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Human Epidermal Growth Factor Receptor 2 (HER2)-Directed Therapies Administered After Trastuzumab Deruxtecan (T-DXd) Remain Effective in Patients With Metastatic Breast Cancer (mBC): Exploratory Analysis From DESTINY-Breast02 and -03

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Objective

- To determine the duration of treatment (DoT), used as a surrogate for treatment outcomes of subsequent lines of therapy, administered after discontinuation of T-DXd for any reason, in patients with HER2-positive mBC

Conclusions

- This descriptive, exploratory analysis shows clinically meaningful DoT across various HER2-directed therapies administered after T-DXd
- These results are in line with real-world data (RWD) for patients receiving HER2-directed regimens after prior trastuzumab-based therapies other than T-DXd
- These exploratory results suggest that treatment outcomes associated with other HER2-directed therapies are maintained after T-DXd in patients with HER2-positive mBC

Plain Language Summary

Why did we perform this research?
T-DXd, an antibody-drug conjugate that delivers chemotherapy to tumor cells by targeting a protein called human epidermal growth factor receptor 2 (HER2) expressed on the surface of tumor cells,[1,2] has shown strong and durable antitumor activity in patients with previously treated HER2-positive metastatic breast cancer (mBC)[3,4] and other HER2-expressing tumors.[5] However, clinical trial data on outcomes with subsequent therapies after discontinuation of T-DXd are lacking. While some data do exist, there are high attrition rates for patients with HER2+ mBC as they move through subsequent lines of therapy, and there remains a need to better understand the outcomes associated with specific HER2-targeted agents after T-DXd to inform treatment decisions.

How did we perform this research?
This exploratory analysis described long-term outcomes of patients who were included in the randomized, open-label, multicenter, phase 3 DESTINY-Breast02 and DESTINY-Breast03 studies evaluating the efficacy and safety of second-line or later treatment with T-DXd versus treatment of physician's choice (TPC) or trastuzumab emtansine (T-DM1), respectively, in patients with HER2-positive unresectable or mBC.[3,6] In particular, duration of treatment (DoT) of different types of HER2-targeting therapies received by patients from these studies as their next line of treatment after discontinuation of T-DXd for any reason were compared.

What are the implications of this research?
DoT is an accepted indicator that a therapy is still active as patients are only treated for as long as their tumor is responding to the therapy. This analysis shows clinically meaningful DoT across various HER2-directed therapies administered after T-DXd in patients with HER2-positive mBC, suggesting that treatment outcomes associated with other HER2-directed therapies are maintained after T-DXd.

Where can I access more information?
To learn more about the trials in this study, you can visit:
• DESTINY-Breast02: https://www.clinicaltrials.gov/ct2/show/NCT03523585.
• DESTINY-Breast03: https://www.clinicaltrials.gov/ct2/show/NCT03529110.

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Poster

Supplementary material

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

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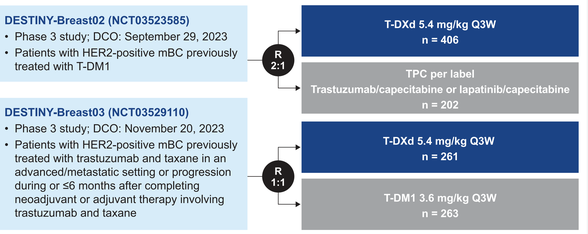
Introduction

- T-DXd is a HER2-targeting antibody-drug conjugate[1,2] that has shown strong and durable antitumor activity in patients with previously treated HER2-positive mBC[3,4] and other HER2-expressing tumors[5]
- Based on results of the DESTINY-Breast01, -02, and -03 trials, T-DXd is approved for the treatment of patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+ and in situ hybridization-positive [ISH+]) breast cancer who have received ≥1 prior anti-HER2–based regimen[6,7]
- RWD provide a useful benchmark for DoT of HER2-directed therapies given after trastuzumab-based therapies[8-11]
  - In a retrospective observational study, 138 patients with HER2-positive mBC had a median time to treatment discontinuation of 3.6 months (95% CI, 3.1-4.2 months) from the start of subsequent therapy after discontinuing trastuzumab emtansine (T-DM1)[8]
  - In another retrospective observational study involving 337 patients with HER2-positive mBC who had received 2 prior anti-HER2–based regimens (including T-DM1), those who received subsequent third-line treatment with trastuzumab-based therapy combined with chemotherapy (CT; n = 288) had significantly longer weighted median overall survival (OS; 20.6 months [95% CI, 18.3-26.4 months]) versus patients who received CT only (n = 49; 10.1 months [95% CI, 7.8-12.3 months])[9]
- An analysis of long-term outcomes data from DESTINY-Breast03 provided an indication of clinical outcomes after discontinuation of T-DXd, demonstrating a median progression-free survival (PFS) from time of randomization to progression on the next line of therapy or death (PFS2) of 45.2 months (95% CI, 39.3 months to not estimable)[12]
  - However, given that PFS1 is the main driver behind PFS2, and because PFS2 encompasses all types of next-line therapies administered after T-DXd, a more detailed analysis is warranted
- Overall, clinical trial data on outcomes with subsequent therapies after discontinuation of T-DXd are lacking. While some data do exist, there remains a need to better understand the treatment outcomes associated with specific HER2-targeted agents after T-DXd to inform treatment decisions given the paradigm shift in oncology towards the use of such agents in the second- and later-line setting[9]
- DoT can be considered a surrogate for treatment outcome as patients typically receive treatment for as long as they respond to treatment or do not discontinue treatment due to any adverse event

