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DESTINY Breast06

Effects of trastuzumab deruxtecan vs choice of chemotherapy on patient-reported outcomes in hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer: results from DESTINY-Breast06

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On behalf of the DESTINY-Breast06 investigators

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Declaration of interests

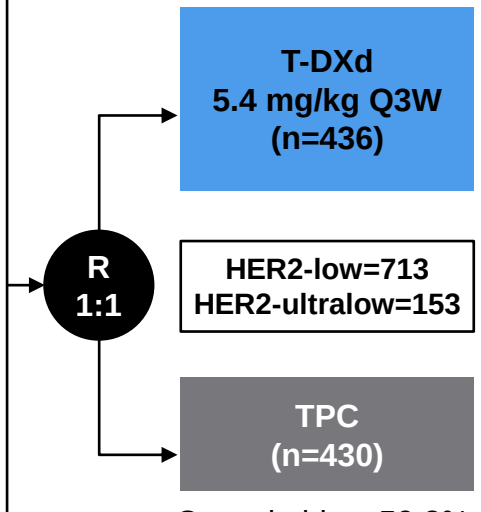
Commercial interests	Nature of relationship
MSD	Receipt of research funding
AstraZeneca	Advisory board participation / receipt of consultation fees

Background: study design and primary results[1]

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study[2]

Patient population
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) **OR** HER2-ultralow (IHC 0 with membrane staining)
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy
- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 mo after starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 mo after starting adjuvant ET



Primary endpoint
- PFS (BICR) in HER2-low

Secondary endpoints included
- PFS (BICR) in ITT (HER2-low + ultralow)
- Overall survival
- Safety and tolerability
- **Patient-reported outcomes** (HER2-low and ITT)

Patients
- **Median age** 57 years; ~40% **ECOG PS ≥1**; ~30% **de-novo mBC**; 67% **liver and related metastases**
- **Median duration of treatment:** T-DXd 11 mo; TPC 5.6 mo
- **Data cutoff:** March 18, 2024

Efficacy
- Median PFS
  - HER2-low: **T-DXd 13.2 mo** vs **TPC 8.1 mo** (hazard ratio **0.62**; P<0.0001)
  - ITT: **13.2 mo** vs **TPC 8.1 mo** (hazard ratio **0.63**; P<0.0001)
- OS data were ~40% mature

Safety
- Grade ≥3 treatment-related AEs: **40.6%** vs **31.4%**
- AE-associated treatment discontinuations: **14.3%** vs **9.4%**

The PRO analysis was conducted in the HER2-low and ITT populations (per the statistical analysis plan). Percentages are based on the number of treated patients in each arm
AE, adverse event; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. NCT04494425. Updated. July 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed September 9, 2024)

PRO endpoints and analyses

Questionnaire	Description	Measures of interest	Analyses	Definition of clinically meaningful change
EORTC QLQ-C30	Oncology-specific	• GHS/QOL • Functioning scales: physical, emotional, role, social, and cognitive • Symptom scales include:* pain, fatigue, nausea/vomiting, diarrhea constipation, appetite loss	• Change from baseline • Time to deterioration	• QLQ-C30/BR45 scales/items: change from baseline of **≥10 points** • Time to deterioration: change from baseline of **≥10 points** at either ≥2 consecutive timepoints‡ or last PRO assessment§ • Event (eg death) by first survival follow-up visit
EORTC QLQ-BR45	Breast cancer-specific	• Multi-item scores including:† skin mucosis symptoms, body image, sexual functioning, arm symptoms, breast symptoms	• Change from baseline	

