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**Original Article**

# Patient-reported outcomes from DESTINY-Breast04: trastuzumab deruxtecan versus physician's choice of chemotherapy in patients with HER2-low mBC

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## Abstract

**Background:** The phase 3 DESTINY-Breast04 trial demonstrated superior efficacy and acceptable safety with trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy in previously treated patients with human epidermal growth factor receptor 2 (HER2)–low metastatic breast cancer (mBC). We report the patient-reported outcomes (PROs), focusing on the hormone receptor–positive cohort.

**Patients and Methods:** Patients were randomized 2:1 to T-DXd (5.4 mg/kg intravenously every 3 weeks) or physician's choice of chemotherapy and prospectively assessed for PRO measures. Change from baseline and time to definitive deterioration (TDD) were calculated from the EORTC QLQ-C30 and QLQ-BR45 and the EQ-5D-5L questionnaires.

**Results:** Baseline global health status/quality of life (GHS/QoL) scores were similar between groups (T-DXd, 331 patients; physician's choice, 163 patients); there were no clinically meaningful changes while on either treatment (median duration: T-DXd, 8.2 months; physician's choice, 3.5 months). Median TDD for GHS/QoL was delayed with T-DXd vs physician's choice (11.4 vs 7.5 months, respectively; hazard ratio, 0.69; 95% CI, 0.52-0.92). Median TDD for all prespecified PROs, including pain, favored T-DXd. In an additional analysis, the median TDD was shorter for nausea and vomiting with T-DXd vs the physician's choice.

**Conclusions:** Trastuzumab deruxtecan maintained GHS/QoL scores despite a longer treatment course compared with standard chemotherapy and delayed definitive deterioration across all prespecified PROs vs the physician's choice. Appropriate management of adverse events and use of preventive measures (ie, antiemetic prophylaxis) may further support patient health-related quality of life. These findings reinforce the benefit of T-DXd as an option for patients with HER2-low mBC. ClinicalTrials.gov: NCT03734029

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**Key words:** metastatic breast cancer; quality of life; trastuzumab deruxtecan; HER2-low; patient-reported outcomes; antibody-drug conjugate.

### Implications for practice

DESTINY-Breast04 demonstrated superior efficacy and acceptable safety of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in previously treated patients with HER2-low metastatic breast cancer (mBC). This analysis reports the prespecified patient-reported outcomes (PROs) captured in DESTINY-Breast04. Health-related quality of life (QoL) was maintained during the entire treatment period for T-DXd or TPC, and time to definitive deterioration of QoL favored T-DXd vs TPC on all primary PROs of interest, including pain symptoms. Appropriate management of adverse events and use of preventive measures (ie, antiemetic prophylaxis) may support health-related QoL. These PRO results reinforce the use of T-DXd as a treatment option for patients with HER2-low mBC.

## Introduction

For patients with metastatic breast cancer (mBC), clinical treatment decisions are based on strategies to extend life expectancy, relieve cancer-related symptoms, and optimize health-related quality of life (QoL).[1,2] Classic clinical endpoints in oncology trials (eg, overall survival [OS], progression-free survival [PFS], and adverse events [AEs]) provide requisite information about the efficacy and safety of novel treatments and inform care guidelines.[3,4] Although these endpoints have historically dominated the paradigm that determines care pathways, patient-reported outcomes (PROs) are now commonly seen as meaningful complementary endpoints that offer important information concerning the impact of a treatment on patients' health-related QoL.[3-8] Together, classic clinical endpoints and PROs from clinical trials can help capture the full therapeutic profile of a new treatment, ultimately leading to better patient outcomes.[3,5,9-11]

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate approved for second- or later-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) mBC.[12,13] In 2022, patients with HER2-low (defined as HER2 immunohistochemistry 1 + or 2 + and in situ hybridization–negative) mBC were established as a population that could benefit from HER2-directed therapies[14] based on the phase 3 DESTINY-Breast04 trial results and subsequent approval of T-DXd for second- or later-line treatment of patients with HER2-low mBC who previously received chemotherapy.[15] At the primary efficacy analysis of DESTINY-Breast04 (data cutoff, January 11, 2022), in the hormone receptor–positive (HR+) cohort, treatment with T-DXd vs physician's choice of chemotherapy (physician's choice) showed a median PFS (primary endpoint) of 10.1 months (95% CI, 9.5-11.5 months) vs 5.4 months (95% CI, 4.4-7.1 months), respectively (hazard ratio, 0.51; 95% CI, 0.40-0.64, $P < .001$) and a median OS (key secondary endpoint) of 23.9 months (95% CI, 20.8-24.8 months) vs 17.5 months (95% CI, 15.2-22.4 months; hazard ratio, 0.64; $P = .003$).[14] Results from the all-patients cohort (key secondary endpoints) and the hormone receptor–negative (HR−) cohort (exploratory endpoints) were consistent with these findings.[14] Although T-DXd demonstrated efficacy and had a manageable and acceptable safety profile in patients with HR+/HER2-low mBC, it was also associated with drug-related treatment-emergent AEs (TEAEs), the most common of which were nausea (T-DXd, 73.0%; physician's choice, 23.8%), fatigue (47.7%, 42.4%), and neutropenia (33.2%, 51.2%).[14] Interstitial lung disease/pneumonitis occurred in 12.1% of patients treated with T-DXd (45/371; 8 cases were grade ≥ 3 [5 were grade 3; 3 were grade 5]).[14] We report the prospectively defined secondary PRO endpoints and hospitalization events from DESTINY-Breast04, focusing on the HR+/HER2-low cohort.

