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Exploratory Pooled Safety Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2+ or HER2-low Unresectable and/or Metastatic Breast Cancer in DESTINY-Breast Trials

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Objective

- To evaluate the safety profile of T-DXd in patients with HER2+ and HER2-low mBC across the DESTINY-Breast01/02/03/04 trials

Conclusions

- In this pooled analysis, the safety profile of T-DXd was consistent in patients with HER2+ and HER2-low mBC across the DESTINY-Breast01/02/03/04 clinical trials
- Adjudicated drug-related ILD/pneumonitis rates were similar in the pooled T-DXd analysis after <3 (11.7%) or ≥3 (13.0%) prior therapy regimens, with most events across all studies adjudicated as grade 1 or 2
- In the pooled T-DXd group, patients with moderate renal impairment (CrCl, 30-59 mL/min) at baseline had a higher rate of adjudicated drug-related ILD/pneumonitis (most grade 1 or 2), and earlier time to onset than those with normal or mild impairment. Patients with moderate renal impairment should be monitored carefully
- Exposure-adjusted incidence rates (EAIRs) of grade ≥3 TEAEs were lower in the pooled T-DXd group than with TPC in DESTINY-Breast02 and DESTINY-Breast04 and T-DM1 in DESTINY-Breast03

Plain Language Summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)–targeting antibody-drug conjugate (ADC) that is approved to treat patients with metastatic breast cancers (mBC) expressing high levels or low levels of the HER2 protein.[1,2] T-DXd demonstrated clinical efficacy and acceptable and generally manageable safety in the DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 clinical trials in patients with HER2-positive mBC (immunohistochemistry [IHC] score 3+ or score 2+ and in situ hybridization (ISH) positive), and in the DESTINY-Breast04 clinical trial in patients with HER2-low mBC (IHC 1+ or 2+/ISH negative).[3-6] During the trials, the most common side effects experienced by patients treated with T-DXd were nausea, fatigue, and neutropenia. Interstitial lung disease (ILD)/pneumonitis, a heterogenous collection of disorders that cause inflammation or fibrosis in the lungs and may be fatal, has been reported in patients treated with T-DXd, and it must be carefully monitored according to guidelines. So far, no studies have been done to evaluate the safety of T-DXd using data that were pooled from these DESTINY-Breast clinical trials.

How did we perform this research?
Safety data from patients treated with T-DXd 5.4 mg/kg every 3 weeks in the DESTINY-Breast01/02/03/04 clinical trials were pooled and analyzed to evaluate drug-related adverse events and adjudicated, drug-related ILD/pneumonitis. The effect of renal function at baseline on the incidence of ILD/pneumonitis was also investigated.

What were the findings of this research and what were the implications?
The results showed that the safety profile of T-DXd was consistent in patients with HER2+ and HER2-low mBC in the DESTINY-Breast01/02/03/04 clinical trials. The duration of treatment with T-DXd was twice as long as the comparator treatments in the trials. When this difference in treatment exposure was accounted for, the rates of grade 3 or higher adverse events were lower with T-DXd than with trastuzumab emtansine (T-DM1), another HER2-targeting ADC, or physician's choice of chemotherapy. Overall, ILD/pneumonitis was reported in 12.7% of patients in the pooled T-DXd safety analysis group, and the rates of ILD/pneumonitis were similar or higher after 3 or more prior therapy regimens than after fewer than 3 therapy regimens in all trials except DESTINY-Breast03. ILD/pneumonitis was more common and more severe, and occurred earlier, in the subgroup of patients who had moderate renal impairment at baseline (patients with severe renal disease were excluded from the trials). T-DXd demonstrated an acceptable and generally manageable safety profile, and there were no new safety findings in this large pooled population of patients from the DESTINY-Breast clinical trials. Patients should be monitored carefully for the onset of ILD/pneumonitis, particularly considering a potentially increased risk in those with moderate renal impairment.

