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Exposure-Efficacy and Exposure-Safety Analysis of Trastuzumab Deruxtecan in Patients With Advanced/Metastatic HER2+ Breast Cancer: Analyses From Phase 3 Studies DESTINY-Breast02 and DESTINY-Breast03

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Objectives

- To evaluate the relationship between trastuzumab deruxtecan (T-DXd) pharmacokinetic exposure and efficacy/safety endpoints in patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC) who received T-DXd 5.4 mg/kg once every 3 weeks (Q3W)

Conclusions

- Exposure-response analyses support a clinically meaningful progression-free survival (PFS) and overall survival (OS) benefit with T-DXd 5.4 mg/kg in patients with HER2+ BC and an acceptable and generally manageable safety profile
  - Clinically meaningful efficacy in the T-DXd arm relative to the control arm was observed in both DESTINY-Breast02 (DB-02; PFS, 17.8 months with T-DXd vs 6.9 months with treatment of physician's choice [TPC]) and DESTINY-Breast03 (DB-03; PFS, 28.8 months with T-DXd vs 6.8 months with trastuzumab emtansine [T-DM1])[1,2]
  - Using data from DB-02 and DB-03, exposure-efficacy analyses supported a flat exposure-response relationship for PFS because of the narrow exposure range resulting from the single dose level (5.4 mg/kg Q3W) of T-DXd in HER2+ BC
  - T-DXd exposure was a significant predictor of OS in DB-02 but not in DB-03
  - Exposure-safety analyses across 12 clinical trials (phases 1-3) showed any-grade and grade ≥3 interstitial lung disease (ILD) event rates were low but increased with increasing T-DXd exposures; event rates for T-DXd 5.4 mg/kg are comparable with prior studies
- Overall, these model-based analyses continue to support T-DXd 5.4 mg/kg Q3W dosing in patients with previously treated HER2+ BC

Introduction

- T-DXd is approved for the treatment of adult patients with unresectable or metastatic HER2+ BC who have received a prior anti-HER2–based regimen, HER2-low BC who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, non–small cell lung cancer whose tumors have activating *ERBB (HER2)* mutations and who have received a prior systemic therapy, and locally advanced or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen[3]
- Using data from 5 phase 1 and 2 clinical trials, previous exposure-response analyses for key efficacy and safety endpoints supported the recommended dose of T-DXd 5.4 mg/kg Q3W in patients with HER2+ BC[4]
- We present outcomes of an updated analysis to evaluate exposure-efficacy relationships for T-DXd 5.4 mg/kg Q3W in DB-02 and DB-03 and exposure-safety relationships across 12 clinical trials with T-DXd, including phase 3 trials

Methods

Exposure-Efficacy Analyses

- Exposure-efficacy relationships were evaluated in 648 patients who were treated with T-DXd 5.4 mg/kg Q3W in DB-02 (n = 394) and DB-03 (n = 254)
  - DB-02 was a multicenter, randomized, open-label, phase 3 study of T-DXd (n = 406) versus TPC (n = 202) in patients with HER2+, unresectable and/or metastatic BC who were previously treated with T-DM1 (data cutoff: June 30, 2022)[1]
  - DB-03 was a multicenter, randomized, open-label, phase 3 study of T-DXd (n = 261) versus T-DM1 (n = 263) in patients with HER2+, unresectable and/or metastatic BC who were previously treated with trastuzumab and a taxane (data cutoff: May 21, 2021)[2]
- Semiparametric Cox proportional hazards models were used to evaluate the exposure-efficacy relationship for primary efficacy endpoints (PFS by blinded independent central review and OS)
- T-DXd exposure metrics included maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the serum concentration-time curve (AUC) at cycle 1 and steady state (AUC_{ss}), and the average serum concentration to the time of efficacy event ($C_{avg\text{-}TOE}$)
- When an exposure-efficacy relationship was identified, covariate analysis was performed using patient characteristics (such as age, baseline tumor size, body weight) as additive terms in Cox regression models