## Materials and methods

### Study design

DESTINY-Breast04 (ClinicalTrials.gov, NCT03734029) is an open-label, randomized, multicenter, phase 3 trial investigating the efficacy and safety of T-DXd vs physician's choice of chemotherapy in patients with unresectable and/or metastatic HER2-low breast cancer; methods and primary results from the trial were published previously.[14] Patients were randomly assigned 2:1 to receive T-DXd (5.4 mg/kg intravenously every 3 weeks) or physician's choice (oral capecitabine or intravenous eribulin, gemcitabine, paclitaxel, or nab-paclitaxel).[14]

### PROs endpoints

Patient-reported outcomes were assessed as additional prespecified secondary objectives in DESTINY-Breast04 and were evaluated at the following time points: at baseline, before patients received treatment but after they had knowledge of their randomization assignment; on day 1 of cycles 1 to 3 and every 2 cycles subsequently; at the end of treatment; at the 40-day follow-up visit; and at every 3-month follow-up visit (Figure S1).[14] The primary PRO measure of interest was the global health status/quality of life scale (GHS/QoL) score from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (a validated oncology-specific questionnaire).[16,17] Secondary PRO endpoints of interest from the EORTC QLQ-C30 included functioning (ie, physical, emotional, and social) and symptom (ie, pain) subscale scores. Symptom subscale scores for nausea/vomiting and fatigue were also included as additional endpoints. Additional endpoints included both role and cognitive functioning subscale scores and single-item symptom scores (ie, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

Breast and arm symptom scales from the EORTC Quality of Life Questionnaire-Breast 45 (QLQ-BR45), a breast cancer–specific companion questionnaire to EORTC QLQ-C30,[18,19] were also secondary PRO endpoints of interest. Additional endpoints included functional subscale scores (ie, body image, sexual functioning, sexual enjoyment, future perspective) and single-item symptom scores (ie, systemic therapy side effects, upset by hair loss). The EuroQol 5-dimension, 5-level (EQ-5D-5L) questionnaire comprises a visual analog scale (VAS) by which patients rate their health, as well as a descriptive system with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[20] See Supplementary Materials for additional methods.

### Statistical analysis

Primary analyses included change from baseline (CFB) and time to definitive deterioration (TDD) for EORTC QLQ-C30 GHS/QoL and prespecified functioning and symptom subscale scores; and CFB and TDD for EORTC QLQ-BR45 symptom subscale scores. A ≥ 10-point CFB in mean scores was considered clinically meaningful.[21] TDD was defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event (a ≥ 10-point change of the subject-specific score in the direction of deterioration [positive for symptom scales, negative for all others] on ≥ 2 consecutive visits or at last available visit) was first seen.

Change from baseline in all the prespecified subscales from EORTC QLQ-C30 and EORTC QLQ-BR45 was descriptively summarized, and differences in means between T-DXd and physician's choice groups and the corresponding 2-sided 95% CI at selected time points are presented. The survival distributions were estimated using the Kaplan-Meier method and included median TDD and the proportion of patients without definitive deterioration at specific time points. A stratified Cox regression model was used to estimate hazard ratios of TDD and 95% CIs and adjusted for stratification factors (ie, HER2 status, number of prior lines of chemotherapy, and HR/cyclin-dependent kinase status). Because PROs were not included in the hierarchical testing plan for DESTINY-Breast04, reported *P* values are nominal and not adjusted for multiplicity.

## Results

### Patient characteristics

Patients for DESTINY-Breast04 were recruited from 208 sites in 20 countries.[14] A total of 713 patients with HER2-low mBC were screened between December 27, 2018, and December 31, 2021; 557 patients underwent randomization to T-DXd (*n* = 373) or physician's choice (*n* = 184).[14] In total, 88.7% (331/373) of patients randomly assigned to T-DXd and 88.6% (163/184) to physician's choice had HR+ disease.[14] At primary data cutoff (January 11, 2022), among all patients, 15.6% (58/373) were still receiving T-DXd vs 1.7% (3/184) still receiving physician's choice. Patient demographics and baseline clinical characteristics were similar between treatment groups and across hormone receptor status cohorts (Table 1; Tables S1 and S2).[14]

In the HR+ cohort, patients in the physician's choice group received either eribulin (53.4%), capecitabine (20.9%), nab-paclitaxel (11.0%), gemcitabine (7.4%), or paclitaxel (7.4%).[14] In both treatment groups, patients in the HR+ cohort had prior exposure to a median of 3 lines of systemic therapy (endocrine therapy or chemotherapy) for metastatic disease.