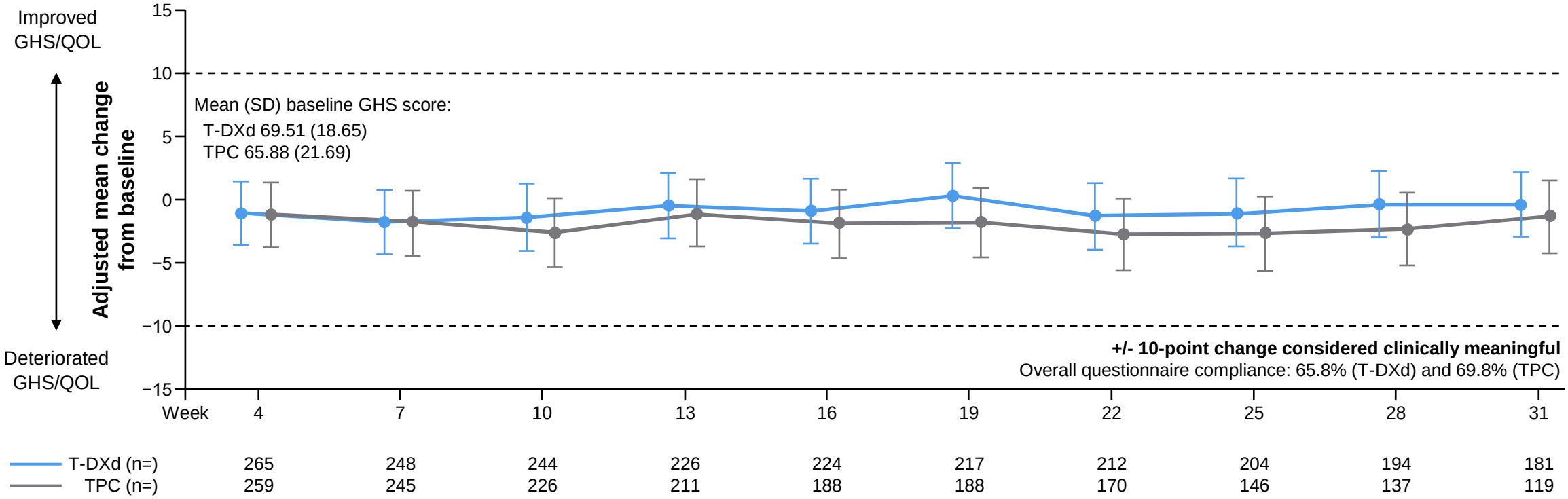
PRO endpoint assessment schedule

Cycle 1 (baseline)	Every 3 weeks	End of treatment	Every 3 weeks	PFS2

PRO assessments began before infusion on Day 1 of Cycle 1; 1 cycle = 21 days. Baseline PROs were completed after patients were aware of their treatment assignment.
*Plus additional single items assessing dyspnea and insomnia; †plus additional scales (breast satisfaction, endocrine therapy symptoms, endocrine sexual symptoms, systemic therapy side effects) and additional single items (sexual enjoyment, future perspective, upset by hair loss); ‡≥14 days apart; §patients with no clinically meaningful deterioration were censored at the time of last PRO assessment
EORTC, European Organisation for Research and Treatment of Cancer; GHS, Global Health Status; PFS2, second progression or death; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Questionnaire breast cancer-specific module; QLQ-C30, Quality of Life Core 30 questionnaire; QOL, quality of life

Overall GHS/QOL was maintained over 31 weeks with T-DXd and TPC in the ITT population; data were consistent in HER2-low

