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ORIGINAL ARTICLE

Patient-reported outcomes and hospitalization data in patients with HER2-positive metastatic breast cancer receiving trastuzumab deruxtecan or trastuzumab emtansine in the phase III DESTINY-Breast03 study

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Background: In the DESTINY-Breast03 clinical trial, trastuzumab deruxtecan (T-DXd) showed superior progression-free survival and overall survival versus trastuzumab emtansine (T-DM1) and manageable safety in patients with human epidermal growth factor receptor 2 (HER2)-positive (HER2+) metastatic breast cancer. Here, patient-reported outcomes (PROs) are reported along with hospitalization data.

Patients and methods: Patients in DESTINY-Breast03 were assessed for prespecified PRO measures, including European Organization for Research and Treatment of Cancer quality of life (EORTC-QoL) questionnaires [the oncology-specific EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and breast cancer-specific EORTC QLQ-BR45] and the generic EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) visual analogue scale. Analyses included change from baseline, time to definitive deterioration (TDD), and hospitalization-related endpoints.

Results: EORTC QLQ-C30 baseline global health status (GHS) scores for T-DXd ($n = 253$) and T-DM1 ($n = 260$) were similar, with no clinically meaningful change (<10-point change from baseline) while on either treatment (median treatment duration: T-DXd, 14.3 months; T-DM1, 6.9 months). TDD analyses of QLQ-C30 GHS (primary PRO variable) and all other prespecified PROs (QLQ-C30 subscales, the QLQ-BR45 arm symptoms scale, and the EQ-5D-5L visual analogue scale) suggested T-DXd was numerically favored over T-DM1 based on TDD hazard ratios. Of all randomized patients, 18 (6.9%) receiving T-DXd versus 19 (7.2%) receiving T-DM1 were hospitalized, and the median time to first hospitalization was 219.5 versus 60.0 days, respectively.

Conclusions: In DESTINY-Breast03, EORTC GHS/QoL was maintained on both therapies throughout treatment, indicating that despite the longer treatment duration with T-DXd versus T-DM1, health-related QoL did not worsen on T-DXd. Furthermore, TDD hazard ratios numerically favored T-DXd over T-DM1 in all prespecified variables of interest including pain, suggesting T-DXd may delay time until health-related QoL deterioration compared with T-DM1. Median time to first hospitalization was three times longer with T-DXd versus T-DM1. Together with reported improved efficacy and manageable toxicity, these results support the overall benefit of T-DXd for patients with HER2+ metastatic breast cancer.

Key words: breast cancer, hospitalization, quality of life, trastuzumab deruxtecan, trastuzumab emtansine

INTRODUCTION

The human epidermal growth factor receptor 2 (HER2) oncogene is overexpressed in ~20% of breast cancers[1,2] and, if not treated with anti-HER2 therapeutics, is associated with shorter overall survival (OS) and a higher risk of recurrence compared with HER2-negative (HER2−) disease.[3] In addition to its prognostic role, HER2 has also been extensively evaluated as a therapeutic target in breast cancer.

In the first interim analysis of PFS for the phase III DESTINY-Breast03 study (data cut-off: May 21, 2021), the HER2-targeted antibody–drug conjugate trastuzumab deruxtecan (T-DXd) demonstrated a clinically meaningful improvement in progression-free survival (PFS) and OS

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versus trastuzumab emtansine (T-DM1) in previously treated patients with HER2-positive (HER2+) metastatic breast cancer (mBC).[4] After a median treatment duration of 14.3 and 6.9 months, and a median duration of study follow-up of 16.2 and 15.3 months for T-DXd and T-DM1, respectively, the median PFS by blinded independent central review (BICR) was not estimable (NE) with T-DXd [95% confidence interval (CI) 18.5 months to NE; $n = 261$] versus 6.8 months with T-DM1 [95% CI 5.6-8.2 months; $n = 263$; hazard ratio (HR), 0.28 (95% CI 0.22-0.37; $P < 0.001$)], demonstrating the superiority of T-DXd for treating this population.[4]

Consistent with the known safety profile of T-DXd in various HER2+ cancers, treatment-emergent adverse events (TEAEs) were manageable in the DESTINY-Breast03 study. The most common drug-related TEAEs were gastrointestinal, including nausea (72.8%) and vomiting (44%) in the T-DXd group (versus 27.6% and 5.7% in the T-DM1 group). Most grade ≥3 drug-related TEAEs occurring in patients receiving T-DXd were hematological, such as neutropenia (19.1%), thrombocytopenia (7%), and leukopenia (6.6%).[4] In line with the safety results from previous studies of T-DXd in HER2+ breast cancer,[5] adjudicated drug-related interstitial lung disease (ILD)/pneumonitis occurred in 10.5% of patients receiving T-DXd and 1.9% of those receiving T-DM1; all cases were grade ≤3.[4] On the basis of these efficacy and safety results from DESTINY-Breast03, T-DXd was approved for the treatment of unresectable or metastatic HER2+ breast cancer after ≥1 line of prior anti-HER2-based regimen(s) in the metastatic setting or with recurrence <6 months after neoadjuvant/adjuvant therapy.[6-8]

Apart from efficacy and safety metrics, patient-reported outcomes (PROs) have become increasingly important ancillary measures in breast cancer clinical studies, given that both the disease and its treatments can negatively affect patients' health-related quality of life (HRQoL).[9] PRO endpoints incorporate patient self-assessments of symptoms and functional deficits into the risk/benefit analysis of a drug's therapeutic value.[10] Hospital admission is another clinically important event that speaks to overall patient health and healthcare utilization/costs. Assessing hospitalization events can inform best practices for managing/reducing disease burden in at-risk individuals, thereby providing insights that may optimize monitoring and mitigate future hospital admissions and costs for healthcare services.[11] Here, we present the health economics and outcomes research (HEOR) results from the first interim analysis of the DESTINY-Breast03 study, comparing the impact of T-DXd and T-DM1 on PROs and hospitalization events to determine the effect of treatment on patients' HRQoL.