Where can I access more information?
To learn more about the trials in this study, you can visit:
- DESTINY-Breast01, https://clinicaltrials.gov/ct2/show/NCT03248492
- DESTINY-Breast02, https://clinicaltrials.gov/ct2/show/NCT03523585
- DESTINY-Breast03, https://clinicaltrials.gov/ct2/show/NCT03529110
- DESTINY-Breast04, https://clinicaltrials.gov/ct2/show/NCT03734029

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Introduction

- Approval of trastuzumab deruxtecan (T-DXd) for the treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) or HER2-low unresectable breast cancer (BC) or metastatic BC (mBC)[1,2] was based on efficacy data from the DESTINY-Breast01/02/03/04 clinical trials in which T-DXd demonstrated durable antitumor activity[3-6]
- The most common treatment-emergent adverse events (TEAEs) in the T-DXd clinical trials were nausea, fatigue, and neutropenia[3-6]
- T-DXd has been shown to increase the risk of interstitial lung disease (ILD)/pneumonitis, which has been identified as an adverse event (AE) of special interest that requires close monitoring and management[3-6]
- There are no previously published pooled safety data for T-DXd in patients with mBC

Methods

- This pooled analysis included patients with HER2+ (DESTINY-Breast01/02/03) or HER2-low (defined as immunohistochemistry [IHC] 1+ or 2+ with in situ hybridization [ISH] not amplified [-]) (DESTINY-Breast04) locally advanced unresectable BC or mBC
  - DESTINY-Breast01 was an open-label, 2-part, multicenter, phase 2 study of T-DXd in patients (n = 184 received T-DXd 5.4 mg/kg) with HER2+ unresectable BC or mBC that progressed on or after treatment with trastuzumab emtansine (T-DM1) or patients who were intolerant of T-DM1[3] (data cutoff: March 26, 2021)
  - DESTINY-Breast02 was an open-label, randomized (2:1), multicenter, phase 3 study comparing T-DXd (n = 404 treated patients) with treatment of physician's choice (TPC; n = 195 treated patients) in patients with HER2+ unresectable BC or mBC who were previously treated with T-DM1[4] (data cutoff: June 30, 2022)
  - DESTINY-Breast03 was an open-label, randomized (1:1), multicenter, phase 3 study comparing T-DXd (n = 257 in safety analysis) with T-DM1 (n = 261 in safety analysis) in patients with HER2+ unresectable BC or mBC who were naive to T-DM1 but previously treated with trastuzumab and a taxane[5] (data cutoff: July 25, 2022)
  - DESTINY-Breast04 was an open-label, randomized (2:1), multicenter, phase 3 trial comparing the efficacy and safety of T-DXd (n = 371 in safety analysis) with that of TPC (n = 172 in safety analysis) in patients with HER2-low unresectable BC or mBC[6] (data cutoff: March 1, 2023)
- The following safety measures were evaluated across the DESTINY-Breast01/02/03/04 trials:
  - Drug-related TEAE incidence and severity, rates of treatment discontinuation and dose reduction, and deaths
  - Adjudicated drug-related ILD/pneumonitis incidence, severity, time to onset, duration, resolution, and outcomes
  - Onset of adjudicated, drug-related ILD/pneumonitis according to renal status at baseline
  - Effect of visceral disease at baseline on the incidence of TEAEs

Results

Patients

- A total of 1216 patients treated with T-DXd 5.4 mg/kg were pooled across the DESTINY-Breast01/02/03/04 trials (**Table 1**)

Table 1. Demographics and Baseline Characteristics in the Pooled T-DXd Group

Baseline Characteristic	Pooled T-DXd (N = 1216)
Age, median (range), years	55 (22-96)
Female, n (%)	1210 (99.5)
Region, n (%)	
Europe	437 (35.9)
Asia	468 (38.5)
North America	169 (13.9)
Rest of world	142 (11.7)
Presence of visceral disease,[a] n (%)	
Yes	1006 (82.7)
No	210 (17.3)
Renal function status,[b] n (%)	
Normal	665 (54.7)
Mild	417 (34.3)
Moderate	128 (10.5)
Missing/not included[b]	6 (0.5)
ECOG PS, n (%)	
0	679 (55.8)
1	535 (44.0)
2	2 (0.2)
Number of prior regimens in the metastatic setting, median (range)	3 (0-27)

[a]Defined as any target or nontarget tumor in prespecified lesion locations.
[b]Patients had to have adequate renal function (CrCl ≥30 mL/min, calculated using the Cockcroft-Gault equation) to enter the trials. Normal renal function was defined as CrCl ≥90 mL/min, mild impairment was defined as CrCl 60-89 mL/min, and moderate impairment was defined as CrCl 30-59 mL/min in accordance with guidelines.[7,8] In DESTINY-Breast04, a protocol deviation and an error concerning laboratory migration resulted in data from 6 patients not being included in the subgroup analysis for renal impairment at baseline.