Methods

- DESTINY-Breast02 (NCT03523585) and DESTINY-Breast03 (NCT03529110) are randomized, open-label, multicenter, phase 3 trials designed to evaluate the efficacy and safety of second-line or later treatment with T-DXd versus treatment of physician's choice (TPC) or T-DM1, respectively, in patients with HER2-positive (IHC 3+ or 2+/ISH+) unresectable or mBC (**Figure 1**)[3,13]
- Patients in DESTINY-Breast02 had to have disease progression following prior T-DM1, taxane, and trastuzumab ± pertuzumab.[13] Patients in DESTINY-Breast03 had to have disease progression following prior taxane and trastuzumab ± pertuzumab[3]
- This study used a descriptive, exploratory approach to compare DoTs defined as the start date of the first post systemic anticancer treatment + 1 subtracted from the end date of the first post systemic anticancer treatment. If the analysis end dates of all therapies within the treatment are missing, then the later value is defined as the participant's last known alive date
- The analysis here presents different HER2-directed therapies such as trastuzumab monotherapy, trastuzumab-based combinations, pertuzumab-based combinations, T-DM1, and HER2 tyrosine kinase inhibitor (TKI)–containing combinations that were received by patients as their next line of treatment after discontinuation of T-DXd for any reason

Figure 1. DESTINY-Breast02 and DESTINY-Breast03 Study Designs[3,12-14]



Results

Patient Demographic and Baseline Characteristics

- A summary of key demographic and baseline characteristics of patients randomly assigned to treatment in DESTINY-Breast02 and DESTINY-Breast03 is provided in **Table 1**
- In both studies, characteristics were representative of the mBC population and were balanced across treatment arms
- At the September 29, 2023, data cutoff (DCO) in DESTINY-Breast02, median follow-up duration since the assignment of 406 patients to T-DXd was 30.2 months (range, 0.8-60.7 months), with treatment ongoing in 55 patients (13.6%)[14]
- At the November 20, 2023, DCO in DESTINY-Breast03, median follow-up duration since the assignment of 261 patients to T-DXd was 43.0 months (range, 0.0-62.9 months), with treatment ongoing in 50 patients (19.5%)[12]

Patient Discontinuation Data

- A summary of the primary reasons for discontinuation of treatment in DESTINY-Breast02 and -03 and subsequent therapies administered is provided in **Table 2**
- In DESTINY-Breast02, 349/404 patients (86.4%) who received treatment with T-DXd and 195/195 patients (100.0%) who received TPC discontinued treatment due to any reason. Overall, 247/349 patients (70.8%) in the T-DXd arm and 148/195 patients (75.9%) in the TPC arm received any posttrial systemic anticancer treatment
- In DESTINY-Breast03, 207/257 patients (80.5%) who received treatment with T-DXd and 251/261 patients (96.2%) who received T-DM1 discontinued treatment due to any reason. Overall, 144/207 patients (69.6%) in the T-DXd arm and 198/251 patients (78.9%) in the T-DM1 arm received any posttrial systemic anticancer treatment

