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Updated Results From DESTINY-Breast01, a Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in HER2-Positive Metastatic Breast Cancer

Shanu Modi,[1] Cristina Saura,[2] Toshinari Yamashita,[3] Yeon Hee Park,[4] Sung-Bae Kim,[5] Kenji Tamura,[6] Fabrice Andre,[7] Hiroji Iwata,[8] Yoshinori Ito,[9] Junji Tsurutani,[10,11] Joohyuk Sohn,[12] Neelima Denduluri,[13] Christophe Perrin,[14] Kenjiro Aogi,[15] Eriko Tokunaga,[16] Seock-Ah Im,[17] Keun Seok Lee,[18] Sara A. Hurvitz,[19] Javier Cortes,[20] Caleb Lee,[21] Yali Liu,[21] Lin Zhang,[21] Javad Shahidi,[21] Antoine Yver,[21] Jose Baselga,[22] and Ian E. Krop[23]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Kanagawa Cancer Center, Yokohama, Japan; [4]Samsung Medical Center, Seoul, Korea ; [5]Asan Medical Center, University of Ulsan College of Medicine Seoul, Korea ; [6]Shimane University Hospital Innovative Cancer Center, Izumo, Japan; [7]Gustave Roussy, Université Paris-Sud, Villejuif, France; [8]Aichi Cancer Center Hospital, Nagoya, Japan; [9]The Cancer Center Institute Hospital of JFCR, Tokyo, Japan; [10]Kindai University Faculty of Medicine, Osaka, Japan; [11]Advanced Cancer Translational Research Institute, Showa University, Tokyo, Japan; [12]Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea ; [13]The US Oncology Network, Virginia Cancer Specialists, Arlington, VA; [14]Centre Eugène Marquis, Rennes, France; [15]NHO Shikoku Cancer Center, Matsuyama, Japan; [16]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [17]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [18]National Cancer Center Korea, Gyeonggi, Korea ; [19]University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; [20]IOB Institute of Oncology, Grupo Quiron, Madrid and Barcelona, Spain and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [21]Daiichi Sankyo, Inc, Basking Ridge, NJ; [22]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD; [23]Dana-Farber Cancer Institute, Boston, MA

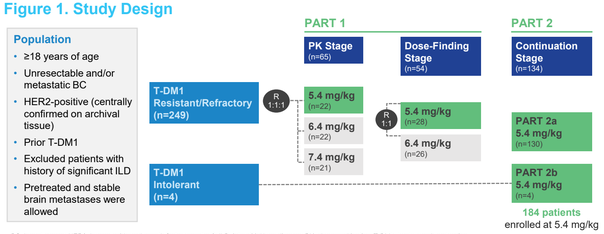
BACKGROUND

- T-DXd is an antibody-drug conjugate consisting of a humanized monoclonal anti-HER2 antibody joined to a potent topoisomerase I inhibitor payload via a cleavable tetrapeptide-based linker[1,2]
- In the phase 2 DESTINY-Breast01 study, T-DXd demonstrated remarkable antitumor activity and a tolerable safety profile in pre-treated patients with HER2-positive metastatic breast cancer (with a data cutoff of August 1, 2019)[3]
- Based on these results, T-DXd was approved for the treatment of adult patients with HER2-positive, unresectable or metastatic breast cancer who have received ≥2 prior anti-HER2–based regimens in the metastatic setting (US)[4] or had prior chemotherapy and are refractory to or intolerant of standard treatments (Japan)[5]
- Here we present updated study results at the most recent data cutoff (June 8, 2020)

METHODS

- DESTINY-Breast01 (NCT03248492) is a phase 2, open-label, multicenter, 2-part study evaluating T-DXd in adult patients with HER2-positive (centrally confirmed; immunohistochemistry [IHC] 3+ or in-situ hybridization [ISH]+), unresectable or metastatic breast cancer (Figure 1)
- The primary endpoint was confirmed objective response rate (ORR) by independent central review (ICR) per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 in patients treated with T-DXd 5.4 mg/kg q3w
- Secondary endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), pharmacokinetics and safety
- T-DXd is associated with an important identified risk of interstitial lung disease (ILD); these events are independently adjudicated and actively managed by patient monitoring, dose modification, and adherence to the ILD management guidelines, which were updated over the course of the study

Figure 1. Study Design



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

RESULTS

Patients

- A total of 184 patients who had received ≥2 anti-HER2–based regimens received T-DXd 5.4 mg/kg q3w
- Demographic and baseline clinical characteristics are shown in Table 1

