice (7·0 *vs* 5·5 months; HR 0·7610 [95% CI 0·6064–0·9551], p=0·0172).

Hospitalisation rates were similar between the trastuzumab deruxtecan (92 [23%] of 406) and treatment of physician's choice (41 [20%] of 202) groups, as was the duration of hospital stay per patient (median 11 days [IQR 6–20] in the trastuzumab deruxtecan group and 10 days [6–15] in the treatment of physician's choice group; appendix p 12), although the median duration of treatment with trastuzumab deruxtecan was 11·3 months (6·2–20·5) versus 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.[8] The median time to first hospitalisation was 133 days (56–237) in the trastuzumab deruxtecan group versus 83 days (30–152) in the treatment of physician's choice group (appendix p 12). Six (1%) patients in the trastuzumab deruxtecan group and three (1%) patients in the treatment of physician's choice group were admitted to an ICU, with a median length of ICU stay of 7·5 days (6–17) for trastuzumab deruxtecan and 2 days (1–2) for treatment of physician's choice.

Discussion

Instruments that measure PROs are used to assess HRQoL through a multifaceted approach and range from

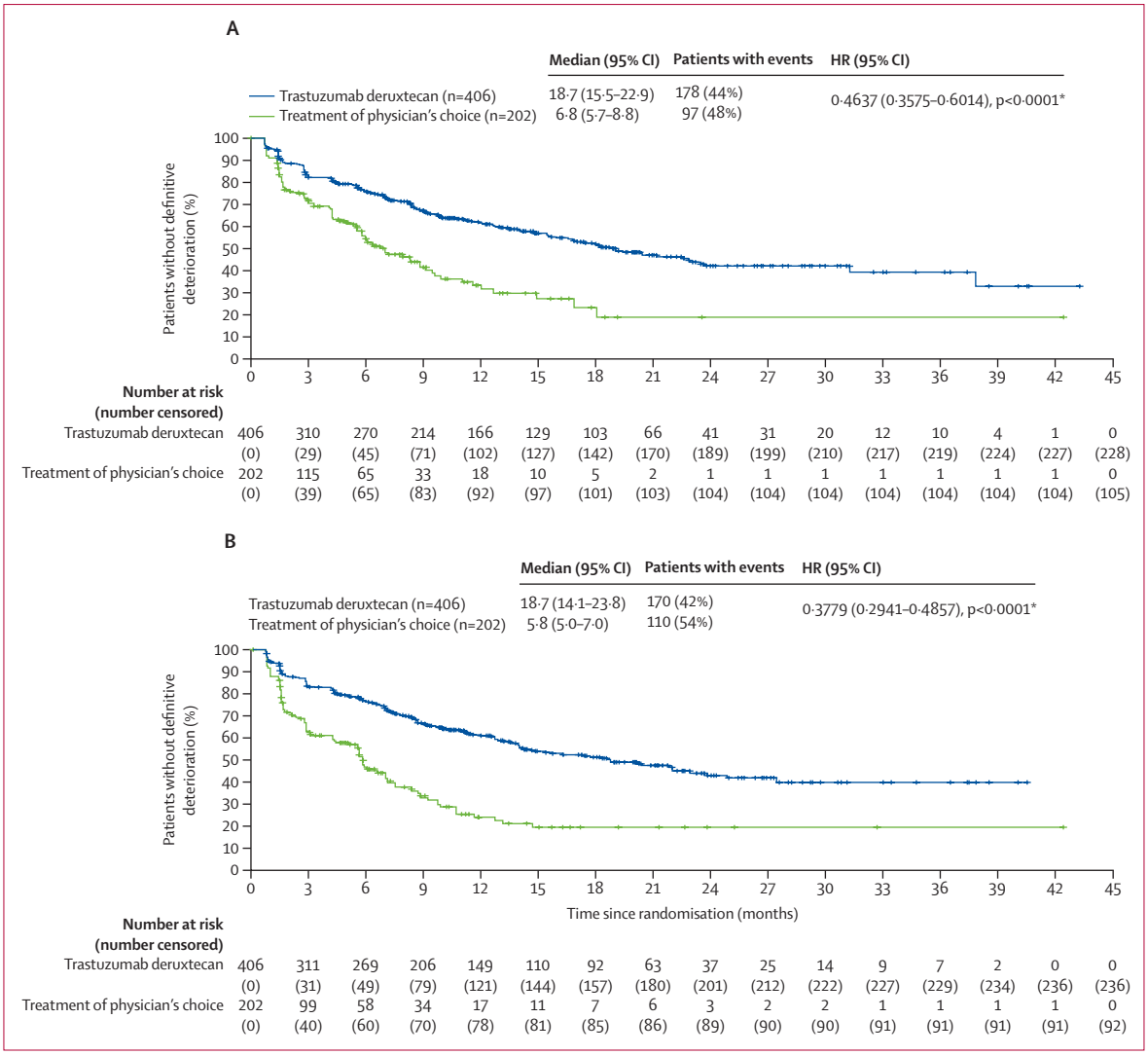

Figure 3: **Kaplan–Meier analysis for time to definitive deterioration of EORTC QLQ-C30 physical functioning (A) and pain symptoms (B)**
EORTC=European Organisation for Research and Treatment of Cancer. HR=hazard ratio. QLQ-C30=Quality of Life Core 30 questionnaire. *Nominal p values are two-sided and based on a stratified log-rank test and not adjusted for multiple testing.