DoT of Anti-HER2 Therapies After T-DXd

- The DoT across first systemic anti-HER2 therapies administered after T-DXd in patients from DESTINY-Breast02 and DESTINY-Breast03 are shown in **Figure 2**
  - In DESTINY-Breast02, the most common first systemic anti-HER2 therapies administered after T-DXd were HER2 TKI–containing combinations, trastuzumab-based combinations, trastuzumab monotherapy (where monotherapy refers only to the anti-HER2 therapy and does not exclude patients also receiving other types of therapy such as chemotherapy), and pertuzumab-based combinations
  - In DESTINY-Breast03, the most common first systemic anti-HER2 therapies administered after T-DXd included T-DM1, trastuzumab-based combinations, and HER2 TKI–containing combinations
- When considering HER2-directed therapies given to ≥10 patients after discontinuation of T-DXd, median DoT was longest with pertuzumab-based combinations (7.0 months) in DESTINY-Breast02 and HER2 TKI–containing combinations (9.0 months) in DESTINY-Breast03

Table 1. Demographics and Baseline Characteristics of Patients in DESTINY-Breast02 and DESTINY-Breast03[3,12-14]

Characteristic	DESTINY-Breast02		DESTINY-Breast03	
	T-DXd n = 406[a]	TPC n = 202	T-DXd n = 261	T-DM1 n = 263
Age, median (range), years	54.2 (22.4-88.5)	54.7 (24.7-86.5)	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, n (%)	403 (99.3)	200 (99.0)	260 (99.6)	262 (99.6)
Race, n (%)				
White	257 (63.3)	127 (62.9)	71 (27.2)	72 (27.4)
Asian	122 (30.0)	56 (27.7)	152 (58.2)	162 (61.6)
Black or African American	10 (2.5)	7 (3.5)	10 (3.8)	9 (3.4)
American Indian or Alaskan Native	2 (0.5)	0	—	—
Native Hawaiian or Pacific Islander	0	1 (0.5)	—	—
Other[b]	15 (3.7)	11 (5.4)	28 (10.7)	20 (7.6)
Region, n (%)				
Europe	152 (37.4)	78 (38.6)	54 (20.7)	50 (19.0)
Asia	112 (27.6)	52 (25.7)	149 (57.1)	160 (60.8)
North America	41 (10.1)	23 (11.4)	17 (6.5)	17 (6.5)
Other	101 (24.9)	49 (24.3)	41 (15.7)	36 (13.7)
HER2 status (IHC), n (%)				
3+	326 (80.3)	159 (78.7)	234 (89.7)	232 (88.2)
2+ (ISH+)	79 (19.5)	41 (20.3)	25 (9.6)	30 (11.4)
2+ (ISH− or NE)	1 (0.2)	1 (0.5)	—	—
1+ (ISH+)	0	1 (0.5)	1 (0.4)	0
NE	—	—	1 (0.4)	1 (0.4)
ECOG PS, n (%)				
0	228 (56.2)	121 (59.9)	154 (59.0)	175 (66.5)
1	177 (43.6)	81 (40.1)	106 (40.6)	87 (33.1)
2	1 (0.2)	0	—	—
Missing	—	—	1 (0.4)	1 (0.4)
Positive hormone receptor status, n (%)	238 (58.6)	118 (58.4)	131 (50.2)	134 (51.0)
Visceral disease, n (%)	316 (77.8)	160 (79.2)	184 (70.5)	185 (70.3)
Baseline brain metastases, n (%)	74 (18.2)	36 (17.8)	43 (16.5)	39 (14.8)
Median number of prior lines of systemic therapy in the metastatic setting (range)[c]	2 (0-10)	2 (1-8)	2 (0-16)	2 (0-15)
Prior systemic cancer therapy, n (%)				
Trastuzumab	404 (99.5)	202 (100)	260 (99.6)	262 (99.6)
T-DM1	404 (99.5)	202 (100)	1 (0.4)	0
Pertuzumab	318 (78.3)	156 (77.2)	162 (62.1)	158 (60.1)
Hormone therapy	164 (40.4)	87 (43.1)	109 (41.8)	112 (42.6)
HER2 TKI	26 (6.4)	17 (8.4)	42 (16.1)	36 (13.7)
Other anti-HER2 therapy (except HER2 TKI)	11 (2.7)	6 (3.0)	2 (0.8)	3 (1.1)
Efficacy endpoint results				
Confirmed ORR by BICR, n (% [95% CI])	283 (69.7 [65.0-74.1])	59 (29.2 [23.0-36.0])	206 (78.9 [73.5-83.7])	97 (36.9 [31.0-43.0])
DOR, median (95% CI), months	19.6 (15.9-not estimable)	8.3 (5.8-9.5)	30.5 (23.0-not estimable)	17.0 (14.1-23.7)
CBR by BICR (95% CI), %	82.3 (78.2-85.9)	46.0 (39.0-53.2)	—	—
Treatment duration, median (range), months	11.3 (0.7-60.7)	~4.5 (0.1-50.6)	18.2 (0.7-56.6)	6.9 (0.7-55.2)