METHODS

Study design

DESTINY-Breast03 (ClinicalTrials.gov NCT03529110) is an open-label, multicenter, phase III study investigating the efficacy and safety of T-DXd versus T-DM1 in patients with HER2-positive, unresectable, and/or metastatic breast cancer (Figure 1). The study's design and interim efficacy and safety results have been published previously.[4]

This study was sponsored and designed by Daiichi Sankyo and funded by AstraZeneca and Daiichi Sankyo. 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 Harmonization 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.

Patients and treatments

Eligible patients had experienced disease progression on or after trastuzumab and a taxane in the advanced/metastatic setting, or within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane. Exclusion criteria included the presence of clinically active central nervous system metastases, previous treatment with an HER2 antibody–drug conjugate, or a history of noninfectious ILD for which they had received glucocorticoids or suspected ILD that could not be ruled out by imaging at screening. Full inclusion and exclusion criteria can be found in the study protocol.[4]

Patients were randomly assigned 1 : 1 to receive T-DXd (starting dose 5.4 mg/kg) or T-DM1 (starting dose 3.6 mg/kg), each administered intravenously every 3 weeks (=1 cycle). Study treatment continued until withdrawal of subject consent, progressive disease, or unacceptable toxicity.

HEOR endpoints

Secondary objectives of DESTINY-Breast03 included the evaluation of HEOR endpoints for patients treated with T-DXd versus T-DM1, including PROs and hospitalizations. PRO endpoints were assessed before infusion on day 1 of cycles 1-3 and then every 2 cycles (5, 7, 9, etc.); at the end of treatment; at day 40 (+7 days) following the last infused dose of T-DXd or T-DM1 (or before starting new anticancer treatment, whichever comes first); and then 3 months (±14 days) after the 40-day follow up (Figure 1). The primary PRO variable of interest was the global health status (GHS)/QoL score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Secondary PRO variables of interest included physical, emotional, and social functioning subscale scores and pain symptom subscale scores of the EORTC QLQ-C30, symptoms scale scores of the breast cancer-specific instrument EORTC QLQ-BR45, and the visual analogue scale (VAS) score of the EuroQoL 5-dimension 5-level questionnaire (EQ-5D-5L). Hospitalization measures of interest included date of admission to hospital, primary reason for hospitalization, and status/date of discharge. Main analyses included change from baseline (CFB) for EORTC-QLQ-C30 GHS scores; time to definitive deterioration (TDD) for EORTC QLQ-C30 GHS and select functioning/symptom subscale scores; EORTC QLQ-BR45 symptoms subscale scores and EQ-5D-5L VAS scores; and both time to