generic assessments, such as the EQ-5D-5L, to disease-specific ones, such as the EORTC QLQ-BR45. These tools are used to elicit data on patients' perceptions of their health condition, which are increasingly used in the regulatory approval process to measure treatment benefits and risks.[10,16–18] Our study describes PROs from the DESTINY-Breast02 trial of trastuzumab deruxtecan compared with treatment of physician's choice in patients with HER2-positive metastatic breast cancer whose disease had previously progressed on trastuzumab emtansine. We show that patients receiving trastuzumab deruxtecan had a longer time to definitive deterioration for GHS-QoL than those receiving treatment of physician's choice and that, from the patient's perspective, trastuzumab deruxtecan was favoured over treatment of physician's choice in all prespecified PRO endpoints.

Having developed resistance to trastuzumab emtansine, the DESTINY-Breast02 patient population had few efficacious treatment options, and they had a fairly high prevalence of visceral disease and brain metastases. Changes from baseline scores for the EORTC QLQ-C30 GHS-QoL, the primary PRO variable of interest, suggested that GHS-QoL was maintained over the course of treatment, with no clinically significant decrease observed in either treatment group. The GHS-QoL changes from baseline scores with trastuzumab deruxtecan were higher during the study than those from patients receiving treatment of physician's choice, suggesting that treatment with trastuzumab deruxtecan was more manageable for patients. Higher rates of durable responses have been observed with trastuzumab deruxtecan than with treatment of physician's choice,[8] which could be linked to

