Exploratory biomarker analysis of trastuzumab deruxtecan versus physician's choice of chemotherapy in HER2-low/ultralow, hormone receptor–positive metastatic breast cancer in DESTINY-Breast06

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Introduction

- The DESTINY-Breast06 trial led to US Food and Drug Administration and European Medicines Agency approval of trastuzumab deruxtecan (T-DXd) for the treatment of patients with hormone receptor–positive (HR+), human epidermal growth factor receptor-2 (HER2)-low or HER2-ultralow unresectable or metastatic breast cancer (mBC) who have progressed after receiving ≥1 endocrine therapy and are not considered suitable for endocrine therapy as the next line of treatment[1-3]
- PI3K/AKT pathway, *ESR1*, and *BRCA1/2* mutations are potentially actionable biomarkers that can inform treatment decision-making in this setting[4-8]
- We report an exploratory circulating tumor DNA (ctDNA) analysis of DESTINY-Breast06 evaluating clinical outcomes according to baseline genomic status (data cutoff: March 18, 2024)

Conclusions

- In the DESTINY-Breast06 biomarker-evaluable population, T-DXd demonstrated a greater progression-free survival (PFS) benefit than physician's choice of chemotherapy (TPC) regardless of baseline PI3K/AKT pathway, *ESR1*, or *BRCA1/2* mutation status. Objective response rate (ORR) and second progression-free survival/time from randomization to second progression or death (PFS2) also favored T-DXd over TPC regardless of baseline mutation status
- There was a potentially greater efficacy benefit with T-DXd in the *BRCA1/2* mutation subgroup than all other subgroups, albeit with a small sample size
- Findings in the biomarker population were consistent with the intent-to-treat (ITT) population[1] and provide evidence that T-DXd is an effective treatment for patients with HER2-low or HER2-ultralow mBC after ≥1 endocrine-based therapy regardless of PI3K/AKT pathway, *ESR1*, or *BRCA1/2* mutation status

Methods

DESTINY-Breast06: a randomized, multicenter, open-label, phase 3 clinical trial (NCT04494425).[1]

Patient population
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH–) **OR** HER2-ultralow (IHC 0 with membrane staining) status
- Chemotherapy naïve in the mBC setting

Prior lines of therapy
- ≥2 lines ET ± targeted therapy for mBC **OR**
- 1 line for mBC **AND**
  - Progression ≤6 mo of starting first-line ET + CDK4/6i **OR**
  - Recurrence ≤24 mo of starting adjuvant ET

R 1:1

- T-DXd 5.4 mg/kg Q3W (n = 436)
- TPC (n = 430)
  - Capecitabine (59.8%)
  - Nab-paclitaxel (24.4%)
  - Paclitaxel (15.8%)

HER2-low = 713
HER2-ultralow = 153

Baseline characteristics[a]
- Median age ~58 years; ECOG PS ≥1 ~40%
- De-novo mBC ~31%; liver metastases ~67%; visceral disease ~85%; primary endocrine resistance[b] ~31%

Primary endpoint
- PFS (BICR) in HER2-low:
  - Median **13.2 mo T-DXd** vs 8.1 mo TPC (hazard ratio, 0.62; *P* <0.001)[c]

Secondary endpoints
- PFS (BICR) in ITT (HER2-low + HER2-ultralow):
  - Median **13.2 mo T-DXd** vs 8.1 mo TPC (hazard ratio, 0.64; *P* <0.001)[d]
- OS: data maturity ~40% at first interim analysis
- PFS2 (INV)
- Safety and tolerability

Exploratory endpoint
- Biomarkers

Exploratory baseline biomarker analysis:
- PI3K/AKT (*AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function), *ESR1*, and *BRCA1/2* mutations
  - Germline and somatic *BRCA1/2* mutations were considered if there was evidence of prior actionability
  - Germline mutations in other genes were considered as variation of uncertain significance/ineligible for subsequent association analysis
  - ≥20 events were required across arms to ensure robust interpretation of clinical outcomes
  - No corrections for tumor fraction; analysis was applied to baseline samples and detection/non-detection of alterations only, and gene deletions were not considered
  - No formal significance testing; no corrections for multiple testing

ctDNA analysis set[e]
GuardantOMNI™ 500-gene liquid biopsy assay
(n = 682)