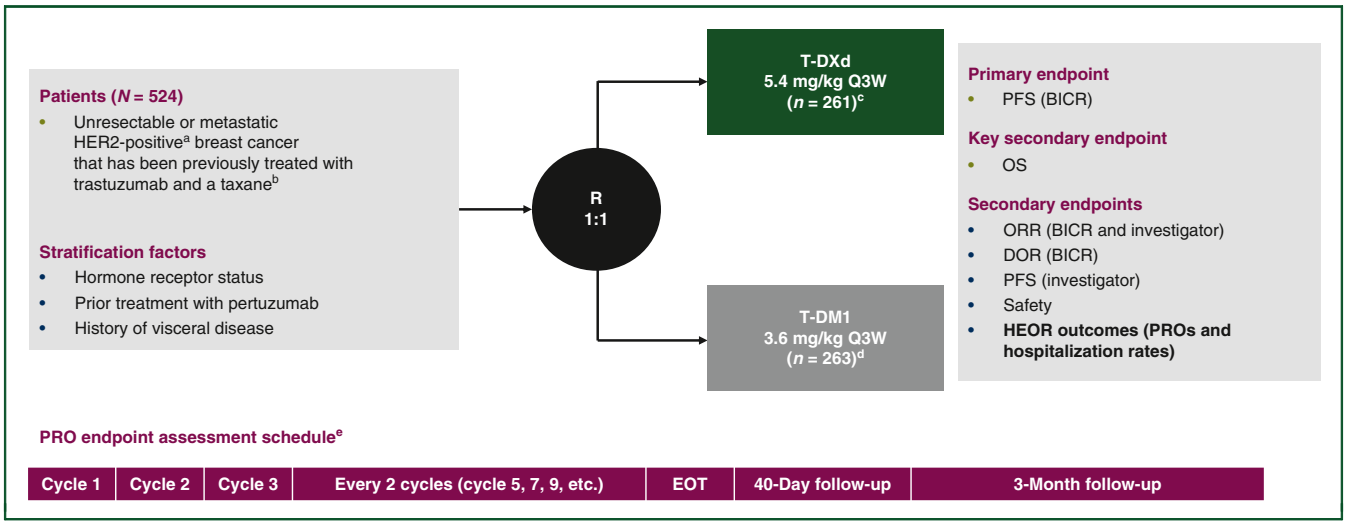

Figure 1. DESTINY-Breast03 study design.
BICR, blinded independent central review; DOR, duration of response; EOT, end of treatment; HEOR, health economics outcomes research; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation.
[b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane.
[c]Four patients were randomly assigned but not treated.
[d]Two patients were randomly assigned but not treated.
[e]1 Cycle = 21 days; T-DXd or T-DM1 administered on day 1 of each cycle; questionnaires completed before treatment on day 1 of cycles indicated.

first hospitalization and length of stay for hospitalization assessments.

Statistical analyses

To assess the primary PRO of interest, EORTC QLQ-C30 GHS/QoL scores were calculated at each assessment.[12] Secondary analyses were based on CFB in GHS/QoL and all prespecified subscales obtained from EORTC QLQ-C30 and QLQ-BR45, which were selected based on those deemed to be of high clinical and/or patient interest and analyzed using a linear mixed-effect model for longitudinal data to assess the treatment effect over time, including terms for treatment, randomization stratification factors, time of visit, and treatment by time of visit interaction.[4] Since the QLQ-BR45 scoring algorithm has not yet been validated, all data captured with QLQ-BR45 were scored using the algorithm for QLQ-BR23. For the mixed-effects model, patients with baseline and at least one postbaseline assessment were included. Analysis only included assessments up to the time point where there were at least 50 patients on each treatment. EORTC QLQ-C30 GHS/QoL and functioning scores and EQ-5D-5L VAS scores range from 0 to 100, such that a high GHS/QoL or VAS score represents a high QoL and a high score for a functional scale represents a high level of functioning. Symptom subscale scores of the EORTC QLQ-C30 and BR45 instruments were reported such that a high score for symptom scales represents a high level of symptomatology. Data that were missing for the GHS/QoL scale score of the EORTC QLQ-C30 were analyzed using a pattern mixture model combined with multiple imputation. A 10-point CFB in GHS/QoL scores was considered clinically meaningful.[13]

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 $\geq$10-point CFB of the specific score in the direction of deterioration (positive for symptom scales, negative for all others), and deterioration on two or more consecutive visits or at last visit] is first seen, indicating clinically meaningful changes in HRQoL.[14,15] Note that death was also considered as deterioration of symptoms/HRQoL if it occurred by the first survival follow-up (3 months from the 40-day follow-up) when there were no baseline evaluable QoL and/or no postbaseline QoL assessments, or there were baseline and at least one postbaseline QoL assessments but no definitive deterioration was identified per above definition. Two-sided *P* value, HR, and 95% CI comparing TDD between the two treatment groups are based on a stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factors (hormone receptor status, prior treatment with pertuzumab, and history of visceral disease). As PROs were not included in the hierarchical testing plan for DESTINY-Breast03, reported *P* values are nominal. The survival distributions were estimated using the Kaplan—Meier method and the results are presented graphically.

For hospitalization-related endpoints, time to first hospitalization, and reason for hospitalization, discharge diagnosis, intensive care unit stay, and length of stay are reported based on case report form collection by site.

RESULTS

Patient characteristics and treatment

Between 20 July 2018 and 23 June 2020, 524 subjects were randomized at 169 study sites in 15 countries to receive

either T-DXd ($n = 261$) or T-DM1 ($n = 263$).[4] Demographics and baseline clinical characteristics were balanced between treatment arms (Table 1).[4] At data cut-off (21 May 2021), 132 (51.4%) patients in the T-DXd arm and 47 (18.0%) patients in the T-DM1 arm were still receiving study treatment.[4]

PROs

Most patients in both treatment groups completed the QoL questionnaires as prescribed in the trial, with >97% compliance at baseline, >82% compliance from cycles 3-27 (after which the number of patients on treatment in the T-DM1 arm dropped below 20 and PRO comparisons were no longer informative), and >90% compliance at the follow-up. Completion rates were low at cycle 2 (38.2% and 43.8% in the T-DXd and T-DM1 arms, respectively) as the requirement for HEOR assessment at this cycle was implemented after study initiation. Baseline scores were similar across most instrument scales between patients receiving T-DXd and T-DM1 (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.04.516).

GHS/QoL scores were maintained in patients on treatment with T-DXd (Figure 2 and Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.04.516; a lower score indicates a worse GHS/QoL). The mean change in the EORTC QLQ-C30 GHS/QoL score from baseline, including assessments up to the time point where there were at least 50 patients on each of the treatments, was −1.88 [standard deviation (SD), 17.60; $n = 71$; cycle 25] in the T-DXd arm and 0.67 (SD, 24.10; $n = 50$; cycle 19) in the T-DM1 arm. The least-squares mean CFB through the time at which at least 50 patients remained on each treatment (cycle 19) in the EORTC QLQ-C30 GHS/QoL score was 1.2 [standard error (SE), 1.51] and −2.9 (SE, 2.12) in the T-DXd and T-DM1 arms, respectively. Patients treated with T-DXd experienced numerically longer median TDD of QLQ-C30 GHS/QoL scores at 16.8 months compared with 14.4 months with T-DM1 [HR (95% CI), 0.85 (0.65-1.11)] (Figure 3).

