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Trastuzumab deruxtecan versus trastuzumab emtansine in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer: Final analysis from DESTINY-Breast03

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Objective

- To report efficacy and safety results from the 5-year follow-up analysis of DESTINY-Breast03, a phase 3 trial of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane

Conclusions

- The final analysis of DESTINY-Breast03 (data cutoff [DCO], June 27, 2025) confirms the long-term survival outcomes of T-DXd compared with T-DM1 in patients with HER2-positive mBC whose disease had progressed after prior treatment with trastuzumab and a taxane
  - Median progression-free survival (PFS) by investigator assessment was 29.0 months in the T-DXd group compared with 7.8 months in the T-DM1 group; the estimated 5-year PFS rate was 37.6% and 10.0%, respectively
  - Median overall survival (OS) was 56.4 months in the T-DXd group and 42.7 months in the T-DM1 group; the estimated 5-year OS rate was 48.1% and 36.9%, respectively
- The safety profile of T-DXd was similar to that shown in previous reports,[1-3] and no new safety signals were observed with longer follow-up
  - The rate of adjudicated drug-related interstitial lung disease (ILD) was 17.5% with T-DXd, with 2 new events (grade 1 and 3) since the last DCO (November 20, 2023); no grade 4 or grade 5 events were reported during the trial
- These data demonstrate the long-term efficacy outcomes and a consistent safety profile of T-DXd compared with T-DM1, continuing to support the use of T-DXd as the standard of care for patients with HER2-positive mBC whose disease progresses after trastuzumab and taxane therapy

Plain Language Summary

Why did we perform this research?
Approximately 20% of breast cancer tumors express high levels of a protein called human epidermal growth factor receptor 2 (HER2).[1,2] Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets HER2.[3,4] DESTINY-Breast03 was performed to compare the treatment benefits and safety of T-DXd with trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer that cannot be removed by surgery (unresectable) or has spread to other areas of the body (metastatic).[5-7] Previous results from DESTINY-Breast03 showed T-DXd to be more beneficial than T-DM1.[5-7] The objective of the current analysis was to compare the treatment benefits and safety of T-DXd with those of T-DM1 after a 5-year follow-up period in patients participating in DESTINY-Breast03.

How did we perform this research?
In the DESTINY-Breast03 study, 524 patients with unresectable or metastatic breast cancer were randomly given either T-DXd 5.4 mg/kg (261 patients) or T-DM1 3.6 mg/kg (263 patients). Because a significant treatment benefit was shown with T-DXd compared with T-DM1 in previous results,[5,6] efficacy results were assessed by the investigators.

What were the findings of this research?
T-DXd had better treatment benefits than T-DM1. The median (middle in a range) length of time that patients lived with their cancer before the disease got worse or caused death (known as median progression-free survival) was 3.7 times longer in patients treated with T-DXd than in those treated with T-DM1 (29.0 and 7.8 months, respectively). The median (middle in a range) length of time that patients survived after starting study treatment (known as median overall survival) was 56.4 months (~4.7 years) with T-DXd and 42.7 months (~3.6 years) with T-DM1, and was approximately 13.7 months longer in the T-DXd group than in the T-DM1 group. It was estimated that after 5 years, 48.1% of patients receiving T-DXd would survive compared with 36.9% of patients receiving T-DM1. In addition, the safety profile of T-DXd was consistent with the known safety profile in this longer follow-up period, with no increase in the rate of side effects observed over time. Adjudicated drug-related interstitial lung disease, which is an adverse event of special interest for T-DXd, occurred in 17.5% of patients in the T-DXd group and 3.1% of patients in the T-DM1 group since the beginning of the study; there were no ILD events that were life-threatening or fatal in either group.

What are the implications of this research?
Findings from this final analysis were mostly similar to previous results,[5-7] and continue to support the use of T-DXd as standard of care in patients with HER2-positive metastatic breast cancer whose disease continued to get worse after trastuzumab and taxane treatment.

