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Trastuzumab deruxtecan versus trastuzumab emtansine in Asian patients with HER2-positive metastatic breast cancer

Hiroji Iwata[1] | Binghe Xu[2] | Sung-Bae Kim[3] | Wei-Pang Chung[4] | Yeon Hee Park[5] | Min Hwan Kim[6] | Ling-Ming Tseng[7] | Chi-Feng Chung[8] | Chiun-Sheng Huang[9] | Jee Hyun Kim[10] | Joanne Wing Yan Chiu[11] | Toshinari Yamashita[12] | Wei Li[13] | Anton Egorov[14] | Soichiro Nishijima[15] | Shunsuke Nakatani[15] | Yuji Nishiyama[15] | Masahiro Sugihara[15] | Javier Cortés[16,17,18] | Seock-Ah Im[19]

Correspondence
Hiroji Iwata, Department of Breast Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.
Email: hiwata0422@gmail.com

Funding information
Daiichi Sankyo

Abstract

The global phase 3 DESTINY-Breast03 study (ClinicalTrials.gov; NCT03529110) showed statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) with trastuzumab deruxtecan (T-DXd) over 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. Here, we report a subgroup analysis of Asian patients enrolled in DESTINY-Breast03. In total, 309 patients (149 in the T-DXd arm and 160 in the T-DM1 arm) from Asian countries and regions were randomized. At data cutoff (July 25, 2022), the median duration of follow-up in the Asian subpopulation was 29.0 months with T-DXd and 26.0 months with T-DM1. The PFS (determined by blinded independent central review) hazard ratio was 0.30 (95% confidence interval 0.22–0.41) favoring T-DXd over T-DM1 (median PFS 25.1 vs. 5.4 months). Median OS was not reached in the T-DXd arm and was 37.7 months in the T-DM1 arm. The median treatment duration was 15.4 months with T-DXd and 5.5 months with T-DM1. The incidence of grade ≥3 drug-related treatment-emergent adverse events was similar between both treatment arms (49.0% vs. 46.5%) and was consistent with the overall DESTINY-Breast03 population. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 12.9% of patients treated with T-DXd and 2.5% treated with T-DM1, with a higher incidence in Japanese patients; none of these were grade ≥4 events.

Abbreviations: ADC, antibody–drug conjugate; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CrCl, creatinine clearance; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILD, interstitial lung disease; mBC, metastatic breast cancer; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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For affiliations refer to page 3086.

These efficacy and safety data reinforce the favorable benefit–risk profile of T-DXd in HER2-positive mBC, including in the Asian subgroup.

KEYWORDS
breast cancer, East Asia, ErbB-2 receptor, trastuzumab deruxtecan, trastuzumab emtansine

1 | INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer worldwide, accounting for 11.7% of all cancer diagnoses.[1] Historically, BC incidence has been low in Asian countries; however, the incidence is now increasing, with approximately 25.0% of all BC cases occurring in East Asia and 11.3% in South Central Asia.[2] BC is also the fifth most common cause of cancer-related deaths (~685,000 fatalities or 6.9% of all cancer deaths),[1] with East, South Central, and South East Asia accounting for ~50.0% of all global BC deaths.[2] Approximately 17% of BC malignancies involve an overexpression of human epidermal growth factor receptor 2 (HER2),[3] which is characterized by an aggressive form, and is historically associated with a poor prognosis.[4]

Standard first-line treatment for patients with HER2-positive metastatic BC (mBC) includes dual HER2 antibody therapy with trastuzumab and pertuzumab in combination with a taxane.[5–7] This combination is the recommended first-line treatment of HER2-positive recurrent or mBC in both the Pan-Asian adapted European Society of Medical Oncology (ESMO) Clinical Practice Guidelines and the Japanese Breast Cancer Society Clinical Practice Guidelines.[8,9] Trastuzumab emtansine (T-DM1) was approved in 2013 as second-line therapy for patients who progressed after first-line therapy with trastuzumab.[10] T-DM1 is a trastuzumab-based antibody–drug conjugate (ADC) that includes the antimicrotubular cytotoxic agent emtansine, and it demonstrated consistent survival benefits in the second-line setting in the phase 3 EMILIA study compared with lapatinib and capecitabine (progression-free survival [PFS] 9.6 vs. 6.4 months, hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.55–0.77; $p < 0.001$).[11] In addition to T-DM1, the combination of pyrotinib and capecitabine has also been approved in China as a second-line standard-of-care treatment for HER2-postive mBC,[12] based on findings from the phase 3 PHOEBE trial, which compared this combination with lapatinib plus capecitabine (PFS 12.5 vs. 6.8 months, HR 0.39; 95% CI 0.27–0.56; $p < 0.0001$).[13]

Trastuzumab deruxtecan (T-DXd) is a novel ADC in which the humanized anti-HER2 monoclonal antibody trastuzumab is covalently linked to a topoisomerase I inhibitor payload through a cleavable tetrapeptide-based linker.[14] In the phase 2, single-arm DESTINY-Breast01 trial, T-DXd demonstrated durable antitumor activity in heavily pretreated patients with HER2-positive mBC.[15] The DESTINY-Breast02 trial was then conducted as a confirmatory trial for DESTINY-Breast01, showing that T-DXd significantly prolonged PFS versus the physician's choice of treatment in patients with HER2-positive mBC refractory to T-DM1 (PFS 17.8 vs. 6.9 months, HR 0.36; 95% CI 0.28–0.45; $p < 0.0001$).[16] Based on the results of DESTINY-Breast01, T-DXd was approved in the United States,[17] Japan,[18] Republic of Korea,[19] and the European Union[20] for the treatment of adults with unresectable or metastatic HER2-positive BC who have received ≥2 prior anti-HER2-based regimens in the metastatic setting.