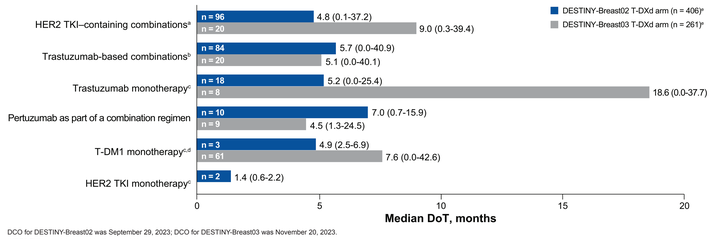
[a]2 patients were randomly assigned to receive T-DXd but were not treated.
[b]Includes patients who reported multiple races.
[c]Not including hormone therapy.

Table 2. Reason for Treatment Discontinuation and Anticancer Therapies Administered After Discontinuation in DESTINY-Breast02 and DESTINY-Breast03[3,12-14]

	DESTINY-Breast02		DESTINY-Breast03	
	T-DXd n = 406[a]	TPC n = 202[b]	T-DXd n = 261[c]	T-DM1 n = 263[d]
Treatment duration, median (range), months	11.3 (0.7-60.7)	~4.5 (0.1-50.6)	18.2 (0.7-56.6)	6.9 (0.7-55.2)
Treatment status, n (%)				
Ongoing	55 (13.6)	0	50 (19.5)	10 (3.8)
Discontinued	349 (86.4)	195 (100.0)	207 (80.5)	251 (96.2)
Primary reason for treatment discontinuation, n (%)				
Progressive disease	193 (47.8)	144 (73.8)	107 (41.6)	183 (70.1)
Adverse event	82 (20.3)	14 (7.2)	61 (23.7)	24 (9.2)
Withdrawal by patient	37 (9.2)	17 (8.7)	22 (8.6)	14 (5.4)
Clinical progression	26 (6.4)	17 (8.7)	5 (1.9)	16 (6.1)
Death	5 (1.2)	1 (0.5)	4 (1.6)	4 (1.5)
Lost to follow-up	2 (0.5)	0	1 (0.4)	0
Physician decision	2 (0.5)	1 (0.5)	2 (0.8)	8 (3.1)
Protocol deviation	1 (0.2)	1 (0.5)	1 (0.4)	0
Other	1 (0.2)	0	4 (1.6)	2 (0.8)
Type of treatment received after discontinuation, n (%)[e]				
Systemic	247 (70.8)	148 (75.9)	144 (69.6)	198 (78.9)
Radiation	43 (12.3)	25 (12.8)	26 (12.6)	43 (17.1)
Surgery	10 (2.9)	7 (3.6)	6 (2.9)	15 (6.0)
Discontinued T-DXd due to any adverse event, n (%)	82 (20.2)	—	61 (23.4)	—
Received 1st line of subsequent therapy (did not have PD on T-DXd)[e]	55 (67.1)	—	42 (68.9)	—
Received 2nd line of subsequent therapy (did not have PD on 1st line)[e]	8 (9.8)	—	7 (11.5)	—

[a]2 patients were randomly assigned to receive T-DXd but were not treated.
[b]7 patients were randomly assigned to receive TPC but were not treated.
[c]4 patients were randomly assigned to receive T-DXd but were not treated.
[d]2 patients were randomly assigned to receive T-DM1 but were not treated.
[e]The denominator for calculating the percentage was the number of patients who discontinued T-DXd due to any adverse event.

Figure 2. DoT of First Systemic Anti-HER2 Therapies After T-DXd in Patients From DESTINY-Breast02 and DESTINY-Breast03



DCO for DESTINY-Breast02 was September 29, 2023; DCO for DESTINY-Breast03 was November 20, 2023.
[b]HER2 TKI–containing combinations could have contained trastuzumab.
[c]Trastuzumab-based combinations did not include a TKI.
[a]As only first systemic anti-HER2 therapy administered, which does not exclude patients also receiving other types of therapy such as chemotherapy.
[d]Patients in DESTINY-Breast02 had been treated with T-DM1 prior to receiving T-DXd.
[e]Intention-to-treat population.

Abbreviations

BICR, blinded independent central review; CBR, clinical benefit rate; DCO, data cutoff; DoR, duration or response; DoT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ITT, intention-to-treat; mBC, metastatic breast cancer; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; R, randomization; RWD, real-world data; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TPC, treatment of physician's choice.

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Disclosures

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DESTINY Breast02/03