Biomarker-evaluable population[f]
(n = 625)

- T-DXd (n = 318)
- TPC (n = 307)

[a]As averaged across treatment groups in the ITT population.
[b]Defined as relapse that had occurred during the first 2 years of adjuvant ET or progressive disease that had occurred during the first 6 months of first-line ET for mBC.[9]
[c]The hazard ratio and its CI were estimated from a stratified Cox proportional hazards model, adjusting for prior CDK4/6i use (yes vs no) and HER2 IHC expression (IHC 1+ vs IHC 2+/ISH−).
[d]The hazard ratio and its CI were estimated from an unstratified Cox proportional hazards model.
[e]Excluded 121 patients from Brazil, China, and Denmark because local regulations restrict use of patient samples for genomic testing for exploratory purposes, 54 patients with samples not received, and 9 patients who failed quality check.
[f]Excluded 57 patients with putative low tumor content.

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Plain language summary

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

Poster presented at Miami Breast Cancer Conference, March 5-8, 2026, Miami, FL, by Alyssa Morgan, PharmD, BCOP.
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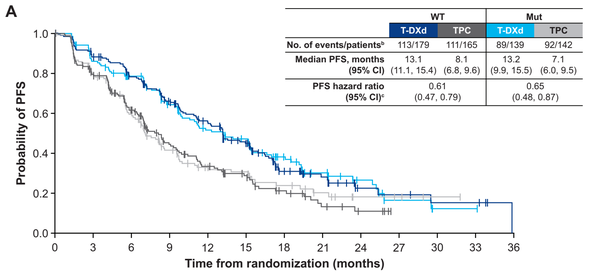
Results

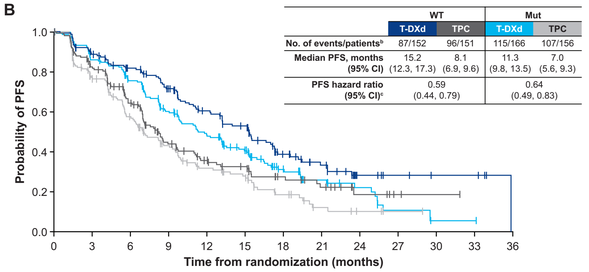
T-DXd improved PFS versus TPC regardless of baseline PI3K/AKT pathway[a] (A), *ESR1* (B), and *BRCA1/2* (C) mutation status.

A



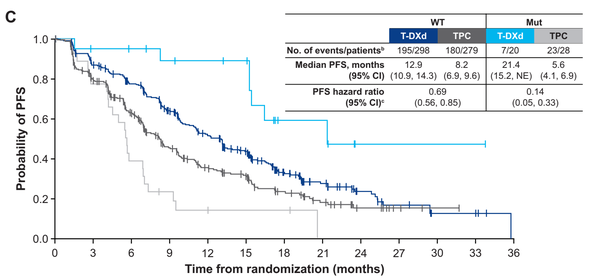
	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients[b]	113/179	111/165	89/139	92/142
Median PFS, months (95% CI)	13.1 (11.1, 15.4)	8.1 (6.8, 9.6)	13.2 (9.9, 15.5)	7.1 (6.0, 9.5)
PFS hazard ratio (95% CI)[c]	0.61 (0.47, 0.79)		0.65 (0.48, 0.87)	

B



	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients[b]	87/152	96/151	115/166	107/156
Median PFS, months (95% CI)	15.2 (12.3, 17.3)	8.1 (6.9, 9.6)	11.3 (9.8, 13.5)	7.0 (5.6, 9.3)
PFS hazard ratio (95% CI)[c]	0.59 (0.44, 0.79)		0.64 (0.49, 0.83)	

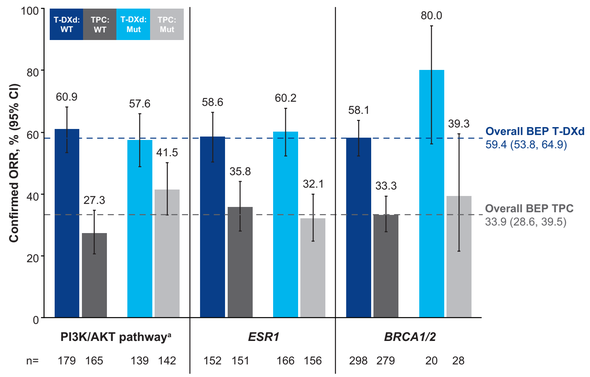
C



	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients[b]	195/298	180/279	7/20	23/28
Median PFS, months (95% CI)	12.9 (10.9, 14.3)	8.2 (6.9, 9.6)	21.4 (15.2, NE)	5.6 (4.1, 6.9)
PFS hazard ratio (95% CI)[c]	0.69 (0.56, 0.85)		0.14 (0.05, 0.33)	