The DESTINY-Breast03 study was designed as a head-to-head comparison of the efficacy and safety of T-DXd with that of T-DM1 as a second-line treatment for patients with HER2-positive mBC.[21] At the time of the first prespecified interim analysis (May 21, 2021), the median duration of follow-up was 16.2 months with T-DXd and 15.3 months with T-DM1. T-DXd demonstrated a statistically significant improvement in PFS compared with T-DM1 (HR for disease progression or death 0.28; 95% CI 0.22–0.37; $p < 0.001$).[21] A trend toward improvement in overall survival (OS) was observed (HR 0.55; 95% CI 0.36–0.86; $p = 0.007$), although statistical significance was not reached due to data immaturity; the overall response rate (ORR) was also higher with T-DXd versus T-DM1 (79.7% vs. 34.2%).[21] In the second interim analysis of DESTINY-Breast03, T-DXd showed continuous benefit in prolongation of PFS (28.8 vs. 6.8 months; HR 0.33; 95% CI 0.26–0.43; $p < 0.0001$), statistically significantly longer OS (not reached in both arms; HR: 0.64; 95% CI 0.47–0.87; $p = 0.0037$), and a higher ORR (79.0% vs. 35.0%) than T-DM1.[22] Although the incidence of grade ≥3 treatment-emergent adverse events (TEAEs) was similar in patients receiving T-DXd and T-DM1, T-DXd was associated with a higher incidence of low-grade interstitial lung disease (ILD) or pneumonitis compared with T-DM1.[21,22] At the time of the current analysis, T-DXd is globally recognized as the standard-of-care for second-line treatment of mBC in place of T-DM1. However, the toxicity profiles of targeted BC treatments can vary across different racial populations.[23,24] Specifically, detailed data on the efficacy and safety of T-DXd in Asian populations are currently limited.

Here, we report the results of a subgroup analysis of Asian patients enrolled in the DESTINY-Breast03 study.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The study design and methods of the open-label, multicenter, randomized, active-controlled, phase 3 DESTINY-Breast03 study (ClinicalTrials.gov identifier: NCT03529110) have been reported previously.[21,22] Briefly, this study enrolled adults (age ≥18 years) with centrally confirmed/pathologically documented HER2-positive unresectable or mBC that was previously treated with trastuzumab

and a taxane in the advanced or metastatic setting or that had progressed within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane. Patients were randomized (1:1) to receive T-DXd 5.4 mg/kg or T-DM1 3.6 mg/kg intravenously every 3 weeks. T-DXd and T-DM1 were administered in 21-day treatment cycles until progressive disease, unacceptable toxicity, or patient/physician decision to withdraw. Key exclusion criteria were previous treatment with an anti-HER2 ADC, including T-DM1, in the metastatic setting; uncontrolled or clinically significant cardiovascular disease; ongoing ILD or pneumonitis, history of ILD or pneumonitis that required steroids, or suspected ILD or pneumonitis that could not be ruled out by imaging at screening; and spinal cord compression or brain metastases that were symptomatic or required treatment with steroids or anticonvulsants.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the International Council for Harmonization consolidated Guideline E6 for Good Clinical Practice and other applicable regulations. The study protocol, amendments, and informed consent forms were approved by the Independent Ethics Committees or Institutional Review Boards at each study site. Written informed consent was collected from all participants before initiating the study.

2.2 | Outcomes

The primary endpoint was PFS, determined by a blinded independent central review (BICR). The key secondary endpoint was OS; other secondary endpoints included: ORR, defined as the proportion of patients who achieved a confirmed best overall response of complete response (CR) or partial response (PR), based on BICR and investigator assessment; duration of response (DOR) based on BICR and investigator assessment; PFS based on investigator assessment; and safety. Clinical benefit rate (CBR), based on BICR, and PFS on the next line of therapy (PFS2) were exploratory efficacy endpoints.

Safety assessments included TEAEs and serious adverse events (AEs), which were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. TEAEs were defined as AEs that occurred or worsened in severity after initiating the study drug until 47 days after the last study dose, and also as any serious AEs with an onset or worsening ≥48 days after the last study dose, if considered related to the study treatment. All cases of potential ILD/pneumonitis were adjudicated by the data cutoff.

2.3 | Statistical analysis

This analysis included data from all patients enrolled from Asian countries and regions in the DESTINY-Breast03 study (data cutoff: July 25, 2022). For the ILD analysis, data for patients enrolled from Japan were also provided separately. The full analysis set included all randomized patients, and the safety analysis set included all randomized patients who received at least one dose of study treatment. Baseline characteristics, response rates, and safety were assessed using descriptive statistics. Continuous data were summarized for each treatment group using medians and ranges (minimum and maximum). Categorical data were summarized using the number and percentage of patients. The survival distribution of PFS, OS, and PFS2 was estimated by the Kaplan–Meier method, and the two-sided CIs of median survival times were calculated using the Brookmeyer and Crowley method. Estimates of HRs of PFS, OS, and PFS2 and their two-sided 95% CIs were determined using the unstratified Cox proportional hazards regression model; no formal hypothesis testing was performed. Statistical analyses were performed using SAS software, version 9.4.