### Patient-reported outcomes

In the HR+ cohort, patient compliance for the questionnaires was high: > 92% at baseline assessment and > 80% for cycles 2-27. Patient compliance at the end of treatment and at the 40-day and 3-month follow-up visits was also > 80% for both groups. The cycle after which the number of patients fell below 10% of baseline enrollment, and CFB results were then no longer considered informative, was cycle 13 for physician's choice and cycle 27 for T-DXd; data between groups were thus interpretable through cycle 13, although data for the T-DXd group were interpretable through cycle 27.

The EORTC QLQ-C30 GHS/QoL scores for the 2 HR+ treatment groups were similar at baseline (Table S3). The mean CFB for GHS/QoL score remained stable (within ± 10 points) over the course of treatment with T-DXd (up to 27 cycles) and physician's choice (up to 13 cycles) (Figure 1). The mean (standard deviation) CFB at cycle 13, when interpretations between the 2 groups were last feasible, was 2.7 (21.5) for T-DXd vs 3.3 (21.7) for physician's choice; the CFB at cycle 27 for T-DXd was 2.3 (19.1) (Table S3). The median TDD of GHS/QoL was longer among patients who received T-DXd (11.4 months [95% CI, 8.8-16.3]) vs physician's choice (7.5 months [95% CI, 5.9-9.5]; hazard ratio, 0.69 [95% CI, 0.52-0.92]; *P* = .0096) (Figures 2 and 3A).

Median TDD for secondary PRO measures of interest among the EORTC QLQ-C30 subscales also favored patients receiving T-DXd over physician's choice (Figure 2). The median TDD for pain symptoms was 16.4 months (95% CI, 13.1-21.5) for T-DXd vs 6.1 months (95% CI, 4.2-7.5) for physician's choice (hazard ratio, 0.40 [95% CI, 0.30-0.54]; *P* < .0001) (Figures 2 and 3B). For physical functioning, median TDD was 16.6 months (95% CI, 11.3-21.5) vs 7.5 months (95% CI, 4.9-9.5; hazard ratio, 0.53 [95% CI, 0.40-0.70]; *P* < .0001), respectively (Figures 2 and 3C). Furthermore, median TDD was longer for both emotional and social functioning scores with T-DXd vs physician's choice (Figure 2). The median TDD for emotional functioning was 19.2 months (95% CI, 16.3-24.5) with T-DXd and 10.5 months (7.1-not estimable) with physician's choice (hazard ratio, 0.69 [95% CI, 0.50-0.96]; *P* = .0266); median TDD for social functioning was 12.8 months (95% CI, 10.4-15.2) vs 6.0 months (95% CI, 4.4-7.7; hazard ratio, 0.59 [95% CI, 0.45-0.77]; *P* = .0001), respectively.

From the EORTC QLQ-BR45, median TDD for arm symptoms (eg, pain, swelling, difficulty moving) favored T-DXd over physician's choice (Figure 2). Specifically, median TDD for arm symptoms was 14.4 months (95% CI, 11.9-23.0) vs 8.7 months (95% CI, 5.6-not estimable; hazard ratio, 0.62 [95% CI, 0.45-0.85]; *P* = .0027), respectively. For breast symptoms, median TDD for T-DXd and physician's choice was not estimable (hazard ratio 0.70 [95% CI, 0.46-1.1]; *P* = .1008).

The impact of treatment on common drug-related TEAEs (EORTC QLQ-C30: fatigue; nausea and vomiting) over time was further evaluated as an additional analysis. Fatigue scores remained stable over time in both treatment groups (Table S3), with prolonged TDD for T-DXd vs physician's choice (hazard ratio, 0.61 [95% CI, 0.47-0.79]; *P* = .0002) (Figure 2). The median TDD of nausea/vomiting scores was shorter among patients who received T-DXd (5.7 months [95% CI, 3.8-8.4]) vs physician's choice (9.3 months [95% CI, 7.5-17.1]; hazard ratio, 1.46 [95% CI, 1.09-1.96; *P* = .0128). While there was an increase in nausea and vomiting score from baseline for patients in the T-DXd group, the change was only clinically relevant in cycles 3 and 5, after which scores decreased and then remained stable over time from cycle 7 to cycle 27 (Figure 4).