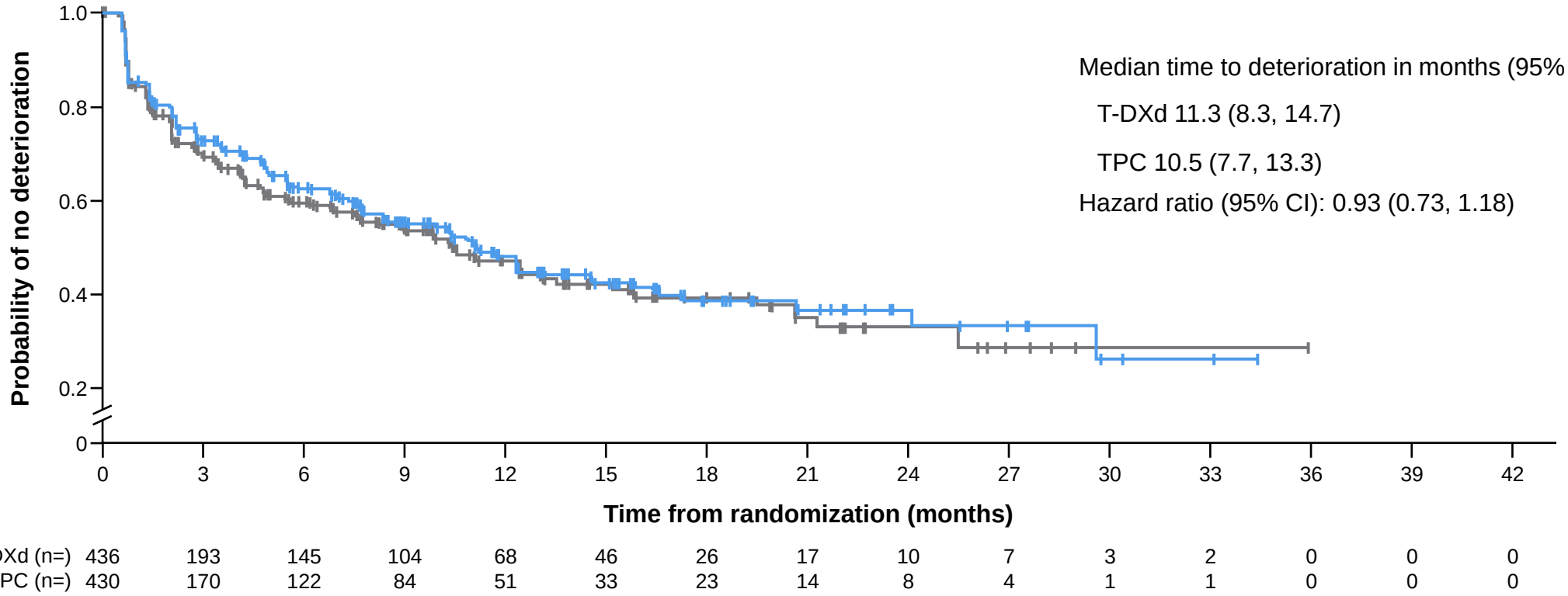
Mean change from baseline in QLQ-C30 GHS/QOL over 31 weeks or until PD (whichever earlier): ITT (HER2-low and HER2-ultralow)



Bars represent 95% confidence intervals. Baseline is defined as the last assessment on or prior to randomization, or before the first dose if assessment only available after randomization. CFB analysis was performed by using an MMRM with treatment, visit, treatment-by-visit interaction, prior CDK4/6i use (yes vs no), HER2 IHC expression (IHC 0 with membrane staining vs IHC 1+ vs IHC 2+/ISH−), and prior taxane use in the non-metastatic setting (yes vs no) as fixed effects, baseline score as a covariate, and the baseline-by-visit interaction. An unstructured covariance matrix was assumed, and the Kenward-Roger approximation was used to estimate the degrees of freedom. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CFB, change from baseline; GHS, Global Health Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; ITT, intent-to-treat; MMRM, mixed model of repeated measures; PD, progressive disease; QLQ-C30, Quality of Life Core 30 questionnaire; QOL, quality of life; SD, standard deviation; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Time to deterioration in QLQ-C30 GHS/QOL was similar with T-DXd and TPC