Where can I access more information?
To learn more about the DESTINY-Breast03 study, you can visit https://clinicaltrials.gov/ct2/show/NCT03529110

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Poster

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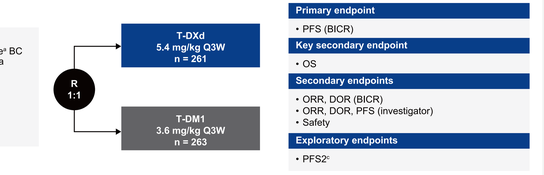
Introduction

- In the randomized DESTINY-Breast03 study (NCT03529110), the HER2-directed antibody-drug conjugate T-DXd showed statistically significant and clinically meaningful improvement in PFS and OS compared with T-DM1 in patients with HER2-positive mBC previously treated with trastuzumab and a taxane[1-3]
  - At the first interim analysis (DCO, May 21, 2021), the primary endpoint of PFS by blinded independent central review (BICR) was met (hazard ratio [HR], 0.28; $P < 0.001$); median PFS by BICR was not reached versus 6.8 months with T-DXd and T-DM1, respectively[1]
  - At the second interim analysis (DCO, July 25, 2022), median PFS by BICR was 28.8 months and 6.8 months with T-DXd and T-DM1, respectively (HR, 0.33; nominal $P < 0.0001$), and median OS was not reached in either group (HR, 0.64; $P = 0.0037$)[2]
  - In an exploratory long-term survival analysis (DCO, November 20, 2023), the median OS was 52.6 months and 42.7 months with T-DXd and T-DM1, respectively[3]
- Based on DESTINY-Breast03 results, T-DXd was approved for the treatment of patients with HER2-positive mBC who have received a prior anti-HER2–based regimen in either the metastatic setting or in the neoadjuvant/adjuvant setting and experienced disease recurrence during therapy or within 6 months of completing therapy[4]
- T-DXd is the recommended second-line therapy for patients after prior treatment with trastuzumab and a taxane[5]
- We report the 5-year follow-up and final efficacy and safety analysis of DESTINY-Breast03

Methods

- DESTINY-Breast03 was a randomized, multicenter, open-label, phase 3 trial (**Figure 1**)
  - Patients were assigned 1:1 to receive T-DXd 5.4 mg/kg or T-DM1 3.6 mg/kg intravenously every 3 weeks
- Exploratory analysis at 5 years (final analysis DCO, June 27, 2025) included PFS, PFS from the time of randomization to progression on the next line of therapy or death (PFS2), OS, confirmed objective response rate (cORR), duration of response (DOR) (all investigator assessed), and safety

Figure 1. DESTINY-Breast03 Study Design[1-3]



[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation.
[b]Progression during therapy or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
[c]Time from randomization to disease progression on the next line of therapy or death.

Results

Patients

- Overall, 524 patients were randomly assigned (261 to T-DXd; 263 to T-DM1), with the last patient enrolled on June 23, 2020
- At the final analysis DCO, June 27, 2025, the median (range) duration of follow-up in the study was 43.0 months (0.0-80.6 months) overall, 50.9 months (0.0-80.6 months) in the T-DXd group, and 35.4 months (0.0-80.4 months) in the T-DM1 group
- 24 patients (9.3%) in the T-DXd group and 2 patients (0.8%) in the T-DM1 group remained on treatment at the DCO
  - The most common reasons for patient discontinuation were progressive disease (T-DXd, 44.7%; T-DM1, 70.9%) and adverse events (AEs; T-DXd, 26.8%; T-DM1, 10.0%)

Efficacy by Investigator Assessment

- Median (range) treatment duration was 18.2 months (0.7-76.0 months) with T-DXd, and 6.9 months (0.7-65.1 months) with T-DM1 (difference, 11.3 months)
  - Median (range) number of treatment cycles initiated was 24.0 (1-108) with T-DXd and 10.0 (1-94) with T-DM1
- Efficacy outcomes as assessed by the investigator at 5 years of follow-up were consistent with results of previous analyses, including cORR and median PFS (**Figure 2**)[1-3]
  - The cORR (95% CI) was 78.9% (73.5%, 83.7%) with T-DXd (34 complete responses [13.0%]) and 36.9% (31.0%, 43.0%) with T-DM1 (13 complete responses [4.9%]) (difference, 42.0% [95% CI, 34.0, 50.1])
  - Median DOR (95% CI) was 31.8 months (23.1, 53.4 months) with T-DXd and 17.0 months (14.1, 23.7 months) with T-DM1 (difference, 14.8 months)