Exposure-Safety Analyses

- Exposure-safety analyses were conducted using an integrated dataset across 12 phase 1 to 3 clinical trials (N = 2216, 68.7% BC), including the phase 3 trials, DB-02, DB-03, and DESTINY-Breast04 (DB-04)
- Parametric and semiparametric time-to-event models were used to describe the exposure-safety relationship for primary safety endpoints (any grade and grade ≥3 adjudicated drug-related ILD)
- T-DXd or DXd exposure metrics included AUC_{ss} for any grade ILD and C_{max} at steady state ($C_{max,ss}$) for grade ≥3 adjudicated drug-related ILD
- When an exposure-safety relationship was identified, covariate analysis was performed using patient characteristics (such as age, baseline tumor size, body weight) as additive terms in Cox regression models
- A covariate subgroup with a probability and CI that does not overlap the full population median is interpreted as a significant deviation and therefore a predictor of efficacy/safety outcomes
- Exploratory analyses were conducted for other safety endpoints, including grade ≥3 treatment-emergent adverse events (TEAEs), using data from DB-02 and DB-03

Results

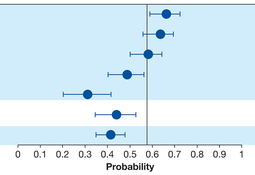
Exposure-Efficacy Analyses

- 648 patients from DB-02 and DB-03 were included in the exposure-efficacy analyses (median age, 54 years; proportion of female patients, 99.4%)
- Although there was a trend for lower PFS in patients with lower exposure, there were no statistically significant relationships between T-DXd exposure metrics and PFS over the range of exposures
- In DB-02, significant predictors of reduced PFS at 24 months were a history of central nervous system (CNS) metastases (n = 114), baseline tumor size, and mild/moderate hepatic impairment (n = 207) (**Figure 1A**)
- A history of CNS metastases (n = 59) and baseline tumor size were significant predictors of reduced PFS at 24 months in DB-03 (**Figure 1B**)
- Tumor baseline size at the 95th percentile corresponded with lower response rates, but this should be considered within the broader context of multiple predictors and patient-specific factors influencing the relative efficacy of T-DXd in different patient subgroups

Figure 1. PFS Probability for Significant Covariates at 24 Months in (A) DB-02 and (B) DB-03

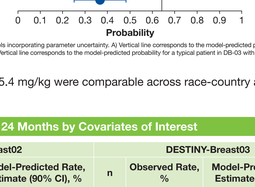
A

Parameter	Percentile	Value	Probability
Baseline target tumor size, mm	5th	13	0.633
	25th	26.2	0.632
	50th	47	0.580
	75th	79	0.491
	95th	138.2	0.312
History of CNS metastases			0.439
Mild/Moderate hepatic impairment			0.416



B

Parameter	Percentile	Value	Probability
Baseline target tumor size, mm	5th	14.7	0.725
	25th	26	0.688
	50th	41	0.634
	75th	64.8	0.536
	95th	122.7	0.261
History of CNS metastases			0.361



Dot and horizontal line correspond to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. A) Vertical line corresponds to the model-predicted probability for a typical patient in DB-02 with baseline tumor size of 47 mm, no history of CNS metastases, and normal hepatic function. B) Vertical line corresponds to the model-predicted probability for a typical patient in DB-03 with median baseline tumor size of 41 mm, and no history of CNS metastases.

- Simulated PFS event probabilities at 24 months for T-DXd 5.4 mg/kg were comparable across race-country and region categories in patients with BC (**Table 1**)

Table 1. Observed and Model-Predicted Rates of PFS at 24 Months by Covariates of Interest