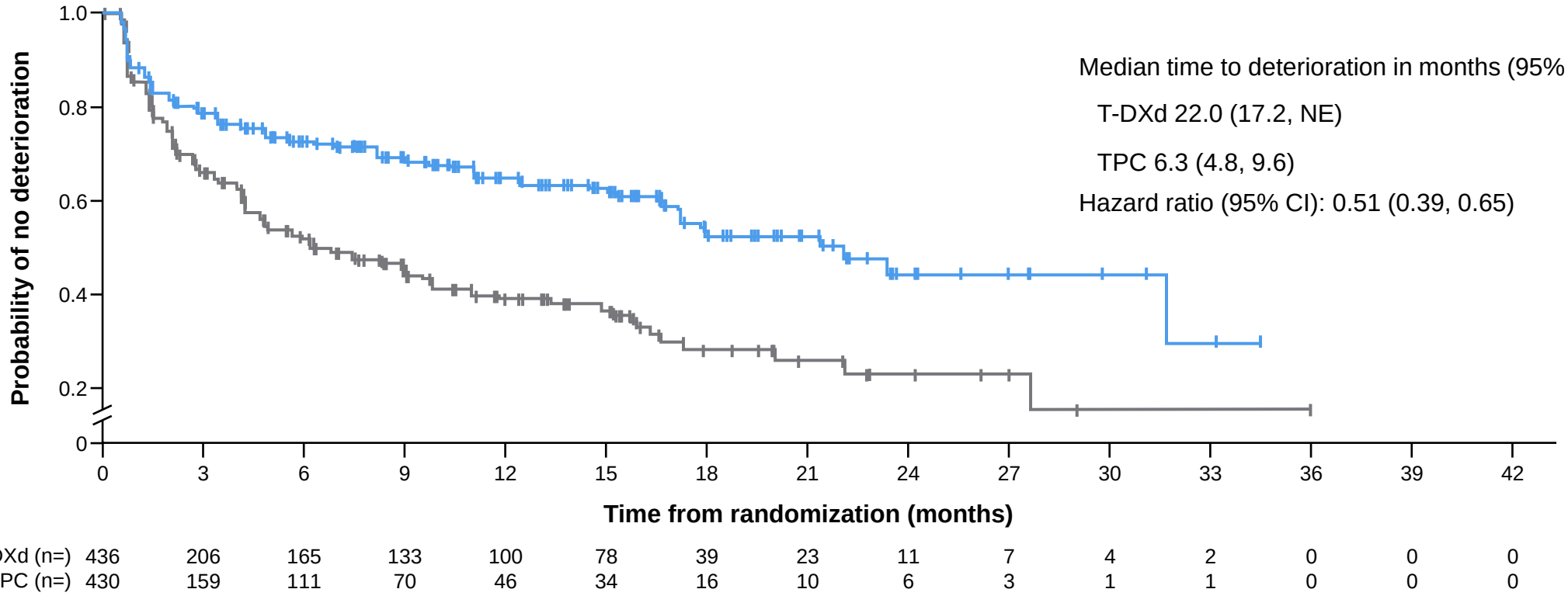
Time to deterioration in QLQ-C30 GHS/QOL: ITT population



Vertical tick mark indicates a censored observation
CI, confidence interval; GHS, Global Health Status; ITT, intent-to-treat; QLQ-C30, Quality of Life Core 30 questionnaire; QOL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

T-DXd reduced the risk of clinically meaningful deterioration in pain by 49% vs TPC

Deterioration in QLQ-C30 pain: ITT

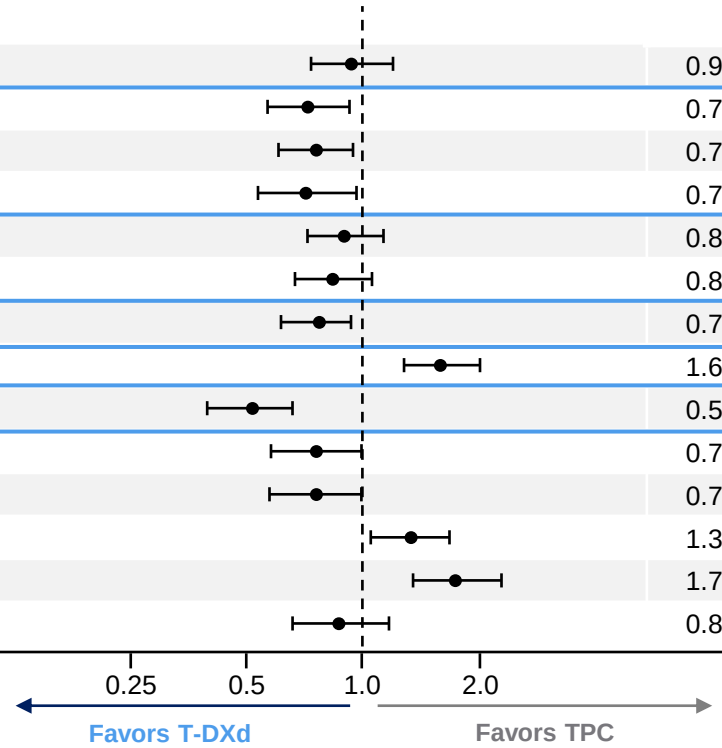


Vertical tick mark indicates a censored observation
CI, confidence interval; ITT, intent-to-treat; NE, not evaluable; QLQ-C30, Quality of Life Core 30 questionnaire; QOL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

