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Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer: Updated Survival Results from a Phase 2 Trial (DESTINY-Breast01)

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Background

- Approximately 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2)[1]
- T-DXd is approved for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting[2]
- DESTINY-Breast01 (NCT03248492) is an international, multicenter, open-label phase 2 study of T-DXd in patients with HER2-positive metastatic breast cancer (MBC); the results from this study supported global regulatory approval[3,4]
- Data from prior data cutoffs (primary: August 1, 2019[3]; initial update: June 8, 2020[4]) showed that patients receiving T-DXd had durable responses
  - At the initial update (June 8, 2020) presented at the 2020 San Antonio Breast Cancer Symposium, confirmed overall response rate (ORR) was 61.4%, duration of response (DOR) was 20.8 months, median progression-free survival (PFS) was 19.4 months, and median overall survival (OS) was 24.6 months[4]
  - Safety results were also consistent with previously reported data on T-DXd[3,4]
- Previous reports of median OS were limited by high percentages of censored patients; updated, mature survival results at the most recent data cutoff (March 26, 2021) are reported here

Conclusions

- With 6 months of additional follow-up, and more than half of the patients now with OS events, T-DXd demonstrated an estimated median OS of 29.1 months and a high landmark survival at 12, 18, and 24 months (85%, 75%, and 58%, respectively)
- These updated results continue to demonstrate a significant and sustained survival benefit of T-DXd in heavily previously treated patients with HER2-positive MBC (median prior lines of treatments, 6)
- Safety results were consistent with the known safety profile of T-DXd[3,4]
- T-DXd is currently undergoing further investigation in randomized controlled clinical trials assessing patients with:
  - HER2-positive BC (DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast05, DESTINY-Breast07, and DESTINY-Breast09)
  - HER2-low BC (DESTINY-Breast04 and DESTINY-Breast06)

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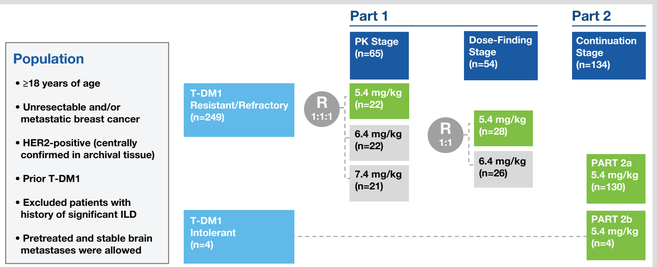
Methods

- DESTINY-Breast01 evaluated T-DXd in adult patients with HER2-positive (centrally confirmed; immunohistochemistry [IHC] 3+ or in-situ hybridization [ISH]+), metastatic or unresectable BC (**Figure 1**)
  - Patients whose disease progressed on or after trastuzumab emtansine were included in the study
  - Of the 253 patients who enrolled, 184 received T-DXd 5.4 mg/kg (primary analysis set)
- The primary endpoint was ORR, and additional endpoints included DOR, PFS, and OS

Figure 1. DESTINY-Breast01 Study Design



BC, breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; PK, pharmacokinetic; R, randomization; T-DM1, trastuzumab emtansine.

Results

Patients

- A total of 184 patients were assessed; ages ranged from 28 to 96 years and the median number of prior lines of therapy in the metastatic setting was 6 (range, 2-27)
- Baseline demographic and clinical characteristics are shown in **Table 1**
- As of March 26, 2021, the median duration of follow-up was 26.5 months (range, 0.7-39.1), 6 months longer than that of the previous most recent analysis (**Table 2**)
- In total, 15% (n = 28) of patients remained on treatment and 85% (n = 156) discontinued
  - Discontinuations were due to progressive disease (46%, n = 85), adverse events (19%, n = 35), patient withdrawal (6%, n = 11), physician decision (4%, n = 8), death (4%, n = 7), or other (5%, n = 10)

