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ORIGINAL ARTICLE

Trastuzumab deruxtecan in previously treated patients with HER2-positive metastatic breast cancer: updated survival results from a phase II trial (DESTINY-Breast01)☆

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Background: Primary analysis of the multicenter, open-label, single-arm, phase II DESTINY-Breast01 trial (median follow-up 11.1 months) demonstrated durable antitumor activity with trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) previously treated with trastuzumab emtansine (T-DM1). We report updated cumulative survival outcomes with a median follow-up of 26.5 months (data cut-off 26 March 2021).

Patients and methods: Patients with HER2-positive mBC resistant or refractory to T-DM1 received T-DXd 5.4 mg/kg intravenously every 3 weeks until disease progression, unacceptable adverse events, or withdrawal of consent. The primary endpoint was confirmed objective response rate (ORR) by independent central review (ICR). Secondary endpoints included overall survival (OS), duration of response (DoR), progression-free survival (PFS), and safety.

Results: The ORR by ICR was 62.0% [95% confidence interval (CI) 54.5% to 69.0%] in patients who received T-DXd 5.4 mg/kg every 3 weeks ($n = 184$). Median OS was 29.1 months (95% CI 24.6-36.1 months). Median PFS and DoR were 19.4 months (95% CI 14.1-25.0 months) and 18.2 months (95% CI 15.0 months-not evaluable), respectively. Drug-related treatment-emergent adverse events (TEAEs) were observed in 183 patients (99.5%), and 99 patients (53.8%) had one or more grade $\geq$3 TEAEs. Adjudicated drug-related interstitial lung disease/pneumonitis occurred in 15.8% of patients ($n = 29$), of which 2.7% ($n = 5$) were grade 5.

Conclusions: These updated results provide further evidence of sustained antitumor activity of T-DXd with a consistent safety profile in heavily pretreated patients with HER2-positive mBC.

Key words: HER2 positive, metastatic breast cancer, trastuzumab deruxtecan, overall survival

INTRODUCTION

The phase II DESTINY-Breast01 trial (NCT03248492) assessed trastuzumab deruxtecan (T-DXd) 5.4 mg/kg in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) with promising efficacy results. The confirmed objective response rate (ORR) was 60.9% [95% confidence interval (CI) 53.4% to 68.0%] in the primary data cut-off (DCO 1 August 2019) and 61.4% (95% CI 54.0% to 68.5%) in the initial update (DCO 8 June 2020).[1,2] Primary results of DESTINY-Breast01 supported approval of T-DXd in third-line settings (December 2019) by the US Food and Drug Administration.[3,4] Based on the results from DESTINY-Breast03, the indication for T-DXd was updated to include patients with HER2-positive mBC who received a prior anti-HER2-based regimen in the metastatic setting or developed disease recurrence during/within 6 months after therapy in the neoadjuvant/adjuvant setting.[4]

Median overall survival (mOS) was not reached in the primary analysis of DESTINY-Breast01. We report updated cumulative survival outcomes (DCO 26 March 2021).

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☆Note: This study was previously presented in part at the 2021 European Society for Medical Oncology (ESMO) congress [Saura CM, Modi S, Krop I, et al. 279P Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer (MBC): updated survival results from a phase II trial (DESTINY-Breast01). *Ann Oncol.* 2021;32:S485-S486].

PATIENTS AND METHODS

Study design and patients

The study design was previously published.[2] Women aged ≥18 years with pathologically documented HER2-positive mBC resistant or refractory to trastuzumab emtansine (T-DM1) with an Eastern Cooperative Oncology Group performance status score of 0 or 1 were included. HER2 positivity (centrally confirmed on archival tissue) was defined according to the American Society of Clinical Oncology/College of American Pathologists guidelines. Patients with a history of noninfectious interstitial lung disease (ILD)/pneumonitis treated with glucocorticoids, current or suspected ILD/pneumonitis, or untreated/symptomatic brain metastases were excluded. The study was approved by the institutional review board at each participating site. All patients provided written informed consent.