Additional analyses of VAS scores from the EQ-5D-5L questionnaire yielded a prolonged median TDD for HR+ patients who received T-DXd vs physician's choice (Figure 2); median TDD was 12.0 months (95% CI, 9.9-15.2) vs 6.8 months (95% CI, 4.9-11.4; hazard ratio, 0.73 [95% CI, 0.54-0.97]; *P* = .0288), respectively. Change from baseline and TDD for additional PRO measures from the EORTC QLQ-C30

**Table 1.** Demographics and baseline characteristics in the HR+ cohort.[14]

| Baseline characteristics | T-DXd (*n* = 331) | Physician's choice (*n* = 163) |
|---|---|---|
| Age, median (range), years | 56.8 (31.5-80.2) | 55.7 (28.4-80.0) |
| Race, *n* (%)[a] | | |
| Asian | 131 (39.6) | 66 (40.5) |
| Black | 7 (2.1) | 2 (1.2) |
| Missing data | 0 | 1 (0.6) |
| Other | 37 (11.2) | 16 (9.8) |
| White | 156 (47.1) | 78 (47.9) |
| Ethnic group, *n* (%)[a] | | |
| Hispanic or Latino | 14 (4.2) | 5 (3.1) |
| Non-Hispanic or Non-Latino | 267 (80.7) | 137 (84.0) |
| Not applicable | 41 (12.4) | 17 (10.4) |
| Unknown | 9 (2.7) | 4 (2.5) |
| Region, *n* (%) | | |
| Asia | 128 (38.7) | 60 (36.8) |
| Europe or Israel | 149 (45.0) | 73 (44.8) |
| North America | 54 (16.3) | 30 (18.4) |
| HER2-low status, *n* (%)[b] | | |
| IHC 1+ | 193 (58.3) | 95 (58.3) |
| IHC 2+/ISH− | 138 (41.7) | 68 (41.7) |
| ECOG performance status, *n* (%)[c] | | |
| 0 | 187 (56.5) | 95 (58.3) |
| 1 | 144 (43.5) | 68 (41.7) |
| Metastasis at baseline, *n* (%) | | |
| Brain | 18 (5.4) | 7 (4.3) |
| Liver | 247 (74.6) | 116 (71.2) |
| Lung | 98 (29.6) | 58 (35.6) |
| Visceral | 298 (90.0) | 146 (89.6) |
| Lines of therapy for metastatic disease, *n* (%) | | |
| 1 | 23 (6.9) | 14 (8.6) |
| 2 | 85 (25.7) | 41 (25.2) |
| ≥ 3 | 223 (67.4) | 108 (66.3) |

HR+ status was based on interactive voice-response system data at the time of randomization.
[a]Race and ethnic group were reported by the patients. Available options for race included: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other. Patients could select multiple races. In countries that did not allow collection of this information, the patient's race and/or ethnicity was categorized as "Not Applicable."
[b]Low expression of HER2 was defined as a score of 1+ on IHC analysis or as an IHC score of 2+ and negative results on ISH.
[c]Performance status scores on the ECOG scale range from 0 (no disability) to 5 (death).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; physician's choice, physician's choice of chemotherapy.

and EORTC QLQ-BR45 for the HR+ cohort are shown in Supplementary Materials (Table S3, Figure S2). Median TDD results from the all-patients and HR− cohorts also favored T-DXd vs physician's choice (Tables S4 and S5).

### Hospital utilization

In the HR+ cohort, hospitalization rates were similar between treatment groups; 27.5% (91/331) of patients receiving T-DXd and 20.2% (33/163) of patients receiving physician's choice were hospitalized during the trial (Table S6). Time to first hospitalization was delayed with T-DXd (151.0 days [range, 0-742]) vs physician's choice (53.5 days [range, 5-282]); median duration of hospital stay per patient was similar between groups at 10 days and 7 days, respectively.

## Discussion

In DESTINY-Breast04, treatment for patients who received T-DXd lasted for more than twice as long as that for patients who received physician's choice (median treatment duration: 8.2 vs 3.5 months, respectively),[14] and GHS/QoL (primary PRO of interest) was maintained compared with baseline scores during the entire treatment period for both groups