Anticancer Systemic Treatment After Trial

- Among patients who discontinued treatment, 161 of 233 (69.1%) in the T-DXd group and 203 of 259 (78.4%) in the T-DM1 group received subsequent systemic anticancer therapy (**Table 1**)
  - In the T-DXd group, 81 patients (50.3%) received T-DM1 after discontinuing trial treatment
  - In the T-DM1 group, 78 patients (38.4%) received T-DXd after discontinuing trial treatment
- The median PFS2 assessed by the investigator at 5 years of follow-up was consistent with results of the previous DCO[3] (**Figure 3**)

Table 1. Anticancer Systemic Treatment After Trial

	T-DXd n = 261	T-DM1 n = 263
Type of treatment[a,b]		
Systemic	161 (69.1)	203 (78.4)
Radiation	30 (12.9)	51 (19.7)
Surgery	6 (2.6)	16 (6.2)
Patients receiving any subsequent systemic anticancer treatment[b,c]	161 (69.1)[a]	203 (78.4)[a]
Trastuzumab	66 (41.0)	111 (54.7)
T-DXd	22 (13.7)	78 (38.4)
T-DM1	81 (50.3)	29 (14.3)
Pertuzumab	19 (11.8)	33 (16.3)
Taxane	27 (16.8)	45 (22.2)
Taxane and trastuzumab	14 (8.7)	40 (19.7)
Other anti-HER2 (includes anti-HER2 TKI and other anti-HER2 antibody or ADC)	63 (39.1)	106 (52.2)
Anti-HER2 TKI	58 (36.0)	99 (48.8)
Other anti-HER2 antibody or ADC	18 (11.2)	22 (10.8)
Hormone therapy	31 (19.3)	43 (21.2)
Other systemic therapy	108 (67.1)	164 (80.8)
Progression on first subsequent anticancer therapy[d]		
Yes	71 (42.8)	105 (51.0)
No	95 (57.2)	101 (49.0)

Values are n (%).
[a]The denominator to calculate the percentage is based on the number of patients who discontinued randomized treatment in the T-DXd (n = 233) or the T-DM1 group (n = 259).
[b]Patients may have been treated with more than 1 type of subsequent anticancer therapy.
[c]For treatments listed under this category, the denominator used to calculate the percentage is based on the number of patients receiving any subsequent systemic anticancer treatment in the T-DXd (n = 161) or T-DM1 group (n = 203).
[d]The denominator to calculate the percentage is based on the number of patients who received any subsequent anticancer therapy (T-DXd, n = 166; T-DM1, n = 206).

Figure 2. Investigator-Assessed PFS

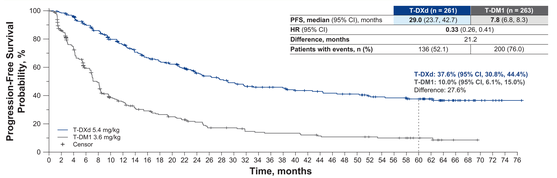
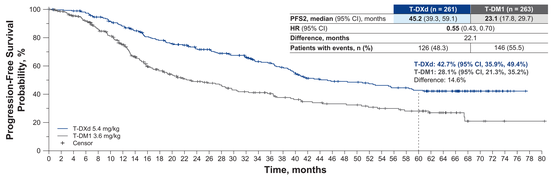