3 | RESULTS

3.1 | Patients

Between July 20, 2018 and June 23, 2020, 524 patients were randomized in the DESTINY-Breast03 study; of these, 309 patients (59.0%) were from Asian countries and regions (149 in the T-DXd arm and 160 in the T-DM1 arm; Figure S1). The demographics and clinical characteristics of patients were well balanced between treatment arms at baseline (Table 1). Patients were aged between 20.2 and 80.6 (median 53.9) years and 99.7% were female. Among the 309 patients, 84 were from the Republic of Korea, 68 from Japan, 65 from China, 71 from Taiwan, and 21 from Hong Kong. Patients had received a median of 2 prior lines of treatment in the metastatic setting, with 41.7%, 20.1%, and 38.2% having received 1, 2, and ≥3 prior lines, respectively; 58.6% of patients had received pertuzumab therapy. Overall, 22.3% of patients had a history of brain metastases, and 17.5% had brain metastases at baseline.

At data cutoff (July 25, 2022), 35 patients (23.8%) were continuing treatment with T-DXd and 10 patients (6.3%) with T-DM1 (Figure S1). The median (range) duration of study follow-up in the Asian population was 29.0 (0.1–46.9) months with T-DXd and 26.0 (0.0–45.0) months with T-DM1.

3.2 | Efficacy

Median PFS (assessed by BICR) was 25.1 months (95% CI 16.8–not estimable [NE]) with T-DXd and 5.4 months (95% CI 4.1–6.9) with T-DM1 (HR 0.30 [95% CI 0.22–0.41] in favor of T-DXd; Figure 1). The 12- and 24-month PFS rates were 71.2% (95% CI 62.9–78.0) and 50.4% (95% CI 41.3–58.9), respectively, in the T-DXd arm and 25.0% (95% CI 17.8–32.9) and 18.0% (95% CI 11.6–25.6), respectively, in the T-DM1 arm. Investigator-assessed median PFS was 26.3 months (95% CI 19.5–NE) with T-DXd and 7.0 months (95% CI 5.5–8.1) with T-DM1 (HR 0.30; 95% CI 0.22–0.41; Figure S2). A consistent PFS benefit (assessed by BICR) in favor of T-DXd was also observed across all the subgroups analyzed, including those based on hormone receptor status, previous pertuzumab treatment, baseline visceral disease, lines of previous therapy, and baseline brain metastases (Figure 2).

TABLE 1 Baseline characteristics of Asian patients included in the DESTINY-Breast03 study.

	T-DXd *n* = 149	T-DM1 *n* = 160
Age, median (range), years	54.0 (30.0–77.5)	53.4 (20.2–80.6)
Sex, *n* (%)		
Male	1 (0.7)	0
Female	148 (99.3)	160 (100.0)
Region, *n* (%)		
Republic of Korea	37 (24.8)	47 (29.4)
Japan	37 (24.8)	31 (19.4)
China	35 (23.5)	30 (18.8)
Taiwan	31 (20.8)	40 (25.0)
Hong Kong	9 (6.0)	12 (7.5)
HER2 status by immunohistochemistry, *n* (%)		
3+	138 (92.6)	142 (88.8)
2+	10 (6.7)	17 (10.6)
1+	0	0
Not evaluable	1 (0.7)	1 (0.6)
ECOG PS, *n* (%)		
0	81 (54.4)	107 (66.9)
1	68 (45.6)	53 (33.1)
Hormone receptor, *n* (%)		
Positive	68 (45.6)	74 (46.3)
Negative	81 (54.4)	86 (53.8)
History of brain metastases, *n* (%)	33 (22.1)	36 (22.5)
Brain metastases at baseline, *n* (%)	24 (16.1)	30 (18.8)
History of visceral disease, *n* (%)	114 (76.5)	116 (72.5)
Visceral disease at baseline, *n* (%)	116 (77.9)	116 (72.5)
Renal function at baseline, *n* (%)		
Within the normal range (CrCl ≥90 mL/min)	75 (50.3)	80 (50.0)
Mild impairment (CrCl ≥60, <90 mL/min)	61 (40.9)	64 (40.0)
Moderate impairment (CrCl ≥30, <60 mL/min)	13 (8.7)	16 (10.0)
Severe impairment (CrCl ≥15, <30 mL/min)	0	0
End-stage renal disease (CrCl <15 mL/min)	0	0
Prior lines of therapy in the metastatic setting, median (range)[a]	2.0 (1.0–10.0)	2.0 (1.0–15.0)
Number of lines, *n* (%)		
1	64 (43.0)	65 (40.6)
2	30 (20.1)	32 (20.0)
3	23 (15.4)	30 (18.8)
4	8 (5.4)	14 (8.8)
≥5	24 (16.1)	19 (11.9)
Any prior cancer therapy, *n* (%)		
Trastuzumab	149 (100.0)	160 (100.0)
Trastuzumab emtansine	0	0
Pertuzumab	89 (59.7)	92 (57.5)
Other anti-HER2	34 (22.8)	33 (20.6)
Anti-HER2 tyrosine kinase inhibitor	34 (22.8)	33 (20.6)
Other anti-HER2 antibody or antibody–drug conjugate	0	1 (0.6)
Hormone therapy	57 (38.3)	59 (36.9)
Other systemic therapy	109 (73.2)	107 (66.9)

Abbreviations: CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Rapid progressors on neoadjuvant therapy were included; line of therapy does not include endocrine therapy.

Median OS was not reached (95% CI NE–NE) in the T-DXd arm and was 37.7 months (95% CI 30.3–NE) in the T-DM1 arm (HR 0.62; 95% CI 0.42–0.91; Figure 3). The 12- and 24-month OS rates were 93.8% (95% CI 88.4–96.7) and 76.6% (95% CI 68.7–82.8), respectively, in the T-DXd arm and 84.0% (95% CI 77.1–89.0) and 65.9% (95% CI 57.6–73.0), respectively, in the T-DM1 arm.