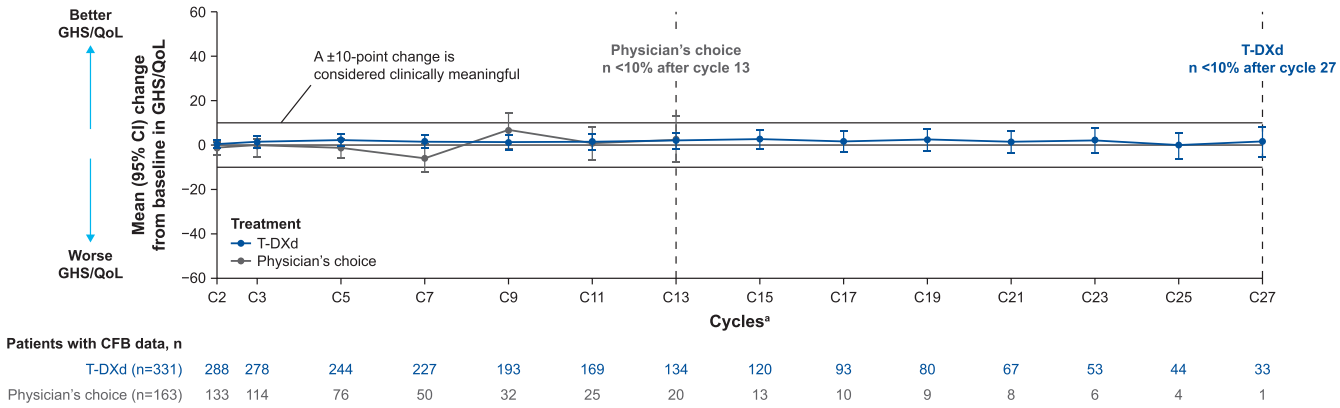


**Figure 1. GHS/QoL change from baseline with T-DXd and physician's choice of chemotherapy over time in the HR+ cohort.** C, cycle; CFB, change from baseline; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hormone receptor; physician's choice, physician's choice of chemotherapy; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DXd, trastuzumab deruxtecan. HR+ status was based on interactive voice-response system data at the time of randomization. GHS/QoL score is from the EORTC QLQ-C30. Scores range from 0 to 100; a higher score represents higher ("better") GHS/QoL. Data between T-DXd and physician's choice treatment groups are only interpretable through cycle 13 (after which the number of patients with available change from baseline data fell below 10% in the physician's choice group). Data in the T-DXd treatment group are interpretable through cycle 27 (after which the number of patients with available change from baseline data fell below 10%). [a] On day 1 of cycle.

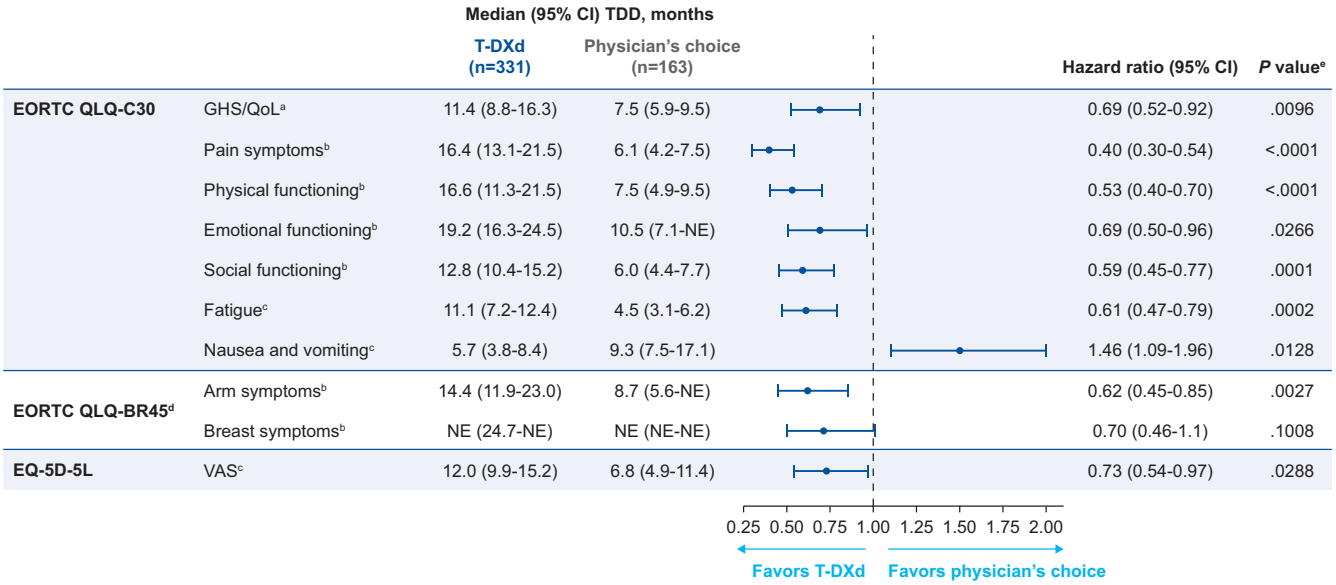


**Figure 2. Forest plot of time to definitive deterioration in PRO measures of interest with T-DXd and physician's choice of chemotherapy in the HR+ cohort.** EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hormone receptor; NE, not estimable; physician's choice, physician's choice of chemotherapy; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale. HR+ status was based on interactive voice-response system data at the time of randomization. Clinically meaningful definitive deterioration was defined as a change of ≥ 10 points from baseline, at either 2 or more consecutive time points, last PRO assessment, or death by the first survival follow-up visit. [a] Primary PRO variable of interest. [b] Secondary PRO variable of interest. [c] TDD of fatigue, nausea/vomiting, and EQ-5D-5L VAS were additional analyses. [d] Scored using the EORTC QLQ-BR23 algorithm. [e] Nominal *P* value not adjusted for multiple testing.