Vertical lines indicate censored observations; CIs for medians were derived based on the Brookmeyer-Crowley method; BICR was assessed according to RECIST 1.1.
[a]Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations.
[b]Number of patients with mutation.
[c]Hazard ratios and CIs were based on a Cox proportional hazards model with no stratification factors, and ties were handled by the Efron approach (a hazard ratio <1 favored T-DXd vs TPC).

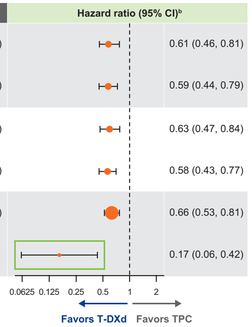
Confirmed ORR was improved with T-DXd versus TPC regardless of baseline PI3K/AKT pathway, *ESR1*, or *BRCA1/2* mutation status.



Confirmed ORR CIs were calculated using the Clopper-Pearson method; BICR was assessed according to RECIST 1.1; confirmed ORR in ITT population: T-DXd, 57.3% (95% CI 52.5, 62.0); TPC, 31.2% (95% CI 26.8, 35.8).[1]
[a]Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations.

Delay in PFS2 favored T-DXd versus TPC regardless of PI3K/AKT pathway, *ESR1*, or *BRCA1/2* mutation status.

		No. of events/patients		Median PFS2, mo (95% CI)		
		T-DXd	TPC	T-DXd	TPC	Hazard ratio (95% CI)[b]
PI3K/AKT pathway[a]	WT	96/179	102/165	19.2 (17.3, 23.7)	14.9 (12.7, 17.1)	0.61 (0.46, 0.81)
	Mut	76/139	103/142	19.5 (15.7, 26.4)	13.6 (11.4, 15.2)	0.59 (0.44, 0.79)
ESR1	WT	82/152	102/151	20.0 (17.0, 23.8)	14.6 (11.8, 16.4)	0.63 (0.47, 0.84)
	Mut	90/166	103/156	19.4 (17.1, 25.3)	13.7 (12.5, 16.7)	0.58 (0.43, 0.77)
BRCA1/2	WT	165/298	183/279	19.2 (17.3, 20.8)	14.9 (12.7, 16.7)	0.66 (0.53, 0.81)
	Mut	7/20	22/28	33.7 (27.7, NE)	11.8 (8.4, 14.6)	0.17 (0.06, 0.42)



Size of circle is proportional to no. of events; PFS2 was defined by investigators according to local standard clinical practice as time from randomization to second progression (earliest progression event following first subsequent therapy) or death; PFS2 was calculated using the Kaplan–Meier technique; CIs for median were derived based on the Brookmeyer-Crowley method.
[a]Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations.
[b]The hazard ratio and CI were calculated using a Cox proportional hazards model with no stratification factors, and ties were handled by the Efron approach (a hazard ratio <1 favored T-DXd vs TPC).

Abbreviations

AKT, protein kinase B, BEP, biomarker-evaluable population; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator; ISH−, in situ hybridization–negative; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; Mut, mutation; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival/time from randomization to second progression or death; PI3K, phosphoinositide 3-kinase; Q3W, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type.

Acknowledgments

We thank the patients and their families for participation, study site staff for their contributions, and members of the independent data monitoring committee and the interstitial lung disease adjudication committee.

Medical writing support, under the direction of the authors, was provided by Jade Murdoch, MChD/BChD, of Helios Medical Communications, part of Helios Global Group, and Sara Duggan, PhD, of ApotheCom, and was funded by AstraZeneca in accordance with Good Publication Practice (GPP) guidelines (http://www.ismpp.org/gpp-2022).

Disclosures

The presenting author, Alyssa Morgan, PharmD, BCOP, is an employee of AstraZeneca.

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