Median TDD was longer with T-DXd versus T-DM1 across EORTC QLQ-C30 subscales, EORTC QLQ-BR45 symptom scales, and the EQ-5D-5L VAS, and the point estimates of HRs between the two treatments favored T-DXd for these measures (Figure 3). Kaplan−Meier analyses of TDD showed persistent separation between the treatment populations within 3-6 months of treatment start, both on the breast cancer symptom level [per EORTC QLQ-BR45 arm symptom scale: HR (95% CI), 0.6759 (0.5133-0.8900); nominal $P = 0.0048$, not adjusted for multiple testing; Figure 4] and in overall QoL [per the VAS score of the EQ-5D-5L instrument: HR (95% CI), 0.6869 (0.5200-0.9073); nominal $P = 0.0077$, not adjusted for multiple testing; Figure 5].

Finally, the impact of the most common drug-related TEAEs observed in T-DXd-treated patients on the study (i.e. nausea, vomiting, and fatigue)[4] was assessed in *post hoc* exploratory analyses. On the EORTC QLQ-C30 symptom subscales for nausea/vomiting, the TDD was shorter with T-DXd versus T-DM1 [median (95% CI) TDD, 7.3 months (4.4-12.5 months) versus NE (NE, NE); HR (95% CI), 2.11 (1.60-2.78); nominal $P < 0.0001$, not adjusted for multiple testing], with T-DXd-treated patients experiencing higher levels of symptomatology in the nausea/vomiting subscale during the first few cycles of treatment [mean CFB at cycle 7 = 10.95 (SD, 22.34); $n = 207$; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.04.516]. Among those receiving T-DXd, one patient discontinued treatment due to vomiting, and none discontinued due to nausea (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.04.516). On the fatigue symptom subscale, TDD was prolonged in patients receiving T-DXd [median (95% CI) TDD, 15.9 months (12.1-19.8 months) versus 10.3 months (6.2-15.2 months) with T-DM1; HR (95% CI), 0.78 (0.60-1.00); nominal $P = 0.0480$, not adjusted for multiple testing]. Overall, mean CFB in the fatigue symptom subscale was maintained with T-DXd (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.04.516).

Table 1. Baseline patient characteristics

Baseline characteristics	T-DXd $n = 261$	T-DM1 $n = 263$
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Region, *n* (%)		
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Europe	54 (20.7)	50 (19.0)
Rest of world	41 (15.7)	36 (13.7)
Hormone receptor status,[a] *n* (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
HER2 status,[b] *n* (%)		
3+	234 (89.7)	232 (88.2)
2+	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
Visceral disease,[a] *n* (%)		
Yes/No	184 (70.5)/77 (29.5)	185 (70.3)/78 (29.7)
Prior treatment of mBC,[c] *n* (%)	240 (92.0)	234 (89.0)
Pertuzumab	162 (62.1)	158 (60.1)
Prior lines of therapy for metastatic disease,[d] *n* (%)		
0-1	132 (50.6)	126 (47.9)
2+	129 (49.4)	137 (52.1)

From *New England Journal of Medicine*, Cortés J, Kim SB, Chung WP, et al., 'Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer,' volume 386, pages 1143-1154.[4] Copyright © (2022) Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

HER2, human epidermal growth factor receptor 2; ISH, *in situ* hybridization; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Based on information at stratification.

[b]HER2 status was evaluated by immunohistochemical analysis at a central laboratory. HER2 ISH-positive refers to positive results on *in situ* hybridization. HER2 status could not be evaluated for one patient in each treatment group.

[c]Excluding hormone therapy.

[d]Patients who had had rapid progression (i.e. progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy.

Hospitalization events

Hospitalization rates at the primary analysis were similar between the T-DXd arm (18/261; 6.9%) and T-DM1 arm