Table 1. Demographics and Baseline Clinical Characteristics

Characteristic	T-DXd 5.4 mg/kg (N=184)[a]
Age, median (range), years	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+	 83.7 15.2 / 1.1
Presence of visceral disease, %	91.8
Prior treatment, median (range) Trastuzumab / T-DM1, % Pertuzumab, % Other anti-HER2 antibodies or ADCs, % HER2 tyrosine kinase inhibitors, % Hormone therapy, % Other systemic therapy, %	6 (2-27) 100 / 100 65.8 6.0 50.5 48.9 99.5

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

EFFICACY RESULTS

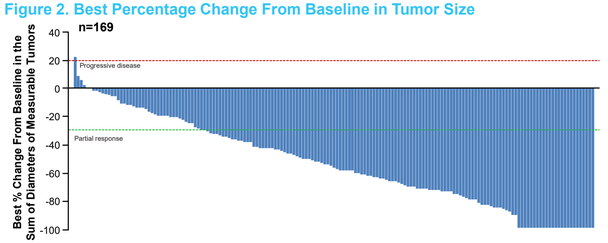
- Median follow-up was 20.5 months (range, 0.7-31.4 months), representing an additional 9.4 months from the prior analysis; 20.1% of patients remained on treatment, with 80 patients (43.4%) on treatment for >12 months and 11 (6.0%) on treatment for >24 months
- With increased maturity of the data duration of responses increased, now with a **median DOR of 20.8 months** (Table 2; Figure 3); 65.2% of patients were censored
  - The confirmed objective response rate was 61.4% (95% CI, 54.0%-68.5%) (Table 2; Figure 3)
- Median PFS increased to 19.4 months (95% CI, 14.1 months-NE; Table 2; Figure 4); 62.0% of patients were censored
- The estimated percent of patients alive at 12 and 18 months was 85% (95% CI, 79%-90%) and 74% (95% CI, 67%-80%), respectively
  - Preliminary median OS was 24.6 months (95% CI, 23.1 months - not estimable; Figure 5)
  - mOS was estimated at 35% maturity, with 119 patients censored and only 17 patients at risk at 24 months; additional follow-up is required for more mature OS data

Table 2. Summary of Efficacy

Intent-to-treat analysis	August 2019 data cutoff T-DXd 5.4 mg/kg (N=184)	June 2020 data cutoff T-DXd 5.4 mg/kg (N=184)
Duration of follow-up, median (range)	11.1 months (0.7-19.9 months)	20.5 months (0.7-31.4 months)
Patients remaining on treatment	42.9% (n=79)	20.1% (n=37)
Confirmed ORR by ICR	60.9% (n=112) (95% CI, 53.4%-68.0%)	**61.4% (n=113)** (95% CI, 54.0%-68.5%)
CR	6.0% (n=11)	6.5% (n=12)
PR	54.9% (n=101)	54.9% (n=101)
SD	36.4% (n=67)	35.9% (n=66)
PD	1.6% (n=3)	1.6% (n=3)
Not evaluable	1.1% (n=2)	1.1% (n=2)
Duration of response, median	14.8 months (95% CI, 13.8-16.9 months)	**20.8** months[a] (95% CI, 15.0 months-NE)
Time to response, median	1.6 months (95% CI, 1.4-2.6 months)	
PFS, median	16.4 months (95% CI, 12.7 months-NE)	19.4 months (95% CI, 14.1 months-NE)

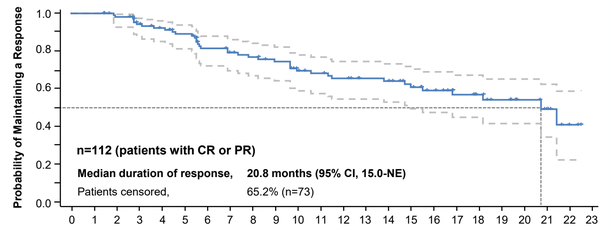
CR, complete response; ICR, independent central review; NE, not estimable; ORR, objective response rate (CR + PR); PD, progressive disease; PR, partial response; SD, stable disease.
[a] One patient had a PR prior to the 08 Jun 2020 cutoff date which was confirmed after the cut-off date. The patient had a confirmed best overall response of PR on the first PR date in the central data but was not included in the analysis of duration of response.

Figure 2. Best Percentage Change From Baseline in Tumor Size



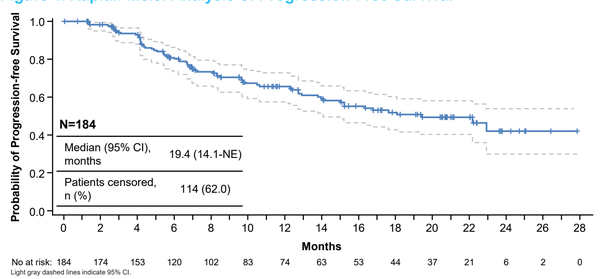
By independent central review.