Procedures

Patients received T-DXd 5.4 mg/kg intravenously every 3 weeks until disease progression, unacceptable adverse events, or withdrawal of consent.

Endpoints

The primary endpoint was confirmed ORR by independent central review (ICR). Additional endpoints included duration of response (DoR), progression-free survival (PFS), OS, and time to response (TTR). Treatment-emergent adverse events (TEAEs) were categorized using the Medical Dictionary for Regulatory Activities, version 23.0, and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03. ILD/pneumonitis was evaluated by an independent adjudication committee. Statistical analyses were previously described.[2]

RESULTS

Patients

Between October 2017 and September 2018, 184 patients received at least one dose of T-DXd 5.4 mg/kg (Figure 1). At DCO, 28 patients remained on treatment. The main reasons for treatment discontinuation were disease progression (46.2%), adverse events (19.0%), and withdrawal of consent (6.0%). Median follow-up and treatment duration were 26.5 months (range 0.7-39.1 months) and 10.1 months (range 0.7-39.6 months), respectively. Table 1 lists patients' baseline characteristics.

Median prior regimens was 6.0 (range 2-27). All patients previously received trastuzumab and T-DM1; 54.3% received other HER2-targeted treatments, 65.8% received pertuzumab, and 48.9% received hormone therapy.

Efficacy

Confirmed ORR by ICR was 62.0% (95% CI 54.5% to 69.0%), with 54.9% and 7.1% of patients achieving partial and complete responses, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.12.001).

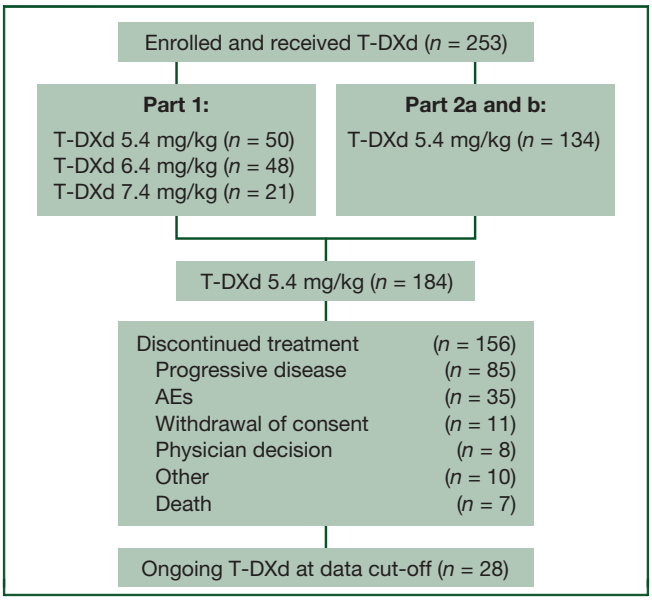

Figure 1. Patient disposition.
Part 1 of the study consisted of two sequential stages: pharmacokinetics and dose finding. Based on these results, a dose of T-DXd 5.4 mg/kg was recommended for part 2 of the study. Part 2 consisted of an evaluation of the efficacy and safety of T-DXd in patients treated at the recommended dose who had tumor progression during or after the administration of T-DM1 (part 2a) and in those who had discontinued T-DM1 for reasons other than progressive disease (part 2b).
AEs, adverse events; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

mOS was 29.1 months (95% CI 24.6-36.1 months), and 51.6% of patients had OS events (Figure 2A). Median PFS was 19.4 months (95% CI 14.1-25.0 months), and 41.3% of patients had PFS events (Figure 2B).

Most patients' tumors reduced in size following T-DXd treatment (Figure 2C). Median confirmed DoR was 18.2 months (95% CI 15.0 months-not evaluable; Figure 3), and median TTR was 1.6 months (95% CI 1.4-2.7 months).