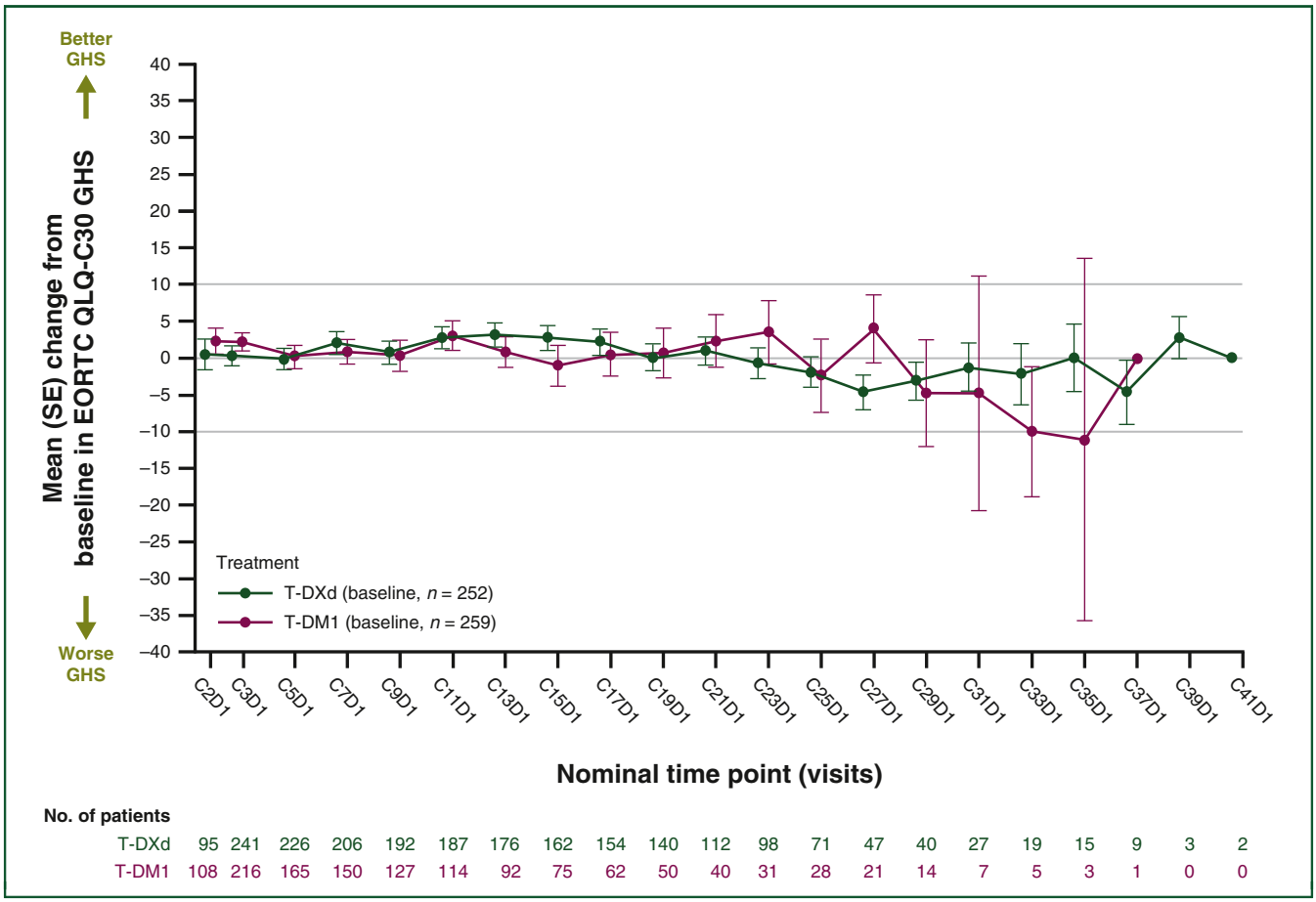

Figure 2. EORTC QLQ-C30 GHS change from baseline over time in patients treated with T-DXd versus T-DM1. Scores range from 0 to 100; a higher score represents higher ('better') GHS/overall QoL. At data cut-off (21 May 2021), the median (range) treatment duration was 14.3 (0.7-29.8) months for patients receiving T-DXd and 6.9 (0.7-25.1) months for patients receiving T-DM1.

C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health scale; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; SE, standard error; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

(19/263; 7.2%), and the median duration of hospital stay was also comparable (10.5 and 9.0 days, respectively; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.04.516). The median time to first hospitalization, however, was approximately three times longer for patients receiving T-DXd (219.5 days; range, 0-723 days) versus T-DM1 (60.0 days; range, 0-399 days; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.04.516).

DISCUSSION

PRO data from the first interim PFS analysis of DESTINY-Breast03 suggest that HRQoL was sustained with T-DXd across prespecified global measures and cancer-specific subscales, in accordance with its efficacy benefit in HER2+ mBC.[4] The median treatment duration was approximately twice as long with T-DXd (14.3 months) compared with T-DM1 (6.9 months), highlighting the importance of considering the effects of treatment on patients' HRQoL.[4] In both treatment arms, the EORTC QLQ-C30 GHS/QoL scale score, the primary PRO variable of interest in this study, did not show clinically significant CFB for the duration of treatment and follow-up, indicating that HRQoL was maintained on T-DXd despite a longer treatment duration.

The EORTC QLQ-C30 GHS/QoL and all other prespecified functional and symptom-based subscales of interest demonstrated HR point estimates for TDD that numerically favored T-DXd (HR range, 0.68-0.86), suggesting that T-DXd treatment delayed the deterioration of HRQoL in patients with HER2+ mBC. In an assessment of PRO symptom scales, TDD was numerically prolonged with T-DXd compared with T-DM1 in the EORTC QLQ-C30 fatigue symptom subscale. In the nausea/vomiting subscale, even though TDD was numerically shorter, scores for T-DXd-treated patients reverted toward baseline after cycle 7 and there was only one discontinuation due to vomiting and none due to nausea. This is consistent with the clinical profile in which the incidence of nausea/vomiting TEAEs peaked during initial treatment cycles, then became stable over time.[16]

PRO data are increasingly used to provide evidence supporting drug approval, particularly in oncology clinical studies.[17] The US Food and Drug Administration and European Society for Medical Oncology consider PROs in support of safety and efficacy in most types of oncology studies