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	T-DXd 5.4 mg/kg (N = 184)[a]
Age, years, median (range)	55.0 (28-96)
Female, %	100
Region, % Asia/North America/Europe	 34.2/28.8/37.0
ECOG performance status 0/1/2, %	55.4/44.0/0.5
Hormone receptor positive/negative/unknown, %	52.7/45.1/2.2
HER2 expression, %[b] IHC 3+ IHC 2+; ISH+/IHC 1+; ISH+ Missing	 83.7 15.2 1.1
Presence of visceral disease, %	91.8
Prior treatment for metastatic disease Median (range) Trastuzumab/T-DM1, % Pertuzumab, % Other anti-HER2, % Hormone therapy, % Other systemic therapy, %	 6 (2-27) 100/100 65.8 54.3 48.9 99.5

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All 184 patients received ≥1 dose of T-DXd.
[b]HER2 status was centrally assessed in archival tissue according to guidelines of the American Society of Clinical Oncology/College of American Pathologists.

Table 2. Summary of Efficacy

Intent-to-Treat Analysis	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Median duration of follow up (range), months	11.1 (0.7-19.9)	20.5 (0.7-31.4)	26.5 (0.7-39.1)
Patients remaining on treatment, n (%)	79 (42.9)	37 (20.1)	28 (15.2)
Confirmed ORR[a] by ICR, n (%) 95% CI	112 (60.9) 53.4-68.0	113[b] (61.4) 54.0-68.5	114 (62.0) 54.5-69.0
CR	11 (6.0)	12 (6.5)	13 (7.1)
PR	101 (54.9)	101 (54.9)	101 (54.9)
SD	67 (36.4)	66 (35.9)	65 (35.3)
PD	3 (1.6)	3 (1.6)	3 (1.6)
Not evaluable	2 (1.1)	2 (1.1)	2 (1.1)
Median DOR (95% CI), months	14.8 (13.8-16.9)	20.8[b] (15.0-NE)	18.2 (15.0-NE)
Median TTR (95% CI), months	1.6 (1.4-2.7)		
Median PFS (95% CI), months	16.4 (12.7-NE)	19.4 (14.1-NE)	19.4 (14.1-25.0)
Median OS (95% CI), months	NE (NE-NE)	24.6 (23.1-NE)	29.1 (24.6-36.1)

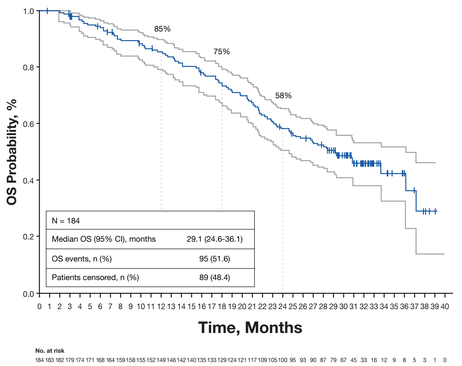
CR, complete response; DCO, data cutoff; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response.
[a]ORR = CR + PR.
[b]One patient had a PR prior to the June 8, 2020 cutoff date that was confirmed after the cutoff date. The patient had a confirmed best overall response of PR on the first PR date in the central data but was not included in the analysis of DOR.

Results (continued)

Efficacy

- As of March 26, 2021, median duration of OS follow-up was 31.1 months (95% CI, 30.7-32.0)
- The updated median OS was 29.1 months (95% CI, 24.6-36.1), and with greater data maturity, more than half of the patients had OS events (95/184, 51.6%) (**Figure 2**)
  - Estimated 12-month OS was 85% (95% CI, 79-90)
  - Estimated 18-month OS was 75% (95% CI, 67-80)
  - Estimated 24-month OS was 58% (95% CI, 51-65)

Figure 2. Kaplan-Meier Analysis of Overall Survival (OS)



- A summary of efficacy results is shown in **Table 2**
- Best percent change from baseline in target lesions is shown in **Figure 3**
- At data cutoff, median PFS was 19.4 months (95% CI, 14-25), which was unchanged from the prior June 2020 data cutoff, with 76 (41%) PFS events (**Figure 4**)
- Median DOR was 18.2 months (95% CI, 15-NE) at the updated data cutoff (March 2021) (**Figure 5**)