Safety

As of 26 March 2021, investigator-reported drug-related TEAEs had occurred in 99.5% of patients; 53.8% of those TEAEs were grade ≥3 (Table 2). Most common TEAEs were generally gastrointestinal or hematologic (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.12.001). Cumulative drug-related TEAEs associated with drug discontinuation, dose reduction, or dose interruption were reported in 33 (17.9%), 43 (23.4%), and 60 patients (32.6%), respectively. Drug-related TEAEs associated with death were reported by investigators in three patients (1.6%); two deaths were due to pneumonitis, and one death was due to respiratory failure. No new cases of left ventricular dysfunction were reported.

Adjudicated drug-related ILD/pneumonitis was reported in 29 patients (15.8%) (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.12.001), including one new case (grade 3) since the 8 June 2020 DCO, which was ongoing and managed according to ILD/pneumonitis management guidelines; the patient was withdrawn from

Table 1. Patient demographics and clinical characteristics

Characteristic	T-DXd 5.4 mg/kg $n = 184$[a]
Median age (range), years	55.0 (28-96)
Age group, *n* (%)	
<65 years	140 (76.1)
≥65 years	44 (23.9)
Female, *n* (%)	184 (100.0)
Region, *n* (%)	
Asia	63 (34.2)
North America	53 (28.8)
Europe	68 (37.0)
ECOG PS, *n* (%)	
0	102 (55.4)
1	81 (44.0)
2	1 (0.5)
Hormone receptor, *n* (%)	
Positive	97 (52.7)
Negative	83 (45.1)
Unknown	4 (2.2)
HER2 expression,[b] *n* (%)	
IHC 3+	154 (83.7)
IHC 2+/IHC 1+, ISH+	28 (15.2)
Missing	2 (1.1)
History of visceral disease at baseline, *n* (%)	169 (91.8)
History of brain metastases,[c] *n* (%)	24 (13.0)
Presence of brain metastases at baseline,[c] *n* (%)	7 (3.8)
Sum of diameters of target lesions, median (range), cm^2	5.8 (1.2-24.5)
Median number of prior treatments for metastatic disease (range)	6 (2-27)
Prior treatment for metastatic disease, *n* (%)	
Trastuzumab	184 (100.0)
T-DM1	184 (100.0)
Pertuzumab	121 (65.8)
Other anti-HER2	100 (54.3)
Hormone therapy	90 (48.9)
Other systemic therapy	183 (99.5)
Best response to prior T-DM1 therapy, *n* (%)	
CR	5 (2.7)
PR	35 (19.0)
SD	39 (21.2)
PD	66 (35.9)
Not evaluable	39 (21.2)

Data cut-off 26 March 2021.

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]All 184 patients received one or more dose of T-DXd.

[b]HER2 status was centrally assessed on the most recent archival tissue according to the American Society of Clinical Oncology/College of American Pathologists guidelines.

[c]Includes treated and asymptomatic brain metastases.

treatment.[5] The outcome of the patient with the grade 3 ILD event was reported as recovered/resolved. A total of four patients received T-DXd retreatment after recovering from grade 1 ILD; three of these patients did not experience recurrence of ILD and one patient had recurrence of grade 1 ILD, which was reported as recovered. Five deaths (2.7%) were attributed to drug-related ILD/pneumonitis by an independent adjudication committee.

DISCUSSION

In this update of DESTINY-Breast01, mOS was 4.5 months longer (29.1 months; 26 March 2021) than the previous DCO (24.6 months; 8 June 2020), demonstrating durable antitumor activity and prolonged survival with T-DXd in pretreated patients with HER2-positive mBC. ORR, DoR, and PFS were consistent with previous DCOs.[1,5] The results of this study support the use of T-DXd in heavily pretreated patients with HER2-positive mBC.