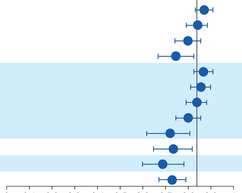
Category	DESTINY-Breast02			DESTINY-Breast03		
	n	Observed Rate, %	Model-Predicted Rate, Estimate (90% CI), %	n	Observed Rate, %	Model-Predicted Rate, Estimate (90% CI), %
Race-country						
Non-Asian	277	43.3	41.0 (36.3-46.0)	106	58.3	52.4 (46.2-59.1)
Asian non-Japan	74	38.3	44.4 (39.2-50.0)	112	47.3	52.3 (46.0-58.3)
Asian Japan	43	39.2	39.3 (33.0-45.8)	36	56.7	55.6 (48.2-62.6)
Region						
Europe	146	43.5	41.6 (36.6-46.6)	52	57.9	55.4 (49.0-61.9)
Asia	108	39.6	42.7 (37.3-48.0)	146	50.8	53.0 (47.3-59.2)
North America	40	51.2	39.4 (33.1-46.0)	17	51.0	49.3 (37.5-59.7)
Rest of the world	100	40.3	41.0 (35.9-46.2)	39	58.5	49.9 (41.7-57.1)

- There was a significant relationship between T-DXd exposure metrics and OS ($P < 0.01$) in DB-02 but not in DB-03
- In DB-02, CNS metastases, mild/moderate hepatic impairment, tumor size at the 95th percentile, HER2 IHC 2+ BC, and age at the 95th percentile were significant predictors of reduced OS at 24 months (**Figure 2A**)
- In DB-03, presence of liver metastases, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥1, and tumor size at the 95th percentile were significant predictors of reduced OS at 24 months (**Figure 2B**)

Figure 2. OS Probability for Significant Covariates at 24 Months in (A) DB-02 and (B) DB-03

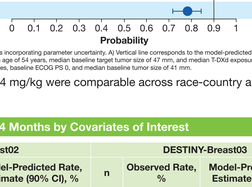
A

Parameter	Percentile	Value	Probability
T-DXd trough concentration cycle 1, µg/mL	5th	2.7	0.701
	25th	4.8	0.783
	50th	6.8	0.84
	75th	8.5	0.879
	95th	12.2	0.935
Age, years	5th	36	0.899
	25th	45	0.873
	50th	54	0.84
	75th	63	0.8
	95th	72.3	0.749
Baseline target tumor size, mm	5th	13	0.868
	25th	26.2	0.856
	50th	47	0.837
	75th	79	0.803
	95th	138.2	0.723
HER2 IHC 2+			0.737
History of CNS metastases			0.692
Mild/Moderate hepatic impairment			0.728



B

Parameter	Percentile	Value	Probability
Baseline target tumor size, mm	5th	14.7	0.924
	25th	26	0.913
	50th	41	0.898
	75th	64.8	0.867
	95th	122.7	0.756
Liver metastases			0.802
ECOG PS ≥1			0.784



Dot and horizontal line correspond to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. A) Vertical line corresponds to the model-predicted probability for a typical patient in DB-02 with HER2 IHC 3+ breast cancer, no history of CNS metastases, normal hepatic function, median age of 54 years, median baseline target tumor size of 47 mm, and median T-DXd exposure for 5.4 mg/kg Q3W. B) Vertical line corresponds to the model-predicted probability for a typical patient in DB-03 with no liver metastases, baseline ECOG PS 0, and median baseline tumor size of 41 mm.

- Simulated OS event probabilities at 24 months for T-DXd 5.4 mg/kg were comparable across race-country and region categories in patients with BC (**Table 2**)

Table 2. Observed and Model-Predicted Rates of OS at 24 Months by Covariates of Interest

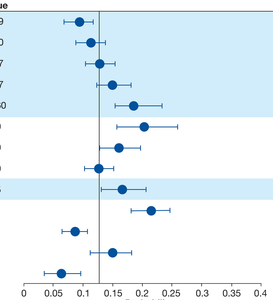
Category	DESTINY-Breast02			DESTINY-Breast03		
	n	Observed Rate, %	Model-Predicted Rate, Estimate (90% CI), %	n	Observed Rate, %	Model-Predicted Rate, Estimate (90% CI), %
Race-country						
Non-Asian	277	64.8	66.0 (61.4-70.5)	106	77.6	77.1 (72.1-82.1)
Asian non-Japan	74	73.1	68.8 (63.3-73.8)	112	77.4	75.5 (69.9-80.5)
Asian Japan	43	59.3	61.3 (53.8-68.0)	36	77.8	82.4 (77.0-86.9)
Region						
Europe	146	66.4	67.1 (62.3-71.6)	52	80.1	82.3 (77.2-86.4)
Asia	108	66.3	65.9 (60.6-70.6)	146	77.2	77.5 (72.2-81.8)
North America	40	54.8	62.4 (54.5-69.7)	17	69.3	69.2 (57.2-78.9)
Rest of the world	100	67.9	65.7 (60.5-70.7)	39	73.9	73.9 (66.3-80.7)