	Patients with deterioration events, n (%)		Median (95% CI) time to definitive deterioration, months		HR (95% CI)	Nominal p value*
	Trastuzumab deruxtecan (n=406)	Treatment of physician's choice (n=202)	Trastuzumab deruxtecan (n=406)	Treatment of physician's choice (n=202)		
EORTC QLQ-C30						
GHS-QoL†	205 (50%)	106 (52%)	14·1 (10·4–18·7)	5·9 (4·3–7·9)	0·56 (0·44–0·71)	<0·0001
Physical functioning‡	178 (44%)	97 (48%)	18·7 (15·5–22·9)	6·8 (5·7–8·8)	0·46 (0·36–0·60)	<0·0001
Emotional functioning‡	160 (39%)	79 (39%)	21·4 (16·9–NE)	10·7 (6·9–15·4)	0·67 (0·51–0·88)	0·0041
Social functioning‡	176 (43%)	99 (49%)	18·7 (13·9–28·8)	6·3 (4·9–8·8)	0·54 (0·42–0·70)	<0·0001
Pain‡	170 (42%)	110 (54%)	18·7 (14·1–23·8)	5·8 (5·0–7·0)	0·38 (0·29–0·49)	<0·0001
EORTC QLQ-BR45§						
Arm symptoms‡	178 (44%)	90 (45%)	18·3 (13·9–21·2)	8·8 (6·1–11·6)	0·57 (0·44–0·75)	<0·0001
Breast symptoms‡	91 (22%)	55 (27%)	NE (30·3–NE)	18·1 (12·5–NE)	0·42 (0·29–0·59)	<0·0001
EQ-5D-5L						
VAS‡	188 (46%)	98 (49%)	16·6 (13·6–20·2)	7·3 (5·8–10·6)	0·59 (0·46–0·76)	<0·0001

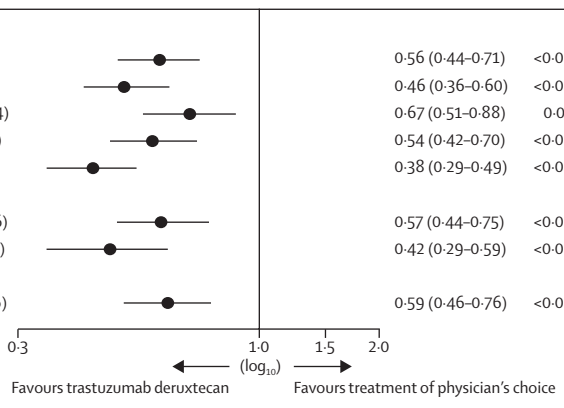

Figure 4: **Summary of time to definitive deterioration in the prespecified PRO variables**
EORTC=European Organisation for Research and Treatment of Cancer. GHS=global health status. HR=hazard ratio. PRO=patient-reported outcome. QLQ-BR45=Quality of Life Breast cancer questionnaire. QLQ-C30=Quality of Life Core 30 questionnaire. QoL=quality of life. VAS=visual analogue scale. *Nominal p values are two-sided and based on a stratified log-rank test and not adjusted for multiple testing. †Primary PRO variable of interest. ‡Secondary PRO variable of interest. §Scored using the QLQ-BR23 algorithm.

the maintenance of GHS-HRQoL beyond that achieved with treatment of physician's choice.

Time to definitive deterioration is a frequently used endpoint to evaluate the effect of two different treatments on HRQoL.[19] The time to definitive deterioration for QLQ-C30 GHS-QoL was longer with trastuzumab deruxtecan than with treatment of physician's choice, suggesting a benefit to patient HRQoL with trastuzumab deruxtecan. These results, considered in conjunction with the median treatment duration (11·3 months with trastuzumab deruxtecan *vs* approximately 4·5 months with treatment of physician's choice), suggest that trastuzumab deruxtecan might maintain patient HRQoL while extending progression-free survival (median progression-free survival: 17·8 months for trastuzumab deruxtecan *vs* 6·9 months for treatment of physician's choice; HR 0·36, p<0·0001) and overall survival (median overall survival: 39·2 months for trastuzumab deruxtecan *vs* 26·5 months for treatment of physician's choice; HR 0·66, p=0·0021).[8] GHS-QoL was assessed in all enrolled patients, regardless of whether they showed a durable response to treatment. Although the rate of patient withdrawal for reasons other than disease progression was higher in the trastuzumab deruxtecan group than the treatment of physician's choice group, the median progression-free survival and duration of response with trastuzumab deruxtecan were longer than the median treatment duration,[8] suggesting a continuous treatment effect that might have impacted HRQoL outcomes.