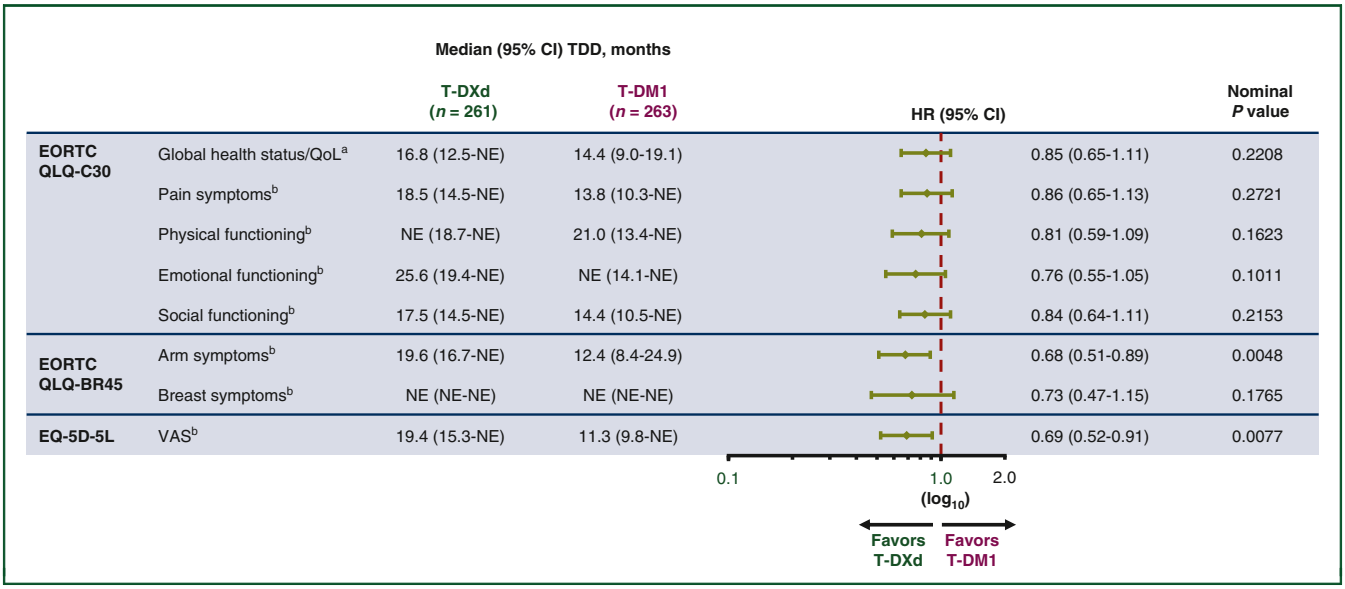

Figure 3. Difference in median TDD between patients treated with T-DXd versus T-DM1 in patient-reported QoL measures. PRO measures are reported such that a high GHS/QoL or VAS score represents a high QoL, a high score on functional scales represents a high level of functioning, and a high score on symptom scales represents a high level of symptomatology. 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 is first observed (i.e. a change exceeding +10 points for symptom scales, or a change exceeding −10 points for GHS, VAS, and functional scales, with deterioration on two or more consecutive visits or at last visit). *P* values are not adjusted for multiple testing.

CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health scale; HR, hazard ratio; NE, not estimable; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast Cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TDD, time to definitive deterioration; VAS, visual analogue scale.

[a]Primary PRO variable of interest.

[b]Secondary PRO variable of interest.

and strongly recommend use of validated PRO measures as a regular part of clinical care to better characterize treatment toxicities and enable earlier intervention.[7,9,18,19] Including PRO data in clinical guidelines may ensure wider acceptance of guideline recommendations among patients while enhancing implementation through health policy.[17] In hormone receptor-positive/HER2− mBC, for example, PROs have been used to support a drug's risk/benefit profile in most recent clinical trials leading to approval. A meta-analysis found that HRQoL was included as a secondary endpoint in 14 of 17 studies preceding approvals in this population.[20] In the majority of these studies, global HRQoL was maintained (although not significantly improved) by experimental treatments relative to baseline. When compared with control treatments, there was a consistent trend toward delays in TDD versus comparator treatments in the evaluable studies, with 2/10 studies achieving significant HRs favoring the experimental treatment.[20] Beyond informing drug approvals, PRO data like these can aid physicians in the dialogue with patients on their prospects for carrying on with their current lifestyle and level of well-being. In addition, specific symptom or functioning subscales together with existing frameworks for holistic patient engagement could help physicians weigh drug choice against treatment priorities with their patients, depending on individual symptom burden and functional expectations.

One of the most common concerns for patients is their symptom burden, with pain in particular being a frequently-reported outcome affecting HRQoL that is used to guide clinical decisions.[20] In DESTINY-Breast03, the median TDD was numerically improved for all prespecified scales, including pain, in patients receiving T-DXd versus T-DM1, and HRQoL was maintained while on treatment based on CFB in GHS/QoL scores. Moreover, the prolonged time to first hospitalization in the T-DXd arm may suggest a reduced burden for healthcare providers, hospitals, healthcare systems, payers, society, and patients. Low rates of hospitalization in both arms, however, limit data interpretation.