(T-DXd, 27 cycles; physician's choice, 13 cycles), supporting that the longer, more effective treatment with T-DXd translated to favorable maintenance of patient health-related QoL, as suggested by mean CFB data for the HR+ cohort. Moreover, even with a substantially longer treatment duration (during which risk for treatment-related TEAEs can accumulate), T-DXd was favored over physician's choice for maintaining health-related QoL, as indicated by prolonged median TDD for GHS/QoL scores. Median TDD for secondary prespecified PRO variables of interest also favored T-DXd, including TDD of pain, suggesting that multiple aspects of health-related QoL were maintained longer before deterioration for patients receiving T-DXd vs physician's choice. This favorable outcome in pain symptoms is particularly important since pain can have a substantial impact on health-related QoL, including in patients with breast cancer.[22] Furthermore, patients in the T-DXd group had a 2.8-fold longer time to first hospitalization compared with the physician's choice group, which can have meaningful personal and economic implications.

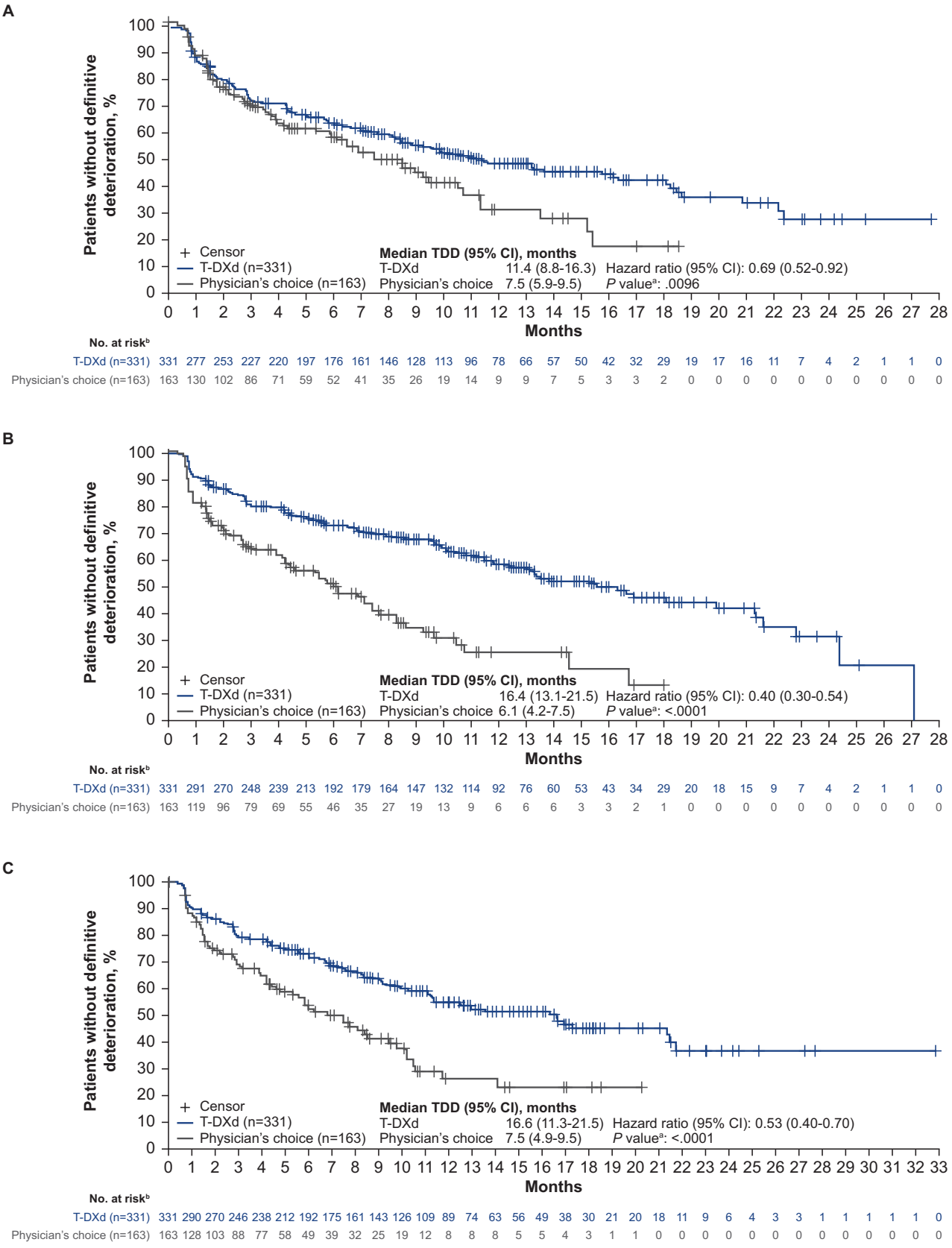


**Figure 3. Kaplan-Meier plot of time to definitive deterioration of (A) GHS/QoL, (B) pain, and (C) physical functioning with T-DXd and physician's choice of chemotherapy in the HR+ cohort.** EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; physician's choice, physician's choice of chemotherapy; PRO, patient-reported outcome; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan. GHS/QoL, pain symptoms, and physical functioning are scales of the EORTC QLQ-C30. Clinically meaningful definitive deterioration was defined as a change of ≥ 10 points from baseline at either 2 or more consecutive time points, last PRO assessment, or death by the first survival follow-up visit. [a] Nominal *P* value not adjusted for multiple testing. [b] All patients were included in the analysis; patients without baseline assessments were censored per the statistical analysis plan.