The use of T-DXd in patients resistant or refractory to T-DM1 is further supported by results from the phase III DESTINY-Breast02 trial, in which T-DXd demonstrated superiority to conventional chemotherapy-based treatment with an mOS of 39.2 months compared to 26.5 months with treatment of physician's choice [hazard ratio 0.66 (95% CI 0.50-0.86); $P = 0.0021$] at a median follow-up of 21.5 months.[6] Both DESTINY-Breast01 and DESTINY-Breast02 trials further support the clinical benefit of T-DXd after use of a previous antibody—drug conjugate (T-DM1). The results of these trials add to the body of evidence for T-DXd in the treatment of HER2-positive mBC following its approval for use as second-line or later therapy based on DESTINY-Breast03.[3,4]

Other trials in patients with two or more prior lines of therapy have reported mOS between 21.6 and 24.7 months in patients with heavily pretreated HER2-positive mBC; however, cross-trial comparisons should be interpreted carefully given the study differences.[7-10] In the TH3RESA trial, mOS was 22.7 months with T-DM1 in patients with HER2-positive advanced breast cancer (BC) previously treated with trastuzumab and lapatinib (advanced setting), a taxane (any setting), and two or more HER2-directed regimens (advanced setting).[7] In the HER2CLIMB trial, mOS with tucatinib or placebo plus trastuzumab and capecitabine in patients with HER2-positive mBC previously treated with trastuzumab, pertuzumab, and T-DM1 (any setting) was 24.7 and 19.2 months, respectively.[8] Similarly, mOS was 21.6 months with chemotherapy plus margetuximab in the SOPHIA trial, compared with 19.8 months with chemotherapy plus trastuzumab in patients with progressive disease following two or more prior lines of HER2-targeted therapy and one to three lines of nonhormonal mBC therapy.[9] In the NALA trial, mean OS with capecitabine plus neratinib or lapatinib was 24.0 and 22.2 months, respectively, in patients who had previously received two or more HER2-directed regimens.[10]

A confirmed ORR was achieved in 62% of patients in DESTINY-Breast01. This is supported by results from DESTINY-Breast02, in which a confirmed ORR was reported in 70% of patients in the T-DXd group versus 29% of patients in the treatment of physician's choice group.[6] Trials of other therapies have reported rates ranging from 14% to 41%.[9-12] However, cross-trial comparisons must be interpreted cautiously given the differences in patient populations; TH3RESA, SOPHIA, and NALA enrolled patients with a median of 2-4 prior lines of HER2-targeted therapies, whereas DESTINY-Breast01 enrolled patients with a median of 6 prior lines of HER2-targeted therapies. HER2CLIMB enrolled a higher proportion of patients with active and nonactive brain metastases compared to the other trials.[9,10,12] In addition, the proportion of patients