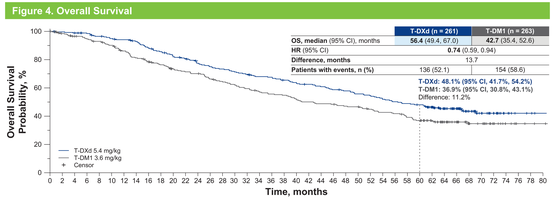
Figure 3. Investigator-Assessed PFS2



Overall Survival

- T-DXd continued to show clinically meaningful improvement in OS versus T-DM1 at 5 years, with a >1-year difference in median OS (56.4 months [95% CI, 49.4, 67.0 months] with T-DXd and 42.7 months [95% CI, 35.4, 52.6 months] with T-DM1 [difference, 13.7 months]) (**Figure 4**)
  - The 5-year (60-month) OS rate was 48.1% with T-DXd and 36.9% with T-DM1 (difference, 11.2%)

Figure 4. Overall Survival



Safety

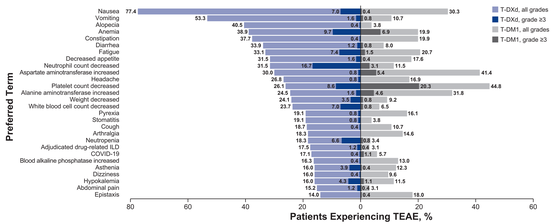
- Rates of treatment-emergent adverse events (TEAEs) were consistent with those at the prior DCO[3] (**Table 2**)
- Total exposure was 538.31 patient-years with T-DXd and 234.94 patient-years with T-DM1
  - Exposure-adjusted incidence rates per patient-year were lower with T-DXd than T-DM1 for any-grade TEAEs (0.48 vs 1.06), grade ≥3 TEAEs (0.29 vs 0.58), and serious TEAEs (0.15 vs 0.25)
- 45 patients (17.5%) in the T-DXd group and 8 patients (3.1%) in the T-DM1 group had adjudicated drug-related ILD
  - With longer follow-up since the previous analysis,[3] there were 2 new events of adjudicated drug-related ILD (grade 1 and grade 3) in the T-DXd group
  - Overall, no events of grade 4 or 5 adjudicated drug-related ILD were reported in either group during the trial
- The most common grade ≥3 TEAEs were neutrophil count decreased (16.7%) and anemia (9.7%) with T-DXd and platelet count decreased (20.3%) and anemia (6.9%) with T-DM1 (**Figure 5**)

Table 2. 5-Year Safety Results

	T-DXd n = 257	T-DM1 n = 261
Total exposure, patient-years	538.31	234.94
Drug-related any-grade TEAEs	252 (98.1)	228 (87.4)
Drug-related grade ≥3 TEAEs	132 (51.4)	111 (42.5)
Drug-related serious TEAEs	40 (15.6)	21 (8.0)
Drug-related TEAEs leading to permanent discontinuation	64 (24.9)	20 (7.7)
Drug-related TEAEs leading to dose reduction	74 (28.8)	40 (15.3)
Drug-related TEAEs leading to dose interruption	117 (45.5)	49 (18.8)
Drug-related fatal TEAEs	0	0
Adjudicated drug-related ILD	45 (17.5)	8 (3.1)
Grade 3	3 (1.2)	1 (0.4)
Grade 4 or 5	0	0
Any-grade TEAEs	256 (99.6)	249 (95.4)
EAIR per patient-year	0.48	1.06
Grade ≥3 TEAEs	155 (60.3)	136 (52.1)
EAIR per patient-year	0.29	0.58
Any serious TEAE	79 (30.7)	59 (22.6)
EAIR per patient-year	0.15	0.25

Values are n (%) unless otherwise noted.

Figure 5. Most Common TEAEs (≥15% of Patients in Either Treatment Group)



Abbreviations

ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BICR, blinded independent central review; cORR, confirmed objective response rate; COVID-19, coronavirus disease 2019; CR, complete response; DCO, data cutoff; DOR, duration of response; EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; mBC, metastatic breast cancer; NE, not evaluable; PFS, progression-free survival; PFS2, progression-free survival from time of randomization to progression on the next line of therapy or death; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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