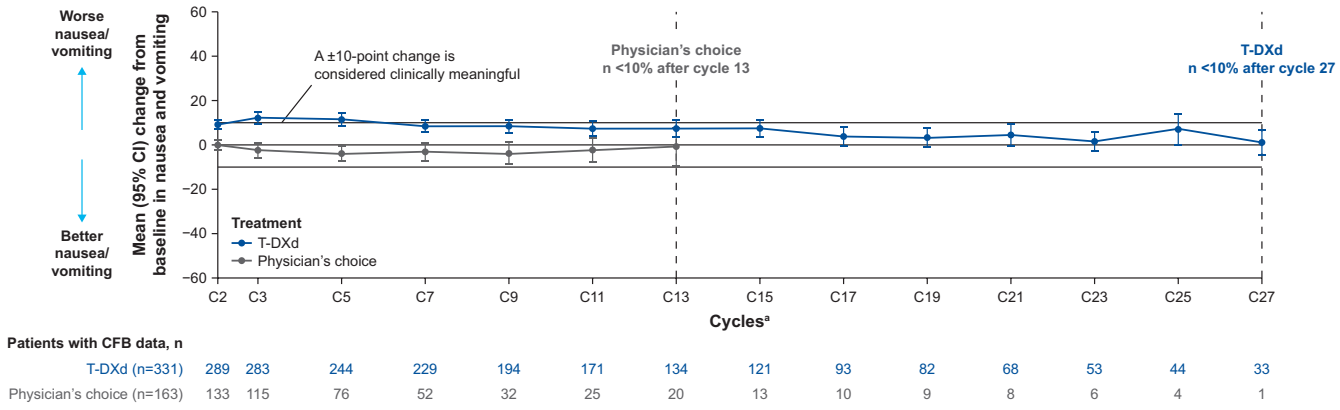


**Figure 4. Nausea and vomiting change from baseline with T-DXd and physician's choice of chemotherapy over time in the HR+ cohort.** C, cycle; CFB, change from baseline; EORTC, European Organization for Research and Treatment of Cancer; physician's choice, physician's choice of chemotherapy; QLQ-C30, Quality of Life Core 30 questionnaire; T-DXd, trastuzumab deruxtecan. Nausea and vomiting is a score from the EORTC QLQ-C30. Scores range from 0 to 100; a higher score represents higher ("worse") symptomology. Data between T-DXd and physician's choice treatment groups are only interpretable through cycle 13 (after which the number of patients with available change from baseline data fell below 10% in the physician's choice group). Data in the T-DXd treatment group are interpretable through cycle 27 (after which the number of patients with available change from baseline data fell below 10%). [a] On day 1 of cycle.

The effect of T-DXd over time on EORTC QLQ-C30 nausea and vomiting was worse than with physician's choice; however, patients treated with T-DXd had a clinically significant increase in nausea and vomiting only during early cycles, after which scores decreased and then remained stable over time. This aligns with the primary report of the current study in which predominantly low-grade (grade 1 or 2) nausea (68.5%) and vomiting (32.6%) were among the most common drug-related TEAEs with T-DXd; grade ≥ 3 drug-related nausea and vomiting was reported by 4.6% and 1.3% of patients, respectively.[14] A recent presentation on detailed safety findings from DESTINY-Breast04 reported that 1 patient (0.3%) receiving T-DXd discontinued because of drug-related nausea and 1 (0.3%) because of vomiting vs none in the physician's choice arm, and that median duration of nausea was 10 days and 5 days for patients receiving T-DXd and physician's choice, respectively.[23] Although antiemetics (eg, 5-hydroxytryptamine receptor antagonists, neurokinin-1 receptor antagonists, and/or steroids [eg, dexamethasone]) were recommended per physician discretion and administered in accordance with prescribing information or institutional guidelines, the use of antiemetic prophylaxis in DESTINY-Breast04 was not mandatory.[23] Among all patients in DESTINY-Breast04, only 50.9% of patients in the T-DXd arm and 37.2% in the physician's choice arm received antiemetic prophylaxis.[23] Despite findings of elevated gastrointestinal symptoms in the first few cycles of treatment among patients who received T-DXd compared with physician's choice, GHS/QoL scores favored T-DXd and remained stable over the course of treatment. Nonetheless, special attention to and treatment of nausea and vomiting may better support patients on treatment with T-DXd and improve patient outcomes. Indeed, appropriate management of these symptoms has been shown to have a positive impact on health-related QoL.[24] It has been proposed that effective prevention and management of nausea and vomiting has a favorable effect on the patient's overall experience with T-DXd, especially if patients receive T-DXd for an extended duration; therefore, management of nausea and vomiting should begin at treatment initiation.[25] Additionally, a comprehensive approach that encompasses both preventive measures and treatment strategies for acute and delayed nausea is warranted because the timing of symptom emergence could vary across treatment cycles.[25] Finally, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis have now categorized T-DXd as highly emetogenic. In addition, the European Society for Medical Oncology guidelines categorized T-DXd at the high end of the moderate emetic-risk category.[26] Therefore, it is essential to provide appropriate management for nausea in accordance with these guidelines.[26,27]