The HRs for time to definitive deterioration favoured trastuzumab deruxtecan over treatment of physician's choice (HR range 0·38–0·67) across all prespecified subscales, including QLQ-C30 pain symptoms. Pain is an important symptom to consider from the perspective of the patient because it has a bearing on the disease burden and is closely associated with health status.[19] Effective management of cancer-related pain improves patient perception of their health care, and a growing number of trials report the time to definitive deterioration for pain scores to assess the impact of treatment on patient HRQoL.[19,20] In our study, patients in the trastuzumab deruxtecan group had significantly delayed time to definitive deterioration in the EORTC QLQ-C30 pain symptoms subscale compared with treatment of physician's choice (HR 0·3779, nominal p<0·0001), and fewer patients had a deterioration event in pain symptoms with trastuzumab deruxtecan than with treatment of physician's choice, which is of particular interest given the profound impact of pain on HRQoL.[20]

The potential impacts of side-effects of treatment with trastuzumab deruxtecan or treatment of physician's choice were further contextualised through the non-prespecified QLQ-C30 scales. Nausea and vomiting are common cancer-drug-related treatment-emergent adverse events, and in the trastuzumab deruxtecan group of DESTINY-Breast02, 293 (73%) of 404 patients had treatment-emergent nausea and 152 (38%) had treatment-emergent vomiting, compared with 73 (37%) and 25 (13%) of 195 patients in the treatment of physician's choice group.[8] Changes from baseline scores for QLQ-C30 nausea or vomiting with trastuzumab deruxtecan showed a clinically significant increase in early treatment cycles. However, after cycle 3, scores returned to within 10 points of the baseline scores, where they remained stable over time. When DESTINY-Breast02 was initiated, antiemetic agents were not part of the recommendations in the protocol. To provide more

supportive care to the enrolled patient population with a high disease burden, recommendations for prophylactic antiemetics were later included, with 292 (72%) of 404 participants in the trastuzumab deruxtecan group and 60 (31%) of 195 patients in the treatment of physician's choice group receiving antiemetics during the study.[8] This recommendation might have contributed to the stabilisation of QLQ-C30 nausea or vomiting scores in the trastuzumab deruxtecan group as well as the overall GHS-QoL scores favouring trastuzumab deruxtecan despite the early gastrointestinal symptoms observed with trastuzumab deruxtecan. QLQ-C30 fatigue symptom scores were lower with trastuzumab deruxtecan than with treatment of physician's choice, indicating that fatigue symptoms did not worsen with trastuzumab deruxtecan. Furthermore, unlike with treatment of physician's choice, patients in the trastuzumab deruxtecan group showed no clinically significant increase of QLQ-C30 diarrhoea symptoms scores, suggesting that diarrhoea symptoms were more manageable with trastuzumab deruxtecan.

Although the number of hospitalisation events, median length of hospital stay, and rates of ICU admissions were similar between the trastuzumab deruxtecan and treatment of physician's choice groups, the median time to first hospitalisation was delayed with trastuzumab deruxtecan, suggesting a reduced burden for patients and health-care services. However, additional studies on the cost-effectiveness of trastuzumab deruxtecan in this population are needed. Furthermore, because the length of ICU stay was longer with trastuzumab deruxtecan than with treatment of physician's choice and the rates of hospitalisation were low in both treatment groups, interpretation of these data is difficult.

PROs from the DESTINY-Breast03 trial, which was conducted to investigate trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer, and PROs from the DESTINY-Breast04 trial, which was conducted to investigate trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-low (immunohistochemistry score 2+ and in-situ hybridisation-negative, and immunohistochemistry score 1+) metastatic breast cancer have recently been disclosed with outcomes similar to those in this analysis.[21,22] In both studies, GHS-QoL scores were maintained in both treatment groups, with no clinically relevant change (median treatment duration for DESTINY-Breast03: 14·3 months for trastuzumab deruxtecan and 6·9 months for comparator; median treatment duration for DESTINY-Breast04: 8·2 months for trastuzumab deruxtecan and 3·5 months for comparator). Time to definitive deterioration analysis for GHS-QoL and all other prespecified subscales in both studies showed that trastuzumab deruxtecan was favoured over the comparator on the basis of HRs. In concordance with PROs from DESTINY-Breast03 and DESTINY-Breast04, PROs from DESTINY-Breast02 demonstrate that, in addition to improving overall survival and progression-free survival relative to the standard of care, trastuzumab deruxtecan is not detrimental to HRQoL.