Patients in the T-DXd arm had a higher ORR compared with those in the T-DM1 arm (75.8% [95% CI 68.2–82.5] vs. 31.3% [95% CI 24.2–39.0]; Table 2). In the T-DXd arm, 31 (20.8%) and 82 (55.0%) patients had CR and PR, respectively, compared with 12 (7.5%) and 38 (23.8%) patients, respectively, in the T-DM1 arm. Stable disease (SD) was achieved by 30 patients (20.1%) in the T-DXd arm and 67 patients (41.9%) in the T-DM1 arm, resulting in a CBR of 86.6% (95% CI 80.0–91.6) and 40.0% (95% CI 32.3–48.0), respectively. Median DOR was not reached (95% CI 16.9–NE) with T-DXd and was 13.8 months (95% CI 8.2–34.7) with T-DM1.

3.3 | Safety

The median treatment duration was 15.4 months (range 0.7–44.0) with T-DXd and 5.5 months (0.7–39.3) with T-DM1. Safety was

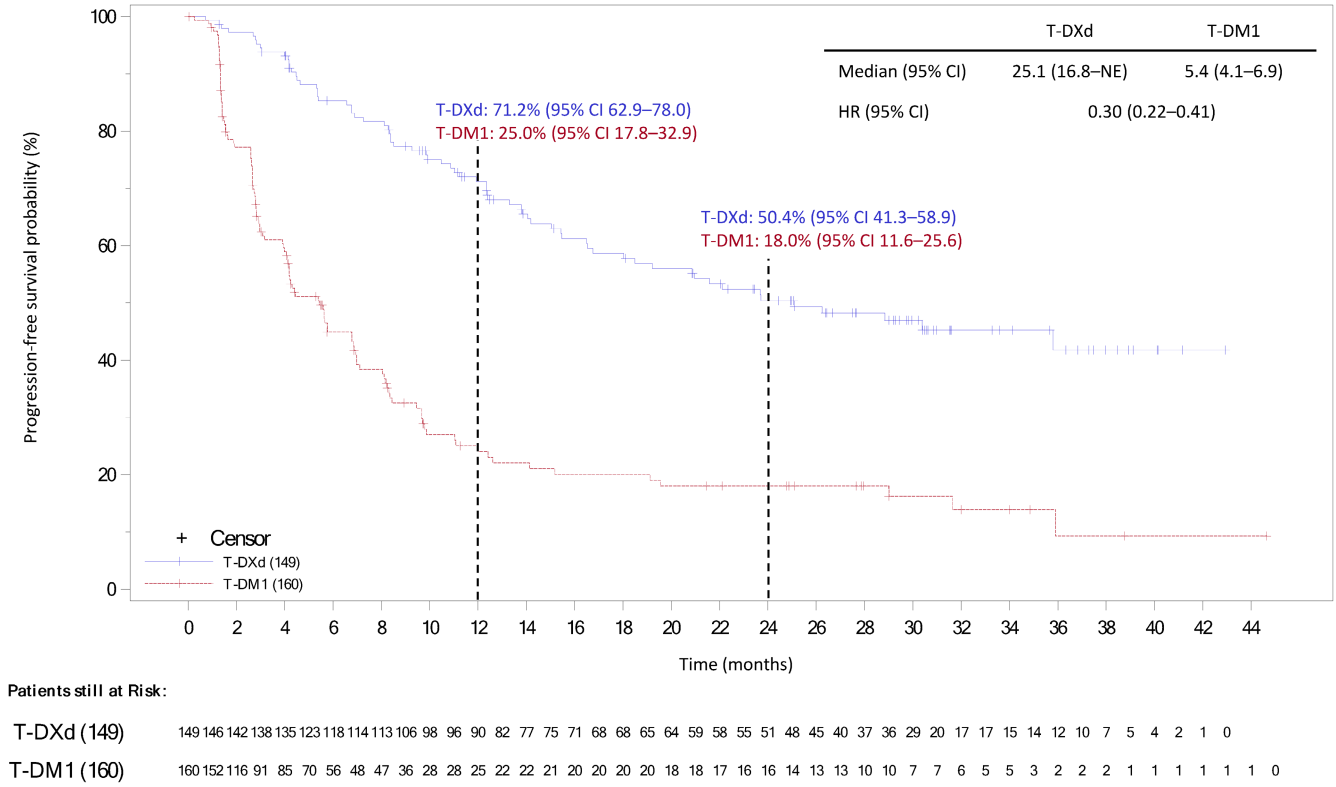

FIGURE 1 Kaplan–Meier analysis of progression-free survival, assessed by blinded independent central review, among Asian patients enrolled in the DESTINY-Breast03 study. CI, confidence interval; HR, hazard ratio; NE, not estimable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Subgroup	No. of patients	No. of events/No. of patients		Median PFS, months (95% CI)		Hazard ratio for disease progression or death (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		69/149	114/160	25.1 (16.8–NE)	5.4 (4.1–6.9)	0.30 (0.22–0.41)
Hormone receptor status						
Positive	149	35/72	56/77	23.7 (16.5–NE)	5.6 (2.8–8.2)	0.34 (0.22–0.52)
Negative	159	33/76	58/83	30.4 (15.0–NE)	5.4 (4.0–6.8)	0.27 (0.17–0.42)
Previous pertuzumab therapy						
Yes	181	42/89	70/92	23.7 (14.2–NE)	4.4 (3.9–6.9)	0.29 (0.20–0.44)
No	128	27/60	44/68	25.1 (15.4–NE)	5.6 (2.9–8.2)	0.32 (0.20–0.53)
Visceral disease at baseline						
Yes	232	59/116	89/116	21.0 (15.0–30.4)	4.2 (2.9–5.7)	0.27 (0.19–0.38)
No	77	10/33	25/44	NE (22.1–NE)	8.3 (4.4–29.0)	0.31 (0.15–0.65)
Lines of previous therapy[a]						
<3	216	47/104	76/112	26.3 (18.5–NE)	6.8 (4.1–8.2)	0.33 (0.23–0.48)
≥3	93	22/45	38/48	18.0 (12.4–NE)	4.2 (2.8–5.7)	0.25 (0.14–0.44)
Brain metastases at baseline						
Yes	54	18/24	22/30	13.3 (9.3–18.5)	2.8 (2.6–6.8)	0.17 (0.07–0.41)
No	255	51/125	92/130	NE (21.6–NE)	5.6 (4.2–8.1)	0.29 (0.21–0.41)

