188P

A Health-Related Quality of Life (QOL) Analysis From DESTINY-Breast04: Trastuzumab Deruxtecan (T-DXd) Versus Capecitabine (CAP) in Patients With Hormone Receptor–Positive (HR+), HER2-Low Metastatic Breast Cancer (mBC)

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Objective

- To report a health-related quality of life (QoL) analysis of trastuzumab deruxtecan (T-DXd) versus capecitabine in patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2 (HER2)–low metastatic breast cancer (mBC) who were preassigned by the investigator to receive capecitabine before randomization in DESTINY-Breast04

Conclusions

- The mean change from baseline (CFB) for Global Health Status/Quality of Life (GHS/QoL) indicated that health-related QoL was maintained throughout treatment with both T-DXd and capecitabine, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) questionnaire
- Median time to definitive deterioration (TDD) results suggest that treatment with T-DXd, compared with capecitabine, delays worsening of most prespecified patient-reported outcome (PRO) measures of interest, including pain symptoms (hazard ratio, 0.42; 95% CI, 0.23-0.78)
- The observed safety profile of T-DXd was consistent with that of the primary report
- Appropriate management of adverse events and the use of preventive measures (ie, antiemetic prophylaxis for nausea and vomiting) may further support patient health-related QoL
- Although the sample size was small, and despite longer treatment duration with T-DXd versus capecitabine, the results support a benefit in most measures of health-related QoL with use of T-DXd compared with capecitabine in patients with HR+/HER2-low mBC treated with 1 or 2 prior lines of chemotherapy

Plain Language Summary

Why did we perform this research?
Some breast cancers express low levels of the protein human epidermal growth factor receptor 2 (HER2) and are known as HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization negative).[1,2] Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate designed to target and kill tumor cells that express HER2.[3,4] In the phase 3 DESTINY-Breast04 clinical trial, T-DXd treatment resulted in improved efficacy and safety outcomes compared with the treatment of physician's choice in all patients with HER2-low metastatic breast cancer (mBC) treated with 1 or 2 prior lines of chemotherapy, including those in the hormone receptor–positive (HR+) cohort.[3] Patient-reported outcomes were also assessed to examine the impact of treatments on patients' health-related quality of life (QoL). The analysis presented here was done to investigate the impact of T-DXd compared with capecitabine, one of the physician's choice of treatment options, on health-related QoL in patients with HR+/HER2-low mBC.

How did we perform this research?
Eligible patients were preassigned to receive capecitabine before randomization to ensure adequate allocation to the physician's choice group. At randomization, these patients were then assigned to receive either T-DXd 5.4 mg/kg or capecitabine. Patients enrolled were asked to periodically complete questionnaires to assess their health-related QoL at prespecified time points before, during, and after treatment.

What were the findings of this research?
Patients' global health scores showed that overall health-related QoL was maintained with T-DXd and with capecitabine. The time to definitive deterioration was longer in patients who received T-DXd according to most prespecified subscales of the questionnaire, including pain and arm symptoms, compared with patients receiving capecitabine. These findings suggest that there is a benefit seen in most of the health-related QoL measures with T-DXd, compared with capecitabine, for patients with HR+/HER2-low mBC.

Where can I access more information?
To learn more about the DESTINY-Breast04 study, you can visit https://clinicaltrials.gov/ct2/show/NCT03734029

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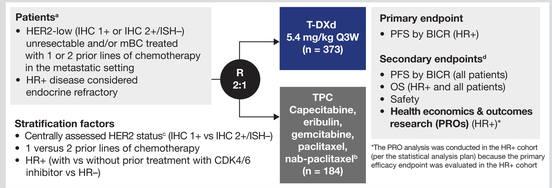
Introduction

- Results of the DESTINY-Breast04 trial showed that patients with HR+/HER2-low mBC treated with T-DXd experienced significantly improved progression-free survival (PFS) and overall survival (OS) compared with treatment of physician's choice (TPC; capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)[1]
  - Median PFS was 10.1 versus 5.4 months (hazard ratio, 0.51; $P < 0.001$) and median OS was 23.9 versus 17.5 months (hazard ratio, 0.64; $P = 0.003$) for T-DXd versus TPC, respectively (data cutoff: January 11, 2022)[1]
  - Median treatment duration was 8.2 months (range, 0.2-33.3 months) with T-DXd and 3.5 months (range, 0.3-17.6 months) with TPC[1]
- To complement efficacy and safety data and to better understand treatment impact on functioning and well-being, secondary PRO endpoints from DESTINY-Breast04 were analyzed
  - Compared with TPC, T-DXd delayed deterioration of prespecified PROs, including pain, and was favored over TPC for maintaining health-related QoL in patients with HR+/HER2-low mBC[2]
- Patients in DESTINY-Breast04 were preassigned by the investigator to 1 of 5 TPC options before randomization; within each TPC subgroup, patients were then randomly assigned to receive treatment with either T-DXd or the respective TPC treatment
  - This allowed for randomized treatment comparisons, including comparison of T-DXd with capecitabine
- Capecitabine is an effective chemotherapy treatment for mBC that has an established favorable safety profile with generally manageable side effects,[3-5] which may affect the degree of negative impact on health-related QoL; therefore, the impact of capecitabine compared with that of T-DXd on health-related QoL is of interest