Figure 3. Kaplan-Meier Analysis of Duration of Response



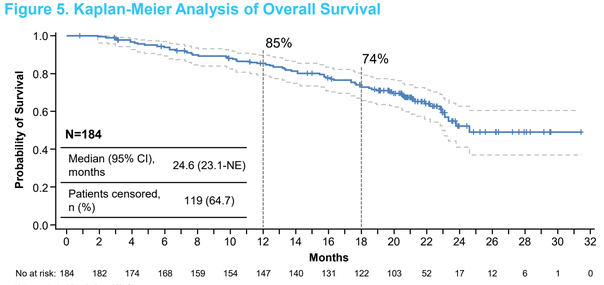
Light gray dashed lines indicate 95% CI.

Figure 4. Kaplan-Meier Analysis of Progression-Free Survival



Light gray dashed lines indicate 95% CI.

Figure 5. Kaplan-Meier Analysis of Overall Survival



Light gray dashed lines indicate 95% CI.

SAFETY RESULTS

- The overall safety profile of T-DXd was consistent with what has been previously reported
- T-DXd continues to demonstrate a generally tolerable safety profile with few treatment discontinuations due to adverse events with longer treatment (median treatment duration, 10.1 months [range, 0.7-29.5 months]) (Table 3)
- 3 new cases of T-DXd–related ILD as determined by an independent adjudication committee were reported (Table 4). Most first ILD events occurred during the first 12 months of treatment (Figure 6); among the patients who did not have an ILD event for ≥12 months, only 1 subsequently developed ILD; 2 cases were pending adjudication at data cutoff
- There was 1 additional case of left ventricle ejection fraction (LVEF) decrease (grade 2) and no new TEAEs of cardiac failure reported since the prior analysis
  - 4 total events of LVEF decrease (3 grade 2 and 1 grade 3)
  - 2 total cardiac failures (1 grade 1 and 1 grade 2) with no LVEF decrease was observed during treatment

Table 3. Overall Safety Summary

Type of Adverse Event, n (%)[a]	August 2019 data cutoff T-DXd 5.4 mg/kg (N=184)	June 2020 data cutoff T-DXd 5.4 mg/kg (N=184)
Any TEAE Drug-related	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)
Dose adjustments		
TEAE associated with discontinuation Drug-related	28 (15.2) 27 (14.7)	34 (18.5) 33 (17.9)
TEAE associated with dose reduction Drug-related	43 (23.4) 40 (21.7)	44 (23.9) 39 (21.2)[b]
TEAE associated with dose interruption Drug-related	65 (35.3) 53 (28.8)	75 (40.8) 60 (32.6)
Death		
TEAE associated with death[c] Drug-related	9 (4.9) 2 (1.1)	10 (5.4) 3 (1.6)

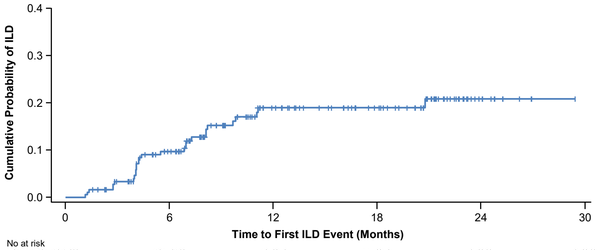
TEAE, treatment-emergent adverse event.
[a]Relationship to study drug was determined by the treating investigator. [b]Based on updated investigator assessment. [c]Each of the following TEAEs was associated with a fatal outcome: respiratory failure, acute respiratory failure, disease progression, general 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 ILD/Pneumonitis[a]

Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

[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.

Figure 6. Cumulative Probability of Adjudicated Drug-related Any-grade ILD[a]



[a] In Patients With HER2-Positive Breast Cancer (T-DXd 5.4 mg/kg).

CONCLUSIONS

In this updated analysis of the single-arm, phase 2 DESTINY-Breast01 study with 9.4 months of additional follow-up (20.5 months median duration of follow-up):

- T-DXd continued to demonstrate clinically meaningful and durable efficacy with an unprecedented median duration of response of 20.8 months
  - T-DXd treatment resulted in a robust survival outcome, with 18-month landmark OS of 74%
- T-DXd showed a generally tolerable safety profile, consistent with previous results, with few treatment discontinuations due to TEAEs with longer treatment
  - In this analysis, the risk of adjudicated drug-related ILD appears lower after approximately 12 months on treatment, suggesting that the risk of developing ILD is not related to a cumulative dose of T-DXd; continued attention to pulmonary symptoms and careful monitoring is warranted
- The consistent benefit/risk profile provides confidence in treatment efficacy, which will be further evaluated in the ongoing randomized, controlled, phase 3 DESTINY-Breast02 study of T-DXd vs investigator's choice of treatment (NCT03523585)

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DISCLOSURES

This study was sponsored by Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for T-DXd (DS-8201).

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