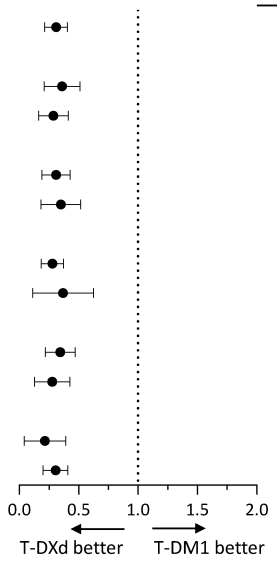

FIGURE 2 Progression-free survival in prespecified subgroups. [a]Lines of previous therapy did not include endocrine therapy. CI, confidence interval; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

assessed in 147 patients who received T-DXd and in 159 who received T-DM1 (Table 3). In the respective treatment arms, drug-related grade ≥3 TEAEs occurred in 49.0% and 46.5% of patients, and drug-related serious TEAEs occurred in 10.9% and 7.5% of patients. There were no deaths due to drug-related TEAEs in either treatment arm. The most common drug-related TEAEs of any grade with T-DXd

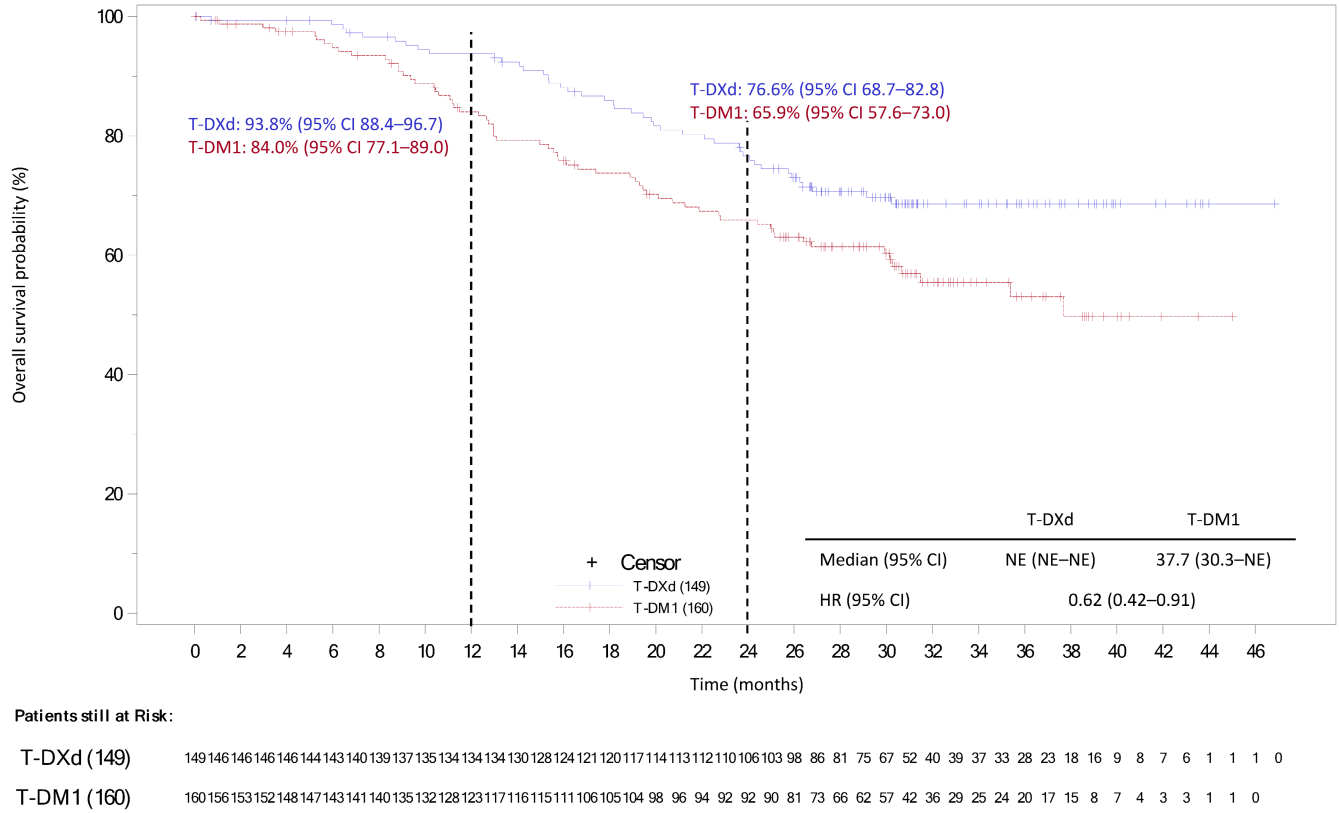

FIGURE 3 Kaplan–Meier analysis of overall survival among Asian patients enrolled in the DESTINY-Breast03 study. CI, confidence interval; HR, hazard ratio; NE, not estimable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

TABLE 2 Best overall response in the full analysis set.