Figure 3. Best Percent Change From Baseline in Target Lesions

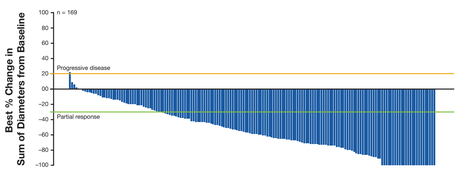


Figure 4. Kaplan-Meier Analysis of Progression-Free Survival (PFS)

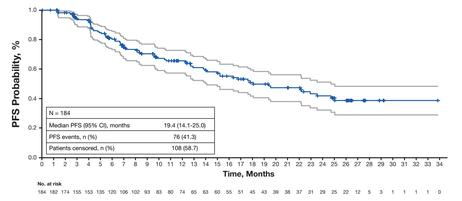
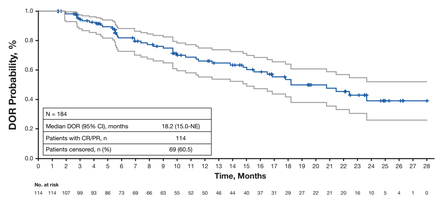


Figure 5. Kaplan-Meier Analysis of Duration of Response (DOR)



Safety Summary

- As most patients had previously discontinued treatment, the overall safety profile of T-DXd was consistent with prior results[3,4]
- These results continue to demonstrate a generally tolerable safety profile in patients treated with T-DXd (**Table 3**)
- One new case of grade 1 T-DXd–related interstitial lung disease (ILD) as determined by independent adjudication committee was reported since the last data cutoff (**Table 4**)
  - With ongoing follow-up, there were no additional reported cases of grade ≥3 ILD/pneumonitis events

Table 3. Overall Safety Summary

Type of Adverse Event,[a] n (%)	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Any TEAE Drug-related	183 (99.5) 183 (99.5)	183 (99.5) 183 (99.5)	183 (99.5) 183 (99.5)
TEAE grade ≥3 Drug-related	105 (57.1) 89 (48.4)	113 (61.4) 97 (52.7)	116 (63.0) 99 (53.8)
Dose adjustments			
TEAE associated with discontinuation Drug-related	28 (15.2) 27 (14.7)	34 (18.5) 33 (17.9)	35 (19.0) 33 (17.9)
TEAE associated with dose reduction Drug-related	43 (23.4) 40 (21.7)	44 (23.9) 39 (21.2)[b]	46 (25.0) 43 (23.4)
TEAE associated with dose interruption Drug-related	65 (35.3) 53 (28.8)	75 (40.8) 60 (32.6)	77 (41.8) 60 (32.6)
Death			
TEAE associated with death[c] Drug-related	9 (4.9) 2 (1.1)	10 (5.4) 3 (1.6)	10 (5.4) 3 (1.6)

DCO, data cutoff; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Relationship to study drug was determined by the treating investigator.
[b]Based on updated investigator assessment.
[c]Each of the following TEAEs was associated with a fatal outcome: respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock hemorrhagic; 1 patient had 2 TEAEs associated with death: acute kidney injury and acute hepatic failure.

Table 4. Drug-related Interstitial Lung Disease/Pneumonitis[a]

Interstitial Lung Disease, n (%)	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Grade 1	5 (2.7)	6 (3.3)	7 (3.8)
Grade 2	15 (8.2)	16 (8.7)	16 (8.7)
Grade 3	1 (0.5)	1 (0.5)	1 (0.5)
Grade 4	0	0	0
Grade 5	4 (2.2)	5 (2.7)	5 (2.7)
Any grade/total	25 (13.6)	28 (15.2)	29 (15.8)

DCO, data cutoff; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

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Disclosures

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References

1. Ferlay J et al. GLOBOCAN 2012 v1.0. 2013.
2. Enhertu [summary of product characteristics]. Munich, Germany: Daiichi Sankyo Europe GmbH; 2021.
3. Modi S et al. *N Engl J Med*. 2020;382:610-621.
4. Modi S et al. *Amer Assoc Cancer Research*. 2021;81(4):PD3-06.