The PRO findings presented here complement the primary efficacy analyses from DESTINY-Breast04 and align with secondary PRO endpoints from 2 recent phase 3 trials of T-DXd in patients with HER2+ mBC: DESTINY-Breast02 and DESTINY-Breast03.[28,29] In addition to showing improvement in PFS and an acceptable safety profile for patients with HER2+ mBC,[28,29] findings from DESTINY-Breast02 and DESTINY-Breast03 demonstrated that GHS/QoL was maintained for the duration of treatment with T-DXd and that TDD for prespecified PRO measures was longer with T-DXd vs comparators, including for pain.[30,31] These favorable observations in pain symptoms across studies of T-DXd in breast cancer are noteworthy given that pain management is an important consideration in clinician decisions.[32] Furthermore, the PRO findings with T-DXd in DESTINY-Breast03 were in comparison to trastuzumab emtansine, which is associated with AEs that are generally low grade and manageable.[29,30,33-35] The current DESTINY-Breast04 analysis further supports the health-related QoL benefit of T-DXd through comparison with standard chemotherapy treatments, which can be associated with major safety concerns.[36,37] Specifically, in patients with early-stage invasive breast cancer, increased incidence rates of severe/very severe pain, nausea, diarrhea, constipation, and dyspnea have been observed in patients who received chemotherapy vs those who did not.[37] Thus, the PRO findings from DESTINY-Breast04 are important in that they suggest maintenance and improvement in QoL, particularly pain symptoms, with T-DXd over standard chemotherapy and support the overall benefit of T-DXd in HER2-low/HR+ mBC.

To our knowledge, this report is the first peer-reviewed evaluation of PROs in patients with HER2-low mBC and offers novel insights into patients' experiences with T-DXd and comparator chemotherapies. A strength of the study is that the PRO endpoints and analyses were prespecified in DESTINY-Breast04; prospective inclusion of well-documented PRO measures encourages methodologic rigor for PRO analyses in clinical trials and validates the importance of capturing the patient experience.[3,4,38] Patients were highly compliant with health-related QoL assessments throughout the duration of the trial, allowing for in-depth assessment of their experiences over time.

One limitation is that CFB and TDD results may be affected by an imbalance between arms in missing PRO data patterns over time. Additionally, although the trial's open-label design could be considered a limitation because of potential bias from patient responses,[39] a recent review suggests that patient perspectives are not affected by treatment concealment design (blinded vs open-label). Other studies have also shown that patients do not report their experience differently after knowing their treatment assignment.[40-44] Finally, no prespecified PRO subgroup analyses were conducted for this study.

From the patient's perspective, T-DXd maintained health-related QoL and delayed definitive deterioration across prespecified PRO scales vs standard chemotherapy treatments. These findings complement the primary efficacy and safety results from DESTINY-Breast04. Furthermore, after a 32-month median follow-up in DESTINY-Breast04 (data cutoff, March 1, 2023), sustained improvement and a generally manageable safety profile with T-DXd vs physician's choice suggest that long-term treatment with T-DXd is feasible.[45] Importantly, appropriate management of AEs and use of preventive measures (ie, antiemetic prophylaxis for nausea and vomiting) may improve treatment tolerability and further support patient health-related QoL. Together, these results support the use of T-DXd as a standard of care for patients with HR+/HER2-low mBC.

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## Author contributions

Naoto T. Ueno (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Francesco Cottone (Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Kyle Dunton (Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), William Jacot (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Toshinari Yamashita (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Joohyuk Sohn (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Eriko Tokunaga (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Aleix Prat (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Junji Tsurutani (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Yeon Hee Park (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Hope S. Rugo (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Binghe Xu (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Fatima Cardoso (Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Zahi Mitri (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Reshma Mahtani (Data acquisition, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Cecilia Orbegoso Aguilar (Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Feng Xiao (Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), Nadia Harbeck (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), David A. Cameron (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript), and Shanu Modi (Conception/design of the work, Analysis and interpretation of the data, Writing and reviewing of the manuscript, Approved the final version of the manuscript)

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## Conflicts of interest

**N.T.U.** reports grant funding, consulting fees, and honoraria from Daiichi Sankyo.

**F.C.** is an employee of Daiichi Sankyo IT.

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## Data availability

Anonymized individual participant data (IPD) on completed studies and applicable supporting clinical study documents may be available upon request at https://vivli.org/. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of the company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/.

## Supplementary material

Supplementary material is available at *The Oncologist* online.

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