	T-DXd *n* = 149	T-DM1 *n* = 160
Best response by BICR, *n* (%)		
CR	31 (20.8)	12 (7.5)
PR	82 (55.0)	38 (23.8)
SD	30 (20.1)	67 (41.9)
PD	2 (1.3)	36 (22.5)
Not evaluable	4 (2.7)	7 (4.4)
Confirmed ORR (CR + PR), *n* (%)	113 (75.8)	50 (31.3)
95% CI	68.2–82.5	24.2–39.0
CBR (CR + PR + SD), *n* (%)	129 (86.6)	64 (40.0)
95% CI	80.0–91.6	32.3–48.0

Abbreviations: BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

were nausea (66.0%), neutropenia (49.0%), fatigue (45.6%), and vomiting (42.9%; Table 3). The incidence of each of these events was lower with T-DM1 (21.4%, 15.7%, 23.9%, and 4.4%, respectively). The most common drug-related grade ≥3 TEAEs with T-DXd were neutropenia (25.9%), thrombocytopenia (12.9%), leukopenia (10.2%), anemia (9.5%), and fatigue (8.8%), whereas the most common drug-related grade ≥3 TEAEs with T-DM1 were thrombocytopenia (34.6%), aspartate aminotransferase increased (6.9%), alanine aminotransferase increased (5.7%), and neutropenia (5.7%).

Adjudicated drug-related ILD or pneumonitis occurred in 19 patients (12.9%) treated with T-DXd and four patients (2.5%) treated with T-DM1. In the T-DXd arm, six patients (4.1%) had grade 1 events, 12 (8.2%) had grade 2, and one (0.7%) had a grade 3 event; there were no grade 4 or 5 events. In the T-DM1 arm, there were two grade 1 and grade 2 events (each 1.3%), and no grade ≥3 events. The median time to first onset of adjudicated drug-related ILD or pneumonitis events was 246.0 days (range 41–674) in the T-DXd arm and 355.0 days (207–499) in the T-DM1 arm. Most patients in both treatment arms recovered by data cutoff (Table S1). In the Japanese population, the incidence of adjudicated drug-related ILD or pneumonitis was 22.2% in the T-DXd arm and 9.7% in the T-DM1 arm (Table 4). There were only low-grade events in both treatment arms (grade 1: 11.1% and 6.5% of patients and grade 2: 11.1% and 3.2% of patients, respectively), and no grade ≥3 events.

3.4 | Post anticancer therapy

During the study, 112 patients (76.2%) in the T-DXd arm and 149 (93.7%) in the T-DM1 arm discontinued treatment. After treatment completion, 81 patients (54.4%) in the T-DXd arm and 116 (72.5%) in the T-DM1 arm received a new systemic anticancer

TABLE 3 Drug-related treatment-emergent adverse events in the safety analysis set.

Drug-related TEAEs, *n* (%)	T-DXd *n* = 147	T-DM1 *n* = 159		
Any grade	144 (98.0)	141 (88.7)		
Grade ≥3	72 (49.0)	74 (46.5)		
Serious TEAEs	16 (10.9)	12 (7.5)		
TEAEs leading to treatment discontinuation	29 (19.7)	11 (6.9)		
TEAEs leading to dose reduction	42 (28.6)	28 (17.6)		
Fatal TEAEs	0	0		
Most common drug-related TEAEs				
System organ class				
Preferred term, *n* (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Neutropenia[a]	72 (49.0)	38 (25.9)	25 (15.7)	9 (5.7)
Anemia[b]	50 (34.0)	14 (9.5)	24 (15.1)	6 (3.8)
Leukopenia[c]	58 (39.5)	15 (10.2)	14 (8.8)	1 (0.6)
Thrombocytopenia[d]	57 (38.8)	19 (12.9)	104 (65.4)	55 (34.6)
Gastrointestinal disorders				
Nausea	97 (66.0)	7 (4.8)	34 (21.4)	1 (0.6)
Vomiting	63 (42.9)	2 (1.4)	7 (4.4)	1 (0.6)
Constipation	37 (25.2)	0	14 (8.8)	0
Diarrhea	27 (18.4)	0	4 (2.5)	0
General disorders and administration site conditions				
Fatigue[e]	67 (45.6)	13 (8.8)	38 (23.9)	1 (0.6)
Metabolism and nutrition disorders				
Decrease appetite	44 (29.9)	2 (1.4)	23 (14.5)	0
Investigations				
AST increased	36 (24.5)	0	60 (37.7)	11 (6.9)
ALT increased	28 (19.0)	2 (1.4)	49 (30.8)	9 (5.7)
Skin and subcutaneous tissue disorders				
Alopecia	57 (38.8)	0	4 (2.5)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan, TEAE, treatment-emergent adverse event.

[a]Includes neutrophil count decreased and neutropenia.

[b]Includes hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.

[c]Includes white blood cell count decreased and leukopenia.

[d]Includes platelet count decreased and thrombocytopenia.

[e]Includes fatigue, asthenia, malaise, and lethargy.

TABLE 4 Adjudicated drug-related interstitial lung disease or pneumonitis[a] in the safety analysis set.