Exposure-Safety Analyses

- There was a statistically significant relationship ($P < 0.001$) between increasing T-DXd exposures from dose levels ranging from 0.8 to 8 mg/kg and increasing hazard of any grade and grade ≥3 ILD
- At Day 360, the incidence rate for any grade ILD with T-DXd 5.4 mg/kg Q3W was higher in patients with lower creatinine clearance, patients with lower oxygen saturation, and Asian patients from Japan (**Figure 3**)

Figure 3. Any Grade ILD Probability for Significant Covariates at Day 360

Parameter	Percentile	Value	Probability
T-DXd AUC_{ss} µg/mL×day	5th	479	0.094
	25th	660	0.113
	50th	787	0.128
	75th	937	0.149
	95th	1160	0.185
Creatinine clearance, mL/min		30	0.203
		60	0.161
		90	0.127
Oxygen saturation, %		95	0.166
Asian Japan			0.215
Asian non-Japan			0.087
Non-Asian North America			0.150
Rest of the world			0.064

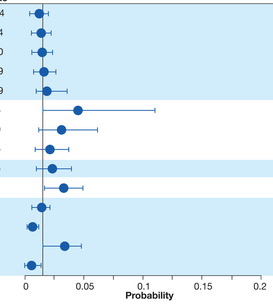


Dot and horizontal line correspond to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical patient (non-Asian from Europe, oxygen saturation of 98%, and median creatinine clearance of 88 mL/min) and median T-DXd exposure for 5.4 mg/kg Q3W in the overall population including all tumor types. Creatinine clearance values correspond to boundaries for normal (90 mL/min), mild (60 mL/min), and moderate (30 mL/min) renal impairment.

- At Day 360, the incidence rate for grade ≥3 ILD with T-DXd 5.4 mg/kg Q3W was higher in patients with lower oxygen saturation, patients with lower albumin levels, and patients with ECOG PS ≥1 (**Figure 4**); grade ≥3 ILD rates were comparable and low across race-country and region
- Findings for ILD and exploratory safety endpoints were generally consistent with previous model-predicted adverse event rates[4]

Figure 4. Grade ≥3 ILD Probability for Significant Any Grade ILD Covariates at Day 360

Parameter	Percentile	Value	Probability
T-DXd $C_{max,ss}$ µg/mL	5th	93.4	0.012
	25th	114	0.014
	50th	130	0.015
	75th	149	0.016
	95th	179	0.019
Albumin, g/L		25	0.045
		30	0.031
		35	0.021
Oxygen saturation, %		95	0.023
ECOG PS ≥1			0.033
Asian Japan			0.014
Asian non-Japan			0.007
Non-Asian North America			0.034
Rest of the world			0.006



Dot and horizontal line correspond to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical patient (non-Asian from Europe, with ECOG PS 0 and oxygen saturation of 98%) and median T-DXd exposure for 5.4 mg/kg Q3W in the overall population including all tumor types.

Abbreviations

AUC, area under the concentration-time curve; AUC_{ss}, area under the concentration-time curve at steady state; BC, breast cancer; $C_{avg\text{-}TOE}$, average serum concentration to time of event; CI, confidence interval; C_{max}, maximum serum concentration; $C_{max,ss}$, maximum serum concentration at steady state; C_{min}, minimum serum concentration; CNS, central nervous system; DB-02, DESTINY-Breast02; DB-03, DESTINY-Breast03; DB-04, DESTINY-Breast04; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; IHC, immunohistochemistry; ILD, interstitial lung disease; OS, overall survival; PFS, progression-free survival; Q, quartile; Q3W, once every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

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Disclosures

Dr. Claire Li is an employee of Daiichi Sankyo Inc.

DESTINY-Breast02/03

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