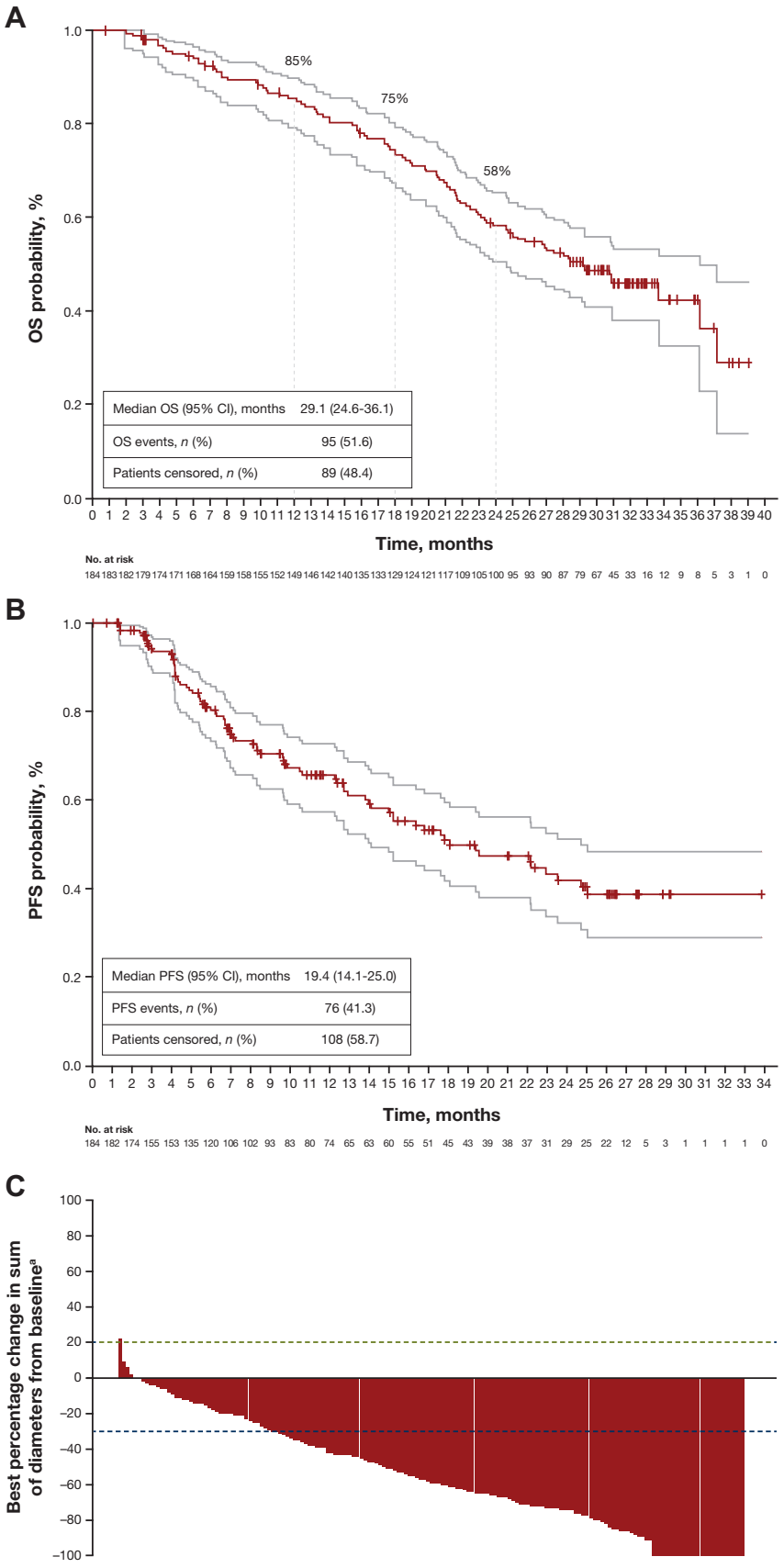

Figure 2. Antitumor activity of T-DXd in DESTINY-Breast01. Efficacy analyses showing (A) overall survival, (B) progression-free survival, and (C) best percentage change from baseline in target lesions in DESTINY-Breast01 ($n = 184$). DCO 26 March 2021. For OS and PFS, the red line represents the overall duration of response probability and the gray lines represent 95% CI upper and lower limits. The green dashed line at 20% denotes progressive disease and blue dashed line at –30% denotes partial response.

CI, confidence interval; DCO, data cut-off; OS, overall survival; PFS, progression-free survival.

[a]By independent central review. A total of 169 patients had both baseline and post-baseline target lesion assessments by independent central review and were included in this analysis.