	Overall Asian population		Japanese population	
	T-DXd *n* = 147	T-DM1 *n* = 159	T-DXd *n* = 36	T-DM1 *n* = 31
Any grade	19 (12.9)	4 (2.5)	8 (22.2)	3 (9.7)
Grade 1	6 (4.1)	2 (1.3)	4 (11.1)	2 (6.5)
Grade 2	12 (8.2)	2 (1.3)	4 (11.1)	1 (3.2)
Grade 3	1 (0.7)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]All cases of potential interstitial lung disease or pneumonitis were adjudicated by the data cutoff.

treatment (Table S2). Post-study systemic anticancer therapies in the T-DXd and T-DM1 arms included trastuzumab (16.8% vs. 32.5% of patients), T-DXd (1.3% vs. 13.1%), T-DM1 (26.8% vs. 2.5%), other anti-HER2 therapies (20.1% vs. 36.3%), and other systemic therapies (36.2% vs. 61.9%). At data cutoff, 34 patients (22.8%) who received T-DXd and 55 (34.3%) who received T-DM1 experienced PD on subsequent systemic anticancer therapies (Table S2). Median PFS2 (from the time of randomization to the first documented progression on next-line therapy) by investigator assessment was 41.2 months (95% CI 41.2–NE) with T-DXd and 19.6 months (95% CI 15.0–28.6) with T-DM1 (HR 0.46; 95% CI 0.32–0.65).

4 | DISCUSSION

Asian patients comprised approximately 60.0% of the overall DESTINY-Breast03 population. This subgroup analysis showed that, in Asian DESTINY-Breast03 patients with HER2-positive mBC previously treated with trastuzumab (with or without pertuzumab) and a taxane, T-DXd had a substantially larger clinical benefit (longer PFS and OS) compared with T-DM1. The median treatment duration was longer with T-DXd than with T-DM1, yet the overall incidence of grade ≥3 or serious TEAEs was similar between the two arms.

In the current analysis, the median duration of PFS (assessed by BICR) was substantially longer with T-DXd than with T-DM1 (25.1 vs. 5.4 months). This PFS benefit was observed across all subgroups analyzed (i.e., hormone receptor status, previous pertuzumab treatment, baseline visceral disease, prior treatment lines, and baseline brain metastases). T-DXd showed a clinically meaningful improvement in OS versus T-DM1, reducing the risk of death by 38.0%. Additionally, T-DXd was associated with a higher confirmed ORR than T-DM1, with 31 patients (20.8%) achieving CR with T-DXd versus 12 (7.5%) with T-DM1.

The results of this subgroup analysis are in line with those seen in the overall DESTINY-Breast03 study population,[21,22] in which T-DXd was associated with a significant and sustained improvement in PFS versus T-DM1 (DESTINY-Breast03, HR 0.33 [95% CI 0.26–0.43][22]; current study, HR 0.30 [95% CI 0.22–0.41]). The reduction in the risk of PD or death by T-DXd versus T-DM1 was slightly higher in this subgroup analysis (70.0%) compared with the overall DESTINY-Breast03 population (67.0%).[22] This subgroup analysis also reported similar OS HR, confirmed ORR, and CBR to the overall population,[22] across various subgroups of patients, suggesting that T-DXd is an

appropriate treatment regimen in Asian patients with HER2-positive mBC.

In the current subgroup analysis, the incidence of drug-related grade ≥3 and serious TEAEs was similar between both T-DXd and T-DM1 treatment arms (49.0% vs. 46.5% and 10.9% vs. 7.5%, respectively). These results were consistent with the overall DESTINY-Breast03 population (drug-related grade ≥3 TEAEs: 47% vs. 42% and drug-related serious TEAEs: 13% vs. 8%).[22] Among the common drug-related TEAEs, the incidences of hematologic toxicities, gastrointestinal disorders, and fatigue were similar between the Asian and overall DESTINY-Breast03 populations; the most common drug-related grade ≥3 TEAEs were neutropenia, thrombocytopenia, leukopenia, and nausea.[21] The safety profile of T-DXd was similar to that reported in DESTINY-Breast01.[15]

ILD and pneumonitis are known risks associated with T-DXd treatment.[21] The incidence of adjudicated drug-related ILD or pneumonitis in the current analysis was 12.9%, with one patient (0.7%) experiencing a grade 3 event. This was similar to the incidence of ILD or pneumonitis reported in the overall DESTINY-Breast03 population (which increased from 10.5% at first analysis to 15% at second analysis),[21,22] and in DESTINY-Breast01 (13.6%).[15] Interestingly, the incidence of T-DXd-related ILD or pneumonitis was higher in the Japanese population (22.2%) compared with the Asian and global DESTINY-Breast03 populations, although no grade ≥3 events were observed in Japanese patients. In a pooled analysis of nine phase 1 and 2 studies involving heavily pretreated cancer patients who received T-DXd monotherapy, the incidence of ILD or pneumonitis was 15.4%, with most events being low-grade and occurring in the first 12 months of treatment.[25] Notably, the Japanese population is prone to drug-induced lung injuries; patients treated with T-DXd in Japan had an increased risk of developing ILD or pneumonitis compared with those treated outside of Japan.[25] The cause of ILD or pneumonitis due to T-DXd has not been identified and may be due to biological factors or differences in monitoring and management practices specific to Japan. However, these findings are consistent with previous studies indicating a higher prevalence of drug-induced lung injuries in Japan compared with other regions,[26,27] which indicates that close monitoring is necessary for ILD or pneumonitis during treatment with T-DXd. The nature of TEAEs associated with T-DM1 were also similar to that reported in the overall DESTINY-Breast03 population.[22]

The limitation of this subgroup analysis is that it is descriptive in nature and solely focused on the patients from East Asian countries and regions. Further, median OS was not reached in the T-DXd arm, although further analyses may establish this.

T-DXd demonstrated a clinically meaningful PFS and OS benefit compared with T-DM1 in an Asian subpopulation of the DESTINY-Breast03 study, and an acceptable and generally manageable safety profile that was consistent with the overall DESTINY-Breast03 population. These data reinforce the favorable benefit–risk profile of T-DXd in all patients with HER2-positive mBC, including in the Asian subgroup.