A key strength of this study is the high compliance rate for PRO questionnaires. Although the open-label design of DESTINY-Breast03 may be considered a limitation for assessing PROs because of the potential bias introduced by the patient's knowledge of treatment,[21] a recent meta-analysis of PROs in cancer studies suggests that blinding has no significant effect on the favorability of an experimental treatment.[22] An additional limitation is that PRO data were not collected beyond the first survival follow-up visit. In future studies, PRO assessments that continue during or after progression could provide additional perspective on how the course of disease impacts HRQoL in this patient population.

The potential for T-DXd treatment to prolong life and sustain HRQoL is important considering that those with HER2-overexpressing disease have historically had worse outcomes among patients with breast cancer.[3] Furthermore, such patient-focused outcomes are highly clinically relevant given the increased access to and use of T-DXd in real-world settings.

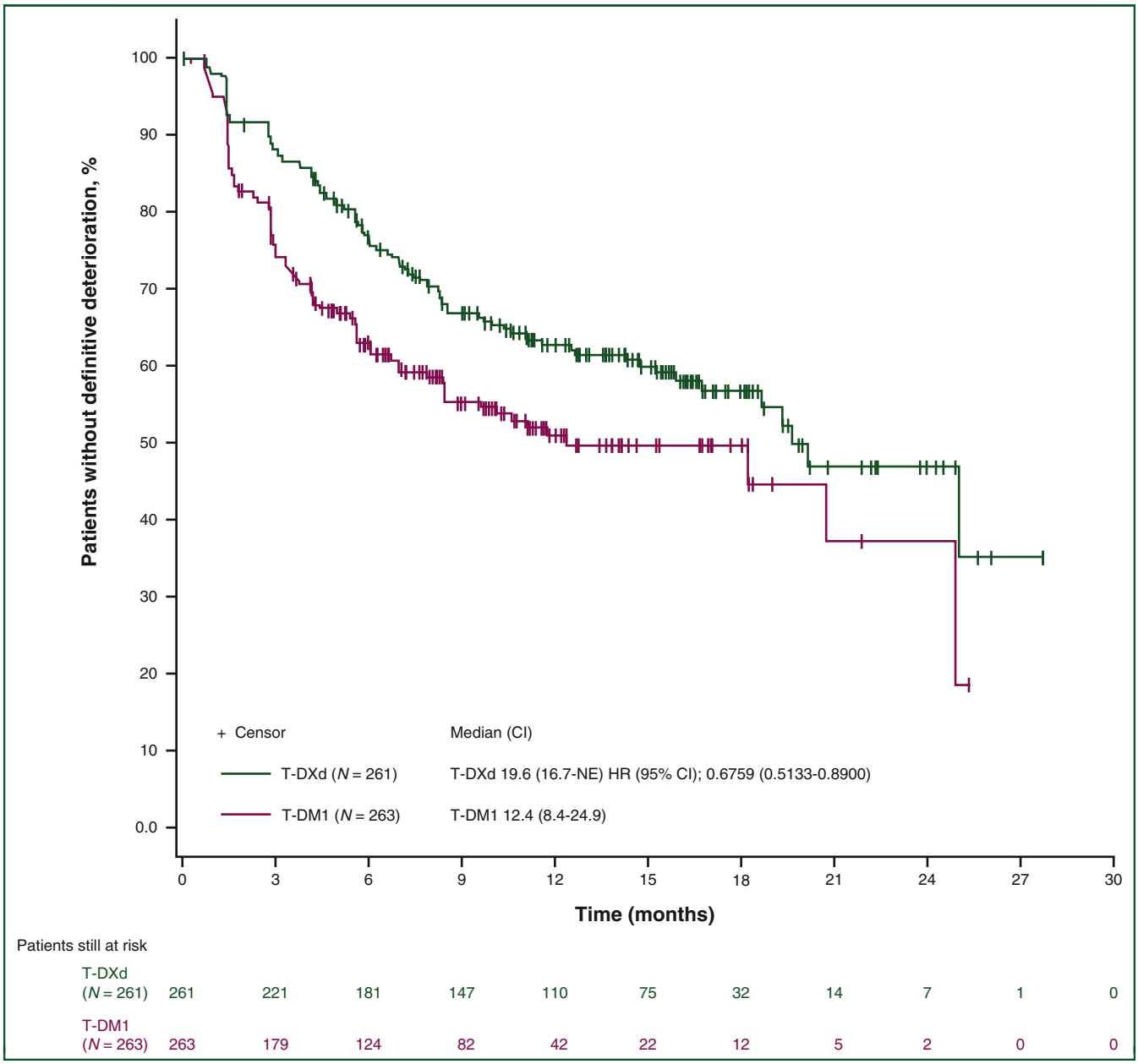

Figure 4. TDD of EORTC QLQ-BR45 arm symptom scores in patients treated with T-DXd versus T-DM1. A high score on symptom scales represents a high level of symptomatology. TDD was defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event is first observed (i.e. a change exceeding +10 points for symptom scales, or a change exceeding −10 points for GHS, VAS, and functional scales, with deterioration on two or more consecutive visits or at last visit). *P* values are nominal and were not adjusted for multiple testing.
CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health scale; HR, hazard ratio; NE, not estimable; QLQ-BR45, Quality of Life Breast Cancer questionnaire; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TDD, time to definitive deterioration; VAS, visual analogue scale.