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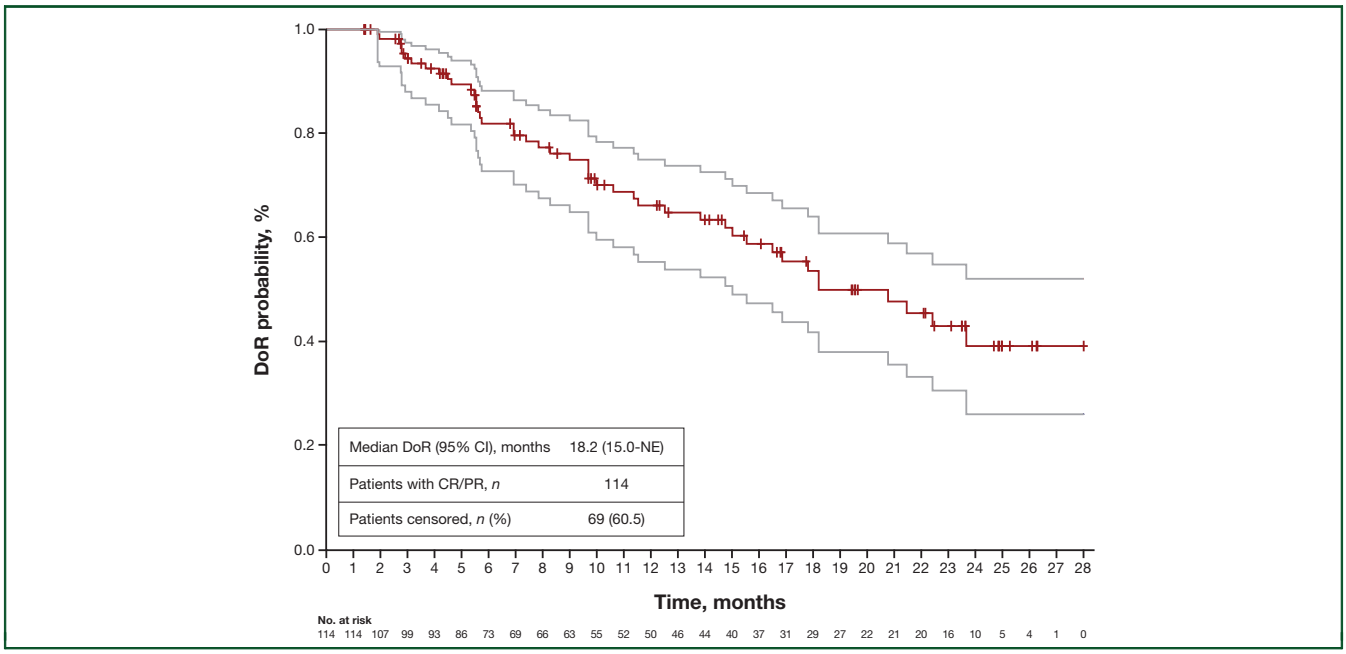

Figure 3. Duration of response.
DCO 26 March 2021. Red line represents overall DoR probability and gray lines represent 95% CI upper and lower limits.
CI, confidence interval; CR, complete response; DCO, data cut-off; DoR, duration of response; NE, not evaluable; PR, partial response.

with previous exposure to T-DM1 and pertuzumab therapies varied across these trials [100% and 100% (HER2CLIMB), 91% and 100% (SOPHIA), and 19%-36% and 7%-36% (NALA)].[9,10,12]

Safety results were consistent with the established safety profile of T-DXd in BC, with no new safety signals.[1,2,5,13] Two additional grade ≥3 drug-related TEAEs and four drug-related TEAEs leading to dose reductions were reported since 8 June 2020, with no new reports of drug discontinuation, dose interruption, or death due to drug-related TEAEs. As previously detailed, patients were proactively monitored for signs and symptoms of ILD and underwent diagnostic tests to rule out other potential etiologies. Cases of suspected or detected ILD/pneumonitis were managed with established ILD management guidelines, including supportive care and immediate steroid treatment, with dose modification of T-DXd as recommended.[2] Most cases were grade 1/2,[2] and there was one additional case of ILD/pneumonitis adjudicated as drug-related (grade 3) reported since 8 June 2020 (this patient was withdrawn from T-DXd). Most TEAEs, including ILD/pneumonitis cases, were observed within the first 12 months of T-DXd treatment, which was consistent with previous reports in this population.[2,5,14]

In conclusion, this updated analysis of DESTINY-Breast01 provides evidence of sustained antitumor activity with T-DXd in heavily pretreated patients with HER2-positive mBC. Further confirmation of the results observed in DESTINY-Breast01 is supported by DESTINY-Breast02.[6]

Table 2. Overall safety of T-DXd

Type of adverse event,[a] *n* (%)	T-DXd 5.4 mg/kg *n* = 184
Any-grade TEAEs	183 (99.5)
Drug-related	183 (99.5)
Grade ≥3 TEAEs	116 (63.0)
Drug-related	99 (53.8)
TEAEs associated with drug discontinuation	35 (19.0)
Drug-related	33 (17.9)
TEAEs associated with dose reduction	46 (25.0)
Drug-related	43 (23.4)
TEAEs associated with dose interruption	77 (41.8)
Drug-related	60 (32.6)
TEAEs associated with death[b]	10 (5.4)
Drug-related	3 (1.6)

Data cut-off 26 March 2021.
T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
[a]Relationship to study drug was determined by the treating investigator.
[b]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; one patient had two TEAEs associated with death: acute kidney injury and acute hepatic failure.