AUTHOR CONTRIBUTIONS

Hiroji Iwata: Data curation; investigation; writing – review and editing. **Binghe Xu:** Data curation; investigation; writing – review and editing. **Sung-Bae Kim:** Data curation; investigation; writing – review and editing. **Wei-Pang Chung:** Data curation; investigation; writing – review and editing. **Yeon Hee Park:** Data curation; investigation; writing – review and editing. **Min Hwan Kim:** Data curation; investigation; writing – review and editing. **Ling-Ming Tseng:** Data curation; investigation; writing – review and editing. **Chi-Feng Chung:** Data curation; investigation; writing – review and editing. **Chiun-Sheng Huang:** Data curation; investigation; writing – review and editing. **Jee Hyun Kim:** Data curation; investigation; writing – review and editing. **Joanne Wing Yan Chiu:** Data curation; investigation; writing – review and editing. **Toshinari Yamashita:** Data curation; investigation; writing – review and editing. **Wei Li:** Data curation; investigation; writing – review and editing. **Anton Egorov:** Investigation; writing – review and editing. **Soichiro Nishijima:** Conceptualization; investigation; writing – review and editing. **Shunsuke Nakatani:** Investigation; writing – review and editing. **Yuji Nishiyama:** Investigation; writing – review and editing. **Masahiro Sugihara:** Conceptualization; formal analysis; investigation; writing – review and editing. **Javier Cortés:** Formal analysis; investigation; writing – review and editing. **Seock-Ah Im:** Data curation; investigation; writing – review and editing.

AFFILIATIONS

[1]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan
[2]Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Department of Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[5]Samsung Medical Center, Seoul, Korea
[6]Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[7]Taipei Veterans General Hospital, Taipei, Taiwan
[8]Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan
[9]National Taiwan University Hospital, Taipei, Taiwan
[10]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Korea
[11]Queen Mary Hospital, Hong Kong, China
[12]Kanagawa Cancer Center, Yokohama, Kanagawa, Japan
[13]The First Hospital of Jilin University, Jilin, China
[14]Daiichi Sankyo Inc., Basking Ridge, New Jersey, USA
[15]Daiichi Sankyo, Co., Ltd., Tokyo, Japan
[16]International Breast Cancer Center, Quironsalud Group, Barcelona, Spain
[17]Medical Scientia Innovation Research, Barcelona, Spain
[18]Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Spain
[19]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

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CONFLICT OF INTEREST STATEMENT

Hiroji Iwata received lecture fees or honoraria from AstraZeneca, received research funds from AstraZeneca and Pfizer, and is an editorial board member of *Cancer Science*. Min Hwan Kim received lecture fees or honoraria from AstraZeneca, Boryung Pharmaceutical, Celltrion, Daiichi Sankyo, Eisai, and MSD and research funds from AstraZeneca and Boryung Pharmaceutical. Chiun-Sheng Huang received research funds from Aston Sci., AstraZeneca, Daiichi Sankyo, EirGenix, Eli Lilly, MSD, Novartis, OBI Pharma, Pfizer, Roche, and Seagen (all research funds of Chiun-Sheng Huang are to the institution) and remunerations (not directly related to research) from Pfizer, Novartis, and Gilead. Jee Hyun Kim received research funds from Ono Pharma Korea to the institution. Toshinari Yamashita received research funds from Chugai, Daiichi Sankyo, Pfizer, Ono Pharma, Eisai, and AstraZeneca and lecture fees or honoraria from Chugai, Daiichi Sankyo, Pfizer, Eli Lilly, and Kyowa Kirin. Javier Cortés received annual value of remuneration from Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Eli Lilly, MSD, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, BioInvent, GEMoaB, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, ExpreS2ion Biotechnologies, Jazz Pharmaceuticals, AbbVie, and BridgeBio as an officer or an advisor; annual value of patent royalties or transfer gains from "Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent (Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED)" and "Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy (Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1. LICENSED)"; lecture fees or honoraria from Roche, Novartis, Eisai, Pfizer, Eli Lilly, MSD, Daiichi Sankyo, AstraZeneca, Gilead, and Stemline Therapeutics; research funds from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. Hoffmann-La Roche, Guardant Health, MSD, Pfizer, Piqur Therapeutics, Iqvia, Queen Mary University of London (all research funds of Javier Cortés are to the institution); and remunerations (not directly related to research) from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead, MSD, and Stemline Therapeutics. Family members of Javier Cortés received annual profit from shares from MAJ3 Capital. Seock-Ah Im received research funds from AstraZeneca, Eisai, Daewoong Pharm, Daiichi Sankyo, Pfizer, Roche, and Boryung Pharmaceutical. Anton Egorov is an employee of Daiichi Sankyo and received annual profit from shares from Daiichi Sankyo. Soichiro Nishijima, Shunsuke Nakatani, Yuji Nishiyama, and Masahiro Sugihara are employees of Daiichi Sankyo. Binghe Xu, Sung-Bae Kim Wei-Pang Chung, Yeon Hee Park, Ling-Ming Tseng, Chi-Feng Chung, Joanne Wing Yan Chiu, and Wei Li have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENTS

Approval of the research protocol by an Institutional Review Board: The study protocol, amendments, informed consent forms, and information sheets were approved by the Independent Ethics Committees or Institutional Review Boards at each study site.
Informed Consent: Written informed consent was collected from all participants before initiating the study.
Registry and the Registration No. of the study/trial: The study (ClinicalTrials.gov; NCT03529110) was conducted in accordance with the ethical standards of the Declaration of Helsinki and the International Council for Harmonization consolidated Guideline E6 for Good Clinical Practice and other applicable regulations.
Animal studies: N/A.

ORCID

Hiroji Iwata https://orcid.org/0000-0002-0242-4718

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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