A key strength of this study was the high rates of patient compliance in completing the PRO questionnaires. However, the data are only reliable until cycle 39 with trastuzumab deruxtecan and cycle 21 with treatment of physician's choice, after which patient numbers were less than 10% of the number at baseline and the data were no longer informative, highlighting the importance of continuous collection of PRO data and patient engagement. Furthermore, the study was not adequately powered to assess efficacy and PRO outcomes in different patient subgroups, such as those with and without brain metastases and visceral disease. Thus, future studies are needed to focus on addressing this need.

There has been some concern over the use of PROs for open-label trials because patients' knowledge of their treatment group might affect their perception of the treatment impact and thus the responses of PRO measures.[10,18,23] However, several studies demonstrated no clinically or statistically significant bias of open-label designs on the results of PROs.[24–29]

In conclusion, data from our study suggest that patients who received trastuzumab deruxtecan had sustained HRQoL. When considered with previous efficacy and safety data from DESTINY-Breast02,[8] our findings provide comprehensive evidence of the benefit of trastuzumab deruxtecan in patients with trastuzumab emtansine-resistant HER2-positive metastatic breast cancer.

Contributors

TF, FA, IK, AE, TT, and S-BK contributed to study conception and design. All authors contributed to data acquisition, quality control, or data analysis, and were involved in the drafting and reviewing of the manuscript for publication. All authors had full access to all the data in the study and final responsibility for the decision to submit to publication. S-BK and WL accessed and verified all the data in the study.

Declaration of interests

TF reports payments to their institution from Roche, Novartis, Pfizer, Daiichi Sankyo, MSD, and Eisai. FC, KD, and WL are full-time employees at Daiichi Sankyo. FA reports institutional research grants from Novartis, Pfizer, AstraZeneca, Eli Lilly, Daiichi Sankyo, and Roche, as well as consulting fees paid to their institution by MedImmune, Gilead, Relay Therapeutics, and Guardant Health. IK reports support for the present manuscript received by their institution from AstraZeneca and Daiichi Sankyo; grants to their institution from Pfizer, Macrogenics, and Genentech/Roche; consulting fees from AstraZeneca, Daiichi Sankyo, Genentech/Roche, Bristol Myers Squibb, Macrogenics, Taiho Oncology, and Seattle Genetics; honoraria from AstraZeneca; participation on a data safety monitoring or advisory board for Novartis and Merck; a leadership or fiduciary role in PureTech; and stock options in PureTech. YHP reports grants from MSD, Pfizer, Roche, AstraZeneca, Gencurix, NGeneBio, and Genome Insight; consulting fees from AstraZeneca, Pfizer, Eli Lilly, Bixink, MSD, Eisai, Roche, Daiichi Sankyo, Menarini, Gilead, and Novartis; payment for lectures, presentations, or educational events from AstraZeneca, Pfizer, Lilly, MSD, Roche, Daiichi Sankyo, and Novartis; support for attending meetings from Pfizer and Roche; participation on a data safety monitoring or advisory board for AstraZeneca, Pfizer, Roche, Gilead, and Novartis; and receipt of equipment or other services from Dong-A ST, Sanofi, Pfizer, and Roche.

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Data sharing

For the **data request** see https://vivli.org/

Anonymised individual participant data and supporting clinical study documents are available upon request. In cases for which 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 online.

For more on **requesting access** see https://vivli.org/ourmember/daiichi-sankyo/

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