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DISCLOSURE

CS reports consulting or advisory roles for AstraZeneca, AX'Consulting, Byondis B.V., Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann-La Roche Ltd, ISSECAM, Medical Statistics Consulting, MediTech, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Pierre Fabre, PintPharma, Puma, Roche Farma, Seagen, and Zymeworks and a leadership role for SOLTI. SM reports consulting or advisory roles for AstraZeneca, Daiichi Sankyo, Genentech, GlaxoSmithKline, Macrogenics, Novartis, and Seagen; research funding from AstraZeneca (inst) and Daiichi Sankyo (inst); and honoraria from AstraZeneca, Daiichi Sankyo, Genentech, Macrogenics, and Seagen. IK reports consulting or advisory roles for AstraZeneca, Bristol Meyers Squibb, Daiichi Sankyo, Genentech, Macrogenics, Merck, Novartis, Roche, Seagen, and Taiho Oncology; research funding from Genentech (inst), Macrogenics (inst), Pfizer (inst), and Roche (inst); honoraria from AstraZeneca; and a leadership role with PureTech. YHP reports consulting or advisory roles for AstraZeneca, Daiichi Sankyo, Eisai, Roche, MSD, Novartis, Pfizer, and Lilly; research funding from AstraZeneca, Gencurix, Novartis, Pfizer, and Roche; and honoraria from Pfizer, Roche, MSD, and Novartis. SBK reports consulting or advisory roles for AstraZeneca, Beigene, Dae Hwa Pharmaceutical Co, Ltd, Daiichi Sankyo, IUS Abxis, Lilly, and Novartis and research funding from DongKook Pharm (inst), Novartis (inst), and Sanofi-Aventis (inst). HI reports consulting or advisory roles for AstraZeneca, Chugai, Daiichi Sankyo, Lilly, MSD, Novartis, Pfizer, and Sanofi and honoraria from AstraZeneca, Chugai, Daiichi Sankyo, Lilly, MSD, and Pfizer. JT reports consulting or advisory roles for AstraZeneca and Daiichi Sankyo; research funding from Chugai (inst), Daiichi Sankyo (inst), Eisai (inst), Lilly (inst), Nihon Kayaku (inst), and Taiho (inst); honoraria from Chugai, Daiichi Sankyo, Eisai, Lilly, Kyowa Kirin, and Taiho; has received support for attending meetings and/or travel from Chugai, Daiichi Sankyo, and Eisai; a leadership role with West Japan Oncology Group; and receipt of equipment, materials, drugs, medical writing, or other services from Daiichi Sankyo. JS reports research funding from AstraZeneca (inst), Boehringer Ingelheim (inst), Lilly (inst), GSK (inst), MSD (inst), Novartis (inst), Pfizer (inst), Roche (inst), and Sanofi (inst) and stock for Daiichi Sankyo. EM, YL, JC, and JS report employment and stock and other ownership interest with Daiichi Sankyo. TY reports research funding from Chugai (inst), Kyowa Kirin (inst), Nippon Kayaku (inst), and Taiho (inst) and honoraria from AstraZeneca, Chugai, Daiichi Sankyo, MSD, Eisai, Lilly, Nippon Kayaku, Kyowa Kirin, Novartis, Pfizer Japan, and Taiho. KT has declared no conflicts of interest.

DATA SHARING

Anonymized individual participant data (IPD) on completed studies and applicable supporting clinical trial documents may be available upon request at https://vivli.org. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc, will continue to protect the privacy of our company and our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo.

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