Conclusion

Overall GHS/QoL in DESTINY-Breast03 was maintained for patients during treatment with T-DXd and T-DM1, indicating that HRQoL was sustained on T-DXd despite a longer treatment duration (median 14.3 months versus 6.9 months with T-DM1). TDD HRs of prespecified PROs were numerically favorable in patients receiving T-DXd compared with those treated with T-DM1, suggesting that HRQoL was maintained longer by those receiving T-DXd versus T-DM1. These PRO outcomes in patients with HER2+ mBC further support the benefit of T-DXd demonstrated by its improved efficacy (including superior PFS and OS) and manageable toxicity when compared with T-DM1 at both this first interim analysis (data cut-off, 21 May 2021) and an updated analysis (data cut-off, 25 July 2022).[4,23]

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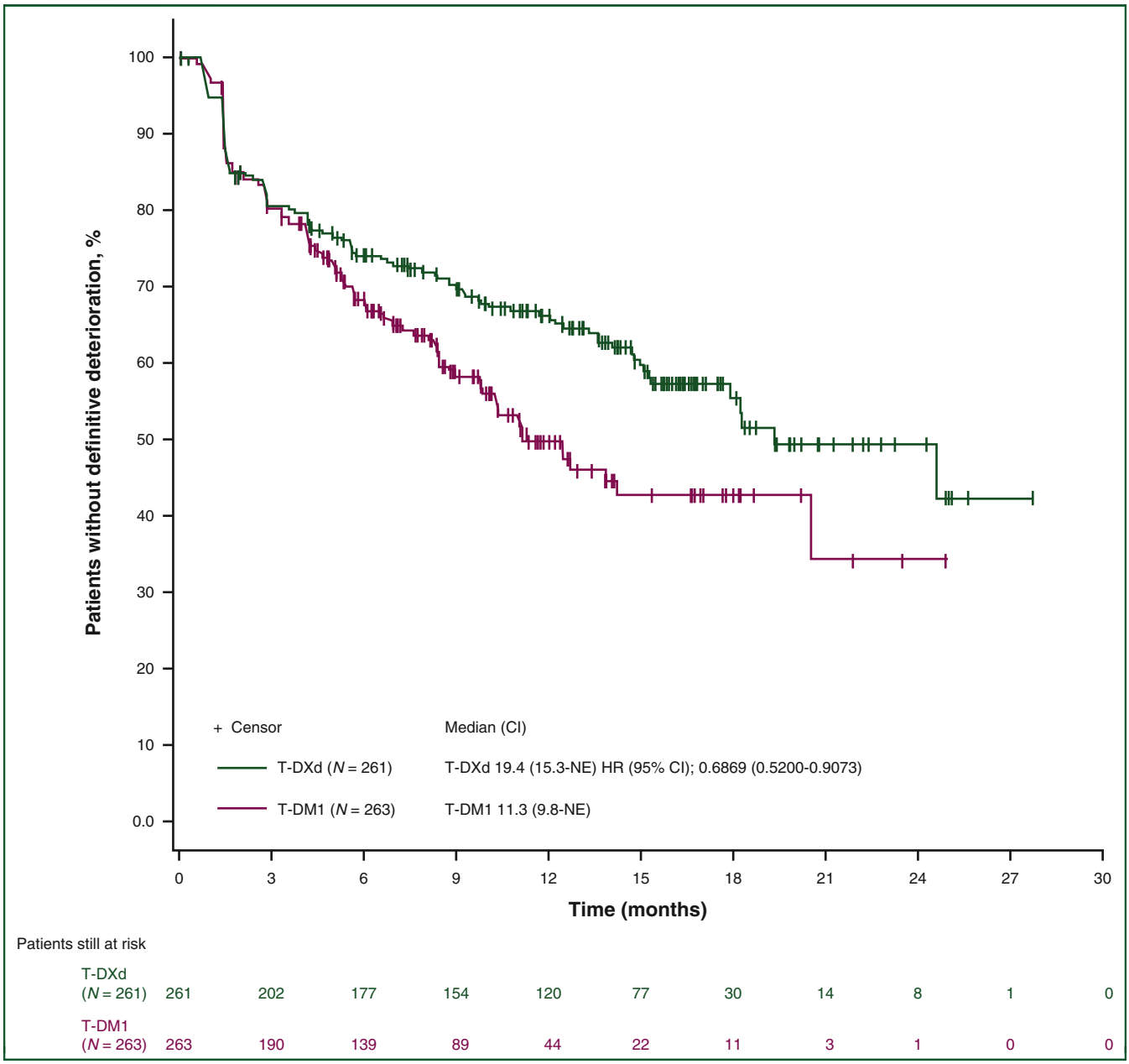

Figure 5. TDD of EQ-5D-5L VAS scores in patients treated with T-DXd versus T-DM1. A high score represents a high QoL. TDD was defined as the number of days between the date of randomization and the date of the assessment at which the definitive deterioration event is first observed (i.e. a change exceeding +10 points for symptom scales, or a change exceeding −10 points for GHS, VAS, and functional scales, with deterioration on two or more consecutive visits or at last visit). *P* values are nominal and were not adjusted for multiple testing.
CI, confidence interval; EQ-5D-5L, EuroQoL 5-dimension 5-level assessment; HR, hazard ratio; NE, not estimable; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TDD, time to definitive deterioration; VAS, visual analogue scale.

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