T-DXd was also associated with reduced risk of clinically meaningful deterioration in functioning and fatigue but increased risk of some GI symptoms

Time to deterioration in PRO measures of interest with T-DXd vs TPC (QLQ-C30 items): ITT

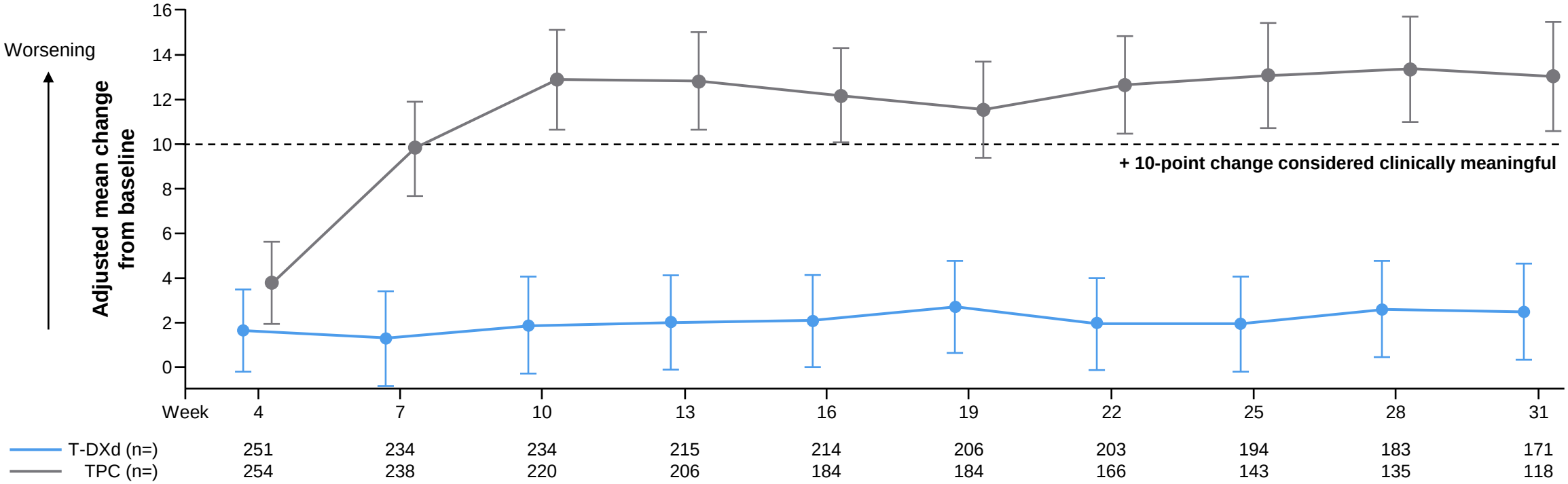
Subscale	Number of events		Months, median (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
GHS / QOL	142/436	137/430	11.3 (8.3, 14.7)	10.5 (7.7, 13.3)	0.93 (0.73, 1.18)
Physical functioning	116/436	137/430	18.0 (15.9, NE)	9.9 (6.9, 15.2)	0.72 (0.56, 0.92)
Role functioning	152/436	174/430	10.3 (6.9, 14.6)	5.5 (4.1, 6.9)	0.75 (0.60, 0.94)
Emotional functioning	91/436	104/430	28.2 (18.6, NE)	17.3 (12.4, NE)	0.71 (0.53, 0.95)
Cognitive functioning	145/436	143/430	11.8 (8.3, 16.6)	9.9 (7.8, 13.8)	0.89 (0.71, 1.13)
Social functioning	142/436	149/430	11.7 (7.6, 16.3)	7.7 (6.2, 10.4)	0.83 (0.66, 1.05)
Fatigue	175/436	201/430	4.3 (3.4, 7.7)	2.9 (2.2, 4.2)	0.76 (0.61, 0.93)
Nausea/vomiting	178/436	132/430	3.5 (2.8, 5.6)	13.8 (7.7, 21.5)	1.60 (1.28, 2.02)
Pain	105/436	157/430	22.0 (17.2, NE)	6.3 (4.8, 9.6)	0.51 (0.39, 0.65)
Dyspnea	98/436	107/430	20.0 (19.3, NE)	20.8 (13.1, NE)	0.75 (0.57, 1.00)
Insomnia	96/436	108/430	NE (17.3, NE)	15.2 (12.4, NE)	0.76 (0.57, 1.00)
Appetite loss	152/436	125/430	8.3 (5.0, 11.7)	13.8 (9.6, 16.1)	1.33 (1.05, 1.69)
Constipation	147/436	96/430	9.2 (5.5, 12.5)	22.0 (15.9, NE)	1.74 (1.34, 2.27)
Diarrhea	101/436	101/430	29.0 (17.2, NE)	16.5 (13.9, 23.4)	0.87 (0.65, 1.16)