Methods

- The study design for DESTINY-Breast04 is presented in **Figure 1**
- PROs were prospectively evaluated at baseline, before treatment (after randomization), on day 1 of cycles 1-3 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 (data cutoff: January 11, 2022)[2]
- PRO endpoints, measures, and analyses are presented in **Table 1**
- TDD in health-related QoL scores were analyzed using an unstratified Cox proportional hazards model for treatment comparisons; median time to event was estimated using the Kaplan-Meier method

Figure 1. DESTINY-Breast04 Study Design[1,2]: A Randomized, Open-Label, Multicenter, Phase 3 Study



*The PRO analysis was conducted in the HR+ cohort (per the statistical analysis plan) because the primary efficacy endpoint was evaluated in the HR+ cohort

[a]If patients had HR+ mBC, prior endocrine therapy was required.
[b]TPC was administered according to the label.
[c]Performed on adequate archived or recent tumor biopsy per American Society of Clinical Oncology (ASCO)/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only assay system.
[d]Secondary endpoints listed here are a simplification of the full study design.

Table 1. PRO Endpoints and Health-Related QoL Analyses

Endpoint	Description	Measures of Interest	Planned Analyses
EORTC QLQ-C30	Oncology-specific questionnaire	• Global health status (GHS)/QoL • Functioning scales: physical, emotional, cognitive, social • Symptom scales: pain, nausea/vomiting[b]	• CFB • TDD[a]
EORTC QLQ-BR45[c]	Breast cancer–specific questionnaire	• Symptom scales: breast, arm	• CFB • TDD[a]

[a]TDD was defined as the number of days between randomization and the assessment at which deterioration was first seen; clinically meaningful definitive deterioration is defined as a change of ≥10 points from baseline at 2 or more consecutive time points, last PRO assessment, or death by the first survival follow-up visit.
[b]Symptom subscale scores for nausea/vomiting were included as exploratory endpoints.
[c]EORTC QLQ-BR45 was scored as QLQ-BR23.

Results

Patients

- Before randomization, a subgroup of 95 patients was preassigned to receive capecitabine to ensure adequate allocation to the TPC arm
  - At randomization, 61 of those patients were assigned to receive T-DXd; 34 patients, capecitabine
- Among all patients preassigned to receive capecitabine, most had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0, had previously received first-line chemotherapy, and received previous treatment with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (**Table 2**)

Table 2. Demographic and Baseline Characteristics

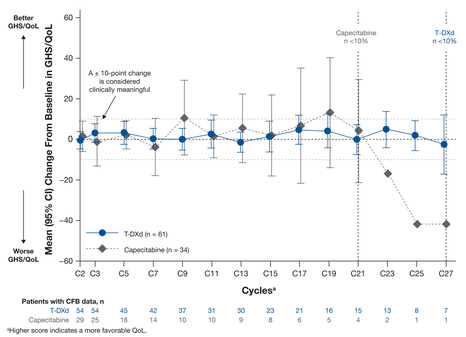
	T-DXd (n = 61)	Capecitabine (n = 34)
Age, median (range), y	56.9 (32.6-76.8)	62.5 (38.2-79.5)
Race, n (%)		
Asian	21 (34.4)	12 (35.3)
Black or African American	3 (4.9)	0
White	29 (47.5)	19 (55.9)
Other	8 (13.1)	2 (5.9)
Missing	0	1 (2.9)
Region,[a] n (%)		
Asia	21 (34.4)	12 (35.3)
Europe and Israel	34 (55.7)	17 (50.0)
North America	6 (9.8)	5 (14.7)
ECOG PS score, n (%)		
0	42 (68.9)	27 (79.4)
1	19 (31.1)	7 (20.6)
HER2 status, n (%)		
IHC 1+	33 (54.1)	16 (47.1)
IHC 2+/ISH–	28 (45.9)	18 (52.9)
Prior lines of chemotherapy, n (%)		
1	45 (73.8)	22 (64.7)
≥2	15 (24.6)	11 (32.4)
Missing	1 (1.6)	1 (2.9)
Prior CDK4/6 inhibitors, n (%)		
Yes	47 (77.0)	26 (76.5)
No	14 (23.0)	8 (23.5)
Prior lines of endocrine therapy in the metastatic setting, n (%)		
1	13 (21.3)	7 (20.6)
2	23 (37.7)	9 (26.5)
≥3	25 (41.0)	18 (52.9)
Prior lines of systemic therapy in any setting, n (%)		
<3	10 (16.4)	7 (20.6)
≥3	51 (83.6)	27 (79.4)
History of CNS metastases, n (%)		
Yes	10 (16.4)	2 (5.9)
No	51 (83.6)	32 (94.1)
Liver metastases at baseline, n (%)	49 (80.3)	26 (76.5)

[a]Region percentages do not summate to 100 due to rounding differences.