T-DXd Safety in DESTINY-Breast01/02/03/04

- The median duration of T-DXd treatment was longest in DESTINY-Breast03, followed by DESTINY-Breast02, DESTINY-Breast01, and DESTINY-Breast04; the overall median (range) treatment duration in the pooled T-DXd group was 10.6 months (0.2-45.1 months) (**Table 2**)
- A similar incidence and severity of TEAEs were reported across the DESTINY-Breast01/02/03/04 clinical trials regardless of HER2 status (HER2+ [DESTINY-Breast01/02/03] or HER2-low [DESTINY-Breast04]) (**Table 2**)
- Median (range) time, in days, to T-DXd discontinuation due to any TEAE was longest in DESTINY-Breast03 (337.0 [104-1163]) compared with DESTINY-Breast01 (187.0 [8-783]), DESTINY-Breast02 (248.5 [2-759]), and DESTINY-Breast04 (149.0 [3-740]), consistent with the longer treatment duration in DESTINY-Breast03

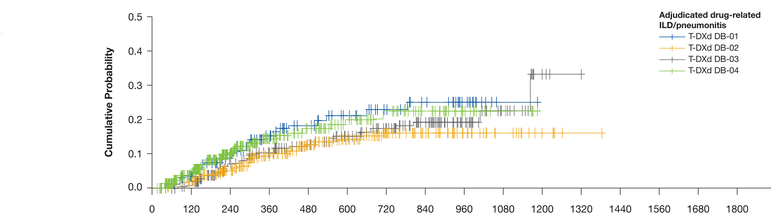
Table 2. Incidence of Any-Grade Drug-Related TEAEs With T-DXd Treatment Across the DESTINY-Breast Clinical Trials

	T-DXd DB-01 (N = 184)	T-DXd DB-02 (N = 404)	T-DXd DB-03 (N = 257)	T-DXd DB-04 (N = 371)	Pooled T-DXd (N = 1216)
Treatment duration,[a] median (range), months	10.1 (0.7-39.6)	11.3 (0.7-45.1)	18.2 (0.7-44.0)	8.2 (0.2-39.1)	10.6 (0.2-45.1)
Patients who had any drug-related TEAE	183 (99.5)	394 (97.5)	252 (98.1)	357 (96.2)	1186 (97.5)
MedDRA preferred term/grouped term (≥20%)[b]					
Nausea	142 (77.2)	277 (68.6)	190 (73.9)	271 (73.0)	880 (72.4)
Fatigue[c]	110 (59.8)	209 (51.7)	123 (47.9)	181 (48.8)	623 (51.2)
Alopecia	86 (46.7)	142 (35.1)	100 (38.9)	141 (38.0)	469 (38.6)
Vomiting	81 (44.0)	131 (32.4)	115 (44.7)	127 (34.2)	454 (37.3)
Neutropenia[c]	63 (34.2)	134 (33.2)	115 (44.7)	125 (33.7)	437 (35.9)
Anemia[c]	49 (26.6)	104 (25.7)	88 (34.2)	127 (34.2)	368 (30.3)
Decreased appetite	57 (31.0)	107 (26.5)	70 (27.2)	106 (28.6)	340 (28.0)
Leukopenia[c]	43 (23.4)	77 (19.1)	85 (33.1)	87 (23.5)	292 (24.0)
Thrombocytopenia[c]	40 (21.7)	82 (20.3)	77 (30.0)	92 (24.8)	291 (23.9)
Diarrhea	45 (24.5)	82 (20.3)	63 (24.5)	83 (22.4)	273 (22.5)
Transaminases increased[c]	32 (17.4)	70 (17.3)	78 (30.4)	93 (25.1)	273 (22.5)
Constipation	33 (17.9)	88 (21.8)	63 (24.5)	80 (21.6)	264 (21.7)
Drug-related TEAE associated with discontinuation	33 (17.9)	58 (14.4)	51 (19.8)	57 (15.4)	199 (16.4)
Drug-related TEAE associated with dose reduction	43 (23.4)	95 (23.5)	65 (25.3)	83 (22.4)	286 (23.5)
Drug-related TEAE associated with an outcome of death	3 (1.6)	4 (1.0)	0	7 (1.9)	14 (1.2)