CI, confidence interval; GHS, Global Health Status; GI, gastrointestinal; ITT, intent-to-treat; NE, not evaluable; PRO, patient-reported outcome; QLQ-C30, Quality of Life Core 30 questionnaire; QOL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Clinically meaningful deterioration of skin and mucosal symptoms observed with TPC but not with T-DXd*

Breast-specific measures of interest (EORTC QLQ-BR45)



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Conclusions and future directions

- Duration of treatment was approximately twice as long with T-DXd versus TPC
- **QOL was maintained during treatment with T-DXd, while time to deterioration was delayed in physical and role functioning, and pain, versus TPC**
- QOL data complement the clinical efficacy/safety of T-DXd after ≥1 endocrine-based therapy in patients with HR+, HER2-low and HER2-ultralow mBC
- GI symptoms reported by patients receiving T-DXd did not appear to be detrimental to overall preservation of QOL and were consistent with the clinician-reported safety data
  - Further investigation of the effect of antiemetic prophylaxis on GI adverse events and associated QOL in patients receiving T-DXd is warranted

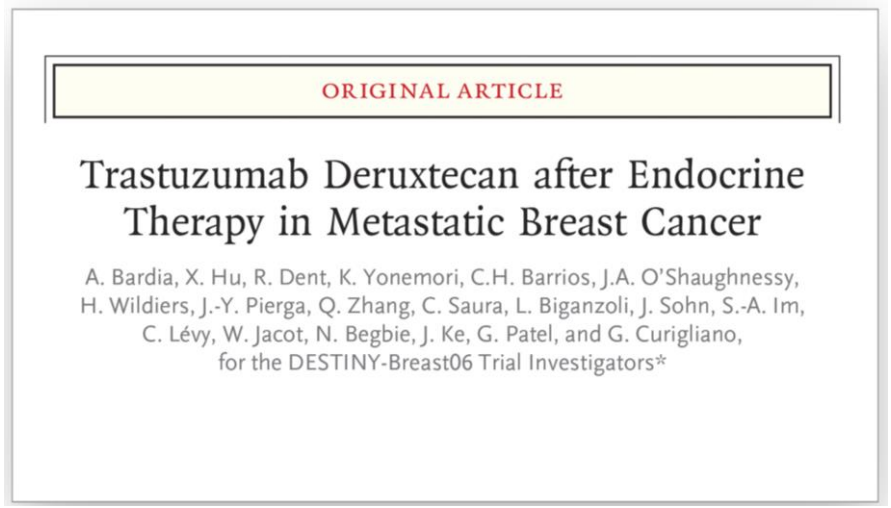
PRO results, describing the patient's perspective, further support T-DXd as a new therapeutic option following ≥1 endocrine-based therapy for patients with HR+, HER2-low and HER2-ultralow mBC

GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; PRO, patient-reported outcome; QOL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

DESTINY-Breast06

Acknowledgments

Thank you to the patients and their families for their participation and the study site staff for their contributions


ORIGINAL ARTICLE

Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer

A. Bardia, X. Hu, R. Dent, K. Yonemori, C.H. Barrios, J.A. O'Shaughnessy, H. Wildiers, J.-Y. Pierga, Q. Zhang, C. Saura, L. Biganzoli, J. Sohn, S.-A. Im, C. Lévy, W. Jacot, N. Begbie, J. Ke, G. Patel, and G. Curigliano, for the DESTINY-Breast06 Trial Investigators*

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What is the purpose of the DESTINY-Breast06 patient-reported outcome (PRO) analysis?