CFB in EORTC QLQ-C30 Measures

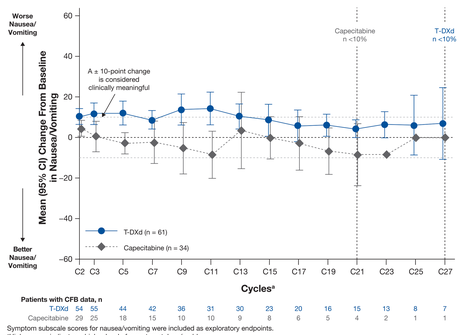
- Among patients who were preassigned to capecitabine, the compliance rate for completing health-related QoL patient questionnaires was >80% throughout treatment
- Baseline mean GHS/QoL score (SD) was 61.5 (20.5) for T-DXd and 62.6 (24.6) for capecitabine
- Mean CFB for EORTC QLQ-C30 measures were maintained throughout the course of treatment for T-DXd and capecitabine (**Figures 2, 3**)

Figure 2. CFB in GHS/QoL Score (EORTC QLQ-C30)



[a]Higher score indicates a more favorable QoL.

Figure 3. CFB in Nausea and Vomiting Score (EORTC QLQ-C30)

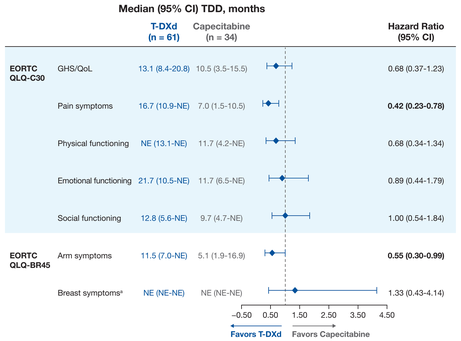


Symptom subscale scores for nausea/vomiting were included as exploratory endpoints.
[a]Higher score indicates a higher level of symptomatology/problems.

TDD in EORTC QLQ-C30 and QLQ-BR45 Measures

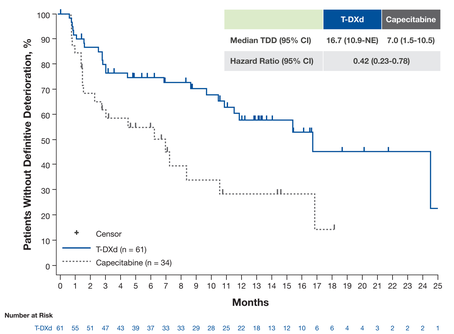
- TDD hazard ratios for most PRO measures of interest favored T-DXd versus capecitabine, including those for pain (hazard ratio, 0.42; 95% CI, 0.23-0.78) and arm symptoms (hazard ratio, 0.55; 95% CI, 0.30-0.99) (**Figures 4, 5**)

Figure 4. TDD in PRO Measures of Interest



[a]Median (95% CI) not estimable due to the low number of patients who experienced deterioration events.

Figure 5. TDD of Pain (EORTC QLQ-C30)



Safety Analysis by Investigator

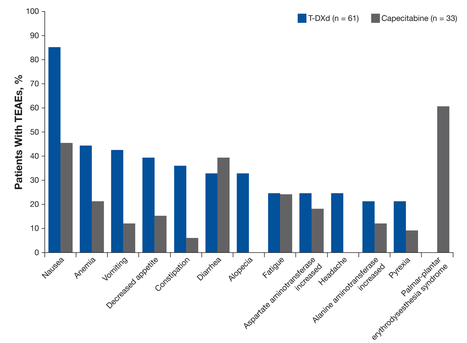
- Median treatment duration was 9.0 months (range, 0.6-28.1 months) with T-DXd and 4.1 months (range, 0.3-17.6 months) with capecitabine (**Table 3**)
- The observed safety profile of T-DXd was consistent with the primary report[1] (**Table 3, Figure 6**)

Table 3. Overall Safety Summary[a]

	T-DXd (n = 61)	Capecitabine (n = 33)
Treatment duration, median (range), months	9.0 (0.6-28.1)	4.1 (0.3-17.6)
Total patient-years of exposure[b]	49.1	16.4
Drug-related TEAEs, n (%)	59 (96.7)	31 (93.9)
Drug-related serious TEAEs, n (%)	8 (13.1)	2 (6.1)
Drug-related TEAEs associated with study drug discontinuation, n (%)	10 (16.4)	3 (9.1)
Drug-related severe TEAEs (CTCAE grade ≥3), n (%)	27 (44.3)	10 (30.3)
Drug-related TEAEs associated with an outcome of death, n (%)	1 (1.6)	0
Drug-related TEAEs associated with dose reduction, n (%)	13 (21.3)	13 (39.4)
Drug-related TEAEs associated with study drug interruption, n (%)	15 (24.6)	11 (33.3)

[a]Safety analyses were performed in patients who received ≥1 dose of a study drug.
[b]Total patient-years of exposure equals the sum of treatment duration of all patients.

Figure 6. TEAEs Reported in ≥20% of Patients Treated With T-DXd or Capecitabine



Abbreviations

CAP, capecitabine; CDK 4/6, cyclin-dependent kinase 4/6; CFB, change from baseline; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-BR45, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL, global health status/quality of life; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice

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Disclosures

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