Values are expressed as n (%) unless otherwise specified.
[a]Treatment duration (months) is defined as (date of last dose – date of first dose + 21)/30.4375.
[b]Reported in ≥20% of patients in any group.
[c]Grouped terms are anemia (anemia, hemoglobin decreased, hematocrit decreased, red blood cell count decreased); fatigue (asthenia, fatigue, lethargy, malaise); leukopenia (leukopenia, white blood cell count decreased); neutropenia (neutropenia, neutrophil count decreased); thrombocytopenia (platelet count decreased, thrombocytopenia); transaminases increased (alanine aminotrasferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test abnormal, liver function test increased, transaminases increased).

- Median treatment duration was approximately 2-fold longer in the pooled T-DXd group (10.6 months) than in the comparator arms in DESTINY-Breast02/03/04 (TPC: 4.6 months, DESTINY-Breast02; 3.5 months, DESTINY-Breast04 and T-DM1: 6.9 months, DESTINY-Breast03)
  - Exposure-adjusted incidence rates (EAIRs) were measured to account for differences in treatment duration exposure in patient-years between T-DXd and comparators and provide a more meaningful comparison (supplementary data are available by scanning the QR code)
  - Grade ≥3 TEAE EAIRs were 0.48 (pooled T-DXd), 0.77 (TPC, DESTINY-Breast02), 0.65 (T-DM1, DESTINY-Breast03), and 1.81 (TPC, DESTINY-Breast04)
- Rates of drug-related TEAEs were consistent regardless of the presence or absence of visceral disease at baseline (defined as any target or nontarget tumor in prespecified lesion locations)
  - In the pooled T-DXd group, grade ≥3 TEAEs were reported in 44.9% of patients (452/1006) with visceral disease at baseline and in 44.8% of patients (94/210) without visceral disease at baseline

Figure 1. Time to Onset of Adjudicated Drug-Related ILD/pneumonitis With T-DXd Treatment



Patients still at risk, n

T-DXd DB-01	184	153	111	83	65	47	37	30	16	1	0	0	0	
T-DXd DB-02	404	356	273	198	153	112	64	44	26	13	4	1	0	
T-DXd DB-03	257	245	197	166	140	120	101	74	38	15	4	1	0	
T-DXd DB-04	371	292	189	107	75	50	36	23	11	4	0	0	0	

Deaths are derived from overall survival. Patients still at risk are those without an event of adjudicated drug-related ILD/pneumonitis or death.

- The overall rate of adjudicated drug-related ILD/pneumonitis in the pooled T-DXd group across the DESTINY-Breast01/02/03/04 clinical trials was 12.7% (**Table 3**)
  - Most ILD/pneumonitis events were grade 1 or 2 (11%), the median (range) time to onset was 176 days (26-960 days), and the median (range) duration was 56.5 days (1-542 days)
  - Rates of any-grade adjudicated drug-related ILD/pneumonitis with T-DXd treatment were similar or higher after ≥3 or <3 prior therapy regimens in the pooled T-DXd group and across the DESTINY-Breast clinical trials; however, the overall number of patients who received <3 prior regimens was comparatively smaller (**Table 3**)
- Across the pooled T-DXd group, patients with adjudicated drug related ILD/pneumonitis events were assessed by the investigators as recovered or resolved for most patients (62.6%), not recovered/not resolved for 28 patients (18.1%)

Table 3. Adjudicated Drug-Related ILD/pneumonitis and Outcomes Across the DESTINY-Breast Studies