The **DESTINY-Breast06** study was designed to compare **trastuzumab deruxtecan** (**T-DXd**) with **chemotherapy** in people with metastatic/advanced breast cancer that had human epidermal growth factor receptor 2 protein at low (**HER2-low**) or very low (**HER2-ultralow**) levels. People could take part in the study if they had received prior hormone therapy, but not **chemotherapy**.

People who received **T-DXd** lived longer without their disease worsening than people who received **chemotherapy** (**13 vs 8 months**).

As part of this clinical trial, **436** people received **T-DXd** and **430** people received **chemotherapy**. Each person was asked to complete questionnaires about their **quality of life** (**QOL**) while receiving treatment. This collected information, known as patient-reported outcomes (**PROs**), is an increasingly important element of clinical trials as it suggests how treatments and their side effects impact people's lives, including their mental and physical wellbeing.

The aim of this analysis was to find out how the **QOL** of people receiving **T-DXd** compared with the **QOL** of people receiving **chemotherapy** using **PRO** questionnaires.

What did the analysis show?

The DESTINY-Breast06 PRO analysis showed that T-DXd helped to maintain the overall QOL of people with advanced breast cancer to a similar extent as chemotherapy. T-DXd preserved physical, emotional, and role* functioning for longer than chemotherapy, with a reduced risk of pain and fatigue deterioration. Compared with chemotherapy, T-DXd led to fewer symptoms of the skin and mouth; however, more gastrointestinal effects (nausea/vomiting, constipation, and loss of appetite) were experienced with T-DXd.

How was the DESTINY-Breast06 PRO analysis performed and what were the outcomes?

Methodology

People were asked to complete PRO questionnaires that used numbered scales to report their symptoms and feelings before, during, and after their treatment. Examples of the questions included:

- During the past week, have you had pain?
- During the past week, have you felt nauseated?
- During the past week, have you had skin problems on or in the area of your affected breast?
- During the past week, were you limited in doing either your work or other daily activities?
- How would you rate your overall QOL during the past week?

Treatment duration

The length of time that half of the people received treatment for (known as the median total treatment duration) was **almost twice as long** for **T-DXd** than **chemotherapy**:

for people given **T-DXd**

for people given **chemotherapy**

Change in specific scores

Areas where T-DXd was better at preserving QOL:

Emotional functioning

Role* functioning

Pain

Physical functioning

Skin, mouth, and extremities symptoms

Fatigue

Areas where chemotherapy was better at preserving QOL:

Appetite loss

Nausea/vomiting

Constipation

*Work, daily, and leisure activities

Overall QOL

Over the 7-month PRO analysis period, people **did not report worsening** of their overall QOL while receiving **T-DXd** and **chemotherapy**.

How do the results of the DESTINY-Breast06 PRO analysis help to improve the treatment of cancer?

Negative impacts on QOL are common for people receiving treatment for hormone receptor–positive, HER2-low and HER2-ultralow advanced breast cancer. The DESTINY-Breast06 PRO analysis found that people who received T-DXd had delayed deterioration in physical, emotional, and role* functioning, compared with chemotherapy, as well as a reduced risk of deterioration in pain and fatigue scores. Although people receiving T-DXd experienced more gastrointestinal side effects, such as nausea and vomiting, this did not appear to negatively impact overall QOL, compared with chemotherapy. The use of drugs that reduce nausea and vomiting could help further in preserving the QOL of people receiving T-DXd.

Where can I access more information?

DESTINY-Breast06 ClinicalTrials.gov identifier **NCT04494425**

This summary is based on a mini-oral presentation by Professor Xichun Hu at the European Society for Medical Oncology (ESMO) Congress 2024 (mini-oral presentation/LBA22): Effects of trastuzumab deruxtecan vs choice of chemotherapy on patient-reported outcomes in hormone receptor–positive, HER2-low or HER2-ultralow metastatic breast cancer: results from DESTINY-Breast06. This summary, and the results of this study, have not yet been peer reviewed. The authors would like to thank the participants and their families who participated in the DESTINY-Breast06 study and the investigators, co-investigators, and study staff. Date of summary: August 2024. The DESTINY-Breast06 study was sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). This plain language summary was prepared by Megan Allard, MSc (Helios Medical Communications, part of Helios Global Group) and was funded by AstraZeneca.