	T-DXd DB-01 (N = 184)	T-DXd DB-02 (N = 404)	T-DXd DB-03 (N = 257)	T-DXd DB-04 (N = 371)	Pooled T-DXd (N = 1216)
Adjudicated highest CTCAE grade, n (%)					
Any grade	29 (15.8)	42 (10.4)	39 (15.2)	45 (12.1)	155 (12.7)
Grade 1	6 (3.3)	11 (2.7)	11 (4.3)	13 (3.5)	41 (3.4)
Grade 2	16 (8.7)	26 (6.4)	26 (10.1)	24 (6.5)	92 (7.6)
Grade 3	2 (1.1)	3 (0.7)	2 (0.8)	4 (1.1)	11 (0.9)
Grade 4	0	0	0	0	0
Grade 5[a]	5 (2.7)	2 (0.5)	0	4 (1.1)	11 (0.9)
Time to onset of first adjudicated drug-related ILD/pneumonitis,[b] days					
n	29	42	39	45	155
Median (range)	134 (35-758)	209.5 (41-638)	246 (33-960)	129 (26-710)	176 (26-960)
Duration of first adjudicated drug-related ILD/pneumonitis,[c] days					
n	19	29	31	37	116
Median (range)	66 (3-542)	58 (1-354)	50 (18-335)	76 (3-525)	56.5 (1-542)
Rate of adjudicated drug-related ILD/pneumonitis after <3 or ≥3 prior regimens, n (%)	<3 (n = 14) / ≥3 (n = 170)	<3 (n = 85) / ≥3 (n = 319)	<3 (n = 112) / ≥3 (n = 145)	<3 (n = 53) / ≥3 (n = 318)	<3 (n = 264) / ≥3 (n = 952)
	2 (14.3)	27 (15.9)	6 (7.1)	36 (11.3)	20 (17.9)	19 (13.1)	3 (5.7)	42 (13.2)	31 (11.7)	124 (13.0)
Investigator-assessed outcome of worst ILD/pneumonitis event at data cutoff,[d] n (%)					
Fatal[a]	4 (13.8)	1 (2.4)	0	3 (6.7)	8 (5.2)
Not recovered/not resolved	7 (24.1)	10 (23.8)	6 (15.4)	5 (11.1)	28 (18.1)
Recovering/resolving	0	3 (7.1)	2 (5.1)	1 (2.2)	6 (3.9)
Recovered/resolved with sequelae	2 (6.9)	3 (7.1)	2 (5.1)	5 (11.1)	12 (7.7)
Recovered/resolved	15 (51.7)	24 (57.1)	29 (74.4)	29 (64.4)	97 (62.6)
Missing/unknown	1 (3.4)	1 (2.4)	0	2 (4.4)	4 (2.6)

[a]Grade was based on the ILD/pneumonitis adjudication committee's adjudication whereas outcome was based on the investigator's report.
[b]Time to first adjudicated drug-related ILD/pneumonitis onset date (days) is defined as the onset date of first ILD/pneumonitis adjudicated as drug-related – first dose date + 1.
[c]Duration is defined as AE end date – AE start date + 1. AE is the event corresponding to the first adjudicated drug-related ILD/pneumonitis for each patient.
[d]The denominator for outcome of the worst ILD/pneumonitis event is based on adjudicated drug-related ILD/pneumonitis and the outcome of the worst ILD/pneumonitis event is based on the investigator-reported outcome of adjudicated drug-related ILD/pneumonitis.

- There was an apparent association between moderate renal impairment at baseline and higher rates of ILD/pneumonitis and earlier onset (**Table 4**)

Table 4. Adjudicated Drug-Related ILD/pneumonitis in the T-DXd Pooled Safety Group According to Renal Status at Baseline

Renal Function Status	Pooled T-DXd (N = 1216)[a]		
	Normal[b] (n = 665)	Mild[c] (n = 417)	Moderate[d,e] (n = 128)
Adjudicated highest CTCAE grade, n (%)			
Any grade	75 (11.3)	48 (11.5)	31 (24.2)
Grade 1	21 (3.2)	13 (3.1)	6 (4.7)
Grade 2	42 (6.3)	30 (7.2)	20 (15.6)
Grade 3	8 (1.2)	2 (0.5)	1 (0.8)
Grade 4	0	0	0
Grade 5	4 (0.6)	3 (0.7)	4 (3.1)
Time to first adjudicated drug-related ILD/pneumonitis onset, median (range), days	250.0 (26-960)	165.5 (41-630)	126.0 (33-632)
Adjudicated drug-related ILD/pneumonitis associated with drug discontinuation, n (%)	54 (8.1)	36 (8.6)	24 (18.8)

[a]In DESTINY-Breast04, a protocol deviation and an error concerning laboratory migration resulted in data from 6 patients not being included in the subgroup analysis by renal impairment at baseline.
[b]CrCl, >90 mL/min.
[c]CrCl, 60-89 mL/min.
[d]CrCl, 30-59 mL/min in accordance with guidelines.[7,8]

Abbreviations

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DB, DESTINY-Breast; EAIR, exposure-adjusted incidence rate; 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; mBC, metastatic breast cancer; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

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DESTINY-Breast